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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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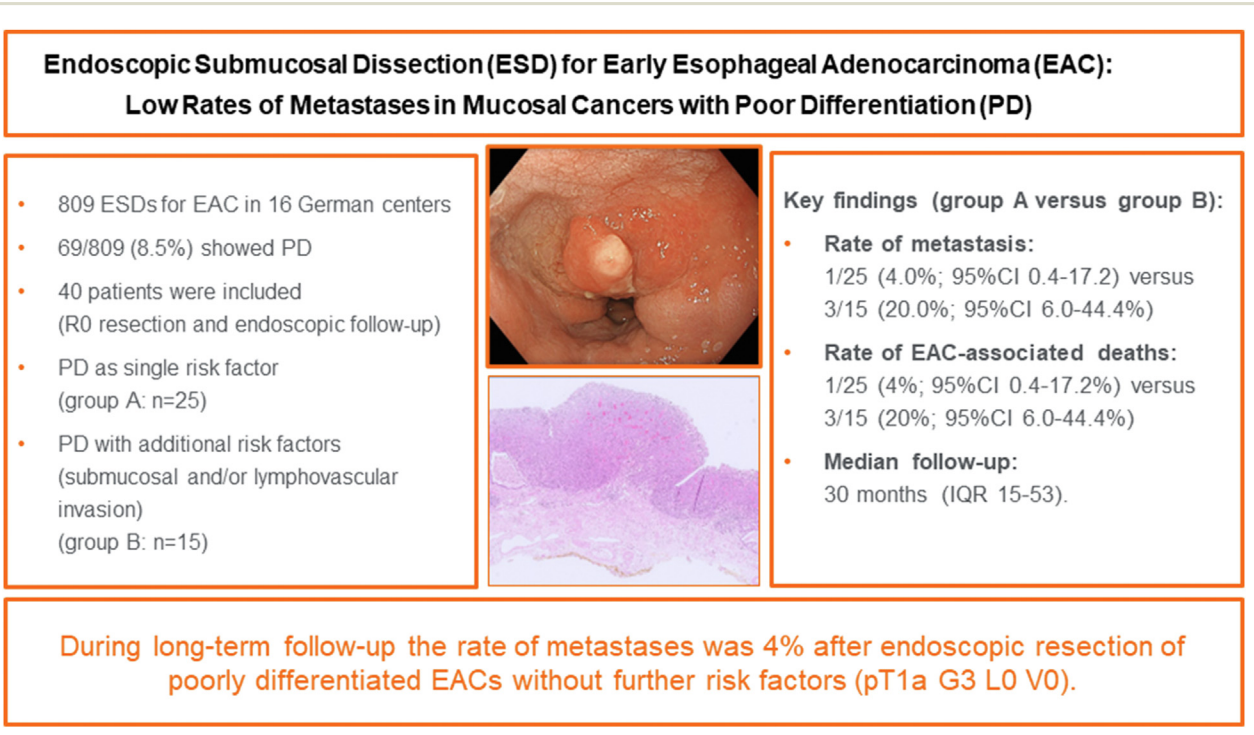
GRAPHICAL ABSTRACT



Background and Aims: Endoscopic resection is accepted as standard treatment for intramucosal esophageal adenocarcinoma (EAC) that is well or moderately differentiated. 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. The aim of this study was to analyze the clinical course of patients after endoscopic resection of EAC with PD.

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: Twenty-five patients with PD as single risk factor (group A) and 15 patients with PD and additional risk factors (submucosal invasion and/or lymphovascular invasion) (group B) were included. The metastasis rate was was 1 of 25 (4.0%; 95% CI, .4%-17.2%) in group A and 3 of 15 (20.0%; 95% CI, 6.0%-44.4%) in group B, respectively

($P = .293$). The rate of EAC-associated deaths was 1 of 25 (4%; 95% CI, .4%-17.2%) versus 3 of 15 (20%; 95% CI, 6.0%-44.4%) in group B ($P = .293$). The overall death rate was 7 of 25 (28.0%; 95% CI, 13.5%-47.3%) versus 3 of 15 (20%; 95% CI, 6.0%-44.4%) ($P = .715$). Median follow-up was 30 months (interquartile range, 15-53 months).

Conclusions: During long-term follow-up, the risk of metastasis is low after endoscopic resection of mucosal EAC with PD as a single risk factor. A conservative approach seems justified in this small patient group. However, the treatment strategy must be determined on an individualized basis until further prospective data are available. (Gastrointest Endosc 2024;100:626-36.)

