Optimising tuberculosis care for refugees affected by armed conflicts

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Analysis of metastases rates during follow-up after endoscopic resection of early "high-risk" esophageal adenocarcinoma

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Background and Aims: After endoscopic resection (ER) of early esophageal adenocarcinoma (EAC), the optimal management of patients with high-risk histologic features for lymph node metastases (ie, submucosal invasion, poor differentiation grade, or lymphovascular invasion) remains unclear. We aimed to evaluate outcomes of endoscopic follow-up after ER for high-risk EAC.

Methods: For this retrospective cohort study, data were collected from all Dutch patients managed with endoscopic follow-up (endoscopy, EUS) after ER for high-risk EAC between 2008 and 2019. We distinguished 3 groups: intramucosal cancers with high-risk features, submucosal cancers with low-risk features, and submucosal cancers with high-risk features. The primary outcome was the annual risk for metastases during follow-up, stratified for baseline histology.

Results: One hundred twenty patients met the selection criteria. Median follow-up was 29 months (interquartile range, 15-48). Metastases were observed in 5 of 25 (annual risk, 6.9%; 95% confidence interval [CI], 3.0-15) high-risk intramucosal cancers, 1 of 55 (annual risk, .7%; 95% CI, 0-4.0) low-risk submucosal cancers, and 3 of 40 (annual risk, 3.0%; 95% CI, 0-7.0) high-risk submucosal cancers.

Conclusions: Whereas the annual metastasis rate for high-risk submucosal EAC (3.0%) was somewhat lower than expected in comparison with previous reported percentages, the annual metastasis rate of 6.9% for high-risk intramucosal EAC is new and worrisome. This calls for further prospective studies and suggests that strict follow-up of this small subgroup is warranted until prospective data are available. (Gastrointest Endosc 2022;96:237-47.)

(footnotes appear on last page of article)

Endoscopic resection (ER) is established as the first-choice treatment for early esophageal adenocarcinoma (EAC) without histopathologic risk factors of lymph node metastases (LNM). Multiple studies and long-term analyses have demonstrated excellent efficacy and safety of ER as an alternative to surgery for these lesions.[1-3] Nevertheless, after radical ER of a tumor with histopathologic risk factors for LNM, optimal management is still unclear. These risk factors include submucosal invasion (T1b), poor tumor differentiation grade (grade 3), and lymphovascular invasion (LVI).

Today, the indication for endoscopic therapy has extended to tumors invading into the superficial submucosa (<500 μm; sm1) with a good to moderate differentiation grade that do not display LVI. For these sm1 tumors without high-risk features, the risk of LNM is <2%,[4,5] and strict endoscopic follow-up is an accepted alternative to esophagectomy.[6,7] A small number of mainly surgical studies have assessed the LNM rates in patients with deep submucosal invasion (ie, ≥500 μm; sm2/3), and/or poor differentiation grade, and/or LVI, reporting a wide range of LNM rates between 16% and 46%.[5,8,9] Therefore, ER is considered insufficient treatment for these patients, and surgery is still advised.

However, these LNM rates are mainly based on historical surgical studies, in which the invasion depth and other

risk features of tumors in the surgical specimen may have been less accurately reported compared with ER specimens. Because histologic assessment of surgical specimens is based on relatively large cuts of 5 mm, invasion depth may have been underestimated if the deepest part of infiltration was not included in slides cut for histologic assessment. Accurate assessment of histologic risk factors was also less relevant, because the esophagectomy had already been performed and the presence or absence of these risk factors would not influence further management. A number of more recent endoscopy-based studies show an LNM risk for submucosal EAC with high-risk features of 0% to 37% during a median follow-up of 23 to 63 months, which is lower than that reported in the surgical series, rendering an invasive esophagectomy possibly unnecessary in a subset of patients.[5,10-12]

Comparatively less is known about the risk of LNM for intramucosal EAC with high-risk features. This disparity drives heterogeneous clinical decision-making and patient management. An alternative to immediate adjuvant surgery may be to survey patients after ER of an EAC with high-risk features and limit further treatment such as chemoradiotherapy and/or surgery to those patients with proven LNM during follow-up. This would require additional evidence about the long-term safety of this conservative strategy from prospective cohort studies. The aim of this study was to assess the outcomes of patients who underwent radical ER for an EAC with high-risk histologic features without metastases at baseline and who were followed endoscopically.

METHODS

The study included patients from the Barrett Expert Center (BEC) registry (Netherlands Trial Register, NL7039), which has been described in detail.[13] In summary, this registry represents outcomes for all patients who underwent endoscopic treatment for Barrett's neoplasia in the Netherlands from 2008 onward. Dutch Barrett's neoplasia care is uniquely organized in 9 BECs with treatment provided by jointly trained endoscopists and pathologists. The BECs comply with a common endoscopic management protocol and gather several times a year to safeguard homogeneity. Furthermore, because every patient in the Netherlands receives treatment in 1 of the BECs, data on treatment and outcomes of all patients treated for Barrett's neoplasia are registered in this uniform, nationwide database.

Patients diagnosed with EAC and histologic risk factors after ER with negative deep resection margins were counseled for endoscopic management or surgery depending on age, comorbidity, and preference following national guidelines.[14,15] None of the included patients participated in the prospective PREFER study (NCT03222635). Our study partly overlaps with 2 earlier reports from our group (n = 52).[5,11]

Study population

For this study, we included all patients who underwent ER of an EAC with high-risk histologic features, with tumor-negative deep resection margins, between January 2008 and October 2019. We distinguished 3 histological subgroups:

- T1a EAC with high-risk features (HR-T1a) was defined as intramucosal adenocarcinoma, with poor differentiation grade (grade), and/or LVI.
- T1b EAC with low-risk features (LR-T1b) was defined as submucosal cancer with superficial invasion in the submucosa (<500 μm; sm1), well to moderately differentiated (grades 1 to 2), without LVI.
- T1b EAC with high-risk features (HR-T1b) was defined as submucosal cancer with deep invasion in the submucosa (≥500 μm; sm2/3), and/or poor differentiation grade (grade 3), and/or LVI presence.

