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Outcome after endoscopic treatment for dysplasia and superficial esophageal cancer – a cohort study

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Abstract

Background:

Dysplasia and superficial esophageal cancer should initially be treated endoscopically. Little is known about post-procedural health-related quality of life (HRQL). The aim of this study was to present our results with endoscopic treatment and post-procedural HRQL.

Material and methods:

From June 2014 to December 2018 all patients treated with endoscopic mucosal resection (EMR) and/or radiofrequency ablation (RFA) for low grade dysplasia (LGD), high grade dysplasia (HGD), T1a and a minority of patients with T1b at Oslo University Hospital were prospectively included. In June 2019 all patients alive were scored according to the Ogilvie dysphagia score as well as the QLQ-C30 and QLQ-OG25 for assessment of HRQL.

Results:

86 patients were treated out of whom 22 (26%) had LGD, 44 (51%) HGD, 13 (15%) T1a and 6 patients (7%) T1b. Histology revealed adenocarcinoma in 18 (21%) and squamous cell carcinoma in one (1%), respectively. The mean follow-up was 22.9 months. Tumor regression or downstaging were archived in 78% of the patients with LGD, 66% of patients with HGD and in 89 % of patients with T1a/b. Five patients (6%) had esophagectomy. There were few and no serious complications. The 90-days mortality was 1%. 52 patients (88%) experienced no dysphagia (Ogilvie score 0). There was no difference in 11 out of the 15 variables in QLQ-C30 when compared to a non-cancerous reference population.

Conclusion:

Endoscopic treatment is safe and efficient for treatment of dysplasia and superficial esophageal cancer. The two-years post-procedural level of HRQL and dysphagia was satisfactory.

Key words: Barrett´s esophagus, LGD, HGD, EMR, RFA, superficial esophageal cancer, dysphagia, health-related quality of life

Introduction

Barrett's esophagus is a premalignant condition where the normal squamous epithelium of the lower esophagus is altered into columnar epithelium by metaplasia. The main risk factor is chronic reflux and it is estimated that 10-15% of all patients with reflux will develop Barrett's esophagus [1]. Patients with Barrett´s esophagus without dysplasia, will have an estimated yearly incidence of about 0.33 % for progression into cancer, while in case of low-grade dysplasia (LGD) or high-grade dysplasia (HGD) the incidence rates vary from 0.4-13% and 6-19%, respectively [2]. With confirmed LGD, the SURF study from 2014, in which 68 patients with LGD were randomized to either radiofrequency ablation (RFA) or surveillance, showed that active treatment reduced the progression to HGD or adenocarcinoma by 25% ($p<0.001$) [3]. Recently, a long-term follow-up study has been presented in which 96% of the patients treated with RFA experienced a sustained clearance after a median follow-up of 74 months [4]. RFA for confirmed LGD is now an integral part in most national [5] and international [6] guidelines.

It is generally recommended that endoscopic treatment is the first-choice therapy for HGD and adenocarcinoma limited to the mucosa (T1a) [6].

First introduced in Japan in 1990 by Inoue [7], endoscopic mucosal resection (EMR) is a safe and efficient technique with few serious complications, for treatment of patients with focal HGD and superficial esophageal cancers, with long-term complete regression rate of 93.8 % and < 2 % serious complications in patients with T1a cancers [8].

RFA is delivered with a focal ablation device (e. g. balloon or focal catheter) in order to destroy the metaplastic tissue. It is efficient in treating dysplastic esophageal mucosa as well as flat lesions without any visual abnormalities [9].

The aim of this study was to evaluate the treatment of dysplasia and superficial esophageal cancer with EMR and/or RFA and the post-procedural health-related quality of life (HRQL).

Materials and methods

From June 2014 to December 2018 patients endoscopically treated for LGD, HGD and T1a cancer at Oslo University Hospital, Ullevål were prospectively included. T1b tumors (submucosa invasion) were only included in case of free resection margins.

Patients with LGD were started on proton pump inhibitor (PPI) and observed for six months prior to new biopsies and a renewed evaluation by two separate experts in histopathology.

