CRT. The majority of PSCCs were located in the hypopharynx. In macroscopic findings, there were various lesion types. The median lesion diameter was 20 mm, ranging from 5 to 50 mm. All PSCC lesions were superficial cancers with no advanced cancers.

Efficacy of 5-FU-CDDP Chemotherapy for PSCC

The treatment for PSCC was determined according to response to CRT for primary ESCC (fig. 3). CRT for ESCC resulted in CR in 8 of the 14 patients. In contrast, only 3 of 14 PSCC lesions were evaluated as CR. The 3 PSCC-CR lesions (38%) were found in the ESCC-CR patients (fig. 3). However, the 3 PSCC-CR lesions were only transiently disappeared, and local recurrence was found in the same region. In the 6 ESCC-non-CR patients, there were no PSCC-CR lesions. Of the 6 patients, 2 who were finally evaluated as partial response for ESCC had transformation of their superficial PSCC to invasive lesions. Therefore, active salvage surgery with laryngopharyngeal and esophageal resection was undertaken in these 2 patients. Of the remaining 4 patients, 2 lesions had no change in size and shape while the other 2 were evaluated as partial response because of decreased tumor size.

ER for PSCC and Complications

ER for PSCC was performed in the 8 patients with ESCC-CR. Histologic findings showed the depth of infiltration was invasive PSCC in 2 patients and cancer in situ in 6 patients. However, no lymphovascular involvement was found in any of the 8 cases with PSCC.

Major complications associated with ER included 1 case of aspiration pneumonia. There were no severe complications such as subcutaneous emphysema, post-ER stricture or delayed bleeding. Of the 8 PSCC lesions, 1 was recurrent 4 months after ER. Because the recurrent lesion was superficial and small, an additional ER was performed with complete resection. The median duration of follow-up after ER was 28 months ranging from 12 to 39 months, and no more recurrences of the PSCC were found.

Survival

The 8 ESCC-CR patients received ER for PSCC and the remaining 6 ESCC-non-CR patients did not. The pretreatment clinical stages of ESCC in 8 ER and 6 non-ER patients were 4 and 1 patient in stage I, 1 and 1 in stage II, 2 and 4 in stage III and 1 and 0 in stage IVA, respectively. There were no differences in clinical staging variety in the ESCC pretreatment evaluation between ER and non-ER patients. Median survivals of ER and non-ER patients were 51 and 14 months, respectively (p = 0.002; log-rank test; fig. 4). The 3-year survival rates of ER and non-ER patients were 63 and 0%, respectively. In contrast, 4 of the 8 ER patients died during follow-up periods. Preclinical stages of the 4 patients were 2 patients in stage I, 1 in stage II and 1 in stage IVA, respectively. The 2 patients in stage I died of radiation-induced pneumonia and cerebral infarction. The patient in stage II died of ESCC progression with lymph node metastases and the remaining patient in stage IVA died of multiple lung metastases.

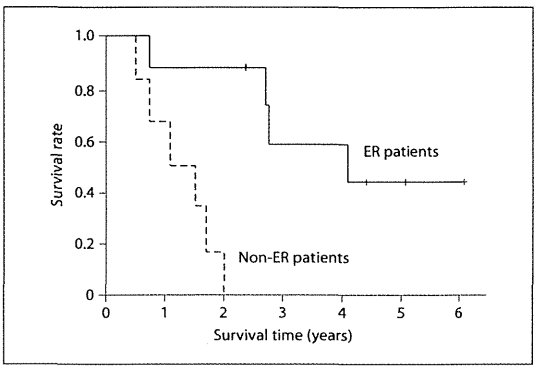

Fig. 4. Overall survival. Median survivals of ER and non-ER patients were 51 and 14 months, respectively (p = 0.002; log-rank test).

After CR confirmation in ESCC, ER was performed in PSCC. The median duration from commencement of CRT to ER in the 8 patients receiving ER was 5.4 months, ranging from 3.8 to 18.9 months. ER was performed in 5 of the 8 patients immediately after CRT since PSCC lesions of the 5 patients were not evaluated as CR. However, the time periods to perform ER after CRT were extended in the remaining 3 PSCC-CR patients from 10 to 18.9 months due to following-up for PSCC-CR. There were no cases in which superficial PSCC transformed to an advanced stage during the follow-up periods. Thus, no functional disorder caused by progression of PSCC, such as difficulty swallowing or speaking, were found in ER patients during all follow-up periods.

Discussion

Of 348 patients with invasive ESCC, 14 (4%) had superficial PSCC detected through endoscopic screening of the oral cavity and pharynx. Standard 5-FU-CDDP CRT targeted for invasive ESCC was administered to the 14

patients with synchronous superficial PSCC and invasive ESCC. After CRT, 8 (57%) were evaluated as CR for invasive ESCC, while only 3 patients with superficial PSCC (21%) achieved transient CR despite receiving 5-FU-CDDP chemotherapy. Therefore, systemic 5-FU-CDDP chemotherapy had no CR potential for superficial PSCC. In contrast, ER for superficial PSCC is quite effective even in a situation after chemotherapy because of minimally invasive treatment with no functional disorder in the pharyngeal region. We propose using novel treatment strategies for synchronous superficial PSCC and invasive ESCC.

Acetaldehyde associated with alcoholic beverage and aldehyde dehydrogenases 2 heterozygous traits can cause pharyngeal and esophageal cancers [7]. According to recent reports regarding multiple cancers, the prevalence of multiple LULs is a biomarker of synchronous or metachronous cancers in the esophagus and head and neck regions [19–21]. In our present study, all 14 patients with synchronous ESCC and PSCC had both daily alcohol consumption and multiple LULs in their esophageal background epithelium. Lugol chromoendoscopy is useful not only to detect superficial ESCC but also to understand the risk of multiple cancers. However, the Lugol solution cannot be routinely sprayed in the region of the pharynx and larynx of patients under conscious sedation because of the stimulation caused by the application of the solution. Thus, we suggest that detecting superficial PSCC by NBI is useful in ESCC patients, especially those with both an alcohol drinking habit and multiple LULs in their esophagus.

5-FU-CDDP treatment has been performed in PSCC patients since the 1980s. The CR rate of this therapy without radiotherapy was 17–20% of locally advanced or metastatic PSCC cases in phase I–II studies [13, 14], and was 5–7% of metastatic or recurrent cases in phase III studies [22, 23]. 5-FU-CDDP treatment alone is likely to be more effective in locally advanced PSCC than in metastatic PSCC. In contrast, there has been no study of 5-FU-CDDP alone in PSCC of early clinical stage, especially stage 0–I. Therefore, the 5-FU-CDDP treatment efficacy in superficial PSCC is uncertain. If the therapy had a high efficacy for superficial PSCC, overlooked superficial PSCC would be cured by the systemic 5-FU-CDDP therapy given to treat ESCC. This is quite a benefit for the patients with these synchronous cancers. As a result, PSCC-CR was found, while no efficacy in continuing CR for superficial PSCC was found in 5-FU-CDDP treatment. In contrast, no progression of PSCC was found in patients having excellent efficacy with CRT for ESCC, although the time periods until CR confirmation for ESCC were required to be at least several months. A good correlation in treatment efficacy between PSCC and ESCC was indicated. It seems that 5-FU-CDDP chemotherapy has a potential in restraining the progression of PSCC. In some recent reports, platinum-based chemotherapy or CRT plus cetuximab were more effective in esophageal and the head and neck cancers [24–26]. CRT combined with cetuximab, a molecular targeted drug, may contribute to a novel treatment strategy for patients with synchronous PSCC and ESCC.