Exclusion criteria were tumor-positive deep resection margin, residual lesion not amendable to re-ER at the first endoscopy after initial ER, metastases (LNM or distant metastases) diagnosed at baseline, and referral for surgery or chemoradiotherapy directly after ER.

Histopathologic evaluation

Histologic evaluation of all ER specimens was performed by pathologists experienced in Barrett's esophagus. After tissue fixation, specimens were cut into 2- to 3-mm strips, processed to paraffin blocks, cut into 4-μm slides, and stained with hematoxylin and eosin and for p53 expression. Hereafter, 4 histologic features were assessed: (1) tumor infiltration depth, with submucosal invasion measured in microns (ie, <500 μm was subclassified as sm1; ≥500 μm as sm2/3. In most, immunohistochemistry using desmin and/or pankeratin staining was performed on a blank hematoxylin and eosin slide with the deepest submucosal tumor invasion.); (2) tumor differentiation grade[16]; (3) presence of LVI (including D2-40 staining in most cases); and (4) status of vertical resection margins and lateral resection margins in cases of en-bloc resection. Three pathologists discovered that Barrett's esophagus independently revised the histopathology of all included T1a cases to ensure no submucosal invasion.

Baseline staging

The joint treatment protocol did not prescribe a standard procedure for baseline staging after ER. Generally, patients underwent endoscopy and EUS ±6 weeks after ER to assess for the presence of residual intraluminal neoplasia and locoregional lymph nodes. Lymph nodes that appeared suspicious as assessed by the treating physician were sampled using EUS-FNA. In addition, a CT of the thorax and abdomen, or a positron emission tomography

(PET)-CT was often performed, to evaluate for the presence of distant metastases.

Follow-up and retreatment

Endoscopic follow-up was performed in the BECs, and intervals were determined by the treating physician because no strict protocol was available. Follow-up consisted of endoscopy ± EUS every 3 to 6 months and FNA in case of suspicious lymph nodes. To guarantee endoscopic imaging quality, most patients were sedated, and high-quality, high-definition endoscopes were used with virtual chromoendoscopy next to normal white-light endoscopy. The Barrett's segment was described using the Prague C & M classification.[17] Targeted biopsy sampling or direct ER was performed if any mucosal irregularity was detected. These irregularities were described using the Paris classification.[18] In addition, random biopsy samples following the Seattle protocol were taken from the (remaining) flat Barrett's segment. PET-CTs were performed in some cases during follow-up at the discretion of the treating physician. Residual Barrett's epithelium was generally kept under surveillance for at least 1 year after ER because of the relatively higher LNM risk in the first 1 to 2 years after resection of a high-risk lesion. Thereafter, eradication treatment of the residual Barrett's neoplasia was initiated in most patients per the physician's discretion.

Endpoints

The primary endpoint was the annual risk for metastases during endoscopic follow-up, stratified for the baseline histopathologic risk group. The secondary endpoint was tumor-related mortality and overall mortality during follow-up. Tumor-related mortality was defined as death directly or indirectly caused by EAC (eg, because of EAC treatment adverse events).

Data collection and management

Medical interns in the final year of their degree collected endoscopy, pathology, and imaging data using the standardized form in all BECs. All patients with endpoints and an additional 70% to 80% were double-checked by dedicated research fellows (all MDs). Missing data and illogical values were completed and corrected where possible. All authors had access to the study data and reviewed and approved the final manuscript. The BEC registry[13] was merged with the nonpublic microdata from Statistics Netherlands to record date and cause of death.

Statistics

Data analysis was performed using the SPSS statistical software package (version 25; SPSS Inc, Chicago, Ill, USA) and R studio for windows (version 3.6.1, Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as mean with standard deviation 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 (CIs).

Length of follow-up was calculated from the date of baseline ER to the most recent endoscopy, EUS, or scan. Annual risk for metastases was calculated as the number of patients with metastases divided by the total follow-up duration in years. Because competing risks were significant in this cohort, we created cumulative incidence curves performing Fine and Gray survival analysis. The time-to-event analysis was the time between baseline ER and occurrence of the event of interest (progression to LNM/distant metastases or EAC-related death), the competing risk (unrelated death), or censoring (the last follow-up endoscopy).

Patient and public involvement

Patients and public were not involved in the research.

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 and patient-informed consent. Patients were approached through an opt-out card with the possibility to object to participation in the registry.

RESULTS

Patient cohort

Between January 2008 and June 2019, 1569 patients underwent ER for a neoplastic lesion in a Barrett's segment (Fig. 1 and Supplementary Fig. 1, available online at www.giejournal.org). One hundred twenty patients met our inclusion criteria, and their baseline characteristics are presented in Table 1. Included patients were subdivided into HR-T1a (25/120; 21%), LR-T1b (55/120; 46%), and HR-T1b (40/120; 33%).

Baseline staging and investigations during follow-up

Most patients underwent baseline staging examinations before initiation of endoscopic follow-up (78% EUS and/or CT) (Table 2). The median duration of follow-up in all 120 patients was 29 months (IQR, 15-48) after baseline ER. Stratified for risk group, the median follow-up duration was 35 months (IQR, 22-53) for HR-T1a, 30 months (IQR, 18-48) for LR-T1b, and 23 months (IQR, 12-50) for HR-T1b (Table 2). Overall, the median number of endoscopies was 5 (IQR, 3-7) with 2 EUSs (IQR, 0-5) per patient. Analyzing results over time, the number of follow-up EUSs appeared to increase over time, especially for HR-T1a EAC (median of 1 EUS per patient in 2008-2011 vs 3 in 2017-2019). An additional PET-CT was