The patient material, including treatment modality (EMR, RFA), number of treatments, assessment of histology, time of follow-up, post-procedure complications, the need for surgery and its outcome were updated in December 2019.

The diagnosis was classified according to ICD-10 [10], by histology and by the TNM 7th classification [11] . In case of Barrett´s metaplasia the Prague classification [12] was used. The Prague classification is a visual assessment of the Barrett (BE) segment, where the circumferential (C) and maximum (M) extent are measured in cm. Biopsies were taken according to the Seattle Protocol [13]: from any visual abnormalities as well as at least four-quadrant biopsies every 2 cm of the BE segment, starting at the upper border of the gastric folds. The diagnosis of BE was only given in cases were the normal squamous epithelium of the lower esophagus was replaced by columnar epithelium with goblet cells (intestinal metaplasia) with a minimum of one cm in length [6]. The lesions were classification according to WHO´s ICD-10 with the use of the following codes: C15.4 malignant neoplasm located in the middle third of the esophagus, C15.5 malignant neoplasm located in the lower third as well as C15.8 overlapping tumors. For a minority of the patients C16.0 neoplasm of the gastroesophageal junction was used. The patients were subdivided into four main groups (TNM 7) [11]: LGD or HGD (malignant cells confined to the epithelium by the basement membrane), T1a (malignant cells invading the lamina propria or muscularis mucosae) and T1b (malignant cells invading into the submucosa). The Japanese SM-subclassification [14], describing the level of tumor depth invasion into the submucosal layer was not applied as EMR is primarily for resections within the mucosa. However, the upper submucosal layer was included in the resections. After the initial diagnosis, all samples were re-examined by a senior gastrointestinal pathologist.

At Oslo University Hospital, we have been using EMR and RFA since 2005 and 2015, respectively. The multiband mucosectomy (Duette, Wilson Cook and Captivator, Boston Scientific) has been performed in all cases. By suctioning the lesion into the cap and releasing a rubber band a pseudopolyp is created, which can be resected using a snare and electrocautery [15].

Duration of follow-up was defined from the time of the first procedure to the end of regulatory controls (5 years) or until the 31st of December 2019, whichever occurred first. After the initial treatment, patients were followed with a renewed gastroscopy every third month for the first year, then annually for a total of five years. For all patients, the initial follow-up was conducted at our hospital. In a total of nine patients (10%) late follow-ups were

at the patient's local hospital. In case of progression of dysplasia during treatment or relapse, the follow-up schedule was reinitiated.

All procedures were conducted by three consultants at the department of gastroenterology. The senior consultant, having twenty years of experience in multiband EMR in the esophagus, supervised the two other consultants. EMR was performed under intravenous sedation (midazolam and alfentanil), while the majority of patients undergoing RFA had deep sedation (propofol) under supervision of an anesthesiologist. Both procedures were mainly undertaken in an outpatient setting. The upper endoscopy was performed with standard white light as well as chromoendoscopy with diluted vinegar and narrow-banding imaging (NBI). Tumors found to be superficial and feasible for endoscopic removal were removed using multiband EMR. In two cases endoscopic submucosal dissection (ESD) were performed. After a minimum of six weeks Barrett's epithelium was eradicated with RFA using Barrx with the 360 RFA balloon and in some cases the focal catheter (Medtronic). Those who had solely dysplastic changes without a visible tumor, underwent RFA only. The number of treatments was recorded as well as their histological and visual outcome.

The short- and long-term complications were prospectively registered by review of the patients´ electronic health record and last updated in December 2019. The occurrence of perforation, bleeding needing transfusion, stricture formation and clinical condition needing hospitalization was registered. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [16] was used for classification of the severity of the adverse events, going from 1 ("mild symptoms, not needing intervention") to 5 (death).

In June 2019 all patients were contacted per letter and invited to take part in our follow-study concerning HRQL and level of dysphagia.

The Ogilvie grading scale [17] was used to determine level of dysphagia. It is a five-graded scale that runs from score 0 (no problem eating normal diet) to score 4 (complete dysphagia, even for liquids). Poor dysphagia was defined as score >1.

