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Treatment of early stage (T1) esophageal adenocarcinoma: Personalizing the best therapy choice

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Abstract

Esophagectomy is considered the primary form of management for esophageal adenocarcinoma (EAC); however, the surgery is associated with high rates of morbidity and mortality. For patients with early-stage EAC, endoscopic resection (ER) presents a potential curative treatment option that is less invasive and carries fewer risks procedure related risks, but it is associated with higher rates of cancer recurrence following the procedure. For some patients, age and comorbidities may prevent them from having esophagectomy as a treatment option, while other patients may be operative candidates but do not wish to undergo esophagectomy for a variety of reasons related to their values and preferences. Furthermore, while anxiety of cancer recurrence following ER may significantly diminish a patient's quality of life (QOL), so might the morbidity surrounding esophagectomy. In addition to considering health status, patient preferences, and impacts on QOL, physicians and patients must also consider what treatments would be both beneficial and available to the patient, considering esophagectomy methods-minimally invasive *vs* open-or the use of chemoradiotherapy in addition to ER. Our article reviews and summarizes available treatment options for patients with early EAC and their potential effects on the health and wellbeing of patients based on the current data. We conclude with a request for more research of available options for early EAC patients, the conditions that determine when each option should be employed, and their effects not only on patient health but also QOL.

Key words: Esophageal cancer; Adenocarcinoma; T1b; Esophagectomy; Endoscopic resection; Chemoradiotherapy; Quality of life

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Core tip: This paper is an important source of information for patients and clinicians faced with a diagnosis of T1b esophageal adenocarcinoma (T1b EAC). This paper explores and then outlines the potential benefits and risks of the numerous treatment options for T1b EAC, highlighting the integral role a patient's individual wishes and values play into making a treatment decision that achieves the greatest outcome for that patient. The review advocates for further research regarding the effects of T1b EAC treatment options on a patient's quality of life.

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INTRODUCTION

Esophageal carcinoma is the eighth most common cancer and the sixth most deadly cancer worldwide^[1]. While esophageal squamous-cell carcinoma (SCC) is the most prevalent type of esophageal carcinoma globally, esophageal adenocarcinoma (EAC) has a higher incidence than SCC within the United States and much of the Western world^[2]. The incidence rate of EAC has increased rapidly since the 1970s, which has corresponded with a rise in the incidence of risk factors for EAC such as obesity, a high-fat diet, chronic gastroesophageal reflux, and Barrett's esophagus (BE)^[3-5]. For the purposes of this review, we focus primarily on treatments for early (T1) EAC.

Esophageal cancer is staged by tumor-node-metastasis based on depth of invasion of the primary tumor, lymph node involvement, and extent of metastatic disease (see [Figure 1](#))^[6,7]. Tumor staging in T1 EAC is further subdivided and reflects the increasing likelihood of lymph node involvement with increasing lesion depth^[7,8]. Specifically, T1 EAC is divided into Tis (carcinoma *in situ*; also known as high-grade dysplasia), T1a (confined to the mucosa, without lympho-vascular involvement), and T1b (involvement of submucosa)^[9-11]. T1b can be substaged further into T1bsm1, T1bsm2, and T1bsm3, each of which represent further invasion into the submucosa, although the reliability of correctly substaging T1b tumors is limited by the precision and accuracy of staging techniques^[12]. Despite the rising incidence of EAC in recent years, 5-year survival rates have improved for a sub-set of patients, specifically those diagnosed with early-stage EAC, for whom the cancer is confined only to the esophagus^[13]. This suggests the importance of examining which treatment modalities for T1 EAC confer the most benefit relative to the trade-off between quality of life (QOL) and risk of recurrence.

