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Curative criteria for endoscopic treatment of oesophageal adenocarcinoma

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ABSTRACT

The incidence of oesophageal adenocarcinoma has been increasing rapidly in the Western world. A well-known risk factor for developing this type of tumour is reflux disease, which can cause metaplasia from the squamous cell mucosa to columnar epithelium (Barrett's Oesophagus) which can progress to dysplasia and eventually adenocarcinoma. With the rise of the incidence of oesophageal adenocarcinoma, research on the best way to manage this disease is of great importance and has changed treatment modalities over the last decades. The gold standard for superficial adenocarcinoma has shifted from surgical to endoscopic management when certain criteria are met. This review will discuss the different curative criteria for endoscopic treatment of oesophageal adenocarcinoma.

1. Introduction

Over the past decades, the incidence of oesophageal adenocarcinoma (AC) has been increasing rapidly. Whereas squamous cell carcinoma (SCC) was the most common type of oesophageal cancer worldwide, in some Western countries such as the United States, the Netherlands and New Zealand adenocarcinoma has surpassed this [1,2]. One of the main risk factors for developing AC in the oesophagus is reflux disease [3]. Longstanding reflux disease can cause metaplasia from the squamous cell mucosa to columnar epithelium (Barrett's Oesophagus) which can progress to dysplasia and eventually adenocarcinoma [3].

Until not so long ago, the treatment of early cancer was a fiery point of debate between surgeons and endoscopists. Oesophagectomy was considered the only treatment option and therefore the gold standard to treat early neoplastic Barrett's Oesophagus (BO). Over the last twenty years, minimally invasive endoscopic interventions have been developed and replaced oesophagectomy as the cornerstone of therapy [4–6]. Endoscopic resection is safe, effective and less invasive than oesophagectomy which is associated with up to 5 % mortality and high rates of morbidity of 50–75 % [7–9].

The current European Society for Gastrointestinal Endoscopy (ESGE) and American Society for Gastrointestinal Endoscopy (ASGE) guidelines divide the endoscopic treatment for resection of BO-associated lesions into two different groups: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) [10,11]. To determine whether a patient is eligible for one of these procedures several criteria concerning the extent of the disease and the risk to develop lymph node metastases have to be met. In this review we will discuss the curative criteria for the endoscopic treatment of oesophageal AC.

2. Criteria for endoscopic treatment of adenocarcinoma

2.1. EMR and ESD

As the ESGE and ASGE guidelines recommend, EMR can be used for removing visible BO-associated lesions ≤20 mm with a low probability of deep submucosal invasion and for larger or multifocal benign (dysplastic) lesions [10]. The most commonly used EMR techniques in the oesophagus are cap-, and ligation-assisted EMR [12]. After marking the target area, cap-assisted EMR uses a submucosal injection to lift the lesion away from the muscle layer. Then suction is applied to caption the lesion into an oblique cap that is placed on the tip of the scope to retract the mucosa [12,13]. Next, a preloaded snare placed in the rim of the cap is closed and the lesion is excised using electrocautery. In ligation-assisted EMR or multiband mucosectomy (MBM) a band ligation device with a cap is attached to the scope and placed over the target

Abbreviations: AC, adenocarcinoma; SCC, squamous cell carcinoma; BO, Barrett's Oesophagus; ESGE, European Society for Gastrointestinal Endoscopy; ASGE, American Society for Gastrointestinal Endoscopy; EMR, Endoscopic Mucosal Resection; ESD, Endoscopic Submucosal Dissection; MBM, Multiband Mucosectomy; EUS, Endoscopic Ultrasound; AI, Artificial Intelligence; LVI, Lymphovascular Invasion; LNM, Lymph Node Metastasis.

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lesion (this can be done with or without lifting of the lesion first using submucosal injection). Next, the lesion is retracted into the banding cap using suction and a band is deployed to capture the lesion, creating a pseudopolyp. This pseudopolyp is subsequently resected using electrocautery snaring. Data comparing both EMR techniques are scarce, although two randomized trials on cap-assisted versus ligation-assisted endoscopic resection showed no differences in rates of adverse events or quality of the resected specimen [14,15]. The selected technique might thereby often be determined by the preference and experience of the endoscopist.

Furthermore, the ESGE and ASGE guidelines recommend using ESD for BO-associated lesions suspicious for submucosal invasion, for malignant lesions >20 mm, and for lesions in scarred/fibrotic areas [10]. The procedure for ESD starts with the placement of marking spots around the neoplasia using the tip of an electrocautery-knife [13]. Next, a submucosal injection with indigo carmine dye or methylene blue is used in the same way as with EMR to lift the lesion from the proper muscle layer and making the separate layers and blood vessels recognizable. After this, a circumferential incision of the mucosal layer is made around the marking dots followed by careful dissection of the submucosal layer from the muscle layer.

