RISK FACTORS AND SCREENING STRATEGIES FOR EARLY DETECTION OF ESOPHAGEAL CARCINOMA

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Abstract

Esophageal cancer is the 8th most frequent type of cancer in the world and the 6th cause of death from cancer, with variable distributions according to geographic region. Initiatives for early detection, treatment, control and monitoring of different pathologies has shown a significant impact on reduction of morbidity and mortality in different pathologies, although there are no established protocols for esophageal cancer screening in general population, risks factors associated with development of this condition are well defined, and this allows identify and prioritize population with highest risk.

Esophageal cancer is the 8th most frequent type of cancer in the world and the 6th cause of death from cancer, with variable distributions according to geographic region (1). The most frequent histological type is squamous cell carcinoma (SCC) accounting for 87% of cases, however, in United States and other western countries adenocarcinoma (EAC) predominates, with 31% and 64% for SCC and ACE respectively (2). EAC usually has a longer survival compared to SCC, especially if it is detected early; it is usually related to Barrett's esophagus (BE) and is located mainly at the distal third of the esophagus and / or at the gastroesophageal junction. BE increases the risk of EAC by 30-40 times. SCC is predominantly located at the upper two thirds of the esophagus (3).

As in most gastrointestinal tumors, esophageal cancer predominates in men, accounting for 70% of cases. Men have 3 to 4-fold higher risk than women of developing SCC and 7 to 10-fold higher risk of developing ACE (1). The incidence

is proportional to age, 60% of cases are reported in patients older than 65 years and only 13% in those younger than 55 (4).

Esophageal cancer has high mortality rate mainly because is rarely diagnosed at early stages. It has been reported that nearly 40% of patients have metastasized at the time of diagnosis; this added to the special anatomical conditions of the mediastinum and the high recurrence rate, confers it a worse prognosis and 5-year survival rate is close to 20% (5). In localized disease, with regional or distant extension, survival is estimated in 30, 13 and 6 months respectively (6).

A better understanding of the etiology and risk factors would allow changing lifestyle and early detection of patients with increased risk of this condition.

Initiatives for early detection, treatment, control and monitoring of different pathologies has shown a significant impact on reduction of morbidity and mortality in different pathologies, although there are no established protocols for esophageal cancer screening in general population, risks factors associated with development of this condition are well defined, and this allows identify and prioritize population with highest risk.

Esophageal cancer is usually preceded by chronic inflammation that injures signaling and cell growth pattern. Alcohol consumption has been shown to increase risk of SCC and BE is considered the most important risk factor for EAC. Several studies have shown an increased risk of EAC in obese patients. Low intake of vitamins A and C, zinc deficiency, hot drinks, and infections such as human papillomavirus also increase SCC incidence (7). Reports on family history and its impact on risk of developing esophageal cancer are conflicting, however, chinese studies (country with a high incidence of SCC), have founded that risk can be at least doubled in those patients who have a first-degree family member with SCC (8); family history of other tumors as: lung, prostate, breast, cervix, oral cavity and pharynx also demonstrated association (9).

Obesity is a known risk factor for EAC, those with a body mass index greater than 40 have a twice fold risk (10). Alcohol and smoking are well established risk factors for AEC and some studies have shown synergic effect. It has not been proven that alcohol increases EAC risk (11).

Regarding diet there is a protective effect from antioxidant properties of fruits and vegetables. Intake of hot drinks, meat, processed and salty food has shown an increased risk of developing esophageal cancer (12). Table 1.

RISK FACTORS FOR ESOPHAGEAL CARCINOMA
Barrett Esophagus
Alcoholism
Obesity (BMI > 40)
Smoking
Diet (Hot drinks, processed and salty food, meat, processed food)
Family history of esophageal, prostate, breast, cervix, oral cavity and oropharynx cancer

Table 1. Risk factors for esophageal carcinoma. Source author.