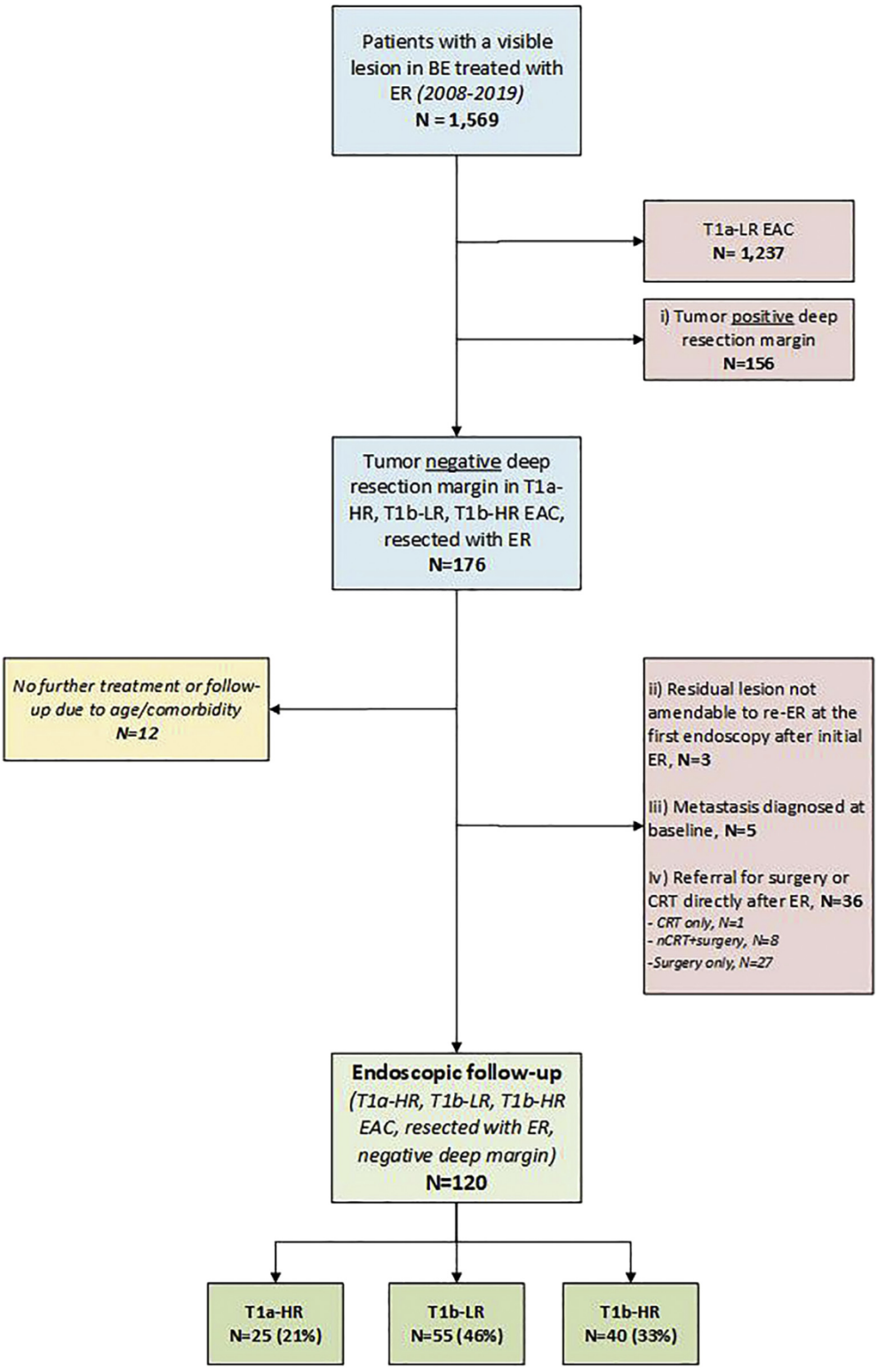


Figure 1. Flow of patients representing the selection of the study cohort. Numbers i to iv state our exclusion criteria as mentioned in Methods. *BE*, Barrett esophagus; *(n)CRT*, (neoadjuvant) chemoradiation therapy; *EAC*, esophageal adenocarcinoma; *ER*, endoscopic resection; *T1a-LR*, mucosal tumor with low-risk histopathologic features such as no lymphovascular invasion and good or moderate differentiation grade; *T1a-HR*, intramucosal tumor with high-risk histopathologic features such as lymphovascular invasion or poor differentiation; *T1b-LR,* submucosal tumor with superficial invasion in the submucosa (<500 μm; sm1), well to moderately differentiated, without lymphovascular invasion; *T1b-HR*, submucosal tumor with either deep invasion in the submucosa (≥500 μm; sm2/3), and/or poor differentiation grade, and/or lymphovascular invasion presence.

TABLE 1. Baseline characteristics of 120 patients included in follow-up analysis

Characteristics	All	High-risk intramucosal tumor	Low-risk submucosal tumor	High-risk submucosal tumor
Total patients	120	25 (21)	55 (46)	40 (33)
Age, y	74 (66-81)	74 (66-82)	76 (69-80)	73 (65-82)
Male sex	99 (83)	21 (84)	43 (78)	35 (88)
Esophageal characteristics				
Barrett's length, cm				
Circumferential	2 (0-5)	2 (1-5)	2 (0-5)	2 (0-5)
Maximal	4 (2-7)	4 (3-8)	5 (2-7)	4 (2-6)
Paris classification (primary component)*				
0-Ip	6 (5)	1 (4)	0	4 (10)
0-Is	32 (27)	2 (8)	8 (15)	15 (38)
0-IIa	65 (55)	12 (48)	29 (53)	11 (28)
0-IIb	7 (6)	3 (12)	3 (6)	1 (3)
0-IIc	8 (7)	1 (4)	4 (7)	2 (5)
Lesion size,† mm	20 (15-30)	20 (20-30)	20 (15-40)	20 (15-30)
Endoscopic resection				
Endoscopic resection technique				
Multiband mucosectomy	83 (70)	20 (80)	41 (75)	22 (55)
Endoscopic cap resection	10 (9)	2 (8)	5 (9)	3 (7)
Endoscopic submucosal dissection	24 (21)	3 (12)	9 (16)	12 (38)
Histopathologic examination of endoscopic resection specimen				
Infiltration depth				
T1m3	25 (21)	25 (100)	—	—
T1sm1 (<500 μm)	70 (58)	—	55 (100)	15 (38)
T1sm2/3 (≥500 μm)	25 (21)	—	—	25 (62)
Differentiation grade				
Good (grade 1)	24 (20)	—	19 (35)	5 (12)
Moderate (grade 2)	54 (45)	1 (4)	36 (65)	17 (43)
Poor (grades 3-4)	42 (35)	24 (96)	—	18 (45)
Lymphovascular invasion				
Absent	97 (81)	16 (64)	55 (100)	26 (65)
Present	23 (19)	9 (36)	—	14 (35)

