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Outcomes after radical endoscopic resection of high-risk T1 esophageal adenocarcinoma: an international multicenter retrospective cohort study

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Methods

We identified patients who underwent radical ER (tumor-negative deep margin) of high-risk T1 EAC, followed by surgery or endoscopic surveillance, between 2008-2019 across 11 international centers.

Results

In total, 106 patients (86 men, 70 ±11 years) were included. Of these, 26 patients (64 ±11 yrs) underwent additional surgery, with residual T1 EAC in 5 (19%) and LNM in 2 (8%) cases. After median 47 (IQR 32-79) months follow-up, 2/26 (8%) developed LNM/distant metastasis (DM), with 1 (4%) EAC-related death. There was 1/26 (4%) unrelated death and 4/26 (15%) were lost to

follow-up.
Eighty patients (71 ±9 yrs) entered endoscopic surveillance. Over 46 (IQR 25-59) months follow-up, 5/80 (6%) developed LNM/DM, with 4/80 (5%) EAC-related deaths. There were 15/80 (19%) unrelated deaths, and 10/80 (13%) were lost to follow-up. Overall rates during follow-up were 6% (95% CI 2-12) for LNM, 7% (95% CI 3-13) for LNM/DM, 5% (95% CI 2-11) for EAC-related mortality, and 20% (95% CI 13-29) for overall mortality.

Conclusion
Our findings present low rates of LNM after radical ER of high-risk T1 EAC, consistent with other endoscopy-focused studies. Post-surgical patients are still at risk for metastasis and disease-specific mortality. These results suggest that endoscopic surveillance is suitable for selected cases, but further prospective studies are needed to refine patient selection and confirm optimal outcomes.

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Table 1. Baseline endoscopic characteristics. ***ESD**: endoscopic submucosal dissection; **EMR**: endoscopic mucosal resection; **HR-T1a**: intramucosal EAC with poor-no differentiation and/or lympho-vascular invasion; **HR-T1b**: submucosal EAC with ≥ 500 µm invasion, poor-no differentiation and/or lympho-vascular invasion; **IQR**: interquartile range; **LR-T1b**: submucosal EAC with <500 µm invasion, well-moderate differentiation and no lympho-vascular invasion; **SD**: standard deviation.*

		HR-T1a	LR-T1b	HR-T1b
Patients		43	27	36
Barrett's Length, cm (Median, IQR)	*Circumferential* *Maximal*	1 (0-3)[1] 4 (2-7)[2]	3 (0-5) 5 (1-8)	1 (0-5)[5] 4 (1-6)[6]
Location Tumor	*Proximal esophagus (≤23cm)* *Mid esophagus (24-32cm)* *Distal esophagus (≥33cm)* *Gastroesophageal junction* *Missing*	- 4 (9%) 30 (70%) 9 (21%)	- 5 (19%) 18 (67%) 4 (15%)	- 5 (14%) 20 (56%) 10 (28%) 1 (3%)
Endoscopic Resection Technique	*EMR* *Multiband mucosectomy* *Endoscopic cap resection* *EMR technique unreported* *ESD*	30 (70%) 26 2 2 13 (30%)	18 (67%) 15 1 2 9 (33%)	14 (39%) 14 - - 22 (61%)
Tumor Infiltration Depth	*Mucosal* *M2* *M3* *M, exact depth unknown* *Submucosal* *Sm1* *Sm2-3* *Sm, exact depth unknown*	 4 (9%) 33 (77%) 6 (14%)	 27 (100%)	 11 (31%) 25 (69%) -
Tumor Differentiation Grade	*G1* *G2* *G3* *G4* *Missing*	2 (5%) 6 (15%) 31 (72%) 3 (7%) 1 (2%)	5 (19%) 22 (81%)	5 (14%) 15 (42%) 15 (42%) - 1 (3%)
Lympho-vascular Tumor Invasion	*Present* *Absent*	17 (40%) 26 (61%)	 27 (100%)	9 (25%) 27 (75%)
Tumor Diameter, mm (mm, SD)		15 (± 8)[3]	27 (± 23)[4]	20 (± 11)[7]

Retrospective high risk T1 EAC cohort

[1]Missing, n=2 (5%)
[2]Missing, n=1 (2%)
[3]Missing, n=7 (16%)
[4]Missing, n=11 (41%)
[5]Missing, n=2 (6%)
[6]Missing, n=2 (6%)
[7]Missing, n=16 (43%)

Table 2. Overview of patients in follow-up, categorized per risk group. ***95%CI****: 95% confidence interval;* ***HR-T1a****: intramucosal EAC with poor-no differentiation and/or lympho-vascular invasion;* ***HR-T1b****: submucosal EAC with ≥ 500 µm invasion, poor-no differentiation and/or lympho-vascular invasion;* ***IQR****: interquartile range;* ***N****: number of patients;* ***NA****: not applicable;* ***LR-T1b****: submucosal EAC with <500 µm invasion, well-moderate differentiation and no lympho-vascular invasion;* ***mo****: months.*

Patients	Duration of Follow-Up[1], Months (IQR)	Diagnosis of Metastatic Disease, N (% [95%CI])	Annual Risk Of Metastasis During Follow-up, % [95%CI]	Time To Metastasis[2], Months (IQR)	Disease-Specific Death During Follow-up, N (% [95%CI])
All (N=106)	47 (27-63)	9 (8% [4-16])	2.2% [1.0-4.2]	29 (12-38)	5 (5% [2-11])
HR-T1a (N=43)	52 (38-65)	4[2] (9% [3-22])	2.2% [0.6-5.6]	12 (NA)	3 (7% [1-19])
LR-T1b (N=27)	50 (29-51)	1 (4% [0.1-19])	0.9% [0.02-4.9]	17 (NA)	1 (4% [0.1-19])
HR-T1b (N=36)	36 (23-51)	4[2] (11% [3-26])	3.9% [1.0-9.6]	33 (NA)	1 (3% [0.1-15])

[1]After initial endoscopic resection

[2]One case diagnosed in esophagectomy specimen

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Keywords:
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Author contributions:
M.W. Chan: Drafting of the manuscript, analyzing of data, and final approval of the version to be published; R.E. Pouw: Supervising of the project, critical revision of the manuscript for important intellectual content, and final approval of the version to be published; All authors contributed data and provided critical feedback to the final manuscript.

Conflicts of interest:
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Abstract

Introduction

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Methods

We identified patients who underwent radical ER (tumor-negative deep margin) of high-risk T1 EAC, followed by surgery or endoscopic surveillance, between 2008-2019 across 11 international centers.

