

## Argon plasma coagulation for superficial esophageal squamous-cell carcinoma in high-risk patients

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### Abstract

**AIM:** To evaluate the usefulness and safety of argon plasma coagulation (APC) for superficial esophageal squamous-cell carcinoma (SESC) in high-risk patients.

**METHODS:** We studied 17 patients (15 men and 2 women, 21 lesions) with SESC in whom endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and open surgery were contraindicated from March 1999 through February 2009. None of the patients could tolerate prolonged EMR/ESD or open surgery because of severe concomitant disease (e.g., liver cirrhosis, cerebral infarction, or ischemic heart disease) or scar formation after EMR/ESD and chemoradiotherapy. After conventional endoscopy, an iodine stain was sprayed on the esophageal mucosa to determine the lesion margins. The lesion was then ablated by APC. We retrospectively studied the treatment time, number of APC sessions per site, complications, presence or absence of recurrence, and time to recurrence.

**RESULTS:** The median duration of follow-up was 36 mo (range: 6-120 mo). All of the tumors were macroscopically classified as superficial and slightly depressed type (0-IIc). The preoperative depth of invasion was clinical T1a (mucosal cancer) for 19 lesions and clinical T1b (submucosal cancer) for 2. The median treatment time was 15 min (range: 10-36 min). The median number of treatment sessions per site was 2 (range: 1-4). The median hospital stay was 14 d (range: 5-68 d). Among the 17 patients (21 lesions), 2 (9.5%) had recurrence and underwent additional APC with no subsequent evidence of recurrence. There were no treatment-related complications, such as bleeding or perforation.

**CONCLUSION:** APC is considered to be safe and effective for the management of SESC that cannot be resected endoscopically because of underlying disease, as well as for the control of recurrence after EMR and local recurrence after chemoradiotherapy.

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**Key words:** Argon plasma coagulation; Superficial esophageal cancer; Squamous-cell carcinoma; High-risk patient; Endoscopic therapy

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## INTRODUCTION

In Japan, 329 314 persons died of malignant neoplasms in 2006; esophageal cancer was the cause of death in 11 345 persons (3.45%). Esophageal cancer is the sixth most common type of cancer in men<sup>[1]</sup>. Squamous-cell carcinoma accounts for 90% of all esophageal carcinomas. Other histologic types, including adenocarcinoma, account for approximately 5%<sup>[2]</sup>. Approximately 90% of all esophageal cancers arise in the thoracic esophagus, and the middle thoracic esophagus is the most frequent location.

Progress in endoscopic diagnostic techniques, such as iodine staining and magnifying endoscopy with narrow band imaging, has led to the detection of increased numbers of superficial carcinomas of the esophagus<sup>[3-8]</sup>. In Japan, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are widely used as standard procedures for the treatment of superficial esophageal squamous-cell carcinoma (SESC)<sup>[9-13]</sup>. Radio-frequency ablation (RFA) is used as an endoscopic treatment for superficial esophageal cancer in Western countries, but it is not used in Japan because this procedure is not covered by the National Health Insurance system for the treatment of superficial esophageal carcinoma<sup>[14]</sup>.

Several studies have reported that argon plasma coagulation (APC) is useful for the management of Barrett's esophagus<sup>[15]</sup>, Barrett's esophageal cancer<sup>[16]</sup> and early gastric cancer<sup>[17,18]</sup>, but few studies have evaluated APC in patients with SESC<sup>[19,20]</sup>. We retrospectively studied the safety and usefulness of APC for SESC in high-risk patients with underlying diseases that precluded EMR and ESD and in those in whom APC was performed to control local recurrence after EMR or chemoradiotherapy.

