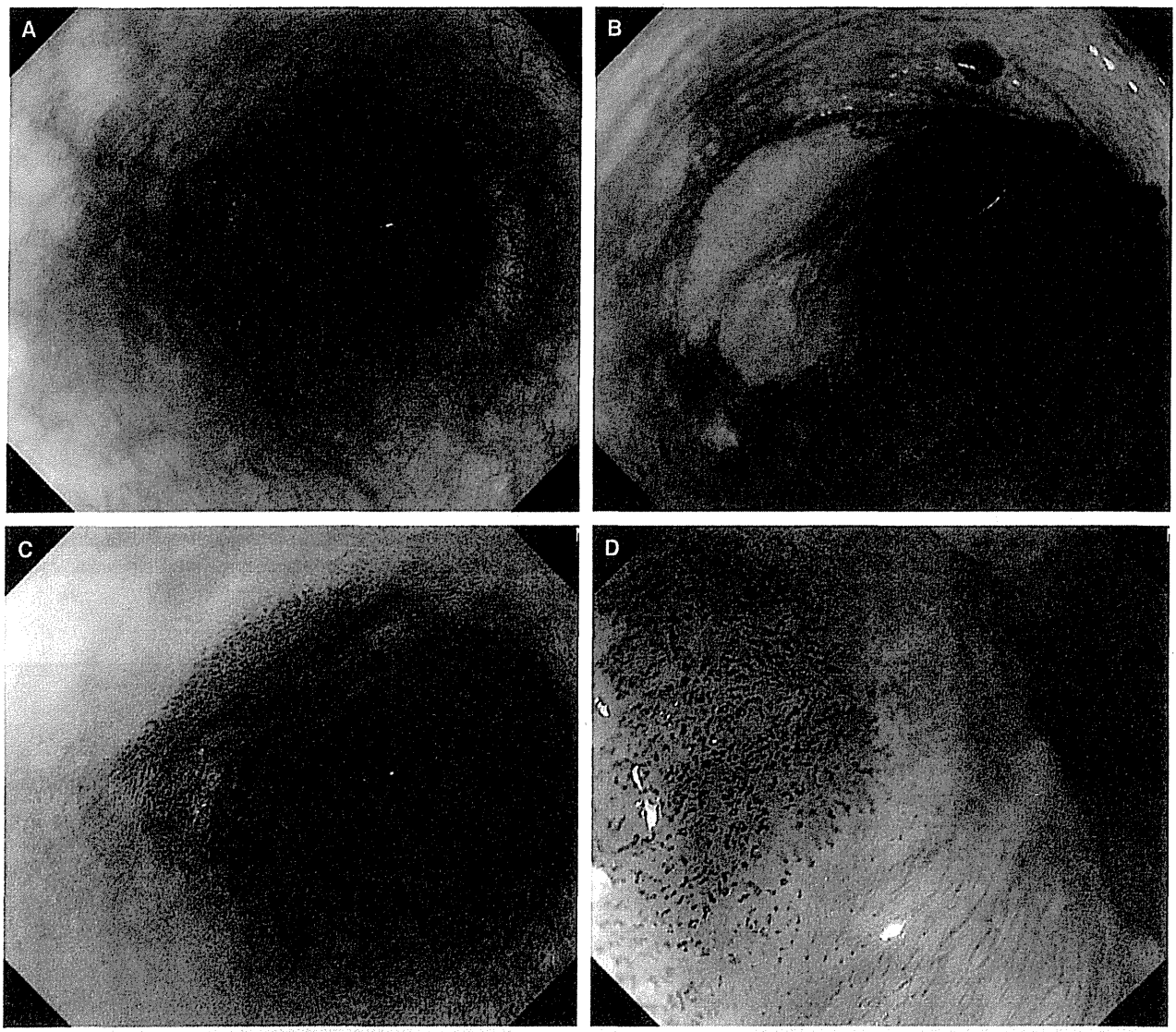

Figure 6 Superficial esophageal squamous cell carcinoma. (A) The cancerous lesion is difficult to identify by conventional white light imaging. (B) Lugol chromoendoscopy clearly reveals the cancerous lesion as a Lugol-voiding lesion. (C) Narrow-band imaging (NBI) shows the cancerous lesion as a well-demarcated brownish area. (D) Magnified NBI shows irregularity of the microvessels in the brownish area while the surrounding background mucosa does not show dilation and tortuous change of the intraepithelial papillary capillary loop (IPCL).

superficial cancer is seen as a brownish area (Fig. 6).[15,16] With magnification, irregularity of the intraepithelial papillary capillary loop (IPCL) is also seen (Fig. 6).[17]

In a prospective multicenter randomized controlled study, Muto *et al.* reported that NBI detected superficial ESCC more frequently than did WLI (97% *vs* 55%, $P < 0.001$).[18] The sensitivity and accuracy of NBI for the diagnosis of superficial ESCC were 97.2% and 88.9%, respectively. Furthermore, even small lesions (<10 mm) were more effectively detected by NBI with magnification than with WLI (94% *vs* 39%, $P = 0.03$).

