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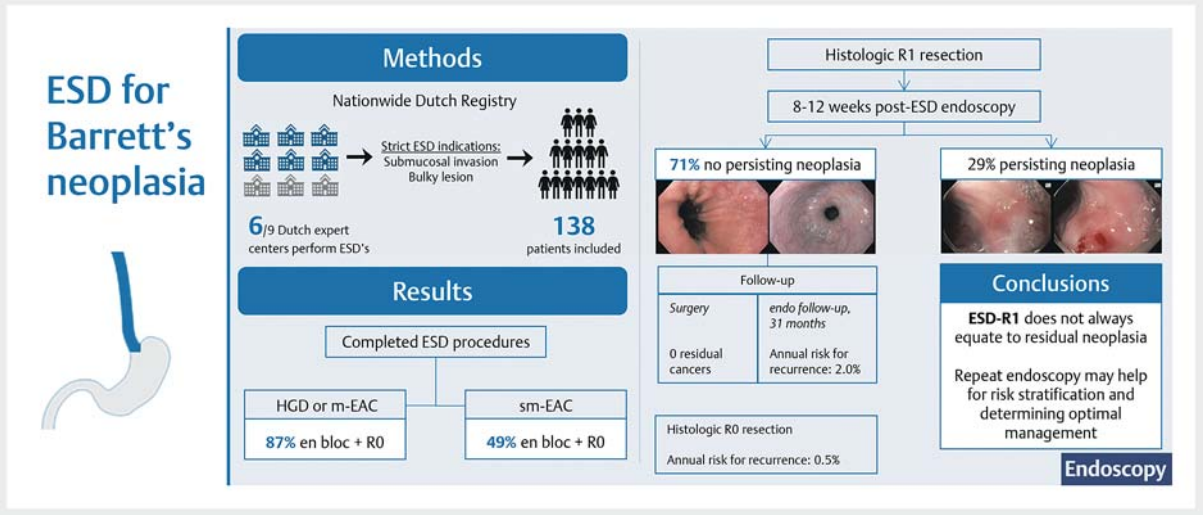
Extending treatment criteria for Barrett's neoplasia: results of a nationwide cohort of 138 endoscopic submucosal dissection procedures

GRAPHICAL ABSTRACT



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ABSTRACT

Background The use of endoscopic submucosal dissection (ESD) is gradually expanding for treatment of neoplasia in Barrett's esophagus (BE). We aimed to report outcomes of all ESDs for BE neoplasia performed in the Netherlands.

Methods Retrospective assessment of outcomes, using treatment and follow-up data from a joint database.

Results 130/138 patients had complete ESDs, with 126/130 (97 %) en bloc resections. Median (interquartile range (IQR)) procedure time was 121 minutes (90–180). Pathology findings were high grade dysplasia (HGD) (5 %) or esophageal adenocarcinoma (EAC) T1a (43 %) or T1b (52 %; 19 % sm1, 33 % ≥ sm2). Among resections of HGD or T1a EAC lesions, 87 % (95 %CI 75 %–92 %) were both en bloc and R0; the corresponding value for T1b EAC lesions was 49 % (36 %–60 %). Among R1 resections, 10/34 (29 %) showed residual cancer, all detected at first endoscopic follow-up. The remaining 24 patients (71 %) showed no residual neoplasia. Six of these patients underwent surgery with no residual tumor; the remaining 18 underwent endoscopic follow-up during median 31 months with 1 local recurrence (annual recurrence rate 2 %). Among R0 resections, annual local recurrence rate during median 27 months was 0.5 %.

Conclusion In expert hands, ESD allows safe removal of bulky intraluminal neoplasia and submucosal cancer. ESD of the latter showed R1 resection margins in 50 %, yet only one third had persisting neoplasia at follow-up. To better stratify R1 patients with an indication for additional surgery, repeat endoscopy after healing of the ESD might be a helpful possible prognostic factor for residual cancer.

Introduction

Endoscopic resection of early neoplasia in Barrett's esophagus (BE) is mostly performed using the multiband mucosectomy technique. Multiple large studies have shown that this technique is a safe and effective treatment for early BE neoplasia (i. e., ≤ sm1) [1, 2]. A technical limitation of using this approach is that lesions larger than 20 mm must be removed using multiple adjacent resections in a so-called piecemeal fashion. For early BE neoplasia (i. e., low grade dysplasia [LGD], high grade dysplasia [HGD]), or esophageal adenocarcinoma [EAC] limited to the superficial submucosa [m1–sm1]), piecemeal resection is an adequate approach [1, 2].

While the risk of lymph node metastasis in mucosal EAC is minimal, this risk increases for cancer invading the submucosa [3, 4]. The risk also depends on other histological factors such as grade of differentiation and presence of lymphovascular invasion (LVI). In addition, adequate histological assessment of the deep resection margin is important to determine the optimal treatment strategy, which may range from endoscopic management to surgery. In the case of submucosal invasion, accurate histologic assessment is thus of the utmost importance, and piecemeal endoscopic resection may compromise this [5]. Furthermore, in the case of bulky polypoid lesions, the intraluminal part of the lesion may fill up the multiband mucosectomy cap, preventing complete removal of the lesion at its base.

Endoscopic submucosal dissection (ESD) might offer a solution in these cases. ESD was pioneered in the early 2000 s in Japan to facilitate en bloc resection and controlled, complete excision of a tumor [6, 7]. ESD entails meticulous tissue dissection in a fluid-expanded submucosal space, offering precise control over resection depth and lateral extent. ESD enables en bloc resection independently of the size of the lesion and its intraluminal extent.

Nevertheless, ESD has inherent disadvantages compared to multiband mucosectomy, most importantly greater technical difficulty, a longer learning curve, and longer procedure times. Multiband mucosectomy is therefore still the preferred approach for most early BE neoplasia, whereas ESD will be preferred in lesions with suspected (deep) submucosal invasion and in lesions where a cap-based approach is technically not feasible [8–10].

An important driver for the use of ESD for early BE neoplasia is the expanding indication of endoscopic treatment for submucosal cancers. Current guidelines advise esophagectomy

for lesions with deep submucosal (sm2–sm3) invasion [8–10] given the risk of local lymph node metastasis, but this is based on surgical studies that are limited in quality and quantity [11, 12]. Recent series of endoscopic treatment of submucosal cancers indicate that this risk may be much lower than generally assumed [4, 13, 14].

