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Favorable effect of endoscopic reassessment of clinically staged T2 esophageal adenocarcinoma: a multicenter prospective cohort study

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ABSTRACT

Background Clinical tumor stage of esophageal adenocarcinoma (EAC) is determined by endoscopic ultrasound and/or computed tomography scan, which have low accuracy for stages T1 and T2, potentially leading to overtreatment. We aimed to assess the proportion of cT2 EACs downstaged to cT1 after endoscopic reassessment (ERA) by an experienced interventional endoscopist.

Methods We performed a prospective multicenter cohort study. Patients with cT2N0M0 EAC were included and underwent ERA. The primary outcome was proportion of cT2 EACs downstaged to cT1 after ERA.

Results 15/25 included patients (60 %) were downstaged from cT2 to cT1 EAC after ERA and underwent attempted endoscopic resection. Endoscopic resection was aborted in 3/15 patients because of tumor invasion into the muscle layer; all three underwent successful surgical resection. Endoscopic resection was successful in 12/15 patients (80 %), all of whom had pT1 tumors. Overall, 10/25 (40 %) were treated with endoscopic resection alone.

Conclusions ERA downstaged about half of the cT2 tumors to cT1, rendering them suitable for endoscopic resection. ERA had substantial clinical impact on therapeutic management, preventing overtreatment in 40 % of patients.

Introduction

Patients with early stage (T1) esophageal adenocarcinoma (EAC) in the absence of poor prognostic criteria, have a good prognosis and can be treated with minimally invasive endoscopic resection [1]. Additional surgery is recommended when poor histological characteristics are present, such as those associated with increased risk of lymph node metastases (LNM) [2].

Endoscopic ultrasound (EUS) is often used for clinical tumor staging because it is superior to computed tomography (CT)

and positron emission tomography (PET) [3]. Although EUS is accurate in staging T3 and T4 EAC, it is less accurate in differentiating between T2 and T1 EAC (sensitivity 43 %–55 %, specificity 80 %–85 %) [4, 5]. This results in a substantial number of patients with pT1 stage who are overstaged as cT2 EAC. As a result, these patients unnecessarily undergo neoadjuvant chemoradiotherapy (nCRT) and surgery, which are associated with increased risks and morbidity [6–8]. Treatment strategies for cT2N0M0 (clinical Tumor-Node-Metastasis stage) EAC are therefore subject to debate, and accurate tumor staging is crucial [6, 9].

It has been observed that endoscopic tumor staging, based on macroscopic tumor characteristics, is superior to tumor staging by EUS in cT2 EAC [6, 10]. Besides endoscopic staging, the endoscopist can also assess whether endoscopic resection is possible [6]. Ideally, this assessment should be performed by an endoscopist with experience in assessing the endoscopic resectability of tumors [6, 10]. The aim of this study was to assess the proportion of cT2 EACs downstaged to cT1 after endoscopic reassessment (ERA) by an experienced interventional endoscopist.

Methods

We conducted a multicenter, prospective observational cohort study in five hospitals specializing in endoscopic resection of early EAC (two academic, three nonacademic). The study was approved by the Medical Ethical Review Committee of the Erasmus Medical Centre in Rotterdam (MEC-2018–1061). All consecutive patients with cT2N0M0 EAC between April 2018 and April 2020 were asked to participate and informed consent was obtained. EAC diagnosis was established by routine clinical work-up, consisting of a standard endoscopy with EUS, CT scan, and/or PET scan. EUS was performed by an experienced endosonographer in the referral or expert center with high-resolution endosonography. EUS-guided fine-needle aspiration was performed in cases of suspected LNM. All staging examinations were systematically reviewed at multidisciplinary tumor board meetings by an expert gastrointestinal (GI) radiologist. If EAC staging had been performed at the referring center, cross-sectional imaging was reassessed by a GI radiologist in the expert center. Exclusion criteria were presence of metastases, cytology-proven LNM, and esophageal stenosis.