The outcomes of ER for superficial PSCC have been reported [27]. Complications, such as laryngeal edema requiring overnight intubation, aspiration pneumonia and sustained dermatitis around the mouth caused by backflow of Lugol solution from the pharynx, were found in 13% of patients after ER [27]. Complications are transient and tolerable in most of cases, and feasibility is confirmed with no functional disorder. In our study, there were no severe complications, with high treatment efficacy for ER during long follow-up periods, although ER was performed in the condition after 5-FU-CDDP chemotherapy. It is important to maintain function with respect to swallowing and/or speaking, and to perform ER under cooperation with head and neck surgeons.

Regarding the treatment strategy, CRT for ESCC should be the initial therapy in patients with both superficial PSCC and ESCC. As the second step, ER for PSCC should be determined after evaluation of CRT for ESCC. A factor deciding the prognosis of patients with the synchronous cancers depends on the CRT effects for ESCC. In our previous study, the prognosis between CR and non-CR cases of ESCC was quite different [28]. In our present study, the median survival time of ER (ESCC-CR) patients was also significantly longer than that of non-ER (ESCC-non-CR) patients. Furthermore, 5-FU-CDDP chemotherapy showed potential in restraining the progression of PSCC including transient CR. If ER was performed initially, the period before commencement of CRT would be delayed. In addition, when complications occurred in ER, the commencement would be further delayed. Therefore, ER for superficial PSCC should be secondary to CRT for invasive ESCC. We suggest that the ER for PSCC contributed to the beneficial prognosis in patients with synchronous superficial PSCC and invasive ESCC. It is uncertain whether all superficial PSCC lesions progress to an advanced stage in the natural history. However, if superficial PSCC was overlooked and progressed to an advanced stage in ESCC-CR patients, it would be difficult to achieve long survival. Furthermore,

when the patients with advanced PSCC receive active treatments, such as surgery or CRT, functional disorder of swallowing or speaking might occur. On this point, ER for superficial PSCC can prevent a progression to an advanced stage, with favorable prognosis.

In our present study, not all patients received magnifying NBI endoscopy in their initial pretreatment evaluation, while superficial PSCC was detected in 4% of 348 patients with newly diagnosed ESCC. From the results of previous studies, Shimizu et al. [29] proposed that superficial PSCC was metachronously found in 2% of ESCC patients receiving EMR through laryngoscopy. Katada et al. [30] reported that superficial PSCC was found in 11% of patients with previous or current ESCC through magnifying NBI observation. In our study, 12 (86%) of the 14 cases of superficial PSCC were detected by magnifying NBI observation. We emphasize that NBI endoscopy in the oral region should be performed in ESCC patients to detect superficial PSCC. A recent report of a multicenter trial suggested that NBI should be the standard examination for the early detection of superficial cancer in the esophagus and head and neck [12]. Furthermore, we demonstrated that magnifying NBI endoscopy was effective in following up patients after treatment since we could detect a transient lesion disappearance or a minor local recurrence. We suggest that NBI should be used not only in the screening observation of the pharynx but also for follow-up endoscopy after treatment with 5-FU-CDDP chemotherapy or ER. However, a limitation is that our study was a single-institute retrospective study.

In conclusion, systemic chemotherapy for superficial PSCC was regrettably found to have no potential in continuing CR, while CRT as targeted to ESCC led to control of superficial PSCC progression. In the present condition, the detection of superficial PSCC is important in making a treatment strategy for synchronous PSCC and ESCC. One of the treatment strategies in patients with the synchronous cancers was that CRT for invasive ESCC should precede ER for superficial PSCC, and that the treatment of superficial PSCC should be decided according to the efficacy of CRT for ESCC. ER for superficial PSCC caused no functional disorders and was effective in curing even the lesions remaining after 5-FU-CDDP chemotherapy. We suggest that curative ER contributes to a beneficial prognosis in patients with ESCC-CR and believe a large-scale clinical trial will be required to establish treatment strategies.

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Disclosure Statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Effect of RECIST revision on classification of target lesions and overall response in advanced gastric cancer patients

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Abstract
Background The Response Evaluation Criteria in Solid Tumors (RECIST) was revised in 2009, based on a large dataset of 6512 patients from 16 trials. However, no gastric cancer patients were included in those data. The purpose of this study was to clarify the difference between RECIST version 1.0 and version 1.1 in advanced gastric cancer.
Methods From 2004 to 2009, 129 consecutive patients with advanced gastric cancer received S-1 plus cisplatin as first-line treatment at the National Cancer Center Hospital East. Ninety-seven of these patients who had had baseline and post-treatment computed tomography scans performed were included in this study. Measurements of tumors were conducted retrospectively.
Results At the baseline of first-line chemotherapy, 172 lymph nodes in 54 patients were considered to be candidate target lesions by RECIST version 1.0. However, only 38 % of the lymph nodes were classified as target lesions by RECIST version 1.1, with 47 % classified as non-target lesions and 15 % classified as non-pathological. By RECIST version 1.0, the proportion of patients with target lesions at the baseline of first-line chemotherapy was 67 % (65/97), and this percentage was significantly reduced according to RECIST version 1.1 (53 %; 51/97) (McNemar's exact test, $P < 0.001$). The findings at the baseline of second-line chemotherapy were similar (reduced from 62 to 49 %; McNemar's exact test, $P = 0.002$). Overall response rates of first-line chemotherapy were 52 % (34/65) according to RECIST version 1.0 and 55 % (28/51) according to version 1.1.
Conclusions The revision of RECIST significantly reduced the proportion of patients classified with target lesions at the baselines of first-line and second-line chemotherapies. No obvious difference in overall response rates was observed.

Keywords RECIST · Gastric cancer · Target lesion

Introduction

The Response Evaluation Criteria in Solid Tumors (RECIST) have been widely used as standard criteria to evaluate the objective responses of chemotherapy, and the RECIST version 1.0 were revised to version 1.1 in 2009 [1, 2]. Major changes in the revised RECIST version 1.1 are as follows. (1) The number of lesions required to assess tumor burden has been reduced from a maximum of 10 to 5 in total, and from a maximum of 5 to 2 per organ. (2) Lymph nodes with a ≥15 mm short axis are considered measurable as target lesions, those with a ≥10 to <15 mm short axis are considered assessable as non-target lesions, and those with a <10 mm short axis are considered non-pathological. (3) Additionally, the definitions of complete response (CR) and progressive disease (PD) were revised. In the response criteria for CR, especially in regard to lymph node evaluation, the requirement for the disappearance of all lesions was revised to any pathological lymph nodes having a reduction in the short axis of <10 mm. In the response criteria for PD,

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RECIST version 1.1 requires a 5 mm absolute increase, in addition to a target lesion with a 20 % increase in the sum of the diameters, to avoid a clinically inappropriate diagnosis of PD when the total sum of lesion diameters is very small [1].

The revision, RECIST 1.1, was based on a large dataset (RECIST data warehouse) of 6512 patients from 16 clinical trials, consisting of 7 breast cancer trials, 4 lung cancer trials, 2 colorectal cancer trials, 2 renal cell carcinoma trials, and 1 gastrointestinal stromal tumor trial, performed between 1993 and 2005 [1, 2]. However, no gastric cancer patients were included in those data.

While surgery remains the only possible cure in patients with early-stage gastric cancer, palliative chemotherapy is the mainstay for patients with inoperable advanced or recurrent cancer. Although there is no globally accepted standard chemotherapy regimen, a fluoropyrimidine plus a platinum agent with or without epirubicin or docetaxel are the protocols used for advanced gastric cancer patients [3]. Based on several randomized controlled trials, a combination of tegafur, gimeracil, and potassium oxonate (S-1) plus cisplatin (CDDP) is widely used and accepted as standard chemotherapy in Japan [4–6].

The purpose of this study was to clarify the differences between RECIST version 1.0 and version 1.1 in terms of the proportions of patients classified with target lesions at the baselines of first- and second-line chemotherapies and the overall response rate (ORR) in advanced gastric cancer patients who received S-1 plus CDDP as first-line chemotherapy.