In the Netherlands, BE care is centralized in nine Barrett Expert Centers (BECs) with a common treatment protocol, a joint training program, and regular meetings with case discussions [9]. Performance of ESD is supercentralized to six high volume centers, all of which have participated in a specific ESD training program and have adhered to strict indications for ESD as an alternative to EMR. In the current study, we report on a nationwide cohort including all ESDs for BE neoplasia performed in expert centers in the Netherlands between 2008 and 2019, in order to evaluate clinical outcomes.

Methods

This retrospective cohort study used data from the Dutch BEC registry (Netherlands Trial Register, NL7039), which has previously been described in detail [15]. Based on the Dutch guideline for management of BE, treatment of early BE neoplasia is restricted to nine BECs and ESD to six superspecialized high volume centers, as mentioned above. In each center, BE care is provided by one or two dedicated endoscopists and pathologists who have undertaken a joint training program, and all centers adhere to a common treatment protocol [16, 17]. The BEC registry has captured outcomes for all patients with Barrett's neoplasia in the Netherlands who underwent endoscopic treatment from 2008 onwards (see "Treatment and follow-up protocol BEC registry," online-only in Supplementary Material).

Ethics

The Institutional Review Board of the Amsterdam University Medical Centers declared that the registry was not subject to the Medical Research Involving Human Subjects Act and waived the need for formal ethical review or patient-informed consent. Patients had been approached through an opt-out card with the possibility to refuse participation in the registry.

Study population

For the current study, we included all patients from the BEC registry who underwent ESD for BE neoplasia between 1 January 2008 and 31 December 2019. Follow-up was updated until 1 August 2021. A total of 30 patients with HGD or low risk EAC who underwent radiofrequency ablation (RFA) and 44 other patients with high risk EAC have been described in previous publications [14, 15].

ESD training

All procedures were performed by expert interventional endoscopists with over 5 years' experience with treatment of BE-related neoplasia, working in six high volume BECs (Amsterdam, Nieuwegein, Utrecht, Eindhoven, Groningen, Rotterdam). ESDs were performed after basic training in the technique under direct supervision by international experts and with multiple sessions on living pigs. Learning thereafter was self-directed using growing experience and regular contact between endoscopists. In 2018 a joint ESD training program was launched to improve ESD skills.

ESD procedure

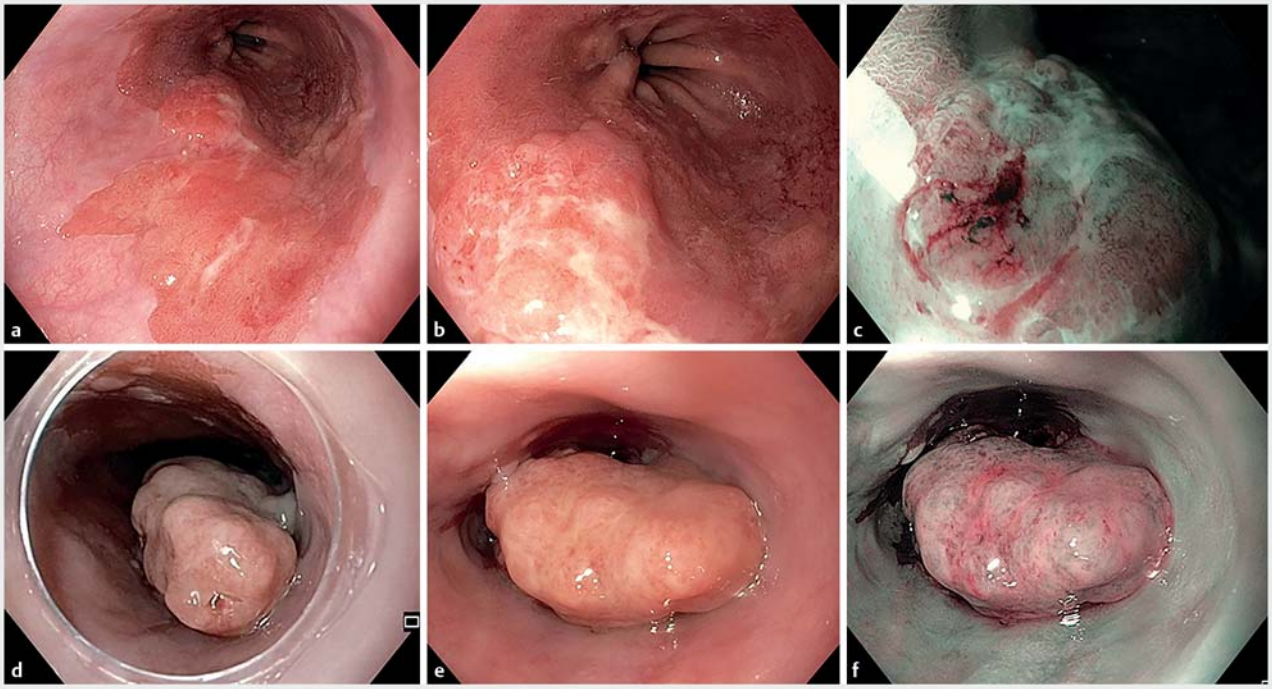
The choice between endoscopic mucosal resection (EMR) or ESD was based on endoscopic imaging, while pre-ESD biopsy diagnosis played no role in the decision. Suspicion of submucosal invasion was based on the subjective assessment by the endoscopist, and generally related to more broad-based sessile lesions (with either a type 0-Is, 0-Ip, or 0-IIc component), having a clearly disrupted mucosal pattern and irregular vascular pattern, and/or reduced movement upon peristaltic contractions (▶ **Fig. 1**).

Procedures were done with patients under general anesthesia with tracheal intubation or with monitored deep sedation using propofol. All were carried out with high definition endoscopes equipped with a distal transparent cap. Erbe electrosurgical generators (Erbe, Tubingen, Germany) were used for each step of the procedure. Different ESD knives were used according to the physician's discretion (DualKnife (J), ITknife2, HookKnife, Olympus Medical, Hamburg, Germany; Flush Knife, Fujifilm, Tokyo, Japan; I-, T- and O-Type HybridKnife, Erbe).