(footnotes appear on last page of article)

The incidence of esophageal adenocarcinoma (EAC) continues to rise, 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 offers a minimally invasive curative treatment option when EAC is diagnosed in early stages without a risk of lymph node metastasis (LNM). Large studies reported excellent long-term results after endoscopic resection of intramucosal EACs without further risk factors such as submucosal (SM) invasion, poor differentiation (PD), or lymphovascular invasion (LVI).[2] For such EACs, the risk of LNM is negligible, and current guidelines recommend endoscopic resection as the curative treatment of choice.[3-5] When histopathologic low-risk factors are not fulfilled, the risk of LNM must 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 (≤500 μm) without further risk factors, small studies reported LNM in about 2%, and endoscopic resection 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 currently recommended for lesions with PD.[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 endoscopic resection. The aim of the current study was to assess the clinical outcome of patients after endoscopic resection for early EACs with PD.

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 (study identifier DRKS00011781). In addition, all patients who underwent ESD for Barrett's neoplasia from April 2008 to June 2023 at the Department of Gastroenterology, University Hospital of Augsburg, were screened. All patients undergoing ESD in the department are enrolled in a local database after informed consent is obtained 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 and the ethical guidelines of the 1975 Declaration of Helsinki.

Inclusion criteria

Study inclusion criteria were as follows: (1) EAC with PD in the resection specimen after ESD for Barrett's neoplasia; (2) written informed consent to the ESD procedure after receipt of detailed information about ESD and alternative treatment strategies; and (3) written informed consent to the enrollment in the database of the German ESD registry or in a local database at the University Hospital of Augsburg.

Exclusion criteria

Study exclusion criteria were as follows: (1) EUS showing invasion depth >T1 and/or suspected LNM; (2) additional surgery, radiotherapy, or chemoradiation after ESD; and (3) concomitant malignant disease without curative treatment option.

Patients with R1 resection at the vertical margin (VM) were excluded from follow-up analysis. The remaining patients were categorized in 2 groups: (1) "PD only" (PD without further high-risk risk criteria [pT1a, G3, L0, V0]); and (2) "PD plus" (PD and additional high-risk criteria [SM invasion and/or LVI]).

Patients with a follow-up period of >6 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, and 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 EMR (eg, in EACs >15 mm or bulky lesions). The lesion 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 before or after endoscopic resection. 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.

HISTOPATHOLOGIC WORKUP

Histopathologic evaluation of endoscopic resection 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 and eosin. Additional staining using immunohistochemistry for D2-40, desmin, or smoothelin was performed individually.

The sizes of the specimen and the EAC are reported. Invasion depth was described as m1 to m4 for mucosal lesions (m1 = no invasion of the superficial muscularis mucosae; m2 = infiltration of superficial muscularis mucosae; m3 = infiltration of the layer in between the superficial and deep muscularis mucosae; m4 = infiltration of the deep muscularis mucosae).[12] For submucosal lesions, the maximum depth of the SM invasion was measured in micrometers. The presence or absence of LVI and R0 resection at the horizontal margin (HM) and the VM is described. In one patient who developed liver metastases, next-generation sequencing was performed to compare the EAC with the metastases. Analysis was performed by using Illumina Oncomine Focus Panel (Thermo Fisher Scientific; 52 genes, DNA, and ribonucleic acid).

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 depending 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, biopsy specimens 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 metachronous neoplasia. Local recurrences and metachronous neoplasia were treated at the discretion of the local endoscopist. Complete eradication of Barrett's esophagus was defined as the absence of visible Barrett's metaplasia after ESD or during follow-up. When the macroscopic appearance was unclear, biopsy specimens 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 (IQRs). Categorical data were compared by using the Fisher exact test. Comparison of continuous data was performed by 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 .05. All calculations were performed by using SPSS version 28.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA).

RESULTS

Patient inclusion

From April 2008 to June 2023, a total of 809 patients underwent ESD for Barrett's neoplasia. PD was diagnosed in the resection specimen of 69 patients (8.5%). Eighteen (26.1%) of 69 patients with R1 resection at the VM were excluded from further follow-up analysis. An additional 11 patients displaying R0 resection at the VM had to be excluded because of further nonendoscopic treatment or missing follow-up data. The remaining 40 patients were included in the follow-up analysis study (Fig. 1). Twenty-five (62.5%) of 40 patients were stratified in the PD only group, whereas 15 (37.5%) of 40 showed additional high-risk features.