2.2. EMR versus ESD

Even though there are very limited randomized prospective trials comparing EMR with ESD, both techniques show their own advantages and disadvantages. EMR presents to be more appropriate for smaller lesions and is relatively simple to execute in less time compared to ESD [16,17]. Moreover, fewer complications are reported with EMR than with ESD [18,19]. One of the main disadvantages of EMR is that if piecemeal resection is necessary, for example for larger lesions, detailed histopathological analysis might be hindered and radical resection cannot be confirmed from a histopathological point of view. Another disadvantage of EMR is the reported higher lesion recurrence rate of 5–20 % [20,21]. Although, these recurrences can usually be treated by re-EMR with a comparable high survival rate as with ESD [22,23].

A great benefit of ESD is that it allows to achieve an R0 resection of any type of lesion regardless of size and it has a very low recurrence rate of less than 1 % [16,18]. Yet, ESD is more time-consuming, advanced endoscopy skills are required and has a higher perforation rate compared to EMR [24]. According to a large study in Japan, there was a 3.3 % perforation rate occurring in patients who underwent oesophageal ESD [25]. Fortunately, the large majority of perforations can be treated endoscopically with application of clips along with antibiotics and nil per mouth, thus without the need for surgery [16,26].

3. Determining tumour invasion during endoscopy

Superficial oesophageal cancer is limited to the mucosa or the submucosa and is considered suitable for endoscopic resection. Determining the probability of submucosal invasion is of importance considering the risk of lymph node metastases increases with the depth of tumour invasion in the oesophagus [27]. Since detection and classification of superficial cancer can be challenging, it should be performed by an experienced endoscopist using high definition white light combined with chromoendoscopy and magnification.

3.1. Gross morphology

When the lesion is identified, the Paris classification can be used to describe the lesion with its concomitant risk of tumour invasion [28,29]. The Paris classification is an international classification system defining type 0 lesions as superficial. This type is categorized into three subtypes: protruding lesions (0-I), non-protruding and non-excavated lesion (0-II) and excavated lesions with/without ulcers (0-III). Type 0-I lesions are divided into subsequently pedunculated (0-Ip) and sessile (0-Is). Type 0-II lesions are further subdivided into slightly elevated (0-IIa), flat (0-IIb), depressed (0-IIc) or combination types. The first two subtypes of 0-II lesions, 0-IIa and 0-IIb, are considered lesions with a low probability of submucosal invasion, thus suitable for endoscopic resection. Lesions with the subtype 0-Is and 0-IIc are suspicious for submucosal invasion, and so en bloc resection should be considered.

Furthermore, the submucosal injection to lift the lesion from the proper muscle layer performed during endoscopic resection as described in *2.1.* Can provide information on the invasion of tumour invasion as well. While this is not a standard diagnostic test that is performed during endoscopy, Kato et al. validated that the amount of lift is related to the depth of invasion in colorectal lesions [30,31]. Lesions in mucosa or lesions infiltrating no deeper than 500 μm in submucosa (m-sm1) usually lift completely, whereas lesions infiltrating deeper layers (sm2-sm3 or > sm3) often lift incompletely or not at all [30–32].

3.2. Surface patterns

To identify adenocarcinoma and its invasion into the mucosa/submucosa, surface patterns are closely inspected with not only white light endoscopy, but also with other techniques. For example, for BO-associated lesions acetic acid can be used to stain the lesion into a more red like colour compared to its non-dysplastic/cancerous surroundings [33,34]. Additionally, optical chromoendoscopy has become available. This technique uses electric endoscopic imaging technologies that provide detailed contrast enhancement of the mucosal surface and blood vessels by a light source illuminating the inspected area without the need of dyes. The most investigated modes of optical chromoendoscopy are narrow-band imaging (NBI) and blue light imaging (BLI), which work on the principle of using light in specific wave-lengths (blue and green light) to visualize neoplasia [35–37]. The depth of penetration into the mucosa depends on the wavelength of the light, due to the absorption of light by haemoglobin. This clarifies why blood vessels are highlighted when viewed with NBI and BLI. A different technique that can be used to identify lesions in the oesophagus is virtual chromoendoscopy, for example i-Scan. This technique works through reconstructing an image provided by the endoscope so that the mucosa looks like it is illuminated by using light in a certain wavelength, without actually changing the wavelength [38].

