Efficacy of Preventive Endoscopic Balloon Dilation for Esophageal Stricture After Endoscopic Resection

Yasumasa Ezoe, MD, Manabu Muto, MD, PhD,† Takahiro Horimatsu, MD,† Shuko Morita, MD,† Shin'ichi Miyamoto, MD, PhD,† Satoshi Mochizuki, MD,‡ Keiko Minashi, MD,‡ Tomonori Yano, MD,‡ Atsushi Ohtsu, MD, PhD,‡ and Tsutomu Chiba, MD, PhD†*

Background and Aim: We earlier reported that mucosal defect involving over three-fourths of the circumference of the esophagus after endoscopic mucosal resection (EMR) is a risk factor for the development of the stricture. Although endoscopic balloon dilation (EBD) is a useful procedure to relieve the stricture, there is no standard strategy for preventing development of the stricture. The aim of this study was to evaluate the efficacy and the safety of preventive EBD.

Methods: From 1993 to 2008, 41 consecutive patients with extensive mucosal defect involving over three-fourths of the esophageal circumference after EMR or endoscopic submucosal dissection (ESD) were investigated. Preventive EBD was carried out for 29 cases within 1 week just after EMR/ESD and was repeated once a week until the mucosal defect was completely healed. The remaining 12 cases were not underwent preventive EBD and used as a historic control. If postEMR/ESD stricture developed regardless of preventive EBD, conventional EBD was given repeatedly until the stricture was completely relieved.

Results: Preventive EBD decreased the incidence of stricture (59% vs. 92%, $P = 0.04$), reduced the severity of stricture [(≤ 2 mm; > 2 mm and ≤ 5 mm; > 5 mm) = (1; 2; 14) vs. (4; 4; 3), $P = 0.01$] and shortened the duration required for resolving the stricture (29 d vs. 78 d, $P = 0.04$) even when stricture developed. There was no complication associated with preventive EBD procedure.

Conclusions: Preventive EBD is an effective procedure to prevent postEMR/ESD stricture. Preventive EBD should be considered when EMR/ESD results in a mucosal defect with a circumference greater than three-fourths of the esophageal lumen.

Key Words: endoscopic mucosal resection, endoscopic submucosal dissection, esophageal stricture, endoscopic balloon dilation, prevention

(*J Clin Gastroenterol* 2011;45:222–227)

Endoscopic mucosal resection (EMR) is being increasingly accepted as one of the standard treatment for superficial esophageal cancer because of its minimal invasiveness and excellent survival rate.[1,2] Furthermore, the endoscopic submucosal dissection (ESD) technique has made it possible to carry out *en-bloc* resection of widespread neoplasia, such as a superficial spreading-type of esophageal squamous cell carcinoma and Barrett esophageal cancer.[3–7] However, extended removal of the esophageal mucosa frequently causes severe stricture.[8,9]

Esophageal stricture may markedly interfere with the oral intake of food and fluids, and thus affect the patients' quality of life adversely. In addition, once severe esophageal stricture has developed, it is difficult to resolve the condition. Although endoscopic balloon dilation (EBD) is usually indicated for benign stricture including the cicatricial stricture caused by EMR/ESD, the effect of EBD is sometimes only temporary and the stricture would reappear.[10,11]

Before 2002, we carried out EBD only when the patients complained of dysphagea by postEMR/ESD stricture, and EBD was repeated until the dysphagea was completely resolved. In 2003, we reported that mucosal defects greater than three-fourths of the circumference of the esophagus after EMR are at high risk of developing esophageal stricture.[12] Since then, we started preventive EBD not to develop stricture, before postEMR/ESD mucosal defects develop scarring.

In this study, we evaluated the effectiveness of preventive EBD for the patients with superficial widespread esophageal cancer who developed mucosal defect extending more than three-fourths of the circumference of the esophagus by EMR/ESD.

PATIENTS AND METHODS

Patients

From February 1993 to June 2008, we experienced 64 consecutive patients with widespread mucosal defects greater than three-fourths of the esophageal circumference as a result of EMR/ESD for esophageal cancer. Written informed consent was obtained from all patients before carrying out EMR/ESD and EBD.

Endoscopic Resection Technique

To remove the lesions endoscopically, EMR[13,14] or ESD[5–7] were carried out.

EBD Technique

All patients received administration of 17.5 to 35 mg of pethidine hydrochloride to reduce the suffering from EBD

Received for publication January 28, 2010; accepted July 23, 2010.
From the *Department of Multidisciplinary Cancer Treatment; †Department of Gastroenterology and Hepatology, Kyoto University, Kyoto; and ‡Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan.
Funding: None.
Conflicts of Interest: None.
Reprints: Yasumasa Ezoe, MD, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan (e-mail: yasuzoe@kuhp.kyoto-u.ac.jp).

procedure. All EBD procedures were carried out using direct visualization and fluoroscopic monitoring. The balloon was positioned across the stenotic site, and then it was inflated carefully with double-diluted contrast agent. During the procedure, patients were closely observed with pulse, blood pressure, and oxygen saturation. When a patient experienced pain during the dilation or when a notch of the balloon placed on the stricture was gradually disappeared, dilation was stopped, and then the balloon was maintained in its inflated state and held close to the tip of the endoscope, and was pushed through the stenotic site as a bougie technique. If the notch of the balloon was rapidly expanded, suggesting a tear at the stenotic site, dilation is immediately stopped and the balloon was deflated, and then the endoscope and deflated balloon were removed.

Four CRE balloon dilators (Boston Scientific Corp. Natick, MA, USA) of different sizes (10 to 12 mm, 12 to 15 mm, 15 to 18 mm, and 18 to 20 mm) were used according to the severity of the stricture. A single balloon was used in each EBD session. When the endoscope could be passed through the site of the mucosal defect, a balloon of 18 to 20 mm was used. When the stricture was less than 10 mm in diameter and larger than 5 mm, a 15 to 18 mm balloon was used. When the stricture was less than 5 mm in diameter and larger than 2 to 3 mm, a 12 to 15 mm balloon was used. When the stricture was a pinhole stricture, a 10 to 12 mm balloon was used. We did not carry out preventive EBD when the luminal diameter was estimated to be greater than 20 mm because the diameter of the lumen would have been greater than that of the fully expanded balloon.

In this study, we defined the EBD procedure carried out immediately after EMR/ESD as "preventive EBD" and that after the development of postEMR/ESD cicatricial stricture as "conventional EBD."

Protocol of the Preventive EBD and Conventional EBD

Preventive EBD was commenced within 1 week after the EMR/ESD and repeated weekly until the complete healing of mucosal defect was observed (Fig. 1). Patients consumed a regular diet during the period of mucosal healing and weekly preventive EBD.

If the postEMR/ESD mucosal defects became scarred with stricture despite repeated preventive EBD, conventional EBD was given repeatedly until the stricture was completely resolved. The time interval of conventional EBD depended on patients' symptom such as dysphagea (usually 2 to 4 wk). The strategy of conventional EBD has not been changed throughout this study period, therefore, the time interval of conventional EBD is not different between 2 groups.

Definition of the Stricture

"Stricture" was defined when a standard 11-mm-diameter endoscope (Q240, 1T240; Olympus Optical Co. Ltd., Tokyo, Japan) could not be passed through the site, or when the patients complaint of dysphagea. Whereas, "complete resolution of the stricture" was defined when a standard diameter endoscope could be passed through the site, and patients' symptoms of dysphagia were completely relieved.

In each EBD sessions in all cases, diameter of stricture was measured by comparing with the diameter of inflated balloon under the fluoroscopic monitoring, and it was classed into 3 groups: more than equal to 2 mm; more than 2 mm and, more than equal to 5 mm; more than 5 mm. The duration required for resolving the stricture was defined as the time interval between the day when the stricture was first observed and the day of complete resolution.

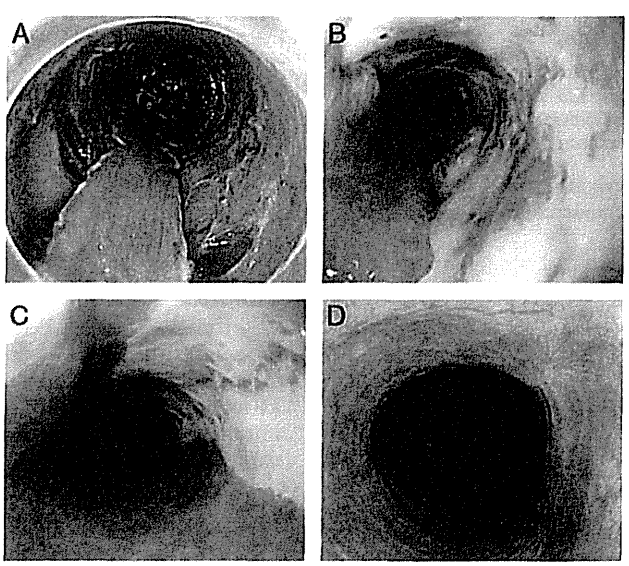

FIGURE 1. A representative case who received preventive endoscopic balloon dilation after a semicircumferential endoscopic submucosal dissection(ESD). A, Semicircumferential mucosal defect immediately after the ESD. B, Mucosal defect 1 week after the ESD. The site gradually developed scarring with mild stricture. C, Mucosal defect 1 month after the ESD. The site developed scarring furthermore, but the stricture was mild. D, PostESD site 2 months after the ESD. The complete healing of the postESD mucosal defect was observed without stricture. The endoscope could be passed through the site and the patient did not complain of any symptom with esophageal stricture.