Until recently, esophagectomy was recommended for all stages of EAC tumors; however, given high rates of morbidity (30%-50%) and mortality (1%-10%) associated with esophagectomy, less aggressive treatment such as endoscopic resection (ER) are increasingly utilized, especially for T1a tumors^[7,8,10,14]. For patients considering esophagectomy, minimally invasive esophagectomy (MIE) is becoming a more frequently used alternative to the traditional and morbid open esophagectomy (OE). MIE is associated with fewer respiratory complications, intensive care unit stays, faster recovery time, and improved patient satisfaction compared to OE; however, the procedure requires an experienced surgeon due to its steep learning curve, and the clinical relevance of MIE's benefits relative to OE has been contested^[15-17]. By contrast, endoscopic therapies offer a promising alternative for patients with stage T1a and, potentially, T1bsm1 lesions^[7,8,10,18]. In fact, according to National Comprehensive Cancer Network 2018 guidelines, endoscopic resection (ER) is the preferred treatment for patients with T1a and T1bsm1 adenocarcinoma without signs of lymph node involvement^[19]. ER may also offer an alternative for patients ineligible for surgery due to advanced age and/or high comorbidity, or those who wish to pursue a less invasive treatment^[10,18,20,21]. Aligned with this view, a recent decision analysis found that for T1b patients older than 70 or patients with high comorbidity, ER, rather than esophagectomy, is the most cost-effective treatment^[22]. However, ER therapies cannot address nodal involvement and therefore carry greater risk of incomplete resection for patients with T1bsm2, T1bsm3, or later tumors, which are more likely to involve lymph nodes^[7]. Additionally, it is challenging to assess submucosal substaging using ER. A full thickness resection of the submucosa is necessary to accurately identify the

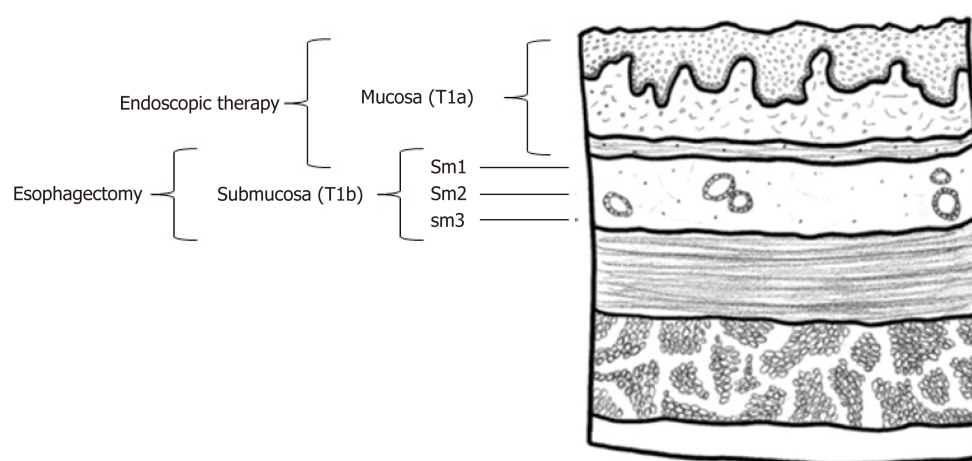


Figure 1 Esophageal adenocarcinoma therapies by tumor stage.

depth of submucosal invasion; ER resections often do not include the full submucosa, and when they do, these specimens may be compromised by saline injection and resection^[23].

Several factors complicate treatment decision-making. Age and age-related comorbidities must be considered as 30% of EAC patients are 75 and older at the time of diagnosis^[24]. Concerns about treatment morbidity and negative side effects are important factors for patients regardless of age^[25]. Imaging techniques such as computerized tomography, positron-emission tomography scan, and endoscopic ultrasound (EUS), run the risk of understaging T1 and T2 lesions, which should be considered when weighing treatment options with varying levels of risk of recurrence^[6,11,25,26]. The extant literature, reviewed in detail below, suggests that the choice of treatment for early-stage (particularly T1b) EAC patients is highly complex; it depends not only on stage and sub-stage, but also on patient preferences for treatment aggressiveness versus cancer risk, and patient characteristics such as age and comorbidity. Table 1^[16,22,25,27-29] summarizes the different treatment options for patients with T1 EAC.

