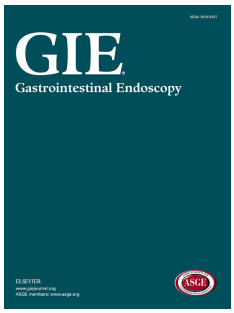

Endoscopic Submucosal Dissection for Early Esophageal Adenocarcinoma: Low Rates of Metastases in Mucosal Cancers with Poor Differentiation

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Endoscopic Submucosal Dissection for Early Esophageal Adenocarcinoma: Low Rates of Metastases in Mucosal Cancers with Poor Differentiation

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Keywords: esophageal adenocarcinoma, endoscopic resection, endoscopic submucosal dissection, poor differentiation, lymph node metastasis

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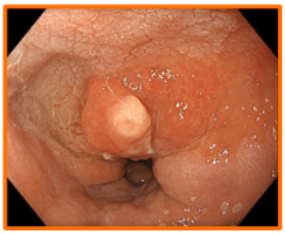
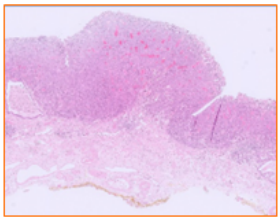
Helmut Messmann: analysis and interpretation of the data, critical revision of the article for important intellectual content; final approval of the article.

Endoscopic Submucosal Dissection (ESD) for Early Esophageal Adenocarcinoma (EAC): Low Rates of Metastases in Mucosal Cancers with Poor Differentiation (PD)

- 809 ESDs for EAC in 16 German centers
- 69/809 (8.5%) showed PD
- 40 patients were included (R0 resection and endoscopic follow-up)
- PD as single risk factor (group A: n=25)
- PD with additional risk factors (submucosal and/or lymphovascular invasion) (group B: n=15)





Key findings (group A versus group B):

- **Rate of metastasis:** 1/25 (4.0%; 95%CI 0.4-17.2) versus 3/15 (20.0%; 95%CI 6.0-44.4%)
- **Rate of EAC-associated deaths:** 1/25 (4%; 95%CI 0.4-17.2%) versus 3/15 (20%; 95%CI 6.0-44.4%)
- **Median follow-up:** 30 months (IQR 15-53).

During long-term follow-up the rate of metastases was 4% after endoscopic resection of poorly differentiated EACs without further risk factors (pT1a G3 L0 V0).

Endoscopic Submucosal Dissection for Early Esophageal Adenocarcinoma:

Low Rates of Metastases in Mucosal Cancers with Poor Differentiation

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Helmut Messmann: analysis and interpretation of the data, critical revision of the article for important intellectual content; final approval of the article.

Abstract

Background and aims: Endoscopic resection (ER) is accepted as standard treatment for intramucosal esophageal adenocarcinoma (EAC) with well or moderate differentiation. Poor differentiation (PD) is judged as a risk factor for lymph node metastasis (LNM) and surgery is recommended. However, the evidence for this recommendation is weak. Study aim was to analyze the clinical course of patients after ER of EAC with PD.

Patients and methods: Patients undergoing endoscopic submucosal dissection for EAC were included from 16 German centers. Inclusion criteria were PD in the resection specimen, R0 resection and endoscopic follow-up. Primary outcome was the metastasis rate during follow-up. Analysis was performed retrospectively in a prospectively collected database.

Results: 25 patients with PD as single risk factor (group A) and 15 patients with PD and additional risk factors (submucosal invasion and/or lymphovascular invasion) were included. The metastasis rate was was 1/25 (4.0%; 95%CI 0.4-17.2) in group A and 3/15 (20.0%; 95%CI 6.0-44.4%) in group B, respectively (p=0.293). The rate of EAC-associated deaths was 1/25 (4%; 95%CI 0.4-17.2%) versus 3/15 (20%; 95%CI 6.0-44.4%) in group B (p=0.293) while the overall death rate was 7/25 (28.0%; 95%CI 13.5-47.3%) versus 3/15 (20%; 95%CI 6.0-44.4%) (p=0.715). Median follow-up was 30 months (IQR 15-53).

Conclusions: During long-term follow-up the risk of metastasis is low after ER of mucosal EAC with PD as single risk factor. A conservative approach seems justified in this small patient group. However, the treatment strategy has to be determined on an individualized basis until further prospective data are available.

Introduction

The incidence of esophageal adenocarcinoma (EAC) is still rising with 85 700 cases reported for 2020 and an expected increase to 141 300 cases in 2040 worldwide. EAC has become the most frequent subtype of esophageal cancer in many western countries.[1] Endoscopic resection (ER) offers a minimally invasive curative treatment option when EAC is diagnosed in early stages without a risk of lymph node metastasis (LNM). Large studies showed excellent long-term results after ER of intramucosal EACs without further risk factors such as submucosal invasion (SM invasion), poor differentiation (PD) or lymphovascular invasion (LVI).[2] For such EACs the risk of LNM is negligible and current guidelines recommend ER as curative treatment of choice. [3,4,5] When histopathological low-risk factors are not fulfilled the risk of LNM has to be balanced against the mortality of surgical esophagectomy which ranges from 4.0% in high-volume centers to 11.4% in low-volume centers.[6] For early EACs with superficial SM invasion (≤500µm) without further risk factors small studies showed LNM in about 2% and ER with strict endoscopic follow-up can be considered as a treatment option.[3,4,7,8] Poor differentiation (PD) has been reported as a risk factor for LNM and surgical resection is recommended for lesions with PD today.[3,5] However, the frequency of PD in early EAC is low and the evidence for current treatment recommendations is weak.[2,9] Data on the clinical impact of PD in early EACs are scarce especially when PD is the single histologic risk factor after ER. The aim of this study was to assess the clinical outcome of patients after ER for early EACs with PD.