Patients and methods

From 2004 to 2009, 129 consecutive patients with advanced gastric cancer received S-1 plus CDDP as first-line treatment at the National Cancer Center Hospital East. S-1 (40–60 mg depending on the patient's body surface area as follows: <1.25 m^2, 40 mg; ≥ 1.25 m^2 and <1.5 m^2, 50 mg; and ≥ 1.5 m^2, 60 mg) was given orally twice daily for 3 consecutive weeks and CDDP was given intravenously at a dose of 60 mg/m^2 on day 8, followed by a 2-week rest period, within a 5-week cycle. Of all 129 patients, 97 patients who met the following criteria were included in this study: histologically confirmed unresectable and recurrent adenocarcinoma of the stomach, having no other malignancy, no history of chemotherapy or radiation therapy except for adjuvant chemotherapy, and tumor assessment by computed tomography (CT) scans performed in our hospital at baseline (within 28 days before the start of treatment) and post-treatment.

All CT scans were performed on a helical CT scanner with intravenous administration of contrast materials, and the slice thickness was 5 mm. The post-treatment CT scans were performed after every 2 cycles of S-1 plus CDDP. The CT image data were directly displayed on monitors and tumor measurements were performed with electronic calipers. We reviewed each patient's medical records and measured tumor size retrospectively using RECIST version 1.0 and version 1.1. Two medical oncologists (N.F. and E.N.) reviewed all CT images independently of the attending physicians. First, E.N. evaluated all CT images based on RECIST versions 1.0 and 1.1. N.F. then reviewed the results. If an inter-observer difference was present, the final judgment was made after sufficient discussion. The overall response was evaluated without interval confirmation.

The differences in proportions of patients with target lesions between the two RECIST versions were evaluated using McNemar's exact test. Corresponding 95 % confidence intervals (CIs) were also calculated, using the Clopper-Pearson method. All P values are two sided. Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

All data were collected retrospectively. The study was performed under an institutional review board waiver in accordance with the Japanese ethical guidelines for epidemiological research.

Results

The characteristics of the 97 patients are shown in Table 1. All 97 patients discontinued S-1 plus CDDP, for the following reasons: 88 patients because of PD, 5 because of adverse events, and 4 for other reasons. Of the 88 patients with PD after S-1 plus CDDP, 74 (84 %) received second-line chemotherapy.

One hundred seventy-two lymph nodes from 54 patients were considered to be candidate target lesions by RECIST version 1.0 at the baseline of the first-line chemotherapy. These lymph nodes were categorized into 3 groups according to the size of the short axis by RECIST version 1.1 as follows: <10 mm; ≥ 10 mm but <15 mm; and ≥ 15 mm (Table 2). According to RECIST version 1.1, only 38 % (66/172) of the lymph nodes were classified as target lesions, 47 % (80/172) were classified as non-target lesions and 15 % (26/172) were classified as non-pathological lesions.

Target lesions at the baselines of the first- and second-line chemotherapies, classified according to RECIST version 1.0 and version 1.1, are summarized in Table 3. The proportion of patients with a target lesion at the baseline of the first-line chemotherapy was 67 % (65/97; 95 % CI 57–76 %) by RECIST version 1.0, and the proportion was reduced to 53 % (51/97; 95 % CI 42–63 %) when classified according to RECIST version 1.1. This reduction was statistically significant (McNemar's exact test, $P < 0.001$).

Table 1 Characteristics of the 97 patients

Characteristic	No. of patients	%
Median age, years (range)	64 (32–79)	
Gender		
Male	64	66
Female	33	34
Performance status		
0	65	67
1	31	32
2	1	1
Histology		
Undifferentiated	57	59
Differentiated	37	38
Not specified	3	3
Prior adjuvant chemotherapy		
Yes	5	5
No	92	95
Disease status		
Unresectable	83	86
Recurrent	14	14
Primary tumor		
Present	73	75
Absent	24	25
No. of organs involved		
1	38	39
2	44	45
≥3	15	16
Metastatic sites		
Lymph node	69	71
Peritoneal	60	62
Liver	31	32
Lung	2	2
Bone	6	6
Other	3	3

Table 2 Categorization of 172 lymph nodes that were candidate target lesions according to RECIST version 1.0

Classification	No. of lymph nodes	%
Non-pathological (short axis <10 mm)	26	15
Non-target (short axis ≥10, <15 mm)	80	47
Target (short axis ≥15 mm)	66	38

RECIST Response Evaluation Criteria in Solid Tumors

Of the 32 patients who did not have any target lesions at the baseline of the first-line chemotherapy, 21 had only peritoneal metastasis, 9 had peritoneal metastasis and lymph node metastasis, 1 had lymph node metastasis only, and 1 had peritoneal, lymph node, and bone metastases.

Table 3 Target lesions at the baselines of first- and second-line chemotherapies

	RECIST version 1.0		RECIST version 1.1	
	No. of patients	%	No. of patients	%
First-line (n = 97)				
Target lesion (+)	65	67	51	53
Target lesion (−)	32	33	46	47
Second-line (n = 74)				
Target lesion (+)	46	62	36	49
Target lesion (−)	28	38	38	51

RECIST Response Evaluation Criteria in Solid Tumors

Table 4 Overall response

	RECIST version 1.0 (n = 65)		RECIST version 1.1 (n = 51)	
	No. of patients	%	No. of patients	%
Overall response	34	52	28	55
Complete response	0	0	1	2
Partial response	34	52	27	53
Stable disease	26	40	19	37
Progressive disease	5	8	4	8

RECIST Response Evaluation Criteria in Solid Tumors

Of the 65 patients who had target lesions based on RECIST version 1.0 at the baseline of the first-line chemotherapy, 29 had only lymph node metastasis as a target lesion and 14 no longer had target lesions according to the RECIST revision. Of the 14 patients who no longer had target lesions after the RECIST revision, 5 patients had only lymph node metastasis; 7 had peritoneal metastasis (which was not considered as a target lesion), with lymph node metastasis; and 2 had bone metastasis with lymph node metastasis.

The proportion of patients with a target lesion at the baseline of the second-line chemotherapy was 62 % (46/74; 95 % CI 50–73 %) as classified by RECIST version 1.0, and this proportion was reduced to 49 % (36/74; 95 % CI 37–61 %) by RECIST version 1.1. The difference between the two RECIST versions in the proportions of patients with target lesions was statistically significant (McNemar's exact test, $P = 0.002$).

Overall response rates (ORRs), and the numbers of patients with CR, partial response (PR), stable disease, and PD after first-line chemotherapy are shown in Table 4. The ORRs of S-1 plus CDDP were 52 % (34/65) according to RECIST version 1.0 and 55 % (28/51) according to version 1.1. In 1 patient, while the overall response classified by

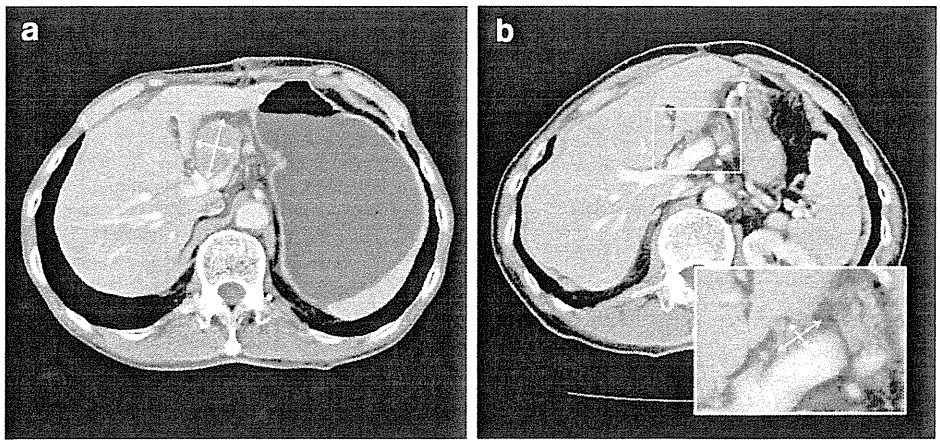

Fig. 1 Discrepancy between Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 and RECIST version 1.1 in the overall response in 1 patient. A partial response classified by RECIST version 1.0 was changed to a complete response by RECIST version 1.1. **a** Lymph node metastasis, as the only target lesion, was 40 mm versus 27 mm (long axis vs. short axis) at the baseline of the first-line chemotherapy. **b** The lymph node had regressed to 14 versus 7 mm 1 year after the initiation of the first-line chemotherapy

RECIST version 1.0 was PR, the overall response classified by RECIST version 1.1 was CR (Fig. 1).

