Endoscopic Therapy of Barrett’s Esophagus and Esophageal Adenocarcinoma

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Abstract

The normal squamous esophageal epithelium reacts as a chronic inflammation to the severe gastro-esophageal reflux. Esophagitis will progress to Barrett metaplasia in 10% of patients who would be of minor clinical interest if it then did not advance to low, high grade dysplasia and invasive carcinoma. The rise of esophageal adenocarcinoma (EAC) incidence surpasses any other cancer, including melanoma, lymphoma and small cell lung cancer. There is no clear proof that medical therapy could prevent the neoplastic progression. It seems that this population has a variable answer to proton pump inhibitors therapy. A multimodal approach of Barrett’s esophagus with high grade dysplasia is required, including endoscopic mucosal resection, photodynamic therapy and thermal ablation. Photodynamic therapy could be used for the management of patients with high grade dysplasia, early EAC, local recurrence post radical therapy, microscopic involvement of tumor borders post radical resection, patient unfit / unwilling to undergo surgery. The palliation of non-resectable EAC by stenting represents the first choice. The correction of the malignant esophageal obstruction improves the symptomatology and life quality, but not survival. Because of the dismal prognosis and the frequent treatment failure of conventional treatment strategies, it seems reasonable to look for new palliative strategies.

Keywords


Introduction

Barrett’s esophagus (BE) represents a premalignant condition which raises 30-50 times the risk for esophageal adenocarcinoma (EAC) development, with an annual incidence of approximately 0.5% [1, 2]. There is a dramatic increase in EAC incidence (4-10% annually) with a 5 years survival of only 10% [3]. Only 3.9% of the patients with EAC are previously diagnosed with BE. A screening study in patients who were addressed to an endoscopy department for a sigmoidoscopy showed that 25% of the male patients older than 50 years had BE [4]. Esophageal carcinogenesis represents a multistep process with a progression from different grades of dysplasia to invasive carcinoma, a progression more probabilistic than deterministic. The time interval necessary for this neoplastic progression is not known accurately, but high grade dysplasia represents a major risk factor for EAC development. Despite some imperfections (sampling error, inter-observers variability) the histological classification of dysplasia on samples of endoscopic biopsy represents the only predictive variant for cancer development in patients with BE. The grade of dysplasia correlates with the risk for cancer development, where high grade dysplasia is associated with the highest risk: about 30-35% of patients develop invasive carcinoma after 5 years [5].

Therapy of Barrett’s esophagus with high grade dysplasia

Esophagectomy

Esophagectomy has been the standard treatment in patients with high grade dysplasia. This approach was based on several studies which showed neoplasia in approximately 40% of resected samples in these patients [6]. The mortality and morbidity rates of esophagectomy are 3-5% and 20-50%, respectively, even when performed in high volume expert centers [7]. But BE and early neoplasia were detected after subtotal esophagectomyies, endoscopic surveillance probably being still necessary in these patients after surgery [8].
**Endoscopic therapy**

Endoscopic therapy has become a viable alternative for patients with high grade dysplasia or early EAC (Figs. 1, 2) due to the low rates of lymphatic or hematogenous dissemination, corroborated with the adverse effects of esophagectomy.

*Endoscopic resection of mucosa* (ERM) implies the local excision of the dysplastic lesion. It is a safe procedure and allows the accurate histopathological staging of the resected samples, the diagnosis being confirmed and the lesion completely resected (Figs. 3-5). Endoscopic resection of the mucosa is recommended for lesions restricted to the mucosa and some experts recommend it also for lesions restricted to the superior 1/3 of the submucosa. According to the Japanese experience, penetration of the superficial submucosa is associated with a risk of 6% for distant metastasis. If there is a deeper invasion of submucosa, the risk for metastasis increases to 47% [9]. Circumferential ERM is associated with a 30-40% rate of esophageal stenosis, which requires endoscopic dilation. Endoscopic resection of mucosa is associated with the risk for neoplasia recurrence during follow up in up to 20% of cases [11].

*Endoscopic ablation* techniques are based on the assumption that the injury of metaplastic and dysplastic epithelium interrupts the physiopathological sequence which determines BE development and restores the normal squamous epithelium.