Patients and methods

Patients were included from the German ESD registry which included 457 patients who

underwent ESD for Barrett's neoplasia in 16 German referral centers from January 2017 to December 2020. The German ESD registry was initiated by the University Hospital of Augsburg and was approved by the ethics committee of the Ludwig-Maximilian-University Munich, Germany (study ID: DRKS00011781). Additionally, all patients who underwent ESD for Barrett's neoplasia from April 2008 to June 2023 at the Department of Gastroenterology, University Hospital of Augsburg, Germany, were screened. All patients undergoing ESD in the department are enrolled in a local database after informed consent prospectively. Patients were included in this analysis when PD was diagnosed histopathologically in the resection specimen. Data were analyzed retrospectively. The study was conducted in accordance with the principles of Good Clinical Practice (GCP) and the ethical guidelines of the 1975 Declaration of Helsinki.

Inclusion criteria

- EAC with PD in the resection specimen after ESD for Barrett´s neoplasia
- Written informed consent to the ESD procedure after detailed information about ESD and alternative treatment strategies
- Written informed consent to the enrolment in the database of the German ESD registry or in a local database at the University Hospital of Augsburg

Exclusion criteria

- EUS showing invasion depth >T1 and/or suspected LNM
- Additional surgery, radiotherapy or chemoradiation after ESD
- Concomitant malignant disease without curative treatment option

Patients with R1 resection at the VM were excluded from follow-up analysis. The remaining patients were categorized in two groups:

- “PD only”: PD without further high-risk risk criteria (pT1a, G3, L0, V0)
- “PD plus”: PD and additional high-risk criteria (SM invasion and/or LVI)

Patients with a follow-up period of more than six months were included and analyzed separately within the different groups.

Patients who underwent surgery were analyzed outside the follow-up analysis regarding LNM in the surgical specimen and surgery-associated mortality.

Outcome criteria

The primary outcome parameter was the rate of metastasis (LNM or distant metastasis) during follow-up. Secondary outcome parameters were overall survival, disease-free survival, and procedural characteristics (R0 resection rate, adverse events, additional endoscopic treatment after ESD).

Diagnostic workup and ESD procedure

Diagnostic endoscopy and the ESD procedure were performed at the different centers at the discretion of the local endoscopist. ESD was chosen when en bloc resection was unlikely using other resection techniques such as endoscopic mucosal resection (EMR) (e.g. in EACs >15mm or bulky lesions). The lesions morphology and the extent of the Barrett’s esophagus were described according to the Paris classification and the Prague classification.[10,11] There was no standard protocol for baseline staging prior or after ER. EUS, CT scans or further diagnostic measures were performed at the discretion of the endoscopist and according to the decision of the local multidisciplinary board. Information regarding baseline and follow-up examinations was obtained from

all centers retrospectively. Adverse events were defined as bleeding, perforation, stricture, or death.

Histopathological workup

Histopathologic evaluation of ER specimens was performed by pathologists at the different centers. All pathologists were experienced in Barrett's neoplasia. Specimens were fixed onto cork with needles, fixed with formalin and cut into parallel sections of 2 mm thickness or less. Routine staining was performed with Hematoxylin Eosin. Additional staining using immunohistochemistry for D2-40, Desmin or Smoothelin was performed individually.

The sizes of the specimen and the EAC were reported. Invasion depth was described as m1-m4 for mucosal lesions (m1 no invasion of the superficial muscularis mucosae, m2 infiltration of superficial muscularis mucosae, m3 infiltration of layer in between superficial and deep muscularis mucosae, m4 infiltration of deep muscularis mucosae).[12] For submucosal lesions the maximum depth of SM invasion was measured in µm. Presence or absence of LVI and R0 resection at the horizontal margin (HM) and the vertical margin (VM) were described. In one case who developed liver metastases next generation sequencing (NGS) was performed to compare the EAC with the metastases. Analysis was performed using Illumina Oncomine Focus Panel (52 genes, DNA and RNA).

Follow-up

In patients with complete eradication of the Barrett's metaplasia follow-up endoscopy was scheduled 3 to 6 months after ESD, 12 months after ESD and annually thereafter. In patients with residual non-neoplastic Barrett's epithelium endoscopic ablation was performed 3 to 6 months after ESD and was repeated every 3 to 6 months until the Barrett´s metaplasia was completely eradicated. Ablation techniques were

radiofrequency ablation (RFA) and argon plasma coagulation (APC). RFA or APC were used dependent on the area of residual Barrett´s (APC for small areas, RFA for large areas). The ablation strategy was not different between the different centers. During follow-up, biopsies were taken when residual or metachronous neoplasia was suspected macroscopically. Local recurrence was diagnosed when neoplasia was confirmed histopathologically at the initial resection site. When neoplasia was confirmed distant from the ESD scar, the lesion was judged as metachronic neoplasia. Local recurrences and metachronous neoplasia were treated at the discretion of the local endoscopist. Complete eradication of Barrett´s was defined as the absence of visible Barrett´s metaplasia after ESD or during follow-up. When the macroscopic appearance was unclear biopsies were taken to confirm the absence of residual Barrett´s epithelium.

EUS and CT scans were performed at the discretion of the local endoscopist taking the patient´s condition and therapy request into account.

Statistical analysis

Categorical variables are presented as absolute numbers and percentages. Continuous metrics are shown as medians and interquartile ranges (IQR). Categorical data were compared using the Fisher's exact test. Comparison of continuous data was performed using the Mann-Whitney-U test. To compare the overall survival distribution of the groups Kaplan-Meier analysis was used and log-rank analysis was performed. The significance level was set at 0.05. All calculations were performed using the SPSS (Statistical Package for Social Sciences) version 28.0 (IBM Crops, Armonk, NY, USA).

Results

Patient inclusion

From April 2008 to June 2023, 809 patients underwent ESD for Barrett's neoplasia. PD was diagnosed in the resection specimen of 69 patients (8.5%). 18/69 (26.1%) patients with R1 resection at the VM were excluded from further follow-up analysis. Further 11 patients showing R0 resection at the VM had to be excluded because of additional non-endoscopic treatment or missing follow-up data. The remaining 40 patients were included in the follow-up analysis study (Figure 1). 25/40 (62.5%) were stratified in the "PD only group" while 15/40 (37.5%) showed additional high-risk features.