Screening and treatment of Barrett's esophagus

Adenocarcinoma is the dominant form of esophageal cancer in developed countries. Its incidence has increased 6 times in the last 40 years and has a poor prognosis with mortality rates almost equal to its incidence. In fact, half of diagnosed patients do not go to other treatment than palliative, however, patients with early stages have better outcomes, mainly associated with new endoscopic techniques (13).

Risk factors

Chronic inflammation of the esophagus is caused by gastroesophageal reflux or other irritants. From this inflammation, intestinal metaplasia (Barrett´s Esophagus,

BE) may develop at distal esophagus. Continued irritation can lead to low-grade dysplasia, which can progress to high-grade dysplasia and later to adenocarcinoma (2).

Clinical risk factors for BE

Although gastroesophageal reflux disease (GERD) is the strongest risk factor, 15-45% of BE cases develop in patients without GERD symptoms. Moreover 15-20% of western population have GERD symptoms, but only 10-15% develop BE. Although BE is clearly a precursor, it only progresses to adenocarcinoma at a rate of 0.12 to 0.6% annually (14).

Considering screening for BE in men with GERD for over 5 years and / or symptomatic frequency of more than once a week, with two or more risk factors for BE or EAC is suggested (age > 50, central obesity, abdominal circumference greater than 102 cm, smoking, first-degree relative with BE history) (15).

Follow-up is not recommended in women with chronic GER symptoms considering low risk of EAC in this population. However, it can be considered in patients with multiple risk factors such as age greater 50, central obesity, abdominal circumference > 88 cm, smoking, first - degree relative with EB or EAC history (15) (16). Table 2.

SCREENING RECOMENDATIOS FOR BARRETT ESOPHAGUS

Men with gastroesophageal reflux> 5 years
or
Men with gastroesophageal reflux with symptomatic frequency of more than once a week

With two or more risk factors for BE or EAC

- Age over 50 years
- Abdominal circumference > 102 cm
- Smoking
- First-degree relative with history of Barrett's esophagus or esophageal adenocarcinoma

Consider in women with chronic GER symptoms and multiple risk factors:

- Age over 50 years
- Abdominal circumference> 88 cm
- Smoking
- First-degree relative with history of Barrett's esophagus or esophageal adenocarcinoma

* **Table 2.** Screening recommendations for Barrett's esophagus. Source author

Endoscopic risk factors

Evidence of esophagitis or anatomic risk factors that worsen reflux (hiatal hernia) have been associated with increase in the progression of BE and EAC. In patients with endoscopic suspicion of BE not confirmed in the pathology, is suggested to carry out endoscopic control in 1 to 2 years for a new evaluation, this taking into account that up to 30% of patients will have a positive result for metaplasia at the second review (15).

Extent of metaplasia determines if it is short or a long segment, short segment is defined as less than 3 cm and long segment greater than 3 cm; long-segment BE patients have been shown to be at increased risk for EAC. Presence of mucosal nodularity, ulcers, and areas of stenosis have also been associated with EAC development (17).

Histological risk factors

Rate of progression to esophageal adenocarcinoma increases about 1% per year for BE patients with low-grade dysplasia and 7% per year for those with high-grade dysplasia (15).

Screening strategies

Screening techniques can be divided into those that allow identifying patients with Barrett 's esophagus and techniques to identify patients with EB diagnosis and highest risk of developing ACE, so they can enter an intensive protocol monitoring and treatment. This requires an endoscopic study and biopsies.

Screening is not recommended for the general population, only for certain risk groups as mentioned previously.

In case of BE is recommended to take four biopsies every two centimeters of metaplasia extension for a total of eight biopsies.
In patients with short-segment BE in whom it is technically impossible to obtain eight samples, is recommended obtain at least four quadrant biopsies for each centimeter of metaplasia extension and one biopsy for each centimeter in the observed reeds (15) (16).

