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A scoping review of the management of esophageal cancer and the shift toward the minimally invasive approach

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Abstract

Esophageal cancer poses a significant global health burden due to its aggressive nature and challenging management. This scoping review aims to explore the evolving landscape of esophageal cancer management, focusing on the shift toward minimally invasive approaches. The review synthesizes current guidelines, staging methods, treatment modalities for early and advanced stages, and surgical options, emphasizing the growing prominence of minimally invasive techniques.

Keywords: Esophageal cancer, minimally invasive approach, esophageal squamous cell carcinoma, esophageal adenocarcinoma

INTRODUCTION

Esophageal cancer remains a formidable health challenge, with its incidence rising steadily across diverse populations worldwide. Globally, it is the eighth most prevalent cancer and the sixth leading cause of cancer-related mortality[1,2]. In particular, the incidence of esophageal adenocarcinoma (EAC) is rising, with contributing factors of global aging and the increased prevalence of risk factors such as obesity, alcohol, and smoking[3]. The complexity of its management necessitates a multidisciplinary approach encompassing

surgery, chemotherapy, radiation, and immunotherapy. Recent years have witnessed a paradigm shift toward adopting minimally invasive strategies in the management of esophageal cancer. This review aims to comprehensively analyze the current landscape of esophageal cancer management, highlighting the increasing preference for minimally invasive approaches and their impact on patient outcomes.

EPIDEMIOLOGY AND PATHOLOGY OF ESOPHAGEAL CANCER

Esophageal cancer is broadly classified into two histological subtypes: esophageal squamous cell carcinoma (ESCC) and EAC. Diagnosis is based on histology from endoscopy and biopsies. In poorly differentiated cancers where differentiation between ESCC and EAC is not possible, immunohistochemical staining is recommended[4].

ESCC is more prevalent in certain regions, such as Asia, while EAC is primarily more common in Western countries, including the United States and Europe. ESCC also tends to occur in the upper and middle thirds of the esophagus, and is associated with risk factors such as smoking, alcohol consumption and dietary factors. Conversely, EAC tends to occur in the lower third of the esophagus and is associated with reflux disease, Barrett's esophagus, and obesity. This differentiation between the two main subtypes is important for both prognostication and guiding subsequent management.

STAGING AND WORKUP FOR ESOPHAGEAL CANCER

Current guidelines for the management of esophageal cancer, including those published by the National Comprehensive Cancer Network (NCCN)[5] and the European Society for Medical Oncology (ESMO)[4], provide fundamental frameworks for treatment. These guidelines advocate for a multidisciplinary approach, incorporating surgery, neoadjuvant, and adjuvant therapies based on the tumor stage and the patient's condition.

Accurate staging of esophageal cancer is paramount for optimal treatment planning. Esophageal cancer is staged with respect to the tumor/node/metastases (TNM) classification as per the American Joint Committee on Cancer (AJCC) guidelines[6], along with histologic grade and anatomic/prognostic groups for both squamous cell carcinoma and adenocarcinoma. Gastroesophageal junction (GEJ) tumors with an epicenter within the proximal 2 cm of the cardia and above (Siewert I/II) are staged as esophageal cancers[7]. Regional lymph nodes extend from the periesophageal lymph nodes to the celiac nodes. There are two main classification systems commonly used in the literature: the AJCC system and that of the Japanese Esophageal Society (JES)[8,9].

Various staging modalities, including endoscopic ultrasound (EUS), computed tomography (CT), and positron emission tomography (PET), play pivotal roles in assessing tumor extent and nodal involvement. Recent advances in imaging technologies have enhanced the precision of staging, facilitating better therapeutic decisions. The NCCN guidelines recommend CT of the chest, abdomen, and pelvis as the initial imaging modality for both locoregional assessment and initial assessment for metastases. PET has a higher sensitivity for the detection of distant metastases than CT[10] and, therefore, is recommended for patients without evidence of M1 disease and considered for surgical resection. In some centers, PET is combined with a contrasted CT, replacing the need for a separate CT scan; however, its availability varies between institutions.