After detailed inspection and delineation of the lesion, markings were placed at 2 mm from the border of the area that should be removed, taking into account potential subsquamous extension. Coagulation markings were generally placed using the tip of the knife. Submucosal lifting was then done, using a mixture of saline or crystalloid/hydroxymethyl cellulose/indigo carmine/adrenaline to expand the submucosal space and to create a safe plane between the mucosa and the muscle layer. Mucosal incision was performed followed by submucosal dissection. Bleeding vessels were treated with the tip of the knife (Coagrasper, Olympus Medical; or bipolar hemostatic grasper HemostatY, Pentax Medical, Hamburg, Germany). According to the protocol, patients were hospitalized for 0–2 days following ESD. High dose proton pump inhibitors (40 mg twice daily) were prescribed along with sucralfate (three times daily) and if available a H2 receptor antagonist ante noctem, for the first 2 weeks after treatment.

Histopathologic work-up

All resection specimens were pinned down on paraffin or foam board prior to fixation in formalin. Specimens were sliced in 2–3-mm sections and processed for histopathological examination. Expert Barrett's pathologists who had participated in dedicated BE training programs [18–20], assessed the samples and reported diagnoses according to the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) classification [21]. The diameter of the lesion, depth of invasion, tumor differentiation, and LVI were recorded. In all submucosal cancers, the depth of submucosal invasion was measured in microns. Lesions with submucosal invasion ≤ 500 µm were defined as sm1, those with deeper invasion as sm2/3 lesions. Any lesion with sm2/3 invasion, poor differentiation grade, and/or LVI was considered a high risk lesion. Re-



▶ **Fig. 1** Typical indications for endoscopic submucosal dissection in Barrett's esophagus-related neoplasia. **a–c** Paris type 0-IIa-IIb lesion with suspicion of submucosal invasion based on the irregular vascular and disrupted mucosal pattern. In addition, reduced movement was observed upon peristaltic contractions. **d–f** A large, bulky, Paris type 0-Is lesion where a cap-based approach was technically not feasible.

section margins were reported in terms of cancer-free vertical and lateral margins and dysplasia-free lateral margins.

If a pathology report had no final conclusion regarding the resection margins, a consensus meeting with three expert pathologists (S.M., J.O., L.B.) was held to establish a final conclusion.

Study endpoints

Procedure-related outcomes included: (i) the en bloc resection rate, defined as the proportion of resections assessed as being en bloc at the end of the ESD procedure; (ii) the R0 resection rate, defined as the proportion of en bloc resections with lateral and vertical resection margins that were R0 (namely, free of cancer, or free of HGD if HGD was the worst diagnosis), stratified for depth of invasion; (iii) lesion histology; and (iv) procedure-related adverse events.

Endpoints were assessed according to an intention-to-treat analysis that included all patients in whom ESD was initiated, and to a per-protocol analysis that included only patients in whom ESD was considered to have been completed.

Endpoints related to follow-up included: (i) the incidence of residual cancer ("persistent neoplasia") as detected during endoscopic follow-up or surgical resection after ESD, for R0 and R1 resections (see **Table 1 s** in Supplementary Material for all definitions); (ii) the incidence of recurrent lesions during follow-up; and (iii) the reliability of an endoscopic assessment for the presence of residual neoplasia after ESD.

Statistical analyses

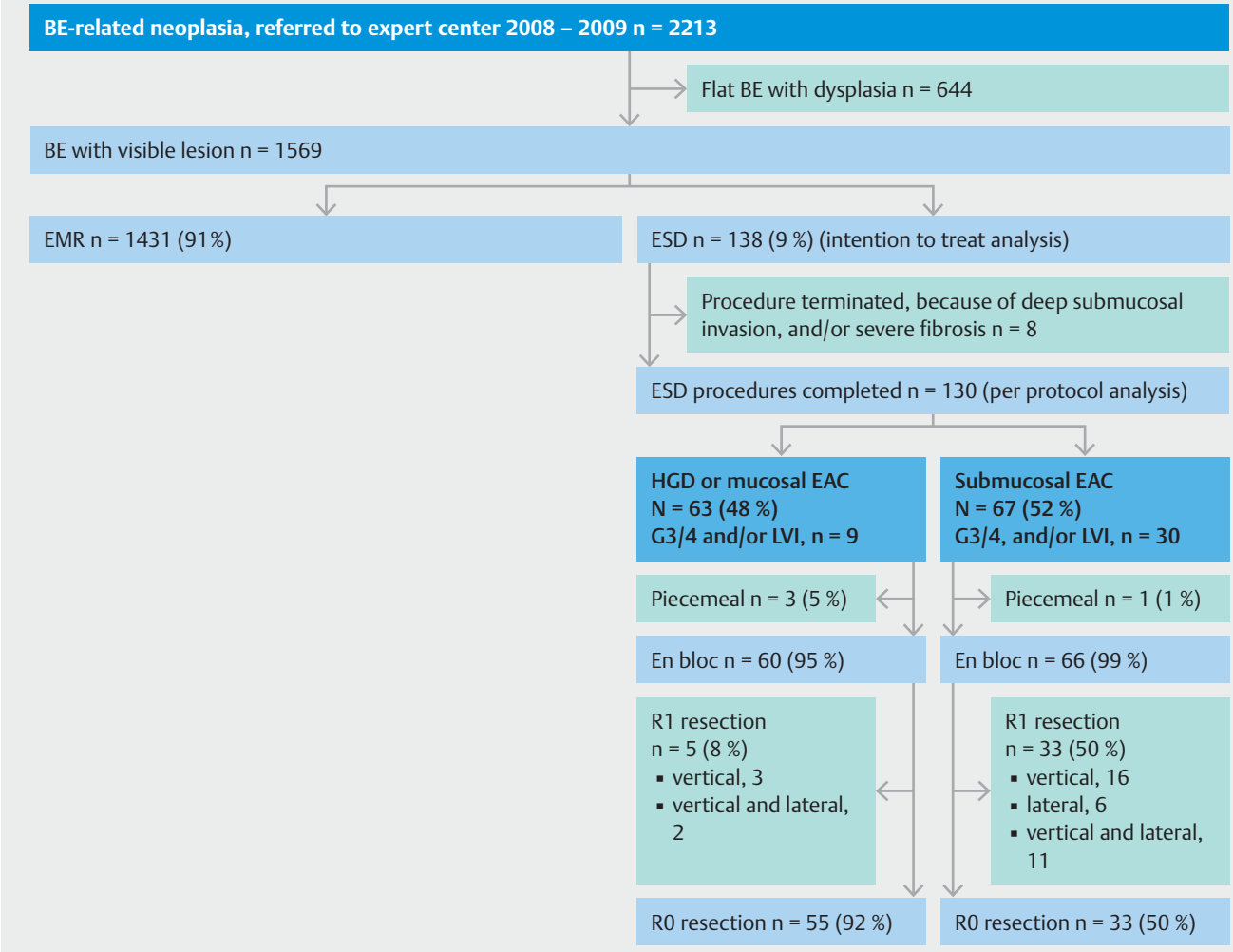
Continuous variables are presented as mean with SD or median with interquartile range (IQR) for normally distributed or skewed data, respectively. Categorical variables are presented as counts with percentages and 95 % confidence intervals (95 % CIs), that were obtained using bias-corrected bootstrapping with 10 000 samples.