Endoscopic reassessment and endoscopic resection

All included patients underwent ERA using the latest series endoscopes, with white-light high-resolution endoscopy and narrow-band imaging, to determine clinical tumor stage. ERA for invasive features was performed by endoscopists with experience in endoscopic resection of early EAC. Most endoscopists merely detect lesions and define upper and lower limits, whereas an endoscopist who actually carries out endoscopic resection looks for the precise borders and assesses the lesion for subtle signs of deep invasion that makes a lesion amenable to endoscopic resection or not. Invasive features included presence of a stricture, deep ulceration, nonprotruding depressed or excavated lesions, and a tumor that was not moving freely with peristalsis. If these features were absent, the tumor was staged cT1 and endoscopic resection was attempted. The type of resection technique was left to the discretion of the endoscopist. Endoscopic submucosal dissection (ESD) was recommended over endoscopic mucosal resection (EMR) for EACs >15 mm, if the tumor was depressed, or when submucosal infiltration was suspected [11].

Histological evaluation

All resection specimens were reviewed by a GI pathologist for tumor differentiation, presence of lymphovascular invasion, tumor depth infiltration (mucosal tumors m1–3; submucosal tumors sm1 [≤500 µm] and sm2/3 [>500 µm]), and tumor involvement of vertical resection margins (R0/R1) [12]. All resection specimens were assessed for whether they fulfilled the criteria for a curative resection [13]. If endoscopic resection was outside curative criteria, additional treatment was discussed in a multidisciplinary tumor board meeting. When EAC tumor stage was estimated as cT2 after ERA, patients underwent subsequent nCRT followed by esophagectomy [8]. In these patients, tumor stage after nCRT based on residual disease (ypTN), and pre-treatment pathological tumor stage (prepT-stage) and N-stage (prepN-stage) were assessed in surgical resection specimens [14].

Follow-up

Patients were followed according to the European Society of Gastrointestinal Endoscopy guidelines if endoscopic resection had been performed [11], and according to the National Comprehensive Cancer Network guidelines if esophagectomy had been performed [15]. In general, this consisted of upper endoscopy every 3–6 months and then annually for curative endoscopic resection [11]. Follow-up was indicated every 3 months in the first year after esophagectomy [15].

Study end points

The primary end point was the proportion of cT2 EACs downstaged to cT1 after ERA. Secondary end points were: 1) proportion of tumors that were successfully treated with endoscopic resection after ERA; 2) proportion of resected pT1 EACs that were within the accepted criteria for a curative endoscopic resection; 3) prepT-stage, prepN-stage, and ypTN-stage in patients treated with nCRT and esophagectomy, and final pathology TN-stage (pTN) in patients treated with esophagectomy only; and 4) sensitivity and specificity of the presence of invasive features during ERA in differentiating T1 from T2 EAC.

Statistical analysis

Baseline characteristics were presented using descriptive statistics. The 95 % confidence intervals (CIs) were calculated for proportions, sensitivity, and specificity, and performed with the epiR package in R, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org). For sensitivity and specificity analyses, patients were only included when final pathologic tumor stage was known. Follow-up data were retrieved until October 2020. Analyses were carried out

using IBM SPSS Statistics version 25 (IBM Corp., Armonk, New York, USA).

Results

Baseline and tumor characteristics

A total of 25 patients with cT2N0M0 EAC were included; no patients were excluded. Baseline and tumor characteristics are presented in ▶ **Table 1**. Tumor stage was determined by EUS in 24/25 patients and by CT scan in 1/25 patients. The median follow-up time was 16.4 months (interquartile range [IQR] 11.0–23.5).