EUS plays an important role in locoregional staging. Firstly, it can be used in the assessment of superficial esophageal cancer that may benefit from endoscopic resection. Its accuracy has been a topic of debate, ranging from 65% to 85% in various meta-analyses[11-13]. Definitive T staging is hence still made from

endoscopic resection. Secondly, EUS plays a crucial role in predicting the resectability of advanced esophageal cancer and assessing its invasion into the pericardium, aorta, or airways. Bronchoscopy may be used as an adjunct if there is suspected airway involvement. A limitation of EUS in staging advanced cancer with intraluminal extension and strictures is its reduced accuracy and increased risk of perforation[13]. EUS may also be used to evaluate lymph nodes outside the radiation field or planned resection area[5]. In such cases, fine needle aspiration/biopsy may be performed for cytological/histological confirmation.

For locally advanced GEJ tumors with infiltration of the cardia, the ESMO guidelines also recommend staging laparoscopy to exclude peritoneal disease, which is found in approximately 15% of cases[14].

The management of esophageal cancer is based predominantly on both tumor staging as well as patient fitness and comorbidities, with the main aim of staging investigations to rule out metastatic disease. The approach to metastatic or unresectable esophageal cancer involves a multidisciplinary approach with a palliative intent, which is outside the scope of this review. The management of resectable esophageal cancer can be broadly classified into early *vs.* advanced esophageal cancer. In the rest of this scoping review, we will touch on the latest literature and advances in the treatment of esophageal cancer, focusing on the emergence of the minimally invasive approach.

APPROACH TO EARLY ESOPHAGEAL CANCER

Early esophageal cancer typically refers to cancer that is confined to the inner layers of the esophageal wall, namely mucosal (T1a) or submucosal (T1b) invasion, without evidence of nodal or distant metastases[15]. The lack of invasion into deeper layers or surrounding tissues confers the possibility of curative intent treatment, and is associated with better prognosis compared to advanced-stage cancer. The management of early esophageal cancer has witnessed significant progress in recent years, with improved advanced endoscopic diagnostic and therapeutic capabilities resulting in a shift toward less invasive treatments aimed at preserving esophageal function and improving patient outcomes.

Indications for endoscopic treatment

Endoscopic treatment options encompass both endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)[15,16]. EMR involves the removal of superficial mucosal lesions using snare techniques and should only be performed if the lesion is smaller than 15 millimeters (mm)[17]. EMR can be broadly classified into either the traditional cap-EMR or multiband mucosectomy/EMR, which involves a cap with multiple rubber bands applied to it[17]. The drawback of EMR is that resection of larger lesions can often only be done in a piecemeal fashion, which is disadvantageous in early esophageal tumors where histopathological assessment of resection margins is key. On the other hand, ESD is a more technically challenging procedure that enables en bloc resection of larger lesions by dissecting within the submucosal layer, allowing for enbloc R0 resection of lesions larger than 15 mm. The indications for endoscopic treatment of esophageal cancer differ slightly for EAC and ESCC, as ESCC has a higher risk of lymph node metastasis compared to EAC[18]. In ESCC, submucosal invasion deeper than 200 μm is associated with a significant risk of lymph node metastasis, and hence, early ESCC should be treated with endoscopic resection only up to a mucosal invasion depth of m2[19] [Table 1]. In early EAC, these criteria can be expanded if submucosal invasion is ≤ 500 μm (sm1), the cancer is well or moderately differentiated, with a lesion size < 3 cm, and without lymphatic invasion[19]. Table 1 below elucidates the different indications for endoscopic resection for both ESCC and EAC.

After resection, histopathological assessment needs to be performed on the resected specimen to confirm curative endoscopic resection. Curative resection is only achieved when all of the following criteria are met:

Table 1. Indications for endoscopic treatment of esophageal cancer

ESCC	
Depth of invasion (T stage)	< T1a m2
Size of lesion	No upper size limit for ESD (< 1.5 cm for EMR)
Circumference	< 2/3 circumference
Differentiation	Well-differentiated
Paris classification[20]	Paris 0-II (flat lesions)
Others	Without lymphatic invasion or ulceration
	No lymph node involvement or distant metastasis
EAC	
Depth of invasion (T stage)	< T1b sm1 (≤ 500 μm)
Size of lesion	< 3 cm for ESD (< 2 cm for EMR)
Differentiation	Well or moderately differentiated
Others	Without lymphatic invasion or ulceration
	No lymph node involvement or distant metastasis

ESCC: Esophageal squamous cell carcinoma; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; EAC: esophageal adenocarcinoma.

negative margins, tumor depth limited to mucosa or submucosa (sm1), tumor is well to moderately differentiated, with no lymphovascular invasion. If not all of these criteria are met, the procedure is not considered curative and further treatment such as surgery is required[21].