Results

A total of 1569 patients with a visible lesion were referred to an expert center between 2008 and 2019 (▶ **Fig. 2**). Of these, only 138 patients (9 %) underwent ESD while 1431 patients (91 %) underwent EMR. The majority of ESDs was performed from 2015 onwards (129/138 procedures). Baseline data of demographics, Barrett segments, lesions, and ESD indications are shown in **Table2 s**. The majority of patients was male (80 %) with a median age of 68 (61–73) years. The median length of lesions was 30 (10–40) mm and the median circumferential extent was 30 % (25 %–50 %). In 65 % of cases, ESD was performed for suspected submucosal invasion.

Procedure

Procedures were performed in Amsterdam (n = 64), Utrecht/Nieuwegein (n = 41), Rotterdam (n = 20), Eindhoven (n = 9), and Groningen (n = 4). Most procedures were performed with the DualKnife (78 %). Median procedure time was 121 minutes (IQR 90–180).



▶ **Fig. 2** Endoscopic submucosal dissection (ESD) for Barrett-related neoplasia: patient flow and ESD outcomes according to neoplasia findings. BE, Barrett's esophagus; EMR, endoscopic mucosal resection; HGD, high grade dysplasia; EAC, esophageal adenocarcinoma; LVI, lymphovascular invasion.

The ESD procedure was completed in 130/138 cases. In the remaining eight patients, the procedure was aborted because of invasion into the muscularis propria and/or severe fibrosis (▶ **Fig. 2**). Of these patients, four subsequently underwent surgery, revealing T3N1, T2N0, and T1bN0 EACs (n = 1, 1, and 2, respectively). The remaining four patients were deemed unfit for surgery, and one died of EAC 18 months after ESD; one died of unrelated causes 12 months after ESD; and two were alive after 12–15 months.

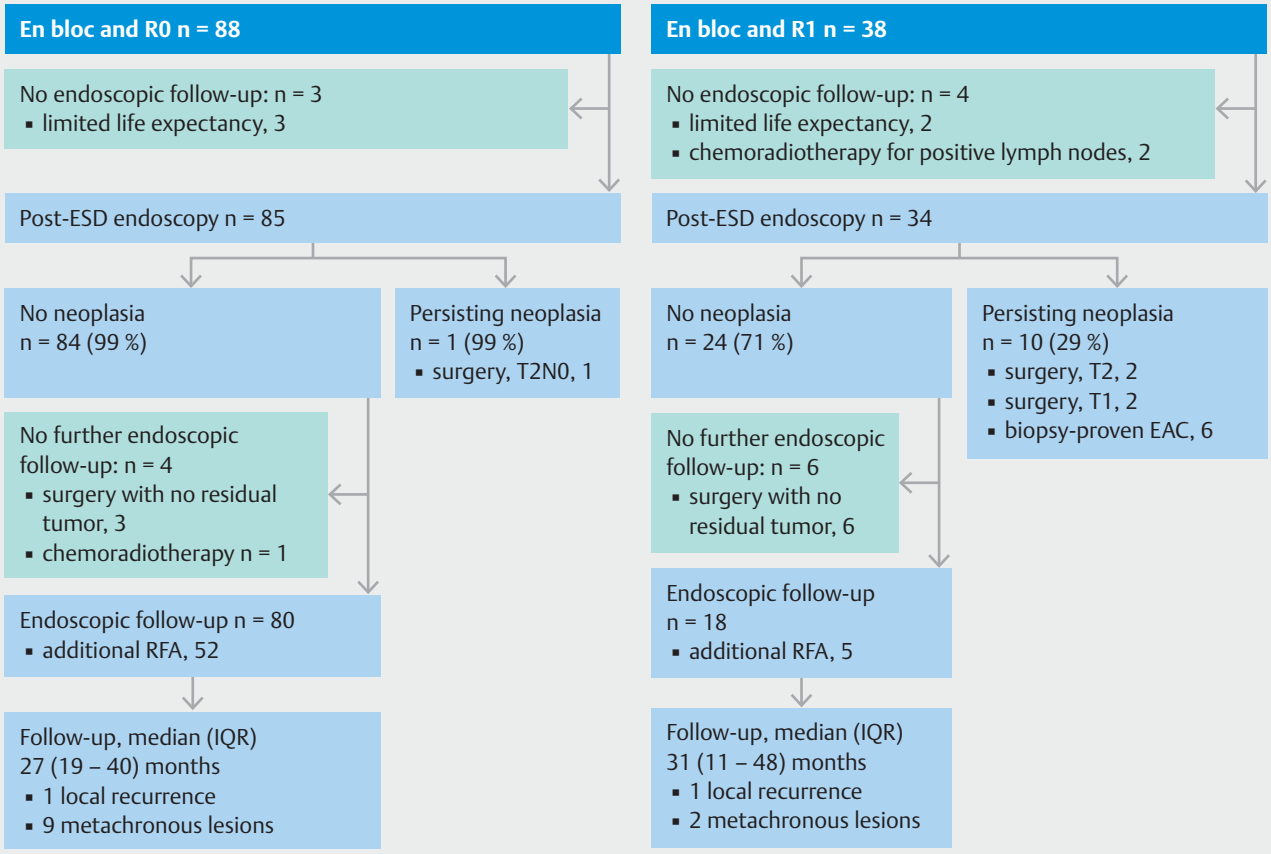
In intention-to-treat analysis, 126/138 ESDs were en bloc resections (91 %).

In per-protocol analysis, including only the 130 cases where ESD was complete, en bloc resection was achieved in 126/130 ESDs (97 %) (▶ **Fig. 2**). In the remaining 4, the lesion was removed in piecemeal fashion with additional ER after ESD, resulting in a complete removal of the lesion assessed during the endoscopy.