If initial endoscopy is negative for BE, is not recommended to repeat it. If the endoscopy demonstrates grade B, C, or D esophagitis, endoscopic evaluation should be repeated after completing 8-12 weeks of proton pump inhibitor therapy to ensure healing and exclude underlying BE (15).

Follow-up: Using advanced imaging techniques such as electronic staining is recommended during follow-up as it increases detection rate of dysplasia by taking directed biopsies at any evident mucosal alteration. All mucosal changes by more trivial that seem must be biopsied (18).

Dysplasia is the main risk marker for EAC in patients with BE, current evidence supports the importance of having confirmation by a second pathologist, for all dysplasia reports (19).
Follow-up interval is determined by the presence and degree of dysplasia. Given the lower rate of progression to EAC of BE without dysplasia, a new endoscopy in 3-5 years seems appropriate. Biopsy protocol in this case requires taking a biopsy from 4 quadrants at 2- centimeter intervals (15).

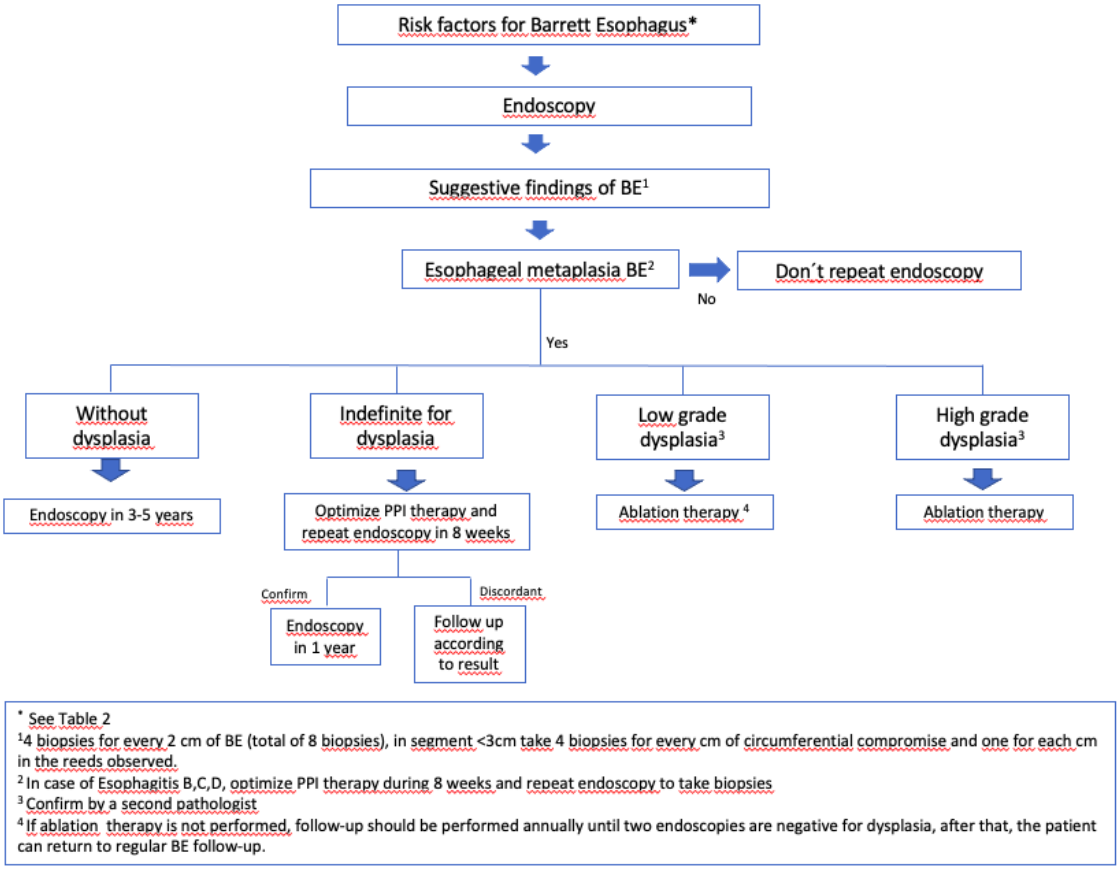
If indefinite dysplasia is reported, is considered reasonable to optimize protom pump inhibitory therapy (double dose) to reduce any type of inflammation and is suggested to perform an endoscopic control in 3 to 6 months, if it is confirmed as indefinite, control is done after one year, and if it changes to high grade dysplasia (HGD) or low-grade dysplasia (LGD) or without dysplasia, the follow-up will be done according to this result (20).