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In total, 106 patients (86 men, 70 ±11 years) were included. Of these, 26 patients (64 ±11 yrs) underwent additional surgery, with residual T1 EAC in 5 (19%) and LNM in 2 (8%) cases. After median 47 (IQR 32-79) months follow-up, 2/26 (8%) developed LNM/distant metastasis (DM), with 1 (4%) EAC-related death. There was 1/26 (4%) unrelated death and 4/26 (15%) were lost to follow-up. Eighty patients (71 ±9 yrs) entered endoscopic surveillance. Over 46 (IQR 25-59) months follow-up, 5/80 (6%) developed LNM/DM, with 4/80 (5%) EAC-related deaths. There were 15/80 (19%) unrelated deaths, and 10/80 (13%) were lost to follow-up. Overall rates during follow-up were 6% (95% CI 2-12) for LNM, 7% (95% CI 3-13) for LNM/DM, 5% (95% CI 2-11) for EAC-related mortality, and 20% (95% CI 13-29) for overall mortality.

Conclusion

Our findings present low rates of LNM after radical ER of high-risk T1 EAC, consistent with other endoscopy-focused studies. Post-surgical patients are still at risk for metastasis and disease-specific mortality. These results suggest that endoscopic surveillance is suitable for selected cases, but further prospective studies are needed to refine patient selection and confirm optimal outcomes.

Introduction

High-risk T1 esophageal adenocarcinoma (EAC) is defined as cancer invading the mucosa (T1a) with presence of poor tumor differentiation or lympho-vascular invasion (LVI), or cancer invading the submucosa (T1b) with or without these high-risk features. The conventional approach for managing high-risk T1N0M0 EAC has been surgical resection, involving esophagectomy and lymphadenectomy, to remove the cancer and potential lymph node metastases (LNM). However, esophagectomy carries considerable mortality (up to 6%) and morbidity rates (1.7-49.5%), and may result in lifelong functional complaints, even in high-volume centers. [1-3]

Recent advancements in endoscopic techniques have facilitated radical endoscopic resection (ER) of early esophageal cancers, even high-risk T1 EAC, using methods like endoscopic submucosal dissection (ESD), which has become even more efficient when combined with traction techniques. [4, 5] The optimal post-ER management for high-risk T1 EAC is still debated due to uncertain but increased risk of LNM. [6] LNM rates of 0-46% for T1 EAC have prompted guidelines to recommend additional esophagectomy with lymph node resection. [7-9] However, a small number of studies exploring endoscopic surveillance as an alternative post-ER approach have demonstrated its feasibility and safety for selected patients with favorable tumor characteristics (<500µm invasion (sm1), no LVI, and well-to-moderate differentiation), particularly for those at high risk of surgical complications. [4, 10, 11] These endoscopy-focused publications report lower LNM rates for T1b EAC (0-16%), compared to earlier surgical series, though small cohort sizes and mostly retrospective designs may have introduced bias. Further research is needed to clarify LNM risk and management outcomes.

This study aimed to assess outcomes in a larger cohort of patients who, following radical ER for T1 EAC with at least one high-risk feature, underwent either surgical resection or entered endoscopic surveillance.

Methods

Study design

This was a retrospective multicenter study involving eleven tertiary referral centers in Europe and Australia, collaborating on large-scale studies on early Barrett's neoplasia management. The Institutional Review Board (IRB) of the Amsterdam University Medical Centers (AUMC) declared that the study registry was not subject to the Medical Research Involving Human Subjects Act, waiving the need for formal ethical review and patient consent. Each participating center's IRB reviewed and approved the protocol.

Study population

We identified patients who underwent ER for T1 EAC with at least one high-risk feature between January 2008 and December 2019. Cases were mostly extracted from existing databases, though one center conducted a manual search. Notably, not all centers had initiated EMR and ESD procedures by 2008.

Patients were included if they had a tumor-negative vertical (deep) resection margin (R0v). Tumor extension at the horizontal (lateral) margin was not considered an exclusion criterion, provided it was an endoscopic radical resection. We categorized cases into three histologic risk groups:

- High-risk T1a EAC (**HR-T1a**): mucosal EAC with poor-to-no differentiation (G3-4) and/or LVI;
- Low-risk T1b EAC (**LR-T1b**): submucosal EAC with superficial invasion (<500 µm; sm1), well-to-moderate differentiation (G1-2) and no LVI;
- High-risk T1b EAC (**HR-T1b**): submucosal EAC with deep invasion (≥500 µm; sm2-3), and/or G3-4, and/or LVI.

Exclusion criteria were: I) tumor-positive (R1v) or inconclusive vertical resection margin ; II) residual/metachronous tumor lesion ineligible for endoscopic re-treatment present at the first endoscopy following ER; III) baseline metastatic disease; IV) prior EAC treatment; V) use of chemo-/ radiotherapy; VI) no follow-up or management initiated; VII) unavailable follow-up data.

This study did not include patients from the prospective PREFER study (NCT03222635), or Dutch patients from prior studies on this topic. [12, 13] There is overlap with prior cohorts by *Graham et al*. [14] (n=8), and *Benech et al*. [15] and *Doumbe-Mandengue et al*. [16] (n=10), though our cohort has a longer follow-up period.

Endoscopic resection

ERs were conducted using cap- or band-assisted EMR techniques, or ESD by endoscopists with experience in managing Barrett's neoplasia (**Figure 1**).

Pathology assessment

ER specimens were assessed by experienced gastro-intestinal pathologists adhering to the seventh edition of the UICC TNM-classification. [17] For T1a tumors, a distinction was made between those invading the lamina propria (m2) and the muscularis mucosae (m3). T1b tumors were categorized by depth of submucosal invasion: <500µm (sm1) or ≥500µm (sm2-3). The ER was considered radical if the vertical margin was tumor-free (R0v). In this study, we re-evaluated the endoscopy and pathology reports of all cases with surgically staged T1 disease initially marked as ER R0v.

Staging examinations

During the inclusion period (2008-2019), staging and follow-up protocols for high-risk T1 EAC varied and included endoscopies (with or without endoscopic ultrasound (EUS)) and CT or PET-CT scans based on physician preference.

Post-ER management

Additional surgery

Surgical strategies, including minimally-invasive and open thoracolaparoscopic esophagectomies, were chosen based on tumor location and surgeon's preference, with lymph node resection documented in most cases. Following surgery, a new TNM staging was determined.