Values are n (%) or median (25th-75th percentiles). —, No patients with these specific histopathologic characteristics.
*Missing, n = 2 (1.7%).
†Missing, n = 17 (14%).

performed in 28 patients (23%) during follow-up (median, 1 [IQR, 1-1]). Per histologic subgroup, PET-CT was performed in 4 of 28 (14%) HR-T1a patients, 7 of 28 (25%) LR-T1b patients, and 17 of 28 (61%) HR-T1b patients.

Twenty-one patients (18% [95% CI, 12-25]) were diagnosed with a visible intraluminal recurrence during regular endoscopic follow-up. The median time to intraluminal recurrence was 10 months (IQR, 9-20).

LNM and distant metastases detected during follow-up

Nine patients (7.5% [95% CI, 3.5-14]) were diagnosed with metastatic disease (LNM, n = 4 [3.3%]) and/or distant metastases (n = 5 [4.2%]) during a median follow-up of 29 months, corresponding to an annual risk of 2.7% (95% CI, .5-7.1). Metastases were detected after a median of 27 months (IQR, 23-38).

TABLE 2. Summary of patients during follow-up divided per risk group (n = 120)

	Follow-up mo	No. of endoscopies	No. of EUSs	Lymph node metastasis/distant metastases during follow-up n (%)	Annual metastasis risk during follow-up % (95% confidence interval)	Time to metastasis mo	Tumor-related death n (%)
High-risk intramucosal tumor (n = 25)	35 (22-53)	6 (3-9)	1 (0-4)	5 (20)	6.9 (3-15)	31 (25-64)	4 (16)
Low-risk submucosal tumor (n = 55)	30 (18-48)	4 (2-7)	1 (0-3)	1 (2)	.7 (0-4)	22 (NA)	1 (2)
High-risk submucosal tumor (n = 40)	23 (12-50)	5 (3-8)	5 (2-8)	3 (8)	3.0 (0-7)	24 (NA)	2 (5)

Values are median (interquartile range) unless otherwise defined. *NA*, Not applicable.

In 5 patients, metastases were detected as part of routinely performed follow-up examinations; 4 of these patients had regional LNM and 1 patient was found to have liver metastases. In the remaining 4 patients in whom metastases were detected, additional examinations were carried out because of symptoms. These detected 1 patient with regional LNM and 3 patients with distant metastases. For the latter group, EUS had been performed a median of 9 months (IQR, 7-11) before the onset of symptoms. All 9 patients with metastases had undergone baseline EUS and/or CT without evidence of metastases. Three of 9 patients (33%) also had intraluminal recurrence at the time of metastatic disease detection. The first patient underwent re-ER for an LR-T1b EAC (same as the initial tumor), whereas the second (initial histopathology showed HR-T1b) and third (initial histopathology HR-T1a) patients underwent re-ER for a visible lesion with high-grade dysplasia. Figure 2 shows the cumulative incidence curves for progression to LNM or distant metastases during follow-up stratified for baseline histology group.

After resection of HR-T1a, 5 of 25 patients (20%) developed metastases during a median of 35 months (IQR, 22-53) of follow-up (annual risk, 6.9%; 95% CI, 3.0-15). The median time to metastases in this group was 31 months (IQR, 25-64).

For patients with LR-T1b, 1 of 55 patients (2%) developed metastases during a median of 30 months (IQR, 18-48) of follow-up (annual risk, .7%; 95% CI, 0-4.0). Time to metastases in this group was 22 months.

Among the HR-T1b patients, 3 of 40 patients (8%) developed metastases during a median of 23 months (IQR, 12-50) of follow-up. The annual risk was 3.0% (95% CI, 0-7.0). The median time to metastases was 24 months. Table 3 displays histopathologic features of these patients per risk group.

EAC-related and -unrelated mortality during follow-up

Of the 9 patients with metastases, 5 developed distant metastases and died. Overall, the risk for EAC-related death was 5.8% (95% CI, 2.4-12) during a median of 70 months (IQR, 55-126).

