Thieme

Lessons from pathological analysis of recurrent early esophageal squamous cell neoplasia after complete endoscopic radiofrequency ablation

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ABSTRACT

Background Endoscopic radiofrequency ablation (RFA) is a treatment option for early esophageal squamous cell neoplasia (ESCN); however, long-term follow-up studies are lacking. The risks of local recurrence and "buried cancer" are also uncertain.

Methods Patients with flat-type ESCN who were treated with balloon-type ± focal-type RFA were consecutively enrolled. Follow-up endoscopy was performed at 1, 3, and 6 months, and then every 6 months thereafter. Endoscopic resection was performed for persistent and recurrent ESCN, and the histopathology of resected specimens was assessed.

Results A total of 35 patients were treated with RFA, of whom 30 (86 %) achieved a complete response, three were lost to follow-up, and five (14 %) developed post-RFA stenosis. Two patients had persistent ESCN and received further endoscopic resection, in which the resected specimens all revealed superficial submucosal invasive cancer. Six of the 30 patients with successful RFA (20 %) developed a total of seven episodes of local recurrence (mean size 1.4 cm) during the follow-up period (mean 40.1 months), all of which were successfully resected endoscopically without adverse events. Histological analysis of the resected specimens revealed that six (86 %) had esophageal glandular ductal involvement, all of which extended deeper than the muscularis mucosae layer. Immunohistochemistry staining for P53 and Ki67 suggested a clonal relationship between the ductal involvement and epithelial cells. None of the tumors extended out of the ductal structure; no cases of cancer buried beneath the normal neosquamous epithelium were found.

Conclusions Because ductal involvement is not uncommon and may be related to recurrence, the use of RFA should be conservative and may not be the preferred primary treatment for early ESCN.

Introduction

Endoscopic radiofrequency ablation (RFA) is increasingly being used to eradicate Barrett's neoplasia [1, 2], as well as the flat type of early esophageal squamous cell neoplasia (ESCN) [3–5]. Previous studies have shown good short-term outcomes of RFA in treating early ESCN, with a complete response rate ranging from 84 % to 97 % at 1 year and a low adverse event rate [3, 4].

The ablation effect of RFA on the human esophageal wall is uniform and superficial, with a maximal ablation depth to the level of the muscularis mucosae layer (~1000 µm) [6, 7]. Compared with other endoscopic treatment modalities such as argon plasma coagulation (APC) [8, 9], photodynamic therapy [10], and endoscopic submucosal dissection (ESD) [11], RFA therapy has several advantages over other ablative therapies, including uniform ablation, controlled depth, and the advantages over ESD, such as lower stricture or perforation risk [12]. However, long-term follow-up studies are still lacking. In addition, the patterns of recurrent and persistent ESCN after initial successful RFA have not been reported. Therefore, studies to elucidate whether RFA therapy is associated with a high recurrence rate, as with other tissue-destructive therapies [8], are warranted.

The major concern with RFA is the lack of post-treatment specimens to evaluate the curability of the whole lesion. Moreover, extension of neoplasia along mucosal surfaces into gland orifices and ducts of esophageal submucosal glands has previously been reported in ESCN [13–15]. However, whether these involved ducts beyond the reach of ablation will create a sheltered "niche," or even lead to a buried squamous cancer, has not been elucidated [15]. Therefore, this study aimed to evaluate the treatment outcomes, identify the risk factors for tumor recurrence, and determine whether buried ESCN exists in recurrent or persistent ESCN after RFA therapy.

Methods

Patient selection

We consecutively enrolled patients with flat-type early ESCN at E-Da hospital from July 2011 to July 2015. The inclusion criteria were: (i) flat-type (0-IIb) lesions; (ii) Lugol-unstained lesions occupying more than half of the circumference with a length longer than 3 cm; (iii) endoscopic ultrasound (EUS) and computed tomography (CT) showing no lymph node or distant metastasis; and (iv) magnifying endoscopy showing the intraepithelial papillary capillary loop as a type IV or V1 pattern according to the classification of microvascular architecture of superficial esophageal carcinoma [16].