Endoscopic surveillance

Conducted at the original ER center, surveillance endoscopies were scheduled at the treating physician's discretion and included imaging (EUS, CT, and/or PET-CT) as needed.

Study endpoints

Primary endpoint: risk of LNM and distant metastases during follow-up. Secondary endpoints: rate of local recurrence requiring surgery in those under endoscopic surveillance, disease-specific, other-cause and overall mortalities during follow-up.

Data collection

Research fellows (MD) or nurses entered baseline and follow-up data on standardized forms in a joint online database (Castor EDC), with each institution maintaining a patient identification file. Missing data and illogical values were completed and corrected where possible. The database closed on July 25, 2023, with all authors reviewing and approving the final data.

Statistics

Statistical analysis was performed using IBM SPSS Statistics Version 28.0.1.1 and R Version 4.4.2. Descriptive statistics included mean with standard deviation (SD/±) for normally distributed variables, and median with interquartile range (IQR) for non-normal variables. Categorical variables are presented as counts with percentages. Exact 95% confidence intervals (CI) for proportions were calculated using the exact binomial test in R to account for non-normal distributions. . To compare subcohorts, in SPSS, the independent samples t-test was used for continuous variables, and the chi-squared test for categorical variables; Fisher's exact test when expected cell counts were <5. All tests were two-sided with a significance level of 0.05.

Follow-up duration was calculated from initial ER to last hospital contact, metastatic event, or death. Endoscopic follow-up was calculated from initial ER to last endoscopy. Kaplan-Meier was used for survival analysis, and the log-rank test tested for differences between subcohorts. Annual risk for recurrent disease was calculated by dividing the number of metastatic cases by total follow-up time in years.

Results

Patient cohort

Between January 2008 and December 2019, 242 patients underwent staging ER for high-risk T1 EAC in Barrett's esophagus, with 106 meeting inclusion criteria (86 men, mean age at time of ER 70 ±11 years). Baseline endoscopic characteristics are presented in **Table 1**. Exclusion details are in **Figure 2**. The excluded cases involved 6 surgical cases initially categorized and included as R0v ER. However, due to evidence of (residual) T1 EAC in the surgical specimen, we reassessed these cases and found clear arguments to register them as R1v or inconclusive, leading to their exclusion (see **Supplementary Table 1**).

Of the 106 patients, 26 (25%) underwent additional surgical resection following ER, while 80 (75%) entered endoscopic surveillance as they were deemed unfit for surgery (n=31), based on patient's preference (n=13) or local guidelines for low-risk T1b (n=20) (16 unknown). Patients in the endoscopic surveillance group (71 ±9 years) were older than those who underwent additional surgery (64 ±11 years) (*P* <.001). Endoscopic surveillance patients were also more frequently diagnosed with HR-T1a and LR-T1b (*P* <.001), with no significant difference in ASA-classification (*P* =.82).

Surgical treatment after endoscopic resection

26 patients (9 HR-T1a, 1 LR-T1b, 16 HR-T1b) underwent esophagectomy median 2 (IQR 1-3) months after ER. Procedures consisted of 14/26 (54%) minimally-invasive thoracolaparoscopic, 6/26 (23%) open transthoracic, 2/26 (8%) open transhiatal, and 1/26 (4%) minimally-invasive transhiatal esophagectomies (3 unknown). Surgical morbidity was 65% (95% CI 49-83) (n=17), with infection being the most common (n=13, 50%), followed by anastomotic leakage (n=3, 12%). The 30-day mortality was 0%.

In the esophagectomy specimens, invasive (residual) intra-luminal cancer was found in five patients (19%; 95% CI 7-39): 4 mucosal and 1 submucosal tumor. Nodal disease was found in two patients (8%; 95% CI 1-25), each with one positive lymph node, with a median of 22 (IQR 17-29) nodes resected. Post-surgical staging showed T0N0M0 (n=19), T1N0M0 (n=5) and T0N1M0 (n=2). Follow-up after surgery was a median of 47 (IQR 32-79) months.

Endoscopic surveillance after endoscopic resection

80 patients (34 HR-T1a, 26 LR-T1b, 20 HR-T1b) entered endoscopic surveillance, with a median of 7 (IQR 4-11) endoscopies over median 41 (IQR 20-59) months. EUS, CT-scan and PET-CT were infrequently performed (median 0; IQR 0-1). Total follow-up was 46 (IQR 25-59) months.

Metastatic disease

During follow-up

Seven out of 106 patients (7%; 95% CI 3-13) developed LNM and/or distant metastasis during follow-up, diagnosed after median 29 (IQR 12-38) months post-ER. The main patient outcomes are shown in **Figure 3**. 2/7 cases in the surgical group showed LNM at 9 and 28 months post-esophagectomy, with one also having distant metastasis. 4/7 patients in the endoscopic group developed LNM, with one simultaneously diagnosed with distant metastasis. The remaining 1/7 patient, under endoscopic surveillance, developed distant metastasis after 38 months. The overall rate of LNM was 6% (95% CI 2-12), and LNM and/or distant metastasis 7% (95% CI 3-13) over 47 (IQR 27-63) months of follow-up. Patient characteristics and subsequent treatment of metastatic disease are displayed in **Supplementary Table 2**.

Overall risk

Considering metastatic events following immediate surgery as well as during follow-up, metastatic rates were 9% (4/43; 95% CI 3-22) for HR-T1a with an annual risk of 2.2% (95% CI 0.6-5.6) during follow-up, 4% (1/27; 95% CI 0.1-19) for LR-T1b with an annual risk of 0.9% (95% CI 0.02-4.9), and 11% (4/36; 95% CI 3-26) for HR-T1b with an annual risk of 3.9% (95% CI 1.0-9.6). See **Table 2** for a detailed summary.

Local intraluminal recurrence

Two out of 80 patients (3%; 95% CI 0.3-9) in the endoscopic surveillance group required esophagectomy due to intraluminal recurrence during follow-up exceeding re-ER limits, with post-surgical diagnoses of T1N0M0 and T3N0M0.

Mortality

During follow-up, five of 106 patients died from EAC-related causes (1 in the surgery group [4%; 95% CI 0.1-20] and 4 in the endoscopic group [5%; 95% CI 1-12]), resulting in a disease-specific mortality rate of 5% (95% CI 2-11).

16 out of 106 patients died of non-EAC-related causes (1 in the surgery group [4%; 95% CI 0.1-20] and 15 in the endoscopic group [19%; 95% CI 11-29]). Other-cause mortality was 15% (95% CI 9-23), with an overall mortality rate of 20% (95% CI 13-29).