Patients and lesions characteristics

Patients and lesions characteristics are summarized in table 1. High-risk features in the "PD plus group" were SM invasion without LVI in 10/15 (66.7%, SM invasion with additional LVI in 3/15 (20%) and LVI in mucosal lesions in 2/15 (13.3%). In cases with SM invasion invasion depth was >500µm in 10/13 (76.9%).

Procedure characteristics and adverse events

32/40 (80%) specimens showed R0 resection while the remaining 8/40 (20%) were diagnosed R1 at the HM (Table 1). Only two of these patients showed local recurrences at the resection scar during follow-up. In 30/40 (75%) and 32/40 (80%) EUS and/or CT scan were performed at baseline, respectively. Adverse events were not observed after ESD.

Additional treatment after ESD

In 11/40 (27%) complete eradication of the Barrett's metaplasia was achieved with ESD. In the remaining 29/40 patients (72.5%) with residual non-neoplastic Barrett's epithelium further endoscopic treatment was recommended (Table 1). In four of these

patients residual neoplasia was diagnosed or morphologically suspected during the first follow-up endoscopy and the residual Barrett's was removed completely by repeated endoscopic resection (ESD in two patients and EMR in another two). In 21 patients ablation was performed every 3 to six months after ESD (RFA alone in 7, RFA and APC in 6, APC alone in 8). With a mean number of 2.2 ablations (range 1-9) complete eradication of the Barrett's metaplasia could be achieved in 20/21 patients and ablation is still ongoing in the remaining one. When complete eradication of the Barrett's metaplasia was achieved, no recurrent metaplasia was diagnosed during further follow-up. No adverse events were observed after repeated endoscopoic resection or ablation. In four patients with residual Barrett's ablation was not performed due to patients refusal.

Follow-up

Median follow-up was 30 months (IQR 15-53) for all patients and did not differ between the "PD only" group (32 months; IQR 14-72) and the "PD plus" group (28 months; IQR 16-44) (p=804). Follow-up data are summarized in Table 2 and Figure 2.

Endoluminal recurrence

Local recurrence was diagnosed in 3/40 patients (7.5%; 95% CI 2.2-18.7%). As mentioned above, two local recurrences were diagnosed after R1 resection at the HM. In both patients biopsies from the scar had shown well-differentiated EAC three and six months after ESD, respectively. Both patients underwent repeated endoscopic resection (ESD and EMR in one case each). Histopathological diagnosis were well-differentiated mucosal EAC in one patient and non-neoplastic Barrett's metaplasia in the other one. The further course was uneventful in both patients. Another patient who

had refused further follow-up after R0 resection of an EAC with deep submucosal invasion and LVI presented with a local endoluminal recurrence, synchronous LNM and distant metastases 27 months after ESD. The patient was treated with best supportive care and died.

Two metachronous EACs were observed during follow-up (5.0%; 95%CI 1.1-15.1%). One of them was diagnosed in the PD only group two years after ESD and was successfully treated by repeated ESD. Histopathology confirmed R0 resection of a mucosal EAC with poor-differentiation (12mm in diameter; invasion depth m1 L0 V0). The initial extent of the Barrett's esophagus had been C9M9 and ablation had not been completed at that time. Another metachronous EAC was confirmed in the PD plus group 9 months after R0 resection of a SM invasive EAC and repeated ESD is scheduled. The Barrett's initial extent had been C3M4 and ablation was not completed so far.

In summary the rate of endoluminal recurrence was 5/40 (12.5%; 95%CI 4.9-25.2%).

Lymph node metastases and distant metastases

The rate of any metastasis was 1/25 (4.0%; 95%CI 0.4-17.2) in the PD only group and 3/15 (20.0%; 95%CI 6.0-44.4%) in the PD plus group, respectively (p=0.293) (Table 2).

LNM were detected in 0/25 patients in the PD only group (0%; 95%CI 0.0-9.5%) while the LNM rate was 1/15 in the PD plus group LNM (6.7%; 95%CI 0.7-27.2%). Diagnosis of LNM was made 18 months after ESD of an EAC with deep SM invasion >500µm (L0V0). Despite esophagectomy the patient developed metachronous liver and

pulmonary metastases 10 months later and died. The Kaplan-meier curve for the cumulative incidence of metastases is shown in Figure 3.

Distant metastases were observed in 1/25 patients in the PD only group (4.0%; 95% CI 0.4-17.2%). In this patient liver metastasis of a moderately differentiated adenocarcinoma were confirmed 65 months after ESD of an EAC 30mm in diameter. LNM or another cancer were not found, and the diagnosis of Cancer of Unknown Primary (CUP) was made because of the long interval after ESD. For the current analysis next generation sequencing was performed to compare the EAC with the metastases. However, due to insufficient quality of the extracted DNA and paucity of residual sample material, the NGS analyses could not successfully be performed. The Hematoxilyn & Eosin-based morphological features had to be compared for the final conclusion and could not rule out metastases of the EAC. Therefore, the case was judged as a recurrence retrospectively. The patient received palliative chemotherapy and died.

In the PD plus group 2/15 patients (13.3%) developed distant metastases during follow-up. In one patient pulmonary and liver metastasis were diagnosed 15 months after ESD of an EAC with deep SM invasion (L0V0). The patient received palliative chemotherapy and died. Another patient presented with adrenal gland metastasis and synchronous LNM 27 months after ESD. Additionally, a local endoluminal recurrence was seen (the patient is described above). He was treated with best supportive care and died.

Survival

10/40 patients (25.0%, 95% CI 13.6-39.8%) died during the study period. The overall death rate was 7/25 (28.0%; 95%CI 13.5-47.3%) in the PD only group and 3/15 (20%; 95%CI 6.0-44.4%) in the PD plus group (p=0.715).