Patients having esophageal stricture, a history of endoscopic resection, surgery, or radiation of the esophagus, uncontrolled coagulopathy, decompensated cirrhosis (Child–Pugh score ≥7), or a high risk of bleeding from esophageal varices were excluded from the study.

The Institutional Review Board of E-Da Hospital approved this study.

Radiofrequency ablation procedure

Prior to RFA, Lugol staining (1.5 %) was performed to determine the location and size of the lesions. The endoscopic RFA procedure was performed as previously described [12], and all procedures were performed by a single endoscopist (W.-L.W.), using a balloon-type RFA system (HALO360 system; Covidien GI Solutions, Sunnyvale, California, USA) as the initial treatment. We used a regimen of ablation (12 J/cm^2) – clean ablation (12 J/cm^2) for all of the procedures, and the treatment area was defined as the area from 1 cm proximal to 1 cm distal to the Lugol-voiding lesion-bearing segment of the esophagus.

After the endoscopic RFA, the patients were given esomeprazole 40 mg daily, and sucralfate suspension 5 mL (200 mg/mL) four times a day for 1 month. Follow-up endoscopy was performed 1 month after RFA to exclude post-operative stenosis, which was defined as failure of a standard endoscope (9.8-mm diameter) to pass through.

Follow-up and treatment of persistent or recurrent ESCN

The flowchart of patient enrollment and follow-up is shown in ▶ **Fig. 1**. After initial RFA, the patients underwent follow-up endoscopy with image-enhancing modalities including Lugol staining and narrow-band imaging (NBI) at 1, 3, and 6 months after the procedure, and every 6 months thereafter. Two biopsies were taken endoscopically from the normal-appearing mucosa over the treatment area and from Lugol-unstained areas or any suspicious lesions. A complete response was defined as the absence of squamous neoplasia from any biopsy specimen taken from the treatment area.

If residual lesions were detected during follow-up endoscopy at 1 or 3 months after initial RFA, one session of focal ablation with the HALO90 System (12 J/cm^2, 2 applications) was applied. If the lesions persisted (persistent ESCN) after balloon-type RFA and focal-type RFA, or recurred after the initial complete response phase, an endoscopic resection was performed to evaluate the histopathology.

Because P53 and Ki-67 molecules are well known to be involved in early esophageal carcinogenesis [17, 18] and cancer proliferation/invasion [19], respectively, we also analyzed the expressions of these two markers in the recurrent ESCN specimens. The expression of P53 (clone DO7, 1:100; Novocastra Leica Biosystems) and of Ki-67 (clone GM010, 1:200; Genemed) in the resected specimens were evaluated by immunohistochemistry staining. Esophageal glandular ductal involvement was defined as the presence of ductal cancerization accompanied by non-neoplastic ductal epithelium lined by a single layer of cuboidal cells [13].