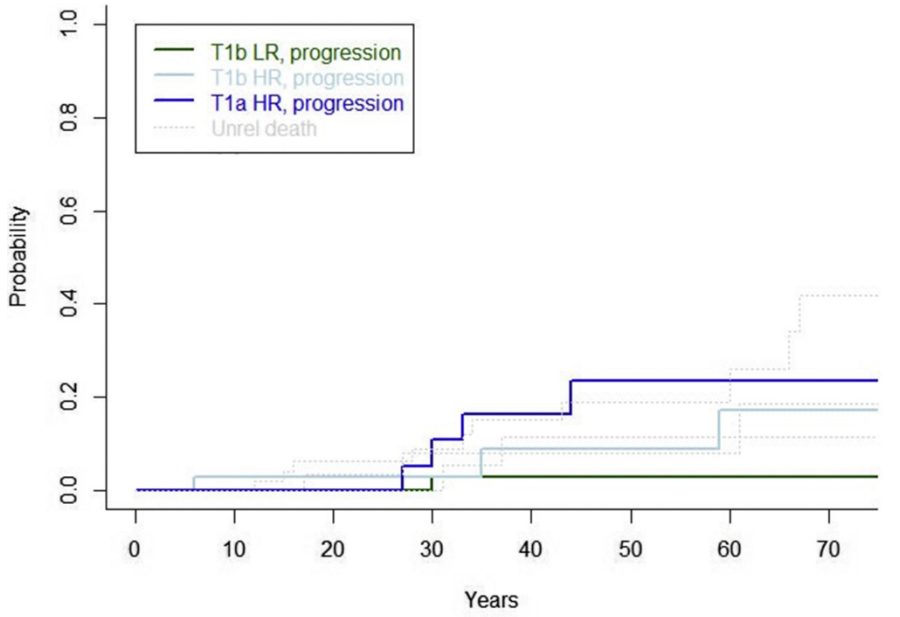
The remaining 4 patients with metastases had LNM and were additionally treated with curative intent, of which 2 patients were treated successfully (ie, 1 patient with neoadjuvant chemoradiotherapy and esophagectomy and 1 patient with definite chemoradiotherapy). The 2 other patients died because of treatment adverse events: 1 of adverse events after esophagectomy and 1 of severe radiation pneumonitis. Supplementary Table 1 (available online at www.giejournal.org) shows an extensive overview of all patients with metastases including outcomes.

Mortality not related to EAC was 13% (95% CI, 8.0-21) during a median of 33 months, and patients died a median of 34 months (IQR, 20-61) after baseline. Figure 3 shows the cumulative incidence curves for EAC-related versus EAC-nonrelated mortality, and Figure 4 shows the cumulative incidence of progression to LNM or distant metastases compared with unrelated death during follow-up, which indicates that the probability to die from unrelated causes was higher than the probability to develop metastases during follow-up. Finally, Table 2 provides a summary of all patients, including outcomes.

DISCUSSION

This study includes outcomes of all 120 patients who underwent endoscopic follow-up after radical ER of an EAC with histopathologic risk features for LNM in the Netherlands. Of 120 patients, 9 (7.5%) developed metastases during a median follow-up of 29 months (IQR, 15-48). The cohort was subdivided in T1a with high-risk features, T1b with low-risk features, and T1b with high risk features in the initial ER specimen. The annual risks for metastases for the histologic subgroups during follow-up were 6.9% (95% CI, 3.0-15), .7% (95% CI, 0-4.0), and 3.0% (95% CI, 0-7.0), respectively. EAC-specific related mortality and -nonrelated mortality were 5.8% and 13% during a median of 70 months (IQR, 55-126).

Our results regarding metastases rates in the LR-T1b group are in line with previously published endoscopy-orientated studies. A study that analyzed long-term outcomes showed a metastasis rate of 2% in patients with LR-T1b EAC during 60 ± 30 months of follow-up.[10] Our analysis, which also showed a metastasis rate of 2%



Nr of Patients	120	101	74	48	33	21	12
Months FU	0	12	24	36	48	60	72

Figure 2. Cumulative incidence curves for progression to metastases versus unrelated deaths per histopathological risk group. *T1b LR,* Submucosal tumor with superficial invasion in the submucosa (<500 μm; sm1), well to moderately differentiated, without lymphovascular invasion; *T1b HR*, submucosal tumor with either deep invasion in the submucosa (≥500 μm; sm2/3), and/or poor differentiation grade, and/or lymphovascular invasion presence; *T1a HR*, intramucosal tumor with high-risk histopathologic features such as lymphovascular invasion or poor differentiation; *FU*, follow-up.

during a median follow-up of 30 months, confirms the data supporting endoscopic management for patients with LR-T1b EAC. Metastases rates in patients with HR-T1b EAC (3/40 [8%] during 23 months of follow-up) were at the lower side of the spectrum compared with existing endoscopic literature (ie, rates differ between 0% and 37% during 23-63 months of follow-up).[5,10-12] In comparison with our study, the previous reported studies focused on submucosal EACs only, whereas the current study also included intramucosal EAC with high-risk features. Furthermore, some studies included patients with a positive deep resection margin in their cohort, whereas this study only included tumor-negative deep resection margins. In addition, in most previous reported studies, metastases rates were analyzed for patients who underwent ER with or without subsequent surgery, whereas our study focused on the metastasis rate after ER during endoscopic follow-up. Our study partly overlaps with 2 previous reports from our group.[5,11]

An explanation for the observed low metastases rates of HR-T1b EACs in this study is that in contrast to previous surgical series, all T1b cancers had to be amendable to ER in the first place, ER had to result in negative deep resection margins, and staging after ER could not show (locoregional) metastases. In this regard, 5 patients who were found to have metastatic disease at baseline staging on EUS-FNA and/or PET-CT were excluded, resulting in a subgroup with a lower metastasis risk compared with surgical retrospective studies without a preselection excluding these high-risk cases. There was 1 HR-T1b patient with LNM found during subsequent surgery after radical ER for a baseline staged N0M0 EAC in this study.

Although we cannot compare the metastasis rate of HR-T1a patients with other studies, we found the annual metastasis rate of 6.9% (5/25 [20%]) to be surprisingly high, especially when compared with T1b cases in this cohort. Because this was unexpected, the T1a cases were reviewed by expert pathologists to confirm the diagnosis.