For assessment of HRQL, the cancer-specific European Organization for Research and Treatment of Cancer (EORTC) core-questionnaire, QLQ-C30 version 3 [18] together with the gastro-esophageal-specific module QLQ-OG25 were used [19]. Both questionnaires are validated for patients with gastro-esophageal cancer [19]. For both the EORTC questionnaires, the patient answer scales with Likert type response categories ranging from 0 ("not at all") to 4 ("very much") and from 1 ("very poor") to 7 ("excellent") for question 29 and 30 in the EORTC QLQ-C30. All scores were linearly transformed to a 0-100 scale where high score represents a high degree of function or a high degree of side effects/problems. For

every scale, the mean value was calculated. Further, number of patients with reduced HRQL (function ≤ 50/ symptoms ≥ 50) was calculated.

Ethics:

This study has been approved by the regional health committee (application: 2018/720, REK NORD) as well as the Hospitals Data Protection Official with legal basis in the General Data Protection Regulation (GDPR) article 6 (1a) as well as article 9 (2j).

Statistical methods:

Descriptive analysis was used for demographic data, in which categorical data where presented as frequencies and proportions and continuous data were presented as mean, median and range. For comparison between HRQL in our patients and a reference population we used a t-test (two-sample mean-comparison test). P-values below 0.05 were considered significant. SPSS version 26 and STATA SE version 16 were used for all statistical analysis.

Results

From June 2014 to December 2018 125 patients were referred to our hospital for assessment regarding endoscopic treatment with EMR and/or RFA, of whom 86 patients (69%) were included in this study (figure 1). The main reasons for exclusions were that no dysplasia could be confirmed (n=17), relapse of esophageal cancer (n=6) and tumors more advanced than T1a (n=10). Mean age of patients at initial treatment was 66 years (32 – 86) of whom 72 (84%) were men. Table 1 reveals the TNM stage and histology of the lesions as well as the prevalence and extent of Barrett's esophagus. In 19 patients with cancer, histology was adenocarcinoma in 18 and squamous cell carcinoma in one, respectively.

Initial treatment

Time of follow-up was mean 22.9 months (0 – 60 months) and median 23 months, being completed in 41 patients (48%) and still ongoing in 38 patients (44%). Seven patients (8%) were lost to follow-up due to not attending in five and deaths unrelated to treatment in two, respectively. Treatment modalities and their results are presented in tables 2 and 3, respectively. Two of the patients that received RFA, had previously ESD performed for an adenocarcinoma (T1b) or an elevated lesion of LGD at another Norwegian hospital. Generally, there was a high degree of complete regression and downstaging of dysplasia: 78% for LGD and 66% for HGD. Seventeen of the 19 patients (89%) with initial superficial cancer

gained complete tumor regression in 16 (84%) and downstaging in one (5%), respectively. Nine patients (10%) experienced progression during treatment, from HGD in six, LGD in two and T1a in one, respectively. The latter patient, a 78-year-old patient with heart disease and obesity, underwent during a period of 24 months four treatments with EMR and two treatments with RFA. At the last endoscopy there was residual tumor not suitable for endoscopic removal. No tumor was seen on CT. Due to comorbidity and advanced age the patient was not found suitable for surgery and referred for radiochemotherapy.
For the whole patient material, number of treatments with EMR and RFA were mean 1.5 (0-4) and 0.7 (0-4), respectively.