Surgery

While endoscopic techniques are suitable for certain early-stage lesions, surgical interventions remain crucial for cases requiring deeper resection or when endoscopic methods are not feasible. Current surgical options for early esophageal cancer include minimally invasive esophagectomy (MIE), particularly thoracoscopic and/or laparoscopic approaches, as well as open surgery. MIE, when appropriate, demonstrates comparable oncological outcomes with reduced morbidity, shorter length of stay, and improved quality of life compared to open surgery[22]. The benefits of the MIE approach will be elucidated in later sections.

Definitive chemoradiotherapy

Definitive chemoradiotherapy (CRT) is an option for patients with early ESCC, especially in those not suited for esophagectomy surgery. The literature shows that the selection of the appropriate treatment modality for early esophageal cancer hinges on meticulous patient evaluation, considering factors such as tumor size, depth of invasion, histological features, and patient comorbidities. Multidisciplinary discussions involving gastroenterologists, oncologists, surgeons, radiologists, and pathologists are integral in determining the optimal approach, aiming for complete tumor eradication while preserving the functional integrity of the esophagus. Both endoscopic and surgical interventions for early esophageal cancer exhibit favorable outcomes, with high rates of complete resection and low recurrence rates in appropriately selected cases[16]. In addition to therapeutic treatment, post-treatment surveillance through endoscopic examinations and imaging studies is also crucial to monitor for recurrence or metachronous lesions, ensuring timely intervention if required.

APPROACH TO ADVANCED ESOPHAGEAL CANCER

Advanced esophageal cancer, characterized by T2 disease (involvement of the muscularis propria) and above or nodal involvement, often necessitates a multimodal treatment approach. Neoadjuvant treatment (both chemotherapy alone and CRT) followed by surgical intervention has emerged as standard of care for such cases[23]. Neoadjuvant treatment plays a pivotal role in downstaging tumors, enhancing resectability, and reducing micrometastases. The treatment for the small subset of patients with T2N0M0 tumors is still

somewhat more controversial, with both neoadjuvant treatment and upfront surgery being viable options to consider[4,5]. The development of optimal multimodal neoadjuvant regimens has resulted in good tumor response in the majority of patients (especially ESCC), and has facilitated the transition to more minimally invasive surgical approaches.

Neoadjuvant CRT

Combined chemotherapy and radiation regimens, typically a platinum-based chemotherapy regime with concurrent radiation, have demonstrated improved pathological response rates and increased rates of R0 resection in esophageal cancer. The chemoradiotherapy for oesophageal cancer followed by surgery study (CROSS) trial was a landmark clinical trial that evaluated the efficacy of neoadjuvant chemoradiotherapy (NCRT) in patients with esophageal cancer, and reported a substantial improvement in overall survival for patients who received NCRT [carboplatin and paclitaxel along with radiotherapy (41.4 Gy in 23 fractions)] followed by surgery compared to those who underwent surgery alone[24], and this survival benefit persisted for up to 10 years post surgery[25]. Subgroup analysis of patients with ESCC in the CROSS trial showed a much better efficacy of NCRT, with a pathological complete response (pCR) rate of 49%[24]. The Phase III Study of Neo-adjuvant Chemoradiotherapy Followed by Surgery for Squamous Cell Esophageal Cancer (NEOCRTEC5010) trial, which utilized a vinorelbine and cisplatin dual chemotherapy regime with a total radiation dose of 40.0Gy, also demonstrated a survival benefit in the NCRT group compared to the surgery alone group[26]. The success of both of these randomized trials has significantly influenced clinical practice, leading to the widespread adoption of NCRT as an integral part of the multimodal treatment strategy for esophageal cancer, particularly ESCC.