## MATERIALS AND METHODS

The study group comprised 17 patients (15 men and 2 women; 21 lesions) who underwent ablation of their tumors by APC at the Department of Gastroenterology, Kitasato University East Hospital, from March 1999 through February 2009 (Table 1). The median age of the subjects was 68 years (range: 57-80 years). At the time of diagnosis, 11 patients were asymptomatic, and SESC was diagnosed incidentally on screening examinations for other diseases (peptic ulcer in 5 patients, esophageal varices in 2, gastritis in 2, after surgery for gastric cancer in 1, and after surgery for tongue cancer in 1). The other 6 patients exhibited symptoms (epigastric pain in 3, heartburn in 2, and hoarse voice in 1), and SESC was diagnosed upon further evaluation. All of the tumors were macroscopically classified as superficial and slightly depressed type (0-II c). The tumor diameter ranged from approximately 1 cm to approximately half of the circumference of the

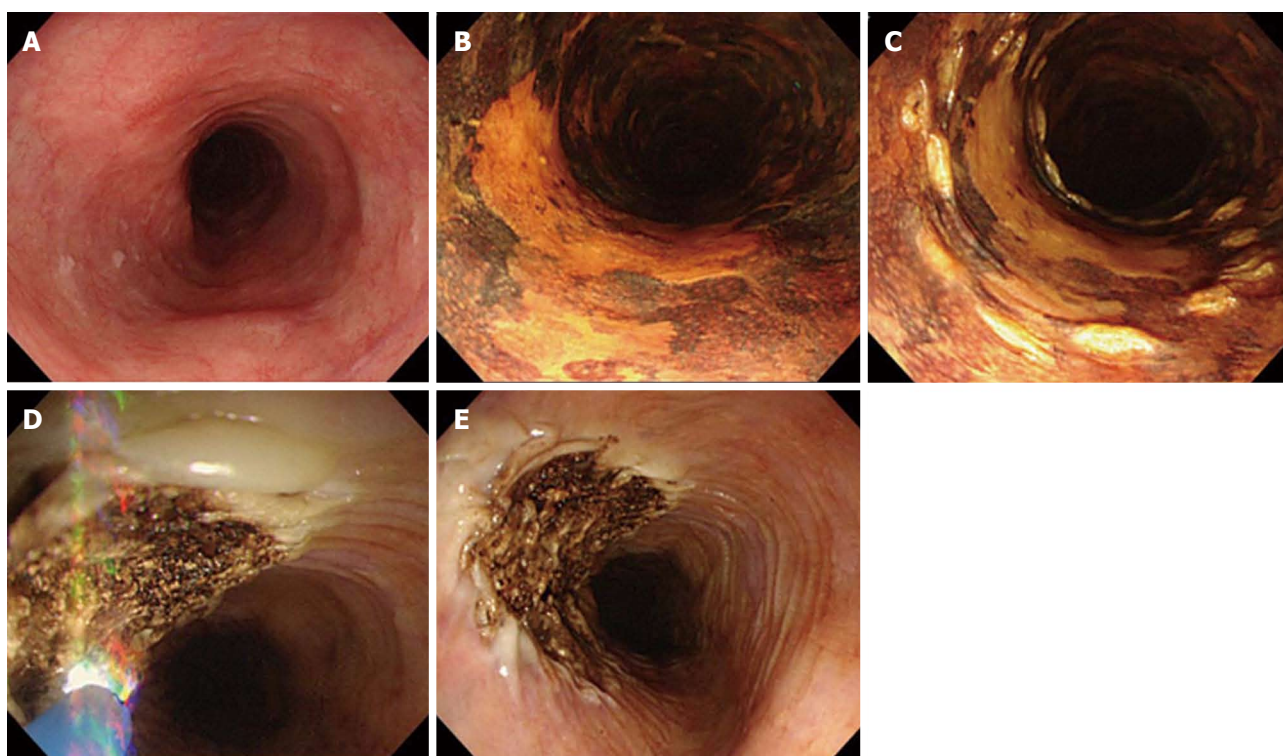
Table 1 Patient and lesion characteristics