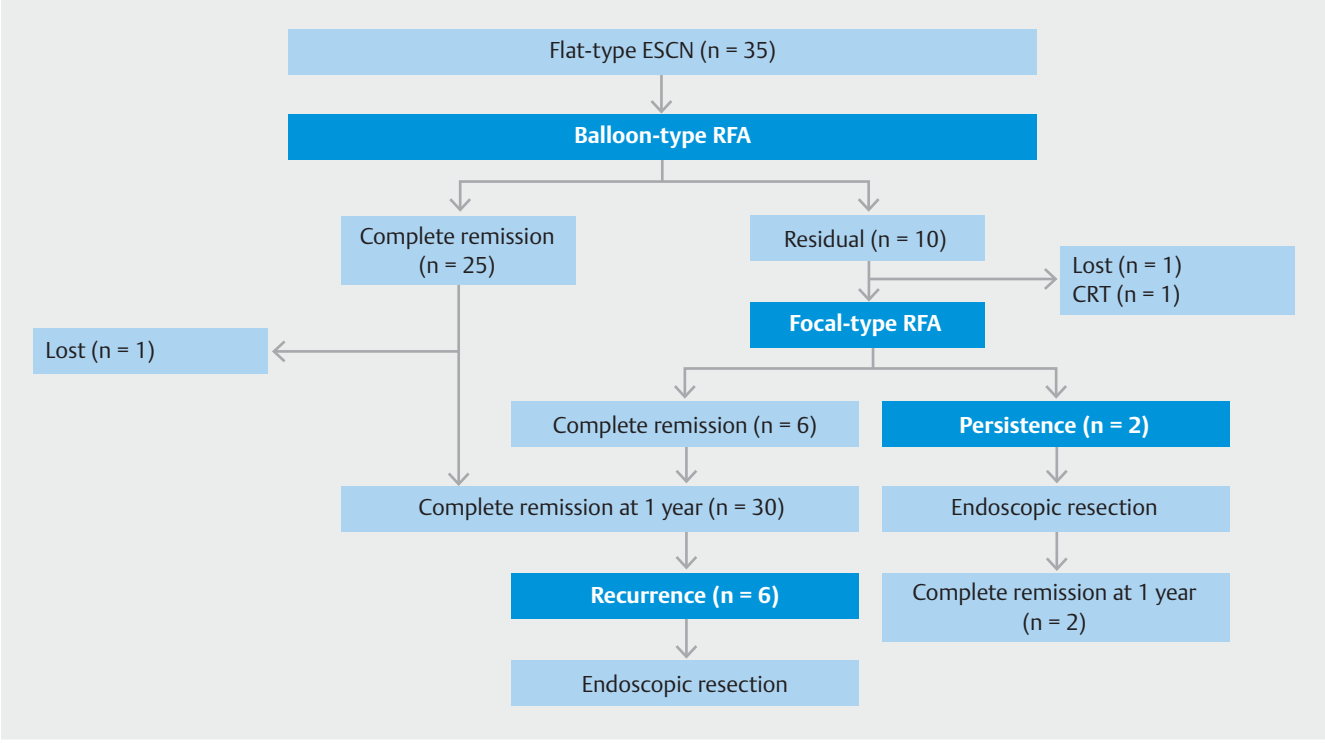
Statistics

Statistical analyses were performed with SPSS software (SPSS for Windows, version 18.0; SPSS Inc., Chicago, Illinois, USA). The cumulative recurrence-free survival was estimated using Kaplan–Meier curves. Cox proportional hazard analysis was used to assess the risk factors of local recurrence after RFA therapy. Significance was set at a P value of less than 0.05.

Results

Clinical characteristics and initial outcomes of the patients

The clinical characteristics and outcomes of 35 patients treated with balloon-type RFA are shown in ▶ **Table 1.** The mean tumor length was 72 ± 43 mm (range 30–170 mm). Twenty-five (71.4 %) patients achieved complete remission (CR) after primary RFA. During the procedure, two patients developed in-



▶ **Fig. 1** Flowchart of patient enrollment and follow-up. ESCN, esophageal squamous cell neoplasia; RFA, radiofrequency ablation; CRT, chemoradiotherapy.

tramural hematomas, and one patient had mucosal laceration during sizing; all of these resolved spontaneously, with no patients requiring further management. No major adverse events such as perforation, bleeding, or mortality were noted. Five patients (14 %) developed post-RFA esophageal stenosis and required balloon dilation (median 3 times; range 2 – 8) to resolve their symptoms.

There were 10 patients who had residual ESCN after primary RFA; the flowchart of their treatment is shown in ▶ **Fig. 1**. Two of these patients withdrew from the study because of decompensated cirrhosis and receiving further chemoradiation therapy for residual lesions, respectively. The other eight patients received focal ablation therapy, of whom six achieved CR thereafter, but two had persistent ESCN and subsequently received further ESD. Pathological assessments of the endoscopically resected specimens from these two persistent lesions revealed superficial submucosal invasive cancer (sm1). Both of these patients achieved CR at 1 year with no tumor recurrence after 20 and 43 months of follow-up, respectively.

A total of 31 patients achieved CR after balloon-type RFA and/or focal-type RFA; however, one patient was lost to follow-up after completing treatment. In total, 30 patients had CR at 1 year and were defined as having had successful RFA therapy.

Follow-up of the patients with successful RFA therapy

The mean follow-up period of the patients who had undergone successful RFA (n = 30) was 40.1 months (range 24 – 66 months). No cases of cancer progression, lymph node metastasis, or disease-related mortality were noted. The recurrence-free survival (mean 56.3 months [95 %CI 49.4 – 63.2]) is shown in ▶ **Fig. 2**.