Due to the variability in outcomes associated with different treatment modalities, decisions in this realm are preference-sensitive; that is, decision-making is contingent on the intersection of patients' values and understandings of treatment options^[30]. As such, the primary aim of this review is to overview the current landscape of early-stage EAC treatment options, including their associated risks of cancer recurrence and morbidity.

ENDOSCOPIC THERAPIES

Endoscopic resection

As a diagnostic technique, ER is more accurate and precise at staging early EAC than imaging methods such as EUS, reducing the risk of under- or over-staging the disease^[31]. ER is a crucial component of treatment decisions for early EAC, as treatment plans are highly dependent on tumor staging and appearance, a topic more thoroughly addressed below.

Curative ER is an option for patients at low risk of lymph node involvement. These patients are characterized by having no or minimal submucosal invasion, no lympho-vascular involvement, negative deep margins, and well- to moderately-differentiated tumor biology; the majority of patients with these characteristics are staged as T1a^[32,33]. ER offers these patients a potentially curative treatment while preserving the esophagus. For later-stage patients, ER serves primarily as a staging procedure, more accurate than available imaging methods^[34]. In T1a patients, the risk of lymph node metastases is comparable to the mortality rate associated with esophagectomy, suggesting that esophagectomy is not appropriate for this population^[9]. Additionally, ER has been shown to yield local control rates exceeding 95% in T1a patients, with survival times comparable to age and sex-matched adults without cancer^[7]. A decision analysis found that ER resulted in more quality-adjusted life years than esophagectomy for T1a patients regardless of age or comorbidity, but for T1b patients, ER was only cost-effective relative to esophagectomy for older patients or patients with high comorbidity^[22]. Thus, evidence suggests that endoscopic therapy is an

Table 1 Treatment of early stage esophageal adenocarcinoma treatment options

Treatment option	Potential benefits	Potential disadvantages
Endoscopic resection with or without radiofrequency ablation	Organ preserving; very low mortality; low morbidity; small, transient effect on quality of life	Does not address potential lymph node metastases; higher risk of recurrence and lower rate of complete response (particularly in T1b patients)
Esophagectomy	High curative rate; higher disease related survival rate; lower recurrence rates; addresses lymph node metastases	High rates of early and long-term morbidity; considerable rates of surgical mortality; large decrement in quality of life; high post-operative pain; complicated surgical procedure with high operative times and financial costs

acceptable first-line treatment with curative intent for T1a patients.

The low (0%-3.9%) risk of nodal metastases for T1a tumors is sufficient to justify using ER as a primary curative treatment, which is up to 98% effective for patients with Barrett's Esophagus (BE) and early neoplasia^[35-37]. T1b tumors, by contrast, carry a 20% risk of lymph node metastasis, indicating that ER alone leaves a patient at considerable risk of unaddressed lymph node metastasis and cancer progression^[36,37].

Endoscopic resection of T1b tumors

The mortality and morbidity associated with esophagectomy may reach unacceptable levels even for those with riskier T1b lesions, especially older patients with comorbidities. Consequently, T1b patients unwilling or unable to undergo esophagectomy may elect to undergo ER. While ER is ineffective for T1b patients with lymph node metastases, it can potentially be curative for T1b patients without nodal involvement.