Subsequent treatment

Five out of the nine patients with T1b cancer underwent minimally invasive esophageal resection (table 4). In a 74-year-old patient with progression into T1b, the operation specimen revealed T1bN1M0. This patient was initially treated for HGD with EMR (four times) and RFA (two times) during 18 months. After the last EMR, histology revealed carcinoma and a tumor that demanded resection 30 months after initial diagnosis. At the last follow-up two years postoperatively, there was no sign of recurrent cancer. Three remaining patients with an initial T1b cancer were not operated due to comorbidity, patient wish and no need for surgery due to free resection margins after EMR.
Among the nine patients with progression during treatment, two underwent surgery while the seven remaining patients (HGD (n=2), T1aN0M0 (n=1), T1bN0M0 (n=1), TxN0M0 (n=1), TxN1M0 (n=1), T3N3M1 (n=1)) did not due to comorbidity from heart disease (n=3), advanced liver cirrhosis (n=1), successfully treated HGD with EMR (n=1), lost to follow-up (n=1) and metastatic disease (n=1), respectively. The latter patient aged 63-years had 17 years prior been treated for a nose cancer with 70Gy and comprehensive resection and reconstructive surgery. Now he had an initial HGD treated with EMR (three times) and RFA (two times) over a period of 19 months. Despite multiple treatments, the biopsies still revealed HGD without visible lesions and a third RFA was performed 22 months after the first treatment. However, at a repeated endoscopy three months later, the biopsies revealed adenocarcinoma and a CT-scan showed liver- and lymph node metastases. He received chemotherapy and died after 12 months.

Complications

In general, there were few complications (table 5), including no esophageal perforations. Seven patients developed strictures who transiently needed balloon dilation.

The procedures were done in an outpatient setting in 80 (93%) out of the 86 patients. Six patients (7%) needed admission due to pain and nausea (n=2), pneumonia (n=1) and bleeding (n=3) of whom two needed blood transfusion. One 76-year old patient with Barrett´s esophagus (C10M10) died of heart failure three months after his first EMR-treatment for an HGD, representing a 90-days mortality of 1%.

Health related quality of life

Fifty-nine out of the 86 patients alive (69%) completed the questionnaires after a mean follow-up of 28 (8-65) months. HRQL, measured by EORTC QLQ-C30 and EORTC QLQ-OG25 in general and subdivided according to treatment modality is shown in Table 6. Proportion of patients with reduced HRQL (function scores (≤ 50) or symptoms score ≥ 50) in 59 patients are visualized in figure 2. Twenty-four percent of the patients answering the questionnaires underwent EMR, 31% RFA and 44% both EMR and RFA. There was no significant difference ($p>0.05$) in 11 out of the 15 variables in QLQ-C30, including the level of dysphagia, weight loss, global quality of life (QoL) and emotional status, neither between the treatment groups nor with respect to a non-cancerous European reference population of 201 men with age 60-69 [20]. For the remaining four variables (physical and cognitive functional scale, constipation and diarrhea), the patients experienced significantly lower HRQL (data not shown). Mean 28 (8-65) months post-procedurally, 52 patients experienced no dysphagia (Ogilvie score 0), while seven patients (12 %) had minor problems eating solid food (Ogilvie score 1), of whom all underwent EMR.

Discussion

In this series of 86 patients with LGD, HGD and superficial esophageal cancer, endoscopic treatment was safe and efficient, giving regression and downstaging rates of 78% and 66% in patients with LGD and HGD, respectively.

Eighty-four percent of patients with superficial esophageal cancer gained complete regression after endoscopic treatment. Only one out of five patients undergoing esophageal resection for a T1b cancer had residual tumor more advanced then T1a in the final operation specimen and was though in need of surgery. There were few and no serious complications and a 90-days mortality rate of 1%. After a mean follow-up time of 28 (8-65) months there were no difference in level of dysphagia, weight loss or global quality of life when compared no non-cancerous reference population [20].

This study is limited by the presents of being a single-center study with a limited number of patients and time of follow-up. Even though 69% of the patients answered the questionaries' regarding HRQL and dysphagia, the low number of participants and the lack of pretreatment assessment prevents us from studying any changes in HRQL and whether or not the results may be generalized for the population of post-endoscopic treated patients with dysplasia and superficial esophageal cancer. In addition, a longer follow-up time could have altered the results regarding treatment success and HRQL.

Complete eradication rates of Barrett's metaplasia (CBE) for patients with HGD are in the literature often not presented solely, but in conjunction with rates for T1a cancers. These rates varies from 80.4%-96.9%, after a mean of two EMR treatments per patient, a mean follow-up time of 22.9-40.6 months and the development of a symptomatic stricture in up to 37.8% of the patients [21-23]. Pech et al [8] have, in a German cohort study of a 1000 T1a patients treated with EMR from 1996-2010, shown a complete remission rate of 96.3 %. Surgery was necessary in 3.7% and 14.5% of the patients developed metachronous lesions or recurrence of cancer which in 82% of the cases were successfully treated endoscopically. This gives a long-term complete remission rate of 93.8% after a mean follow-up time of 56.6±33.4 months. They calculated a 10-year survival rate of 75% and major complications accorded in 1.5% of the patients.