Four deaths were related to recurrent EAC while six were related to other causes (cardiopulmonary disease n=3, other malignancy n=1, others n=2).

The rate of EAC-associated death was 1/25 (4%; 95%CI 0.4-17.2%) in the PD only group and 3/15 (20%; 95%CI 6.0-44.4%) in the PD plus group, respectively (p=0.293). Due to small patient numbers, the overall-death rate and the EAC-associated death rate showed no significant difference (Table 2). Figure 4 and Figure 5 show Kaplan-Meier curves for the overall survival and the disease-free survival, respectively.

Surgically treated patients

22/69 (31.9%) patients with PD in the ESD specimen underwent surgery (esophagectomy in 20 patients and Merendino's procedure in the remaining two). Surgery was performed in 14 patients with R1 resection (all lesions were pT1b cancers) and in eight patients with R0 resection (two patients with pT1a cancers and another six patients with pT1b cancers). The rate of LNM in surgical specimens was 0/2 (0%) for pT1a cancers and 4/20 (20.0%) for pT1b cancers. 3/22 (13.6%) patients who underwent surgery suffered fatal adverse events. All patients had been categorized ASA 3. In summary, in patients who underwent surgery LNM were not found in the "PD only" group but in 20% of the "PD plus" group. The surgical mortality was substantial in this preselected patient group (13.6%).

Discussion

ER is recommended for superficial EAC when histopathological features indicate a negligible risk of LNM. PD has been reported as a relevant risk factor for LNM and surgical resection has to be considered or is recommended today.[3-5] However, PD is a rare finding in ER specimens of EACs, data on the clinical course of these patients are scarce and the evidence for the current treatment recommendation is weak.[2,8]

In our large multicenter study, the rate of PD in endoscopically resected EACs was 8.5%. Previous studies reported lower rates of 5.4% and about 3% in ER specimens.[2,9]

After exclusion of patients with R1 resection at the VM and patients who underwent additional non-endoscopic treatment we included 40 patients with endoscopic follow-up. 25 patients with PD as a single high-risk criterium were stratified in a “PD only” group while while 15 patients with additional high-risk features (SM invasion and/or LVI) were stratified in a “PD plus” group. The “PD plus” group predominantly included SM invasive cancers (86.7%).

Only few studies report on EACs with PD as a single high-risk feature and their data are conflicting. A Dutch multicenter study included 16 patients with “PD only” and reported two cases with metastatic recurrence (12.5%) during a median follow-up of 27 months .[9] A recent multicenter study from the United States which included 45 pT1a EACs with PD and/or LVI showed similar results with a 11.1% rate of extra-esophageal metastasis during a longer median follow-up of 5.7 years. However, EACs with PD or LVI as single risk factor were not differentiated in this study.[13] In contrast, a multicenter study from France included 9 patients with pT1a EACs with PD and/or LVI but observed no recurrence (median follow-up 30 months) .[14] Surgical

data on the LNM rate in esophagectomy specimens of PD EACs are also conflicting. Newton et al identified PD as an independent predictor of LNM and reported on a LNM rate of 3/45 (6.7%) in poorly differentiated pT1a EACs (≥2cm in diameter).[15] A multicenter study from the US included 19 patients who underwent esophagectomy after ER of pT1a EACs. 4/19 (21%) were lesions with PD as single risk factor and no LNM was found in their esophagectomy specimen.[16] Leggett et al identified LVI and R1 resection at the VM but not PD as risk factors for mortality after ER of EACs.[17] A scoring system identified the grade of differentiation, LVI and the lesions size as predictive factors for LNM. In poorly differentiated pT1a lesions without LVI and ≤15mm in diameter, the risk for LNM metastasis was 2.6% compared to a 90-dmortality after esophagectomy of 4.6%.[18]

In our study, the rate of any extraesophageal metastasis during follow-up was 1/25 (4.0%; 95%CI 0.4-17.2) in the PD only group and 3/15 (20.0%; 95%CI 6.0-44.4%) in the PD plus group, respectively (p=0.293).

The substantial risk of metastasis in the “PD plus” group which included mainly pT1b cancers is in line with the published literature and supports the current guideline recommendations for additional surgery after ER of these lesions. In a large surgical study, Newton et al report LNM for pT1b tumors in 33.5% when PD is present and in 43.3% when LVI is present.[15]

In contrast, the low rates of LNM and distant metastasis in the “PD only” group have to be balanced against the surgical mortality. In the literature the mortality of surgical esophagectomy ranges from 4.0% in high-volume centers to 11.4% in low-volume centers.[6] Surgical mortality in our study was 13.6%. One reason may be the preselection of patients with higher age and/or severe comorbidity who were treated initially by ER despite a high probability of high-risk histology.

We observed EAC-associated deaths in 1/25 (4%; 95%CI 0.4-17.2%) in the PD only group and 3/15 (20%; 95%CI 6.0-44.4%) in the PD plus group, respectively (p=0.293). Due to small patient numbers, statistical significance was not reached.

Our study has several limitations which must be clearly addressed. Because of the missing standard protocol for EUS and CT scans metastasis at baseline and/or extraesophageal recurrences during follow-up may have been missed. At baseline, EUS and/or CT were performed in 75% and 80% of the patients, respectively. During follow-up EUS and /or CT were performed in 65% of the patients. However, the follow-up period was long (median 30 months; IQR 15-73) and this fact may reduce this risk of missed mestastases at baseline and during follow-up noticeable.

Furthermore, the patient number is low and the analysis has been performed retrospectively. However, due to the low frequency of PD in ER specimens (only 3.5% of all ERs were “PD only” lesions in our study) it seems difficult to design prospective studies with high patient numbers and a long-term follow-up.

Despite these limitations, the present study is one of the largest studies on EACs with PD which are treated endoscopically and probably the largest study which focuses on PD as a single high-risk feature.