Lymph node metastasis is a robust predictor of recurrence and disease-specific survival, and tumor depth is a predictor of lymph node metastasis^[14,38]. A study ($n = 69$) of T1b patients found that deeper submucosal invasion was associated with poorer outcomes from ER^[39]. Of those at low risk of nodal involvement (T1bsm1) managed with radical ER, there was only one local recurrence; this recurrence was treated with repeat ER, suggesting that ER is a viable option for T1b patients with minimal submucosal invasion. However, of the 30 high-risk patients with deeper submucosal invasion who opted for ER, six developed metastatic disease during follow-up, and five died of cancer. Among higher-risk patients who did undergo esophagectomy, two of 25 patients went on to develop metastases and die of cancer. Because a greater portion of high-risk patients developed metastatic cancer under ER than under surgical management, the authors concluded that esophagectomy remains the optimal treatment for T1b tumors with deep invasion of the submucosa^[39].

Another study ($n = 107$) also demonstrated the curative potential of ER for EAC patients with only mucosal or superficial submucosal involvement and found a 5-year recurrence-free rate of 97% and only one case of lymph node metastasis. However, 18 out of 41 patients with T1bsm2-3 tumors showed lymph node metastases and only 57% were recurrence-free after 5 years^[40]. These data indicate that, on one hand, ER is a valuable curative treatment for T1bsm1 patients with lower morbidity and mortality rates than esophagectomy, but, on the other hand, ER potentially confers higher cancer risk.

For some T1bsm1 patients, the QOL benefit of organ-preserving ER may be worth the potential risk of untreated nodal metastasis, assuming initial staging and substaging were correct. However, once tumor depth reaches T1bsm2-3, rates of lymph node metastases and cancer recurrence become much higher, and esophagectomy should be the primary form of curative treatment^[40]. It is important to reiterate that accurate, precise EAC staging and substaging of T1a and T1b is difficult^[6,11,25,26]. Consequently, the risk of potentially understaging patients should be communicated by the clinician and considered when deciding between conservative ER and esophagectomy, as patients may desire a more aggressive treatment when presented with the possibility that their cancer may be understaged.

As previously mentioned, tumor depth is not the only predictor of lymph node involvement; there are other factors to consider when determining risk of lymph node metastases, including tumor morphology, histologic grade, and lymphovascular invasion^[41,42]. In one study ($n = 85$), T1b tumors were grouped according to depth of submucosal invasion in conjunction with histological grade and lymphovascular invasion. Patients with tumors that were well- or moderately-differentiated and had no lymphovascular invasion had rates of overall and disease-specific survival closer to T1a tumors than to T1b tumors with poor differentiation and T1b tumors with

lymphovascular invasion^[43].

Another study ($n = 66$), examined the effects of ER on T1bsm1 patients defined as low risk, characterized by having macroscopically polypoid or flat lesions and good to moderate tumor differentiation (G1-G2), and found that out of the 61 patients whose remissions were assessed, 53 achieved complete endoluminal remission (CER) and fifty-one achieved long-term remission^[44]. When focal lesions were smaller than 2 cm, the CER rate jumped from 87% to 97%. There were no associated tumor deaths. The rate of major complications from ER was 1.5% with a 0% mortality rate, and biopsy and imaging results showed that only one patient had lymph node metastases^[44]. Ishihara *et al.*^[45] found no metastasis in any of the 32 T1b lesions smaller than 30 mm without lymphovascular involvement and a poorly differentiated component in their study of the risk of metastasis of EAC, concluding such lesions as good candidates for ER.

These studies highlight that T1b tumors have similar prognostic outcomes to T1a tumors if their histology and morphology do not indicate nodal involvement. Furthermore, they identify the importance of considering multiple tumor characteristics to determine the risk of lymph node metastasis. As previously stated, ER techniques may not always accurately stage submucosal involvement; therefore, examining multiple tumor characteristics to inform tumor classification and treatment decisions is important^[23].