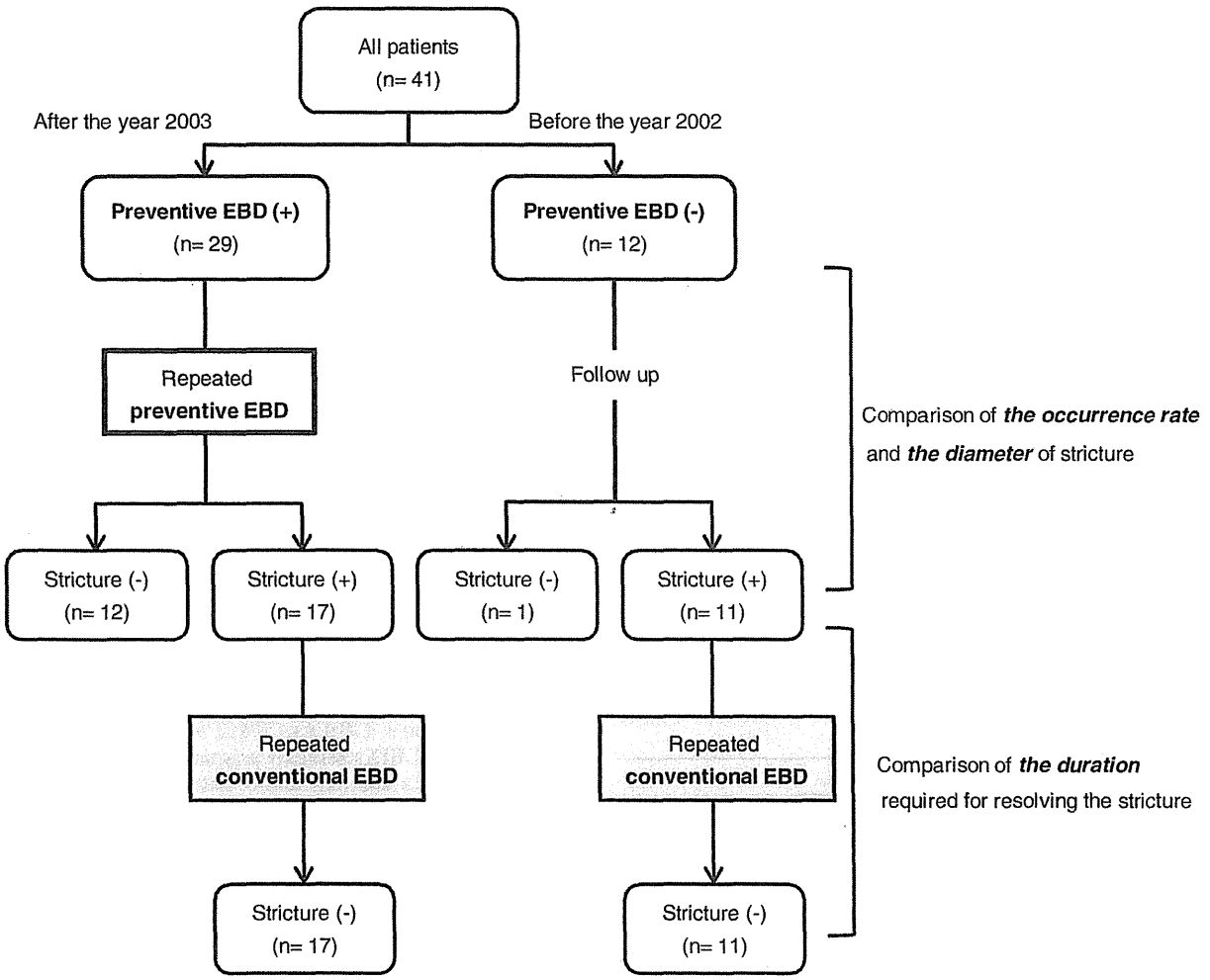

FIGURE 2. Diagram of patients flow.

Evaluation of Preventive EBD

The efficacy of preventive EBD was evaluated retrospectively by comparing the following 3 points between the patients with preventive EBD and those without it (Fig. 2); the occurrence rate of stricture, the diameter of stricture, and the duration required for resolving the stricture by repeated conventional EBD.

Statistical Analysis

Fisher exact test, or its extension when there were more than 2 categories, was used for categorical variables and the Mann–Whitney *U* test was used for continuous variables. Cox proportional hazard model was used for the multivariate analysis. A *P* value of more than equal to 0.05 was considered significant. All statistical analyses were carried out using the Dr SPSS II Statistics software package (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Background

Among the 64 patients with mucosal defects greater than three-fourths of the circumference of the esophagus after EMR/ESD, 3 patients did not attend follow-up consultations, 17 received additional treatment for primary lesions (chemoradiation for deep invasion of the carcinoma or EMR/ESD for local recurrence and incomplete resection), and 3 underwent surgical resection for metachronous gastric cancer immediately after EMR/ESD. We excluded these 23 patients because additional treatments had the potential to make the stricture worse. Finally, we used data from 41 lesions in 41 patients to evaluate the efficacy of the preventive EBD.

Thirty-six lesions were removed by EMR and 5 lesions were removed by ESD procedure. A histopathological diagnosis of squamous cell carcinoma was found in all lesions and 40 lesions were mucosal cancers but 1 submucosal cancer.

Of the 41 patients, 29 underwent preventive EBD and 12 did not. There were no statistical differences in the characteristics of the patients and the mucosal defects except for the endoscopic resection method between patients who underwent preventive EBD and those who did not. Because the ESD was recently established technique, there are no patients treated by ESD in the historical control group. Although the difference was not statistically significant, the rate of circumferential resections tended to be greater in

TABLE 1. Comparison of the Characteristics of Mucosal Defects After Endoscopic Resection in Patients With and Without Preventive EBD

	Preventive EBD		
	(+) n = 29	(−) n = 12	*P*
Sex			
Male	28	11	0.50
Female	1	1	
Age			
Median (range)	64 years (50-74)	60 years (48-80)	0.21
Circumference of the lumen			
Circumferential	10	6	0.49
Semi-circumferential	19	6	
Depth of resected lesion			
Mucosa	28	12	0.34
Submucosa	1	0	
Location			
Upper	3	1	0.30
Middle	13	5	
Lower	13	6	
Length of mucosal defect			
30 mm or less	6	4	0.30
More than 30 mm	23	8	
Median (range)	40 mm (10-110)	45 mm (20-70)	0.38
Endoscopic resection procedure			
EMR	24	12	< 0.001
ESD	5	0	

Number of patients are shown unless specified.
EBD indicates endoscopic balloon dilation; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

conventional EBD group [10/29 (34%) vs. 6/12 (50%), $P = 0.49$] (Table 1).

Profile of Preventive EBD Sessions

Among the 29 patients who underwent preventive EBD, the median number of preventive EBD sessions was 6 (range, 3 to 9) and the period of preventive EBD was 45 days (range, 16 to 65) (Table 3).

Efficacy of Preventive EBD

The number of patients who developed stricture after EMR/ESD was significantly lower in patients who were given preventive EBD than those who were not given preventive EBD [12/29 (59%) vs. 11/12 (92%), $P = 0.04$] (Table 2).

TABLE 2. Comparison of the Occurrence Rate and the Diameter of Esophageal Stricture Between Patients With and Without Preventive EBD

	Preventive EBD		
	(+)	(−)	*P*
No. patients who developed stricture	17/29 (59%)	11/12 (92%)	0.04
The narrowest diameter of the stricture			
≤2 mm	1/17 (6%)	4/11 (36%)	0.01
2 mm < and ≤5 mm	2/17 (12%)	4/11 (36%)	
5 mm <	14/17 (82%)	3/11 (28%)	

Number of patients are shown unless specified.
EBD indicates endoscopic balloon dilation.

The narrowest diameter of stricture in each patient was significantly larger in patients who were given preventive EBD than those who were not given preventive EBD [(≤2 mm; >2 mm and ≤5 mm; >5 mm) = (1; 2; 14) vs. (4; 4; 3), $P = 0.01$] (Table 2).

The number of days to development of stricture was 23 days (21 to 49) in patients without preventive EBD. Similarly, in patients who were given preventive EBD, tendency of stricture development was observed within 2 weeks after EMR/ESD. However, preventive EBD could prevent the patients' symptom such as dysphagea because dilation was carried out at short intervals (once a week) in all patients. Therefore, no patients suffered from dysphagea during the preventive EBD period in this study. Since the patients with preventive EBD complained the symptom of dysphagia after the completion of weekly preventive EBD, the number of days to development of stricture was 51 days (30 to 72). It was significantly longer in patients who underwent preventive EBD than those who did not ($P < 0.001$).

Seventeen patients with preventive EBD and 11 patients without preventive EBD developed esophageal stricture. Then, they were given conventional EBD repeatedly until the stricture was completely relieved. Among them, the duration required conventional EBD was significantly shorter in patients given preventive EBD than in those not given it (29 d vs. 78 d; $P = 0.04$). The number of conventional EBD sessions was smaller in patients with preventive EBD than in those without it, although the difference was not statistically significant (2 times vs. 4.5 times; $P = 0.5$) (Table 3).

The number of total EBD sessions was greater in patients with preventive EBD than in those without it, however, the difference was not statistically significant (8 times vs. 4.5 times; $P = 0.42$) (Table 3).

Safety of EBD Procedure

Among a total of 166 preventive EBD sessions for 29 patients, no complication occurred during the procedure (complication rate of preventive EBD: 0%). Among a total of 189 conventional EBD sessions for 28 patients, a perforation was occurred in 1 conventional EBD session in 1 patient (0.5% per total conventional EBD sessions, 3.6% per patient). The patient was immediately hospitalized and administered intravenous antibiotics. The patient had no symptoms or signs of mediastinitis. The fasting period was 3 days and hospital stay was only 1 week after causal EBD. No other major complication occurred.

