Digestive Endoscopy 2021; ••: ••–•• doi: 10.1111/den.14197

Original Article

Esophageal carcinoma in achalasia patients managed with endoscopic submucosal dissection and peroral endoscopic myotomy: Japan Achalasia Multicenter Study

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Objectives: Indications for peroral endoscopic myotomy (POEM) and endoscopic submucosal dissection (ESD) in patients with achalasia concomitant with esophageal carcinoma (EC) are unclear. This study aimed to clarify the role of POEM in cases of achalasia concomitant with EC and to elucidate the indications for ESD and efficient surveillance for EC.

Methods: We conducted a multicenter cohort study at 14 hospitals in Japan, including 3707 cases of achalasia-related esophageal motility disorders (EMDs). Factors contributing to EC risk, the characteristics of EC, and clinical outcomes of POEM/ESD were analyzed.

Results: In patients undergoing POEM, screening and surveillance endoscopy throughout a 1-year period resulted in diagnosis of 72.1% new EC cases. Of 62 patients with 123 ECs, 40.3% had multiple or metachronous lesions within 37.5 months. EC was predominantly observed in the middle thoracic esophagus (58.5%) and posteriorly (73.2%). POEM had comparable safety and efficacy in cases of concomitant EC even after ESD. Endoscopic en bloc resection was performed in 95.8% and 89.3% of ECs diagnosed before and after POEM, respectively ($P = 0.351$); however, ESD on the POEM-line was impaired by fibrosis. Multivariate analysis revealed risk factors for EC, including regular alcohol consumption, a history of smoking, advanced age, and extended disease duration. Alcohol intake and smoking had a synergistic effect on EC development.

Conclusions: Screening and surveillance of POEM help in detecting EC. ESD is feasible in achalasia, although on the POEM-line is challenging. Surveillance endoscopy for EC is recommended for cases with specific risks and a history of ECs.

Key words: achalasia, endoscopic submucosal dissection, esophageal carcinoma, peroral endoscopic myotomy, squamous cell carcinoma

INTRODUCTION

ACHALASIA IS A primary esophageal motility disorder (EMD) secondary to degeneration of Auerbach's plexus.[1] Impaired relaxation of the lower esophageal sphincter and abnormal esophageal peristalsis lead to

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Received 1 October 2021; accepted 15 November 2021.

retention of large amounts of food and liquid within the esophagus. This pathology induces chronic inflammation that eventually triggers malignant transformation of the esophageal epithelium.[2] Although achalasia confers a relatively high risk of esophageal carcinoma (EC), routine endoscopy is not recommended in patients with achalasia because the absolute risk of EC is not high enough to warrant cost-effective screening.[3–6] Therefore, an effective surveillance system targeting patients at high risk for EC is required. However, analysis of risk factors requires a large number of cases, as the incidence of EC in patients with achalasia is at most as low as 0.59 per 100 person-years.[7]

Due to the development of high-resolution manometry (HRM)[8–10] and minimally invasive peroral endoscopic myotomy (POEM),[11] more cases of achalasia-related EMDs are diagnosed and treated.[12] However, the safety and efficacy of POEM and endoscopic resection (ER), such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), have not been investigated in cases of achalasia with concomitant EC. Both POEM and ER employ similar procedures regarding mucosal incision and submucosal dissection and may interfere with each other.

Achalasia is a rare disease with an incidence of 1.0 per 100,000 person-years.[12,13] Thus, a single-center study cannot provide a statistically significant number of cases. Therefore, to clarify the characteristics and treatment outcomes of EMDs including achalasia, we conducted the Japan Achalasia Multicenter Study (JAMS), involving high-volume centers in Japan. In this study, using the large JAMS database, first, the risk factors of ECs and efficient surveillance for EC were investigated. Further, the characteristics of achalasia concomitant with ECs, and the indications for POEM and ER were clarified.

METHODS

Patients

JAPAN ACHALASIA MULTICENTER Study was conducted across 14 high-volume EMD centers in Japan (Table S1). We included patients diagnosed with EMDs using standard methods, such as HRM, esophagograms, and esophagogastroscopy, and treated between 2010 and 2020. Among them, cases of achalasia and achalasia-related EMDs, including esophagogastric junction outflow obstruction (EGJOO), and major disorders of peristalsis, such as jackhammer esophagus (JE), distal esophageal spasm (DES), and unclassified spastic disorders, were analyzed. JAMS was approved by the ethics committee of the respective institutions (approval number of Niigata University, 2020-0308) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained in the form of an opt-out system on the website.

Data collection

The survey items included age at onset and diagnosis of EMDs, duration of symptoms, sex, body mass index (BMI), alcohol consumption, a history of smoking, Eckardt score, HRM diagnosis, integrated relaxation pressure (IRP), type of achalasia, and esophageal dilation. In cases of EC with achalasia-related EMDs, the age at EC diagnosis, tumor macroscopic type, location (cervical, upper, middle, lower thoracic, and abdominal), direction (0–3, 3–6, 6–9, and 9–12 o'clock), tumor size, histological diagnosis, and treatment course were investigated. Additionally, procedures and outcomes of POEM were analyzed.