Despite the benefits associated with organ preservation, the impact of fear of cancer recurrence on QOL is a factor to consider for T1b patients eligible for ER. One study ($n = 91$) examined QOL and fear of cancer recurrence following endoscopic versus surgical treatment for early-stage EAC (defined as BE with high-grade dysplasia, T1, T1sm, and T2N0M0 tumors) and found no differences in health-related or cancer-specific QOL between treatment groups^[46]. While the surgical group reported significantly more reflux and eating problems, the ER group reported greater fear of cancer recurrence and anxiety^[46]. The authors of the study noted that leaving the esophagus intact may prompt cancer anxiety among patients treated with ER and especially among T1b patients, for whom the chance of incomplete eradication and nodal metastases are higher^[27]. Additionally, a study ($n = 20$) eliciting health state utility values associated with dysplastic BE-related health states from non-dysplastic BE patients reported that the utility of states associated with potential cancer recurrence were comparable to the utility associated with esophagectomy^[47]. Along these lines, a decision analysis comparing ER and esophagostomy outcomes for T1 EAC patients found that the optimal treatment strategy depended most heavily on the post-treatment health state utility values, indicating that for patients with T1b EAC, treatment decisions should be centered around patient preferences^[22]. Together, these studies suggest that patient perceptions of and preferences for cancer risk are important to consider when making treatment decisions for T1b EAC.

Endoscopic eradication therapy: Radiofrequency ablation and cryotherapy

Patients who have early-stage EAC that has developed within a large segment of BE have the option of ER followed by radiofrequency ablation (RFA) or other ablative therapies to eliminate the remaining BE^[34,48-50]. Ablative techniques are important as they reduce the risk of metachronous neoplasia developing in residual BE^[51].

Research with BE patients suggests that RFA is an effective method for eradicating areas with dysplasia or early intramucosal adenocarcinoma^[52]. Although RFA carries a 7.8%-11.3% risk of adverse events (predominantly strictures and bleeding) these events are often low grade, with a low rate (0.6%) of severe adverse events (e.g. perforation)^[53,54]. The impact of RFA on QOL in EAC patients has not been specifically studied. However, one study reported the effects of RFA on patients with dysplastic BE and found that performing RFA improved QOL by reducing anxiety about developing cancer, worry about needing an esophagectomy, stress, impact on daily QOL, dissatisfaction with the condition of their esophagus, and impact on work and family life^[55]. These findings indicate a potential benefit of RFA for patients with T1a or T1bsm1 EAC and for patients with T1bsm2 or sm3 EAC who are unable or unwilling to undergo esophagectomy.

Research suggests cryotherapy is also an effective method of eradication of dysplasia^[50,56]. Cryotherapy is also utilized as treatment for patients with EAC who are unwilling or unable to undergo more aggressive treatments^[57-60]. A 2017 analysis of the safety and efficacy of liquid nitrogen spray for EAC patients who were not candidates for conventional therapy demonstrated complete response rates for 76.3% of T1a patients, 45.8% of T1b patients, and 66.2% for all T1 patients, with a low rate of low-grade strictures (13.6%)^[57]. A 2013 assessment of patients ineligible for conventional EAC therapy found that 75% of patients with T1a EAC and 60% of patients with T1b EAC showed complete endoscopic response, with benign strictures occurring in 13% of patients^[58]. These data suggest that cryotherapy is tolerable and effective for T1

EAC patients who cannot undergo conventional treatments; however, data regarding long-term outcomes are lacking^[59,60].

SURGICAL TREATMENTS

Esophagectomy

Esophagectomy is the mainstay of treatment for resectable esophageal cancer and is indicated for T1b tumors with more than minimal submucosal invasion or later-stage tumors due to increased risk of nodal involvement^[9,10]. The pain and discomfort experienced by patients after surgery has a significant negative effect on a patient's QOL^[61]. Specifically, a 2014 meta-analysis found significant and lasting detrimental effects of surgery on QOL: Social functioning, fatigue, pain, reflux, dyspnea, and coughing problems were significantly worse than pre-operation for at least nine to twelve months after surgery, at times extending beyond one year^[62].