Clinical Course of all Patients After EMR/ESD

Follow up period was calculated between the day of EMR/ESD and the day of patients' final visit. After the complete resolution of stricture, endoscopic examination was carried out every 6 months in all patients. Median follow up period of all patients was 84 months. There were no patients who suffered from dysphagea owing to the recurrence of stricture.

RISK OF STRICTURE

Risk Factors for Stricture Among Patients With Preventive EBD

The method of EMR and the longitudinal length of mucosal defect (>30 mm in length) were significantly

TABLE 3. Comparison of the Duration and the Number of EBD Sessions Required for Resolving the Stricture by Conventional EBD Between Patients With and Without Preventive EBD

	Preventive EBD		
	(+)	(−)	*P*
Period of preventive EBD*	45 d (16-65)	(−)	(−)
Number of days to development of the stricture*	51 d (30-72)	23 d (21-49)	< 0.001
Duration required for resolving the stricture*	29 d (15-169)	78 d (8-1093)	0.04
No. preventive EBD sessions*	6.0 sessions (3-9)	(−)	(−)
No. conventional EBD sessions*	2.0 sessions (2-20)	4.5 sessions (2-35)	0.5
No. total EBD sessions*	8.0 sessions (3-29)	4.5 sessions (0-35)	0.42
No. patients whose stricture was relieved	17/17 (100%)	11/11 (100%)	1

Number of patients are shown unless specified.
*Median (range).
EBD indicates endoscopic balloon dilation.

associated with the increased risk for development of stricture by multivariate analysis (Odds ratio: 20.8, 95% CI: 1.3-328.9 and 12.7, 95% CI: 1.3-126.9, respectively). Circumferential mucosal defects showed a higher rate of stricture than semicircumferential mucosal defects; however, the difference was not statistically significant (Odds ratio: 3.0, 95% CI: 0.2-40.5) (Table 4).

DISCUSSION

Technically, extended esophageal mucosal resection could be carried out. However, the development of the esophageal stricture is one of the most important problem to be solved. To date, there are no well-established methods to prevent the stricture after EMR/ESD. If we can prevent the development of the stricture after EMR/ESD by preventive EBD, the ability of the patients oral intake would be dramatically improved.

In this study, we showed that the preventive EBD reduced the incidence of esophageal stricture in patients who underwent an extensive EMR/ESD. In our preventive EBD protocol, EBD was carried out once a week for about 6 weeks [median; 44 days (16 to 65 d)] until the mucosal defect completely developed scar. Because of this strategy, the number of EBD sessions tended to be greater. Although it did not reach statistical significance ($P = 0.42$), the total number of EBD sessions was nearly twice as high compared with the conventional EBD group (8.0 vs. 4.5). However, the narrowest diameter of stricture was significantly mild in the preventive EBD group compared with the group without it (Table 2), whereas 60% of the patients in the preventive EBD group develop stricture. Clinically, the severity of the stricture is very important, because it critically affects the oral intake condition. Furthermore, the preventive EBD shortened the period to relieve the stricture even when the stricture was developed. These data indicated that the preventive EBD was a beneficial method, and thus should be considered to carry out for the patients who underwent extensive EMR/ESD as a supportive treatment.

TABLE 4. Predictive Factors for Development of Stricture After Endoscopic Resection in Patients who Received Preventive EBD

	Odds Ratio (95% CI)	*P*
Method of endoscopic resection		
ESD	1.0 (reference)	0.03
EMR	20.8 (1.3-328.9)	
Longitudinal length of mucosal defect involving over three-fourth of the esophageal circumference		
≤30 mm	1.0 (reference)	0.03
>30 mm	12.7 (1.3-126.9)	
Circumference of mucosal defect		
Semi-circumferential	1.0 (reference)	0.4
Circumferential	3.0 (0.2-40.5)	

EBD indicates endoscopic balloon dilation.

Perforation and massive bleeding were the most severe complications during the EBD procedure. However, there was no complication associated with preventive EBD procedure in this study. Thus, we could conclude that the preventive EBD was a feasible procedure. Not to develop perforation, we carefully carried out preventive EBD under fluoroscopic monitoring, to confirm with both the size of the stricture and the inflated balloon. When the patients complained of pain or when the balloon expanded exponentially, we stopped dilating the balloon immediately not to develop deep tear or perforation.

There were some imbalances of the characteristics of mucosal defect between 2 groups; the rate of circumferential resections [10/29 (34%) vs. 6/12 (50%), $P = 0.49$] and the rate of ESD resections [5/29 (17%) vs. 0/12 (0%), $P < 0.001$]. Although the difference of the rate of circumferential resections was not statistically significant, the possibility that the results of this study might be influenced by the difference cannot be denied. However, the "circumferential resection" and "noncircumferential resection" were not associated with the risk of development of stricture by the multivariate analysis even in the preventive EBD group. Therefore, it seemed that the imbalance about the rate of circumferential resection between 2 groups was not a major problem. As for the different rate of ESD resections, there are no patients treated by ESD in the historical control group because the ESD was recently established technique. These imbalances between 2 groups are unavoidable limitations of the retrospective review with small sample size.

The rate for stricture was lower in patients who underwent ESD than those who received EMR [1/5 (20.0%) vs. 16/24 (66.7%), $P = 0.03$]. Although the reason for this difference is unknown, 1 possibility is that the potent cautery effect of EMR compared with that of ESD might cause more severe submucosal injury resulting in an

increased risk for development of stricture.[15] Clarification of the precise mechanisms for developing stricture after EMR/ESD is warranted in future studies. In addition, the difference of rate for stricture between 2 groups might be influenced by the lower rate for stricture in ESD patients. However, there are no ESD patients who did not undergo preventive EBD, it is therefore impossible to evaluate real influence from ESD patients for the results of this study.

Temporary stent placement may also be a promising strategy for preventing postEMR/ESD stricture. Self-expandable removable stents or biodegradable stents have been reported to be useful for the treatment of benign stricture such as anastomotic stricture and cicatricial stricture by esophagitis.[16] However, there has been no report on the use of self-expandable removable stents for preventing the postEMR/ESD stricture. Although the biodegradable stents have been reportedly applied for prevention of the postEMR/ESD stricture, a small number of patients, short-term follow-up periods, and a high frequency of stent migration obscured its usefulness.[17,18] Thus, further evaluation of these methods is required to compare their usefulness with the EBD.

The multivariate analysis in patients with preventive EBD showed that the longer longitudinal mucosal defects (> 30 mm) was the significant risk factor for development of the stricture; in contrast, the circumferential mucosal defect was not a significant risk factor. To avoid the treatment induced esophageal stricture, these data are informative when we select the treatment modalities for the extended esophageal cancer; such as EMR/ESD, chemoradiotherapy, radiotherapy, or surgical resection. If patients prefer the remaining the sufficient ability of oral intake, extensive EMR/ESD should not be indicated, because the long term EBD would be needed and the symptom of dysphagia afflicts the patients.

In conclusion, preventive EBD could be a useful and acceptable strategy to reduce the incidence of postEMR/ESD stricture. Because there is no other effective method to prevent stricture after extensive EMR/ESD at present, preventive EBD should be considered for all patients who undergo extensive EMR/ESD. Although almost 60% of patient developed stricture despite the preventive EBD, the severity of the stricture was clearly reduced even when the stricture was developed. Since the number of patients in this study is rather small, and moreover, this was the retrospective study, a prospective study with a large number of cases is required to confirm the effectiveness of preventive EBD procedure for the prevention of postEMR/ESD stricture in patients with early stage esophageal cancer.

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JJCO Japanese Journal of Clinical Oncology

Case Reports

Jpn J Clin Oncol 2011;41(1)121–124
doi:10.1093/jjco/hyq157
Advance Access Publication 6 October 2010

Early Detection of 5-FU-induced Acute Leukoencephalopathy on Diffusion-Weighted MRI

Reiko Akitake[1], Shin'ichi Miyamoto[1,*], Fumiyasu Nakamura[1], Takahiro Horimatsu[1], Yasumasa Ezoe[2], Manabu Muto[1] and Tsutomu Chiba[1]

[1]Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University and [2]Department of multidisciplinary cancer treatment, Graduate school of Medicine, Kyoto University, Kyoto, Japan

*For reprints and all correspondence: Shin'ichi Miyamoto, Department of Gastroenterology and Hepatology, Graduate School of Medicine, Kyoto University, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan. E-mail: shmiyamo@kuhp.kyoto-u.ac.jp

Received February 3, 2010; accepted July 12, 2010

A 59-year-old man treated with 5-fluorouracil and cisplatin for advanced oesophageal cancer presented abnormal behaviour and subsequently developed impairment of cognitive function, dysphagia and dysarthria on the fifth day of the treatment. Although brain computed tomography revealed no abnormal findings, brain magnetic resonance imaging using diffusion-weighted imaging clearly revealed the presence of a high signal intensity in the deep white matter of the bilateral cerebral hemispheres, including the corpus callosum symmetrically. A diagnosis of acute leukoencephalopathy was reached based on these findings. His clinical symptoms normalized four days after the discontinuation of the chemotherapy. Improvement in magnetic resonance imaging findings was delayed compared with that of clinical symptoms; however, the high signal intensity detected in the deep white matter had disappeared completely five months after the onset of symptoms. Early detection of drug-induced leukoencephalopathy is important as the clinical symptoms can be reversed by early discontinuation of the causative drug. Diffusion-weighted magnetic resonance imaging is a useful modality for the early detection and definitive diagnosis of this characteristic encephalopathy.