Endoscopic reassessment

Information about ERA, subsequent management, and tumor stage is presented in ▶ **Fig. 1** and ▶ **Table 2**. The median time between cT2 EAC diagnosis and ERA was 26 days (IQR 0–35). ERA resulted in downstaging from cT2 to cT1 EAC in 15/25 patients (60 %, 95 %CI 39 %–79 %), who all underwent attempted endoscopic resection. The median time between ERA and endoscopic resection was 26 days (IQR 15–32). Successful endoscopic resection was performed in 12/15 patients (80 %), all of whom had pT1 tumors. Five of these 12 patients (▶ **Table 2**, patients 1–5) were within the accepted criteria for curative endoscopic resection, 5 patients (▶ **Table 2**, patients 8–12) preferred a wait-and-see strategy, and 2 patients (▶ **Table 2**, patients 6 and 7) received adjuvant treatment. ESD was aborted in 3/15 patients because of tumor invasion into the muscle layer (▶ **Table 2**, patients 13–15). ▶ **Fig. 2a** shows an example of a cT2 EAC that was downstaged to cT1 during ERA.

In the remaining 10/25 patients (40 %, 95 %CI 21 %–61 %), ERA confirmed cT2 tumor stage based on the presence of invasive features (▶ **Table 2**, patients 16–25). Seven of the 10 patients were treated with nCRT followed by surgery, without proven LNM in surgical resection specimens. Of the remaining three patients, one was treated with chemoradiotherapy followed by active surveillance within a research protocol, one received radiotherapy alone owing to poor condition, and the remaining patient renounced further treatment. ▶ **Fig. 2b** shows a cT2 EAC that was confirmed as cT2 during ERA.

Overall, 15/25 (60 %, 95 %CI 39 %–79 %) cT2 EACs turned out to be histologically proven pT1 or prepT1 EAC. A total of 12 of these 15 cT2 EACs were downstaged to cT1 EAC and therapeutic management changed for all 12 patients. Ten of 25 patients (40 %, 95 %CI 21 %–61 %) were treated with endoscopic resection only. In 13/25 patients (52 %, 95 %CI 31 %–72 %), the interventional endoscopist assessed EAC tumor stage as at least T2 during reassessment endoscopy (n = 10) or attempted ESD (n = 3). Ten of these 13 patients were treated with nCRT and surgery. PrepT-stage was at least T2 in 7/10 patients (70 %).

Sensitivity and specificity of invasive features during ERA

At least one invasive feature was present during ERA in 12/25 patients (▶ **Table 2**). In 2/12 patients (▶ **Table 2**, patients 13 and 14), the lesion moved freely with peristalsis and therefore the benefit of the doubt was given and these lesions were classified as cT1 EAC. The sensitivity of the presence of invasive features during endoscopy in detecting T2 EAC was 86 % (95 %CI 42 %–100 %) and the specificity was 80 % (95 %CI 52 %–96 %) (▶ **Table 3**).