There is scarce knowledge regarding the individual histologic risk factors for metastases (ie, deep submucosal invasion, poor differentiation grade, LVI). One study assessed LNM rates in surgical specimens shortly after ER for HR-T1a EAC (of 5 patients, none had LNM).[19] The same study also analyzed patients with T1b EAC and poor differentiation grade or LVI, showing that, although not significant, the highest odds ratio for nodal involvement was for LVI (5.2) followed by poor differentiation grade (3.0), independent of invasion depth. A second study assessed clinical and histologic variables associated with survival of T1a and T1b EAC patients after endoscopic treatment *with or without subsequent esophagectomy*.[20] Patients with metastasis at baseline and positive resection margin were not excluded. Older age, deep margin involvement, and

TABLE 3. Histopathologic features of patients with metastasis detected during follow-up disaggregated per risk group (n =120)

	High-risk intramucosal tumor (n = 25)			Low-risk submucosal tumor (n = 55)	High-risk submucosal tumor (n = 40)			Total
Histopathologic risk factors	Grades 3/4 and LVI+	Grades 3/4	LVI+	Sm1	Sm1 and LVI+	Sm2/3 and grades 3/4	Sm2/3 and grades 3/4 and LVI+	
No. of patients with LNM+	1	1	0	1	1	0	0	4
No. of patients with LNM+ and DM+	1	1	1	0	0	1	1	5
Total no. of patients with metastases	2	2	1	1	1	1	1	9
	5/25 (20%)			1/55 (2%)		3/40 (8%)		9/120 (7.5%)
Total no. of patients with these high-risk factors	8/25	16/25	1/25	55/55	6/40	6/40	3/40	

LNM, Lymph node metastasis; *LVI*, lymphovascular invasion; DM, distant metastases.

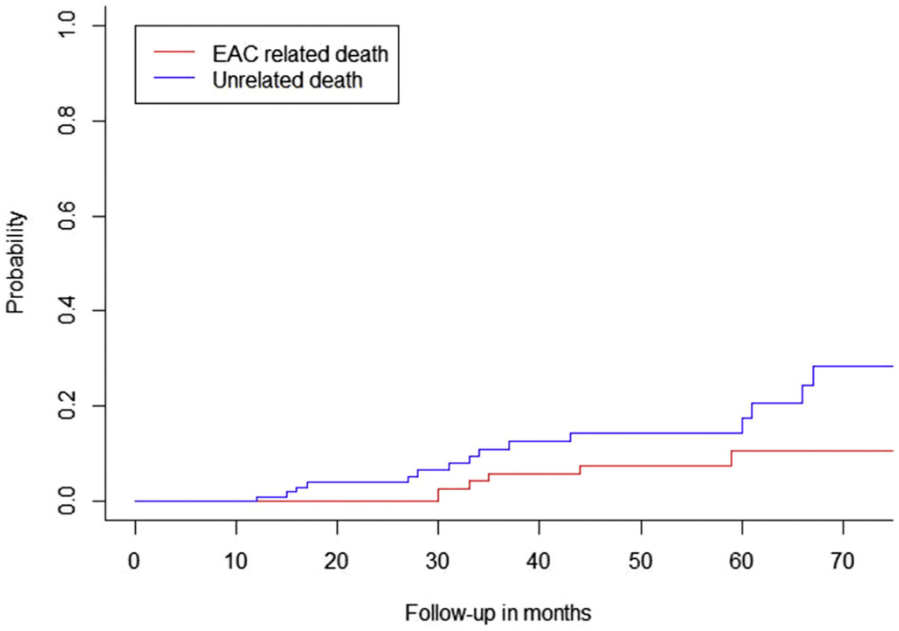


Figure 3. Cumulative incidence curves for EAC-related versus -unrelated death. *EAC*, Esophageal adenocarcinoma.

presence of LVI were associated with decreased (tumor-free) survival (hazard ratio, 1.67; 95% CI, 1-3; $P = .009$).[20]

To assess independent predictors of survival of endoscopic versus *surgically* treated T1b EAC patients, Otaki et al[21] built a Cox proportional hazards model and concluded that having 1 more high-risk histologic feature (ie, deep margin positivity, LVI, poor differentiation) was associated with decreased survival compared with the group without any high-risk features. The 5-year survival rate was higher in patients treated surgically. However, as illustrated by the differences in age and comorbidity score between both groups, patients with poorer life expectancy were followed endoscopically and were not treated with esophagectomy, leading to a biased comparison of overall survival in favor of surgery.[21] Another recently published study developed a prediction tool that estimated the risk of metastases in patients with T1b EAC, also combined with other histopathologic risk factors. The highest risk was found in EAC with LVI (subdistribution hazard ratio of 2.95).[22] In our study, 23 patients had LVI of which 5 (22%) were diagnosed with metastases. On the other hand, 4 of 97 patients (4%) without LVI developed metastases. These data seem to suggest that LVI and poor differentiation grade strongly affect the risk of metastasis. However, the number of events in our study was too low to further analyze the risk of LNM for

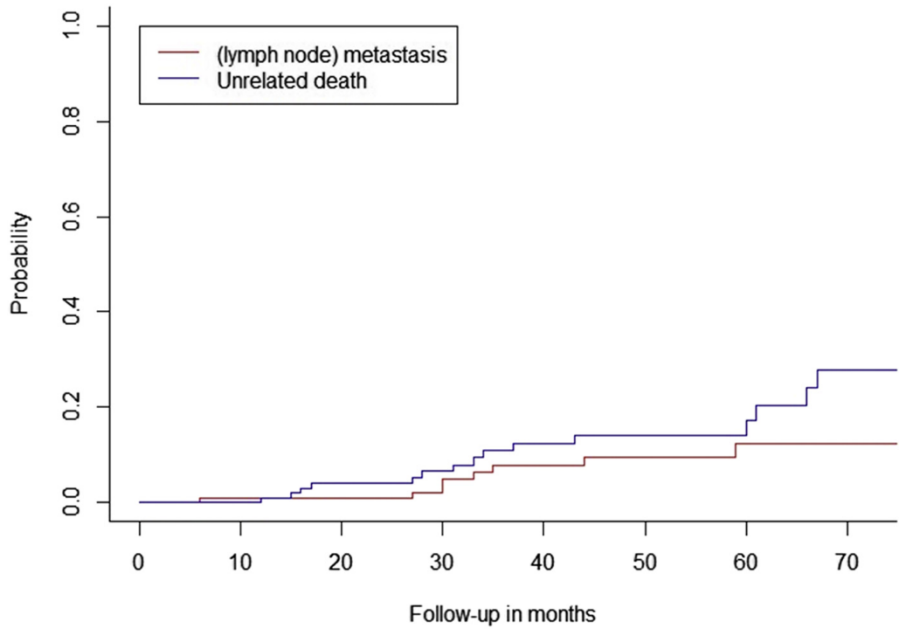


Figure 4. Cumulative incidence curves for lymph node metastases versus unrelated death.

individual histologic risk factors. In addition, comparing our study results with other studies is difficult because of the discrepancy in inclusion and exclusion criteria and study aims.