The screening of second primary ESCC in patients with head and neck cancer is important, and Lugol chromoendoscopy has been used for its detection.[19] In a study reported by Takenaka *et al.*,[20] the specificity of NBI was significantly superior to conventional WLI (95.4% *vs* 84.7%, $P < 0.001$), whereas the sensitivity of NBI and Lugol chromoendoscopy was equivalent (90.9% *vs* 100%, not significant). Further-

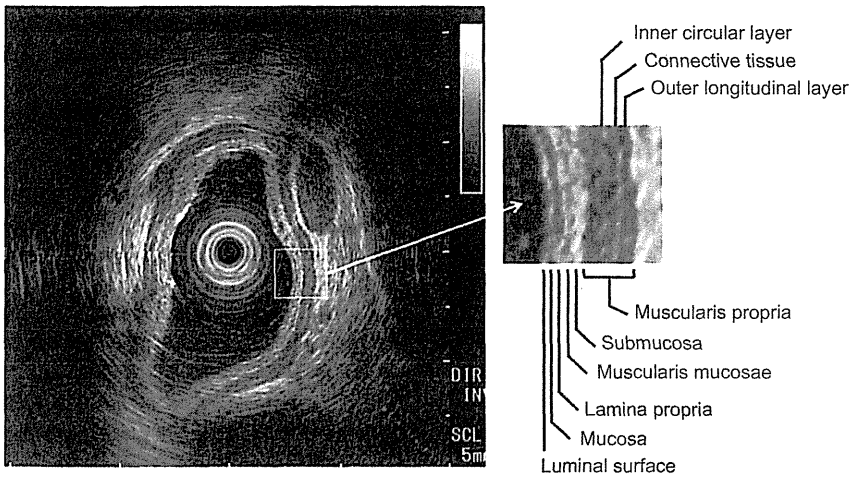

Figure 7 Endoscopic ultrasonography (EUS) image of the normal esophageal wall by 20 MHz miniprobe demonstrates a nine-layered structure (arrow). The first five layers correspond to the echogenic luminal surface (high echo), mucosa (low echo), lamina propria (high echo), muscularis mucosae (low echo), submucosa (high echo). Next are inner circular (low echo) and outer longitudinal layers (low echo) of muscularis propria. They are separated by a thin hyperechoic layer of the connective tissue (high echo).

more, most of the Lugol-voiding lesions overlooked by NBI were low-grade intraepithelial neoplasia or lesions with atypical findings. These results indicate that NBI is a useful and less invasive screening method for ESCC.

In contrast, when NBI is used without magnification, the false-positive rate is high.[21] Therefore, NBI is recommended for use with magnification to provide both higher sensitivity and higher specificity.[20,22]

ENDOSCOPIC ULTRASONOGRAPHY

THE DEPTH OF ESCC invasion into the esophageal wall is closely associated with metastasis to lymph nodes.[23] The frequency of metastasis in the lymph nodes in ESCC that is confined to the mucosa is 3%. The risk increases to 12% for cancer invading the muscularis mucosae, and increases markedly to 26–46% in those with submucosal invasion. Because ESCC confined to the mucosal layer is correlated with a low frequency of metastasis, and because surgery confers a high risk of morbidity and mortality, these patients are considered to be appropriate candidates for minimally invasive treatment by EMR or ESD. ESCC invading the muscularis mucosae is indicated for surgical resection, but may still be treated by ESD. ESCC with submucosal invasion necessitates surgical resection and/or chemoradiotherapy.[24,25]

To estimate the depth of ESCC invasion for superficial ESCC, standard endoscopy with image enhancement and EUS are currently considered the best methods. Other methods, such as the barium meal, computed tomography (CT) and positron emission tomography (PET), are considered less appropriate for superficial ESCC because of their resolution limitations.