Report of LGD requires confirmation by a second pathologist, some authors suggest a new endoscopy after acid suppression with protom pump inhibitories in 3 to 6 months, based on some studies in which up to 50% of these patients may have changes in pathological report, this new endoscopic review should be

performed using chromoendoscopy, this tool allows rule out the presence of lesions that require early mucosal resection with greater precision (21). If it is confirmed that the patient has LGD, two protocols are accepted: follow-up or ablation therapy (15).

If no endoscopic therapy is performed because of patient's decision or conditions that contraindicate it, follow-up should be performed annually until two endoscopies are negative for dysplasia, after that, the patient can return to regular BE follow-up. Biopsy protocol in this case (LGD monitoring) is to take a biopsy from 4 quadrants for each centimeter compromised by BE and any mucosal alteration evidenced by endoscopic mucosal resection should be resected (15).

If high-grade dysplasia (HGD) is reported, it must be confirmed with a second pathologist and therapeutic intervention is required. Some authors suggest performing a new endoscopy in 6 to 8 weeks to evaluate the presence of visible lesions that would need endoscopic resection before ablative therapy (2) (15). Algorithm 1.



Algorithm 1. Diagnosis and monitoring of Barrett's esophagus. Source author.

Treatment

In HGD, ablation therapy is prefered over esophagectomy and close endoscopic follow-up due to its proven efficacy and better safety profile when compared to surgery. In BE with GDB (confirmed by two pathologists) ablative therapy results in clinically and statistically significant reduction in progression to HGD or EAC. Contrary to these scenarios in BE without dysplasia (taking into account its low rate of progression and the complication rate of ablative therapy and its costs) it is not recommended (21).

Regarding which ablation therapy to choose, a wide variety of modalities have been described and have proven to be effective in eradication of intestinal metaplasia. Currently, photodynamic therapy and radiofrecuency have the most

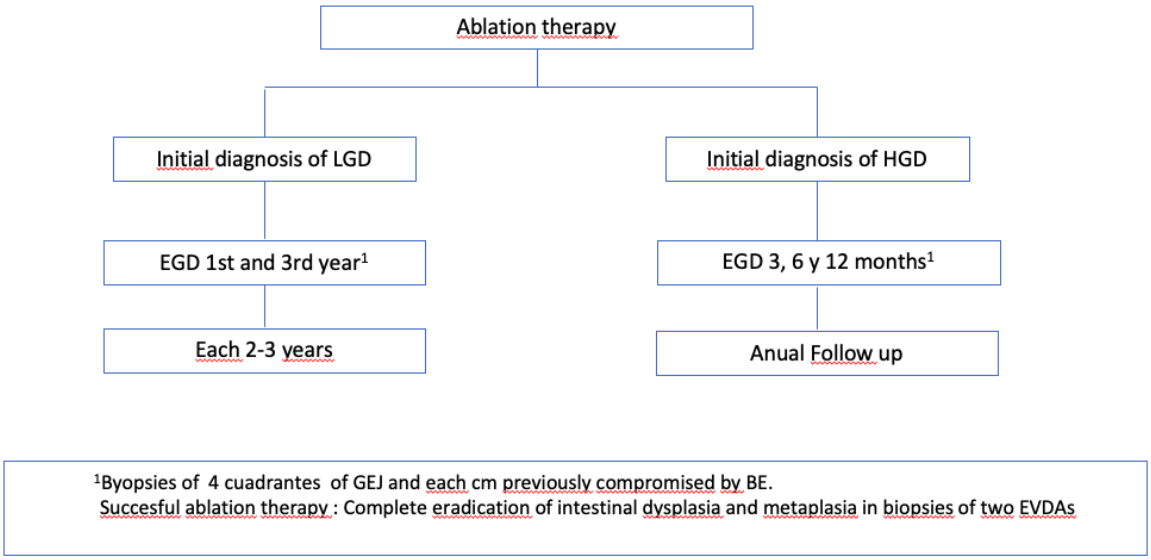
valid evidence for reducing the incidence of EAC. Considering costs and safety profile of photodynamic therapy as well as data supporting safety and efficacy of radiofrequency, this appears to be the prefered modality for most patients. Stenosis and complete eradication rates for photodynamic and radiofrequency therapy are 30% vs. 6% and 77 vs. 90%, respectively (22).