Regardless of the modality for esophagectomy (*e.g.*, open or minimally-invasive), optimal surgical outcomes occur in high-volume centers with highly-skilled and well-practiced surgeons. Esophagectomy in high-volume surgical centers reduces the morbidity, mortality, length of hospital stay, and cost of the procedure^[63]. Additionally, the long-term prognosis of a patient following the surgery is associated with the case-volume of the surgical center, with a higher volume predicting a better prognosis^[64,65]. These data indicate that, when possible, patients may benefit from assuming the additional burden of seeking high-volume hospitals with highly experienced staff and the necessary resources to prevent and manage potential complications.

Open versus minimally-invasive

Treatment esophagectomy consists of two primary surgical techniques: OE and MIE. MIE is performed laparoscopically or thoracoscopically, where access to the abdominal and thoracic cavity is granted via small abdominal incisions. OE, on the other hand, requires a right thoracotomy and laparotomy, which involves large incisions where the ribs and abdominal wall are opened widely. Both OE and MIE carry significant risk of complications; one meta-analysis found complication rates of 48.2% and 41.5% in patients undergoing OE and MIE, respectively^[66]. Although each of these rates are high, the difference between the two was significant and favored MIE. This meta-analysis also found a post-operative mortality risk that again significantly favored MIE, with an average mortality risk of 3.8% and 4.5% for MIE and OE respectively^[66]. MIE has also been shown to result in superior short-term outcomes relative to OE, with reduced blood loss, fewer pulmonary and respiratory complications, lower total morbidity rates, and shorter post-operative hospital stays^[66-71]. Owing to the complexity of the procedure, the operative time for MIE is, however, longer than that of OE^[16]. MIE and OE have not been shown to differ in oncologic outcomes, with comparable lymph node retrieval and overall survival^[72].

Regarding the impact of each procedure on QOL, a systematic review comparing MIE and OE found that, while overall health and social and emotional function more frequently improved following MIE relative to OE, other QOL outcomes were comparably and negatively associated with both surgery types^[73]. Another meta-analysis found that MIE patients reported higher QOL than OE patients immediately after surgery, but evidence for this disparity was less robust 1-year post-operation^[74]. Thus, while MIE may not have as large of an immediate decrement on QOL, MIE, like OE, remains an aggressive procedure that carries risks and can produce complications.

Important to note is the varying accessibility of MIE versus OE. Although there is evidence to suggest superiority of MIE over OE, the choice between surgical techniques may not be available to some patients because of geographic and logistical barriers such as the steep learning curve of MIE and the low availability of surgical tools necessary for MIE^[16,75,76]. Therefore, OE may be the only option for patients who do not have access to centers equipped for MIE or do not have the resources to seek such centers.

EMERGENT TREATMENT STRATEGIES

Chemoradiotherapy and endoscopic resection

As mentioned above, ER is primarily recommended for T1a patients due to concerns regarding the increased rate of lymph node metastases following submucosal invasion^[28]. Lymph node metastases can be addressed through lymphadenectomy

during esophagectomy and/or chemoradiotherapy (CRT). CRT alone is sometimes used as a non-operative treatment in place of surgery for older patients with locally advanced EAC who are unable, unwilling, or not referred to undergo esophagectomy despite the risk of nodal involvement. However, current data show that, compared with esophagectomy, definitive CRT for stage I-III EAC patients is ineffective^[77-83]. Additionally, CRT's impact on QOL and the differences in severe adverse events relative to esophagectomy have not been well documented. With this in mind, ER in combination with chemotherapy or CRT warrants further exploration as a potential organ-preserving alternative to esophagectomy that can address lymph node metastases, particularly in patients who are older and/or have comorbid conditions who are poor operative candidates^[84].