Seven small locally recurrent neoplasms were detected in six patients (20 %) during the follow-up period, all of which developed between 18 and 30 months (median 19 months) after RFA and were subsequently completely treated with endoscopic resection (four endoscopic mucosal resections and three ESDs). Multivariable Cox regression analysis showed that pretreatment histology was the independent risk factor that predicted locally recurrent ESCN (adjusted hazard ratio 12.46 [95 %CI 1.12 – 138.44]; $P = 0.04$) (▶ **Table 2**).

Pathological assessment of the resected specimens from recurrent ESCN

The clinical and histopathological characteristics of the seven recurrent neoplasms are shown in ▶ **Table 3**. The mean size of the recurrent neoplasms was 1.4 cm (range 1 – 2 cm). The mean procedure time for endoscopic resection was 33.6 minutes (range 10 – 100 minutes). There were no procedure-related adverse events; however, two patients had severe submucosal fibrosis that was found during the procedure.

The final histology showed that five of the seven lesions (71 %) were high grade intraepithelial neoplasia. Of note, six of the

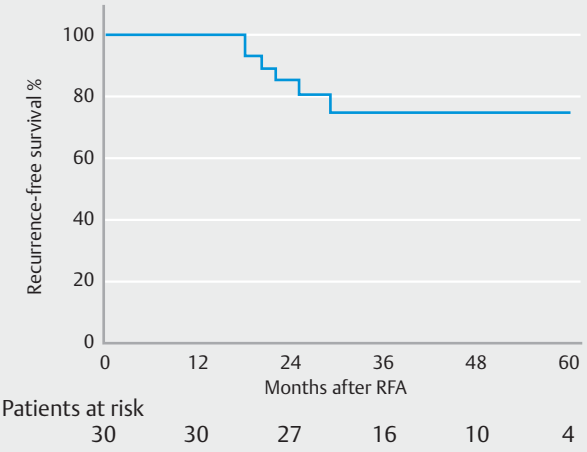
▶ **Table 1** The clinical characteristics and the outcomes of the 35 patients who underwent radiofrequency ablation (RFA).

Age, mean ± SD (range), years	52.3 ± 7.8 (41 – 76)
Sex, male, n (%)	34 (97 %)
BMI, mean ± SD (range), kg/m2	22.6 ± 2.8 (17.5 – 28.4)
Alcohol drinking, n (%)	33 (94 %)
Betel nut chewing, n (%)	26 (74 %)
Cigarette smoking, n (%)	32 (91 %)
Tumor location, n (%)	
▪ Upper	6 (17 %)
▪ Middle	21 (60 %)
▪ Lower	8 (23 %)
Tumor longitudinal length, mean ± SD (range), mm	72 ± 43 (30 – 170)
Circumferential extension of tumor, n (%)	
▪ ≤ 1 /2	20 (57 %)
▪ ≤ 3 /4	7 (20 %)
▪ Total circumference	8 (23 %)
Histology, n (%)	
▪ High grade intraepithelial neoplasia	25 (71 %)
▪ Squamous cell carcinoma	10 (29 %)
Complete response after primary RFA, n (%)	25 (71 %)
Complete response at 12 months, n (%)	32 (91 %)
Adverse events, n (%)	
▪ Perforation	0
▪ Mucosal laceration	1 (3 %)
▪ Intramural hematoma	3 (9 %)
▪ Stricture	5 (14 %)

SD, standard deviation; BMI, body mass index.

seven lesions (86 %) had esophageal glandular ductal involvement that extended deeper than the muscularis mucosae layer but not out of the glandular duct (▶ **Fig. 3**; ▶ **Table 3**). Consistent with the endoscopic findings, we found that all of the areas of ductal involvement developed near the center of the recurrent lesions.

Analysis of P53 and Ki67 expression by immunohistochemistry staining (▶ **Fig. 3**) revealed that six and seven of the lesions, respectively, had strong positive staining. In addition, the expression intensity of both markers was consistent between the epithelial and ductal-involvement neoplastic cells, suggesting that these neoplastic cells had a clonal relationship. The recurrent neoplasms may have arisen from the residual ductal involvement after RFA (▶ **Fig. 4**). Based on the analysis of these resected specimens, no cases of "buried squamous cancer" existed beneath the normal neosquamous epithelium.



