Endoscopic management of Barrett’s esophagus with dysplasia

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Esophageal cancer is the eighth most common form of cancer, and the sixth leading cause of cancer death worldwide. In the western world the incidence of esophageal cancer has increased six-fold, mainly driven by the increase in the number of diagnosed adenocarcinomas. The most important risk-factor for esophageal adenocarcinoma is Barrett’s esophagus (BE), a pre-malignant condition in which the normal squamous lining of the esophagus has been replaced by columnar epithelium containing intestinal metaplasia (IM) as a result of chronic gastro-esophageal reflux disease. General population data are scarce, but the prevalence of BE is estimated to be 1.6% in Europe, compared to estimates between 1.7%-5.6% in the US. Incidence rates vary between 23.1-32.7 per 100,000 person-years. Malignant degeneration of BE is thought to occur in a step-wise fashion: from non-dysplastic IM, to low-grade dysplasia (LGD) then high-grade dysplasia (HGD), eventually resulting in invasive cancer.

In recent years, endoscopic treatment has been established as the primary management strategy over surgery, for BE patients with high-grade dysplasia or early cancers with a low risk of lymph-node metastasis (early BE neoplasia). Endoscopic resection (ER) is the cornerstone of this endoscopic treatment, as it allows for removal of visible lesions and accurate histological assessment of infiltration depth, differentiation grade and lymph-vascular invasion, which is imperative for optimal patient selection. However, removal of visible lesions alone is insufficient as treatment for early Barrett’s neoplasia. Previous studies by our group and elsewhere in Europe estimated the risk of developing metachronous lesions in the BE segment to be 30% within 3 years. Eradication of any residual Barrett’s epithelium is therefore recommended.

A decade ago, a new technique became available for eradication of residual Barrett’s epithelium. This ablation technique consists of stepwise circumferential and focal radiofrequency ablation (RFA) using controlled and uniform delivery of radio-frequency energy. In 2005, our group was the first worldwide to introduce RFA in patients with flat high-grade dysplasia, and after prior ER of early cancer. In pilot studies we demonstrated that radiofrequency ablation was safe and effective for eradication of early neoplasia and the entire Barrett’s segment. In this thesis we describe our long-term experiences with radiofrequency ablation and the combined treatment approach with endoscopic resection for patients with early Barrett’s neoplasia.

Over the last five years, our research focus of RFA has shifted towards an earlier stage in the metaplasia-dysplasia sequence: low-grade dysplasia in Barrett’s esophagus. Guidelines recommend performing endoscopic surveillance every 6 to 12 months, to monitor for neoplastic progression in these patients. A study by our group, however, indicated that in patients with LGD, neoplastic progression occurs at an alarming rate of 13.4% per patient year, provided that the LGD diagnosis has been confirmed by expert pathologists. We therefore speculated that endoscopic treatment for low-grade dysplasia might be of clinical relevance. Large prospective trials from the US already confirmed that radiofrequency ablation was effective and safe for treatment of BE, but studies on its use for LGD were scarce and small sized. In this thesis we describe the results of a multicenter randomized trial comparing radiofrequency ablation with endoscopic surveillance in patients with a confirmed
diagnosis of low-grade dysplasia. In this trial-setting we further investigated the cost-effectiveness of ablation, and we investigated the role of an expert panel of pathologists in the diagnosis of low-grade dysplasia.

OUTLINE OF THIS THESIS

PART I: Treatment of high-grade dysplasia and early Barrett’s cancer

The first part of this thesis describes our long-term experience with endoscopic treatment of high-grade dysplasia and early Barrett’s cancer, and on the technical adaptations which have improved the technique over the past years. In Chapter 1 and 2 we have reviewed the technical background of endoscopic resection (ER) and radiofrequency ablation (RFA) and their indications for use in early Barrett’s neoplasia. In Chapter 3 we report on a prospective multicenter trial which was conducted in 13 European centers. In this EURO-II trial we included 132 patients who were treated with a combined approach of ER followed by RFA for early Barrett’s neoplasm. Chapter 4 describes the long-term durability of this combined use of ER and RFA, which was studied by evaluating patients five years after their initial treatment session. Until now, RFA treatment sessions always demanded much from a patient. RFA procedures are time-consuming and require many introductions of catheter and endoscope. In two randomized trials we evaluated whether efficacy and safety could be maintained, while simplifying the standard treatment regimen. Three different circumferential ablation regimens are compared in Chapter 5. In Chapter 6 we evaluated a simplified focal ablation regimen by using patients as their own control.

PART II: Low-grade dysplasia in Barrett’s esophagus

The second part of this thesis is focused on improving the diagnosis of low-grade dysplasia, and the clinical implications for patients in whom low-grade dysplasia is confirmed by an expert pathologist. In Chapter 7 we studied the validity of an expert pathology panel in the diagnosis of low-grade dysplasia, by relating the review diagnosis to long-term follow-up outcomes. To determine if patients with a confirmed LGD diagnosis may benefit from preventive RFA treatment, we conducted a multicenter randomized clinical trial. In this SURF-trial, described in Chapter 8, we assessed the rate of neoplastic progression in 136 patients allocated to endoscopic surveillance or treatment with RFA. In Chapter 9 we evaluated the cost-effectiveness of RFA as a primary management strategy for this group of patients.