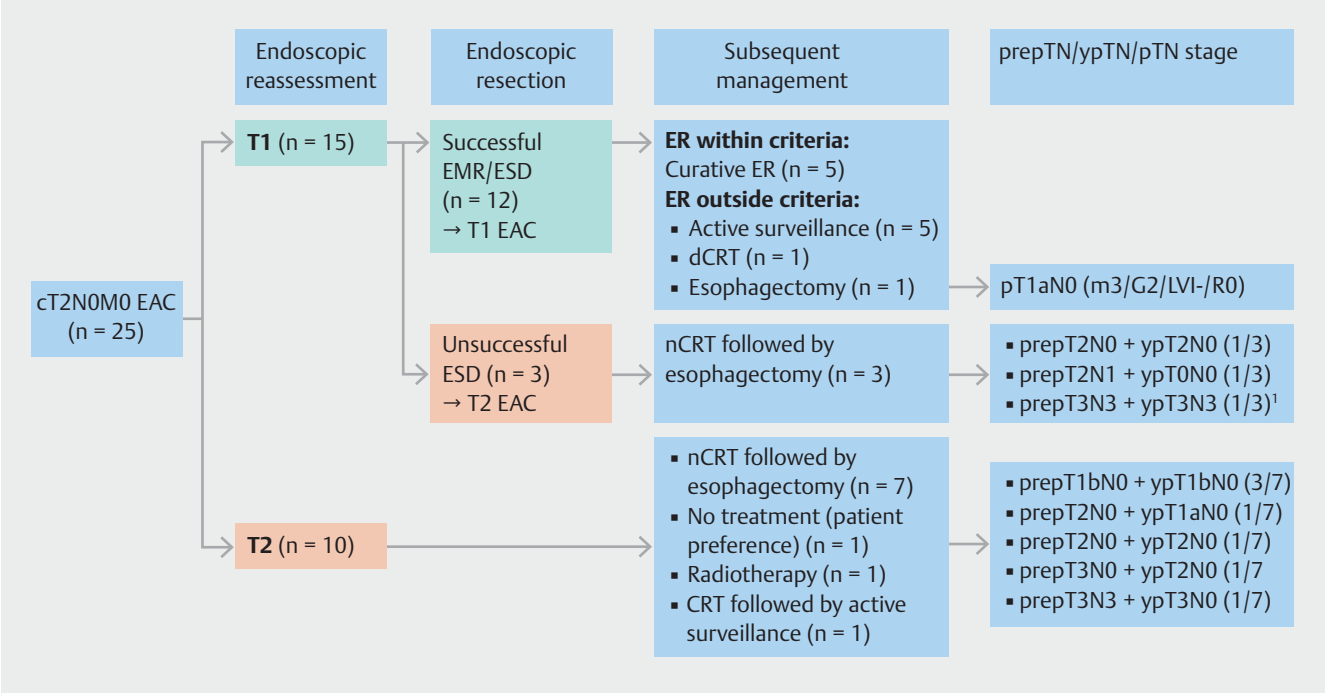
▶ **Table 1** Baseline and tumor characteristics.

Parameter	Total cohort (n = 25)
Patient characteristics	
Sex, n (%)	
▪ Male	22 (88)
▪ Female	3 (12)
Age at diagnosis, median (IQR), years	69 (57–74)
BMI, median (IQR), kg/m2	29 (25–31)
ASA classification, n (%)	
▪ I	4 (16)
▪ II	14 (56)
▪ III	7 (28)
Endoscopic tumor characteristics	
Barrett's present, n (%)	23 (92)
Tumor location, n (%)	
▪ Lower limit of the esophagus	23 (92)
▪ Gastroesophageal junction	2 (8)
Tumor diameter, median (IQR), mm	30 (20–45)
Morphology*	
▪ 0-I (protruded pedunculated)	2 (8)
▪ 0-Is (protruded sessile)	6 (24)
▪ 0-IIa (slightly elevated)	2 (8)
▪ 0-IIc (slightly depressed)	1 (4)
▪ 0-Is-IIa	6 (24)
▪ 0-Is-III	1 (4)
▪ 0-Is + IIa + IIc	3 (12)
▪ Not reported	4 (16)
Tumor differentiation grade (biopsy)	
▪ G1/2	10 (40)
▪ G2/3	3 (12)
▪ G3	1 (4)
▪ Not reported in pathology report	11 (44)

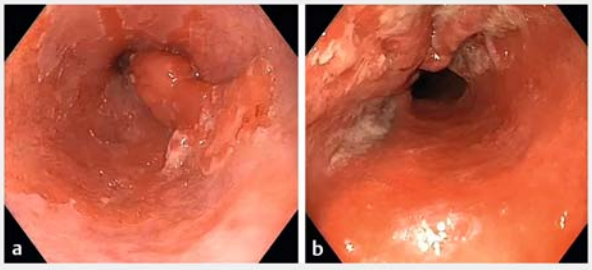
IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists.
* According to the Paris classification [12].

Discussion

The results of our study showed that in patients with a cT2N0M0 EAC, ERA by an experienced interventional endoscopist downstaged about half of the cases to a cT1 EAC that



▶ **Fig. 1** Endoscopic reassessment and subsequent management. EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; ER, endoscopic resection; nCRT, neoadjuvant chemoradiotherapy; dCRT, definitive chemoradiotherapy; CRT, chemoradiotherapy. [1]15/29 resected lymph nodes were positive.