Variables

Duration of symptoms was defined as from onset of disease to date of EC diagnosis or POEM. According to alcohol consumption, patients were categorized into "regular drinkers" and "non-drinkers/occasional drinkers"; furthermore, according to their history of smoking, they were categorized into "current or past smokers" and "non-smokers". Those who were "regular drinkers" and "current or past smokers" were counted. The Eckardt score was used to assess symptom severity.[14] This score comprises the sum of the respective four-point scores for dysphagia, regurgitation, chest pain, and weight loss. A higher score reflects the presence of more severe achalasia-related EMD symptoms (maximum 12). HRM diagnoses were based on the Chicago classification, version 3.0.[15] On esophagography, the type of achalasia was defined as straight or sigmoid type.[16] Esophageal dilation was classified as grade I (<3.5 cm), grade II (3.5 to 6 cm), or grade III (≥6 cm) depending on the diameter of the esophageal lumen.[16] Treatment success was defined as an Eckardt score ≤3 and the absence of repeated interventions.[17] The severity of adverse events was assessed using the Clavien-Dindo classification.[18] Reflux esophagitis was classified according to the Los Angeles classification.[19]

The histological diagnosis of EC was based on the Japanese classification,[20] which categorizes neoplastic lesions confined within the epithelial layer as carcinoma. These are defined as "high-grade dysplasia/carcinoma *in situ*" in Western classification systems.[21,22] Final pathological diagnosis was investigated using pathological TNM classification.[21]

Study 1: Risk factors related to EC development

The characteristics of achalasia-related EMDs were compared between patients with EC and those without (controls). Potential risk factors for EC development included age at onset, duration of symptoms, age at diagnosis, sex, BMI, alcohol consumption, history of smoking, Eckardt score, HRM diagnosis, IRP, type of achalasia, and esophageal dilation. Cox proportional hazard models and Kaplan–Meier estimates were used to compare the impact of these potential risk factors (Fig. 1).

Study 2: Characteristics of EC and outcomes of ESD and POEM

Patient and tumor characteristics in cases of EC with achalasia-related EMDs were analyzed. The procedures and outcomes of ESD and POEM were also compared between patients diagnosed with EC before and after POEM. In patients undergoing POEM, screening endoscopy for the diagnosis and preliminary examination of achalasia is routinely performed preoperatively and intraoperatively. Furthermore, surveillance endoscopy was performed on day 1 to rule out adverse events before starting meals, after 3 months, and after 1 year to assess the short- and long-term efficacy of POEM, and to check for reflux esophagitis.

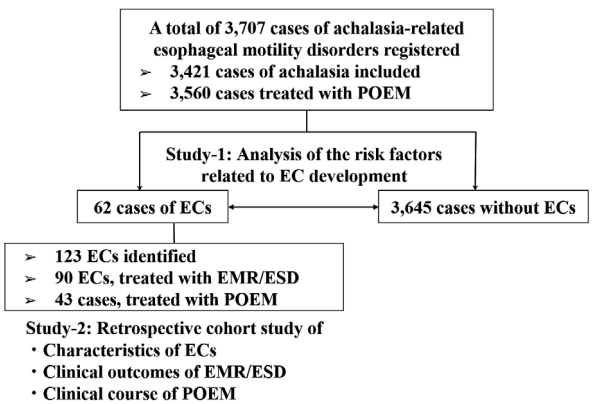

Figure 1 Study flowchart. In total, 3707 cases of achalasia-related esophageal motility disorders were included in this study. Among them, 3421 cases of achalasia and 3560 cases for peroral endoscopic myotomy (POEM) were included. During the study period, 62 patients had 123 esophageal carcinomas (ECs), and risk factors for EC were analyzed in Study 1. Study 2 was performed to elucidate the characteristics of EC, clinical outcomes of endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD), and clinical courses of POEM.

Statistical analyses

All data are presented as medians and interquartile ranges or as numbers of applicable patients and percentages. Categorical values were compared using Pearson's χ^2 test, whereas continuous values were compared using the Mann–Whitney *U*-test. To determine risk factors associated with EC development, we used univariate and multivariate Cox proportional hazard models and calculated hazard ratios (HRs) and 95% confidence intervals (CIs). In the multivariate analysis, we included risk factors with $P < 0.05$ in the univariate analysis. Several continuous candidates (age, duration of symptom, BMI, IRP) were treated as categorical variables according to common cutoff points to facilitate interpretation.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). R version 3.6.1 (R Project for Statistical Computing, Vienna, Austria) was used to generate the Kaplan–Meier estimates. All reported *P* values were two-sided, and $P < 0.05$ was considered significant.

RESULTS

OF 3707 REGISTERED patients with achalasia-related EMDs, 3421 patients with achalasia were included. POEM was conducted in 3560 patients with achalasia-related EMDs (Table S2).