Gender (men/women)	15/2
Mean age (range), yr	68 (57-80)
Location Ce/Ut/Mt/Lt/Ae	0/0/14/7/0
Macroscopic type	0-II c 21
Depth of invasion	T1a (m) 19 T1b (sm) 2
Previous treatment	6 (35.3%) (EMR 3, ESD 1, and CRT 2)
Concomitant disease	13 (76.5%) (liver cirrhosis 5, heart disease 4, cerebral infarction 1, other 3)

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; CRT: Chemoradiotherapy.

esophagus. The preoperative depth of invasion was clinical T1a (mucosal cancer) for 19 lesions and clinical T1b (submucosal cancer) for 2. Histopathologically, all of the tumors were confirmed to be esophageal squamous-cell carcinomas. EMR and ESD could not be performed because of underlying disease in 11 patients (15 lesions). APC was used to treat local recurrence after EMR or multiple metachronous tumors in 4 patients (4 lesions) and to manage local recurrence after chemoradiotherapy in 2 patients (2 lesions). Of the 17 patients, 13 (76.5%) had the following underlying diseases: liver cirrhosis in 5 patients, heart disease in 4, cerebral infarction in 1, after right lung resection with thrombophlebitis in 1, colon cancer operation in 1, and dementia in one patient. After informed consent was obtained from patients in whom anticoagulants could not be discontinued, those in whom prolonged endoscopic therapy was precluded by respiratory failure, and a patient aged 80 years, these patients asked to undergo APC among other possible treatment options. APC was therefore performed.

Before APC, endoscopy was performed to evaluate the macroscopic characteristics of the tumor. Next, 1.5% Lugol's solution (a diluted iodine-potassium solution) was sprayed on the mucosa to assess the lesion margins, and a biopsy specimen was taken and examined histopathologically. Endoscopic ultrasonography (probe, UM-DP20-25R, Olympus, Tokyo, Japan) was also performed before treatment to assess the depth of invasion. The absence of metastasis was confirmed by computed tomography. All of the tumors were macroscopically classified as superficial in type according to the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus by the Japanese Society for Esophageal Disease<sup>[21]</sup>. If possible, oral anticoagulants and antiplatelet agents were discontinued before treatment. APC was performed using an Olympus videoscope, a high-frequency oscillator unit (Erbotom ICC200, 1999 to 2004 or APC 2, 2004 to 2009, Elektromedizin Co. Ltd., Tuebingen, Germany), an argon gas supply unit, and a flexible argon plasma coagulator with an argon gas flow of 2 L/min and a high-frequency output of 40 W. The treatment technique was as follows. After conventional endoscopy, the lesion was stained with iodine (Figure 1A, B), and its circumference was marked by APC (Figure 1C). Subsequently, the entire



**Figure 1** Treatment procedure using argon plasma coagulation. A: Conventional endoscopy; B: Chromoendoscopy with iodine staining; C: Marking by argon plasma coagulation (APC); D: Marked area was treated by APC; E: The region was completely coagulated.

**Table 2** Patients characteristics

No.	Age (yr)	Sex	Depth	Time (min)	Times	Hospitalization days	Interval until recurrence (mo)	Retreatment	Illness
1	66	M	m	14	1	11	-	-	After right lung resection, thrombophlebitis <sup>1</sup>
2	59	M	m	22	4	35	-	-	LC (HCV), esophageal varices
3	68	M	m	26	4	68	7	APC	LC (alcoholic), IHD, remnant stomach
4	67	M	m1	30	1	12	-	-	OMI (three vessel stenosis) <sup>1</sup>
5	67	M	m	15	1	53	-	-	LC (HCV), HCC, esophageal varices, DM
6	79	M	m	10	1	13	-	-	Dementia
7	66	M	sm	34	2	47	-	-	LC (alcoholic), esophageal varices, DM
8	60	M	m	16	2	14	-	-	Arrhythmia, mitral regurgitation
9	74	M	m1	14	3	11	-	-	Cerebral infarction
10	66	M	m2	36	2	17	-	-	Post tongue cancer operation
11	71	M	m1	28	2	12	-	-	Multiple SESC
			m1						
			m1						
12	68	F	m1	15	1	0	-	-	Post colon cancer operation
13	76	M	m1	15	1	5	-	-	lesion of near after ESD scar
14	73	M	m1	15	1	0	-	-	Recurrence after EMR
15	70	M	m1	25	2	16	-	-	IHD <sup>1</sup>
16	57	M	sm1	12	4	12	3	APC	LC, recurrence after CRT
17	80	F	m2	15	2	14	-	-	Senior age, IHD, recurrence after CRT