▶ **Fig. 2a** cT2N0M0 esophageal adenocarcinoma that was assessed as T1 during endoscopic reassessment and later successfully removed by endoscopic submucosal dissection. Pathology: pT1m3G2LVI-R0. **b** cT2N0M0 esophageal adenocarcinoma assessed as T2 during endoscopic reassessment. The tumor had a depressed center and did not move freely with peristalsis. Pathology after neoadjuvant chemoradiotherapy and surgery: ypT2N0 (prepT3N0).

was suitable for endoscopic resection. ERA prevented unnecessary adjuvant treatment in 40 % of patients and therefore had a substantial clinical impact on the management of cT2 EAC. The presence of invasive tumor features during ERA for the detection of T2 EAC had a sensitivity of 86 % (95 %CI 42 %–100 %) and a specificity of 80 % (95 %CI 52 %–96 %). We would suggest standardizing endoscopy reports for these invasive features. We advocate that all cT2-staged EACs should be considered for ERA by an endoscopist with experience in endoscopic resection of early EAC.

Retrospective studies have shown that up to 63 % of pT1 EACs are overstaged as cT2 by EUS [4–6, 9, 16]. Tumor downstaging by ERA may avoid the substantial risk of treatment-related morbidity and mortality of esophagectomy, with or without nCRT, in patients with cT2N0M0 EAC, while maintaining equal curative outcomes when endoscopic resection is performed [7, 17].

In accordance with this study, previous studies have demonstrated that a substantial number of cT2 EACs can be treated with endoscopic resection and are in fact pT1 EACs [6, 18]. Nelson et al. investigated whether patients with cT2N0 EAC benefit from attempted EMR to identify overstaged patients [18]. EMR effectively eradicated pT1 EAC in 56.7 % [18]. However, only small tumors (< 2 cm) with mild fluorodeoxyglucose avidity were included in the study [18], and this may have resulted in an overestimation of the number of overstaged cT2 EACs. The median tumor size in our study was 30 mm and ESD was performed in more than half of patients treated with endoscopic resection. One might hypothesize that more cT2 EACs could be classified as pT1 EAC when ESD is performed. Our results reflect those of Gotink et al. who found that 85 % of cT2N0 EACs were downstaged to cT1 EACs after ERA [6]. Although this percentage is higher than in our study, there was a selection bias in the former study; only patients with cT2 EAC that were considered "promising" underwent ERA [6]. This may have resulted in an overestimation of the number of downstaged cT2 EACs.

It could be argued that ERA should be the first step in determining clinical EAC tumor stage rather than EUS, especially when low EAC tumor stage is expected. May et al. compared the sensitivity and accuracy of endoscopic tumor staging by an

▶ **Table 2** Tumor characteristics, treatment, and outcome of all included patients with cT2N0M0 esophageal adenocarcinoma.