Importance of identifying risk factors for EC in achalasia surveillance

The characteristics of patients with EC ($n = 62$) and those without ($n = 3645$) at the time of achalasia-related EMD diagnosis were compared (Table S3). Duration of symptoms ≥10 years, age at diagnosis ≥65 years, male sex, alcohol intake, smoking, and sigmoid achalasia were significantly more frequent in patients with EC than in controls, whereas Eckardt score ≥7 was significantly less frequent in patients with EC than in controls.

Next, multivariate analysis (Table 1) revealed that duration of symptoms ≥10 years (HR 2.45; 95% CI 1.38–4.35), age at diagnosis ≥65 years (HR 2.43; 95% CI 1.28–4.61), alcohol intake (HR 6.47; 95% CI 3.29–12.7), and smoking (HR 2.97; 95% CI 1.53–5.75) were risk factors for EC development ($P < 0.05$).

Furthermore, Kaplan–Meier curves for the EC risk factors in Table 1 are shown in Figure 2A. Regular alcohol intake and a history of smoking were deemed major risks. The comparisons among combined alcohol intake and smoking, alcohol intake alone, and smoking alone are shown in

Table 1 Factors associated with incidence of esophageal carcinoma in achalasia

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age at onset <20 years	1.524 (0.667–3.482)	0.318		
Duration of symptoms ≥10 years	2.186 (1.276–3.743)	**0.004**	2.451 (1.382–4.348)	**0.002**
Age at diagnosis ≥65 years	1.879 (1.123–3.145)	**0.016**	2.429 (1.281–4.605)	**0.006**
Sex, male	2.386 (1.373–4.147)	**0.002**	0.795 (0.415–1.526)	0.491
Body mass index <18.5	0.907 (0.482–1.709)	0.764		
Alcohol[†]	11.36 (6.556–19.67)	**<0.001**	6.471 (3.289–12.73)	**<0.001**
Smoking[‡]	6.988 (4.036–12.1)	**<0.001**	2.967 (1.531–5.747)	**0.001**
Eckardt score ≥7	0.465 (0.240–0.902)	**0.023**	0.556 (0.283–1.091)	0.088
Type I achalasia on HRM[§]	1.058 (0.512–2.188)	0.878		
Type of achalasia, sigmoid[¶]	1.704 (0.995–2.918)	0.052		
Esophageal dilation[¶]	1.074 (0.622–1.856)	0.798		

[†]Consumption of alcohol every day was counted.
[‡]Cases of experienced or being currently smoking were counted.
[§]HRM diagnosis was analyzed in type I, II, and III achalasia.
[¶]Sigmoid achalasia and esophageal dilation were evaluated in 3421 cases of achalasia.
Bold *P*-values are statistically significant.
CI, confidence interval; HR, hazard ratio; HRM, high-resolution manometry.