When looking at surface patterns for adenocarcinoma, the following items are evaluated; mucosal architectural distortion, microvascular irregularities and ulceration. For the identification of the first two items, a classification system was developed and validated by the Barrett's International NBI group (BING) [39]. In normal tissue, the mucosal architecture has a ridge/villous pattern with multiple longitudinal lines or a circular pattern. If the pattern appears irregular and distorted, this can be classified as abnormal, and the risk of high grade dysplasia or malignancy is increased [39,40]. The vascular pattern can be classified as normal when the blood vessels are situated regularly along or between mucosal ridges and-or those showing normal, long, branching patterns. When the vascular pattern is focally or diffusely distributed not following the normal mucosa, this is classified as irregular [39,40]. The third item concerning the surface pattern in adenocarcinoma, ulceration, is related to a risk of 84 % of having submucosal invasion and therefore has a higher risk of lymph node metastases [41].

3.3. Endosonography

Endosonography (EUS) has been broadly studied to determine differences in tumour invasion in the oesophagus. Overall, it appears to be not accurate enough to distinguish between mucosal (T1a) and submucosal (T1b) tumours. A large meta-analysis on this topic showed heterogeneity present among the included studies suggesting multiple factors affect the diagnostic accuracy (i.e. location and type of the tumour, method (linear vs radial) and frequency of EUS probe and the experience of the endoscopist) [42]. Moreover, a study from 2022

showed a high frequency of overstaging for T1 tumours when using EUS [43]. The Dutch study showed downstaging of 60 % from cT2 tumours to cT1 tumours after endoscopic reassessment by an experienced interventional endoscopist, rendering them suitable for endoscopic resection. After resection, histological analysis showed that 80 % of the downstaged lesions were pT1 tumours. In line, other studies demonstrated that EUS is a suboptimal technique to distinguish between the above mentioned tumours when compared to histological analysis after resection of the tumour [44,45].

3.4. Artificial intelligence

No published articles are found on determining the tumour invasion of oesophageal AC by artificial intelligence (AI). Studies on AI's measurement of infiltration depth in oesophageal SCC, gastric and colon AC have been published. For example, a study on gastric cancer showed a promising sensitivity of 77 % and a specificity of 96 % for distinguishing early gastric cancer from deeper submucosal invasion with higher accuracy than human endoscopists with varying experience [46]. Furthermore, Messmann et al. mention several studies using real-time AI-assisted staging of early squamous cell neoplasia through determination of infiltration depth. These studies show that AI performs similar to expert endoscopists for predicting depth [47]. Research on oesophageal AC regarding infiltrating depth is currently lacking.

4. Histopathological assessment and definitive curative criteria

After resection, histopathological assessment needs to be performed on the resected specimen to determine the definite tumour depth, size, margin status, differentiation grade and presence of lymphovascular invasion (LVI) to decide whether the endoscopic treatment is sufficient or additional treatment interventions are required (i.e. surgery, chemotherapy, radiotherapy). If complete endoscopic resection has been achieved and vertical margins appear to be free of tumour, the tumour depth is limited to the mucosa or ≤500 μm in the submucosa (sm1), the tumour is well to moderately differentiated (G1/2 and there is no LVI, the ESGE and ASGE guidelines recommend that curative resection has been achieved (Fig. 1). No step-up treatment is required. Ablation of the remaining Barrett's mucosa is recommended, because of an increased risk of metachronous neoplastic recurrence [48,49]. If any of the criteria stated above are not met, additional treatment is recommended in most guidelines. These criteria are based on the evidence that after performing endoscopic resection the risk of lymph node metastasis (LNM) is lower compared to the risk of mortality when undergoing oesophagectomy.

4.1. Mucosal tumours

The oesophagus has lymphatic vessels that frequently extend into the mucosa, resulting in the potential of malignant lesions to metastasize not only through the submucosal, but also through the mucosal lymphatics [50]. Nonetheless, mucosal tumours (T1a) are rarely associated with LNM. Multiple retro- and prospective studies showed a risk of 0 % for local recurrence and/or LNM in mucosal tumours in the oesophagus [51–55]. Yet, other retrospective studies and a systematic review reported a prevalence for LNM ranging from 1 to 3 % [56–59]. As Weksler et al. furthermore state, nodal metastases were significantly affected by the tumour differentiation grade, the size of the lesion and the presence of LVI based on a self-made scoring system that predicts the risk of nodal metastases for mucosal and submucosal oesophageal AC [59]. The higher the score, ergo more of the before mentioned predictors are found after histopathological assessment, the higher the risk for LNM. In addition, a study on the outcome of surgical treatment for AC in the gastro-oesophageal junction showed that in univariate analysis *N*-stage, tumour differentiation grade and depth of tumour invasion was a prognostic factor for a recurrence-free period [58]. In multivariate analysis only *N*-stage was a prognostic factor. Two recent studies from 2021 to 2022 that aimed to assess the risk of LNM in oesophageal AC with low versus high risk histological features (absence versus presence of LVI and good/moderate versus poor tumour differentiation) showed conflicting results [60,61]. The study from 2021 showed no LNM, even in high risk tumours [60]. Meanwhile the study from 2022 reported LNM in 7 % of high risk mucosal tumours [61]. Regardless of this conflicting data, with an average risk of 0–3 % for LNM compared to the mortality risk of 0–5 % for oesophagectomy, endoscopic resection is according to most current guidelines the preferred mode of treatment without the need of additional treatment when all curative criteria are met.