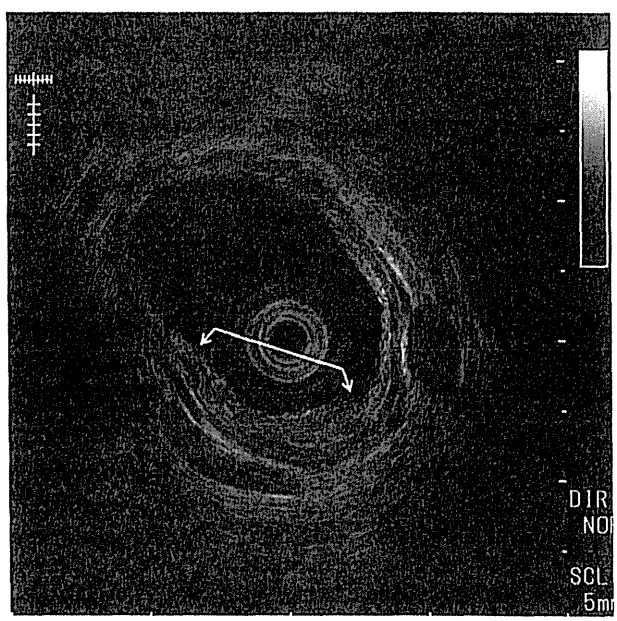

Figure 8 Endoscopic ultrasonography (EUS) image demonstrates a low echoic mass located in the submucosal layer (arrow).

To estimate the depth of invasion, the distinct tissue layers of the esophageal wall should be identified. To visualize them, 20 MHz or 30 MHz miniature probes should be used. These high-resolution probes provide nine-layered echostructures (Fig. 7). Generally, a tumor can be seen as a low echoic mass by EUS (Fig. 8). If the cancerous lesion invades the submucosal layer, EUS delivers a low-echo mass in the high-echo layer and corresponding submucosal layer. A balloon should be attached to the tip of the endoscope to keep deaerated water in the esophageal lumen and prevent

regurgitation to the pharynx. An endoscope with a water jet function is desirable to keep the esophageal lumen wider and to obtain clear images.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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Clinical Trial Notes

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A Phase II Clinical Trial of Endoscopic Submucosal Dissection for Early Gastric Cancer of Undifferentiated Type: Japan Clinical Oncology Group Study JCOG1009/1010

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A Phase II clinical trial has been initiated to evaluate the efficacy and safety of endoscopic submucosal dissection for intramucosal (cT1a) gastric cancer of undifferentiated type. Patients with cT1a gastric cancer with undifferentiated-type adenocarcinoma are eligible for the study. The tumor size should be 2 cm or less without ulceration. The study will enroll a total of 325 patients from 51 institutions over a 4-year period. The primary endpoint is proportion of 5-year overall survival (% 5-year overall survival) in patients with undifferentiated dominant type. The secondary endpoints are overall survival, relapse-free survival, distant metastasis-free survival, % 5-year overall survival without either recurrence or gastrectomy, % en-bloc resection with endoscopic submucosal dissection, % pathological curative resection with endoscopic submucosal dissection, % 5-year overall survival in patients with differentiated dominant type, % 5-year overall survival in patients with pathologically curative resection with endoscopic submucosal dissection and adverse events. This trial was registered at the UMIN Clinical Trials Registry as UMIN000004995.

Key words: clinical trial-trial design – clinical trials – endoscopy-upper GI

INTRODUCTION

Gastrectomy with lymph node dissection has been the standard treatment in patients with early gastric cancer (EGC) in Japan, because complete cure can almost always be achieved (1). On the other hand, endoscopic resection (ER) is an attractive alternative for some EGC because it is a minimally invasive, stomach-conserving procedure and postoperative quality of life is better.

The indications for ER are limited to EGC without lymph node metastasis because the treatment involves only local resection without lymph node dissection. As per the Japanese Gastric Cancer Treatment Guidelines 2010 (ver.3) set forth by the Japan Gastric Cancer Association, the indication for ER is

limited to intramucosal (cT1a) lesions of differentiated (intestinal) type 2 cm or less in diameter, based on the potential for lymph node metastasis and technique for en-bloc resection.

A large retrospective study of surgically resected cases showed that some cT1a (i.e. mucosal cancer without ulceration (UL) regardless of its size and intramucosal cancer with UL 3 cm or less) demonstrated no lymph node metastasis (2). Moreover, recent technical advances in ER, including endoscopic submucosal dissection (ESD) (3), have enabled en-bloc resection of cT1a tumors larger than 2 cm (4). Thus, it is speculated that ER using ESD techniques may cure some patients with differentiated type of EGC beyond the indications described in the current practice guidelines. A multi-institutional clinical trial, by Japan Clinical Oncology Group (JCOG0607), is currently in progress to examine these indications, as previously reported (5).

