

Evaluation of an Endoscopic Mucosal Resection in 38 Patients with Superficial Esophageal Carcinoma

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Abstract : Superficial esophageal carcinoma can be safely resected either surgically or endoscopically. We evaluated the indications for an endoscopic mucosal resection (EMR) and the optimal treatment modality for superficial carcinoma of the esophagus. From January 1995 to January 2004, 38 patients with superficial cancer of the esophagus underwent EMR (n = 38 patients, 44 lesions) utilizing the esophageal EMR-tube method or EMR cap-fitted panendoscope. All 44 superficial esophageal carcinomas were removed. No local recurrence occurred in any of the 17 lesions (38.6%) by a one-piece resection; however, recurrence was detected in five of the 27 lesions (61.4%) removed by a multi-piece resection ($p=0.162$). The five patients demonstrating recurrence underwent a second EMR, radiation therapy or surgery, and no further recurrence was noted in these patients. Seven of the patients who were found to have submucosal cancer also received additional treatment, including a surgical resection, radiotherapy, or chemoradiotherapy. Controllable esophageal bleeding following EMR was apparent in 13.2% of the patients; however, neither stenosis nor perforation was observed. In addition, nine of 38 cases presented multiple primary carcinomas including gastric carcinoma (4 cases), colorectal carcinoma (2 cases), hepatic carcinoma (2 cases) and tongue carcinoma (one case). These results indicate that a local resection with EMR is the preferred treatment for superficial esophageal cancers limited to the lamina propria mucosae. Additional therapy, such as chemoradiotherapy, supports EMR in the treatment of esophageal cancers accompanied by submucosal invasion. Patients with esophageal carcinoma have high risks of developing associated multiple hepatogastroenterological tumors.

Key words : Esophagus, Superficial carcinoma, Endoscopic mucosal resection, Multiple primary cancers

Introduction

Thanks to recent advances in endoscopic techniques, particularly dye-spraying endoscopy with iodine staining, early-stage asymptomatic esophageal carcinomas are now being detected with increasing frequency. As a result, the number of esophageal carcinomas which can be treated simply

by therapeutic endoscopy (which preserves the esophagus) has also increased. We herein present cases of superficial carcinoma of the esophagus which we treated with an endoscopic mucosal resection (EMR) and we also describe the clinical outcome of these cases.

Subjects and Methods

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(2) Part of this study was presented at the 73rd Japan Digestive System Endoscopic Conference Kyushu Branch Symposium, June 2002, in Kumamoto, Japan.

Table 1. Characteristics of Patients (38 cases, 44 lesions)

Sex (male/female)	35/3
Age (year)	67.0 (46~88)
Presence/absence of multiple cancers	9/29 (23.7%)
Tongue carcinoma	1 (asynchronism)
Gastric carcinoma	4 (synchronism, 3 ; asynchronism, 1)
Colorectal carcinoma	2 (synchronism, 1 ; asynchronism, 1)
Hepatocellular carcinoma	2 (synchronism)

Table 2. Analysis of Local Recurrence

		No recurrence (n=39)	Recurrence (n=5)	<i>p</i> value
Lesion site				
Upper-thoracic (%)	7 (15.9)	6	1	
Middle-thoracic (%)	32 (72.7)	29	3	
Lower-thoracic (%)	5 (11.3)	4	1	
Tumor size (cm)	3.0 (1~7)	2.9 (1~7)	3.8 (2~6)	<i>p</i> =0.2175
Number				
Single (%)	33 (86.9)	30	4	
Multiple (%)	5 (13.1)	3	1	
Method of EMR				
EEMR-tube (%)	37 (84)	33	4	
EMRC (%)	7 (16)	6	1	
One-piece resection	17 (38.6)	17	0	<i>p</i> =0.162
Multi-piece resection (%)	27 (61.4)	22	5	