Our results regarding T1a cancers are well comparable to the literature with 84% gaining complete regression after a mean of 1.9 (1-4) treatments with EMR and a mean of 0.9 (0-4) treatments with RFA. Only one patient (8%) experienced progression.

Our primary aim for patients with HGD was not CBE, but to avoid progression requiring surgery and to minimize the occurrence of complications, including development of symptomatic strictures needing treatment. After a mean of 1.4 (0-6) treatments of EMR and 1.4 (0-4) treatments of RFA, 22 patients (50%) developed complete regression of dysplasia, six patients (14%) experienced progression and a total of 4 patients (9%) developed strictures needing treatment. In case of increased follow-up time, the numbers of treatments could have been augmented, thereby increasing the regression rates. A major challenge is to evaluate the treatment of the nine patients (10%) who had progression of their lesions, of whom one developed local and metastatic disease after multiple RFA and EMR procedures. This patient might have been a high-risk patient due to previously radiation therapy for a nose cancer. Further on, the tumor was primary located extramucosal, making the diagnosis extremely difficult. A more extensive follow-up with concomitant CT-scans could have been of value in order to early detect regional lymph node metastasis, thereby being able to consider esophagectomy as a treatment option.

All summarized up 43/44 (98%) of our patients with HGD could be spared for esophagectomy with a minimum of complications.

For 11 out of the 15 variables in QLQ-C30, including level of dysphagia, weight loss, global quality of life (QoL) and emotional status there were no significant difference ($p>0.05$) when compared to a non-cancerous European reference population, two years post-procedurally. For the four remaining variables: physical and cognitive function scale, constipation and diarrhea there was a difference. These variables seem to be unrelated to the procedure itself and the somehow surprisingly outcome could be due to the low number of participants.

Little is known about post-procedural HRQL in patients undergoing endoscopic treatment for dysplasia or superficial esophageal cancer. In one recent study from Schwameis et al [24] 19 patients treated for HGD or superficial esophageal cancer were evaluated using a telephone interview median 90.3 (84-113) months post-procedural. By using the RAND-SF36 they found that QoL was below population means in 4 out of 8 areas, including energy/fatigue, pain, general health and physical functioning. Sixteen percent of the patients experienced dysphagia.

Rosmolen et al [25] compared QoL (measured by SF-36, EORTC QLQ-C30 and EORTC QLQ-OES18) among 42 patients endoscopically treated for BE with HGD and superficial esophageal cancer (≤T1bSM1), 44 patients with non-dysplastic BE, 21 patients undergoing esophagectomy for HGD-T2N0M0 and 19 patients operated for advanced cancer (T1N1M0-T3N1M0). QoL was measured at baseline and at two and six months after treatment. At follow-up there were no difference between the endoscopic and the surveillance group, besides mental health (decreased in the surveillance group). As expected, the surgical groups had significant lower QoL when compared to the endoscopic group for most almost all variables.

A direct comparison between our patients and the patients in the study of Schwameis [24] and Rosmolen [25] is obviously not possible due do difference in time of follow-up and different grading systems. Even though, when comparing our patients with the European reference population [20] we get the impression that HRQL measured 2 years after EMR/RFA is satisfactory.

Our results regarding endoscopic treatment are well in accordance with and does support the updated national [5] and international guidelines [6] for treatment of LGD, HGD and T1a. There is need for further studies with longer time of follow-up for final assessment regarding HRQL in patients undergoing endoscopic treatment.

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Declaration of interest of statement

No potential conflict of interest was reported by the authors.

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Figure 1. Flow-chart displaying referral to our hospital for endoscopic treatment, number of patients included and reasons for exclusion.