Existing research regarding CRT + ER is limited for early-stage EAC patients. Minashi *et al*^[85] found that ER and selective CRT provided to patients with T1b (sm1-2) resulted in a 3-year survival rate of 90.7%, which is comparable to that of surgery. A review of six studies ($n = 168$) in which all patients had superficial esophageal SCC treated with CRT + ER found promising rates of control of local recurrence following treatment, ranging from 0%-9%, and 3-year overall survival rates ranging from 87%-100%^[86]. Patients who developed metachronous esophageal lesions after ER and adjuvant CRT were all successfully treated with salvage ER^[86]. The major limitation of these findings is that the patients in this review had SCC, which tends to have a better response to CRT than EAC; therefore, these results alone cannot be used to justify the use of ER and CRT for T1 EAC^[82]. Another study ($n = 32$) compared outcomes of ER alone, CRT + ER, and esophagectomy in patients with T1b EAC^[87]. This study found an EAC recurrence rate of 11% with CRT + ER, compared to a 38% EAC recurrence rate with ER alone, and a 29% EAC recurrence rate with esophagectomy. Although there was a trend toward better outcomes for CRT + ER, differences in EAC recurrence rates were not statistically significant, potentially due to a lack of statistical power; however, these findings suggest that CRT + ER could be a viable treatment option for T1b EAC patients unable or unwilling to undergo esophagectomy^[87]. Another report assessed the efficacy of salvage ER following CRT in two patients with T2N0M0 EAC who were unfit for esophagectomy^[88]. Both patients achieved complete endoscopic and histological remission after removing residual lesions with ER following treatment with CRT regimen. While this sample size is too small to generalize the results to the early EAC patient population, these results suggest the utility of future work examining the efficacy of CRT + ER in early-stage EAC patients^[88].

Biomarkers and precision medicine

Another avenue of research with promising therapeutic potential is the identification of prognostic and predictive biomarkers of EAC and tailored treatment plans that target these biomarkers. These targeted therapies work by acting on molecular characteristics of a patient's tumor, rather than applying a systemic conventional chemotherapy. Prognostic biomarkers of overall survival for patients with EAC have been identified, and include *SPARC*, *SPP1*, and *MET* gene expression, COX-2 angiogenic factor expression, and HER2 positivity^[89-92]. Some molecular profiles are more common in EACs than others; EGFR (16% of EACs), HER2 (19% of EACs), and MET (6% of EACs), some of the more common biomarkers in EAC, have available targeted therapies, although they have mostly been explored in adenocarcinoma of the gastroesophageal junction^[93]. HER2 positivity and EGFR overexpression are prognostic biomarkers, the presence of which indicate a poorer EAC prognosis as they promote cancer growth^[94,95]. Patients with HER2 positivity are considered for treatment with trastuzumab, which acts on HER2 cells to inhibit tumor cell growth^[96]. Those with EGFR overexpression may be candidates for treatment with cetuximab with chemotherapy, which has shown a trend toward improved survival relative to chemotherapy alone^[93]. Because targeted therapies work only on cells that express a given biomarker, therapies such as trastuzumab and cetuximab are most likely to yield positive outcomes only in the subset of EAC patients with HER2 positivity and EGFR overexpression, respectively^[93,97]. The efficacy of these targeted treatments, which offer the benefits of superior outcomes for a subset of patients and lower toxicity than conventional CRT, merit further study as a potential definitive and/or neoadjuvant treatment for EAC patients.

CONCLUSION

A thorough understanding of available treatment options for early-stage EAC and their effects on survival, health, and QOL is paramount for informing treatment-

related decisions and improving patient outcomes. Many patients diagnosed with early-stage EAC are older, have comorbid conditions, or are eligible to undergo esophagectomy but choose not to have it. Future research concerning these patients' preferences and effects of different treatments on QOL are warranted. Additional exploration of T1b tumor characteristics that can accurately predict whether the tumors are at high or low risk of lymph node metastasis would also aid in treatment choice optimization for T1b patients. The potential for the combination of ER and CRT to provide an effective, organ-preserving treatment for some early-stage EAC patients is important and requires further investigation.

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