Resection outcomes according to histology

Complete ESD was performed for 63 mucosal and 67 submucosal lesions (**Table 3 s**). Mucosal lesions consisted of HGD (7/130; 5 %) or T1a EAC (56/130, 43 %). Among patients with T1a cancer, 9/56 (16 %) had one or more high risk histological features. T1b EAC was present in 67/130 cases (52 %), and 30/67 (45 %) had one or more high risk features. Of the 90 lesions where ESD was performed for suspicion of submucosal invasion, 59 (66 %) were found to have submucosal invasion on histological examination.

For mucosal lesions (HGD and T1a), the rate for resections that were both en bloc and R0 was 55/63 (87 % [75 %–92 %]), both in intention-to-treat and per-protocol analysis. Piecemeal ESD and additional EMR were done in 3 patients. In the 60 patients with en bloc resection, 5 were R1, all with tumor involvement at the vertical margins and 2 also having intramucosal cancer in the lateral margins. Thus among the patients with



▶ **Fig. 3** Outcomes after post-endoscopic submucosal dissection (ESD) endoscopy according to completeness of resection, i. e., R0 (radical, complete) or R1 (nonradical, incomplete). RFA, radiofrequency ablation; IQR, interquartile range.

mucosal lesions and with en bloc resection, the R0 rate was 55/60 (92 % [80 %–97 %]).

For T1b EAC lesions, in intention-to-treat analysis, the rate for resections that were both en bloc and R0 was 33/75 (44 % [32 %–55 %]). The corresponding value in per-protocol analysis was 33/67 (49 % [36 %–60 %]). Overall, 33 patients with en bloc resection had R1 resection with cancer only in the vertical margin (16), only in the lateral margin (6), or in both the vertical and lateral margins (11). Thus among the 66 T1b lesions that were removed en bloc, the R0 rate was 33/66 (50 % [36–61]).

Outcomes after R0 resection

In total, 85/88 patients with R0 resection underwent a follow-up endoscopy at a median 12 (8–13) weeks post ESD (▶ **Fig. 3**). Despite R0 status, a single patient (1 %) was found to have residual cancer at the site of the ESD scar during the first follow-up endoscopy 6 weeks after the ESD (▶ **Fig. 3**, ▶ **Table 1**). This patient had sm2/3 invasion in the initial ESD specimen and subsequent surgery showed T2N0 EAC.

The remaining 84 (99 %) patients with an R0 resection had no remaining neoplasia at first follow-up (▶ **Fig. 3**, ▶ **Table 1**). After the post-ESD endoscopy 3 patients underwent surgery and these patients had no residual tumor in the esophagectomy specimen. One patient had chemoradiotherapy because of positive lymph nodes.

The remaining 80 patients had endoscopic follow-up after ESD and additional RFA for residual BE was performed in 52 (65 %).

During the endoscopic surveillance after ESD (median 27 [19–40] months) one patient developed local recurrence (1.3 %; annual recurrence risk 0.5 % [0 %–1.6 %]). At baseline ESD, the patient with local recurrence had been found to have deep submucosal EAC, well differentiated, without LVI, and with R0 resection. Surveillance endoscopy and endoscopic ultrasound every 3 months was initiated based on the patient's preference. At 18 months after ESD, a new non-flat lesion of 8 mm was observed in the squamous epithelium at the edge of the ESD scar. An attempt at a further ESD was not successful because of deep invasion in the muscularis propria. The patient preferred endoscopic follow-up over surgery.

Outcomes after R1 resection

Of the 38 cases with R1 resection, 34 had follow-up endoscopy (▶ **Fig. 3**) at a median 10 weeks post ESD (IQR 8–11 weeks).

In 24/34 patients (71 %), no residual cancer was found at first endoscopic follow-up. Of these, 6/24 underwent surgery (indi-

▶ **Table 1** Endoscopic submucosal dissection (ESD) for Barrett-related neoplasia: histopathologic assessment and resection status, and persistence of neoplasia at follow-up of median 8 weeks after ESD in 126 patients.

Histological assessment: lesion type and resection status	n (%[1])	Neoplasia free (108 patients) n (%[2])	Persisting neoplasia (11 patients) n (%[2])	No follow-up endoscopy (7 patients) n
HGD/m-EAC (n = 60)		59/59 (100)	0 (0)	1
▪ R0	55/60 (92)	54/54 (100)	0 (0)	1
▪ R1	5/60 (8)	5/5 (100)	0 (0)	0
Sm1-EAC(n = 24)		22/24 (92)	2/24 (8)	0
▪ R0	14/24 (58)	14/14 (100)	0 (0)	0
▪ R1	10/24 (42)	8/10 (80)	2/10 (20)	0
Sm2/3 EAC (n = 42)		27/36 (75)	9/36 (25)	6
▪ R0	19/42 (45)	16/17 (94)	1/17 (6)	2
▪ R1	23/42 (55)	11/19 (58)	8/19 (42)	4

HGD high grade dysplasia; m, mucosal; EAC, esophageal adenocarcinoma; R0, cancer-free lateral and vertical tumor margin); R1, presence of tumor in lateral and/or vertical resection margin (or dysplasia in cases of HGD); sm, submucosal.
[1] As percentage of histological group.
[2] As percentage of endoscopically followed -up subgroup total.

cations for surgery were sm2/3 invasion in the ESD specimen, and 1 also showed lymph node metastasis at EUS); none of these patients had residual esophageal tumor in the surgical specimen. The remaining 18 patients with no neoplasia at first endoscopic follow-up underwent further endoscopic follow-up through a median 31 (11–48) months; there was 1 intraluminal recurrence (5.6%; annual recurrence risk 2% [0%–6%]).

The baseline ESD for this patient with local recurrence had shown m3 EAC with R1 resection histologically. Afterwards, additional EMR was performed for metachronous T1m3 EAC. Follow-up showed normal scar tissue and a short remaining BE segment; biopsies from the scar and remaining BE segment showed no abnormalities. Because of comorbidities, it was then decided to stop standard 3-monthly follow-up endoscopies. A new follow-up endoscopy was performed 2 years later (i.e., 3 years after the initial ESD) and a new visible lesion was found in the ESD scar. Repeat ESD showed deep submucosal EAC with poor differentiation and LVI. The patient was not fit for surgery and endoscopic follow-up was continued.

In the other 10/34 patients with R1 resection (29%), residual cancer was detected endoscopically at first follow-up (▶ **Fig. 3**). In 9 patients the initial ESD had shown T1b EACs with R1 vertical margins, in 3 cases there were also R1 lateral margins, and in 1 patient only the lateral margin was R1. Subsequently 4 patients underwent surgery, revealing T2N1, T2N0, and T1N0 EACs (n = 1, 1, and 2, respectively). The remaining 6 patients had biopsy-proven EAC but were unfit for major surgery and received curative chemoradiotherapy (n = 2) or palliative therapy (n = 4).