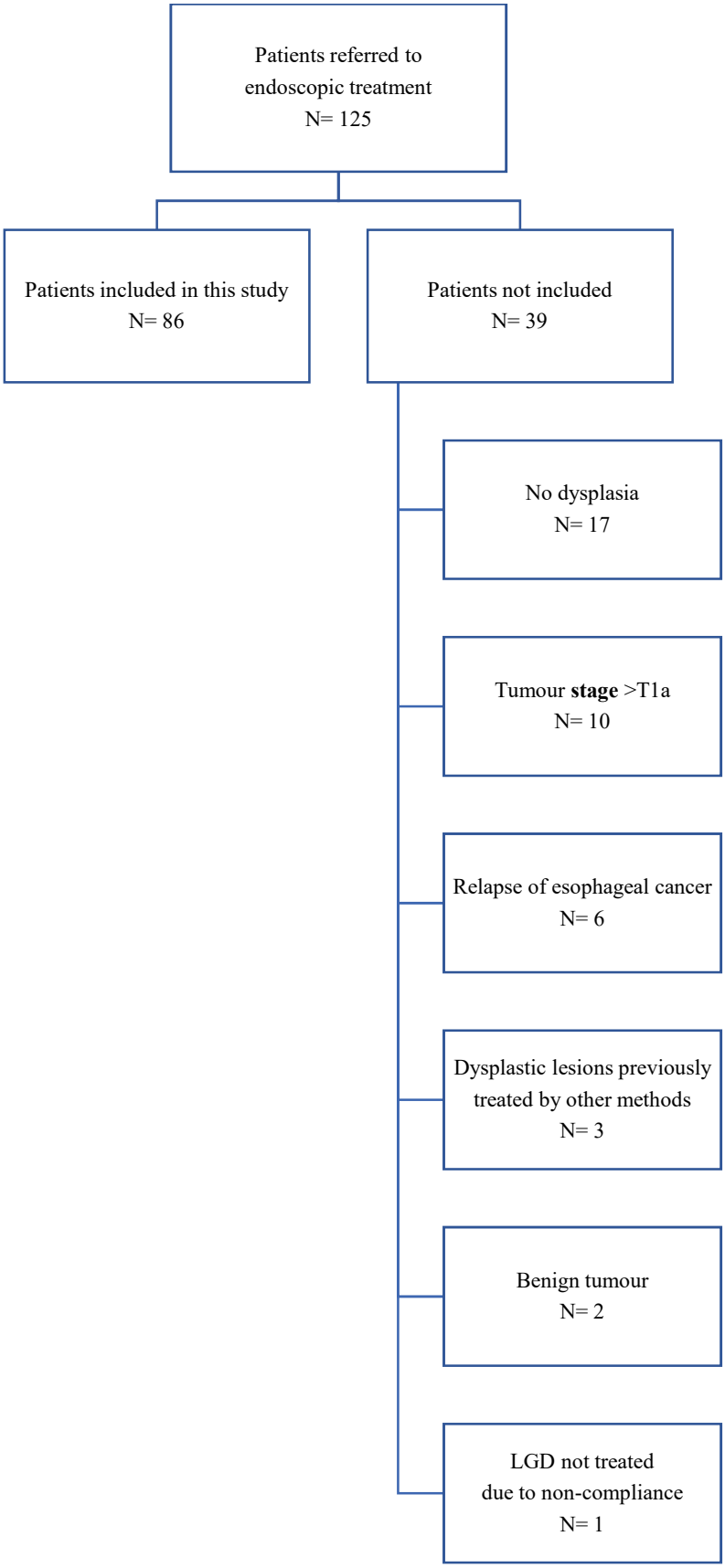

Figure 2. Proportion of patients with reduced HRQL (≤ 50), reduced function (≤50) and high level of symptoms (≥ 50) in 59 patients.