▶ **Fig. 2** The recurrence-free survival curve of the 30 patients who underwent successful radiofrequency ablation (RFA) therapy.

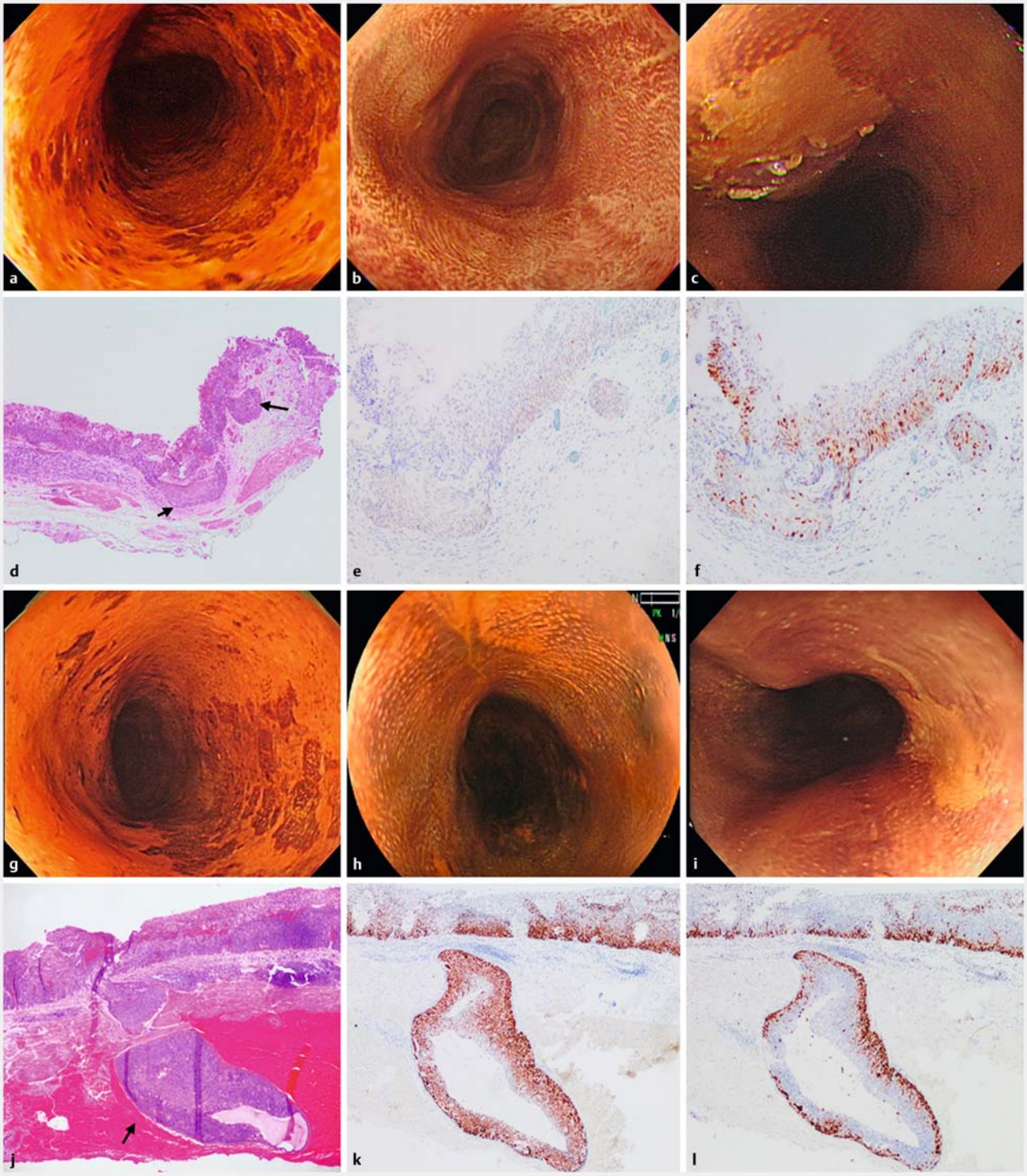
Discussion

Our results showed a good initial outcome of RFA in treating ESCN; however, a high recurrence rate (20 %) was noted. The recurrent ESCN usually appeared as small and round lesions; however, 86 % of them had esophageal glandular ductal involvement extending to the muscularis mucosae or submucosal layer. Because ductal involvement is not uncommon and may be related to recurrence, the use of RFA should be conservative. In addition, if the ESCN persisted after the initial session of balloon-type RFA and one session of focal-type RFA, it was usually found to be deep invasive cancer (sm1).