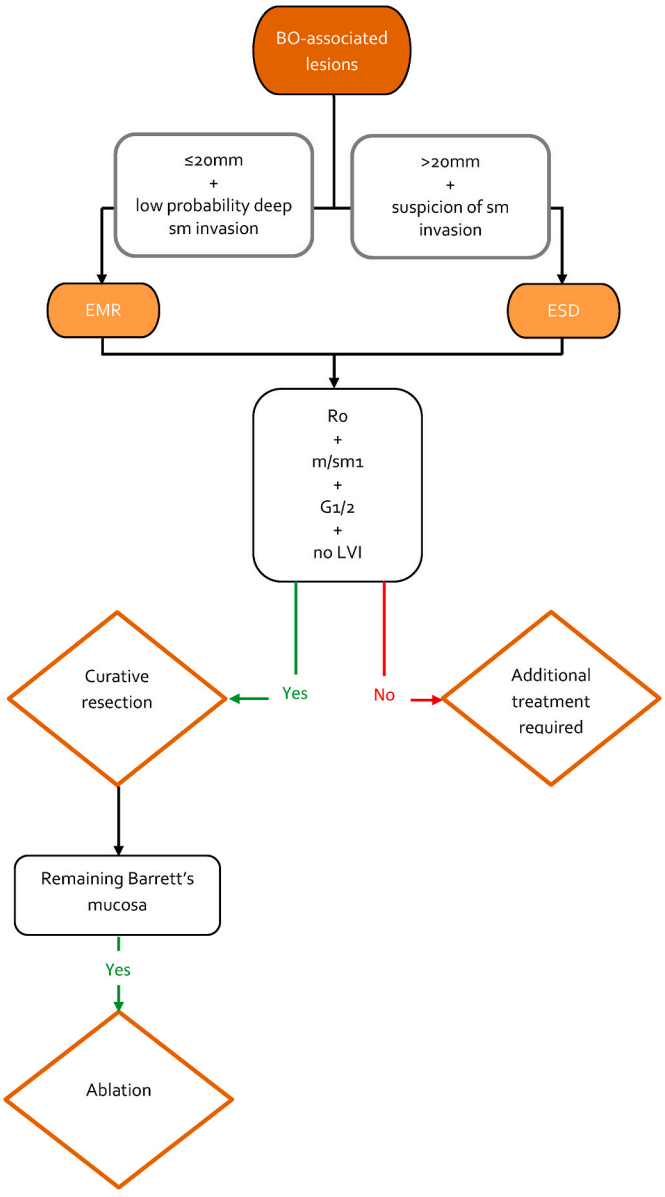

Fig. 1. Flowchart BO-associated lesions
BO = Barrett's Oesophagus; sm = submucosal; EMR = Endoscopic Mucosal Resection; ESD = Endoscopic Submucosal Dissection; R0 = tumour free margins; m = mucosal; G1/2 = good to moderately differentiated tumour, LVI = lymphovascular invasion.