Perioperative chemotherapy

In contrast, the utilization of neoadjuvant chemotherapy (NCT) is mainly for EAC. Its current status is based on three large randomized controlled trials - the Medical Research Council adjuvant gastric infusional chemotherapy (MAGIC) trial[27], the 5-FU, leucovorin, oxaliplatin and docetaxel (FLOT) *vs.* epirubicin, cisplatin and 5-FU (ECF) in patients with locally advanced resectable gastric cancer (FLOT4) trial[28], and the UK Medical Research Council (OE02) trial[29]. The MAGIC trial demonstrated that a perioperative regimen of ECF decreased tumor stage and size, and also significantly improved progression-free and overall survival[27]. However, limitations of the MAGIC trial included poor compliance with the chemotherapy regimen due to high toxicity, and low rates of proper D2 lymphadenectomy dissection. Given the high toxicity of the ECF regimen, the FLOT4 trial evaluated the FLOT chemotherapy regime instead. They demonstrated that FLOT improved both progression-free and overall survival, with a median survival of 50 months compared to 35 months in the ECF/ECX arm[28], and this has since influenced the chemotherapy regimen for gastric and GEJ adenocarcinoma. However, the percentage of esophageal cancer patients in the MAGIC trial was only 14.8%, and the FLOT trial only included gastric and GEJ tumors. The OEO2 trial showed that NCT (two cycles of combination cisplatin and fluorouracil) before surgery improved survival in operable esophageal cancer[30].

Trials comparing NCT to NCRT for EAC demonstrate a significantly higher rate of pCR after NCRT, but the rates of overall survival were similar between the two groups[31,32]. For ESCC, evidence for NCT alone without radiotherapy is still limited in large-scale clinical trials. A recent trial published in China - comparison between NCRT and NCT followed by MIE for treatment of locally advanced resectable ESCC (CMISG1701) - demonstrated that patients who underwent NCRT had better pCR rates, but with similar 1-year overall survival[33]. The JCOG1109 NExT study published in 2022 evaluated the doublet (cisplatin and 5-fluorouracil) and triplet (docetaxel, cisplatin and 5-fluorouracil) chemotherapy regimens and CRT as neoadjuvant treatments[34]. The results showed that the triplet regimen had the highest 3-year overall survival at 72.1%, compared to 62.6% and 68.3% for the doublet and CRT arms, respectively.

Surgery

Surgery remains the cornerstone in the treatment of advanced esophageal cancer post-neoadjuvant therapy, and is often done 4-8 weeks after completion of neoadjuvant therapy. Esophagectomy, often performed via minimally invasive or open techniques, aims at achieving R0 resection and complete tumor removal. The transition toward MIE and robotic-assisted procedures has gained traction, demonstrating comparable oncological outcomes with reduced perioperative complications[22,35]. The various surgical approaches to esophagectomy are further illustrated in the next section. In patients who are not fit for major esophagectomy surgery, the mainstay of treatment is definitive CRT. A randomized trial published in 2013 demonstrated that definitive CRT for ESCC resulted in comparable long-term survival to surgery, with 5-year overall survival of 50% in the definitive CRT group compared to 29.4% in the surgery group (P = 0.147)[36].

Watch-and-wait approach

Recently, the "watch-and-wait" approach for esophageal cancer after CRT has gained attention as an alternative strategy to immediate surgery for patients who show a complete clinical response to NCRT. Studies have shown that a subset of patients (approximately 15%-30%) treated with CRT achieve a complete clinical response, meaning no visible residual disease[37,38]. There are reported similar overall survival rates between patients who opt for the watch-and-wait strategy and those who undergo surgery, indicating that delaying surgery in carefully selected patients does not compromise survival outcomes[39,40]. Of note, the recently published surgery as needed for oesophageal cancer (SANO) trial demonstrated that patients undergoing active surveillance for two years after CRT had comparable survival and improved short-term quality of life compared to standard surgery[40]. Only patients who were deemed as having complete clinical response 10 to 14 weeks after completion of NCRT were recruited into this study. A complete clinical response was defined as no evidence of disease on oesophagogastroduodenoscopy (OGD), PET-CT or EUS. Patients in the active surveillance arm were also required to undergo intensive surveillance termed as clinical response evaluations (CREs) every 3 months in the first year, every 4 months in the second year, every 6 months in the third year, and yearly in the fourth and fifth year. Each CRE includes OGD with bite-on-bite biopsies, PET-CT, and EUS with FNA of suspected lymph nodes[41]. Once recurrence is detected, patients are then offered salvage esophagectomy if there is no evidence of distant metastases. However, it should be noted that up to sixty percent of ESCC patients who achieve complete clinical response following nCRT but refuse esophagectomy develop disease recurrence, with local recurrence being the most common pattern[42]. The risks of performing a salvage esophagectomy are also well demonstrated to be higher, with a 2-fold higher risk of experiencing serious complications and a 1.5-fold higher hazard risk of death and postoperative recurrence[43]. The "watch-and-wait" approach is currently still being evaluated for its long-term oncological results as the long-term follow-up for the SANO trial awaits to be published, but it offers a potential alternative for patients who have a complete response to CRT, avoiding the potential morbidities associated with esophagectomy. However, patients should be appropriately counseled on the intensive post-CRT surveillance regimen required in the watch-and-wait strategy, along with consideration of higher-risk salvage esophagectomy once recurrence develops. Patients should be informed about the potential risk of developing distant metastases during the period of active surveillance. Future studies should focus on factors that can risk stratify and predict for patients who are at high risk of recurrence after CRT, such as post-CRT endoscopic findings[42], which can help guide clinicians regarding the best treatment option for patients.