Key words: acute luekoencephalopathy – 5-fluorouracil – oesophageal cancer – MRI – diffusion-weighted imaging

INTRODUCTION

5-Fluorouracil (5-FU) is widely used in the treatment of a spectrum of solid cancers, such as carcinoma of the head and neck, oesophagus, stomach, intestine and ovaries. Some adverse reactions of the drug, which include toxic effects to the central nervous system, have been reported (1,2). Among them, encephalopathy is rare and may present as disorientation, confusion, agitation, neurosensory hearing impairment, seizure, stupor, and even deep coma. Diffusion-weighted magnetic resonance imaging (DW-MRI) is a useful modality for the early detection and definitive diagnosis of this characteristic encephalopathy. Herein, we reported a case of 5-FU-induced acute leukoencephalopathy.

CASE REPORT

A 59-year-old man who presented with cough and dysphagia was admitted to our hospital. Oesophago-gastroduodenoscopy showed an ulcerative and localized type of tumour in the middle oesophagus with intramural metastasis to the anal side. A biopsy specimen revealed the presence of well-differentiated squamous cell carcinoma. Enhanced computed tomography (CT) demonstrated that the oesophageal wall thickness was invasive to the surrounded organs, with multiple lymph nodes metastasis at the supramediastinum and the bilateral supraclavicular fossa and with paraaortic localization. A diagnosis of stage IVB (TNM classification. cT4N1M1b) advanced oesophageal cancer was established

and the patient received systemic chemotherapy (cisplatin, cis-diaminedichloroplatinum (CDDP); 80 mg/m^2, day 1) and 5-fluorouracil (5-FU; 800 mg/m^2, days 1–5). On the fifth day of the treatment, he presented an abnormal behaviour and subsequently developed impairment of cognitive function, dysphagia and dysarthria. Vital signs and serum examination were normal, with the exception of an elevated level of ammonia (117 μg/dl; normal range, 20–60 μg/dl). No abnormal findings, including brain metastasis, were detected in the CT images (Fig. 1) and T1-weighted magnetic resonance imaging (MRI) (Fig. 2A). T2-weighted MRI faintly revealed the presence of a high signal intensity in the deep white matter of the bilateral cerebral hemispheres, including the corpus callosum (Fig. 2B). In contrast, DW-MRI clearly revealed the presence of a symmetrical high signal intensity at the same anatomical location (Fig. 2C). As drug-induced acute leukoencephalopathy was suspected based on these findings, both 5-FU and CDDP were discontinued at a total dose of 6000 and 1300 mg, respectively. Clinical symptoms disappeared after the discontinuance of the drugs. He was discharged on the twenty-first day, without recurrence of central nervous system toxicity. One month after the onset of the disease, he was asymptomatic and neurological examination was normal. In addition, the high signal intensity detected in the deep white matter of the bilateral cerebral hemispheres had almost disappeared, and there were only some remnants of it at the splenium of the corpus callosum (Fig. 3A). MRI performed at five months after the onset of the symptoms revealed the complete disappearance of the high signal intensity in both the bilateral cerebral white matter and the corpus callosum (Fig. 3B).

DISCUSSION

Leukoencephalopathy initially manifests itself as dizziness, numbness, disorientation, memory deficit, confusion, agitation, cognitive impairment and unsteady gait. In severer cases, stupor, seizure, akinetic mutism, and even comas may occur (3). Drug-induced leukoencephalopathy is mainly caused by various chemotherapeutic agents, which include methotrexate, vincristine, ifosfamide, fludarabine, cytarabine, 5-fluorouracil, cisplatin and the interferons (4). Among them, 5-FU has been reported most frequently as a leukoencephalopathy causative agent. 5-FU is a fluorine-substituted analogue of pyrimidine uracil. The main action of this agent is to block DNA synthesis by reducing the formation of thymidine monophosphate via the inhibition of the thymidylate synthetase and incorporation into RNA. 5-FU readily penetrates the blood-brain barrier; however, 5-FU-induced neurotoxicity is uncommon and has an incidence of less than 5% among patients treated with this agent. In general, 5-FU-induced leukoencephalopathy is more common in females and in patients with malnutrition or liver dysfunction (5). Hyperammonemia, lactic acidosis and hypocapnia were found to be parallel to the development of encephalopathy. Interestingly, these abnormalities were not detected in patients who did not develop encephalopathy (6). The specific mechanism that underlies hyperammonemia is unknown; however, several factors, including renal dysfunction, constipation, weight loss and infection, aggravate this condition (7).

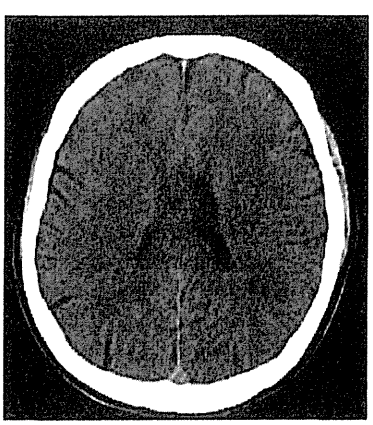

Figure 1. Brain computed tomography performed on the day of the onset of the symptoms showed an absence of abmormalities.

Dyhydropyrimidine dehydrogenase (DPD) is responsible for more than 85% of the catabolism of pyrimidine. Several studies suggest that DPD deficiency, in which the serum and urine levels of uracil and thymidine are increased, may be a risk factor for 5-FU-induced leukoencephalopathy (8).

The common radiological imaging findings of leukoencephalopathy include symmetrical periventricular hypoattenuation on CT scan and diffuse high intensity signal in the white matter and corpus callosum on T2 weighted MRI DW-MRI. DW-MRI is more sensitive than CT scan for the detection of abnormalities in the white matter (9). In the present case, it clearly revealed the presence of a high signal intensity in the deep white matter of the bilateral cerebral hemispheres, including the corpus callosum symmetrically, which was consistent with 5-FU-induced leukoencephalopathy. Cisplatin-induced neurotoxicity is rare and less likely to be present in this case, as the involvement was confined solely to the deep cerebral white matter, and did not extend to the cortex and subcortical white matter (10).

The exact pathological process associated with drug-induced leukoencephalopathy remains unknown. Elevated levels of myelin basic protein in the cerebrospinal fluid (CSF) suggest the presence of myelin destruction (11) (in our case, CSF examination was not performed). *In vitro* and *in vivo* studies suggest that segmental splitting, vacuolization and myelin swelling may occur in humans in the early stage of the disease. It has been known that DW-MRI detects molecular motion of water protons. The accumulation of many small vacuoles within the myelin may interfere with diffusion, thus leading to the appearance of high signal intensity on DW-MRI.

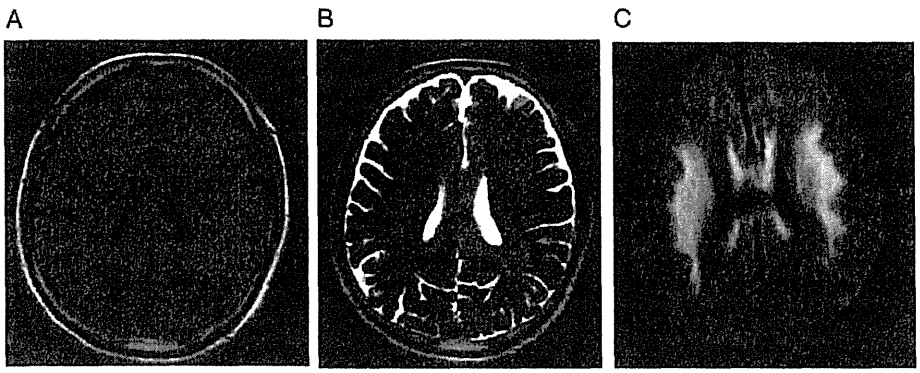

Figure 2. Brain magnetic resonance imaging (MRI) on the day of the onset of the symptoms. (A) No abnormal findings were detected on T1-weighted MRI (B). T2-weighted MRI faintly revealed the presence of a high signal intensity in the deep white matter of the bilateral cerebral hemispheres, including the corpus callosum. (C) In contrast, MRI-diffusion weighted imaging (DWI) clearly revealed the presence of a symmetrical high signal intensity at the same anatomical location. The value of b factor was 1000 s/mm^2.

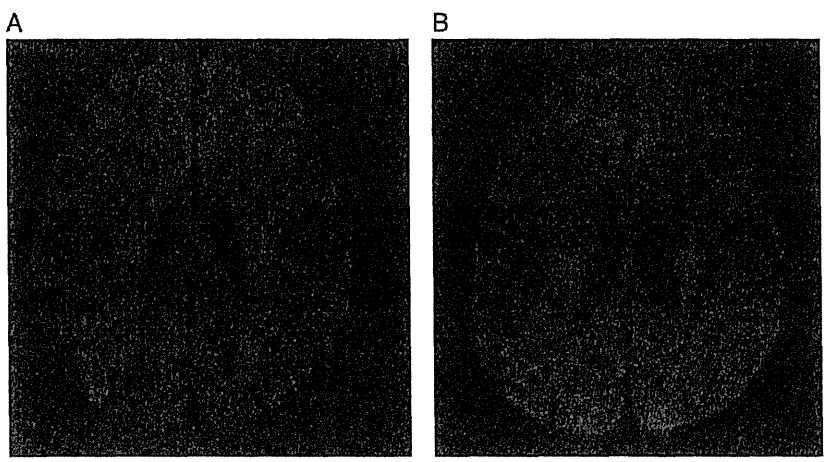

Figure 3. Time course variation of brain MRI-DWI. (A) The high signal intensity detected in the deep white matter of the bilateral cerebral hemispheres and corpus callosum was still slightly visible on MRI-DWI performed one month after the onset of symptoms. (B) These lesions had disappeared completely on the MRI-DWI performed five months after the onset of symptoms.