Kaplan-Meier analysis (**Figure 4**) suggest a potential trend toward better overall survival in the surgery group following ER (log-rank test *P* =.069), considering all causes of death. Disease-specific mortality shows no significant difference between the two treatment subcohorts (*P* =.802).

Discussion

We conducted an international multicenter retrospective cohort study of 106 patients who underwent radical ER for high-risk T1 EAC. In this cohort, EMR was performed more frequently (58%) than ESD (42%), with ESD becoming more common later in the inclusion timeframe (2008-2019). The study encompasses outcomes from 26 patients who underwent additional surgery and 80 patients who entered endoscopic surveillance. Our cohort presents a considerable number of patients with relatively long follow-up periods. Within our study cohort, 29 had follow-up exceeding five years, and ten patients even more than eight years, contributing to a cumulative 440 person-years.

Our findings suggest low metastatic rates during follow-up. Notably, no significant difference in overall mortality rates was observed between surgical and endoscopic surveillance groups, suggesting that additional surgery as post-ER management does not offer survival advantage over conservative endoscopic management. However, the surgical group in our cohort was relatively small, and our results were not adjusted for age, pre-existing comorbidities, or tumor stage. These findings align with previous literature, showing that esophagectomy is not always a definitive curative approach for high-risk T1 EAC, and metastatic disease can still occur. *Westerterp et al.* analyzed 120 T1 EAC patients undergoing esophagectomy (with nodal involvement in 19/120), without chemo- and/or radiotherapy, revealing 18 cases of recurrent disease over a median 44 months follow-up, resulting in ten deaths. [18]. *Molena et al*. reported that among 23 T1b EAC patients undergoing esophagectomy (nodal involvement in 6/23 patients) with a median 37 months follow-up, one patient died of systemic recurrence. [19] *Schölvinck et al*. found two recurrences among 25 patients with high-risk T1b EAC who underwent esophagectomy (nodal involvement in 5/25 patients), over a 49-months follow-up, both fatal. [11] Also, in our cohort, surgery did not appear to improve disease-specific mortality, aligning with the findings of *Otaki et al*. [20] In their large multicenter study involving 141 T1b EAC patients, 68 underwent esophagectomy and 73 were managed endoscopically, indicating no correlation between surgery and improvement of disease-free survival. Importantly, both studies lack standardized follow-up protocols, limiting their conclusions. While in our cohort overall survival seemingly favored the surgical group (**Figure 4**), the older age of the endoscopic group limits direct comparison, as does the absence of a standardized follow-up regimen.

Existing literature suggests that submucosal tumor invasion is likely associated with increased metastatic risks, with HR-T1b tumors carrying a higher risk than LR-T1b tumors. However, our data,

albeit low inclusion numbers, reveal low annual metastatic rates across all three risk groups ranging from 0.8-3.1% (**Table 2**). Regarding T1a EAC specifically, the non-surgical management has long been relatively consensual due to the assumption of very low to non-existent risk of LNM (<1%). [10, 11, 21, 22] However, studies specifically addressing HR-T1a are limited. *Nieuwenhuis et al.* reported a surprisingly high annual risk of LNM (6.9%, 95% CI 3-15) in their cohort of 25 HR-T1a patients undergoing ER (R0v) and surveyed for 35 (IQR 22-53) months. [13] *Benech et al.* included 9 HR-T1a patients undergoing ER (R0v/R1v) who showed no metastatic disease during 35 (IQR 24-61) months follow-up. [15] In contrast, our larger HR-T1a subgroup (n=43) with longer follow-up (median 52 (IQR 37-65) months) exhibited an annual LNM risk of 2.2% (95% CI 0.6-5.6). Surprisingly, the metastatic rate during follow-up stood at 9% (95% CI 3-22), which exceeded our expectations. It is possible that the limited number of inclusions and the lack of histopathology review might account for this, although this data, like the study by *Nieuwenhuis et al.* suggests that mucosal cancers with high-risk features potentially carries a higher risk for metastasis than previously assumed.

Regarding metastatic risk of LR-T1b EAC, previous endoscopic cohort studies focusing on the prolonged outcomes of this patient group have reported rates ranging between 0-2%.[11, 21, 23, 24] Our present analysis echoes these findings, demonstrating a similarly low annual risk of 0.9% (95% CI 0.02-4.9) within this patient group. Although the observed metastatic rate during follow-up might appear relatively high at 4% (95% CI 0.1-19), this assessment is most likely due to the small inclusion size (n=27). Concurrently, despite their limited cohort sizes and retrospective nature, an increasing number of endoscopy-focused studies report relatively low metastatic rates for HR-T1b, ranging from 0-16%. [10, 11, 21, 23, 24] Our findings regarding this patient subgroup align with these recent studies, displaying an annual risk of 3.9% (95% CI 1.0-9.6), which, although relatively low, exceeds the annual risks observed in our HR-T1a and LR-T1b subcohorts, as anticipated. The metastatic rate of 11% (95% CI 3-26), based on a small inclusion number (n=36), also falls within the anticipated range reported in the endoscopy-focused studies. *Gotink et al.* recently published a cohort study comprising 248 T1b EAC patients who underwent ER and/or surgery, assessing LNM presence in surgical resection specimens and during clinical follow-up. [12] In their cohort, one-third of patients experienced metastases within five years. Their scoring system, considering submucosal invasion depth, LVI and tumor size, estimates a possible high metastatic risk of between 5.9-70.1% for T1b EAC. While we do advocate for a personalized risk model to advance personalized care, there are important limitations to their study design, such as the retrospective design covering mostly historical cases (1986-2016), handling of samples (lack of additional slide preparation in surgical specimens and no additional immunohistochemical staining). Moreover, the model relies predominantly on surgical data and may not be directly applicable to patients who underwent ER. Therefore, using these data for therapeutic decision-making is in our opinion not appropriate without external validation of the model in endoscopically treated patients.

The risk of metastatic disease in high-risk T1 EAC has been reported as high as 46% in literature. [7-9] Our rates, aligned with recent endoscopy-focused studies and involving extended follow-up durations, fall within the lower end of this spectrum, indicating low annual recurrence rates during follow-up. The discrepancy between surgical and endoscopy-focused studies may be attributed to differences in handling and processing surgical specimens versus ER specimens for pathological diagnosis. Surgical specimens are cut at wider intervals, while ER specimens are fully embedded, raising the risk of underdiagnosis in surgical specimens. Additionally, advances in endoscopic imaging nowadays allow

detection of more subtle high-risk T1 lesions, which are then treated with ER. These subtle high-risk T1 lesions may have different malignant potential compared to more prominent high-risk T1 lesions historically treated with surgery.