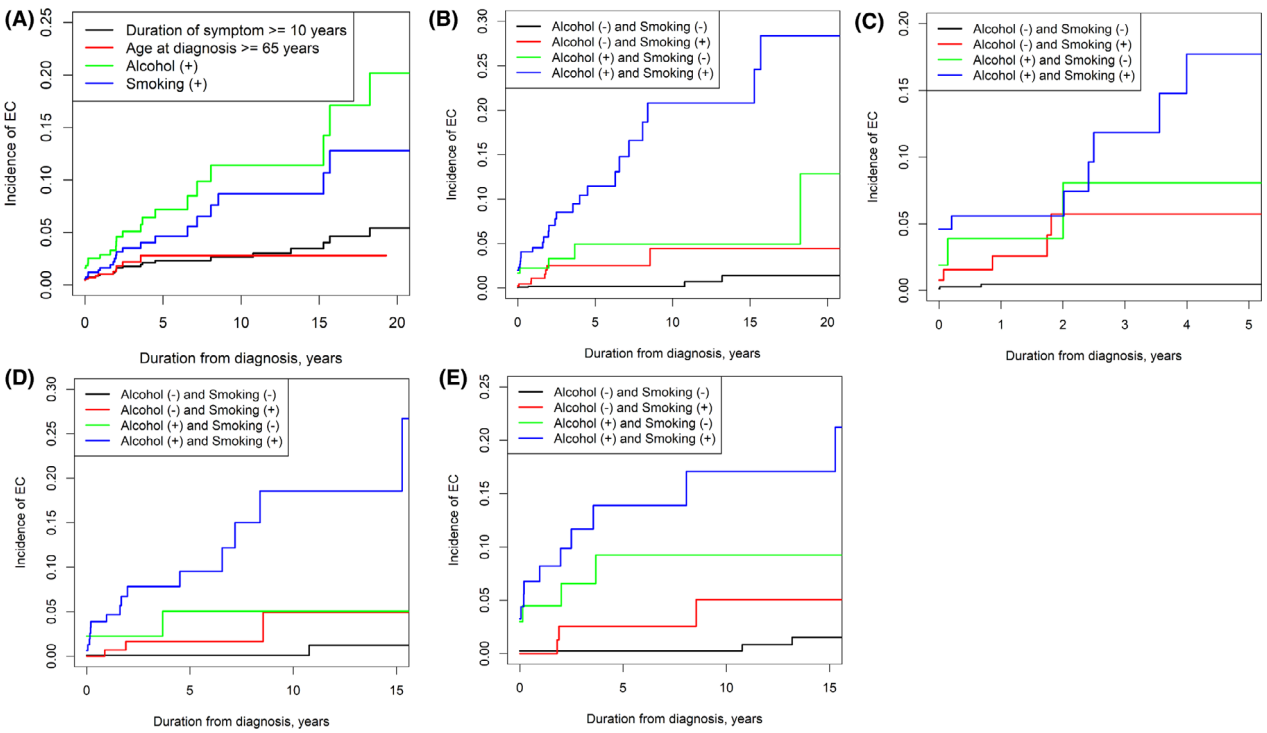

Figure 2 Cumulative incidence of esophageal carcinoma (EC) in cases with achalasia-related esophageal motility disorders (EMDs). Horizontal axis: duration from the diagnosis of achalasia (years). (A) Incidence of EC in relation to alcohol (regular drinking), smoking (current and past history of smoking), age ≥65 years, duration of symptoms ≥10 years. (B) Incidence of EC in relation to combined cases of alcohol and smoking (blue line), alcohol alone (green line), smoking alone (red line), and cases without an alcohol intake and smoking habit (black line). (C) Incidence of EC restricted to age ≥65 years. (D) Incidence of EC restricted to ages from 40 to 64 years. (E) Incidence of EC restricted to cases with duration of symptoms ≥10 years.

Table 2 Characteristics of esophageal carcinoma (n = 123) in cases of achalasia-related EMDs (n = 62)

Number of cases (n = 62)	
Age at diagnosis of esophageal carcinoma	65 (55.0–73.8)
Cases of multiple lesions	15 (24.2%)
Cases of metachronous lesions	16 (25.8%)
Cases of multiple or metachronous lesions	25 (40.3%)
Follow-up period, months	37.5 (14.8, 60.3)
Number of esophageal carcinoma (n = 123)	
Location (Ce: Ut: Mt: Lt: Ae)	0, 17, 72, 30, 4
Directional distribution	1–3 o'clock: 20 3–6 o'clock: 49 6–9 o'clock: 41 9–12 o'clock: 12 Circumferential: 1
Macroscopic types	0-IIa: 1 0-IIb: 68 0-IIc: 42 0-IIa + IIc: 3 0-IIb + IIc: 1 0-IIb + IIa: 1 0-IIc + Is: 1 Type 2: 4 Unknown: 2
Tumor size (mm)	20.5 (14.3, 33.0)
Histological diagnosis	Squamous cell carcinoma: 123 (one with basaloid component) Adenocarcinoma: 0
Treatment	ESD: 98, EMR: 1, CRT: 1, chemotherapy: 1, surgery: 18, follow-up without treatment: 1, plan for ESD: 3
Pathologic TNM classification	Stage 0: 52, Stage IA: 57, Stage IB: 5, Stage IIA: 3[†]

[†]Lymph node metastasis was not detected in the pathological investigation.

Ae, abdominal esophagus; Ce, cervical esophagus; CRT, chemoradiation therapy; EMDs, esophageal motility disorders; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; Lt, lower thorax; Mt, middle thorax; Ut, upper thorax.

Figure 2B. Log-rank analysis showed statistical significance between cases without alcohol intake and smoking, respectively (P < 0.001, <0.001, 0.001). Alcohol intake and smoking had a synergistic effect on EC development. They showed a high consumptive incidence of EC at nearly 0.20 around 10 years after the diagnosis of achalasia, although a single risk had an incidence of 0.05 within a 10-year follow-up period.

Incidence of EC restricted to age ≥65 years are shown in Figure 2C. Kaplan–Meier plots show statistical significance in combined cases with alcohol intake and smoking (P < 0.001), cases with alcohol intake alone (P < 0.001), and cases with smoking alone (P = 0.043) between cases without an alcohol intake and smoking. In regular drinkers with a history of smoking, the incidence of EC was predicted to be more than 0.15 within 5 years. In contrast, in patients who were diagnosed at 40–65 years of age (Fig. 2D), statistical significance was calculated in combined cases of alcohol intake and smoking (P < 0.001), cases with alcohol intake (P < 0.001), and cases with smoking (P = 0.20) between cases without an alcohol intake and smoking. In regular drinkers with a history of smoking, the incidence of EC reached 0.20 within 10 years. Finally, in patients with duration of symptoms ≥10 years (Fig. 2E), incidence of EC was compared in combined cases of alcohol intake and smoking, alcohol intake alone, and smoking alone. Log-rank analysis showed statistical significance between cases without an alcohol intake and smoking (P < 0.001, <0.001, 0.059). In regular drinkers with a history of smoking, the incidence of EC was >0.15 within 15 years. Conversely, in patients without a history of regular drinking and smoking, the incidence of EC was extremely low in all Kaplan–Meier estimates.