Drug-induced leukoencephalopathy is dose- and schedule-dependent and is reversible after drug withdrawal or dose reduction; however, in some cases it may lead to life-threatening complications. In other words, the improvement of clinical symptoms after the withdrawal of the causative drug strongly supports the encephalopathy diagnosis. The disease seems to be associated with two clinical courses, according to the time of onset. The first is an acute phase, which develops within one week after administration of the medication. The second is a subacute phase, which develops within five months after administration of the medication (12,13). The treatment modalities proposed in the literature vary considerably and range from purely supportive measures to the use of corticosteroids, thiamine (2,12,13).

Age-related periventricular hyperintensity must be differentiated from drug-induced leukoencephalopathy. Though these T2-weighted MRI findings are similar to those observed in drug-induced leukoencephalopathy, DWI findings differ between the two conditions. DW-MRI of drug-induced leukoencephalopathy revealed the presence of a hyperintensity in the periventricular white matter, whereas that of age-related periventricular hyperintensity showed an absence of any abnormal findings corresponding to the hyperintensity observed on T2-weighted images. From this point of view, DW-MRI seems to be a very useful modality to differentiate this encephalopathy from another condition.

In conclusion, the development of conscious disturbance or abnormal neurological findings in patients treated with chemotherapeutic agents (especially 5-FU) should lead to the consideration of a drug-induced leukoencephalopathy diagnosis. Moreover, in such cases it is important to perform MRI (especially DW-MRI) immediately to establish a

definitive diagnosis, as the neurological symptoms are reversible after discontinuance of the causative drug.

Conflict of interest statement

None declared.

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Diseases of the Esophagus (2011) **24**, 274–278
DOI: 10.1111/j.1442-2050.2010.01141.x

DISEASES OF THE ESOPHAGUS

Original article

Submucosal tumor appearance is a useful endoscopic predictor of early primary-site recurrence after definitive chemoradiotherapy for esophageal squamous cell carcinoma

C.-H. Tu,[1] M. Muto,[2] T. Horimatsu,[2] K. Taku,[3] T. Yano,[4] K. Minashi,[4] M. Onozawa,[5] K. Nihei,[5] S. Ishikura,[5] A. Ohtsu,[4] S. Yoshida[4]

[1]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, Far Eastern Memorial Hospital, Taipei, Taiwan; and* [2]*Department of Gastroenterology and Hepatology, Kyoto University, Kyoto, Japan, and* [3]*Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan,* [4]*Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan, and* [5]*Division of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

SUMMARY. **Chemoradiotherapy (CRT) for esophageal cancer is disadvantageous because of a high locoregional failure rate. Detecting early small recurrent cancers at the primary site is necessary for potential salvage treatment. However, most endoscopists are inexperienced and therefore, a role for surveillance endoscopy after complete remission (CR) has not been established. We retrospectively evaluated serial surveillance endoscopic images from patients eventually proved to have primary-site recurrence in order to identify useful endoscopic features for early diagnosis. From January 2000 to December 2004, 303 patients with esophageal squamous cell carcinoma underwent definitive CRT, and 133 of them achieved CR. The surveillance endoscopic images stored at intervals of 1–3 months for the 16 patients with recurrence only at the primary tumor site and the 61 patients with no recurrence were collected for reexamination. Among 133 patients who achieved CR, 16 (12%) developed only local recurrence at the primary site. Thirteen of the 16 primary-site recurrent tumors (81%) appeared as submucosal tumors (SMT), with the remaining appearing as erosions or mild strictures. Of biopsy-proven recurrences, 81% were preceded by newly developed lesions such as SMT, erosions, or mild strictures detected by earlier surveillance endoscopies. For all 77 patients achieving CR with no metastasis, 86% of the evolving SMT with negative biopsies were eventually confirmed as cancer at later endoscopies. Thirteen of the 21 evolving lesions were subsequently confirmed as recurrent cancer. Early primary-site recurrence of esophageal cancer after a complete response to CRT is detectable with frequent endoscopic surveillance. SMT appearance is a useful endoscopic sign of early recurrence, as well as a predictor of subsequent diagnosis of recurrence.**

KEY WORDS: **chemoradiotherapy, esophageal cancer, recurrence, surveillance.**

INTRODUCTION

Definitive chemoradiotherapy (CRT) is widely accepted as a standard treatment option in the management of locally advanced esophageal cancer because of its high response rate and significant survival benefit.[1,2] A major drawback to this nonsurgical approach is locoregional treatment failure. At least 40% of patients undergoing CRT experienced local failure, some of whom did not develop distant metastases.[1,3–5]

These primary-site recurrence patients are traditionally managed with salvage esophagectomy for a chance of long-term survival, particularly in those with an earlier pathological stage (T1N0 and T2N0).[6,7] However, high perisurgical mortality and morbidity rates are major concerns.[7,8] Recently developed nonsurgical techniques, such as salvage endoscopic mucosal resection and photodynamic therapy,

Address correspondence to: Dr Manabu Muto, MD PhD, Department of Gastroenterology and Hepatology, Kyoto University, 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. Email: mmuto@kuhp.kyoto-u.ac.jp
List of presentations: Nil.
Author's disclosure of potential conflict of interest: The authors have no potential conflicts of interest.

have the advantages of greater safety and fewer treatment-related sequelae, while conferring promising survival benefits for local failures after definitive CRT.[9,10] Technically, endoscopic mucosal resection and photodynamic therapy are feasible only when the volume of the locally recurrent tumor is small enough to be amenable to these endoscopy-based procedures. Therefore, the application of these newer treatments depends crucially on the ability to identify early recurrent tumors by endoscopy.

A strategy of frequent surveillance endoscopy initiated early after remission of the cancer should theoretically improve the chances of detecting primary-site recurrent tumors in their early stages. This requires the prompt recognition of minute tumors arising from the former neoplastic bed, instead of from the uninvolved normal esophageal mucosa. However, the complete regression of cancer cells results in residual fibrosis, radiation-induced tissue injury, and the distortion of normal microstructures,[11,12] which may render relapsing neoplastic growth morphologically different from typical primary tumors. Apparently, most endoscopists are inexperienced in hunting for these difficult lesions. To our knowledge, no study of the skills in endoscopic detection of such lesions has been published. Not surprisingly, a follow-up endoscopy after the completion of CRT is considered 'optional' in the National Comprehensive Cancer Network clinical practice guidelines for esophageal cancer.[13] We believe that a reliable endoscopic diagnostic technique is necessary to support a strategy of intense endoscopic follow-ups.

As a cancer referral and research hospital, our institute is unique in its implementation of a vigorous endoscopic follow-up program after primary treatment for all patients with esophageal cancer. Therefore, it is possible to analyze the filed imaging data of endoscopic monitoring on the post-CRT mucosa. In the present study, we aimed to identify useful endoscopic findings through reviewing the image data pool to predict recurrent esophageal cancers limited to the primary site after complete remission (CR) is achieved by CRT.

MATERIALS AND METHODS

Patient population

Between January 2000 and December 2004, 303 patients with esophageal squamous cell carcinoma underwent definitive CRT at the National Cancer Center Hospital East, Kashiwa, Japan. The CRT consisted of 50.4–60 Gy irradiation, together with two cycles of continuous infusion with 5-fluorouracil (5FU) and cisplatin. Up to four courses of CRT were added for those patients who showed a good initial response to treatment.[9]

Table 1 Clinical data of 133 patients achieving complete remission with definitive chemoradiotherapy

Characteristic		Number of patients	%
Sex			
Male		110	82.7
Female		23	17.3
Age (years)			
Mean	62		
Range	39–76		
T stage			
T1		30	22.6
T2		21	15.8
T3		70	52.6
T4		12	9.0
N stage			
N0		46	34.6
N1		87	65.4
M stage			
M0		123	92.5
M1		10	7.5
Clinical stage			
I		16	12.0
II		45	33.8
III		62	46.6
IV		10	7.5
Macroscopic classification			
Type 0		30	22.6
Type 1		19	14.3
Type 2		60	45.1
Type 3		24	18.0

Response to treatment was assessed at the completion of CRT. CR was defined when all the following criteria were met: (i) the disappearance of the tumor lesion or ulcer at the primary site, with negative biopsies; (ii) no esophageal stricture or any condition that prevented a thorough endoscopic examination of the whole esophagus; (iii) no remaining measurable disease or distant metastasis on computer tomography and chest roentgenography; and (5) these criteria were met for at least 4 weeks.

Of the 303 patients, 133 (43.9%) were defined as being in CR at the completion of CRT. Of these 133 patients, 110 were men, with a median age of 62 years. Pretreatment staging of their esophageal cancers was determined with the tumor-node-metastasis classification of the International Union Against Cancer.[14] Seventy (52.6%) patients had T3 tumors; most patients had N1 (65.4%) or M0 (92.5%) disease. Forty-five (33.8%) and 62 (46.6%) patients were classified as clinical stages II and III, respectively (Table 1).