Post-ESD endoscopic assessment of local tumor status

Overall, in 119/126 patients with en bloc resection (both R0 and R1 histologically), a dedicated follow-up endoscopy was performed at a median 11 weeks (IQR 8–15 weeks) after ESD.

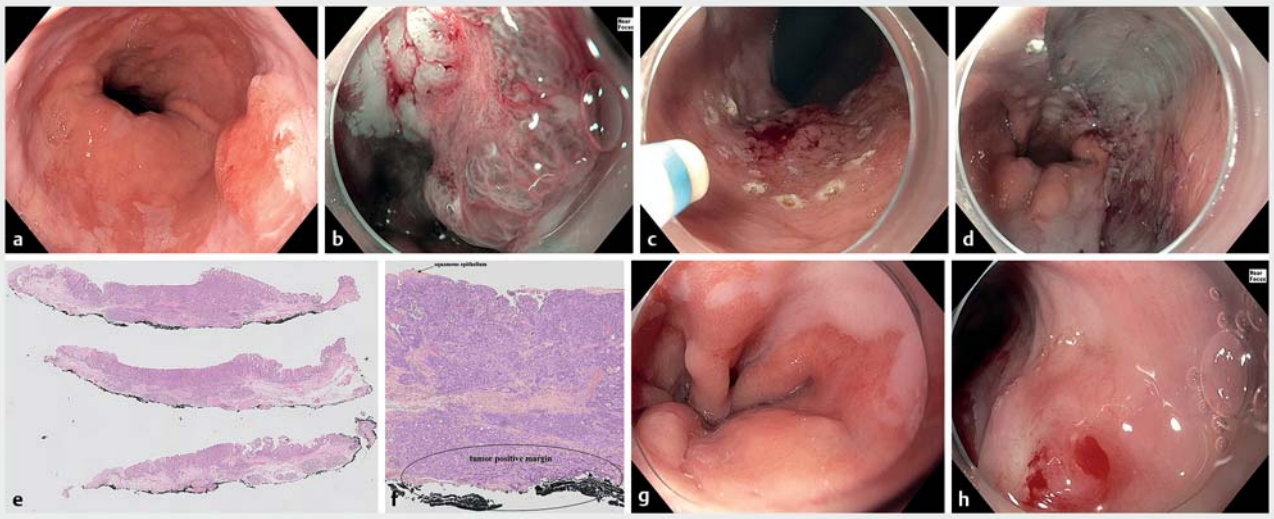
Residual cancer was seen at first follow-up in 11 patients. The risk for residual cancer at this first follow-up endoscopy gradually increased with deeper tumor invasion. None of the mucosal lesions had residual cancer, whereas residual cancer at first follow-up was seen in 8% (2/24) of sm1 EACs and 25% (9/36) for sm2/3 EACs. (▶ **Table 1**, ▶ **Fig. 4**). The 11 cases with residual cancer detected at the first follow-up endoscopy are described in **Table 4 s**.

Among 108 patients without residual cancer at the first post-ESD follow-up endoscopy, 9 underwent surgery with no residual tumor found in their surgical specimens. The remaining 98 patients underwent endoscopic follow-up and during median 27 (15–39) months, 2 patients developed local recurrence (2%, annual recurrence risk 0.9% [0%–2%]) (▶ **Fig. 5**). These two local recurrences have been described above.

Overall, among the patients with no persisting neoplasia at post-ESD endoscopy, with histologic R0 and R1 resection, respectively, 1/84 (1.2%) and 1/24 (4.2%) had recurrent neoplasia ($P = 0.34$).

Adverse events

There were no procedure-related deaths. Post-procedural bleeding occurred in 4 patients (4/138; 2.9% [0.7%–5.8%]. All were managed endoscopically and 1 had additional blood transfusion.



▶ **Fig. 4** Residual (persisting) neoplasia at follow-up endoscopy after ESD, in a case with a tumor-positive basal resection margin in the resection specimen. **a,b** C0M1 Barrett segment with a type 0-IIa-IIc lesion between 1 to 4 o'clock, with narrow-band imaging in zoom mode shows irregular vascularization suspicious of submucosal invasion. **c** Markings were placed using argon plasma coagulation. **d** ESD was performed, with endoscopically complete en bloc resection. **e,f** The microscopic histopathological specimen shows tumor invasion in the basal resection margin. **g,h** At follow-up, irregular tissue was seen in the ESD scar which bled after minimal provocation. The persisting lesion was not amenable to endoscopic treatment, and because of age and comorbidity no further treatment was performed.

A small perforation occurred in 1 patient, and was managed directly during the procedure with a single clip (1/138; 0.7% [0%–2.0%]).

A total of 18 patients developed a stricture (18/138; 13% [7.2%–18.8%]) and these were managed with a median 3 dilations (range 1–12). All the patients who developed esophageal strictures had undergone resection of >50% of the esophageal circumference.