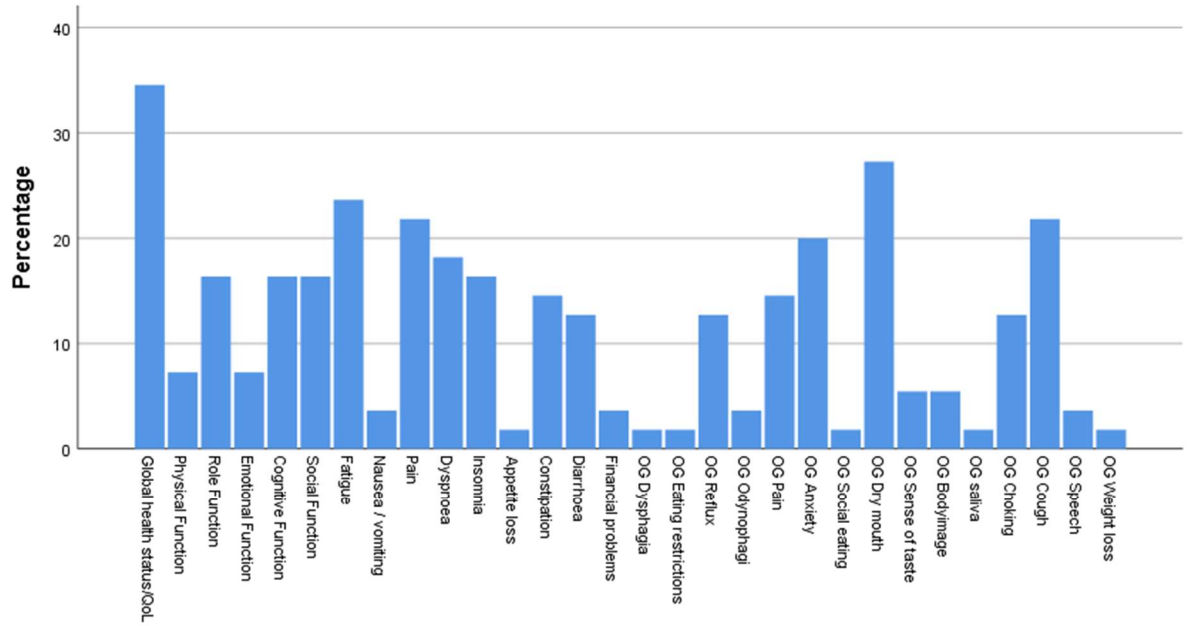

Table 1. Initial TNM, histology and location of the lesions, including the extent of Barrett's esophagus in 86 patients.

TNM	**No patients (%)**
Tis	44 (51)
T1a	13 (15)
T1b	6 (7)
NA	23 (27)
Histopathology	
LGD	22 (26)
HGD	44 (51)
Adenocarcinoma	18 (21)
Squamous cell carcinoma (SCC)	1 (1)
Indefinite for dysplasia	1 (1)
Location of lesion[a]	
Mid esophagus (25-30 cm)	2 (2)
Lower esophagus (30-40 cm)	62 (72)
Overlapping lesions	6 (7)
Gastroesophageal junction	16 (19)
Barrett´s esophagus (intestinal metaplasia)	
Yes	70 (81)
No	14 (16)
Could not be assessed	2 (2)
Length of Barrett´s esophagus[b]	
< 3 cm	24 (34)
3-10 cm	30 (43)
> 10 cm	13 (19)
NA	3 (4)

[a]The distance from the incisors to the proximal edge of the lesion (in cm).
[b]Maximum length (M) according to the Prague classification.
NA=not assessed

Table 2. Initial treatment related to diagnosis in the 86 patients. Number in parenthesis are percentages.

Diagnosis	RFA No patients (%)	EMR	EMR+RFA	ESD+RFA
LGD (n=22)	19 (86)	1 (5)	1 (5)	1 (5)
HGD (n=44)	5 (11)	14 (32)	25 (57)	-
T1a (n=13)	-	6 (46)	7 (54)	-
T1b (n=6)	-	4 (67)	1 (12)	1 (12)
Indefinite dysplasia (n=1)	1	-	-	-

Table 3. Initial results of treatment related to diagnosis in the 86 patients. Number in parenthesis are percentages.