Patient and lesion characteristics

Patient and lesion characteristics are summarized in Table 1. High-risk features in the PD plus group were SM invasion without LVI in 10 (66.7%) of 15, SM invasion with

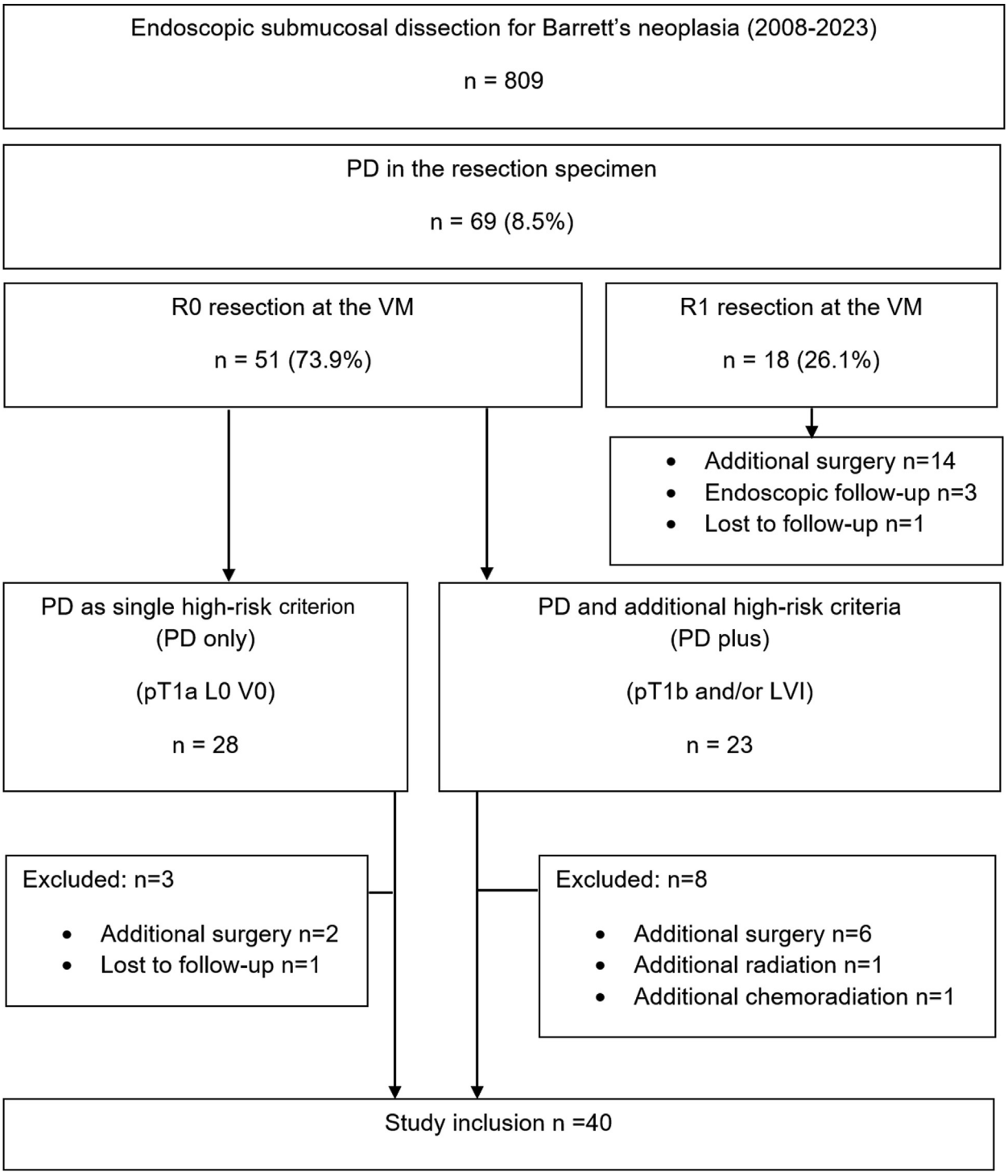


Figure 1. Inclusion of patients. *PD*, Poor differentiation; *VM*, vertical margin; *LVI*, lymphovascular invasion.

additional LVI in 3 (20%) of 15, and LVI in mucosal lesions in 2 (13.3%) of 15 patients. In cases with SM invasion, the invasion depth was >500 μm in 10 (76.9%) of 13 patients.