<sup>1</sup>Anticoagulant therapy; m: Mucosa; sm: Submucosa; m1: Epithelium; m2: Lamina propria mucosae; sm1: Superficial layer of submucosa; APC: Argon plasma coagulation; LC: Liver cirrhosis; IHD: Ischemic heart disease; OMI: Old myocardial infarction; HCC: Hepatocellular carcinoma; DM: Diabetes mellitus; SESC: Superficial esophageal squamous-cell carcinoma; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; CRT: Chemoradiotherapy.

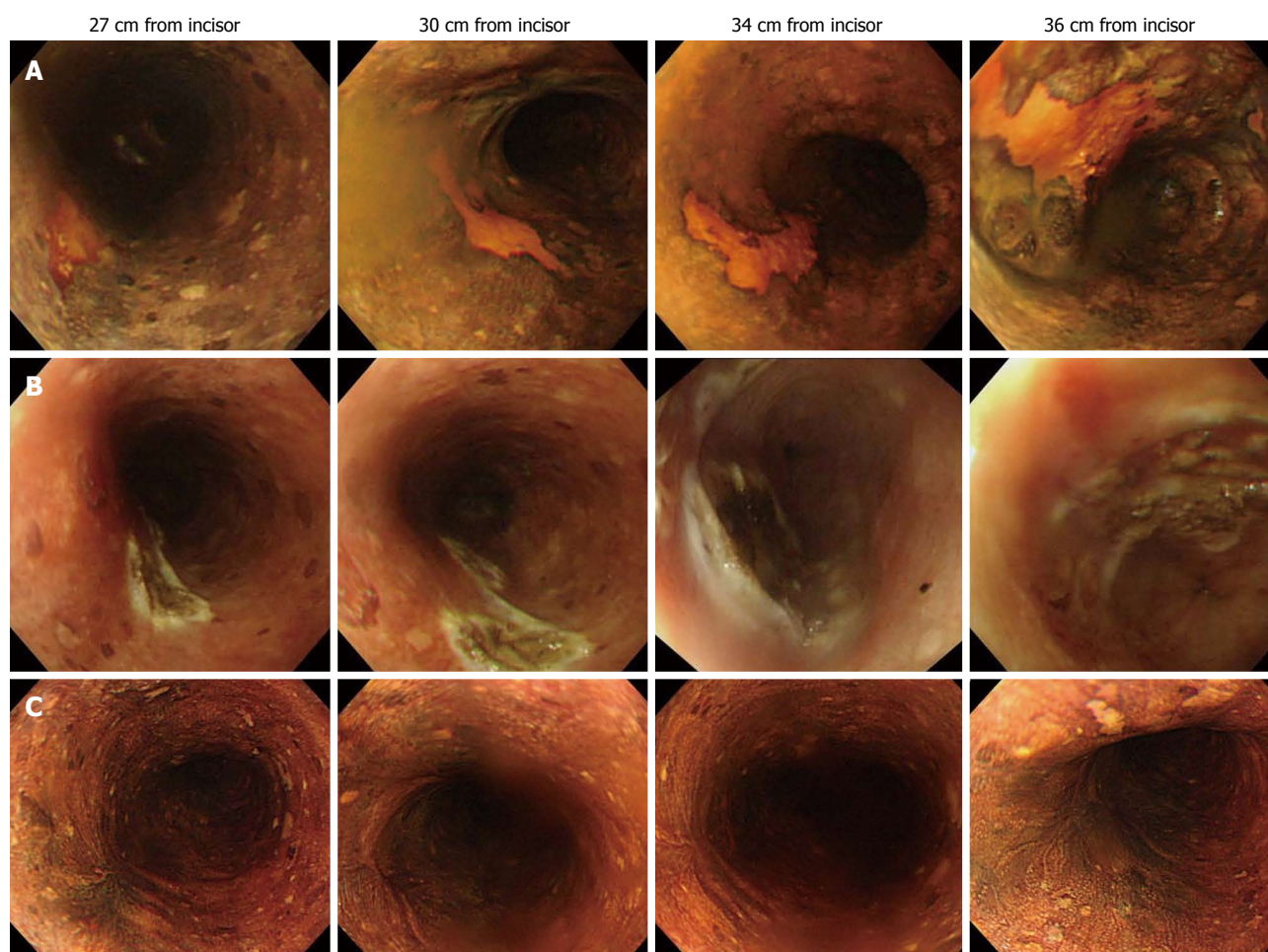
lesion inside the marked area was ablated until it turned black (Figure 1D, E). If residual tumor was suspected on follow-up endoscopy 1 wk after APC, the procedure