Furthermore, within our study, the extensive reassessment of 11 surgically staged T1 EAC cases initially registered as R0v in prior ER revealed the majority (6 of 11 cases) mislabeled as R0v ER in local registries. An in-depth reassessment of for each case highlighted diverse reasons to re-classification as R1v or inconclusive, based on pathology reports unable to confirm tumor-free vertical margins, endoscopy reports indicating metachronous lesion, or incomplete lifting during the ER , preventing radical resection. These findings challenge previous retrospective studies that failed to thoroughly investigate such cases, thereby potentially missing misclassifications that may have contributed to higher reported rates of LNM.

This study has several key limitations. First, its retrospective design introduces potential selection and information biases, compromising the robustness of our findings. Second, there was no standardized baseline staging or follow-up protocols. Inconsistent utilization of EUS for LNM screening, coupled with infrequent imaging for distant metastasis assessment prior to initiating follow-up, could mean some patients already had baseline metastatic disease. Similarly, follow-up metastatic disease may have been undetected due to low frequencies of follow-up imaging, including EUS. Incorporating more rigorous follow-up visits with increased imaging examinations could potentially have identified metastatic disease at earlier, curable stages. Third, although the overall study population was substantial, the smaller subgroup sizes limited comprehensive comparative or predictive assessments for metastatic risk. Moreover, patients who underwent direct surgery without prior ER were not included, potentially skewing metastatic risk. Fourth, central pathology review was performed on only selected five cases (see **Supplementary Table 1**). Fifth, the retrospective nature limited our ability to stratify mortality by pre-existing clinical factors.

Strengths of our study encompass its large, multi-center cohort derived from eleven tertiary-referral centers, making it, to our knowledge, center-wise the largest study on T1 EAC metastatic risk after ER. By including both surgery and endoscopic surveillance patients, it reflects real-world clinical practices where nonsurgical candidates often receive endoscopic surveillance, enhancing the study's applicability. Additionally, the study uniquely focused on a well-defined cohort of high-risk T1 EAC patients who underwent radical ER, excluding R1v and inconclusive resections after thorough reexamination of doubtful surgically staged T1 cases. The extensive median follow-up durations of 47 and 46 months strengthen the validity of our findings. While extended follow-up could potentially alter metastatic rates, this seems improbable given the median post-ER time to diagnosing metastatic disease of 29 (IQR 12-38) months. Prior studies also indicate metastasis appear within two years post-ER. [12, 25]

In summary, our study underscores the feasibility of a conservative, organ-preserving, endoscopic surveillance approach after radical ER for high-risk T1 EAC as a valid alternative to surgical resection, in selected patients without baseline signs of residual cancer or metastatic disease. Our findings emphasize the need for reevaluating existing tumor risk factors to enhance risk stratification. Annual metastasis risks were low, but not negligible across all three risk groups, which is consistent with recent endoscopy-focused studies with low metastatic incidences in high-risk T1 EAC. Nonetheless, robust

prospective data with standardized protocols and prolonged follow-up (PREFER study; NCT03222635) are requisite to ascertain the optimal management strategy and refine guidelines for treating individuals with high-risk T1 EAC.

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Figure legend

Figure 1. Endoscopic images of a high-risk T1b lesion removed with ESD, in an 81-year old patient with significant co-morbidity, who entered endoscopic surveillance post-ER. A. Paris type 0-Is lesion of 25mm in diameter within a Barrett esophagus, delineated with electrocoagulation marks for endoscopic submucosal dissection (ESD); **B.** Mucosal incision at the oral side of the lesion; **C.** Signs of deep submucosal invasion encountered during submucosal dissection; **D, E:** Wound after endoscopic radical resection of the lesion. Histology showed a radically resected (R0), poorly differentiated (G3) esophageal adenocarcinoma, invading into the submucosa over 2mm (sm3), with signs of lymphovascular invasion; **F.** ESD scar healed with squamous mucosal at the restaging endoscopy 8 weeks after ESD.

Figure 2. Flow of patient selection. 242 patients underwent ER for high-risk T1 EAC in Barrett's esophagus, of which 106 met the inclusion criteria. ***EAC**: esophageal adenocarcinoma; **ER**: endoscopic resection; **FU**: follow-up; **G**: tumor differentiation grade, **high-risk**: presence of submucosal infiltration, poor differentiation and/or lympho-vascular invasion; **HR-T1a**: intramucosal EAC with poor-no differentiation and/or lympho-vascular invasion; **HR-T1b**: submucosal EAC with ≥ 500 µm invasion, poor-no differentiation and/or lympho-vascular invasion **LR-T1b**: submucosal EAC with <500 µm invasion, well-moderate differentiation and no lympho-vascular invasion; **LVI**: lympho-vascular invasion; **R1v**: tumor-positive vertical endoscopic resection margin.*

Figure 3. Flow diagram depicting the main follow-up outcomes. Of 106 patients included, 26 underwent additional surgery and 80 entered endoscopic surveillance. ***DM:** distant metastasis; **EAC**: esophageal adenocarcinoma; **ER**: endoscopic resection; **FU**: follow-up; **LNM**: lymph node metastasis.*

Figure 4. Kaplan-Meier survival curves. A. Overall survival; no significant difference between the two subgroups (log-rank test, *P* = .069). **B.** Disease-specific survival; no significant difference between the two subgroups (*P* = .802). ***ER**: (initial) endoscopic resection procedure*

Supplementary Table 1. Following the exclusion of patients at baseline as per the criteria, 11 patients were identified with surgically staged T1 EAC (despite initially classified as radical ER, R0v). These cases underwent comprehensive reassessment through retrievable endoscopy, surgery, and pathology reports, of which five cases underwent additional pathological revision. Case-specific details are listed. The highlighted information reports an upstaged diagnosis of the deep endoscopic resection margin. ***ESD**: endoscopic submucosal dissection; **EMR**: endoscopic mucosal resection; **ER**: endoscopic resection; **G**: tumor differentiation grade, **LVI**: lympho-vascular invasion; **m**: mucosal infiltration; **R0v**: tumor-free vertical endoscopic resection margin; **R1v**: tumor-positive vertical endoscopic resection margin; **sm**: submucosal infiltration.*