EEMR-tube : endoscopic esophageal mucosal resection

EMRC : endoscopic mucosal resection with a cap-fitted panendoscope

Table 3. Macroscopic Features and the Depth of Invasion of Lesions Resected by EMR (38 cases, 44 lesions)

	m1	m2	m3	sm1	sm2
I pl				1*	
II a	1			1	1
II b	2			1	
II c	26	5	1	3	
II a + II c				2	

* : adenoid cystic carcinoma

The subjects comprised 38 patients (35 males and 3 females ; mean age, 67.0 years) with superficial esophagus carcinoma (44 lesions) who underwent EMR between January 1995 and January 2004 (Table 1). Written informed consent for all procedures was obtained from all patients before EMR. Multiple primary carcinomas were detected in nine cases (23.7%) : these included gastric carcinoma in four patients, colorectal carcinoma in two patients, hepatic carcinoma in two patients and tongue carcinoma in one patient. Each clinical case was investigated and compared in terms of lesion site, size, number of lesions, visible type, mode of EMR, rate of multi-piece resection, postoperative pathological diagnosis, presence or absence of additional treatment, EMR-related complications and the presence or absence of disease

recurrence. The depth of invasion was evaluated as follows : epithelial layer (m1), proper mucosal layer (m2), muscularis mucosae (m3), upper third of the submucosal layer (sm1), middle third of the submucosal layer (sm2), lower third of the submucosal layer (sm3), according to a draft of subclassification of superficial esophageal cancer that was formulated by the Japanese Society for Esophageal Disease.¹⁾ Cases characterized by lesions of up to 3 cm in size at the m1 and m2 levels were considered to be absolute indications, while cases with a suspected infiltration of the submucosal layer based on the general medical condition, as well as cases displaying large lesion areas, were considered to be relative indications. A diagnosis of the depth of infiltration was determined by x-ray examinations, endoscopic examinations (toluidine blue

staining) and endoscopic ultrasonography. Follow-up observations were performed by endoscopic examinations at 3, 6 and 12 months after the EMR procedure, and every 6 months thereafter. In addition, chest CT examinations were conducted once a year thereafter.

A statistical analysis was performed with the Fisher's exact test with a 5% significance level.

Results

Of the 44 lesions, 7, 32 and 5 were upper-thoracic (15.9%), middle-thoracic (72.7%) and lower-thoracic lesions (11.3%), respectively. The average lesion size was 3.0 cm, with a maximum diameter of 7 cm, occupying up to 2/3 of the perimeter. Thirty-three cases (86.9%) displayed a single lesion, whereas five cases (13.1%) exhibited multiple lesions. The endoscopic esophageal mucosal resection (EEMR)-tube and Endoscopic mucosal resection using the cap-fitted panendoscope (EMRC) methods were used for 37 (84%) and 7

(16%) lesions, respectively. A one-piece resection and multi-piece resection were conducted for 17 (38.6%) and 27 (61.4%) lesions, respectively. In comparison between the non-recurrent and the recurrent cases, the latter group demonstrated larger lesions; moreover, all the recurrent cases underwent a multi-piece resection (no statistical significance, Table 2).

The largest number of lesions (Table 3) was macroscopically IIc with 35 lesions (79.5%). The frequency of elevated cancer was low. Thirty-four cases of m1 and m2 were observed; moreover, eight cases of sm1 and one case each of sm2 and m3 were detected. The I pl type case featuring sm1 was an adenoid cystic carcinoma.

EMR-related complications (Table 4) included five instances of bleeding (venous bleeding, : 4; arterial bleeding, : 1). Neither perforation nor stenosis was recognized. The four cases with the complications of venous bleeding were successfully treated with endoscopic hemostasis, however, this was not possible in the single case of arterial bleeding, and consequently Sengstaken-Blakemore tubing was required. None of these complications necessitated surgical intervention; in addition, no deaths occurred due to these complications.