was repeated, exercising care to avoid excessive ablation. Thereafter, follow-up endoscopy was performed at approximately 2 mo, 6 mo, 12 mo, 18 mo, 24 mo, and 36



**Table 3** Outcomes of endoscopic argon plasma coagulation treatment (*n* = 21)

Median duration of follow up (mo)	36 (6-120)
Median time required for treatment (min)	15 (10-36)
Median number of treatment sessions(times)	2 (1-4)
Median duration of hospitalization (d)	14 (5-68)
Complications	
Postoperative bleeding	0
Perforation	0
Residual tumor and recurrence	2 (9.5%)

**Figure 2** Case presentation: Superficial esophageal carcinoma with four lesions. A: Endoscopic findings before treatment; B: Endoscopic findings after treatment; C: Endoscopic findings 2 years after treatment.

mo. Recurrence was confirmed by endoscopic examination after the application of iodine staining and biopsy. We retrospectively studied the treatment time, the number of APC sessions per site, the presence or absence of recurrence, the time to recurrence, and complications. The median follow-up period was 36 mo (range: 6-120 mo). Informed consent was obtained from all patients in accordance with the ethical guidelines of the Declaration of Helsinki.

## RESULTS

The patients' demographic characteristics are shown in

Tables 1 and 2. The results of treatment and follow-up are shown in Table 3. The median time per one-treatment session was only 15 min (range: 10-36 min). The median number of treatment sessions per site was 2 (range: 1-4). There were no treatment-related complications, such as bleeding or perforation. The median duration of follow-up was 36 mo (range: 6-120 mo). Among the 21 lesions, 19 (90.0%) showed no evidence of recurrence. The 2 other lesions recurred locally 3 mo and 7 mo after APC, respectively. Both recurrences were treated by repeat APC ablation. At the time of this writing, 1 patient had died of tongue cancer and the others were alive, with no distinct evidence of metastasis or recurrence.

### Case presentation

The patient was a 71-year-old man who had 4 lesions. APC was selected for treatment because prolonged ESD would have been difficult. Superficial and slightly depressed type (0-IIc) lesions unstained with iodine staining were found at 4 sites, located 27 cm, 30 cm, 34 cm, and 36 cm from the incisor teeth (all of the lesions were classified as clinical T1a) (Figure 2A). APC ablation was performed at all 4 sites (Figure 2B). Follow-up endoscopy after 2 years showed no lesions *via* iodine staining and no other evidence of recurrence (Figure 2C).