ID	Reason first diagnostic endoscopy	Invasive endoscopic features	ERA	Management after ERA	Pathologic tumor stage	Subsequent management and outcome (total follow-up period in months)
1	Barrett's surveillance	Not present	cT1	ESD	T1a (M3, G2, LVI-, R0)	Curative ER → follow-up; no recurrence (16.4)
2	Barrett's surveillance	Not present	cT1	EMR	T1a (M3, G2, LVI-, R0)	Curative ER → follow-up: synchronous EAC (pT1m1G1LVI-R0) treated with MBM (27.9)
3	Barrett's surveillance	Not present	cT1	EMR	T1a (M2, G1, LVI-, R0)	Curative ER → follow-up: no recurrence (18.7)
4	Barrett's surveillance	Not present	cT1	ESD	T1a (M3, G2 , LVI-, R0)	Curative ER → follow-up: no recurrence (15.2)
5	Barrett's surveillance	Not present	cT1	EMR	T1a (M2, G1, LVI-, R0)	Curative ER → follow-up: no recurrence (17.0)
6	Barrett's surveillance	Not present	cT1	ESD	T1b (Sm2/3, G3, LVI+, R1)	dCRT → follow-up: no recurrence (10.9)
7	Barrett's surveillance	Not present	cT1	EMR	T1b (Sm2/3, G2, LVI-, R1)	Esophagectomy (pT1aN0)[1] → follow-up: no recurrence (25.5)
8	Weight loss + fatigue	Not present	cT1	EMR	T1b (Sm2/3, G3, LVI+, R0)	Endoscopic surveillance + EUS: no recurrence (26.0)
9	Barrett's surveillance	Not present	cT1	ESD	T1b (Sm2/3, G1, LVI-, R0)	Endoscopic surveillance + EUS: no recurrence (18.5)
10	Accidental finding in the esophagus on PET-CT	Not present	cT1	ESD	T1a (M3, G3, LVI-, R1)	Endoscopic surveillance + EUS: no recurrence (11.0)
11	Barrett's surveillance	Not present	cT1	ESD	T1b (Sm2/3, G3, LVI+, R0)[2]	Palliative treatment due to the presence of metastases (bone and liver) after ESD: deceased due to metastases (5.6)[3]
12	Barrett's surveillance	Not present	cT1	ESD	T1b (Sm2/3, G2, LVI+, R1)	Endoscopic surveillance + EUS: recurrence after 8.3 months → cT2N0M0 treated with CRT (13.1)[4]
13	Vitamin B12 deficiency	Traction of the lesion to one point Central ulcer in the tumor	cT1[5]	ESD aborted: tumor growth in muscle layer	ypT2N0/ prepT2N0	nCRT + esophagectomy: no recurrence (25.8)
14	Barrett's surveillance	Traction of the lesion to one point	cT1[5]	ESD aborted: tumor growth in muscle layer	ypT3N3/ prepT3N3	nCRT + esophagectomy: deceased due to peritoneal metastases (14.0)
15	Barrett's surveillance	Not present	cT1	ESD aborted: tumor growth in muscle layer	ypT0N0/ prepT2N1	nCRT + by esophagectomy: no recurrence (29.0)
16	Melena	Fixed lesion Not moving freely with peristalsis	cT2	Radiotherapy	No pathology	Follow-up: deceased due to peritoneal metastases (9.2)
17	Regurgitation and eructation	Circumference of the tumor: 100 % Tumor growth in the stomach	cT2	nCRT + esophagectomy	ypT1bN0 / prepT1bN0	Follow-up: deceased due to bone metastases (14.5)

▶ **Table 2** (Continuation)

ID	Reason first diagnostic endoscopy	Invasive endoscopic features	ERA	Management after ERA	Pathologic tumor stage	Subsequent management and outcome (total follow-up period in months)
18	Dysphagia	Stenosis Depressed center of the tumor Not moving freely with peristalsis	cT2	nCRT + esophagectomy	ypT2N0/ prepT3N0	Follow-up: no recurrence (24.5)
19	Dysphagia	Stenosis Ulcer	cT2	nCRT + esophagectomy	ypT1aN0/ prepT2N0	Follow-up: no recurrence (17.0)
20	Dysphagia	Stenosis Not moving freely with peristalsis Traction of the lesion to one point	cT2	No treatment (patient preference)	No pathology	No follow-up (patient preference) (3.8)
21	Dysphagia	Stenosis Ulcer	cT2	nCRT + esophagectomy	ypT1bN0/ prepT1bN0	Follow-up: lung metastases after 22.6 months → palliative chemotherapy (22.6)
22	Anemia	Depressed lesion Not moving freely with peristalsis Ulcer	cT2	nCRT + esophagectomy	ypT2N0/ prepT2N0	Follow-up: no recurrence (17.7)
23	Barrett's surveillance	Depressed center of the tumor Not moving freely with peristalsis	cT2	nCRT + esophagectomy	ypT1bN0/ prepT1bN0	Follow-up: no recurrence (15.0)
24	Dysphagia	Fixed lesion Depressed center of the tumor	cT2	CRT + active surveillance	No pathology	Follow-up: no recurrence (8.9)
25	Dysphagia	Stenosis Depressed ulcer Circumference of the tumor: 100 %	cT2	nCRT + esophagectomy	ypT3N0/ prepT3N3	Follow-up: no recurrence (10.3)