In conclusion, our study shows low rates of metastasis and EAC-related deaths after ER of EAC when PD is the only histopathological risk factor. A conservative approach with close endoscopic follow-up seems justified in this small patient group. In patients who underwent surgery LNM were not found in the “PD only” group but in 20% of the “PD plus” group. The surgical mortality was substantial in this preselected patient group (13.6%). The data may be helpful to individualize treatment strategies. However, further data and prospective studies are urgently needed.

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FIGURE LEGENDS

Figure 1: Patients inclusion
(PD poor differentiation, HM horizontal margin, LVI lymphovascular invasion)

Figure 2: Clinical course of patients after ESD for EAC with poor differentiation (PD)

Figure 3: Cumulative incidence of metastasis during the follow-up period

Figure 4: Overall survival for the different groups (PD only versus PD plus)

Figure 5: Disease-free survival for the different groups (PD only versus PD plus)

TABLES

	All patients n=40	**PD only (pT1a L0V0) n=25**	**PD plus (pT1b and/or LVI) n=15**	**p-value**
Patient's characteristics				
Age (years), median (IQR)	69.5 (63.5-75.0)	70 (63.0-77.5)	66 (61.0-73.0)	0.525
Male gender, n (%)	38 (95.0)	24 (96.0)	14 (93.3)	1.000
ASA status 1 / 2 / 3, n (%)	9 / 19 / 12 (22.5 / 47.5 / 30.0)	8 / 14 / 3 (32.0 / 56.0 / 12.0)	1 / 5 / 9 (6.7 / 33.3 / 60.0)	0.005
Barrett's characteristics				

Circumferential length (cm), median (IQR)	1 (1.0-3.0)	1 (1.0-3.5)	1 (1.0-3.0)	0.699
Maximal length (cm), median (IQR)	3 (3.0-6.0)	3 (3.0-6.0)	3 (2.0-7.0)	0.489
Lesions characteristics				
Maximal diameter of EAC (mm), median (IQR)	25 (15-35)	20 (15-30)	25 (15-40)	0.211
Paris classification, n (%)				0.219
0-Ip	2 (5.0)	1 (4.0)	1 (6.7)	
0-Is	5 (12.5)	2 (8.0)	3 (20.0)	
0-IIa	17 (42.5)	12 (48.0)	5 (33.3)	
0-IIa+Is	7 (17.5)	5 (20.0)	2 (13.3)	
0-IIa+IIc	2 (5.0)	0	2 (13.3)	
0-IIb	3 (7.5)	3 (12.0)	0	
0-IIc	3 (7.5)	1 (4.0)	2 (13.3)	
Missing information	1 (2.5)	1 (4.0)	0	
Histopathology				
Depth of invasion, n (%)				
M2	8 (20.0)	8 (32.0)	0	0.016
M3	9 (22.5)	7 (28.0)	2 (13.3)	0.440
M4	10 (25.0)	10 (40.0)	0	0.006
Submucosal invasion	13 (32.5)	0	13 (86.7)	<0.001
Lymphovascular invasion present	5 (12.5)	0	5 (33.3)	0.005
Baseline Staging				
EUS, n (%)	30 (75.0)	19 (76.0)	11 (73.3)	1.000
CT, n (%)	32 (80.0)	18 (72.0)	14 (93.3)	0.219
Neither EUS nor CT, n (%)	3 (7.5)	3 (12.0)	0	0.279
Resection characteristics				

Maximal diameter of the resection specimen (mm), median (IQR)	50 (40-59)	50 (40-53)	50 (40-60)	0.847
R0 resection, n (%)	32 (80.0)	22 (88.0)	10 (66.7)	
R1 resection HM, n (%)	8 (20.0)	3 (12.0)	5 (33.3)	0.126
Adverse events				
Bleeding	0	0	0	1.000
Perforation	0	0	0	1.000
Stricture	0	0	0	1.000

Table 1: Patients, lesions and resection characteristics

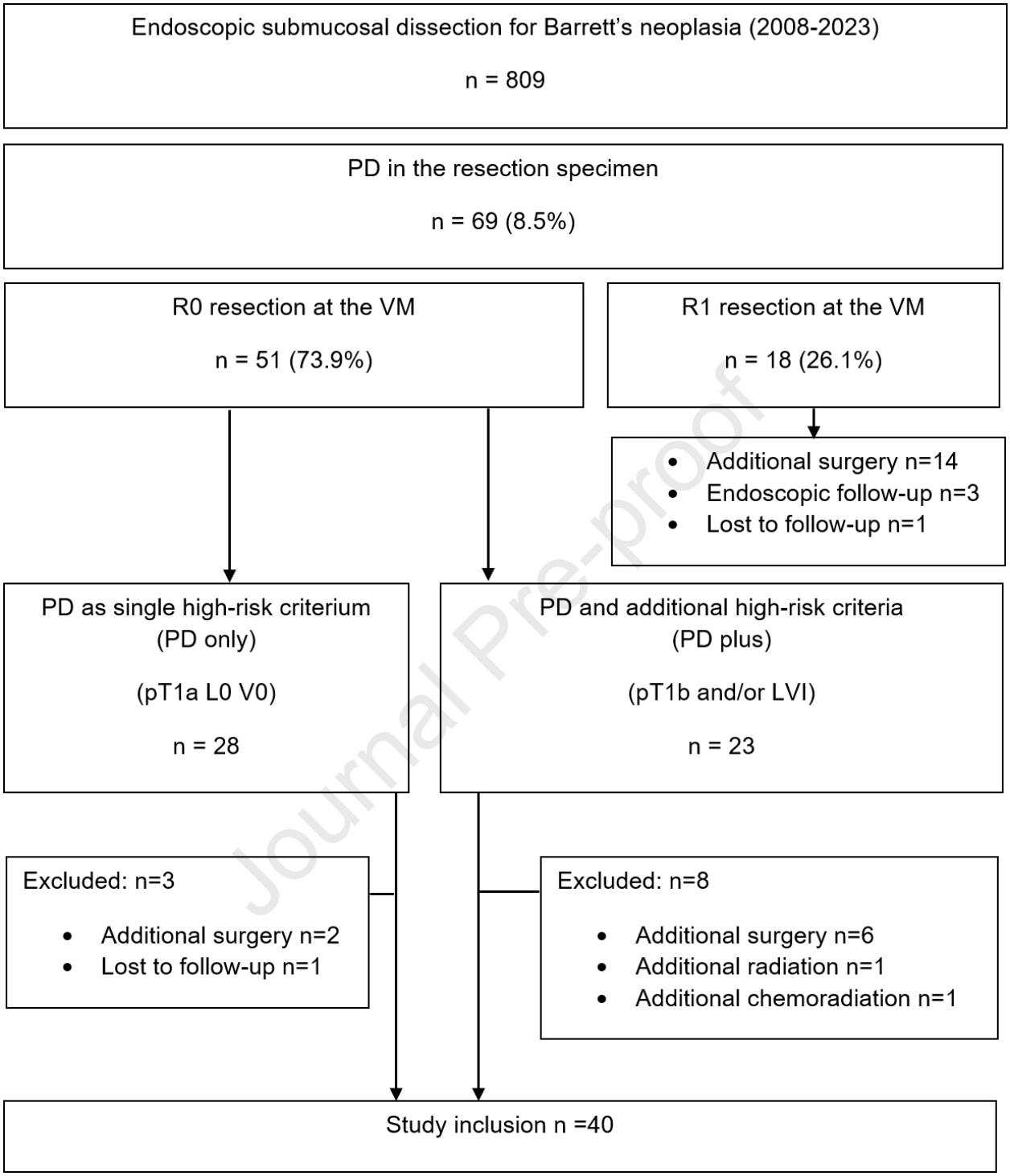
PD poor differentiation, EAC esophageal adenocarcinoma, HM horizontal margin.