Challenges of ESD on the POEM-line

The characteristics of EC (n = 123) in cases of achalasia-related EMDs (n = 62) are summarized in Table 2. The median age at diagnosis was 65 (55.0–73.8) years and ranged from 43 to 87 years. Among 62 cases, multiple and metachronous lesions were observed in 15 (24.2%) and 16 (25.8%) cases, respectively. Multiple or metachronous lesions were observed in 25 cases (40.3%) during a median follow-up period of 37.5 months. EC was mostly located in the middle thoracic esophagus (72, 58.5%) and was commonly seen posteriorly from the 3:00 to 9:00 positions (90, 73.2%). Macroscopic types of superficial EC were predominantly 0–IIb (68, 58.1%) and 0-IIc (42, 35.9%). The histological diagnosis was chiefly squamous cell carcinoma (SCC); however, one case had a basaloid component. No adenocarcinomas were noted.

Of 3560 patients who underwent POEM, 43 patients with 89 ECs were identified. Among them, 17 (39.5%) were first diagnosed with EC during the screening period before POEM. A total of 14 patients (32.6%) were diagnosed within a year after POEM (Fig. S1).

The outcomes of ER were compared between patients diagnosed with EC before (n = 48) and after POEM (n = 28). The en bloc resection rate was 95.8% (46/48)

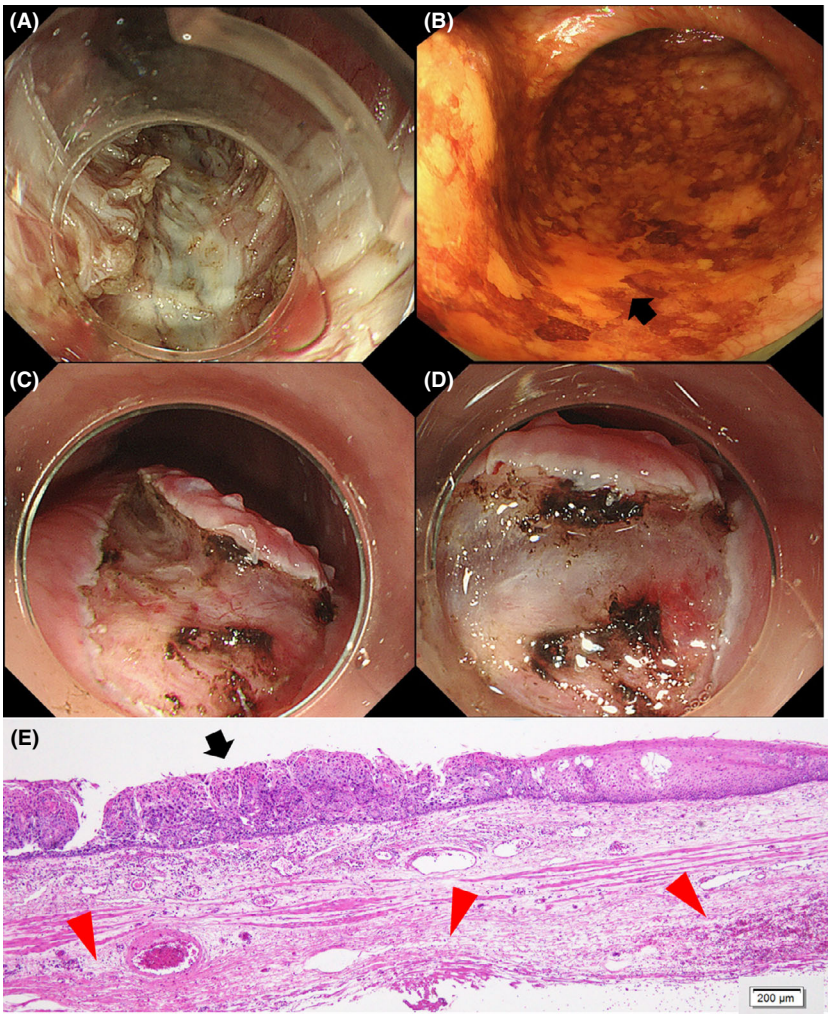

Figure 3 Endoscopic submucosal dissection (ESD) on the line of peroral endoscopic myotomy (POEM). POEM: posterior side myotomy was successfully performed for cases of achalasia (A). Thereafter, superficial esophageal carcinoma (black arrow, unstained area of iodine staining) was detected on the POEM-line (B). The planned ESD could be completed successfully despite severe submucosal fibroses hampering progress of the procedure (C, D). Severe fibrosis (red triangle) was found on final histology (E).

and 89.3% (25/28) in patients with superficial EC diagnosed before and after POEM, respectively. The success rate between both groups was not significant (P = 0.351). Three patients had ECs on the POEM-line. Two patients underwent ESD (Fig. 3), one of whom underwent piecemeal resection because of submucosal fibrosis. The other patient underwent surgery for superficial EC that developed on the POEM-line because ESD was difficult. Histological examination showed severe fibrosis.

The procedure and clinical course of POEM were compared among the group with EC before POEM, group with EC after POEM, and control group without EC (Table 3). The procedure time was shorter in patients diagnosed with EC before POEM than in those diagnosed after POEM (P = 0.018) and controls (P = 0.024). Furthermore, the incidence of reflux esophagitis was lower in patients diagnosed with EC before POEM than in controls (P = 0.025). Other procedure-related outcomes, adverse events, and efficacy were not significantly different among the three groups.