Study design

After achieving CR, initial follow-up endoscopy to confirm CR was scheduled within at most 1–2 months for each patient, accompanied with other necessary studies for the assessment of metastases. After the confirmation of CR, follow-up endoscopy was scheduled every 2–3 months for the first year and every 4–6

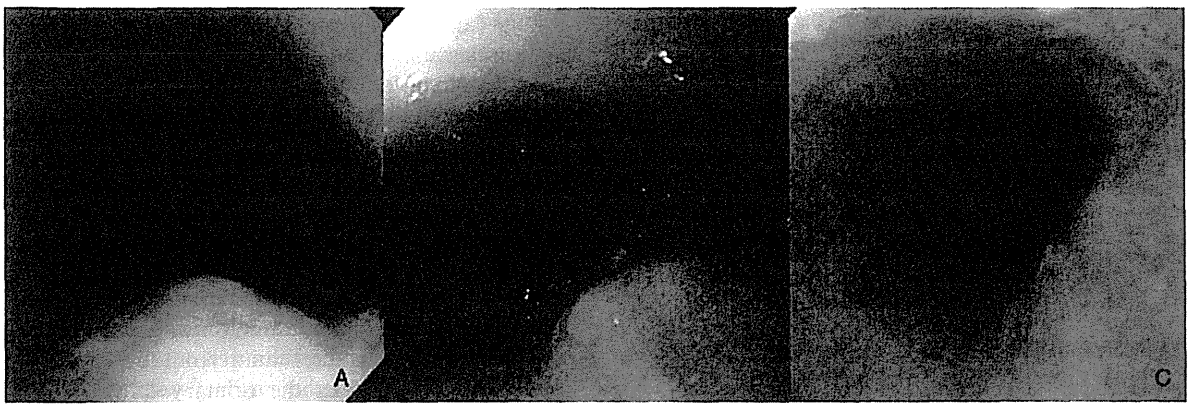

Fig. 1 Initially growing recurrent esophageal cancer at the primary tumor site after complete remission was achieved with chemoradiotherapy may be detected by endoscopy, with features of a submucosal tumor (A), a submucosal tumor with superficial ulcer (B), or a flat erosion (C).

months for 2 years thereafter. Lugol staining and multiple biopsies at the primary site were routinely required.[15] The diagnosis of local recurrence was determined by a positive biopsy.

Of the 133 CR patients, 61 had no recurrence, 56 developed lymph node or distant metastases, and the remaining 16 developed local recurrence at the primary tumor site with no evidence of metastasis. We excluded the 56 patients with lymph node or distant metastases from this study because for them, evaluation of the primary site was not important and only those patients eligible for salvage treatment on local tumors were of interest. Therefore, the endoscopic images of the remaining 77 patients were retrospectively enrolled. This population comprised patients with esophageal squamous cell carcinoma who achieved CR after the initial CRT and developed no metastasis during follow-up, regardless of local recurrence. All of the filed endoscopic images stored after achieving CR, both conventional endoscopy and Lugol-stained chromoendoscopy, were retrospectively collected for reexamination. The stored endoscopic images were evaluated by consensus among three endoscopists experienced in upper gastrointestinal cancer diagnosis (K. T., M. M., K. M.).

RESULTS

Upon the diagnosis of primary-site recurrence for the 16 patients, 13 (81%) had endoscopic findings resembling submucosal tumors (SMT), typically a focal bulge mostly covered by normal-appearing mucosa (Fig. 1A).[16] Eleven of the 13 tumors contained central eroded areas recognized as ulcers or erosions (Fig. 1B and 1C). The remaining three tumors were detected as flat erosions without features of SMT (Table 2).

Images of surveillance endoscopies performed at intervals between CR and the diagnosis of recurrence in the 16 patients were sequentially examined. Newly developed gross lesions at the primary site with negative biopsies were interpreted as recurrent lesions. Evolving lesions were discovered in 13 (81%) patients, including six (38% of the 16 patients) SMT, five (31%) erosions, and two (12%) mild luminal strictures (Table 3).

For all 77 patients achieving CR and free of metastasis, lesions newly developed between CR and the most recent endoscopic surveillance were considered evolving lesions. Therefore, an evolving lesion may be eventually proven to be a recurrence or remain biopsy-negative at the most recent endoscopy. Six of the seven (86%) evolving SMT were subsequently confirmed as recurrent cancer by follow-up

Table 2 Endoscopic findings at primary-site with biopsy-proven recurrence

Endoscopic finding	Number of patients	%
SMT	13	81
SMT with erosion or ulceration	11	
SMT without erosion or ulceration	2	
Erosion	3	19
Total	16	100

SMT, submucosal tumor.

Table 3 Endoscopic findings of newly developed lesion for primary-site recurrent tumors

Preceding newly developed lesions with negative biopsies	Findings at diagnosis of recurrence	Number of patients
SMT	SMT	6
Erosion	SMT	4
Erosion	Erosion	1
Mild stricture	SMT	2
No newly developed lesion	SMT	1
No newly developed lesion	Erosion	2
Total		16

SMT, submucosal tumor.

Table 4 Primary-site biopsy results of the latest surveillance endoscopy for patients who achieved complete remission and remained free of metastasis

Evolving lesion found at preceding endoscopies	Numer of patients (%)	Biopsy result of the latest endoscopy	Number of patients (%)
SMT	7 (9)	Recurrence	6 (86)
		Negative	1 (14)
Erosion	8 (10)	Recurrence	5 (63)
		Negative	3 (37)
Mild stricture	6 (8)	Recurrence	2 (33)
		Negative	4 (67)
No evolving lesion	56 (73)	Recurrence	3 (5)
		Negative	53 (95)
Total	77 (100)		

SMT, submucosal tumor.

endoscopic biopsies. Similarly, five of eight (63%) evolving erosions and two of six (33%) evolving mild strictures were finally confirmed as recurrence. Fifty-six patients were never found to have evolving lesions throughout the follow-up, including three (5%) who were confirmed as recurrence upon the first appearance of an endoscopic lesion. In total, eight of the 21 (38%) patients who developed evolving lesions remained biopsy-negative at their most recent endoscopic follow-up (Table 4).

DISCUSSION

We discovered that the most frequent (81%) endoscopic indicator of primary-site recurrence at its earliest possible stage for a histological diagnosis is SMT. Eighty-one percent of biopsy-proved recurrences were preceded by newly developed lesions such as SMT, erosions, or mild strictures detectable with surveillance endoscopies. Most (86%) evolving SMT with negative biopsies were eventually confirmed as cancer at later endoscopies, but the proportions were lower for other evolving lesions such as erosions (63%) and strictures (33%). This is the first study to describe the morphological changes of early recurring tumors by serial endoscopic observations at short intervals. Our findings will be helpful for improving the skills to detect potentially treatable primary-site recurrence after definitive CRT for esophageal squamous cell carcinoma.

For the endoscopic diagnosis of primary esophageal cancer, several features have been previously described to detect early stage squamous cell carcinoma: localized mucosal erosions in contrast to normal surrounding mucosa; circumscribed mucosal protuberances with irregular configurations; focal areas of mucosal coarsening and congestion; and, rarely, white mucosal plaques.[16] However, these features are not reliable when applied to early recurrent tumors arising from the mucosal bed of a former primary cancer that regressed after CRT. The original esophageal layering and vascular structures have been disrupted by the primary tumor. Furthermore, the expansion and arrangement of recurring neoplastic cells are disrupted by tissue reactions to previous chemotherapy and radiotherapy, as well as by subsequent repair processes. Tumor necrosis, foam cell formation, vascular granulation, inflammatory exudation, and fibrosis are frequent histological sequelae of CRT.[17,18] The minute foci of the initial neoplastic growth may arise from scattered residual cancer cells in deeper tissues, rather than from the superficial mucosal layer, as does the primary cancer.[11] These factors have largely precluded endoscopic ultrasound as a feasible tool in the assessment of residual or recurrent esophageal cancers.[19,20] For the same reason, the endoscopic diagnostic features for recurrent tumors are likely to be different from those for primary tumors.

We speculate that most of the SMT lesions discovered in our study were formed by expanding tumor cells in the submucosal layers, but barely reached the luminal surface because of their depth and constraining fibrosis. Although the overlying mucosa appeared normal, they manifest their first sign by bulging outward. Malignant cells can be captured by biopsy forceps only when they reach the surface in sufficient numbers, or more efficiently, destroy the surface to make an erosion. This might explain why all of the six newly developed SMT yielded negative results at their first biopsies but eventually proved to be recurrences (Table 3).

Several previous studies have aimed to improve the detection of local recurrence by measures other than endoscopy. In addition to pretreatment staging, F-18-fluorodeoxyglucose–positron emission tomography (FDG–PET) is highly sensitive (up to 96%) in detecting recurrent esophageal cancer, but with somewhat lower specificity (68–82%).[21–23] However, its utility in detecting locoregional recurrence is limited by its low specificity (57–75%) for postesophagectomy patients. Postsurgical inflammation and anatomical changes are largely responsible for the false positivity. Detecting small residual or early recurrent cancers is even more challenging because low tumor volume could greatly reduce the sensitivity of FDG–PET. Moreover, such lesions are not distinguishable from post-CRT inflammation or regional lymph-node metastasis.[24,25]

The results of our study disagree with the conventional belief that endoscopy is of limited utility in the management of esophageal cancer after CRT.[13,26] We believe that routine endoscopy, particularly focused on the primary tumor site, is advisable for all patients with esophageal squamous cell carcinoma after the completion of CRT. We also suggest regular endoscopic surveillance at least every three months for those who have achieved CR. The occurrence of

SMT-like lesions after CR is an alarming sign that deserves intensive investigation and follow-up if a modality of salvage treatment is available. Any evolving lesion at the primary site with negative biopsy should be followed closely.

Our retrospective study design has introduced a knowledge bias because the evaluating endoscopists were not totally blinded to the outcomes. Therefore, a randomized controlled trial comparing the clinical outcomes is necessary to establish the role of surveillance endoscopy after definitive CRT for esophageal squamous cell carcinoma.