Discussion

Our data showed that the revision of RECIST significantly decreased the proportions of patients classified with target lesions at the baselines of both the first-line and second-line chemotherapies. The decrease in the numbers of patients classified with target lesions in RECIST version 1.1 was caused by the change in lymph node evaluation. From the RECIST data warehouse, 90.5 % of lymph nodes were considered to be target lesions according to the new guidelines of RECIST version 1.1 [7]. In contrast, in our study, only 38 % of lymph nodes were considered to be target lesions based on RECIST version 1.1. This large difference between studies might be caused by the characteristics of lymph node metastasis from gastric cancer being different from those of the lymph nodes in the RECIST data warehouse. However, the evaluation of lymph nodes in the RECIST data warehouse was based on only 2747 bidimensionally measurable lesions from all 3974 lesions [7]. This selection might have been biased and it might explain the discordance between the RECIST data warehouse results and our study.

A decrease in the number of patients with target lesions may affect the eligibility of patients for a clinical trial, because some trials, particularly phase II studies or phase III studies in which progression-free survival is a primary endpoint, require a target lesion in the eligibility criteria. The proportions of patients with target lesions in clinical trials that do not require a target lesion in the eligibility criteria differ between trials and regions. While the proportion of patients with target lesions was relatively small in recent Japanese trials (59–76 %) [5, 6, 8, 9], the proportion was 96 % in the FLAGS study, which was conducted in the rest of the world [10]. In the AVAGAST study, 73 % of Asian patients had target lesions, while 88 % of European and 77 % of Pan-American patients had target lesions [11]. In the Japan Clinical Oncology Group (JCOG) 9912 study, patients without target lesions had better survivals than those with target lesions [12]. The fact that more patients without target lesions participated in clinical trials in Japanese and other Asian studies might explain why there was a better prognosis in Japanese or Asian patients. This hypothesis needs to be evaluated by data from global clinical trials.

We found that the ORRs of S-1 plus CDDP were similar in RECIST version 1.0 and version 1.1 (52 and 55 %, respectively). In our study, the overall response was determined without interval confirmation, because of the limitation of it being a retrospective study. CT scans were performed after every 2 cycles of S-1 plus CDDP in a practice setting, which was translated into an interval of $\geq$10 weeks, while CT scans are performed at an interval of 4–6 weeks in clinical trials in which the primary endpoint is the ORR. The number of patients classified as responders would increase without response confirmation [2]. Accurate evaluation of differences in the ORRs between RECIST version 1.0 and version 1.1 will require data of clinical trials in which CT scans are performed at a short-term interval.

In conclusion, for advanced gastric cancer patients, the revision of RECIST significantly reduced the proportions of patients classified with target lesions at the baselines of

first-line and second-line chemotherapies. There did not appear to be a difference between the two RECIST versions in the response rates of first-line chemotherapy.

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Conflict of interest None of the authors has financial or personal conflicts of interest to disclose.

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Radial incision and cutting method for refractory stricture after nonsurgical treatment of esophageal cancer

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Strictures remaining after nonsurgical treatment for esophageal cancer are generally more refractory to endoscopic balloon dilation (EBD) when compared with anastomotic strictures. The aim of the present study was to evaluate the efficacy and safety of a radial incision and cutting (RIC) method for the treatment of refractory strictures after nonsurgical treatment of esophageal cancer. All subjects complained of grade 2 or worse dysphagia, even after at least 10 sessions of EBD. Between August 2009 and May 2012, eight consecutive patients with refractory esophageal stricture after nonsurgical treatments, including chemoradiotherapy (CRT) alone (n = 3), CRT followed by salvage endoscopic treatment (n = 3), or endoscopic submucosal dissection (ESD; n = 2), underwent the RIC procedure. After the RIC procedure, dysphagia in all the patients dramatically improved to grade 1 or 0 without any major complications; however, the long-term efficacy was unfavorable as only 37.5% (3/8) demonstrated adequate lumen patency at 3 months, and re-intervention was necessary in six patients (75%).

Introduction

Dysphagia due to stricture is a major problem for patients with esophageal cancer and can reduce their quality of life even if their esophageal cancer has been cured. Endoscopic balloon dilation (EBD) or esophageal dilation with a bougie-type dilator is usually the primary treatment for dysphagia due to esophageal stricture.

We have previously reported a retrospective study of the use of EBD for strictures after curative treatment for esophageal cancer [1]. In that study, EBD was found to be safe and effective for strictures both after esophagectomy and after nonsurgical treatment such as chemoradiotherapy (CRT) or endoscopic mucosal resection (EMR). While over 90% of patients became dysphagia free after repeated EBDs, there was a significant difference in the median time to treatment success between the group with strictures following nonsurgical treatment and the anastomotic stricture group (5.6 vs. 2.3 months, $P = 0.02$).

Furthermore, the group with strictures after nonsurgical treatment contained significantly more subjects with severe refractory strictures that required six or more repeated sessions of EBD compared with the anastomotic stricture group (75% vs. 45%, $P < 0.01$).

Recently, Muto et al. reported the usefulness of the endoscopic radial incision and cutting (RIC) method for refractory esophagogastric anastomotic stricture [2]. In their study, 93.8% (30/32) of patients experienced a dramatic improvement in their dysphagia after the RIC procedure without any major complications. Moreover, the improvement in dysphagia remained 12 months after the RIC procedure in more than 60% of the patients. The RIC method is recognized as a safe and effective treatment for refractory anastomotic stricture after esophagectomy. However, the safety and efficacy of the RIC method for refractory stricture after nonsurgical treatment, such as EMR/ESD or CRT, are unknown.

The aim of this consecutive case series was to evaluate the efficacy and safety of the RIC method for refractory stricture after nonsurgical treatment for esophageal cancer.

Case series

Patients and methods

In this study, the indications for the RIC procedure to treat refractory stricture were as follows: (i) both a complaint of dysphagia (dysphagia score > 2) [3] and the inability to pass an ordinary size of endoscope (9–10 mm in diameter) that had

Table 1 Characteristics of the eight patients with strictures following nonsurgical treatment for esophageal cancer who underwent the radial incision and cutting (RIC) procedure.

Case number	Sex	Age, years	Cause of stricture	Stricture location	Stricture length, cm	Number of prior endoscopic balloon dilation sessions	Period of repeated endoscopic balloon dilations, months
1	Male	59	Endoscopic submucosal dissection	Lower	3	22	8
2	Male	67	Chemoradiotherapy	Cervical	6	60	120
3	Male	60	Chemoradiotherapy + endoscopic mucosal resection	Cervical	2	13	36
4	Male	70	Chemoradiotherapy + endoscopic mucosal resection	Upper	3	17	26
5	Male	72	Chemoradiotherapy	Upper	3	14	7
6	Male	70	Chemoradiotherapy + photodynamic therapy	Upper	3	69	41
7	Male	75	Endoscopic submucosal dissection	Cervical	4	18	4
8	Male	65	Chemoradiotherapy	Middle	3	12	6

not been resolved with at least 10 repeated sessions of EBD; (ii) benign esophageal stricture after CRT, endoscopic treatment (EMR, ESD, photodynamic therapy [PDT]), or combination treatment, such as CRT and PDT; and (iii) Eastern Cooperative Oncology Group (ECOG) performance status < 2. Written informed consent was obtained from all patients. This study protocol was approved by the institutional review board of the National Cancer Center.