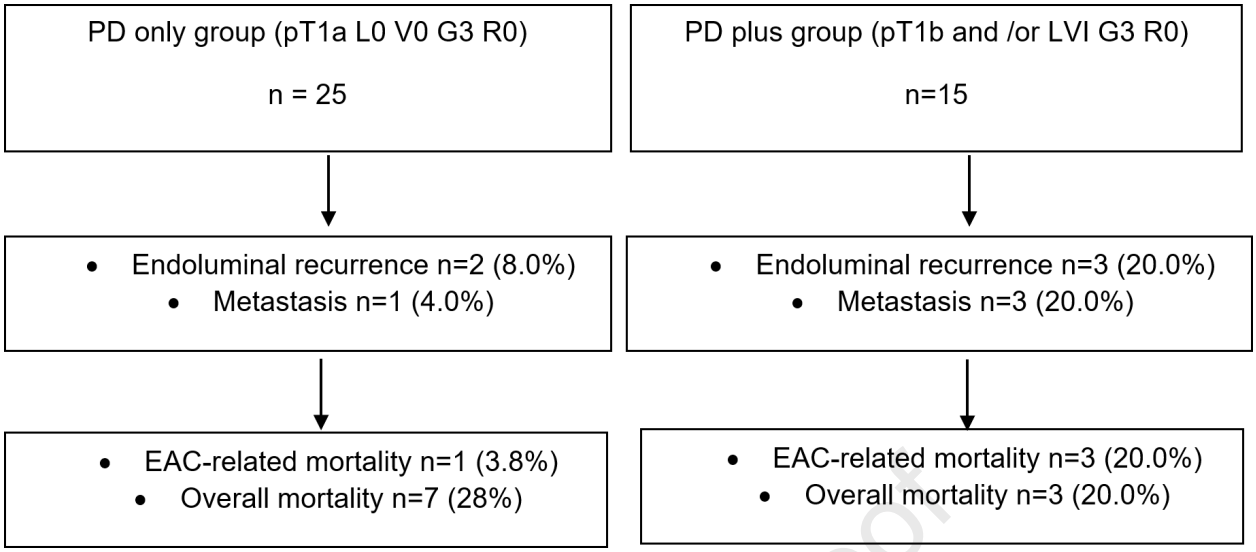
	All patients n=40	**PD only (pT1a L0V0) n=25**	**PD plus (pT1b and/or LVI) n=15**	**p-value**
Complete eradication of Barrett's after ESD, n (%)	11 (27.5)	8 (32.0)	3 (20.0)	0.486
Residual Barrett's after ESD, n (%)	29 (72.5)	17 (68.0)	12 (80.0)	0.486
Further treatment				
Endoscopic resection, n (%)	4 (10.0)	2 (8.0)	2 (13.3)	0.622
Endoscopic ablation, n (%)	21 (52.5)	14 (56.0)	7 (46.7)	0.745
No further treatment, n (%)	4 (10.0)	1 (4.0)	3 (20.0)	0.139
Course during FU				
Staging procedures during FU, median (IQR)				
Number of endoscopies	5 (2-6)	5 (2-8)	3 (2-6)	0.267
Number of EUS	0 (0-1)	0 (0-1)	0 (0-1)	0.659
Number of CTs	0.5 (0-1)	0 (0-1)	1 (1-2)	0.015