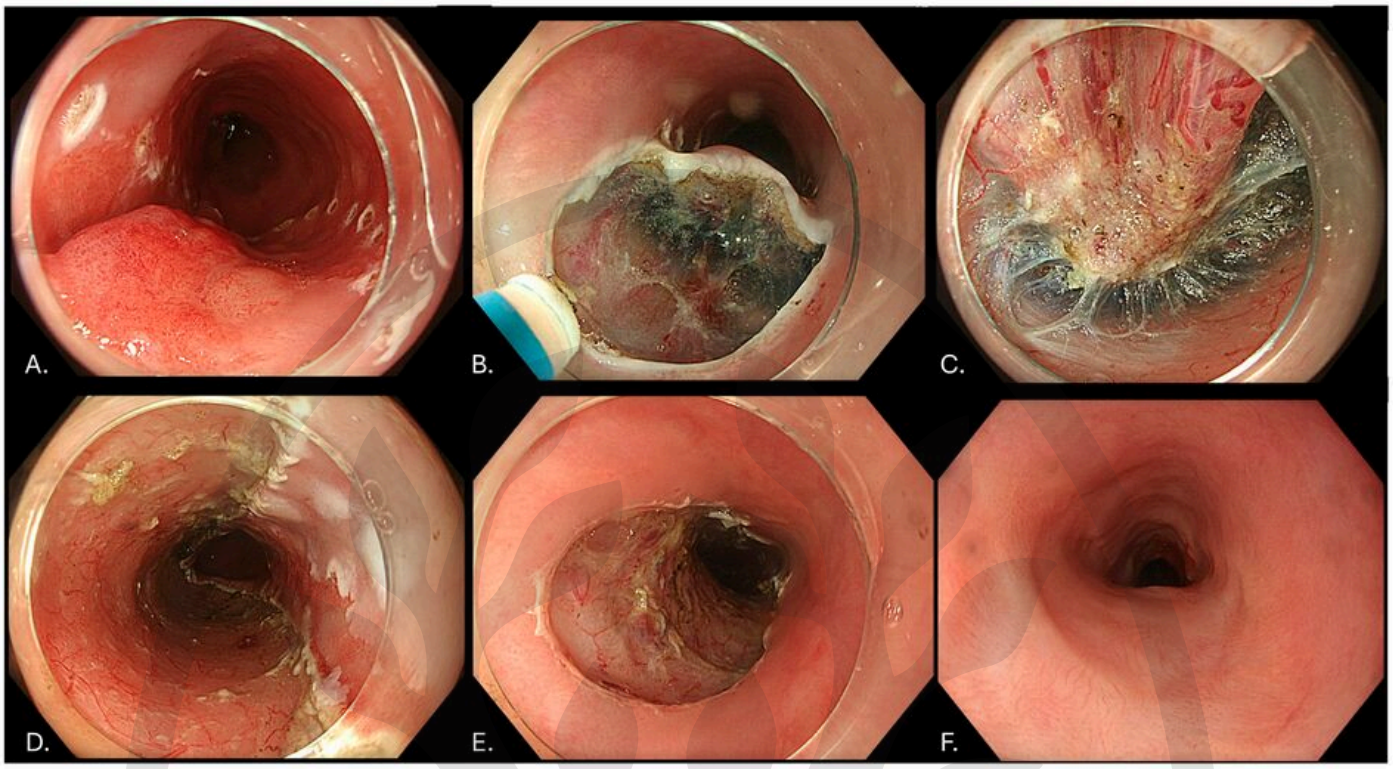
Patients	Initial ER Diagnosis	Surgical TNM Stage	Acquired Information After Data Verification	ER Pathology After Pathology Revision	Patient Selection	Patient Outcome After Follow-up
1	T1sm1, G3, LVI+, R0v	T1bN0 M0	**Endoscopy report of ER procedure described incomplete resection (R1v).** .	-	Excluded	Recurrence-free, alive.
2	T1sm1, G3, no LVI, R0v	T1aN0 M0	**Pathology report of ER specimen described inconclusive ER margin.**	-	Excluded	Recurrence-free, alive.
3	T1sm1, G2, LVI+, R0v	T1bN1 M0	**Pathology report of ER specimen described inconclusive ER margin.**	-	Excluded	**Metastatic disease, EAC death.**
4	T1sm1, G3, no LVI, R0v	T1bN0 M0	Pathology report of ER specimen described radicality of <1mm to ER margin.	**Diagnosis of tumor-positive ER margin (R1v).**	Excluded	Recurrence-free until lost to follow-up.
5	T1sm3, G3, no LVI, R0v	T1aN0 M0	Pathology report of ER specimen described radicality of <1mm to ER margin.	**Diagnosis of tumor-positive ER margin (R1v).**	Excluded	Recurrence-free, alive.
6	T1sm3, G2, no LVI, R0v	T1bN0 M0	Pathology report of ER specimen described radicality of <1mm to ER margin.	**Diagnosis of tumor-positive ER margin (R1v).**	Excluded	Recurrence-free, alive.
7	T1m3, G3, LVI+, R0v	T1aN0 M0	All reports described tumor-free ER margin (R0v).	Tumor-free ER margin confirmed (R0v).	Remained in study cohort	Recurrence-free, alive.
8	T1m3, G1, LVI+, R0v	T1aN0 M0	Pathology reports irretrievable.	Tumor-free ER margin confirmed (R0v).	Remained in study cohort	Recurrence-free, non-EAC death.
9	T1sm1, G3, LVI+, R0v	T1aN0 M0	ER pathology report described radicality of 0.2mm to ER margin.	-	Remained in study cohort	Recurrence-free, alive.
10	T1m3, G3, no LVI, R0v	T1aN0 M0	ER pathology report described radicality of 0.3mm to ER margin.	-	Remained in study cohort	Recurrence-free, alive.
11	T1m2, G4, LVI+, R0v	T1aN0 M0	ER pathology report described tumor-positivity in some ER fragments, but insufficient to alter R0v status.	-	Remained in study cohort	**Metastatic disease, EAC death.**