The RIC procedure was performed largely in accordance with the previous report [2]. After the patient had received intravenous pethidine hydrochloride (17.5 – 35 mg), the RIC method was performed with an improved-type insulation-tipped knife (KD-611 L, IT knife-2, Olympus, Tokyo, Japan) under endoscopic observation with a 9.2-mm diameter endoscope (GIF Q260, Olympus). Details of the RIC procedure in this study were as follows: (i) a vertical incision was made radially to the stricture with the IT knife-2; (ii) the incised area was sliced off with IT knife-2; (iii) the surface of the tight fibrotic area was shaved with a short-pronged blade IT knife-2 until the endoscope could pass the stricture (◎ **Video 1**).

In this study, subjects had longer and tighter strictures than are usual with anastomotic strictures and it was technically difficult to perform the RIC procedure in some areas; hence, we chose the improved-type knife [4]. After the procedure, maintenance EBD was performed once a week until the ulcer following the RIC procedure had formed a scar.

The dysphagia symptoms of the patients were evaluated and given a dysphagia score before and after the RIC procedure, where 0 denoted the ability to eat a normal diet; 1, the ability to eat some solid food; 2, the ability to eat semisolids only; 3, the ability to swallow liquids only; and 4, complete dysphagia [3]. Perforation and bleeding requiring intervention or transfusion were defined as major complications. A dysphagia score of grade 2 or worse and the inability to pass an ordinary endoscope through the stricture during follow-up were defined as restenosis.

Video 1

The radial incision and cutting (RIC) procedure including a vertical incision being made radially to the stricture with an IT knife-2, the incised area being sliced off, and the surface of the tight fibrotic area being shaved with a short-pronged blade of an IT knife-2 until the endoscope is able to pass the stricture.

online content including video sequences viewable at:
www.thieme-connect.de

Results

Between August 2009 and May 2012, eight consecutive patients with refractory esophageal stricture after nonsurgical treatments underwent the RIC procedure. Patient characteristics before the RIC procedure are presented in ◎ **Table 1**. All patients were male, and their median age was 68.5 years (range 59 – 75). The treatment for the esophageal cancer that had caused the stricture was CRT alone in three patients, CRT followed by salvage EMR or PDT in three, and ESD in two. The stricture was at the cervical esophagus in three patients, upper thoracic esophagus in three, middle esophagus in one, and lower esophagus in one. The median length of the stricture was 3 cm (range 2 – 6). Prior to the RIC procedure, a median of 17.5 sessions of EBD (range 12 – 69 sessions) had been performed within a median period of 17 months (range 4 – 120).

The treatment outcomes for the RIC procedure are presented in ◎ **Table 2**. Before the RIC procedure, all patients complained of dysphagia that was grade 2 or worse (grade 2 in five patients, grade 3 in two patients, and grade 4 in one patient). After the RIC procedure the dysphagia of all patients had dramatically improved to grade 1 or 0. A representative case (#8) of a patient with refractory stricture after CRT is shown in ◎ **Fig. 1**.

A median of 2.5 sessions (range 0 – 4) of maintenance EBD was performed after the RIC procedure. No major complications were experienced during or after the RIC procedure. The median follow-up time after the RIC procedure was 28.5 months (range 4 – 32). The 3-month lumen patency (dysphagia score of grade 1 or better) for the patients was 37.5 % (3/8). At the last follow-up, restenosis had occurred in six patients (75 %). All of these six patients had undergone repeat RIC procedures between 1 and 32 times.

Discussion

In this study, the severe dysphagia due to refractory stricture after nonsurgical treatment for esophageal cancer was dramatically improved with the RIC procedure in all eight cases, and no major complication such as perforation or bleeding related to the RIC method occurred.

The short-term effect and safety of the treatment in this group were similar to the outcomes for patients with anastomotic stricture; however, the long-term lumen patency with the RIC procedure was not as satisfactory in patients with refractory stricture after nonsurgical treatment. In the present study, the 3-month lumen patency (dysphagia score of grade 1 or better) was 37.5 %

Table 2 Outcomes following radial incision and cutting (RIC) treatment for the eight patients with strictures following nonsurgical treatment for esophageal cancer.

Case number	Dysphagia score		Maintenance endoscopic balloon dilations after the RIC procedure, n	Major complications	Restenosis	Time to restenosis	Number of repeat RIC sessions after restenosis	Follow-up period after the RIC procedure, months
	Before the RIC procedure	After the RIC procedure						
1	2	0	3	None	No	–	–	30
2	3	0	1	None	Yes	28 days	21	32
3	2	1	1	None	Yes	84 days	16	30
4	2	0	4	None	No	–	–	13
5	2	0	3	None	Yes	75 days	32	28
6	2	0	0	None	Yes	12 months	6	29
7	3	1	2	None	Yes	48 days	1	15
8	4	0	4	None	Yes	84 days	1	4

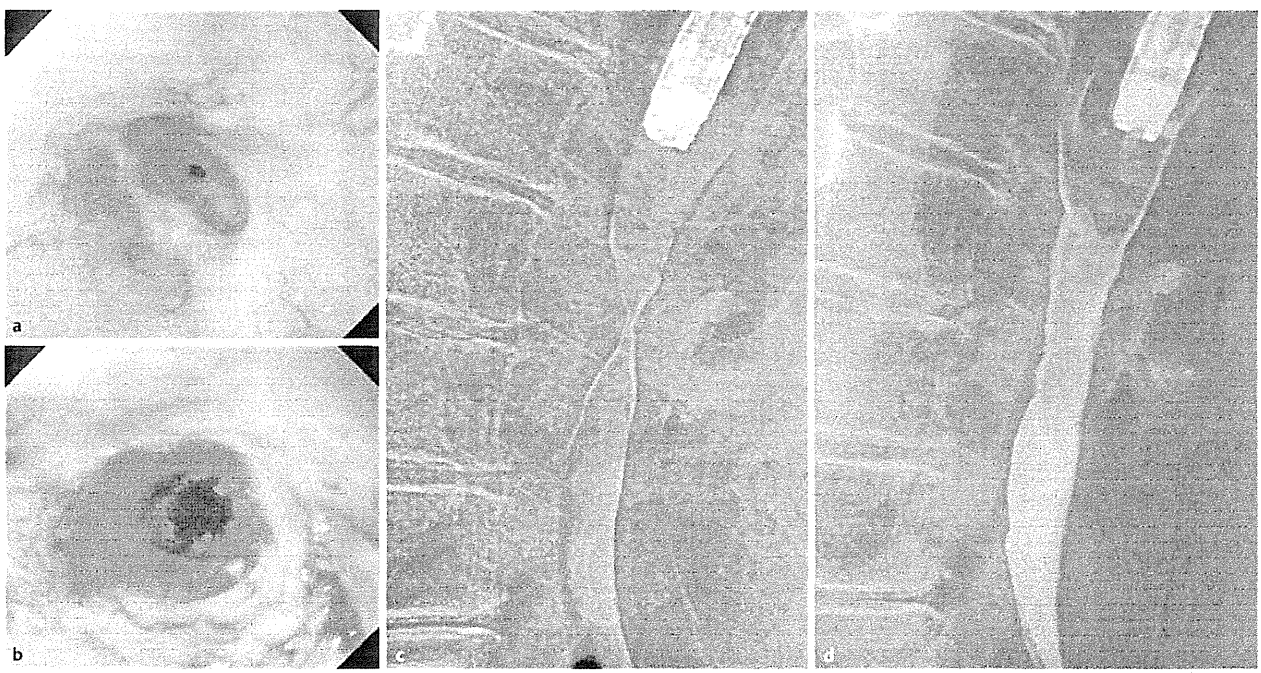

Fig. 1 Representative appearances in a 65-year-old man with refractory esophageal stricture following chemoradiotherapy (CRT) treated by the radial incision and cutting (RIC) method. **a** The endoscopic appearance of a severe esophageal stricture after CRT in the middle esophagus. The patient was unable to drink water and relied on a gastrostomy tube. The stricture had not been resolved by 12 sessions of endoscopic balloon dilation within a 6-month period. **b** The endoscopic appearance of the esophageal stricture shortly after the RIC procedure. An ordinary-sized endoscope could now be passed through the stricture. **c** An esophogram before the RIC procedure showing a severe stricture with a length of 3 cm in the middle esophagus. **d** A repeat esophogram shortly after the RIC procedure showing complete resolution of the esophageal stricture. Following the RIC procedure, the patient was able to eat normal solid food.