Additional treatment was administered in eight patients (Table 5). Submucosal infiltration of carcinoma was detected in EMR-resected pathologi-

Table 4. EMR-related Complications

	Number of cases (%)
Bleeding	5 (13.2)
Perforation	0
Stenosis	0
None	33 (86.8)

Table 5. Patients treated by both the EMR and additional treatments

Patient	Age/Sex	Depth	ly	v	Additional therapy	n	Follow-up period (mo)
1	66/M	sm1	0	0	Radiotherapy		36
2	65/M	m1	0	0	Radiotherapy		29
3	69/F	sm1	0	0	Chemoradiation		16
4	78/F	sm2	1	0	Chemoradiation		14
5	72/M	sm1*	1	1	Radiotherapy		10
6	66/M	sm1	1	0	Surgery	—	94
7	58/M	sm1	1	0	Surgery	—	52
8	65/M	sm1	1	0	Surgery	+	44

* : via vessel invasion

Table 6. Clinical course of patients with recurrent cancers

Case	Tumor size	Mode of Resection	Depth	Recurrent Period (mo)	Additional treatment	Recurrence after 2nd therapy	
1	88/M	3cm	Multiple-piece resection	m1	13	EMR	—
2	64/F	5cm	Multiple-piece resection	m2	6	EMR	—
3	68/M	3cm	Multiple-piece resection	m1	18	EMR	—
4	73/M	2cm	One-piece resection	m1	4	Multiple EMRs, Radiotherapy	+
5	46/M	5cm	Multiple-piece resection	sm1	12	Surgery	

cal tissue in seven cases (1 case via vessel infiltration). In addition, five of the seven patients (71.4%) demonstrated vascular invasion. Surgery was performed in three instances as a follow-up treatment; furthermore, chemoradiotherapy and radiation therapy were performed in two cases each. One case demonstrated an m1 status, however, because of the large lesion area and fibrosis from EMR, repeated EMR was not possible. As a result, radiation therapy was selected as an alternative treatment modality. No disease recurrence and no deaths occurred among the eight individuals undergoing follow-up treatment.

Repeated EMR was conducted for three lesions among the five recurrent cases (11.3%, Table 6) and no additional recurrence was detected in these cases. Case 5 failed to appear at the clinic for one year after the EMR procedure, and the patient was subsequently diagnosed to have progressive carcinoma 15 months after the initial treatment; surgical intervention was then prescribed. Case 4 underwent multiple EMRs in conjunction with APC treatment, however, the localized lesions could not be permanently treated. Repeated recurrence occurred at a later date, but since EMR was becoming increasingly difficult due to fibrosis, external irradiation (60 Gy) was added to the treatment regime. Despite the absence of localized recurrence, metastasis was observed in the chest tracheal lymph node and the patient died 64 months after the initial treatment.

Discussion

Since the initial establishment of an endoscopic mucosal resection as a treatment for superficial esophageal carcinoma in 1988,²⁾⁻⁵⁾ this technique has been widely applied in m1 and m2 cases which lack lymph node metastasis due to its ability to provide a superior QOL based on its low invasion level in comparison with conventional surgical procedures, and the consequent preservation of the esophagus.

In previous studies, three of 154 lesions (1.9%)⁶⁾ and two of 65 lesions (3.1%)⁷⁾ were found to display localized recurrence following EMR for superficial esophageal carcinoma. Furthermore, all recurrent cases involved a multi-piece resection.

In the present investigation, the recurrent group exhibited a larger lesion size; consequently, a greater number of multi-piece resections were conducted. Therefore, all recurrent cases originated from the multi-piece resection group. Most localized recurrent cases tend to be diagnosed approximately one year after surgical intervention.⁶⁾⁸⁾ The non-lifting sign is an effective treatment indicator for localized recurrent lesions, while patients lacking the non-lifting sign are treated with repeated EMR, while the non-lifting sign-positive cases are treated with chemoradiotherapy, laser irradiation and Argon plasma coagulation (APC).⁶⁾⁸⁾ The EEMR tube method was selected since it enables a larger volume of resection and covers a larger esophageal flexural area; EMRC was selected in instances in which EEMR tube application proved difficult. However, these manual techniques possess limitations in terms of the size of the resection; thus, the implementation of hooking EMR as developed by Oyama *et al.*,⁹⁾ which enables a large size, one-piece resection, is highly desirable. Hooking EMR can eliminate multi-piece resections, thus resulting in a reduced risk of localized disease recurrence.