Precision medicine and immunotherapy

The watch-and-wait strategy represents a potential management option for patients with complete clinical response after CRT, but the majority of patients still have persistent residual disease. Despite the advances in CRT regimens, the complete response rates remain poor and recurrence rates remain high in advanced

esophageal cancer. The development of precision medicine has helped to revolutionize the field of esophageal cancer treatment, by enabling genomic profiling of tumor tissues to identify specific genetic alterations that can allow targeted therapy. Precision medicine also encompasses the identification of biomarkers such as programmed death-ligand 1 (PD-L1) expression that can be used to predict responses to targeted therapy. Immunotherapy, particularly immune checkpoint inhibitors, has emerged as a promising avenue in the field of targeted therapy for esophageal cancer. The overexpression of various receptors including human receptor growth factor receptor 2 (HER2), vascular endothelial growth factor receptor (VEGFR), and epidermal growth factor receptor (EGFR) have been reported in esophageal cancer, and have given rise to many potential treatment targets for new drug therapy, both as standalone therapies and in combination with other modalities. Three landmark clinical trials - study of nivolumab in unresectable advanced or recurrent esophageal cancer (ATTRACTION-3)[44], Study of pembrolizumab (MK-3475) versus investigator's choice standard therapy for participants with advanced esophageal/esophagogastric junction carcinoma that progressed after first-line therapy (KEYNOTE181)[45], and study of SHR-1210 versus investigator's choice standard therapy for participants with advanced esophageal cancer (ESCORT)[46] have confirmed the efficacy of pembrolizumab, camrelizumab, and nivolumab as second-line treatment for advanced/metastatic esophageal cancer. Building on the promising results of immunotherapy in second-line treatment, studies (KEYNOTE-590, Checkmate-649) have evaluated the addition of immunotherapy as a first-line treatment for unresectable esophageal cancers, demonstrating improved survival outcomes[47,48]. Currently, adjuvant nivolumab is also being offered as standard of care in patients who have undergone nCRT followed by esophagectomy with residual pathological disease, after the publication of the results from the landmark Checkmate-577 trial. The Checkmate-577 trial demonstrated a disease-free survival of up to 22.4 months in the adjuvant nivolumab group as compared to only 11 months in the placebo group[49], paving the way for the use of adjuvant nivolumab in patients who have undergone curative intent treatment. The field of immunotherapy is rapidly evolving, with numerous other ongoing phase III trials (Keystone-002[50], ESCORT-NEO/NCCES0[51]) evaluating the addition of neoadjuvant immunotherapy in the setting of resectable esophageal cancer. The results of these trials are eagerly awaited, but not the focus of this scoping review.