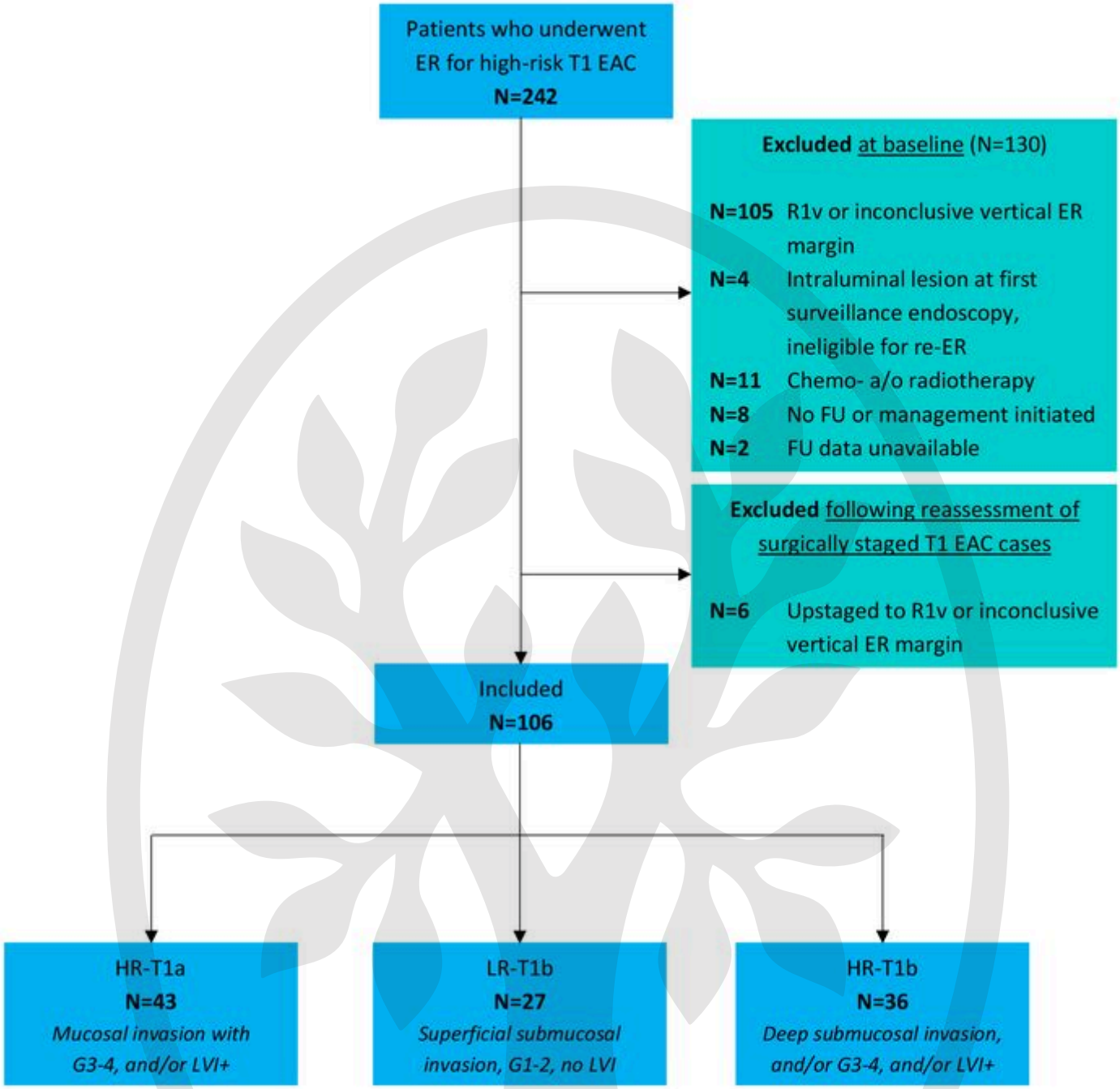
Supplementary Table 2. Patients that developed metastatic disease during follow-up. ***ASA:*** *American Society of Anesthesiologists;* ***CRT:*** *chemoradiotherapy;* ***EAC:*** *esophageal adenocarcinoma;* ***ER****: (initial) endoscopic resection procedure;* ***FU****: follow-up;* ***G****: tumor differentiation grade,* ***HR-T1a****: intramucosal EAC with poor-no differentiation and/or lympho-vascular invasion;* ***HR-T1b****: submucosal EAC with ≥ 500 µm invasion, poor-no differentiation and/or lympho-vascular invasion;* ***LNM****: lymph node metastasis;* ***LR-T1b****: submucosal EAC with <500 µm invasion, well-moderate differentiation and no lympho-vascular invasion;* ***LVI****: lympho-vascular invasion;* ***m****: mucosal infiltration;* ***mo****; months;* ***NA****: not applicable;* ***sm****: submucosal infiltration.*