DISCUSSION

THIS LARGE-SCALE MULTICENTER study highlights the clinical potential of screening and surveillance endoscopy for EC in patients undergoing POEM. Our

Table 3 Safety and efficacy of peroral endoscopic myotomy (POEM) in cases of concomitant esophageal carcinoma diagnosed before and after POEM

	Cases of EC diagnosed before POEM (n = 22)	Cases of EC diagnosed after POEM (n = 21)	$P^{\dagger}$	Controls without EC (n = 3517)	$P^{\ddagger}$
Procedure time, ≥60 min	11 (57.9%)	19 (95.0%)	**0.018**	2795 (81.0%)	**0.024**
Posterior myotomy	18 (81.8%)	12 (60%)	0.222	2728 (77.9%)	0.856
Esophageal myotomy, >5 cm	16 (76.2%)	17 (85.0%)	0.697	2956 (85.3%)	0.386
Gastric myotomy, >2 cm	9 (42.9%)	9 (45.0%)	1.000	1918 (55.4%)	0.353
Adverse event, all[§]	1 (4.5%)	4 (20.0%)	0.164	237 (6.7%)	1.000
Adverse event, ≥IIa[§]	0 (0.0%)	2 (10.0%)	0.209	138 (3.9%)	1.000
Treatment success	21 (95.5%)	17 (85.0%)	0.333	3009 (92.8%)	1.000
Reflux esophagitis	7 (38.9%)	6 (37.5%)	1.000	1873 (65.2%)	**0.025**
Symptomatic GERD	0 (0.0)	3 (15.8%)	0.230	491 (15.7%)	0.059

[†]*P*-value was calculated between cases of EC pre- and post-POEM.
[‡]*P*-value was calculated between cases of EC pre-POEM and controls without EC.
[§]Adverse event was evaluated by Clavien-Dindo classification into I–V (7 degrees).
Bold *P*-values are statistically significant.
Missing value for analysis: Procedure time, 69; Direction of myotomy, 17; Length of myotomy, 54; Adverse event, 2; Treatment success, reflux esophagitis, and symptomatic GERD could be analyzed in 3281, 3150, and 3162 followed-up patients.
EC, esophageal carcinoma; GERD, gastroesophageal reflux disease.

findings indicated that a well-designed POEM was safe and effective in patients diagnosed with EC before POEM, and that ESD was feasible in patients with achalasia-related EMDs, although ESD for EC on the POEM-line was challenging. Our study further elucidated that duration of symptoms ≥10 years, age ≥65 years at diagnosis, regular alcohol consumption, and history of smoking are risk factors for EC. Therefore, organized surveillance endoscopy may be recommended in cases with a combination of these risk factors and with a history of EC.

As POEM is an endoluminal endoscopic surgery, screening endoscopy is crucial for diagnosing achalasia, ruling out pseudo-achalasia, and determining the POEM procedure (e.g. direction and length of myotomy). Further, surveillance endoscopy is necessary to monitor for adverse events and safely restart the oral intake. Our results indicate that repeated screening and surveillance endoscopies of POEM may increase the detection of superficial ECs. Even in cases of remnant liquid or food in the esophagus before POEM, EC in earlier stages can be detected immediately after POEM due to improved visibility.

Risk factors for EC development were clarified in a multivariate analysis using numerous EC cases in achalasia-related EMDs. In addition to the general risk factors for SCC, such as aging, alcohol intake, and smoking, this analysis identified achalasia-specific factors such as duration of symptoms. Most ECs have been reported to develop >10 years after symptom onset.[23,24] In our study, regular alcohol consumption and a history of smoking were identified as major risk factors. Moreover, the synergistic effect of alcohol intake and smoking, as reported by a previous study on general esophageal SCC,[25] was confirmed. Although dilated or sigmoid esophagus on esophagography are significant to reflect long disease duration, high-risk cases can be narrowed using the simple factors abovementioned. Moreover, high multiple and metachronal incidence of EC is possibly affected by achalasia-specific conditions, and those with a history of smoking and alcohol intake are more vulnerable than the general population.

The efficacy of EMR/ESD was elucidated in achalasia-related EMDs, although superficial ECs developing on the POEM-line should be treated carefully. Achalasia triggers inflammation in the mucosa, particularly in the epithelium, due to poor esophageal emptying.[26] Therefore, fibrosis in the submucosal layer is rare and possibly limited to end-stage cases.[27] This study also indicated that in addition to the middle thoracic esophagus reported in general SCCs,[28] posterior side was the main location of EC in patients with achalasia; this could be avoided in the POEM procedure for cases at risk for EC. The posterior side is possibly more affected by food and liquid retention, and the anterior side may be better considered for cases at risk for post-POEM ECs. Well-designed POEM for EC cases was safe, effective, and less time-consuming. This is because in patients with concomitant ECs, the myotomy length could be arranged shorter, not to interfere ESD for ECs, although our result did not show statistical significance of esophageal myotomy length. Short myotomy was reported to be equally effective with less RE rates.[29]