Discussion

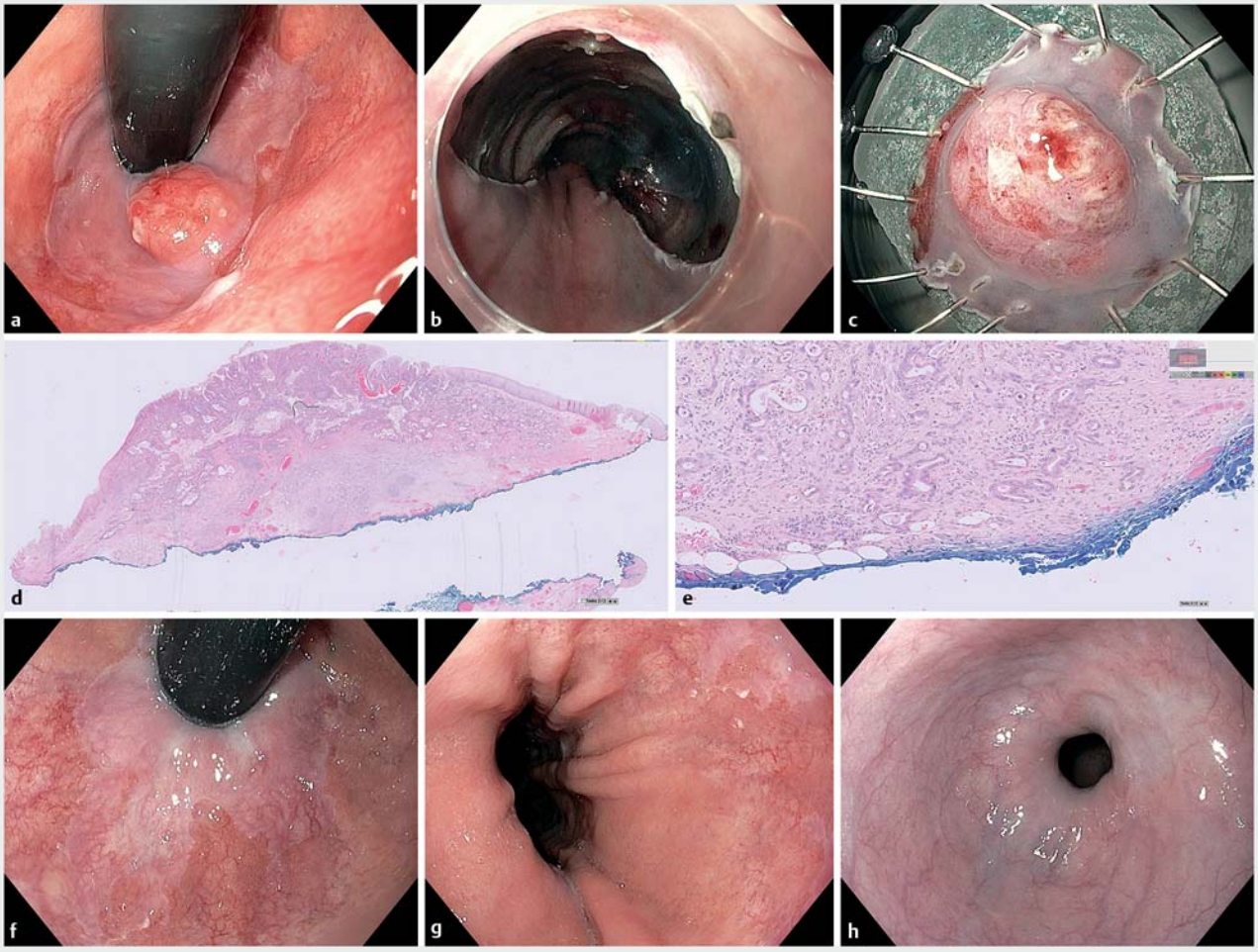
We report all 138 ESDs performed for BE neoplasia in the Netherlands between 2008 and 2019. An important driver for the expanding use of ESD for early BE neoplasia is the opportunity for endoscopic treatment for submucosal cancers, as submucosal dissection enables deeper radical resection than cap-based techniques. Importantly, it is generally assumed that deeper and more controlled resection with ESD also provides a better specimen for histological evaluation and risk assessment for lymph node metastasis. This expanding indication is reflected in the indications for ESD in the current series: suspected submucosal invasion was the main indication for ESD in 65% of cases and in this subgroup 66% indeed was found to have a submucosal cancer. Our series includes 67 cases with submucosal cancer making it the largest published ESD cohort for removal of submucosal EAC (T1b).

The technical outcomes of our study, such as rates for en bloc/R0 resection and adverse events, comport well with other ESD series and do not provide much new information (**Table 5 s**). However, our study presents important new findings for ESD of submucosal cancers.

We found that ESD of submucosal cancers was associated with a positive vertical resection margin in half of cases, a rate significantly higher than for mucosal cancers (8%). However, upon esophagectomy or after multiple endoscopic follow-up sessions, residual cancer was detected in only a minority of these R1 cases. Whereas all guidelines dictate esophagectomy for cancers with a tumor-positive deep resection margin after ESD, our data suggest that this may not be appropriate.

How can we explain the discrepancy of a tumor-positive deeper resection margin of the ESD specimen and the observed low frequency of persisting local tumor? There are a number of potential explanations for this finding: (i) inaccuracy in the histological diagnosis of R1 resection; (ii) ESD-related artefacts causing overdiagnosis of R1 cases; and (iii) a direct ablative effect of ESD-related electrocoagulation on any residual cancer tissue and/or indirect effects by compromised vascularization of any residual neoplasia.

A recent study assessed pathologist concordance in the digital histologic evaluation of 62 endoscopic resection specimens by 13 expert pathologists [22]. Focusing on basal margin radicality (i.e., histological assessment of completeness of resection, discordance, defined as disagreement by at least 1 pathologist, was found in 31% of specimens. The authors propose review by a second pathologist for specimens containing high risk features and suggest how diagnostic criteria can be improved. In our series, ESD specimens were assessed by expert pathologists who participated in the aforementioned study. Although a second review was not yet standard of care, for the purpose of this study all cases with uncertain assessment of the vertical resection margins were discussed in a consensus meeting with three pathologists.



▶ **Fig. 5** A patient without residual (persisting) neoplasia at first follow-up endoscopy, but having a histologically tumor-positive basal resection margin (R1). **a** Type 0-Is lesion in C0M2 Barrett's esophagus (BE) segment in white-light endoscopy in retrospective view. **b** Submucosal dissection of the lesion and the entire BE tongue. **c** The lesion of 25 mm in diameter was excised en bloc with complete endoscopic removal. **d,e** Histologic assessment revealed tumor invasion in the basal resection margin. **f** Endoscopy at 6–8 weeks post-ESD revealed normal squamous epithelium with a scar at 2 to 3 o'clock. **g,h** During 12 months of follow-up, no (recurrent) neoplasia was detected. After 12 months the patient had died because of cardiovascular disease.

Assessment of radicality (that is, histologically assessed completeness of resection) of ESD specimens may also be compromised by ESD-specific difficulties. During the procedure the endoscopist might coagulate the basal margin of the ESD specimen, because of bleeding, or for prophylactic coagulation of vessels, or accidentally during the submucosal dissection, especially in the final phase of dissection when orientation is sometimes difficult. These coagulation effects might complicate an accurate assessment of whether a resection is R0 or R1. The histologic distinction between an R1 diagnosis based on focal coagulation effects versus an R1 diagnosis based on true dissection through the tumor with confirmation by the endoscopist, requires specific awareness and expertise of the pathologist when evaluating ESD specimens.