Procedure characteristics and adverse events

Thirty-two (80%) of 40 specimens showed R0 resection; the remaining 8 (20%) were diagnosed R1 at the HM (Table 1). Only 2 of these patients showed local recurrences at the resection scar during follow-up. In 30 (75%) and 32 (80%) of 40 patients, EUS and/or CT scans were performed at baseline, respectively. Adverse events were not observed after ESD.

Additional treatment after ESD

In 11 (27%) of 40 patients, complete eradication of the Barrett's metaplasia was achieved with ESD. In the remaining

TABLE 1. Patient, lesion, and resection characteristics

Characteristic	All patients ($N = 40$)	PD only (pT1a L0V0) ($n = 25$)	PD plus (pT1b and/or LVI) ($n = 15$)	*P* value
Patient characteristics				
Age, y	69.5 (63.5-75.0)	70 (63.0-77.5)	66 (61.0-73.0)	.525
Sex, male	38 (95.0)	24 (96.0)	14 (93.3)	1.000
ASA status I/II/III	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)	.005
Barrett's characteristics				
Circumferential length, cm	1 (1.0-3.0)	1 (1.0-3.5)	1 (1.0-3.0)	.699
Maximal length, cm	3 (3.0-6.0)	3 (3.0-6.0)	3 (2.0-7.0)	.489
Lesion characteristics				
Maximal diameter of EAC, mm	25 (15-35)	20 (15-30)	25 (15-40)	.211
Paris classification				.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				
M2	8 (20.0)	8 (32.0)	0	.016
M3	9 (22.5)	7 (28.0)	2 (13.3)	.440
M4	10 (25.0)	10 (40.0)	0	.006
Submucosal invasion	13 (32.5)	0	13 (86.7)	<.001
LVI present	5 (12.5)	0	5 (33.3)	.005
Baseline staging				
EUS	30 (75.0)	19 (76.0)	11 (73.3)	1.000
CT scan	32 (80.0)	18 (72.0)	14 (93.3)	.219
Neither EUS nor CT scan	3 (7.5)	3 (12.0)	0	.279
Resection characteristics				
Maximal diameter of the resection specimen, mm	50 (40-59)	50 (40-53)	50 (40-60)	.847
R0 resection	32 (80.0)	22 (88.0)	10 (66.7)	
R1 resection HM	8 (20.0)	3 (12.0)	5 (33.3)	.126
Adverse events				
Bleeding	0	0	0	1.000
Perforation	0	0	0	1.000
Stricture	0	0	0	1.000

Values are median (interquartile range) or n (%).
PD, Poor differentiation; *LVI*, lymphovascular invasion; ASA, American Society of Anesthesiologists; *EAC*, esophageal adenocarcinoma; *HM*, horizontal margin.

29 patients (72.5%) with residual non-neoplastic Barrett's epithelium, further endoscopic treatment was recommended (Table 1). In 4 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 2 patients and EMR in another 2). In 21 patients, ablation was performed every 3 to 6 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 of 21 patients, and ablation is ongoing in the remaining one. When complete eradication of the