4.2. Submucosal tumours

For lesions infiltrating the submucosa (T1b) the risk of LNM

increases. One of the most investigated risk factors for LNM is the extent of tumour invasion in the submucosa. When the lesion has invaded ≤500 μm in the submucosa (sm1) or invaded ≥500 μm in the submucosa (sm2/3), the risk for LNM is 0–9 % and 0–38 % respectively [53,55,62–64]. Especially surgical studies on LNM, as opposed to endoscopic studies, show high rates of metastases in submucosal tumours. This might be an overestimation due to the older aspect of the surgical studies. In these time periods, the exact tumour invasion in the surgical specimens did not change the mode of treatment for patients with oesophageal AC. Additionally, there is a large difference in the amount of resected submucosa which might make it difficult for the pathologist to identify the deepest point of tumour invasion in large surgical specimens. Therefore, tumour invasion can be understaged with a higher rate of LNM compared to an endoscopically resected specimen. In like manner, the surgical specimen is cut in 5 mm slices for histopathologic assessment, compared to 2 mm slices with an endoscopically resected specimen allowing a less detailed inspection of the tumour and its invasion resulting in the same understaging as mentioned in the latter sentence [65]. Moreover, multiple studies showed that LVI and poor tumour differentiation (G3) were also associated to the presence of LNM [56,66,67]. For example, a meta-analysis of 23 studies from 2000 to 2018 reported a significantly increased risk for LNM for patients with a lesion containing LVI with an odds-ratio of 5.72 [66]. Several studies reported a significantly increased risk for LNM for patients with poorly differentiated lesions with odds-ratios ranging from 2.2 to 9.73 [56,68,69]. A recent multicentre cohort study from 2021 made an individual risk calculator to predict LNM in patients with submucosal oesophageal AC [70]. The model showed a good discriminative ability where the risk for LNM increased with tumour invasion depth (every increase of 500 μm), LVI and tumour size (for every increaser of 10 mm) with hazard ratios of 1.08, 2.95 and 1.23 subsequently. In a study published in 2014 on the risk of LNM in patients with T1b sm1 EAC patients meeting all histological criteria (well/moderately differentiated, no LVI) the risk of LNM was 2 % compared to 9 % for tumours that showed one or more poor prognostic criteria [62]. Since a metastasis rate of 9 % is higher than the mortality rate for oesophagectomy, additional staging and treatment is recommended in most guidelines. This should be carefully balanced against individual mortality and morbidity risks related to surgery. Watchful waiting strategies are also being evaluated. This will be discussed in the next chapter.

5. Summary

In oesophageal cancer, AC is becoming more common in Western countries compared to the stable higher incidence of SCC for the Eastern World. One of the main risk factors for developing oesophageal AC is reflux disease which can cause metaplasia from the squamous cell mucosa to columnar epithelium (Barrett's Oesophagus) that can progress to dysplasia and eventually adenocarcinoma. The rising incidence of oesophageal adenocarcinoma is an important point of research and management of this disease has changed over the last decades in most guidelines from mainly surgical treatment to endoscopic treatment when certain criteria are met. Endoscopic treatment can be divided into EMR for smaller lesions (≤20 mm) with a low probability of deep submucosal invasion and ESD for larger lesions (>20 mm) suspicious for submucosal invasion and for lesions in fibrotic areas. If complete endoscopic resection has been achieved and vertical margins appear to be free of tumour, the tumour depth is limited to the mucosa or ≤500 μm in the submucosa (sm1), the tumour is well to moderately differentiated (G1/2) and there is no LVI, the ESGE and ASGE guidelines recommend that curative resection has been achieved. These criteria are based on the evidence that after performing endoscopic resection the risk of lymph node metastasis (LNM) is lower compared to the risk of mortality when undergoing oesophagectomy. Further research on LNM after endoscopic resection to substantiate these criteria is needed. Ablation of the remaining Barrett's mucosa is recommended, because of an increased risk of metachronous neoplastic recurrence.

Practice points

- EMR can be used for removing visible BO-associated lesions ≤20 mm with a low probability of deep submucosal invasion and for larger or multifocal benign (dysplastic) lesions.
- ESD can be used for removing BO-associated lesions suspicious for submucosal invasion, for malignant lesions >20 mm, and for lesions in scarred/fibrotic areas.
- If complete endoscopic resection has been achieved and vertical margins appear to be free of tumour, the tumour depth is limited to the mucosa or ≤500 μm in the submucosa (sm1), the tumour is well to moderately differentiated (G1/2) and there is no LVI, most guidelines recommend that curative resection has been achieved.
- The curative criteria for endoscopic treatment of oesophageal AC are based on the evidence that the risk of lymph node metastasis is lower compared to the risk of mortality when undergoing oesophagectomy.
- Ablation of the remaining Barrett's mucosa is recommended, because of an increased risk of metachronous neoplastic recurrence.

Research agenda

- All curative criteria for endoscopic treatment of oesophageal AC are based on the risk of LNM. Though many studies show large ranges for this risk. More studies are needed to narrow this range and validate the criteria more accurately.
- More research on the separate influence of the different criteria (tumour invasion, differentiation grade, presence of LVI) on LNM is desirable to determine the individualized risk for patients with oesophageal AC.
- AI is an upcoming system which might be able to assist an endoscopist with recognizing and grading lesions in the oesophagus. There is a need for more extensive research in this field in the future.

Declaration of competing interest

None.

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