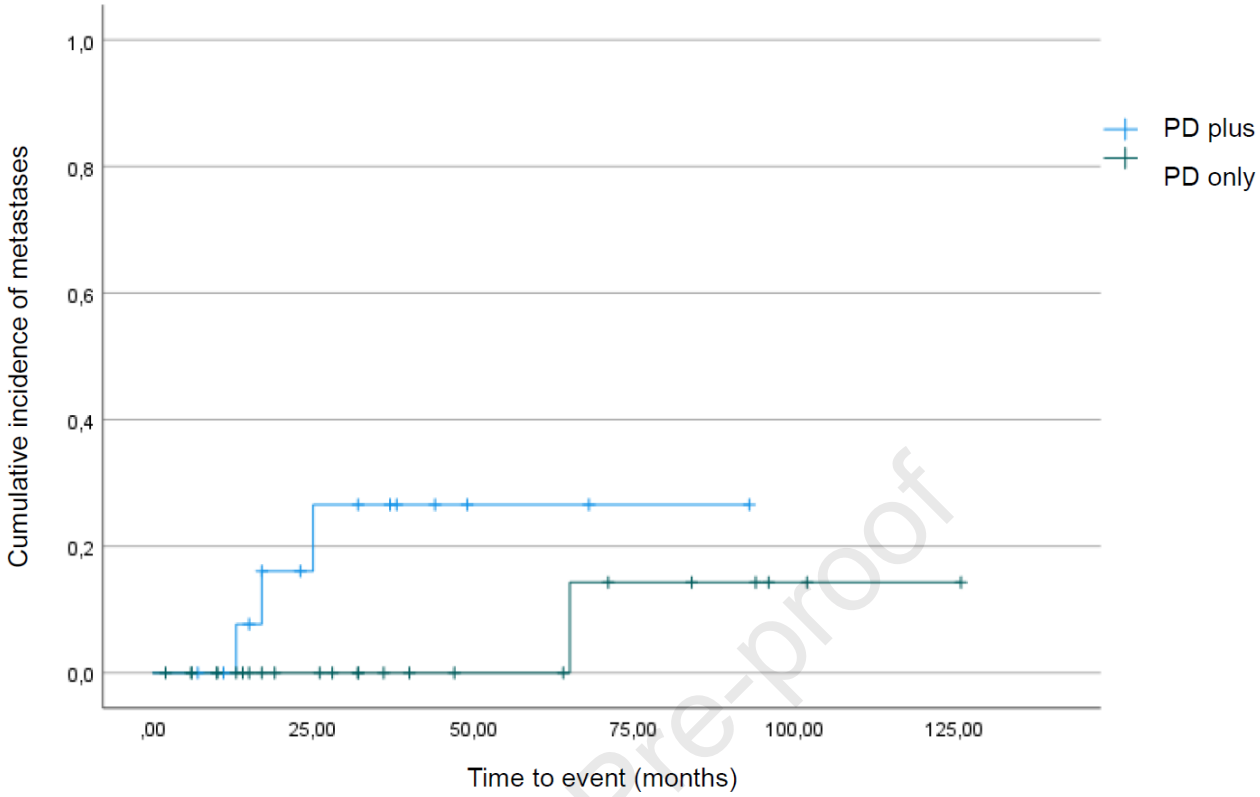
Endoluminal recurrence, n (%; 95% CI)				
Any endoluminal recurrence	5 (12.5; 4.9-25.2)	2 (8.0; 1.7-23.3)	3 (20.0; 6.0-44.4)	0.345
Local recurrence	3 (7.5; 2.2-18.7)	1 (4.0; 0.4-17.2)	2 (13.3; 2.9-36.3)	0.545
Metachronous neoplasia	2 (5.0; 1.1-15.1)	1 (4.0; 0.4-17.2)	1 (6.7; 0.7-27.2)	1.000
Metastasis, n (%; 95% CI)				
Any metastasis	4 (10.0; 0.4-22.0)	1 (4.0; 0.4-17.2)	3 (20.0; 6.0-44.4)	0.293
LNM	1 (2.5; 0.03-11.1)	0 (0; 0.0-9.5)	1 (6.7; 0.7-27.2)	0.375
Distant metastasis	2 (5.0; 1.1-15.1)	1 (4.0; 0.4-17.2)	1 (6.7; 0.7-27.2)	1.000
LNM and distant metastasis	1 (2.5)	0 (0; 0.0-9.5)	1 (6.7; 0.7-27.2)	0.375
Death, n (%; 95% CI)	10 (25.0; 13.6-39.8)	7 (28; 13.5-47.3)	3 (20.0; 6.0-44.4)	0.715
Cause of death				
EAC, n (%)	4 (10.0)	1 (4.0)	3 (20.0)	0.139
Other Cancer, n (%)	1 (2.5)	1 (4.0)	0	1.000
Cardiopulmonary, n (%)	3 (7.5)	3 (12.0)	0	0.279
Other, n (%)	2 (5.0)	2 (8.0)	0	0.519
Survival				
Overall survival at 2 years, % (95%-CI)	92.5 (81.3-97.8)	92.0 (76.7-98.3)	93.3 (72.8-99.3)	1.000
Overall survival at 5 years, % (95%-CI)	82.5 (68.7-91.8)	84.0 (66.3-94.3)	80.0 (55.6-94.0)	1.000
Disease-free survival at 2 years, % (95%-CI)	94.4 (83.4-98.8)	100,0 (81.5-100)	91.7 (75.9-98.2)	0.543
Disease-free survival at 5 years, % (95%-CI)	88.9 (75.7-96.1)	100,0 (81.5-100)	83.3 (65.1-94.1)	0.278
Follow-up (months), median (IQR)	30 (15-53)	32 (14-72)	28 (16-44)	0.804