Adenocarcinoma was not identified in this study because the prevalence of adenocarcinoma is lower in Japan than that in western countries.[30] Therefore, the risk of

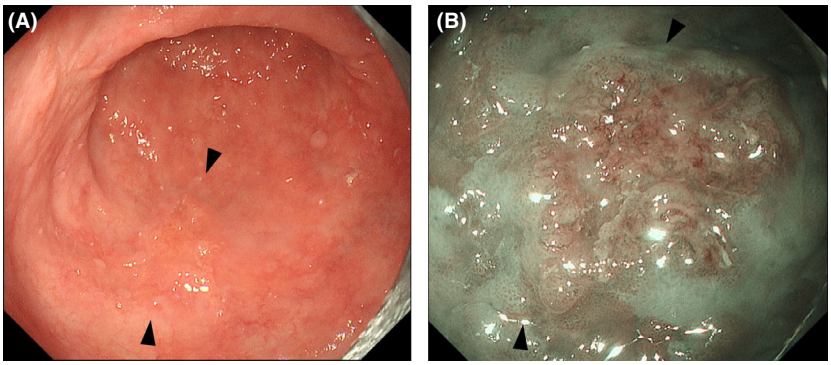

Figure 4 A case of advanced esophageal carcinoma detected after peroral endoscopic myotomy. (A) On the posterior side of the dilated lower thoracic esophagus, 0-IIa + IIc lesion was detected (black triangle). (B) The tumor was well-demarcated, as noted on endoscopy with narrow band imaging. Surgery confirmed that there was squamous cell carcinoma invading into the muscularis propria.

adenocarcinoma after interventions may not need excessive attention; however, given that long-term follow-up data are lacking in Japan, hence, required.

This study has several limitations. First, as this was a retrospective study, the interval of surveillance endoscopy was not fixed between cases. However, in cases of POEM, well-organized screening, and surveillance was performed from the perioperative period to around 1 year after the procedure. Nevertheless, blind spots due to sigmoid achalasia or food retention impaired EC detection. Additionally, chronic inflammation of the background epithelium also complicated the diagnosis of EC (Fig. 4). Therefore, careful examination is required, particularly in cases with several risk factors, to prevent a delay in diagnosis. Future studies should focus on the surveillance program using narrow band imaging or iodine staining and also investigate the overall and cause specific survival data. Second, there were several missing data regarding patient characteristics (BMI and Eckardt score). This was a potential source of bias. However, the rates of items with missing values were low, and the large data scale could compensate for the imperfections. This study was conducted as high-volume centers with HRM and POEM, which may also cause the selection bias for relative abundance of early ECs rather than advanced ECs. Third, the number of EGJOO, DES, and JE was not enough; hence, further prospective study focusing on these disorders is recommended.

In conclusion, advanced age, smoking, alcohol consumption, and long disease duration are risk factors for EC development. Therefore, organized surveillance may be considered in cases with a combination of risk factors and cases with a history of EC. In patients diagnosed with EC, well-designed POEM is safe and effective by freely arranging the direction and length of myotomy. Further, ER for EC in achalasia is feasible.

ACKNOWLEDGMENT

WE WOULD LIKE to thank Editage (http://www.editage.com) for editing and reviewing this manuscript for English language.

CONFLICT OF INTEREST

AUTHOR H.I. IS the president of the Japan Gastroenterological Endoscopy Society. The other authors declare no conflict of interest for this article.

FUNDING INFORMATION

THIS STUDY WAS partially supported by the JGA Clinical Research Grants (grant number: 2021-1). The funding played no role in the study design, analysis, or decision to publish the manuscript.

REFERENCES

1 Park W, Vaezi MF. Etiology and pathogenesis of achalasia: The current understanding. *Am J Gastroenterol* 2005; **100**: 1404–14.
2 Boeckxstaens GE, Zaninotto G, Richter JE. Achalasia. *Lancet* 2014; **383**: 83–93.
3 Vaezi MF, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG clinical guidelines: Diagnosis and management of achalasia. *Am J Gastroenterol* 2020; **115**: 1393–411.
4 Oude Nijhuis RAB, Zaninotto G, Roman S *et al.* European guidelines on achalasia: United European Gastroenterology and European Society of Neurogastroenterology and Motility