TABLE 2. Follow-up after ESD of poorly differentiated EAC

Further course after ESD	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	11 (27.5)	8 (32.0)	3 (20.0)	.486
Residual Barrett's after ESD	29 (72.5)	17 (68.0)	12 (80.0)	.486
Further treatment				
Endoscopic resection	4 (10.0)	2 (8.0)	2 (13.3)	.622
Endoscopic ablation	21 (52.5)	14 (56.0)	7 (46.7)	.745
No further treatment	4 (10.0)	1 (4.0)	3 (20.0)	.139
Course during FU				
Staging procedures during FU				
No. of endoscopies	5 (2-6)	5 (2-8)	3 (2-6)	.267
No. of EUS	0 (0-1)	0 (0-1)	0 (0-1)	.659
No. of CT scans	.5 (0-1)	0 (0-1)	1 (1-2)	.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)	.345
Local recurrence	3 (7.5; 2.2-18.7)	1 (4.0; .4-17.2)	2 (13.3; 2.9-36.3)	.545
Metachronous neoplasia	2 (5.0; 1.1-15.1)	1 (4.0; .4-17.2)	1 (6.7; .7-27.2)	1.000
Metastasis, n (%; 95% CI)				
Any metastasis	4 (10.0; .4-22.0)	1 (4.0; .4-17.2)	3 (20.0; 6.0-44.4)	.293
LNM	1 (2.5; .03-11.1)	0 (0; .0-9.5)	1 (6.7; .7-27.2)	.375
Distant metastasis	2 (5.0; 1.1-15.1)	1 (4.0; .4-17.2)	1 (6.7; .7-27.2)	1.000
LNM and distant metastasis	1 (2.5)	0 (0; 0-9.5)	1 (6.7; .7-27.2)	.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)	.715
Cause of death				
EAC	4 (10.0)	1 (4.0)	3 (20.0)	.139
Other cancer	1 (2.5)	1 (4.0)	0	1.000
Cardiopulmonary	3 (7.5)	3 (12.0)	0	.279
Other	2 (5.0)	2 (8.0)	0	.519
Survival, % (95% CI)				
Overall survival at 2 y	92.5 (81.3-97.8)	92.0 (76.7-98.3)	93.3 (72.8-99.3)	1.000
Overall survival at 5 y	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 y, % (95% CI)	94.4 (83.4-98.8)	100.0 (81.5-100)	91.7 (75.9-98.2)	.543
Disease-free survival at 5 y, % (95% CI)	88.9 (75.7-96.1)	100.0 (81.5-100)	83.3 (65.1-94.1)	.278
FU, mo	30 (15-53)	32 (14-72)	28 (16-44)	.804

Values are n (%) or median (interquartile range) unless otherwise indicated.
ESD, Endoscopic submucosal dissection; *EAC*, esophageal adenocarcinoma; *PD*, poor differentiation; *LVI*, lymphovascular invasion; *FU*, follow-up; *CI*, confidence interval; *LNM*, lymph node metastasis.

Barrett's metaplasia was achieved, no recurrent metaplasia was diagnosed during further follow-up. No adverse events were observed after repeated endoscopic resection or ablation. In 4 patients with residual Barrett's, ablation was not performed due to patient refusal.

Follow-up

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

Endoluminal recurrence

Local recurrence was diagnosed in 3 of 40 patients (7.5%; 95% CI, 2.2%-18.7%). As mentioned earlier, 2 local recurrences were diagnosed after R1 resection at the HM. In both patients, biopsy specimens from the scar had shown well-differentiated EAC 3 and 6 months after ESD, respectively. Both patients underwent repeated endoscopic