Conversion therapy

Substantial progress in the multimodality treatment approaches, including immunotherapy, for initially unresectable ESCC has led to the consideration of conversion therapy with curative intent for selected cases. Conversion therapy is a concept well-known in the management of unresectable gastric and GEJ adenocarcinomas, and is defined as surgery aiming for R0 resection after systemic treatment for cancers that were initially deemed unresectable[52]. It has gained traction recently in the field of treatment of initially unresectable gastric cancer, with large-scale trials such as CONVO-GC-01[53] and AIO FLOT 3 trial[54] showing favorable outcomes in selected groups of patients. For ESCC, a multinational conference involving East Asia experts was held to establish a consensus for conversion therapy, which is defined as surgery or CRT aimed at achieving a cure after the initial treatment of initially unresectable tumors due to either local invasion into adjacent organs or distant metastases[55]. Retrospective studies have demonstrated the safety and efficacy of conversion therapy for ESCC with distant metastases, with 5-year overall survival rates ranging from 24.4% to 31.7%[56,57]. A phase 3 trial is currently underway (JCOG1510) to evaluate the trimodality induction regime of docetaxel, cisplatin, and 5-fluorouracil followed by conversion surgery, compared to definitive CRT for locally advanced unresectable ESCC[58]. There is currently still no consensus regarding conversion therapy for ESCC, and more studies are required to evaluate the long-term oncological benefits of conversion therapy, various treatment protocols, and indications.

SURGICAL OPTIONS

This part of the scoping review will focus on the surgical management of esophageal cancer, including the various operative approaches, the extent of lymphadenectomy, and the shift toward minimally invasive (including robotic) techniques.

Surgical approaches

Esophagectomy is a major surgical procedure that involves the removal of part or the entire esophagus en bloc together with adequate lymphadenectomy, followed by reconstruction of the gastrointestinal tract to maintain enteral continuity. The esophagus spans three different body cavities - the neck, thorax, and abdomen - and, hence, the different approaches to esophagectomy depend on which cavity is accessed and the extent of lymphadenectomy required. Traditionally, there are three main approaches to esophagectomy: the transthoracic approaches (Ivor Lewis and McKeown) and the transhiatal approach. The transthoracic approach offers better visualization of the tumor and enables a complete intrathoracic lymph node resection with better long-term oncologic outcomes; however, it necessitates entry into the thorax with its associated increased risks of perioperative pulmonary complications. The transhiatal approach does not require thoracic entry, but it is usually reserved only for distal esophageal and GEJ tumors that do not require significant thoracic dissection and lymphadenectomy. Previous randomized trials evaluating the transthoracic and transhiatal approaches for lower esophageal tumors have not shown significant differences in terms of overall survival[59]. Recently, transcervical mediastinoscopy-assisted esophagectomy has emerged as a novel and viable alternative to the traditional transthoracic route, and has shown to be comparable to the usual transthoracic approaches in terms of oncological outcomes and complication rates[60,61]. This technique allows dissection of thoracic lymph nodes without the need for thoracic entry and is especially suitable for elderly and poor surgical-risk patients[60]. Surgical approaches should be individualized based on the patient's characteristics and the nature of the disease.

In terms of positioning for the thoracic phase, the prone, semiprone, and lateral decubitus positions have been described in the literature. The traditionally described left lateral decubitus position has the advantage of having a similar surgical field compared to open surgery, and allows for easy conversion to thoracotomy if required. However, drawbacks include the need for an additional port for lung retraction, limited exposure to the posterior mediastinum, and accumulation of blood in the operative field. Conversely, the advantages of the prone position include providing good visibility and access to the posterior mediastinal structures without requiring lung retraction. Hence, the prone position has been adopted as an alternative approach by some surgeons, citing advantages such as improved ergonomics and operative exposure, shorter surgical time, and decreased pulmonary morbidity[62-64].

Extent of lymphadenectomy

Oncological surgery entails adequate clearance of the draining lymph node basin in order to reduce recurrence and improve survival. There are currently two staging systems, the 8th staging system by AJCC[8] and the 12th Japanese classification by JES[9], that are currently being applied for esophageal cancer patients. The latest 12th Japanese classification by JES, published in 2022, is now similar to the UICC/AJCC staging and divides N into N0-N3 according to the number of positive lymph nodes[9]. This 12th JES edition has only been published in Japanese thus far, with the English edition planned to be published in the near future. Supraclavicular lymph nodes are also now classified as distant lymph nodes rather than regional lymph nodes in the latest JES classification. However, they are classified as M1a since they are expected to be removed surgically during three-field lymphadenectomy, and are distinguished from other distant non-resectable metastases M1b. Both systems have been validated in clinical practice in terms of predicting prognosis and overall survival[65]. The approach to lymphadenectomy in esophageal cancer surgery involves different strategies: standard two-field, extended two-field, and three-field lymphadenectomy [Table 2].