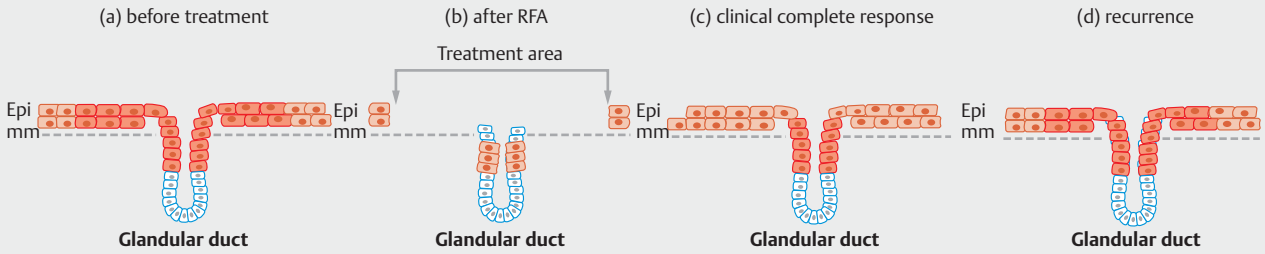
These lesions could not be totally eradicated by repeated RFA; however, they were all safely and completely treated with endoscopic resection. Therefore, if RFA is applied, we suggest that endoscopic resection is an appropriate rescue strategy for the management of recurrent or persistent ESCN after RFA therapy.

This study is the first to demonstrate ductal involvement in recurrent ESCN and the first to evaluate the possibility of buried cancer after RFA therapy. Esophageal submucosal glands are generally scattered throughout the entire esophagus. They are drained by ducts that are lined by a single layer of cuboidal epithelium and penetrate the muscularis mucosae and epithelium to open into the esophageal lumen [13].

Ductal involvement may serve as a pathway for tumor spread to the deeper layer [14]; however, the natural history and clinical implications of ductal involvement in early ESCN are still uncertain. One previous study evaluated the clinical significance of ductal involvement in an analysis of 201 surgically resected superficial esophageal squamous cell carcinomas (SCCs) [13]. The authors found that among 83 lesions with mucosal carcinoma, ductal involvement occurred in 11 (13.8 %), of which six (7.2 %) had ductal involvement extending to the submucosal layer. This carcinoma did not reach the submucosa through stromal invasion and there was no lymph node metas-



▶ **Fig. 3** Representative cases of recurrent esophageal squamous cell neoplasia (ESCN) treated with successful radiofrequency ablation (RFA) therapy. **a** Example of a lesion occupying the near-total circumference (unstained part) on Lugol chromoendoscopy. **b** No residual unstained lesions are seen after balloon-type RFA therapy (a biopsy confirmed complete remission). **c** A small recurrent neoplasm was detected in the treatment area 22 months after initial RFA therapy. **d** Histological analysis of the post-endoscopic mucosal resection specimen showed high grade intraepithelial neoplasia, with two areas of ductal involvement over the center of the lesion (arrows). **e** P53 immunostaining was weakly positive on both the ductal involvement and epithelial neoplastic cells. **f** Ki67 immunostaining was strongly positive in the recurrent ESCN. **g** A circumferential Lugol-unstained lesion. **h** Complete remission after RFA. **I** A small recurrent neoplasm was found at 25 months. **j** The resected specimen showed high grade intraepithelial neoplasia, with ductal involvement extending to the submucosal layer (arrow). Strongly positive immunostaining was seen with both: **k** P53; and **l** Ki67.