### DISCUSSION

APC is a non-contact technique that uses argon gas to induce tissue coagulation. In the field of gastrointestinal endoscopy, APC has been used to arrest gastrointestinal bleeding<sup>[22]</sup>, ablate Barrett's esophagus<sup>[14]</sup>, perform sclerotherapy of esophageal varices, and treat early gastric cancer<sup>[17,18]</sup>. At present, EMR and ESD are the endoscopic treatments of choice for superficial esophageal cancer, and studies of APC in patients with SESC are scarce<sup>[19,20]</sup>.

However, EMR and ESD are associated with an increased risk of bleeding in patients with liver cirrhosis or esophageal varices and those who are receiving anti-coagulant therapy<sup>[23]</sup>. Akiyama *et al*<sup>[24]</sup> used endoscopic variceal ligation for minute cancer of the esophagogastric junction accompanied by esophageal varices associated with a high risk of bleeding. ESD is thus often difficult to perform safely<sup>[25,26]</sup>.

In this study, we evaluated the usefulness and safety of APC in 11 patients (15 lesions) in whom EMR was precluded by concurrent disease, 4 with recurrence after EMR, and 2 with local recurrence after chemoradiotherapy. Of the 17 patients, 13 (76.5%) had underlying diseases, such as cardiopulmonary disease and liver cirrhosis (Table 1). Two patients (9.5%) experienced tumor recurrence but received repeat APC with no subsequent recurrence. No patient experienced complications such as bleeding or perforation.

Gastrointestinal perforation caused by APC has been reported<sup>[27,28]</sup>. Grund *et al*<sup>[29]</sup> performed APC in a large series of patients and reported that the incidences of gastrointestinal perforation and intestinal emphysema were 0.25% and 0.46%, respectively. The possibility of complications should thus be borne in mind when APC ablation is performed.

Patients with recurrence after EMR or local recurrence after chemoradiotherapy have scars caused by prior treatment, increasing the risk of perforation on repeat EMR. Nomura *et al*<sup>[30]</sup> used APC to control local recurrence after chemoradiotherapy and recurrence after EMR. Both conditions could be treated safely within a short time. Two of 10 patients experienced recurrence, but APC exhibited a low risk of perforation and allowed oral intake to be resumed earlier than EMR. APC was therefore recommended for patients in whom EMR is difficult to perform. In our study, APC was completed

safely and within a short time.

Photodynamic therapy is another option for the endoscopic treatment of superficial esophageal cancer but requires pretreatment and light shielding after application<sup>[31,32]</sup>. In contrast, APC is more convenient and straightforward, with a simple treatment procedure.

In conclusion, our results showed that APC effectively ablated SESC in patients with underlying disease and in those in whom EMR and ESD were not feasible. By repeating APC as required, the tumors were reliably ablated. APC is thus considered to be a safe and effective treatment that can be accomplished within a relatively short time. To confirm our results, additional prospective studies of larger numbers of patients are needed.

### COMMENTS

#### Background

In Japan, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are standard treatments for superficial esophageal squamous-cell carcinoma (SESC). However, the use of these procedures is contraindicated by underlying disease in certain patients.

#### Research frontiers

Argon plasma coagulation (APC) is useful for the management of Barrett's esophageal cancer and early gastric cancer, but few studies have evaluated APC in patients with SESC.

#### Innovations and breakthroughs

APC effectively ablated SESC in patients with underlying disease, as well as in those for whom EMR and ESD were not feasible.

#### Applications

APC is considered to be safe and effective for the management of superficial carcinoma of the esophagus that cannot be resected endoscopically because of underlying disease, as well as for the control of recurrence after EMR and local recurrence after chemoradiotherapy.

#### Peer review

In this study, the authors performed retrospective study that assessed the clinical usefulness and safety of APC for SESC in high risk patient. This study showed APC would be one of the good option to treat SESC especially in high risk patient, although further prospective study in large sample size is necessary to conclude it.

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