Table 2. Comparing the different lymphadenectomy strategies for esophageal cancer surgery

Extent of lymphadenectomy	Definition of lymphadenectomy	Advantages and disadvantages
Standard two-field lymphadenectomy	Upper abdominal lymph nodes (paracardial, lesser curvature, greater curvature, left gastric, common hepatic, and celiac lymph nodes) + mediastinal lymphadenectomy (until the level of carina) - subcarinal nodes (107), middle paraesophageal nodes (108), bilateral hilar lymph nodes (109), lower paraesophageal nodes (110), diaphragmatic nodes (111), and posterior mediastinal lymph nodes (112)	Advantages: purported reduced risk of complications such as RLN injury; widely recognized and practiced with substantial clinical evidence supporting its efficacy Disadvantages: does not achieve complete mediastinal nodal clearance, studies have shown higher recurrence rates and reduced survival
Extended two-field lymphadenectomy	Standard two-field lymphadenectomy + total mediastinal lymphadenectomy (including lymph nodes above the carina) - upper paraesophageal nodes (105), nodes along the bilateral RLNs (106)	Advantages: achieves complete mediastinal nodal clearance (especially for ESCC with a tendency for higher incidence of upper mediastinal LN involvement) Disadvantages: increased surgical risks (such as RLN injury); more technically challenging, longer operative time
Three-field lymphadenectomy	Extended two-field lymphadenectomy + cervical lymphadenectomy (cervical paraesophageal lymph nodes (101), including lymph nodes along the recurrent nerve in the neck) + deep cervical lymph nodes (102) + supraclavicular nodes (104)	Advantages: addresses all three potential sites of lymph node metastasis; some studies show better survival compared to two-field lymphadenectomy Disadvantages: longer operative time and increased morbidity (RLN injury risk); no global consensus regarding oncological benefits (especially for EAC)

Numbers in brackets represent the lymph node stations. RLN: Recurrent laryngeal nerve; ESCC: esophageal squamous cell carcinoma; LN: laryngeal nerve; EAC: esophageal adenocarcinoma.

Lymph node sites mentioned in Table 2 are classified according to the Japanese classification of esophageal cancer, 12th edition[9].

While more extensive lymphadenectomy theoretically aims to achieve better nodal clearance and staging, the trade-off includes increased surgical complexity, the potential for higher morbidity, and uncertain significant improvements in long-term survival compared to standard approaches. Currently, surgical strategies depend on the distribution pattern of nodal metastases; however, there is still no global consensus on the extent of lymphadenectomy. The paper by Akiyama *et al.* in 1994 described the localization and frequency of lymphatic spread in squamous cell carcinoma of the thoracic esophagus and compared long-term survival between two- and three-field lymph node dissection[66]. It was concluded that the survival rate was significantly better in patients with extensive three-field dissection. Three-field lymphadenectomy gained further popularity after a nationwide study in Japan reported improved overall 5-year survival compared with two-field lymphadenectomy[67]. Hence, for ESCC, Japanese surgeons have standardized the 2- or 3-field lymphadenectomy according to the location of the tumor[68].

Globally, the benefit of three-field lymphadenectomy remains unclear. This is especially so in the Western world, where adenocarcinoma accounts for 85% of all esophageal cancers. Worldwide, other randomized trials have compared two- and three-field lymphadenectomy, but the results are either conflicting due to underpowered studies[69,70], or do not demonstrate any significant clinical benefit[71]. Moreover, the benefits of extended lymphadenectomy remain debatable especially in the era of neoadjuvant therapy, as the effect of neoadjuvant treatment on dissemination and pattern of lymph node distribution is still unclear. The post hoc analysis of the CROSS trial demonstrated a crucial observation that the number of resected lymph nodes correlated with survival in patients who underwent surgery alone, but lost significance in patients

who received neoadjuvant treatment[72]. Tailoring the extent of lymphadenectomy to individual patient characteristics and tumor stage remains crucial, with ongoing research aiming to define the optimal nodal dissection strategy in esophageal cancer surgery.