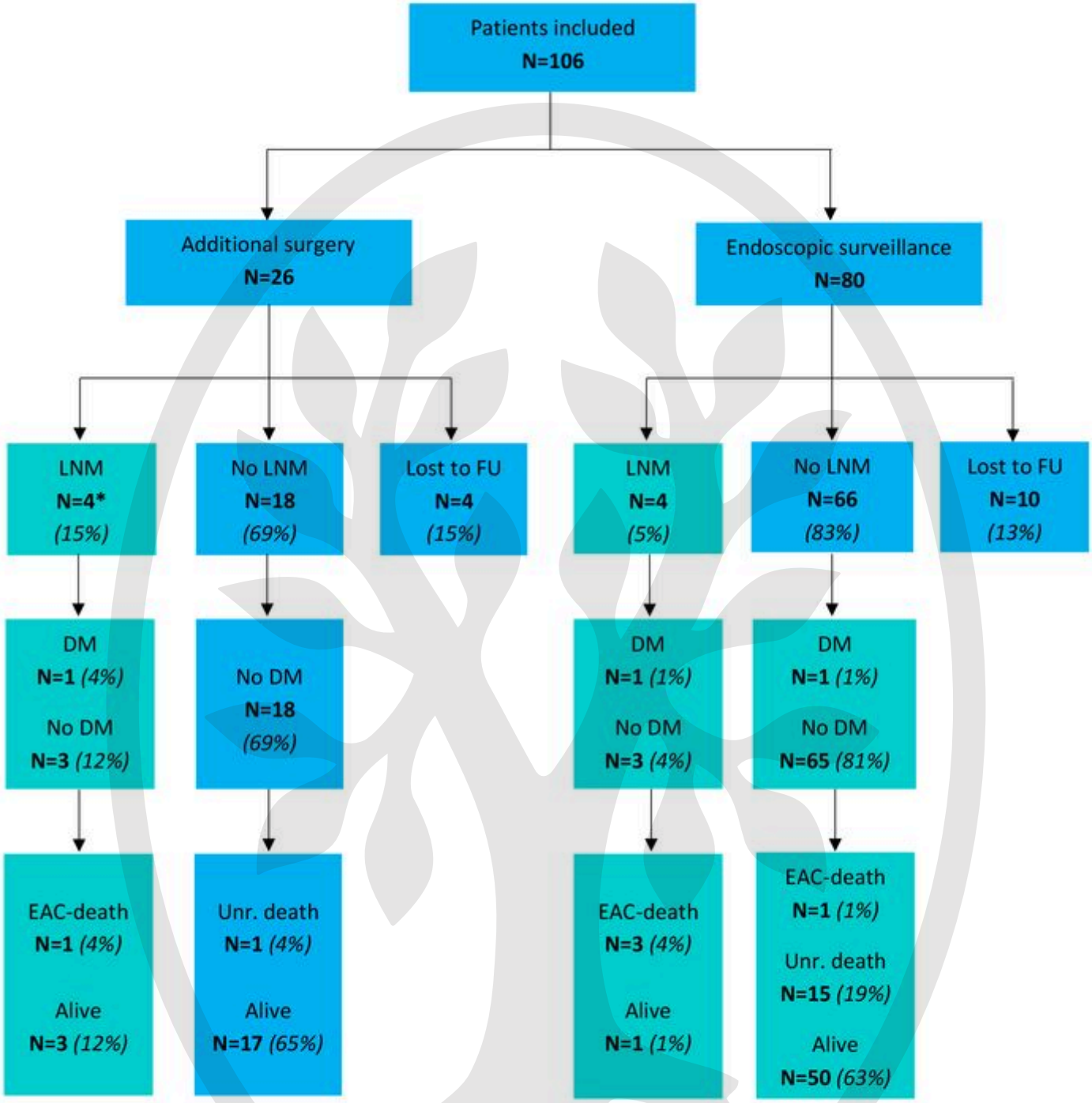
Case	Age at ER	ASA at ER	Baseline ER Diagnosis	Risk Group	Post-ER Policy	Type of Metastatic Disease	Follow-Up Till Diagnosis	Additional Therapy After Diagnosis	Outcome
1	62	II	T1sm1, G3, no LV	HR-T1b	Surgery	LNM (mediastinal) during FU	29 mo after ER/ 28 mo after surgery	CRT	Alive
2	56	III	T1m2, G4, LVI+	HR-T1a	Surgery	LNM and distant metastasis (bone) (simultaneously diagnosed) during FU	12 mo after ER/ 9 mo after surgery	Palliative care	**EAC-related death (20 mo after ER)**
3	69	III	T1sm2 G3, LVI+	HR-T1b	Endoscopic surveillance	LNM (truncal) during FU	39 mo after ER	CRT	Alive
4	66	II	T1sm1, G2, LVI+	HR-T1b	Endoscopic surveillance	LNM (truncal) during FU	33 mo after ER	Palliative care	**EAC-related death (37 mo after ER)**
5	78	II	T1m3, G3, no LVI	HR-T1a	Endoscopic surveillance	LNM (mediastinal) during FU	9 mo after ER	Palliative care	**EAC-related death (11 mo after ER)**
6	69	II	T1m3, G3, no LVI	HR-T1a	Endoscopic surveillance	Distant metastasis (liver) during FU	38 mo after ER	Palliative care	**EAC-related death (38 mo after ER)**
7	77	II	T1sm1, G2, no LVI	LR-T1b	Endoscopic surveillance	LNM and distant metastasis (simultaneously diagnosed, locations unknown) during FU	17 mo after ER	CRT	**EAC-related death (19 mo after ER)**

Supplementary Table 3. Each study center's contribution in the number of patients included for the analysis.

Study center	Number of study patients included
1	12 (11%)
2	5 (5%)
3	5 (5%)
4	6 (6%)
5	21 (20%)
6	2 (2%)
7	1 (1%)
8	11 (10%)
9	25 (24%)
10	8 (8%)
11	10 (9%)
Total	**106**

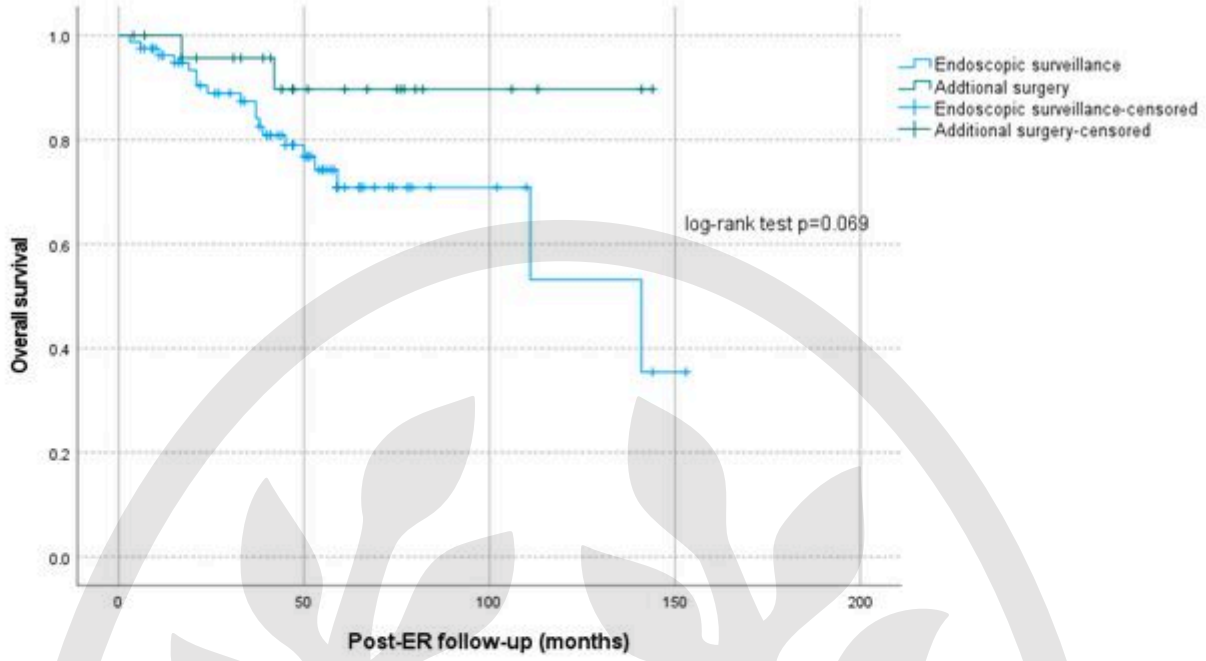






*2 of 4 cases diagnosed in the esophagectomy specimen

A.



B.