(3/8), and restenosis that required intervention with RIC procedures had occurred in six patients (75%). In contrast, for refractory anastomotic stricture, the 6-month lumen patency rate has been reported to be 63%, and a repeated RIC procedure for restenosis was required in only 43.8% of patients [2].

The difference in long-term lumen patency between post-nonsurgical and anastomotic strictures may be due mainly to the length of the respective strictures. While the strictures were longer than 2 cm for all patients in this study, in the previous study approximately 85% of strictures were 5 mm or shorter [2]. From our previous report on balloon dilation, refractory strictures after nonsurgical treatment consisted of a significantly larger number of long strictures (> 2 cm) compared with those seen in anastomotic strictures (44% vs. 2%, $P<0.001$). CRT radiation fields are usually wide to cover the entire tumor, and post-EMR strictures tend to occur after the resection of large areas, longer than 3 cm and more than three-fourths of the circumference of the lumen [5]. We believe that severe fibrosis in a large area after radiation or mucosal resection results in strictures with longer and tighter features than common anastomotic strictures.

Intralesional steroid injection after endoscopic dilation is reported to be an effective treatment for strictures that are resistant to balloon dilation [6, 7]. In addition, there are several reports concerning the prevention of strictures by oral administration or local injection of steroids after ESD for large tumors [8, 9]. In these studies, the incidence of strictures after ESD for complete or semicircumferential lesions of the lumen followed by medication with steroids was significantly lower compared with ESD alone.

The administration of steroids after the RIC procedure has the potential to reduce restenosis and would be valuable to investigate further.

Another approach for refractory esophageal stricture is stent placement. Kim et al. reported on a retrospective analysis of 55 patients who underwent temporary metallic stent placement for refractory esophageal strictures [10]. In their study, approximately 80% of the subjects had corrosive strictures and 70% of the patients suffered grade 3 or 4 dysphagia. The mean dysphagia score was reduced after stent placement (from 2.8 to 1.3), and the stent patency rates at 3 and 6 months after placement were 43% and 38% respectively. The major problem after metallic stent placement was hyperplastic tissue reaction causing fistula formation and restenosis after stent removal.

Recently, a biodegradable stent made of polydioxanone has been developed that is absorbable and does not need to be removed after placement. Repici and colleagues reported favorable results for a prospective study of refractory esophageal stricture in which the 6-month dysphagia-free rate was 45% (9 of 20 patients) without any major complications [11]. In Japan, this biodegradable stent is not yet available. Therefore, we are currently conducting a multi-institutional prospective study for esophageal stricture mainly after nonsurgical treatment for esophageal cancer that is refractory to repeated balloon dilation and/or the RIC method (UMIN000008054).

In conclusion, dysphagia in patients with refractory stricture after nonsurgical treatment for esophageal cancer was dramatically improved with the RIC method, without any major complications. However, the long-term lumen patency rate was unfavorable and is a major problem to be resolved for this method of treatment when used for refractory strictures after nonsurgical treatment.

Competing interests: None.

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日消誌　2013；110：1731―1737

今月のテーマ　食道表在癌の診断と治療

食道癌ESD　up-to-date

矢野友規　小田柿智之　森本浩之
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要旨：食道癌に対するESDは，EMRと比較するとより広範な病変に対して一括切除が可能で局所再発率が低く，根治性の面で優れていることから急速に普及しており，前向き試験での検証も行われつつある．ESDによる穿孔を中心とした合併症頻度は，EMRと差がなく安全性は同等という報告が多いが，長い治療時間を要する高度な手技であり，初心者が行う体制は慎重に構築する必要があり，トレーニング法の確立は重要である．また，適応拡大において最も大きな課題であったESD後の食道狭窄は，ステロイド投与などの予防法の開発や，再生医療の応用で克服されつつある．食道癌に対するESDの論文報告を中心に概説し，今後の課題について考察した．

索引用語：食道癌，ESD，狭窄予防

はじめに

食道表在癌に対する内視鏡治療は，2000年代になって内視鏡的粘膜下層剥離術（ESD）が導入されはじめ[1)2)]，内視鏡的粘膜切除術（EMR）と比較すると広範な病変も一括切除できるようになったため，急速に普及し，最近では長期成績も報告されつつある．2012年4月版の食道癌診断・治療ガイドライン[3)]では，内視鏡治療は一括切除が原則とされ，EMRで一括切除が困難な広範な病変ではESDでの治療が推奨されている．一方で，ESDはEMRと比較すると出血，穿孔などの偶発症の頻度も多く，施行に当たっては予防や対処法の十分な理解とトレーニングが必要であるとされている．また，食道表在癌に対する内視鏡治療後の食道狭窄は，粘膜欠損が広範になるほど頻度が増えることが知られており，適応拡大における最も大きな課題であった．近年ステロイド投与を中心とした予防法が開発されその有効性が報告されており，課題が克服されつつある．本稿では，食道癌に対するESDの最新情報について論文報告を中心にレビューし，概説する．

I　食道癌に対するESDの適応と治療成績

1．ESDの適応

食道癌診断・治療ガイドラインでは，食道表在癌に対する内視鏡治療の適応は，リンパ節転移の観点から，癌の深達度別にT1a-EP，LPMは絶対適応，T1a-MMまたはT1b-SM1（200μm未満）は相対適応，T1b-SM2以深は適応外と位置づけている．さらに，切除後の病理評価で，T1a-MMで脈管侵襲陽性またはINFcや垂直断端陽性の場合，またはSMと評価された場合には，外科手術や化学放射線療法（chemoradiotherapy；CRT）

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Up to date of ESD for esophageal cancer
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などの追加治療を考慮すべきとされている[3]. Shimizuらは，16例のpT1a-MMまたはpT1b-SM1に対してEMR＋CRTの治療成績についてretrospectiveな解析を報告しており，観察期間中央値43カ月の時点で5年全生存率は100%であった[4]. 本報告は少数例でのretrospectiveな解析ではあるが，JCOG（日本臨床腫瘍研究グループ）消化器内視鏡グループでは，多施設でEMR/ESD＋CRTの第Ⅱ相試験を行っており，すでに症例登録は終了し最終解析待ちの状態である. T1a-MMかつ脈管侵襲陽性またはpT1b症例に対する追加治療としてのCRTの有効性は，本試験の結果で評価されることになる.