If the histologic assessment of completeness of resection is compromised by significant uncertainty, how can we reliably assess whether neoplasia has been left behind after ESD? Our data suggest that an imaging endoscopy, with white-light endoscopy (WLE), narrow-band imaging (NBI), and zoom mode, and histologic sampling 8–12 weeks post ESD might help. Regarding the 108 patients who had no abnormal findings during this post-ESD endoscopy, only 2 developed local recurrence at the site of the ESD scar during a median endoscopic follow-up of 27 months (annual recurrence risk 2 %), and no residual cancer was detected in the surgical resection specimen of any of the 9 patients who underwent surgery. On the other hand, all the patients who had a residual cancer detected in their surgical specimen had been identified as having residual neoplasia during this post ESD-endoscopy.

This endoscopy at 8–12 weeks post-ESD might have a further advantage. It may not only prevent unnecessary esophagectomy in patients with "false-positive R1," but it may also identify patients with a truly incomplete resection. In our study, 3 of the 5 patients with deep submucosal invasion and residual

neoplasia were diagnosed with T2 EAC upon esophagectomy, which was carried out without neoadjuvant therapy. Although data are scarce, neoadjuvant chemoradiotherapy might potentially have been beneficial in these patients [23].

In our series, suspected submucosal invasion was the most frequent indication for ESD. In our opinion, this is only a valid indication for ESD if patients who are found to have a completely resected submucosal cancer in their resection specimen are considered for subsequent endoscopic follow-up instead of surgical treatment. If such patients are nevertheless subjected to esophagectomy, as most guidelines still dictate, the justification for performing a complex endoscopic procedure may be questioned. Our indications also resulted in 8/138 cases (6 %) in whom the procedure was aborted because of deep invasion into the muscularis propria and/or severe fibrosis. This number may be relatively high, resulting from our strategy of providing an attempt at ESD in advanced cases also, especially when patients were unfit for surgery. In our study, esophagectomy after aborted ESD was conducted without complications.

Three-monthly post-ESD surveillance with high definition endoscopy and endoscopic ultrasound (according to the PREFER study protocol, ClinicalTrials.gov Identifier NCT03222635) is gaining acceptance as an alternative strategy to esophagectomy for selected patients with submucosal EAC. This strategy is based on the studies indicating that the risk for local lymph node metastases in submucosal cancer is lower than generally assumed [24]. Performing prophylactic surgery after radical ESD for submucosal cancer in all patients is most likely associated with overtreatment for the majority of patients who have no local lymph node metastasis after adequate baseline staging with positron emission tomography-computed tomography (PET-CT) and EUS.

Based on the current study, a similar reasoning might hold for patients with an R1 resection of a submucosal cancer. As shown in our results, R1 resection is more common after ESD for submucosal lesions as compared to mucosal lesions, at rates of 50 % and 8 %, respectively. When indications for ESD are expanded to submucosal lesions, a histologic R1 assessment will be increasingly common. If we extrapolate our findings, esophagectomy for all R1 resections may result in overtreatment for up to 71 % of patients with a R1 resection after ESD. It may potentially also result in a risk for undertreatment for those who do harbor T2 or deeper tumor invasion. As discussed, an endoscopy 8–12 weeks post ESD might help in assessment of local tumor status and would therefore be a logical addition to making an effective strategy for endoscopically resected submucosal cancers in BE.

We acknowledge that the number of ESDs performed by endoscopists in the current study may be low as compared to expert centers that have implemented ESD at an earlier stage. Especially given the long learning curve for ESD, endoscopists in those centers will be more experienced and outcomes may potentially be better. However, BE care in the Netherlands is strictly centralized with superspecialization for ESD in high volume centers only. The growing popularity and gradual expansion of ESD in Europe means that it is highly likely that ESDs in Europe will generally be performed by less experienced endoscopists than those in the current study.

This is the largest series for ESD of submucosal lesions currently available for BE neoplasia and is relevant given the gradual shift from surgical treatment to endoscopic management of submucosal cancers. Our nationwide cohort includes all ESDs ever performed for early BE neoplasia in the Netherlands. All procedures were performed in centralized settings by experienced endoscopists and for homogeneous indications only, after meetings in multidisciplinary settings. All ESD specimens were evaluated by dedicated BE pathologists.

The study also has limitations. No central pathology review was performed and this might have introduced variability in our results. Nevertheless, all ESD specimens were assessed by pathologists who participated in dedicated training programs and had many years of experience in the diagnosis of BE neoplasia, and cases with initial “doubtful vertical resection margins” did undergo central revision. Suspicion for submucosal invasion was a subjective assessment.

The 8–12 weeks post-ESD endoscopy was not a standard procedure in our treatment protocol and was missing in 7 patients. Although this post-ESD endoscopy was reliable in all patients with post-ESD strictures in the current study, the numbers are low. There was no standardized protocol for surveillance after ESD and follow-up was performed according to the physician’s discretion. As a result, the initiation of surveillance, surveillance intervals, and choice for EUS, CT scan, or endoscopy were heterogeneous. Unfortunately, we were therefore unable to assess reliably the long-term risks for lymph node and/or distant metastasis. The overall study population was relatively large, but some subgroup analysis included only few patients. Furthermore, endoscopic follow-up was median 27 months and this might have been too short to draw definitive conclusions about the local tumor status. Confirmation of our findings in a larger group of patients with longer follow-up is therefore required.

Because of the limited sample size and broad CIs, we did not account for an additional source of variation due to potential clustering within centers. Roughly, outcomes appeared comparable over the five centers (data not shown).

In conclusion, ESD is safe in expert hands and allows effective treatment of selected cases of early Barrett’s neoplasia. ESD may play a significant role in the expanding indications for endoscopic treatment of submucosal cancers. Our data suggest that the histologic assessment of completeness of resection (radicality, that is, R0 or not R0) of ESD specimens is challenging, and that a tumor-positive deep resection margin does not necessarily imply that vital residual neoplasia has been left behind. An R1 assessment will be an increasingly common phenomenon when indications for ESD are expanded to submucosal lesions. For cases with a histological R1 resection, careful endoscopic examination 8–12 weeks post-ESD may help in selecting the optimal treatment approach.

Clinical trial

Retrospective analysis of prospectively collected data | Registration number (trial ID): NL7039 | Type of study: Cohort study

Competing interests

BW received financial support for IRB-approved research from C2Therapeutics/Pentax Medical. JB received financial support for IRB-approved research from C2Therapeutics/Pentax Medical, Medtronic, and Aqua Medical. The other authors declared no competing interests.

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