▶ **Fig. 4** Schematic of the possible pathogenesis of recurrent esophageal squamous cell neoplasia (ESCN) after radiofrequency ablation (RFA) therapy. **a** Before RFA treatment, the ESCN has esophageal glandular ductal involvement extending deeper than the muscularis mucosae (mm) layer. **b** After RFA, the neoplastic cells still reside in the glandular duct below the level of the muscularis mucosae. **c** After neo-epithelization, ductal involvement cells cannot be detected, with apparent clinical complete remission having been achieved. **d** Gradually, the neoplastic cells progress and extend from the duct, leading to tumor recurrence.

▶ **Table 2** Independent factors predicting local recurrence by univariable and multivariable Cox hazard regression analysis.

Factor	Variable	Number of cases	95 %CI	Hazard ratio	*P* value
Univariable					
Age	> 50 vs. ≤ 50 years	14/16	0.17 – 4.18	0.84	0.83
Tumor length	> 7 vs. ≤ 7 cm	13/17	0.20 – 4.99	1.01	0.99
Tumor circumference	Total vs. non-total	5/25	0.73 – 18.08	3.63	0.12
Location	Middle vs. other	17/13	0.15 – 3.65	0.74	0.71
Pretreatment histology	SCC vs. HGIN	8/22	1.21 – 89.85	10.4	0.03
Multivariable					
Tumor circumference	Total vs. Not-total	5/25	0.13 – 4.56	0.76	0.76
Pretreatment histology	SCC vs. HGIN	8/22	1.12 – 138.44	12.46	0.04

CI, confidence interval; SCC, squamous cell carcinoma; HGIN, high grade intraepithelial neoplasia.

tasis or impact on survival. Therefore, they concluded that ductal involvement is of little significance in esophageal SCC.

In the era of endoscopic treatment, ductal involvement may however have significant implications on the outcomes of patients treated with RFA. Because the maximal tumor ablation depth is the muscularis mucosae layer [6], ductal involvement will not be eradicated. According to a recent study that analyzed a total of 65 ESD specimens from lesions meeting the selection criteria of RFA studies, two of the 17 RFA-eligible cases showed ductal extension of neoplasia into submucosal glands [15].

In the current study, five of the 30 patients (16.7 %) had ductal involvement that presented within the recurrent tumors. In addition, the ductal involvement was always located at the center of the lesions, and the ductal involvement and epithelial neoplastic cells may have a clonal relationship. It is possible that most of the recurrent neoplasms may have arisen from residual ductal involvement after RFA (▶ **Fig. 4**), and this could be detected on endoscopy from 1.5 to 2.5 years after treatment. Fortunately, as in a previous report [13], the ductal involvement always remained in situ and no tumors showed invasion through the ductal involvement. Therefore, this RFA treatment cohort is the best model to realize their natural course, and ductal involvement is an important issue before considering RFA therapy.

Currently, ductal involvement cannot be detected before endoscopic treatment using conventional endoscopy, EUS, or even image-enhanced endoscopy. Future studies to identify the risk factors and the pathological characteristics of ductal involvement are necessary and may guide clinical decision-making with regards to endoscopic treatment and surveillance. Whether some new imaging modalities, such as volumetric laser endomicroscopy [20], could detect the ductal involvement or the dilated involved ducts may also require further investigation.

Previous studies have reported that RFA has good efficacy in treating early ESCN [3, 4,21]; however, long-term follow-up studies are lacking. Some studies have suggested a protocol with focal-type RFA every 3 months until CR is achieved [3, 4,21]. However, our results showed that persistent ESCN was associated with a deep cancer invasion depth to the submucosal layer (sm1). A repeated RFA strategy may be risky be-

▶ **Table 3** The clinical and histopathological characteristics of the seven recurrent squamous cell neoplasms that occurred in six patients after successful radiofrequency ablation (RFA).