Post treatment follow-up

After complete eradication of intestinal metaplasia, recurrence can be 8-10% per year and more than 20% at 2-3 years. Most recurrences do not have dysplasia but up to 25% may have it. Recurrence rate is usually similar and independent of ablation therapy used. Endoscopic follow-up in patients with history of HGD must be done at 3, 6, 12 months and then every year. Endoscopic follow-up in patients with history of LGD is performed at one year, at the third year, and then every 2 to 3 years (15) (21). Algorithm 2.

Follow-up should be permanent; s not recommended to stop it as long-term recurrences have been documented. Factors that favor recurrence are: older age, associated large hiatal hernia, and high-grade dysplasia before ablation.

Successful ablation therapy is defined as complete eradication of dysplasia, as well as intestinal metaplasia in the esophagus, for this it is necessary to take biopsies of 4 quadrants of GEJ and each centimeter previously compromised by BE. Two negative biopsy sessions are required to consider complete eradication (16).



Algorithm 2 . Follow-up of patients treated with ablation therapy. Author source.

Squamous cell carcinoma

Although is not the most common type of carcinoma of esophagus in West countries, EC (Escamocelular carcinoma) remains the most prevalent type of esophageal carcinoma in the world.

Risk factor's

Most important risk factors for EC are environmental. Smoking increases risk of developing the disease. Alcohol is another important risk factor with a relative risk increase of 2 to 8, depending on the volume of alcohol consumed. Consumption of food rich in nitrogenous components has an OR of 2 for development of this condition (2).

Screening techniques

Is believed that esophageal squamous dysplasia is a precursor for EC, however, there are no prospective studies to confirm this theory. Chromoendoscopy is a key tool in diagnosis of pre neoplastic squamous lesions (2). Sensitivity and specificity of white light for detection of high-grade dysplasia and cancer is 62% and 79%, respectively, compared with a much higher sensitivity when using chromoendoscopy of 96% (23).

Due to low incidence in Western countries, screening strategy is not clearly effective, however, these are applied in regions of high incidence (30 cases per 100,000 people / year) (24) . Two endoscopic strategies have been established as cost effective. In areas with low-income levels and limited access to healthcare system, researchers recommend a screening endoscopy at age of 50, with follow-up every 5 years for low-grade dysplasia and every 3 years for high-grade dysplasia. In developed countries, 3 screening endoscopies are recommended at 5-year intervals starting at age of 40 (2).

Early esophageal cancer

Fifth of patients with esophageal carcinoma are diagnosed with localized disease incidentally during a screening endoscopy or monitoring other conditions. Inspection with white light can miss some lesions and therefore evaluation using chromoendoscopy and target biopsies to identified lesions is recommended. This strategy has shown a sensitivity > 90% and specificity > 80% for detection of high-grade dysplasia and early esophageal adenocarcinoma (25).