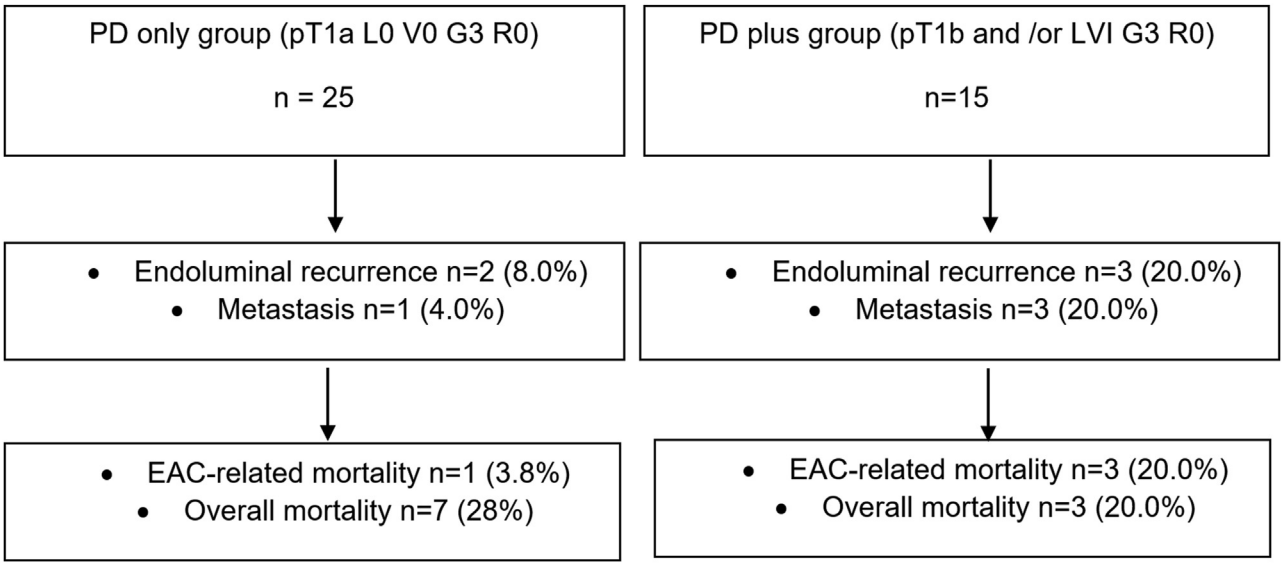


Figure 2. Clinical course of patients after endoscopic submucosal dissection for esophageal adenocarcinoma (EAC) with poor differentiation (PD).

resection (ESD and EMR in 1 case each). Histopathologic diagnosis were well-differentiated mucosal EAC in 1 patient and non-neoplastic Barrett's metaplasia in the other patient. The further course was uneventful in both patients. Another patient who had refused additional follow-up after R0 resection of an EAC with deep SM 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 2 years after ESD and was successfully treated by repeated ESD. Histopathology confirmed R0 resection of a mucosal EAC with poor differentiation (12 mm in diameter; invasion depth, m1 L0V0). 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 initial extent of the Barrett's esophagus had been C3M4, and ablation was not completed so far.

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

Lymph node metastases and distant metastases

The rate of any metastasis was 1 of 25 (4.0%; 95% CI, .4%-17.2%) in the PD only group and 3 of 15 (20.0%; 95% CI, 6.0%-44.4%) in the PD plus group, respectively ($P = .293$) (Table 2).

LNM were detected in none of the 25 patients in the PD only group (0%; 95% CI, 0%-9.5%), whereas the LNM rate was 1 of 15 in the PD plus group (6.7%; 95% CI, .7%-27.2%). Diagnosis of LNM was made 18 months after ESD of an EAC with deep SM invasion >500 μm (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 of 25 patients in the PD only group (4.0%; 95% CI, .4%-17.2%). In this patient, liver metastasis of a moderately differentiated adenocarcinoma were confirmed 65 months after ESD of an EAC 30 mm in diameter. LNM or another cancer was not found, and the diagnosis of Cancer of Unknown Primary 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 next-generation sequencing analyses could not successfully be performed. The hematoxylin and eosin–based morphologic features had to be compared for the final determination 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 (13.3%) of 15 patients developed distant metastases during follow-up. In 1 patient, pulmonary and liver metastases 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. In addition, a local endoluminal recurrence was seen (this patient was described earlier). He was treated with best supportive care and died.

Survival

Ten of 40 patients (25.0%; 95% CI, 13.6%-39.8%) died during the study period. The overall death rate was 7 of 25 (28.0%; 95% CI, 13.5%-47.3%) in the PD only group and 3 of 15 (20%; 95% CI, 6.0%-44.4%) in the PD plus group ($P = .715$). Four deaths were related to recurrent