Several limitations of this study must be addressed. First, the retrospective setting of this study could have resulted in selection and information bias. In addition, this was a preselected cohort, in which frail and/or elderly patients with a higher likelihood of dying of causes not related to EAC were more likely to have been offered endoscopic follow-up instead of surgery. This may play a role in our higher EAC-nonrelated mortality rate (13%) versus EAC-related mortality (5.8%). Furthermore, different ER techniques were used during the years, such as endoscopic submucosal dissection, which has become more frequent from 2018 and onward. This may make the cohort less homogeneous.

Second, the baseline and follow-up strategy was heterogeneous because of a lack of strict guidelines and policy changes over time, and the median number of EUSs per patient was low (Supplementary Table 2, available online at www.giejournal.org). This may have led to an unjustified inclusion of patients who actually already had metastases at baseline. In addition, metastases that developed during follow-up may have been missed, because the median time to detection of metastases (27 months) was comparable with the overall median follow-up duration (29 months). Eventually, 9 patients were diagnosed with metastases during follow-up in our study. Because of heterogeneous follow-up, the moment of detection—and therefore the stage and the possibility to initiate curative treatment—may be less reliable. Nonetheless, we still found 4 of 9 patients who developed LNM only that were detected at curable stages. Two of these 4 patients died of treatment adverse events, which indicates the complex trade-off between these competing strategies. Despite a few patients in this cohort having distant metastases at detection, we believe the stringent follow-up after radical resection of early high-risk EAC, performed by dedicated endoscopists only and following strict guidelines when to conduct EUS-FNA, remains a valid strategy in a subset of patients.

Third, this cohort was preselected and contained small numbers per LNM risk group. Therefore, it is not suitable to perform comparative or predictive analysis on LNM regarding specific (histopathologic) features or types of (subsequent) endoscopic treatment in this study.

Fourth, histopathology review was only performed for HR-T1a cases. Finally, the median follow-up of 29 months (IQR, 15-48) is relatively short. Although studies have shown that most metastases are found during the first 2 years of follow-up, only 4 of 9 metastases in this study were detected within 24 months of follow-up.[9,23] As previously mentioned, this might be a consequence of heterogeneous follow-up.

Strong points of this study are the uniquely harmonized setting of the BECs with care provided by jointly trained endoscopists and pathologists, and registration in a uniform database. This study reflects current clinical practice because some patients with high-risk EAC are deemed unfit for surgery or prefer endoscopic management. These patients are offered endoscopic management after extensive informed consent by both the gastroenterologist and surgeon. This study adds value to the available literature because it describes the largest cohort of endoscopic

management outcomes in early high-risk EAC, including HR-T1a patients. It reflects a *clean* cohort of patients who underwent *radical* ER with subsequent endoscopic follow-up, with a rather long median follow-up duration after treatment. In comparison with other studies assessing metastases in high-risk EAC, the number of included patients is reasonably large.

Our study provides additional data regarding metastasis risk during endoscopic follow-up of patients with early EAC with histologic risk factors. Whereas the observed annual metastasis rate for HR-T1b EAC (3.0%) is somewhat lower than expected in comparison with previous reported percentages, the observed annual metastasis risk of 6.9% for HR-T1a EAC is new and worrisome. Our findings and optimal management strategies for these patients warrant further prospective evaluation (PREFER study, NCT03222635).

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Abbreviations: BEC, Barrett Expert Center; CI, confidence interval; ER, endoscopic resection; EAC, esophageal adenocarcinoma; HR-T1a, high-risk intramucosal tumor; HR-T1b, high-risk submucosal tumor; LR-T1b, low-risk submucosal tumor; LNM, lymph node metastases; LVI, lymphovascular invasion; PET, positron emission tomography.

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APPENDIX

SUPPLEMENTARY TABLE 1. Overview of patients with metastases during follow-up (n = 9)

Patient no. and diagnosis	LR-T1b/HR-T1a / HR-T1b	Histopathology at baseline	EUS at baseline (y/n)	Imaging at baseline (y/n)	Follow-up policy	Timeline of endoscopic resection from LNM to DM (mo)	When and how detected	Location metastasis	Therapy	TNM stage	Final outcome
Patients with LNM (all negative deep resection margins at baseline)											
1. LNM+	LR-T1b	T1b sm1 grade 2 LVI–	Yes	Yes, PET-CT	EUS 6-monthly GDS 3-monthly	22	Regular follow-up EUS (FNA)	Truncal node mass	CRT and surgery	ypT0N0M0	Died after surgery because of adverse events (4 mo after surgery)
3. LNM+	HR-T1b	T1b sm1 grade 2 LVI +	Yes	No	EUS/GDS 3-monthly	6	Regular follow-up EUS (FNA)	1 mediastinal node	CRT and surgery	ypT1aN0M0	Successful CRT/surgery; +1 y after therapy
2. LNM+	HR-T1a	T1a m3 grade 2 LVI+	Yes	Yes, CT	EUS/GDS 3-monthly	27	Patient complaints (weight loss, hoarseness) > CT	1 mediastinal node	CRT	ypT0N1M0	Successful CRT; +2 y after therapy
4. LNM+	HR-T1a	T1a m3 grade 3 LVI–	Yes	Yes, CT	GDS 3-monthly EUS only 2 times (baseline and discovery LNM)	41	Planned EUS (FNA) after magnetic resonance imaging liver for other reasons	1 mediastinal node	CRT	pT0N1M0	Died 4 days after last radiation therapy (complicated course with radiation pneumonitis)
Patients with DM											
5. LNM/DM+	HR-T1a	T1a m3 grade 2 LVI+	Yes	No	GDS annually	86	Patient complaints (icterus, weight loss) > CT and liver biopsy	Multiple organs (liver, bones, lungs, omentum)	Palliative care	pT0N2M1	Died
6. LNM/DM+	HR-T1a	T1a m3 grade 2 LVI +	Yes	Yes, PET-CT	EUS/GDS 3-monthly	31	Regular follow-up EUS (FNA) and CT	Liver	Palliative care	pT0N1M1	Died
7. LNM/DM+	HR-T1a	T1a m2 grade 3 LVI–	Yes	Yes, CT	EUS/GDS 3-monthly	23	Patient complaints (weight loss and abdominal pain) > PET-CT	Liver	Palliative care	pT0N1M1	Died