Cornerstone of early esophageal cancer is endoscopic resection. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are resection methods that allow stablish depth of invasion. Endoscopic resection also provides information about differentiation grade and lymphovascular invasion (26).

Patients with short segments of nodular dysplasia and superficial lesions of EAC or EC are amenable to endoscopic management by EMR. ESD has similar indications with advantage of providing a deeper resection and therefore performing an en bloc resection with curative results; however, ESD is associated with longer surgical times and a greater number of complications. ESD is indicated in lesions larger than 15 millimeters to achieve en bloc resection (27).

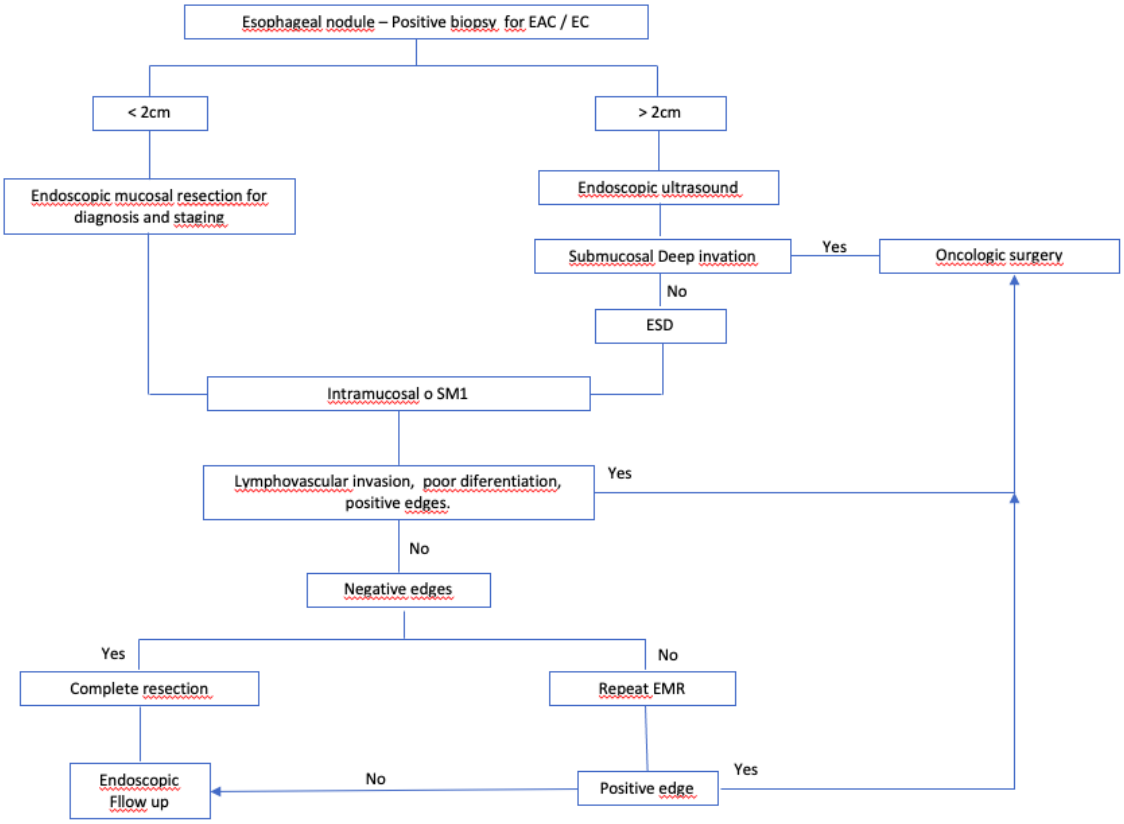
Endoscopic eradication therapy can have complete eradication rates R0> 90% in T1a esophageal carcinomas, therefore it is recommended over surgery when in situ and T1a EAC and EC are detected.
Studies have shown that endoscopic resection is effective in erradicating HGD or T1a EAC in 91-98% of cases. There are data suggesting that cure and survival

rates after endoscopic resection at T1a stages are comparable to those reported after surgical treatment, but with lower morbidity and mortality (28).