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Radiotherapy and Oncology 101 (2011) 410–414

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Pain control in head and neck radiotherapy

Multicenter phase II study of an opioid-based pain control program for head and neck cancer patients receiving chemoradiotherapy

Sadamoto Zenda [a,m,*], Kazuto Matsuura [b], Hiroyuki Tachibana [c], Akihiro Homma [d], Tadaaki Kirita [e], Nobuya Monden [f], Shigemichi Iwae [g], Yojiro Ota [h], Tetsuo Akimoto [a,i], Hiroshi Otsuru [j], Makoto Tahara [a], Kengo Kato [k], Masao Asai [l]

[a] Division of Radiation Oncology, National Cancer Center Hospital East, Chiba; [b] Division of Head and Neck Surgery, Miyagi Cancer Center; [c] Division of Radiation Oncology, Aichi Cancer Center Hospital; [d] Department of Otolaryngology – Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Sapporo; [e] Department of Oral and Maxillofacial Surgery, Nara Medical University, Nara-Kashihara; [f] Division of Head and Neck Oncology, Shikoku Cancer Center, Ehime; [g] Department of Head and Neck Surgery, Hyogo Cancer Center; [h] Division of Oral and Surgery, Shizuoka Cancer Center; [i] Department of Radiation Oncology, Tokyo Women's Medical University; [j] Department of Dentistry Oral Surgery, National Hospital Organization Tokyo Medical Center; [k] Department of Otolaryngology – Head and Neck Surgery, Tohoku University Graduate School of Medicine, Sendai; [l] Division of Head and Neck Surgery, National Cancer Center Hospital, Tokyo; and [m] Department of Head and Neck Surgery, Tokyo Medical and Dental University, Japan

ARTICLE INFO

Article history:
Received 25 March 2011
Received in revised form 7 September 2011
Accepted 20 September 2011
Available online 14 October 2011

Keywords:
Head and neck cancer
Chemoradiotherapy
Supportive care
Morphine

ABSTRACT

Background: The aim of this multi-center phase II study was to clarify the clinical benefit of an opioid-based pain control program for head and neck cancer patients during chemoradiotherapy.

Patients and methods: Head and neck cancer patients who were to receive definitive or postoperative chemoradiotherapy were enrolled. The opioid-based pain control program consisted of a three-step ladder, with basic regimens of:

Step 1: acetaminophen at 500–1000 mg three times a day.
Step 2: fast-acting morphine at 5 mg three times a day before meals for a single day.
Step 3: long-acting morphine administered around-the-clock, with a starting dosage of 20 mg/day and no upper limit set in principle.

Patients and methods: The primary endpoint of this study was compliance with radiotherapy.

Results: A total of 101 patients from 10 institutions were registered between February 2008 and May 2009 and included in the analysis. The major combination chemotherapy regimen was cisplatin alone (76%). The rate of completion of radiotherapy was 99% and the rate of unplanned breaks in radiotherapy was 13% (13/101, 90% confidence interval: 9.9–16.5%). Median maximum quantity of morphine used per day was 35 mg (range 0–150 mg).

Conclusions: Use of a systematic pain control program may improve compliance with CRT.

Several recent randomized phase III studies have confirmed the value of radiotherapy and concurrent high-dose single-agent cisplatin in almost all stages of locally advanced head and neck cancer [1–5], and platinum-based chemotherapy and concurrent radiotherapy regimens with or without induction chemotherapy are widely used in clinical practice [6–8].

One of the most common and debilitating toxicities among head and neck cancer patients is radiation-induced mucositis [9,10], and severe acute mucositis often results in unplanned treatment breaks, clinic visits and hospitalizations [11,12]. Unplanned breaks in radiotherapy for head and neck cancer are associated with significantly worse locoregional control [13–15]. Even short breaks may have a negative influence: in one retrospective analysis of 2225 patients from four centers [13], for example, an unplanned break of only 1 day resulted in a 0.68% lower 2-year local control rate, while other authors estimated that the tumor control rate is at least 1% lower for every day that radiation treatment is interrupted [16,17].

To investigate whether a systematic pain control program might help decrease unplanned treatment breaks by suppressing radiation-induced pain, we developed an opioid-based pain control program for the systematic management of radiation-induced pain. The aim of this multicenter phase II study was to clarify the clinical benefit of this opioid-based pain control program for head and neck cancer patients during chemoradiotherapy.

* Corresponding author at: Radiation Oncology Division, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan.
E-mail address: szenda@east.ncc.go.jp (S. Zenda).

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doi:10.1016/j.radonc.2011.09.016

Patients and methods

This multi-center phase II trial was approved by the institutional review boards of all participating institutions before patient enrollment occurred.

Eligibility

Enrollment criteria included histologically confirmed squamous cell carcinoma of the head and neck, age 20–75 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, normal organ function, scheduled receipt of definitive or postoperative radiotherapy (>50 Gy) with platinum-based chemotherapy, and no cancer pain at the time of recruitment. Written informed consent to treatment was obtained from all patients before the initiation of any treatment.

Treatment

All study patients were recommended to undergo percutaneous endoscopic gastrostomy (PEG) before the start of radiotherapy. The main protocol was called the 'opioid-based pain control program', which consisted of a three-step ladder (Fig. 1).

Prescription Step 1

The basic regimen for mild pain was acetaminophen at 500–1000 mg three times a day. Loxoprofen sodium or diclofenac sodium was avoided on the basis that their adverse effects on renal function might have influenced compliance with platinum-based chemotherapy.

Prescription Step 2

The basic regimen for mild-intermediate pain was fast-acting morphine e.g. anhydrous morphine sulfate at 5 mg three times a day before meals. The main aim of this prescription was to avoid full dependence on PEG at an early phase of CRT. This regimen could be used concurrently with Prescription Step 1. If oral intake became impossible soon after the initiation of CRT, this regimen could be skipped and the patient moved directly from Step 1 to Step 3.

Prescription Step 3

The basic concept in this step was the use of long-acting morphine around the clock. The starting dosage was 20 mg/day, and no upper limit was set. The rescue dose was set as 1–6 of the main morphine dosage. In principle, intravenous administration of morphine was not performed; in case oral intake became difficult, sustained-released morphine sulfate in fractional doses administered via PEG was recommended instead.

Appropriate use of medications to control side effects of morphine was strongly recommended in Steps 2 and 3. Pain strength was evaluated at least weekly by physicians or nurses using the grading system for mucositis/stomatitis (functional/symptomatic) in Common Terminology Criteria of Adverse Events version 3.

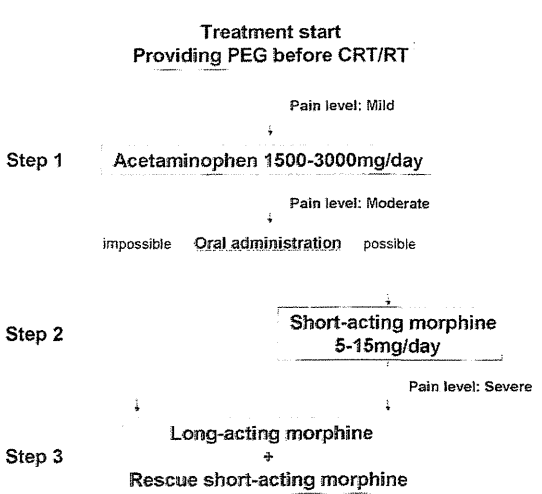

Fig. 1. Opioid-based pain control program. The main decision tree of the opioid-based pain control program is shown.

Toxicity

With regard to the acute toxicity of chemoradiotherapy, adverse events were coded according to the Common Terminology Criteria of Adverse Events version 3. Morphine-induced side effects were evaluated with regard to nausea, constipation, sleepiness, urinary retention, and respiratory depression.

Patient education about use of PEG

To allow CRT to be performed on schedule with minimum hospitalization, it was necessary that patients were able to use PEG alone at home. Expert nurses, including Wound, Ostomy and Continence (WOC) nurses, conducted educational sessions with all patients about how to use PEG during CRT.

PEG management ability was evaluated in each patient at the end of radiotherapy in a three-level score of perfect, possible with family support, and impossible.

Treatment evaluation and statistical analysis

The primary end point of this study was compliance with radiotherapy.

An unplanned treatment break in radiotherapy was defined as an interruption to radiotherapy of 1 day or more, excluding weekends or planned machine maintenance. In our group experience of definitive chemoradiotherapy from 2002 to 2006, 25% of all patients had treatment interruptions (unpublished data). With regard to postoperative radiotherapy, 24% of all patients had treatment interruptions which resulted in a total duration of treatment of more than 7 weeks in EORTC 22931 study [3]. On these basis, our present pain control program was considered worthy of additional study only provided that the true rate of interruption of radiotherapy was 20% or less, and not worthy of additional study if the true rate was 35% or more. With 80% power and a one-sided type-I error of 5%, the minimum number of patients required to evaluate the primary endpoint was 79.

We then calculated that 15% of patients might have a treatment break or cancellation due to reasons other than the failure of supportive management and that 10% might be excluded by violation of the protocol or other reasons. We therefore calculated a total sample size of 110 patients.

Patient demographic, pathologic, and clinical characteristics were described in terms of the mean, standard deviation, median, range, and percentage.

Results

Patient characteristics

One hundred and ten patients from 10 institutions were registered between February 2008 and May 2009. Nine patients were excluded from analysis because of patient discretion ($n = 5$) and change in strategy after registration ($n = 4$). The remaining 101 patients are characterized in Table 1. Median age was 60 years (range

Table 1
Patient characteristics.