Diagnosis	Complete regression	Downstaging	Stable disease	Progression	Not controlled
LGD (n=22)	16 (73)	1 (5)	2 (9)	2 (9)	1 (5)
HGD (n=44)	22 (50)	7 (16)*	5 (11)	6 (14)	4 (9)
T1a (n=13)	12 (92)	-	-	1 (8)	-
T1b (n=6)	4 (67)	1 (17)	-	-	1 (17)
Indefinite dysplasia (n=1)	1 (100)	-	-	-	-

*Six of the patients had downstaging to LGD

Table 4. Results of delayed surgical treatment in five out of nine patients with T1b cancer.

Lesion	No of patients	Operated	Operation specimen
Initial T1b	6	3	T0N0M0 (n=2) T1aN0M0 (n=1)
Progression into T1b	3	2	T1bN1M0 (n=1) HGD (n=1)

Table 5. Number of patients with short and long-term complications according to treatment modality

	EMR	RFA	Total
Bleeding needing blood transfusions (grade 3[a])	2	-	2
Hospitalization (grade 3)	2	4	6
Stricture needing dilatation (grade 2)	4	3	7

[a]Adverse events classified according to CTCAE version 4.03.

Table 6. HRQL measured by (EORTC QLQ-C30 and EORTC QLQ-OG25) in 59 patients.

Questionnaires, scales and single items (item numbers) Mean score (± SD)		**Number of patients (%) with reduced HRQL (function ≤ 50/ symptoms ≥ 50)**	**Number of patients with reduced HRQL (function ≤ 50/ symptoms ≥ 50) according to treatment**		
EORTC QLQ-C30		total	EMR (n = 14)	RFA (n = 18)	EMR + RFA* (n = 27)
Functional scales					
Global QoL (29,30)	66 (26)	22 (37)	8	7	7
Physical (1-5)	83 (21)	5 (8)	2	1	0
Role (6-7)	81 (26)	11 (19)	5	3	3
Emotional (21-24)	84 (20)	5 (8)	2	3	0
Cognitive (20,25)	78 (22)	10 (17)	3	5	2
Social (26,27)	80 (24)	11(19)	6	3	2
Symptom scales					
Fatigue (10,12,18)	31 (25)	14 (24)	4	5	5
Pain (9,19)	22 (25)	13 (22)	5	3	5
Nausea-vomiting (14,15)	7 (14)	2 (3)	1	1	0
Single items					
Dyspnoea (8)	31 (28)	11 (19)	3	5	3
Insomnia (11)	24 (32)	11 (19)	5	3	3
Appetite loss (13)	8 (19)	2 (3)	1	0	1
Constipation (16)	20 (28)	9 (15)	2	2	5
Diarrhoea (17)	18 (25)	7 (12)	2	3	2
Financial-difficulty(28)	9 (18)	3 (5)	2	1	0
EORTC QLQ-OG25					
Symptom scales					
Dysphagia (1-3)	3 (9)	1 (2)	1	0	0
Eating restrictions (4-7)	11 (17)	1 (2)	1	0	0
Reflux (8,9)	18 (25)	8 (14)	3	2	3
Odynophagia (10,11)	8 (18)	2 (3)	2	0	0
Pain (12,13)	16 (22)	9 (15)	5	0	4
Anxiety (14,15)	28 (26)	14 (24)	5	4	5
Single items					
Social Eating (16)	7 (21)	2 (3)	2	0	0
Dry mouth (17)	29 (31)	15 (25)	3	5	5
Sense of taste (18)	10 (19)	3 (5)	2	1	0
Body image (19)	9 (20)	5 (8)	4	1	0
Saliva (20)	10 (16)	1 (2)	1	0	0
Choking (21)	14 (23)	7(12)	1	3	3
Cough (22)	29 (28)	13 (22)	4	4	5
Speech (23)	7 (18)	2 (3)	0	0	2
Weight loss (24)	6 (18)	2 (3)	1	1	0
Hair loss (25)	-----	---	---	---	---

ORTC QLQ-C30 and EORTC QLQ-OG25: A high score for functional scales and the global quality of life (QoL) scale imply a high level of function, while a high score for the symptom scales and single items imply high level of problem. Missing data in 38 patients for Hair loss, not possible to evaluate