(*continued on the next page*)

SUPPLEMENTARY TABLE 1. Continued

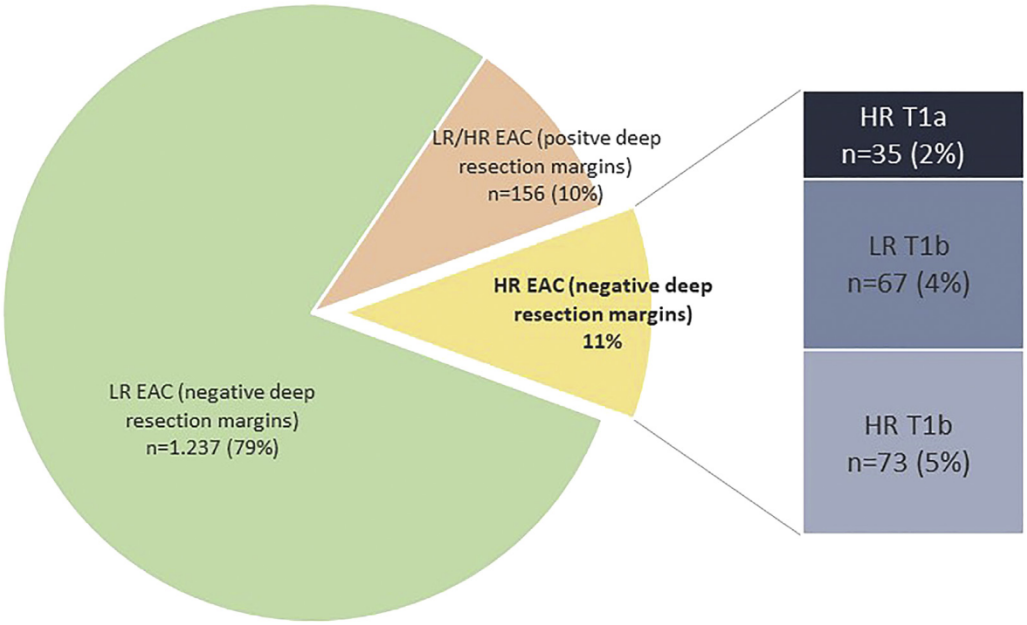
Patient no. and diagnosis	LR-T1b/ HR-T1a / HR-T1b	Histopathology at baseline	EUS at baseline (y/n)	Imaging at baseline (y/n)	Follow-up policy	Timeline of endoscopic resection from LNM to DM (mo)	When and how detected	Location metastasis	Therapy	TNM stage	Final outcome
8. LNM/ DM+	HR-T1b	T1b sm2/3 grade 3 LVI+	Yes	Yes, CT	EUS/GDS 3-monthly	34	Patient complaints (ileus, ascites) > CT	Omentum	Palliative care	pT0N1M1	Died
9. LNM/ DM+	HR-T1b	T1b sm2 grade 3 LVI–	Yes	Yes, CT	EUS/GDS 3-monthly	24	Regular follow-up EUS (FNA) + CT	First mediastinal nodes, later DM in lungs	CRT in 2017; 2 y after CRT: lung metastasis found on follow-up CT > palliative care	ypT0N2M1 (2019)	Died

HR-T1a, High-risk intramucosal tumor; *HR-T1b*, high-risk submucosal tumor; *LR-T1b*, low-risk submucosal tumor; *LNM*, lymph node metastasis; *LVI*, lymphovascular invasion; *PET*, positron emission tomography; *DM*, distant metastases; *GDS*, gastroduodenoscopy; *CRT*, chemoradiotherapy.

SUPPLEMENTARY TABLE 2. Baseline staging examinations per histopathologic risk group

	High-risk intramucosal tumor (n = 25)	Low-risk submucosal tumor (n = 55)	High-risk submucosal tumor (n = 40)
Patients with baseline EUS + CT	13 (52)	21 (38)	33 (82)
Patients with baseline EUS only	4 (16)	11 (20)	6 (15)
Patients with baseline CT only	—	4 (73)	1 (3)
Total	17 (68)	36 (65)	40 (100)

Values are n (%). —, No patients in this risk group with baseline CT only.



Supplementary Figure 1. Barrett Expert Center patient population (2008-2019). *EAC*, Esophageal adenocarcinoma; *T1b LR,* submucosal tumor with superficial invasion in the submucosa (<500 μm; sm1), well to moderately differentiated, without lymphovascular invasion; *T1b HR*, submucosal tumor with either deep invasion in the submucosa (≥500 μm; sm2/3), and/or poor differentiation grade, and/or lymphovascular invasion presence; *T1a HR*, intramucosal tumor with high-risk histopathologic features such as lymphovascular invasion or poor differentiation;