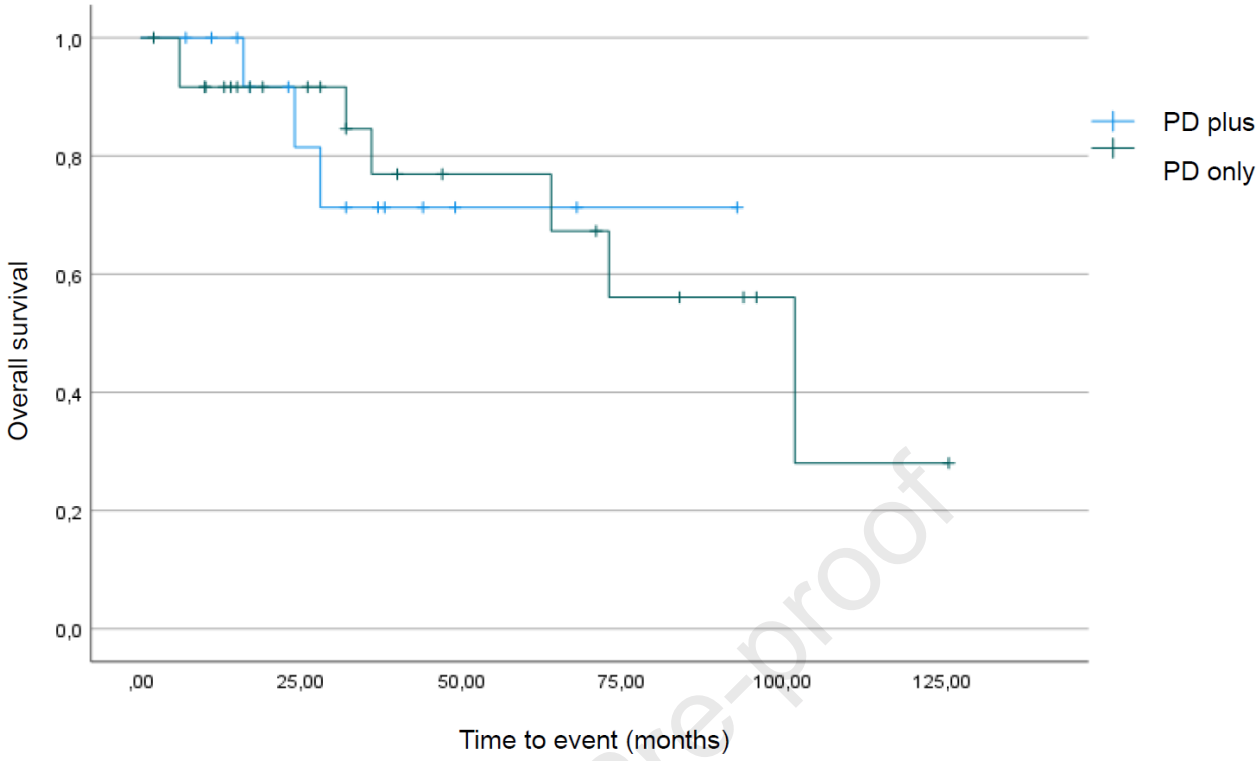
Table 2: Follow-up after ESD of poor differentiated EAC.

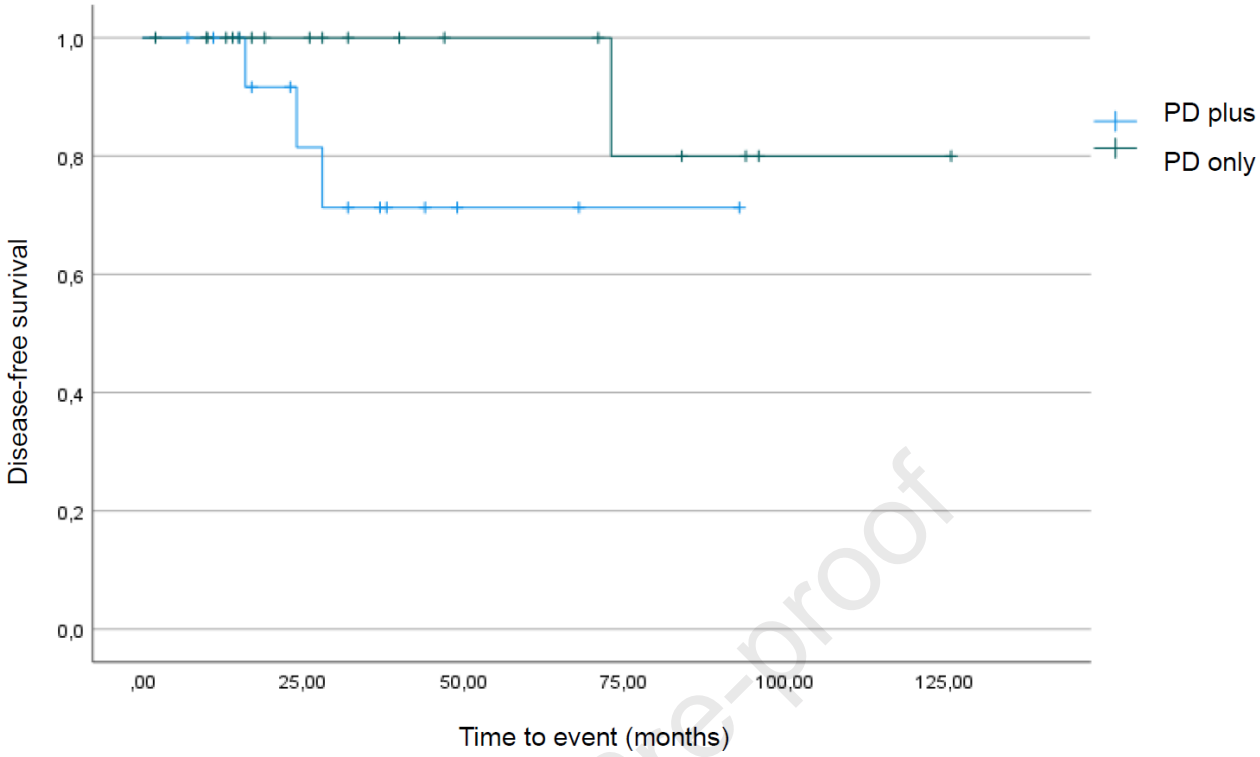
FU follow-up, EAC esophageal adenocarcinoma, ESD endoscopic submucosal dissection, LNM lymph node metastasis)











Acronyms and abbreviations

APC argon plasma coagulation

EAC esophageal adenocarcinoma

EMR endoscopic mucosal resection

ER endoscopic resection

ESD endoscopic submucosal dissection

EUS endoscopic ultrasound

HM horizontal margin

IQR interquartile range

LNM lymph node metastasis

LVI lymphovascular invasion

PD poor differentiation

RFA radiofrequency ablation

SM submucosal

VM vertical margin