2. ESDの治療成績（EMRとの比較）

食道表在癌に対してESDとEMRを直接比較した大規模なprospective studyは認めないが，多数例でのretrospectiveな比較は報告されている. Ishiharaらは，20mm以下の食道表在癌171例に対する治療成績をESDとEMR（EMR-C法と2-channel法）でretrospectiveに比較検討し，報告している[5]. ESDが一括切除率100%，治癒切除率97%と，EMR（一括切除率：EMR-C法87%，2-channel法71%，治癒切除率：EMR-C法71%，2-channel法46%）と比較して有意に根治性が高かった. また治療時間は有意にESDが長かったが，合併症の頻度には違いはなかった. 一方15mm未満の病変ではEMR-C法は経験の乏しい内視鏡医でも高い根治性を示し，治療選択肢として認められると結論されている. Takahashiらも，300例（ESD 116例，EMR 184例）の食道表在癌で単施設でのretrospectiveな比較を報告している[6]. こちらの報告は，より大きな病変が中心の検討で，平均腫瘍径はEMR；20±11mm（範囲：4～60），ESD；30±16mm（範囲：4～95）であった. ESDはEMRと比較して有意に一括切除率が高く，局所再発率が低かった（ESD vs EMR：一括切除率；100% vs 53.3%，p＝0.0009，局所再発率；0.9% vs 9.8%，p＝0.0065）. また，治療時間はESDの方が有意に長く，穿孔の頻度は高かったが有意差は認めなかった（ESD vs EMR：平均治療時間；73.9±45.8分 vs 44.4±32.6分，p＝0.0007，穿孔；2.6% vs 1.6%，p＝0.68）. 以上より，食道表在癌に対するESDはEMRと比較して有意に根治性が高く，安全性は同等であると結論している.

3. ESDの治療成績（prospective study，長期成績）

食道表在癌に対するESDは歴史が浅く，prospective studyや長期成績の報告は少ない. Higuchiらは，食道表在癌に対する安全性と効果を明らかにする目的で，単施設での非ランダム化第Ⅱ相試験を行い，その治療成績を報告している[7]. Primary endpointはR0切除率，secondary endpointは安全性と内視鏡による深達度正診率とされている. 必要症例数は，閾値R0切除率60%，期待値80%，αエラー5%，検出力90%で50例と算出され，52例56病変が登録された. 腫瘍径中央値は20mm（範囲：4～55）で，一括切除率は100%，R0切除率は94.6%でprimary endpointは達成された. 安全性については，有症状の食道狭窄を5例（9.6%）認めたが，術中術後いずれにおいても穿孔を含めた重篤な合併症は認めていない. もう1つのsecondary endpointである深達度正診率は76.8%（43/56，95%信頼区間65.8～87.8）であった. このHiguchiらによる報告は，食道表在癌に対するESDを多数例で評価した最初のprospective studyであり，単施設での成績ではあるが，今後の治療開発においても参考になる貴重なデータである.

Onoらは，84例107病変の表在癌に対するESDの長期成績をretrospectiveに解析して報告している[8]. ESD後84例中15例に，病理結果に基づいた追加治療が施行されている. その後の経過観察で，2例のpT1a-MM例で遠隔再発をしており，3例の食道癌死を認め，観察期間中央値約20カ月での，5年の全生存率，疾患特異生存率は，pT1a-EP，LPM例では95%，100%で，pT1a-MM以深例では56%，85%であった. この報告は，長期成績を結論づけるには，やや不十分な観察期間であり，より長期間観察例での解析が必要である.

II 治療困難例に対するESD

1. 食道胃接合部癌，Barrett's食道腺癌に対するESD

食道胃接合部（EGJ）は，食道の生理的狭窄部でもあり，症例によっては逆流性食道炎の影響やヘルニアなどによる偏位があり，内視鏡治療のアプローチが困難な場所として知られている．Yoshinagaらは，EGJ表在癌（Siewert分類Type II）24例25病変に対するESDの治療成績をまとめて報告している[9]．24例中Barrett's食道を15例（62.5%）で認め，うち1例のみlong segment Barrett'sであった．平均腫瘍径は16.5mm（範囲：3～60）で，全例で一括切除が得られ，治癒切除率は72.0%であった．治癒切除が得られた症例は，観察期間中央値30カ月で局所再発や転移は認めなかったが，SM深部浸潤癌による非治癒切除で追加外科手術を拒否した1例はESDから3年後に肺転移をきたした．穿孔や遅発性出血などの合併症は認めなかったが，2例（8%）で拡張術を必要とする狭窄を認めた．Barrett's食道におけるESDの治療成績については，本邦での疾患頻度の低さと欧米でのESD普及率の低さから，報告は少ない．Neuhausらは，Barrett's食道のhigh grade intraepithelial neoplasia（HGIN）や粘膜内腺癌（MAC）に対する，ESD＋ラジオ波焼灼術（RFA）の治療成績を報告している[10]．30例で解析され，HGIN 6例，MAC 24例，腫瘍径中央値20mm（範囲：10～30），背景Barrett's食道の長径中央値は2cm（範囲：1～9）であった．治療時間中央値は，75分（範囲：22～206）で，一括切除率は90%，内視鏡的治癒切除率96.7%であった．合併症は，軽微な遅発性出血を2例認めたのみで穿孔は認めなかった．RFAはESD後のフォローアップで腫瘍が消失していることが組織学的に確認され，腸上皮化生が残存している症例に対しては行われるプロトコールになっており，10例で施行された．観察期間中央値17カ月で経過観察された28例中27例（96.4%）で組織学的な腫瘍完全消失が維持できていた．技術的な難しさや治療時間の長さなど，克服すべき課題はあるが，ESDはEMRと比べると，大きな病変を一括切除することによって正確な組織診断ができることや局所再発率の低さなどの優位性は強調されており，今後欧米での普及も期待される．

2. CRT後遺残再発例に対するサルベージESD

食道癌CRT後は局所遺残再発率が高く，局所遺残再発に対するサルベージ治療はCRTの根治性を高める意味でも重要である．遺残再発を早期で診断すればサルベージ治療としてEMRを行うことも可能で，EMRで治癒切除が得られれば長期生存が得られる可能性が報告されている[11][12]．CRT後のEMRについては，放射線による組織の線維化が強く高度な技術を要することが知られている．サルベージ治療としてESDを行う試みも報告されている[13][14]．いずれも少数例での症例報告ではあるが，高い一括切除率が得られ，穿孔などの重篤な合併症は認めていない．

III 食道癌に対するESDのトレーニング

学会発表や論文報告での食道癌に対するESDの治療成績は，症例数の多い施設での経験豊富な術者のデータであることが多く，合併症の頻度は先述のようにEMRと比較してそれほど高くない．しかしながら，食道は胃と比較すると呼吸や心拍動の影響を受けやすく，管腔が狭く壁が薄い．出血による影響で視野が悪くなりやすく，視野が悪い状態での雑な処置によって容易に穿孔する．周囲に重要な臓器が多いため，穿孔した場合には気胸，膿胸，縦隔気腫，縦隔膿瘍などの重篤な合併症に繋がりやすい．初心者がESDを行う体制は慎重に構築する必要がある．Godaらは，ESDのエキスパート9名に対するESDのトレーニングについてのアンケート調査を報告している[15]．ほとんどのエキスパートが，食道ESDを行う条件として胃でのESD技術が習熟しているべきと回答しており，食道癌に対するESDは胃癌に対するESDより難しいと考えられている．胃のESDでは，20～50例の経験でラーニングカーブがフラットになると報告されており[16]～[18]，食道ESDを始める条件になり得る．また，初心者がはじめに行う症例としては，20mm未満，1/