ERA, endoscopic reassessment; ESD, endoscopic submucosal dissection; LVI, lymphovascular invasion; ER, endoscopic resection; EMR, endoscopic mucosal resection; EAC, esophageal adenocarcinoma; EUS, endoscopic ultrasound; PET-CT, positron emission tomography-computed tomography; CRT, chemoradiotherapy; dCRT, definitive chemoradiotherapy; nCRT, neoadjuvant chemoradiotherapy.
[1] Lesion in esophagectomy specimen was probably a synchronous mucosal EAC.
[2] Mixed adeno-neuroendocrine carcinoma confirmed after ESD.
[3] First CT-scan did not show metastases.
[4] Active surveillance chosen based on patient preference.
[5] Lesion moved freely with peristalsis, therefore EAC was assessed as cT1.

experienced interventional endoscopist with tumor staging performed by EUS for early esophageal cancer [10]. Although not statistically significant, the sensitivity and accuracy of endoscopic tumor staging (82.9 % and 83.4 %) were slightly superior to those of EUS (79.8 % and 79.6 %) [10].

To our knowledge, this is the first prospective, multicenter, cohort study of ERA for cT2 EAC, which is a major strength of our study. Furthermore, there was no selection bias because no patients were excluded based on tumor characteristics. A major limitation of the present study is the small sample size, with only 25 patients included over 2 years. On the one hand, this might be explained by the relative low prevalence of cT2 EAC [6]. On the other hand, we may have only included the tip of the iceberg because many patients with cT2 EAC do not undergo ERA. The participating centers were all expert centers that usually treat patients who have been referred by other hos-

▶ **Table 3** Presence and absence of invasive features during endosco-py and final pathologic tumor stage of esophageal adenocarcinoma.

	≥T2 EAC	T1 EAC	Total[1]
Invasive features present	6	3	9
Invasive features absent	1[2]	12	13
Total	7	15	22

EAC, esophageal adenocarcinoma; CI, confidence interval.
Diagnostic characteristics of the presence of invasive features in detecting T2 EAC were: sensitivity 86 % (95 %CI 42–100), specificity 80 % (95 %CI 52–96), positive predictive value 67 % (95 %CI 30–93), and negative predictive value 92 % (95 %CI 64–100).
[1] Calculated for 22 patients; 3 patients were excluded from the analysis because no final pathologic tumor stage was known.
[2] Patient #15 in ▶ **Table 2**.

pitals. Most endoscopists in nonexpert centers are not trained to assess whether cT2 EAC is suitable for endoscopic resection [10]. As a consequence, these patients are not referred to an expert center for an attempt at endoscopic resection. Although one could argue that the small sample size will limit the generalizability of our results, our results confirmed the low accuracy of EUS in staging early EAC and showed that ERA downstaged 60 % of cT2 EACs, of which 80 % were pT1 EACs.

We recommend ERA by an experienced interventional endoscopist for all cT2N0M0-staged EAC patients. ERA had a substantial clinical impact on therapeutic management, downstaging about half of the cases to T1 EAC in the current study. Although ERA prevented invasive adjuvant treatment in 40 % of patients, the curative resection rate of downstaged tumors was 33 %.

Clinical trial

Trial Registration: Netherlands National Trial Register | Registration number (trial ID): NL7181 | Type of study: Prospective, Multicenter, Cohort Study

Competing interests

The authors declare that they have no conflict of interest.

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