EMR-related accidents include bleeding, stenosis and perforation. Bleeding was observed in the current investigation; however, neither stenosis nor perforation was detected. In the subgroup of patients with mucosal defects involving more than three fourths of the circumference, a defect longer than 30 mm was significantly associated with the development of esophageal stenosis.¹⁰⁾ No cases with mucosal defects involving more than three fourths of the circumference were observed present in this study. Moreover, perforation mainly occurs in instances of multi-piece resection, following suction of the defective mucous membrane during the primary resection stage. Accordingly, the localized infusion of adequate amounts of saline solution prior to EMR and re-snaring, effected by the momentary release of the snare and the unfastening of the mistakenly-strangled muscularis propria, are effective modalities for preventing perforation.¹¹⁾

Regarding the indications for EMR for superficial esophageal carcinoma, lesions with a level of m1 or m2 infiltration were considered to be an ab-

solute indication due to their lack of lymph node metastasis. In addition, the application of EMR for m3 and sm1 esophageal carcinoma has also recently been investigated. Makuuchi *et al.*¹²⁾ found lymph node metastasis in three of 61 m3 esophageal carcinomas (5.0%) and in seven of 43 sm1 carcinomas (17.1%). Based on these numbers, 80% of these cases exhibited no lymph node metastasis. As a result, such cases should be treated by EMR. However, the rate of correct pre-operative lymph node metastasis diagnosis is only about 80%¹²⁾ which is not very high. Regarding prediction factors, they reported that visual type 0-IIc+IIa type and 0-III type, cases with recognized vascular invasion (50% with positive lymph node metastasis) in the pathological diagnosis, inf γ , and poorly differentiated types are associated with a high probability of lymph node metastasis.¹²⁾ In the present study, case 7 from the additional treatment group (surgical treatment:3 sm1 cases) demonstrated vascular invasion in 0-IIc+IIa type; additional surgery was conducted although no lymph node metastasis was detected. However, surgical intervention in case 8 revealed lymph node metastasis. Therefore, a correct diagnosis of lymph node metastasis prior to surgery in m3 and sm1 esophageal carcinomas is extremely difficult.

In addition to surgical intervention, additional treatment choices include radiotherapy and radiochemotherapy. Muro *et al.*¹³⁾ performed radiation chemotherapy in the 71 cases of superficial esophageal carcinoma (m2 : 1, m3 : 2, sm1 : 24, sm2 : 22, sm3 : 22); moreover, 66 of the 71 cases (93%) demonstrated a complete remission (CR). Chemo-radiotherapy is comparatively more effective than radiotherapy alone.¹⁴⁾¹⁵⁾ Radiotherapy or chemo-radiotherapy was conducted in five cases in the present study; all five patients displayed CR with no disease recurrence. However, a postoperative high risk of disease recurrence and multiple lesions has been reported.¹³⁾ As a result, the current cases all require a careful follow-up over an extended period of time.

Esophageal carcinoma is characterized by a high frequency of recurrence. In particular, a brindled esophagus, which demonstrates numerous small non-stained areas after iodine staining, is known to exhibit a high risk of multiple esophageal

carcinomas.¹⁶⁾¹⁷⁾ Three early-stage carcinomas were detected in what appeared to be a brindled esophagus in the current investigation. Furthermore, esophageal carcinoma displays a high incidence of cancer overlap with other organs, and gastric carcinoma, carcinomas of the head and neck region, and colorectal carcinoma are the most prevalent. Among head and neck carcinomas, hypopharyngeal carcinoma is quite common.^{18)–21)} Consequently, esophageal cases involving EMR treatment require follow-up for allochronic esophageal carcinoma, as well as carcinomas of the head region, such as pharyngeal carcinoma, during endoscopic examinations.²²⁾

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