**Photodynamic therapy (PDT)** has been the most investigated of all the ablative techniques developed for BE with high grade dysplasia and for early EAC treatment. Photodynamic therapy involves the administration of a photosensitizer which accumulates in the tumoral...
tissue. Activation of the photosensitizer is achieved by endoscopically applied laser directly to the malignant tumor. This results in the formation of free oxygen radicals in the tumor tissue leading to ischemic necrosis of the tumor cells. A prospective randomized study showed a significant difference for the study group treated with PDT and omeprazole comparative with the group treated with omeprazole only regarding the ablation of high grade dysplasia (77% vs. 39%, \( p=0.004 \)) and the recurrence of neoplasia (15% vs 29%, \( p=0.027 \)) [13, 14]. The patients followed maximum three PDT sessions, at least at 3 months interval. After PDT with Photofrin and red light, the adverse effects were minimal and the median survival was 60.5 months. The technique might be used in elderly patients and / or with significant comorbidities.

**New treatment concepts**

The PDT was used as neoadjuvant with ERM for BE removal, reducing the risk for recurrent neoplastic lesions [15]. The combination of these two therapies is logical because one of the main difficulties of early cancer treatment is the accurate staging. The ERM allows an accurate staging of the tumour invasion, EMR being the only interventional technique which allows histological sampling. Photodynamic therapy follows ERM at one month intervals in order to remove the residual dysplastic mucosa.

The main objective of endoscopic therapy should be the complete removal of BE epithelium in patients with BE and high grade dysplasia or early EAC. Currently, the intense surveillance of these patients is mandatory for early diagnosis of recurrent lesions.

**Palliative treatment of esophageal adenocarcinoma**

Up to 50% of the patients are diagnosed with non-resectable cancer and the key of these patients’ management is the palliation of dysphagia [19] (Figs. 6, 7). Although surgery could palliate these patients’ symptoms, the morbidity and mortality of the procedure restrict it to patients without advanced disease. Chemotherapy could improve dysphagia and prolong survival, but additional procedures for the palliation of dysphagia are necessary [20]. During chemotherapy, due to the tumor necrosis, bronchus fistulae develop with or without erosion of the blood vessels’ wall (Fig. 8). The bleeding may be fatal or lead to aspiration pneumonia if not stopped in proper time. The most efficient treatment is the final esophageal stenting which allows the fistula closing, bleeding control and esophageal recanalization (Fig. 7).

Patients with severe or persistent dysphagia could benefit from endoscopic therapy. The largest experience belongs to self-expandable metallic stents. These are put in place endoscopically under fluoroscopic control and induce significant immediate improvement of dysphagia in 90% of patients [21]. The adverse effects of stenting are migration, bleeding, and perforation [22].
without resistance (Figs 9-11). Placement of metal stents for these tumours is associated with specific problems, because the distal part of the stent projects freely into the fundus of the stomach and thus cannot fix itself to the wall [22]. Sometimes only the superior pole marking is mandatory (Fig. 12). Thus, the distal end of the stent will surpass and keep the cardia opened. A self-expandable metallic stent deployed across the gastroesophageal junction leads to gastroesophageal reflux in most patients [22].

In case of significant morbidity stents with an antireflux valve should be considered. Several stents with an antireflux function have been developed, but they are expensive and have some limitations.

Esophageal cancer locoregional staging is usually assessed using endoscopic ultrasound; the endoscopic miniprobes with a 20 MHz frequency allow local staging by accurately discriminating T2 stages from early T stages (T1) suited for EMR (Fig. 13). However, the miniprobes are not very accurate for the regional staging (tumoral lymphadenopathies).

Another palliative endoscopic approach is the ablative
technique (PDT, laser ablation, argon plasma coagulation). Photodynamic therapy could be more easily applied than stenting in cervical esophageal cancer. The improvement of the dysphagia rate is 83-90% [23]. Studies which compared stenting with the ablative therapies presented different conclusions. A small randomized study in 39 patients (stenting vs laser therapy and radiotherapy) showed that the latter is more efficient [24]. Another study in 65 patients showed a prolonged survival in patients with thermoablation comparative with stenting [25]. The stents have a low cost, but determine a greater deterioration of life quality.

Conclusions

Photodynamic therapy should be considered a first line potential therapy in patients with BE and high grade dysplasia. Combining ERM and PDT is useful for the complete removal of the metaplastic mucosa. It is time to use this technique on a large scale and adopted by the gastro-oncological community. There is no doubt about its efficiency and adequacy for many patients.

The palliation of non-resectable EAC by stenting represents the first choice. The easing of the malignant esophageal obstruction improves the symptomatology and quality of life, but not survival. Because of the dismal prognosis and the frequent treatment failure of conventional treatment strategies, it seems reasonable to look for new palliative strategies.

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