Endoscopic eradication of Barrett's oesophagus with early neoplasia

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INTRODUCTION
The last decades, endoscopic treatment of early neoplasia in Barrett’s oesophagus has evolved as a valid and less invasive alternative to surgical resection in patients with a low risk of lymph node metastasis. Endoscopic resection (ER) is the cornerstone of endoscopic therapy, since it not only allows for curative removal of neoplastic lesions, but also enables an accurate histological diagnosis required to select patients with a low risk of lymphatic spread.

ER was pioneered in Japan, mainly for the resection of gastric lesions and squamous oesophageal neoplasia. In the Western countries, ER has increasingly been applied for the treatment of early gastro-oesophageal neoplasia, mostly associated with Barrett’s oesophagus. Promising results of ER for removal of early Barrett’s neoplasia published in the last years have made ER the treatment of choice for this indication. Technical developments and increasing possibilities for structured training in ER have resulted in more widespread implementation of ER.

In 2000 we started to use ER as monotherapy for neoplastic lesions in Barrett’s oesophagus, but we found that a significant number of patients required additional treatment for recurrent neoplasia in the remainder of their Barrett’s oesophagus. We then started studying different approaches to prevent recurrent lesions after focal ER of neoplasia. First, we evaluated the use of photodynamic therapy (PDT) with 5-aminolevulinic acid to eradicate all Barrett’s mucosa. This treatment protocol, however, was abandoned in 2003 when we found that most patients still had residual Barrett’s mucosa after PDT and a sustained remission of neoplasia was only achieved in 27% of patients. By then, we had gained more experience with widespread ER, which led to a treatment approach for which the whole Barrett’s segment was removed during subsequent ER sessions. This stepwise radical endoscopic resection protocol (SRER) was proven to be safe and effective in our hands, although the procedure was found to be technically demanding and associated with a significant rate of oesophageal stenosis. As a result, only patients with a Barrett’s segment shorter than 5 cm were deemed eligible for this protocol. In 2004, we therefore engaged in research on the use of a promising new ablation technique: stepwise circumferential and focal radiofrequency ablation (RFA) using the HALO system. Our group was the first worldwide to use it in combination with ER of endoscopically visible abnormalities. Two pilot studies at our centre demonstrated that this approach was highly effective and safe for eradication of all neoplasia and all intestinal metaplasia.

After the single center studies performed in Amsterdam to evaluate SRER and RFA for treatment of early Barrett’s neoplasia, we studied both treatment approaches in a European multicentre setting. This unique collaboration between a number of leading European centres, allowed for inclusion of large numbers of patients from different backgrounds, treated by different endoscopists with expertise in the field of Barrett’s neoplasia. The results of those studies are described in this thesis.

OUTLINE OF THIS THESIS
Part A “Endoscopic Resection”
The first part of this thesis is focused on endoscopic resection (ER) of early neoplasia in the upper gastrointestinal tract. Chapter 1 is a review on different ER techniques and their indications in the upper gastrointestinal tract. Prior to ER, endoscopic ultrasound (EUS) is often used for loco-regional staging of neoplasia. In Chapter 2 we evaluate the clinical value of EUS, next to endoscopic inspection and diagnostic ER, during work-up for endoscopic treatment of early oesophageal neoplasia in 131 patients. As described in Chapter 2, ER not only allows for removal of neoplastic lesions, but it also enables accurate histological staging of the removed lesion. In Chapter 3 we describe a randomized study comparing the safety and efficacy of the ER-cap and multiband mucosectomy (MBM) technique, for piecemeal ER of early Barrett’s neoplasia. After focal ER of neoplasia, there is a risk of 30% that patients develop metachronous lesions in the remainder of the Barrett’s oesophagus (BO). To prevent this, the remainder of the Barrett’s segment can be removed during subsequent ER sessions. In Chapter 4 we report on the combined experience of four European centers with this approach of stepwise radical endoscopic resection (SRER) in 169 patients.

Part B “Radiofrequency Ablation”
The second part of this thesis evolves around radiofrequency ablation (RFA), starting with Chapter 5, a review on the technical background of RFA and its role in the treatment of BO. Chapter 6 describes the first experiences at the Academic Medical Center in Amsterdam with RFA, with or without prior ER for visible lesions, in 44 patients with BO containing early neoplasia. To evaluate if the promising results of RFA could be reproduced in other centres, a multicentre study at 3 European sites was initiated. Chapter 7 reports on the results of this EURO-I study, which included 24 patients. Given the promising results of ER for focal lesions followed by RFA of the remaining Barrett’s segment, a randomized trial was performed to compared this approach to SRER in patients with early neoplasia in a BO <5 cm in length. The results of this study are reported in Chapter 8. For patients with a BO measuring up to 12 cm in length, a prospective cohort study in 13 European centres was initiated. This EURO-II study, described in Chapter 9, included 130 patients who were treated for early neoplasia in BO by a combination of ER and RFA. The efficacy of RFA to eradicate pre-existing genetic abnormalities in BO was studied by immunohistochimical staining and FISH. In addition, biopsy sampling depth and presence of buried Barrett’s in biopsies, keyhole biopsies and ER specimens from post-RFA neosquamous mucosa were evaluated. The results of this study are described in Chapter 10.

Chapter 11 evaluates the presence of post-RFA buried Barrett’s in biopsies from endoscopically normal neosquamous mucosa, and discusses artifacts that may lead to a false positive histological finding of buried Barrett’s.