No. of patients	101
Age	
Median (years, range)	60 (23–75)
Gender	
Male/female	89/12
Performance status	
0–1/2	101/0
Primary site	
Nasopharynx	24
Oropharynx	26
Hypopharynx	27
Larynx	6
Tongue, oral cavity	13
Unknown	5
Clinical stage	
II	12
III	10
IV	49
Recurrence	5
Postoperation	25
Radiotherapy setting	
Postoperative RT	25
Definitive RT	76
Treatment strategy	
IC → CRT	21
CRT	78
RT alone	2
Radiation dose	
Median (range)	70 (54–70)
Combination chemotherapy	
Cisplatin alone	77
Cisplatin and 5-FU	12
Cisplatin and docetaxel	1
Other platinum	9

Abbreviations: IC, induction chemotherapy; CRT, chemoradiotherapy; RT, radiotherapy.

23–75). The major primary site was the pharynx (76%), followed by the nasopharynx (24%), oropharynx (26%) and hypopharynx (27%).

With regard to treatment strategy, 76 patients (75%) received radiotherapy as an initial approach, and the remaining 25 (25%) in a postoperative setting. Median radiation dose was 70 Gy (range 54–70) and the major combination chemotherapy regimen was cisplatin alone (77/101, 76%).

Treatment compliance

One hundred of 101 patients completed radiotherapy. The remaining patient was scheduled for irradiation with 66 Gy, but this was cancelled at 62 Gy because of patient discretion. The rate of unplanned breaks in radiotherapy was 13% (13/101, 90% confidence interval: 9.9–16.5%), owing to acute toxicity in 2, PEG trouble in 2, emergency tracheostomy in 1, gastric ulcer in 1, unplanned machine trouble in 2, patient discretion in 3, and other reasons in 2. Of these, the median interval of radiation interruption was 1 day (range 1–4 days), and no unplanned break of more than 1 week was seen.

Morphine regimen

Morphine use is shown in Table 2. From the initiation of treatment to 1 month after the end of radiotherapy, median total morphine use per patient was 815 mg (0–6284 mg), and median maximum use per day was 35 mg (0–150 mg). Median radiation dose at the start of morphine was 28.8 Gy. The frequency of morphine-induced side effects of nausea, constipation, sleepiness, urinary retention, and respiratory depression was 26%, 32%, 12%, 0%, and 0%, respectively.

Table 2
Toxicity.

	Grade (CTCAE ver.3.0)				
	1	2	3	4	% 3 and 4
Leucopenia	18	45	20	0	20
Neutropenia	21	41	11	1	12
Anemia	35	33	13	1	14
Thrombocytopenia	29	14	5	0	5
Nausea	32	33	10	0	10
Mucositis					
CE	13	33	54	0	53
FS	8	32	61	0	60
Neuropathy					
S	1	2	0	0	0
M	0	0	0	0	0
Xerostomia	46	39	3	0	3
Dermatitis	25	52	24	0	24
Febrile neutropenia	–	–	1	0	1
Weight loss	19	22	0	0	0

Abbreviations: CTCAE, Common Terminology Criteria of Adverse Events; CE, clinical exam; FS, functional/symptomatic; S, sensory; M, motor.

The rate of patient use of Step 2 or Step 3 programs to control pain during CRT was 83% (84/101), while the rate of use of morphine at one month after the end of radiotherapy was 26% (26/101). A schema of the frequency of use of each prescription is shown in Fig. 2.

Toxicity

Toxicity profile during CRT is shown in Table 3. No fatal hematological events were seen. With regard to non-hematological toxicity, mucositis/stomatitis and dermatitis were the most common acute toxicities. Grades 2 and 3 dermatitis events were seen in 52 (52%) and 24 patients (24%), respectively, while no fatal events were seen.

With regard to mucositis/stomatitis, grade 3 events in the categories 'clinical exam' and 'functional/symptomatic' occurred in more than half of the patients. Grade 2 weight loss was seen in 22 patients (22%), while no grade 3 weight loss was seen.

No treatment-related deaths were seen.

The data about PEG

Ninety-eight of 101 patients (97%) were provided PEG, mostly via the direct method. There were four events (4%) of PEG-associated infection or peritonitis during the observation period. At the end of radiotherapy, 92 patients had used PEG in daily life, of whom 84 (91%) were able to manage PEG by themselves, 5 could do so with family support, and 3 could not manage on an outpatient basis.

On the other hand, of 83 patients who survived over 1 year without primary tumor, the rate of PEG dependence at 1 year after RT was 8.4% (7/83).

Discussion

The aim of this phase II study was to clarify the safety and efficacy profile of a systematic pain control program for head and neck cancer patients during chemoradiotherapy. Results suggested that this program might contribute to improving compliance with CRT in these patients.

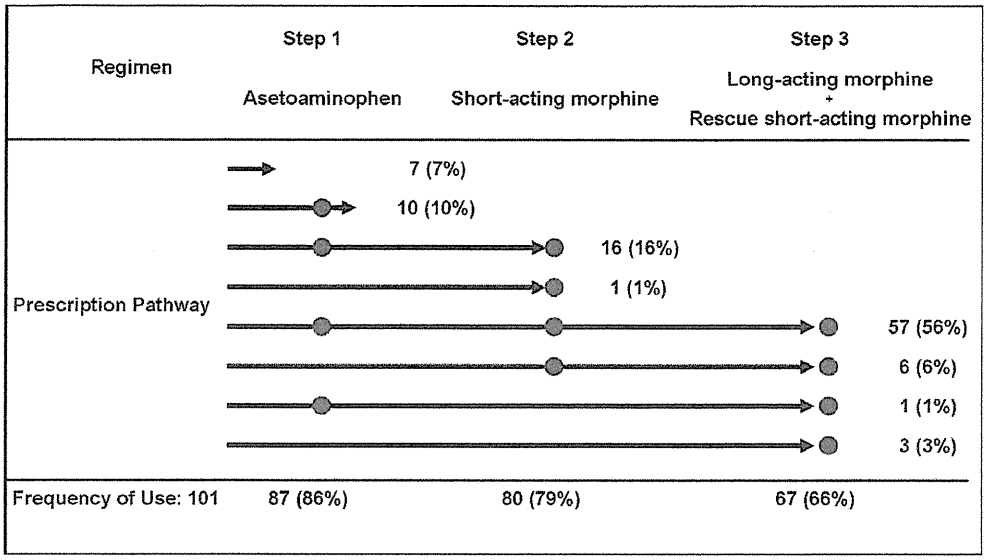

Fig. 2. The summary of prescriptions. Eight prescription pathway patterns were identified. Steps 1–3 was the most common route. Sixty-seven (66%) patients required Prescription Step 3 (long-acting morphine based regimen).

Table 3
Morphine use.

Rate of morphine use	84/101 (83%)
Median total quantity of morphine use per patient	815 mg (0–6286)
Median maximum quantity of morphine use per day	35 mg (0–150)
Morphine-free rate at 1 month after RT	75/10 (74%)
Morphine-induced SE	
Nausea	22 (26%)
Sleepiness	10 (12%)
Urinary retention	0 (0%)
Constipation	27 (32%)
Respiratory depression	0 (0%)

Abbreviations: RT, radiotherapy; SE, side effect.

The primary endpoint of this study was compliance with radiotherapy. Although many retrospective analyses have shown that unplanned treatment breaks have a significant negative impact on treatment outcome [13–15,18], only limited information about this is available from recent prospective trials. In the EORTC 22931 study [3], for example, 24% of all patients had treatment interruptions resulting in a total duration of treatment of more than 7 weeks. Lefebvre et al. [19] reported a randomized control trial which compared sequential chemotherapy and radiotherapy with alternating chemotherapy and radiotherapy, and showed that 23% of the alternating arm patients experienced an interruption to or delay in radiotherapy.

In our study, the rate of unplanned breaks in radiotherapy was 13% and the completion rate was 99%. Although therapeutic intensity in our study was not inferior to that of these two trials, our treatment compliance was better. These results suggest that systematic pain control programs may have a good impact on treatment compliance.

We consider that the provision of percutaneous endoscopic gastrostomy (PEG) before the start of radiotherapy was necessary to allow completion of the treatment schedule. However, complete dependence on PEG soon after starting CRT might result in a decrease in laryngo-pharynx function [20–23]. Taking fast-acting morphine three times a day preprandially at Step 2 might help avoid complete dependence on PEG at an early phase of CRT. In our study, the rate of PEG dependence at 1 year after RT was only 8.4% (7/83). We think the appropriate PEG use does not cause dysphagia in head and neck cancer patients treated with radiotherapy.

With regard to morphine use, the rate of patients using morphine to control pain during CRT was 83% (84/101), and the median maximum quantity of morphine use per day was 35 mg (0–150 mg). In contrast, the rate of patients using morphine at one month after the end of radiotherapy was 26% (26/101). These results suggest that radiation-induced pain worsened rapidly during radiotherapy but improved equally rapidly after the end of radiotherapy.

As an additional benefit of our systematic pain control program, the decrease in differences among physician orders facilitated the duties of nurses. Moreover, unusual changes in pain under this systematic program provided sensitive insight into the possibility of accidents, such as infection. We consider these changes as additional factors that also influenced our good results.

Finally, this program is relatively simple and can be easily implemented without special tools. Although few sustained-release morphine products suitable for administration via PEG are presently available, increased availability will facilitate broad application of the program. This opioid-based pain control program can therefore be widely used in other institutions.

Conclusion

Our opioid-based systematic pain control program during CRT may be helpful for improving compliance with CRT.

We are now planning a randomized control study to determine whether this program has a significant impact on treatment outcomes, including quality of life and overall survival.

Conflict of interest

We have no conflict of interest.

Acknowledgment

This study was supported by the Ministry of Health, Labour and Welfare grant-in-aid for cancer research.

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