T1b EAC lesions have risk of lymph node metastasis as high as 15-25%. This risk may vary depending on invasion depth of the submucosa, with minimal risk of lymphovascular invasion for lesions limited to the upper third of the submucosa (Sm1); invasion beyond this segment is a predictor of lymph node metastatic involvement and could therefore be a contraindication for endoscopic resection. Endoscopic resection is an option when it comes to T1b / SM1 lesions without high-risk characteristics (poorly differentiated grade 3 or 4 carcinoma, lymphovascular or perineural invasion, and positive deep margins) (25).

Despite aforementioned advantages, complications are also more frequent, including bleeding in 6.7% of cases and perforation in 4.6% (29).

Endoscopic ultrasonography performed before any treatment is important for initial staging of neoplastic disease, as it provides information on deep invasion (T), lymph node involvement (N) and occasionally metastasis (M) (27). Algorithm 3



Algorithm 3 . Diagnosis and monitoring of Ca of the esophagus early

Advanced esophageal cancer

Patients with esophageal carcinoma require a multidisciplinary evaluation of their disease and specific staging. Those with metastatic involvement are considered unresectable and surgical procedures with curative intent are not recommended. At this point, treatment focuses on symptom control (30).

Dysphagia

Insertion of an endoscopic stent provides long-lasting relief from obstructive symptoms secondary to the tumor. They can be covered or not covered, latter one with a lower rate of migration.

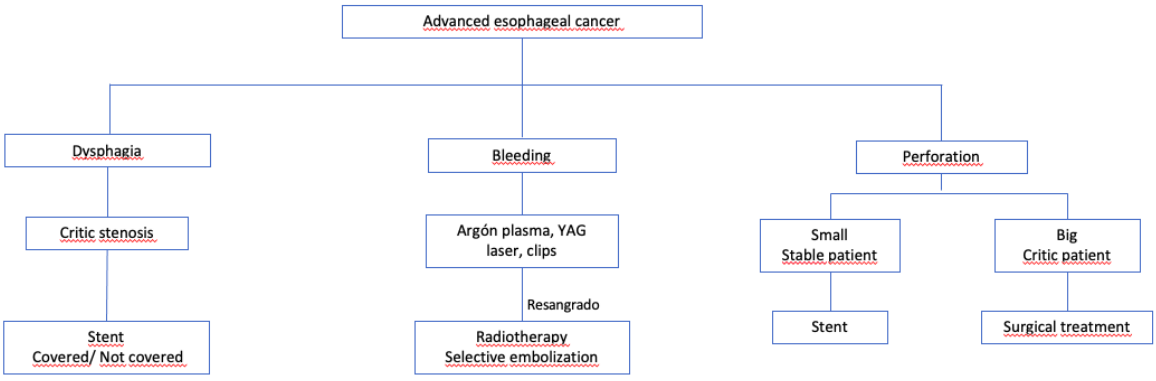
Patients undergoing esophageal stent insertion due to tumor obstruction have a marked improvement in dysphagia, and up to 95% of cases are able to tolerate fluids after the procedure (31).

Bleeding

It is a common complication of advanced tumor disease, usually due to tumor erosion in nearby vessels. Endoscopic therapy is the first line of palliative treatment, argon plasma, cryoablation, YAG laser, and endoscopic clips are the most commonly used methods. If endoscopic therapy fails to control bleeding, other modalities such as radiation therapy for diffuse tumor bleeding or selective embolization may be used (30).

Perforation

In small contained perforations, use of a stent can be considered, if the patient is stable, is the recommended approach. Surgical management is generally required for large perforations or critically ill patients (31). Algorithm 4.



Algoritmo 4. Manejo endoscópico de las complicaciones del cáncer de esófago avanzado

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