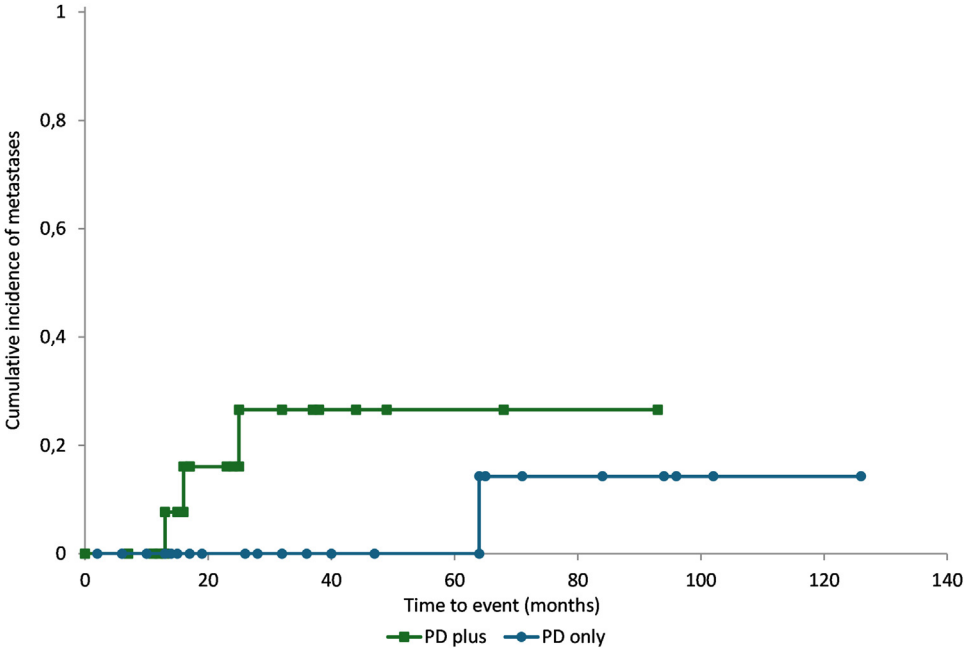


Figure 3. Cumulative incidence of metastasis during the follow-up period. *PD*, Poor differentiation.

EAC, and 6 were related to other causes (cardiopulmonary disease, n = 3; other malignancy, n = 1; others, n = 2).

The rate of EAC-associated death was 1 of 25 (4%; 95% CI, .4%-17.2%) in the PD only group and 3 of 15 (20%; 95% CI, 6.0%-44.4%) in the PD plus group, respectively (P = .293). Due to small patient numbers, the overall death rate and the EAC-associated death rate showed no significant difference (Table 2). Figures 4 and 5 present Kaplan-Meier curves for overall survival and disease-free survival, respectively.

Surgically treated patients

Twenty-two (31.9%) of 69 patients with PD in the ESD specimen underwent surgery (esophagectomy in 20 patients and Merendino's procedure in the remaining 2 patients). Surgery was performed in 14 patients with R1 resection (all lesions were pT1b cancers) and in 8 patients with R0 resection (2 patients with pT1a cancers and another 6 patients with pT1b cancers). The rate of LNM in surgical specimens was 0 (0%) of 2 for pT1a cancers and 4 (20.0%) of 20 for pT1b cancers. Three (13.6%) of 22 patients who underwent surgery experienced fatal adverse events. All patients had been categorized as American Society of Anesthesiologists class III. In summary, in patients who underwent surgery, LNM was 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

Endoscopic resection is recommended for superficial EAC when histopathologic 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 currently.[3-5] However, PD is a rare finding in endoscopic resection 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 endoscopic resection specimens.[2,9]

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

Only a 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 2 cases with metastatic recurrence (12.5%) during a median follow-up of 27 months.[9] A recent multicenter study from the United States that 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.[13] However, EACs with PD or LVI as a single risk factor were not differentiated in this study. 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]

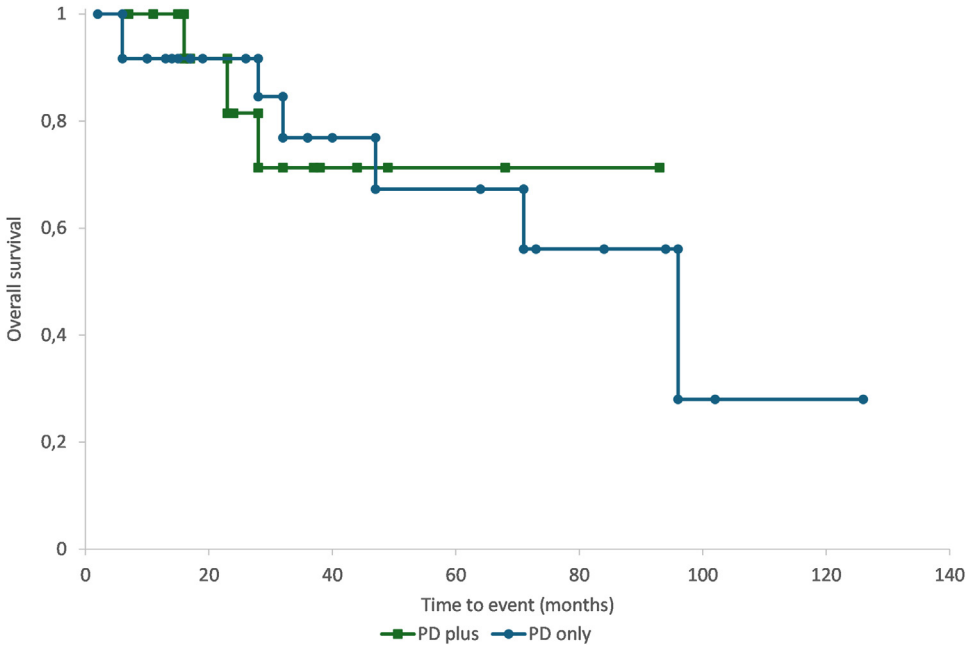


Figure 4. Overall survival for the different groups (poor differentiation [PD] only vs PD plus).