Lesion number	Age, years	Pretreatment histology	Interval, months	Size, cm	Location	Endoscopic resection	Procedure time, minutes	Adverse events	Submucosal fibrosis	Histology	Ductal involvement present	Deepest level of ductal involvement
1	47	SCC	22	1.4	Upper	EMR	15	–	–	HGIN	Yes	mm
2	49	SCC	20	2.0	Middle	ESD	100	–	+	HGIN	No	–
3	65	SCC	25	1.5	Middle	ESD	30	–	–	HGIN	Yes	sm
4*	52	HGIN	18	1.0	Middle	EMR	10	–	–	HGIN	Yes	sm
5*	52	HGIN	18	1.5	Middle	ESD	60	–	+	HGIN	Yes	mm
6	53	SCC	29	1.5	Middle	EMR	10	–	–	SCC (LPM)	Yes	mm
7	41	SCC	18	1.0	Lower	EMR	10	–	–	SCC (LPM)	Yes	mm
Mean ± SD	51.2 ± 7.8	–	21.9 ± 4.3	1.4 ± 0.3	–	–	33.6 ± 34.4	0	2/7	–	6/7 (86 %)	–

SCC, squamous cell carcinoma; EMR, endoscopic mucosal resection; HGIN, high grade intraepithelial neoplasia; mm, muscularis mucosae; ESD, endoscopic submucosal dissection; sm, submucosa; LPM, lamina propria mucosal invasion.

* Developed in the same patient.

cause the lesions will not be completely ablated and this may delay treatment or even potentially lead to cancer progression or buried cancer.

In our study, rescue endoscopic resection was applied for persistent ESCN before the 6th month after initial RFA therapy, and no cases of cancer progression or buried cancer were noted. To avoid neoplastic progression, we believe that endoscopic resection is the most appropriate rescue therapy for persistent ESCN after RFA therapy, and these findings may have an important implication in clinical management. In the nine cases treated with rescue endoscopic resection for persistent and recurrent ESCN after previous RFA, two had severe submucosal fibrosis; however, no adverse events developed. Of particular note, the recurrent neoplasms were usually small (mean 1.4 cm), and therefore they could be resected safely and easily.

The major concern of RFA therapy is the lack of specimens to evaluate the curability of the whole lesion after ablation, and therefore the indication for RFA in treating ESCN should be carefully considered. In this study, we enrolled 35 patients, all of whom had flat-type ESCN, including 25 patients with high grade intraepithelial neoplasia and 10 with SCCs. Among the 10 patients with biopsy-confirmed SCC (pretreatment stage T1aN0), two developed persistent SCC after RFA and were proven to be sm1 invasive cancers by subsequent endoscopic resection; five developed recurrences, four of whom had ductal involvement.

These findings highlight the limitations of pretreatment staging, even though we enrolled only patients with flat-type lesions. Similarly to our previous study analyzing post-ESD specimens, we found that 30 % of the patients had histological upstaging compared with the pretreatment histology [12]. The incomplete eradication rate was relatively high in treating esophageal SCCs with RFA and the risk of delayed therapy, cancer progression, or buried cancer may exist. Therefore, the use of RFA for superficial esophageal SCCs should be carefully considered and may not currently be justified. On the other hand, among the patients with high grade intraepithelial neoplasia who received regular follow up (n = 22), only one developed recurrence with ductal involvement. Therefore, RFA seems to be suitable only for the treatment of high grade intraepithelial neoplasia.

Prior to the RFA procedure, we used Lugol staining to define the lesions. The effects of Lugol staining on the formation of post-RFA stenosis are controversial. One study showed it has a protective effect in human [4], but another study in a porcine model reported that it increases the stenosis risk [22]. Our study used a "Lugol-RFA – clean-RFA" regimen, and the stricture risk (14 %) is similar to the previous study [3, 4]. The stricture risk may be associated with the ablation regimen and the length of the treatment area [4, 5]. Further study is required to determine the best strategy of RFA therapy.

There are several limitations to this study. First, the number of patients is relatively small. However, we found that endoscopic resection may be appropriate rescue therapy for persistent and recurrent lesions and that it should be performed early to avoid delayed treatment and prevent cancer progression. Second, the prevalence of ductal involvement in this study

may be underestimated owing to the relatively short follow-up period. Future studies to determine the prevalence and risk factors for ductal involvement in patients with ESCN are warranted. Third, we found no buried cancers beneath the neosquamous epithelium, which may be because we resected the persistent and recurrent ESCN early. Further studies with a longer follow-up period may be necessary to validate whether buried squamous cancers really exist after RFA therapy.

Acknowledgments

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Competing interests

None.

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