Shift to the minimally invasive approach

While open esophagectomy has been the historical standard, hybrid and totally minimally invasive approaches have gained popularity due to their associated benefits, including reduced blood loss, shorter hospital stays, and faster recovery, while demonstrating comparable oncological outcomes[22]. These advancements mark a notable departure from traditional open techniques, and are also part of an ongoing global move toward enhanced recovery after surgery (ERAS) programs, which provide a structure for multidisciplinary care and have been shown to improve postoperative outcomes[73]. The multicentre randomized controlled phase III (MIRO) trial published in 2011 demonstrated that performing the abdominal phase laparoscopically instead of the traditional open technique, resulted in a lower incidence of perioperative major complications, specifically pulmonary complications, and heralded the benefits of a hybrid minimally invasive approach to esophagectomy[74]. The five-year follow-up study for the MIRO trial also demonstrated comparable overall survival between the two groups[75]. However, the open approach to the thoracic phase was still associated with significant pulmonary morbidity, and hence, there was a further shift to a totally MIE approach. the multi-center traditional invasive *vs.* minimally invasive esophagectomy (TIME) trial showed the superiority of a totally MIE approach as compared with open esophagectomy in terms of intraoperative blood loss, acute immunological response, postoperative pain scores, postoperative pulmonary infections, length of hospital stay, and quality of life[76]. Additionally, lymph node harvest and long-term oncological outcomes in terms of disease-free and overall survival were shown to be comparable between the two groups[76]. Since then, multiple systematic reviews and meta-analyses have compared both open esophagectomy and MIE, and have found an overall reduction in postoperative complications, especially pulmonary complications, in the MIE group[77,78].

Emergence of the robotic approach

The emergence of robotic-assisted surgery, particularly robotic-assisted minimally invasive esophagectomy (RAMIE), presents a promising frontier in esophageal cancer management[35]. The enhanced dexterity and visualization capabilities of robotic surgery offer potential advantages over conventional laparoscopic approaches. The ROBOT (robot-assisted minimally invasive thoracolaparoscopic esophagectomy *vs.* open transthoracic esophagectomy for resectable esophageal cancer) trial published in 2019 compared RAMIE with open esophagectomy, and demonstrated a lower percentage of overall surgery-related and cardiopulmonary complications with lower postoperative pain, better short-term postoperative functional recovery, and a better short-term quality of life in the RAMIE group[79]. Oncological outcomes were also comparable between the two groups. When comparing MIE *vs.* RAMIE, the existing data are still sparse and conflicting, and long-term data are lacking. Some meta-analyses have demonstrated the superiority of RAMIE over MIE in terms of short-term outcomes of pneumonia and vocal cord palsy[79]; however, other studies have shown no significant differences between the two in terms of oncological outcomes and postoperative complications[80,81]. The literature is also divided in terms of operative time, with some studies showing a significantly shorter operative time in the RAMIE group[82], whereas the converse was true in others[83,84]. The results for ongoing randomized trials [RAMIE trial[85], REVATE (robotic-assisted esophagectomy *vs.* video-assisted thoracoscopic esophagectomy) trial[86], ROBOT-2 trial[87]] evaluating the long-term outcomes for RAMIE *vs.* MIE are still being eagerly awaited. Proponents of RAMIE tout the shorter learning curve required compared to conventional MIE[88,89]; however, this should also be weighed against overall cost effectiveness[90].

CONCLUSION

This scoping review underscores the evolving landscape of esophageal cancer management, emphasizing the increasing adoption of minimally invasive approaches across various stages of the disease. The incorporation of these techniques demonstrates promising outcomes in terms of reduced morbidity and comparable oncological efficacy. The benefits of the MIE approach have been well elucidated in the current literature, espousing comparable long-term oncological outcomes with reduced risks of perioperative complications. However, further research and long-term outcome studies are imperative to validate and refine the role of RAMIE in optimizing esophageal cancer care.

DECLARATIONS

Authors' contributions

Assisted in the literature review, drafted the manuscript, created the figures and tables, and coordinated manuscript completion: Yeo CS

Assisted in the literature review and manuscript drafting: Wong JSH

Led manuscript creation and provided guidance on direction and manuscript drafting/editing: Oo AM

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