recommendations. *United European Gastroenterol J* 2020; **8**: 13–33.
5 Zaninotto G, Bennett C, Boeckxstaens G *et al*. The 2018 ISDE achalasia guidelines. *Dis Esophagus* 2018; **31**: 1–29.
6 Evans JA, Early DS, Fukami N *et al*. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointest Endosc* 2012; **76**: 1087–94.
7 Hirota WK, Zuckerman MJ, Adler DG *et al*. ASGE guideline: The role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006; **63**: 570–80.
8 Clouse RE, Staiano A, Alrakawi A, Haroian L. Application of topographical methods to clinical esophageal manometry. *Am J Gastroenterol* 2000; **95**: 2720–30.
9 Fox M, Hebbard G, Janiak P *et al*. High-resolution manometry predicts the success of oesophageal bolus transport and identifies clinically important abnormalities not detected by conventional manometry. *Neurogastroenterol Motil* 2004; **16**: 533–42.
10 Pandolfino JE, Ghosh SK, Rice J, Clarke JO, Kwiatek MA, Kahrilas PJ. Classifying esophageal motility by pressure topography characteristics: A study of 400 patients and 75 controls. *Am J Gastroenterol* 2008; **103**: 27–37.
11 Inoue H, Sato H, Ikeda H *et al*. Per-oral endoscopic myotomy: A series of 500 patients. *J Am Coll Surg* 2015; **221**: 256–64.
12 Sato H, Yokomichi H, Takahashi K *et al*. Epidemiological analysis of achalasia in Japan using a large-scale claims database. *J Gastroenterol* 2019; **54**: 621–7.
13 Samo S, Carlson DA, Gregory DL, Gawel SH, Pandolfino JE, Kahrilas PJ. Incidence and prevalence of achalasia in Central Chicago, 2004–2014, since the widespread use of high-resolution manometry. *Clin Gastroenterol Hepatol* 2017; **15**: 366–73.
14 Eckardt VF. Clinical presentations and complications of achalasia. *Gastrointest Endosc Clin N Am* 2001; **11**: 281–92.
15 Kahrilas PJ, Bredenoord AJ, Fox M *et al*. The Chicago classification of esophageal motility disorders, v3.0. *Neurogastroenterol Motil* 2015; **27**: 160–74.
16 Japan Esophageal Society. Descriptive rules for achalasia of the esophagus, June 2012: 4th Edition. *Esophagus* 2017; **14**: 275–89.
17 Shiwaku H, Inoue H, Sato H *et al*. Peroral endoscopic myotomy for achalasia: A prospective multicenter study in Japan. *Gastrointest Endosc* 2020; **91**: 1037–44.e2.
18 Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–13.
19 Lundell LR, Dent J, Bennett JR *et al*. Endoscopic assessment of oesophagitis: Clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; **45**: 172–80.
20 Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: Part I. *Esophagus* 2017; **14**: 1–36.
21 Rice TW, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: Application to clinical practice. *Ann Cardiothorac Surg* 2017; **6**: 119–30.
22 WHO Classification of Tumours Editorial Board. *WHO Classification of Tumours*, 5th ed., Vol. **1**. Lyon: International Agency for Research on Cancer, 2019.
23 Leeuwenburgh I, Scholten P, Alderliesten J *et al*. Long-term esophageal cancer risk in patients with primary achalasia: A prospective study. *Am J Gastroenterol* 2010; **105**: 2144–9.
24 Ponds FA, Moonen A, Smout A *et al*. Screening for dysplasia with Lugol chromoendoscopy in longstanding idiopathic achalasia. *Am J Gastroenterol* 2018; **113**: 855–62.
25 Takezaki T, Shinoda M, Hatooka S *et al*. Subsite-specific risk factors for hypopharyngeal and esophageal cancer (Japan). *Cancer Causes Control* 2000; **11**: 597–608.
26 Sato H, Takahashi K, Nakajima N *et al*. Full-layer mucosal histology in achalasia: Histological epithelial wave is characteristic in "pinstripe pattern"-positive achalasia. *Neurogastroenterol Motil* 2018; **30**: e13168.
27 Wu Q-N, Xu X-Y, Zhang X-C *et al*. Submucosal fibrosis in achalasia patients is a rare cause of aborted peroral endoscopic myotomy procedures. *Endoscopy* 2017; **49**: 736–44.
28 Watanabe M, Toh Y, Ishihara R *et al*. Comprehensive registry of esophageal cancer in Japan, 2014. *Esophagus*. Published online: 22 Sep 2021; DOI: 10.1007/s10388-021-00879-1.
29 Ghazaleh S. Short versus standard peroral endoscopic myotomy for esophageal achalasia: A systematic review and meta-analysis. *Ann Gastroenterol* 2021; **34**: 634–42.
30 Amano Y, Kinoshita Y. Barrett esophagus: Perspectives on its Diagnosis and management in Asian populations. *Gastroenterol Hepatol (NY)* 2008; **4**: 45–53.

SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Figure S1 Management of esophageal carcinoma in patients treated with POEM. There was a total of 43 patients with 89 esophageal carcinomas during the study period. Out of 43 cases, 31 (72.1%) were identified during screening through 1-year surveillance after POEM. In the ECs for endoscopic resection, the *en bloc* resection rate was 95.8% (46/48) in superficial EC diagnosed before POEM and 89.3% (25/28) in superficial EC after POEM, respectively, without significance ($P = 0.351$).

Table S1 Affiliations, ethics committee approval number in 14 participating facilities.

Table S2 Patients characteristics of achalasia-related esophageal motility disorders.

Table S3 Characteristics of cases of esophageal carcinoma ($n = 62$) in achalasia-related esophageal motility disorders ($n = 3707$).