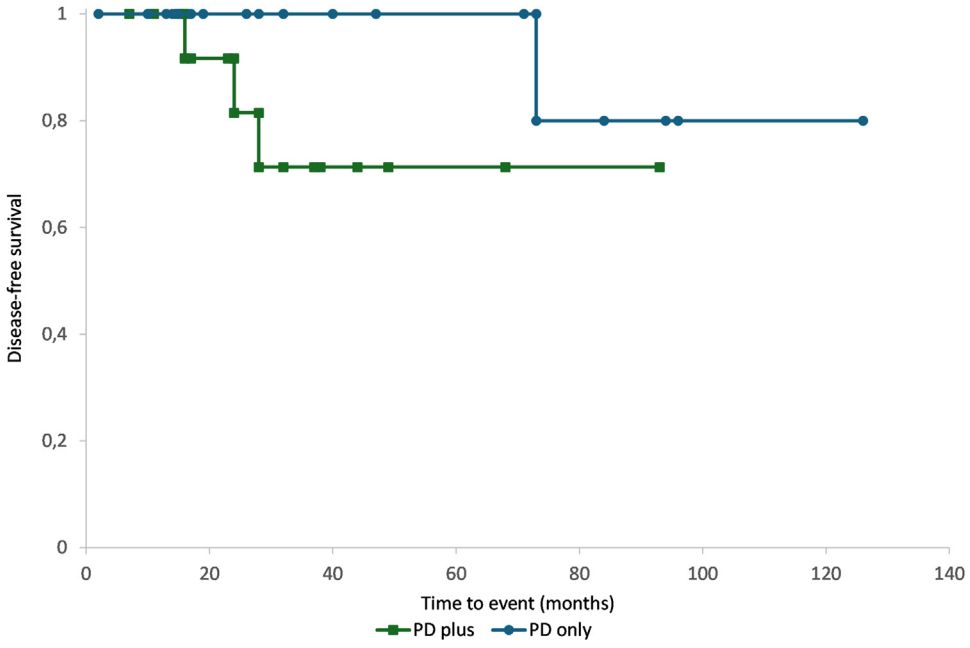


Figure 5. Disease-free survival for the different groups (poor differentiation [PD] only versus PD plus).

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

In the current study, the rate of any extra-esophageal metastasis during follow-up was 1 of 25 (4.0%; 95% CI, .4%-17.2%) in the PD only group and 3 of 15 (20.0%; 95% CI, 6.0%-44.4%) in the PD plus group, respectively ($P = .293$).

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 endoscopic resection of these lesions. In a large surgical study, Newton et al[15] reported LNM for pT1b tumors in 33.5% when PD is present and in 43.3% when LVI is present.

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 endoscopic resection despite a high probability of high-risk histology.

We observed EAC-associated deaths in 1 (4%; 95% CI, .4%-17.2%) of 25 patients in the PD only group and 3 (20%; 95% CI, 6.0%-44.4%) of 15 patients in the PD plus group, respectively ($P = .293$). Due to small patient numbers, statistical significance was not reached.

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

In addition, patient numbers were low, and the analysis was performed retrospectively. However, due to the low frequency of PD in endoscopic resection specimens (only 3.5% of all endoscopic resections 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 current study is one of the largest studies on EACs with PD that are treated endoscopically and probably the largest study that focused on PD as a single high-risk feature.

In conclusion, our study shows low rates of metastasis and EAC-related deaths after endoscopic resection of EAC when PD is the only histopathologic 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%). Although the data may be helpful for individualizing treatment strategies, further data and prospective studies are urgently needed.

DISCLOSURE

All authors disclosed no financial relationships.

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Abbreviations: APC, argon plasma coagulation; EAC, esophageal adenocarcinoma; ESD, endoscopic submucosal dissection; HM, horizontal margin; IQR, interquartile range; LNM, lymph node metastasis; LVI, lymphovascular invasion; PD, poor differentiation; RFA, radiofrequency ablation; SM, submucosal; VM, vertical margin.

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