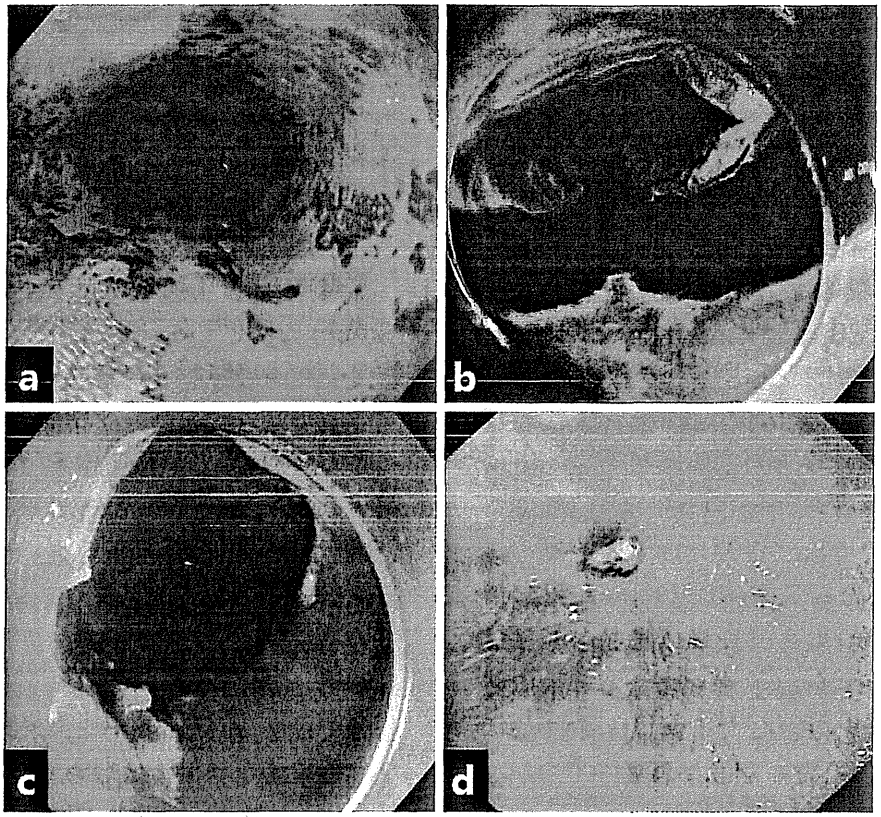

Figure 1. 食道全周性 ESD 後の狭窄　a：全周性の食道表在癌，b：粘膜切開後，c：ESD 直後の全周性粘膜欠損，d：約 1 カ月後の食道狭窄．

2 周未満，胸部中部食道右壁の症例が適していると，多くのエキスパートが回答していた[15]．食道 ESD の技術におけるラーニングカーブについてはほとんど報告がなく，今後検討が必要である．また，欧米への普及の観点からも，トレーニング法の確立は非常に重要である．

IV　食道 ESD 後の狭窄に対する治療と予防法の開発

1. 食道癌 ESD 後の狭窄とその治療

食道表在癌に対する内視鏡治療後の晩期合併症として食道狭窄があり，EMR での経験から粘膜を 3/4 周以上かつ 3cm 以上切除すると深刻な狭窄をきたすことが知られている[19]．ESD の治療成績では，狭窄の頻度は 10～20% 程度と報告され，狭窄の危険因子としては，EMR 同様に 3/4 周以上の粘膜欠損や長径の長さがあげられている[7)8)20)21)]．ESD 後に食事の通過障害をともなう狭窄をきたした場合は，一般的に内視鏡的バルーン拡張術（EBD）やブジーで治療する[22)～24)]．EBD は，簡便で，穿孔の頻度は 1% 程度と安全な治療法であるが，術後の吻合部狭窄と比べると EMR/ESD 後は難治性狭窄例が多く，狭窄改善までに長期間，頻回な EBD が必要になると報告されている[23)]．Takahashi らは，EMR/ESD 後の狭窄に対してブジーを行った症例で，穿孔の危険因子を検討している[24)]．76 例に対して計 648 回のブジーを行い，1.1%（7/648）の穿孔をきたし，穿孔例全例が EGJ から 5cm 以内の病変であり，多変量解析による独立した危険因子は，下部食道と複数回の拡張を要した症例であったと結論している．

2. 狭窄予防法の開発

ESD 技術の進歩により広範な病変の切除も可能になったが，切除後に深刻な狭窄（Figure 1）をきたすことは適応拡大における一番大きなリミテーションであった．最近，食道 ESD の領域で最も活発に開発が進んでいるのは，ステロイド投与を中心とした切除後の狭窄予防法である（Table 1）．Hashimoto らは，ESD 後の粘膜欠損にト

Table 1. 主なESD後狭窄予防法のまとめ

報告者	方法	治療スケジュール	症例数	周在性	狭窄割合	文献
Hashimoto	ステロイド局注	ESD 3, 7, 10日後にトリアムシノロン1カ所2mgを計18～62mg局注	21	3/4～亜全周	19%	25
Hanaoka	ステロイド局注	ESD当日，トリアムシノロン1カ所2.5～5mgを計100mg局注	30	3/4～亜全周	10%	26
Yamaguchi	ステロイド内服	ESD 3日後からプレドニゾロン30mg/日開始，減量しながら8週間服用（30mg，25mgは2週，その後5mg/1週で減量）	19	3/4～全周	5%	27
Ohki	細胞シート移植	ESD 16日前に患者の口腔粘膜採取，16日間培養，ESD直後に粘膜欠損部に細胞シートを移植	10	1/2～亜全周	10%	31

リアムシノロンを局注する方法で狭窄予防を試み，その治療成績を報告している[25]．21例の亜全周性粘膜欠損をきたした症例に対して局注を行ったところ，コントロールの無治療群と比較して有意に狭窄の頻度が低く（局注群19% vs 無治療群75%，$p<0.001$），バルーン拡張の回数も少なかった（局注群平均1.7回 vs 無治療群平均6.6回）．Hanaokaらは，3/4周以上亜全周の粘膜欠損となった30例を対象にステロイド局注の有効性を評価するprospective studyを行った[26]．Primary endpointは，ESD後狭窄割合であった．方法は，ESD直後にトリアムシノロン100mgを局注した．狭窄割合は10%（3/30）で，必要としたバルーン拡張中央値は0回（範囲：0～2）．局注に関連した合併症は認めなかった．Yamaguchiらは，ステロイド内服によるESD後狭窄予防法の有用性を報告している[27]．ステロイドはESD 3日後からプレドニゾロン30mg/日で開始し，徐々に減量しながら8週間服用するレジメンで投与し，亜全周症例19例（3例は全周）で有効性を検討した．狭窄割合は5%（1/19）で，EBDは平均1.7回（範囲：0～7），ステロイド内服にともなう合併症は認めず，良好な治療成績であった．Satoらは，同様のレジメンを予防的EBDと併用し，全周性ESDに対する治療成績をEBD単独とretrospectiveに比較検討して報告している[28]．平均長径6cm以上の全周症例で検討し，全例狭窄はしていたが，EBD単独と比較すると劇的にEBD回数（13.8±6.9回 vs 33.5±22.9回，$p<0.001$），期間（4.8±2.3カ月 vs 14.2±15.7カ月，$p=0.005$）を減らすことができていた．ステロイド投与は，局注法，内服法いずれも極めて有効な方法であり，今後は最適な投与方法やレジメンが検証されていくものと思われる．さらには，再生医療を応用した狭窄予防法も開発されており，いくつか報告されている[29)~31)]．Ohkiらは，自己の口腔粘膜細胞シートを食道ESD後の粘膜欠損に移植し，上皮を早期に再生させ狭窄を抑制させる方法を開発し，その有用性をヒトで探索的に検討した試験の結果を報告している[31]．1/2周以上の粘膜欠損をきたした9例が登録され，移植は全例で成功した．再上皮化が完成するまでの期間の中央値は3.5週で，亜全周の粘膜欠損となった1例を除いて狭窄した症例は認めなかった．再生医療技術を応用した画期的な方法であり，今後，さらなる発展が期待される一方で，その位置づけや，一般化の可否を明らかにすることが課題である．

おわりに

近年，食道ESDに関するさまざまな新しい知見が報告されている．ESDは根治性が高く，食道表在癌に対する治療として普及している．今後の課題としては，さらなる適応拡大の是非，長期予後，欧米への普及，初心者へのトレーニング法の確立などがあげられる．さらに，狭窄予防法の開発については最近目覚ましく進歩しており，今後最適なステロイド投与法の検証，再生医療の位置づけなどが明らかにしていくべき課題と考えられる．

本論文内容に関連する著者の利益相反
：なし

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