With regard to EGC of undifferentiated (diffuse) type, a consensus could not be reached as to which lesions present a negligible risk of lymph node metastasis in the above-mentioned retrospective analysis because of the small sample size (2). Hirasawa et al. (6) recently reviewed additional surgical data 9 years after the initial publication. They concluded that intramucosal EGC of undifferentiated that are 2 cm or less in size, without lymphovascular invasion and UL, presented a negligible risk of lymph node metastasis. In addition, Yamamoto et al. (7) reported excellent results with regard to ESD for undifferentiated-type EGC, with a high proportion of curative resection. From the results of these two reports, we speculated that ER using ESD techniques would be an appropriate indication for certain EGC of undifferentiated type. A multi-institutional Phase II trial (JCOG1009/1010) was therefore initiated to evaluate the efficacy and safety of ESD for EGC of undifferentiated type beyond currently accepted indications (Fig. 1). JCOG1009/1010 is a collaborative study between the two JCOG study subgroups: JCOG1009 is a part of the study by the Gastrointestinal Endoscopy Study Group (GIESG) and JCOG1010 is a part of the study by Stomach Cancer Study Group (SCSG) of the JCOG. JCOG1009/1010 has one common protocol and one primary analysis.

The JCOG Protocol Review Committee approved the protocol in December 2010. The study was registered in the UMIN Clinical Trial Registry [www.umin.ac.jp/ctr/] as UMIN000004995, and activated in February 2011.

JCOG1009/1010 PROTOCOL

Purpose

The aim of this study is to evaluate the efficacy and safety of ESD for intramucosal gastric cancer of undifferentiated type, clinically diagnosed as intramucosal cancer 2 cm or less in size without ulceration.

Study Setting

Multi-institutional (51 centers), single-arm, Phase II trial.

Resources

This study is supported by the Grants-in-Aid for Cancer Research (20S-3 and 20S-6), the National Cancer Center Research and Development Fund (23-A-16 and 23-A-19) and Health and Labour Sciences Research Grant for Clinical Cancer Research (22–021) from the Ministry of Health, Labour and Welfare, Japan.

Endpoints

The primary endpoint is proportion of 5-year overall survival (% 5-year OS) in patients with undifferentiated dominant-type EGC diagnosed in the ESD specimen (Fig. 1). The secondary endpoints are OS, relapse-free survival (RFS), distant metastasis-free survival, % 5-year survival without either recurrence or gastrectomy, % en-bloc resection with ESD, % pathologically curative resection with ESD, % 5-year OS in patients with differentiated dominant-type EGC diagnosed in the ESD specimen, % 5-year OS in patients with pathologically curative resection with ESD and adverse events.

In this trial, OS is defined as the time from registration to death from any cause, and it is censored at the last contact day for a living patient. RFS is defined as the time from registration to either the first event of recurrence or death from any cause, and it is censored at the last day when the patient is alive without recurrence. Adverse events are evaluated according to Common Terminology Criteria for Adverse Events version 4.0—JCOG. The criteria for pathologically curative resection are described in 'Decision criteria after ESD' section.

Inclusion Criteria

Patients are eligible for inclusion in the study if they meet all of the following criteria: (i) histologically proven components of undifferentiated (diffuse)-type adenocarcinoma (por or sig) of the stomach in biopsy specimen; (ii) confirmation of the horizontal margin by cancer-free endoscopic biopsy around the lesion, which should be examined at each participating institution; (iii) non-recurrent single tumor; (iv) clinical T1a (intramucosal); (v) tumor size 2 cm or less; (vi) absence of ulcer findings endoscopically; (vii) low likelihood for luminal stenosis after ESD; (viii) clinical N0/M0 by abdominal CT scan; (ix) age 20–80 years old; (x) performance status (ECOG) of 0 or 1; (xi) no prior gastrectomy and no reconstructive surgery involving the stomach for esophageal cancer; (xii) no prior chemotherapy (including hormone therapy) or radiation therapy for any other malignancies; (xiii) sufficient organ function and (xiv) written informed consent.

Exclusion Criteria

Patients are excluded from the study if they meet any of the following criteria: (i) simultaneous or metachronous (within

	cT1a (mucosa)			
	UL (−)		UL (+)	
	≤20 mm	>20 mm	≤30 mm	>30 mm
Differentiated (intestinal)	Absolute indication by the guideline	Expanded indication, being evaluated in JCOG0607	expanded indication being evaluated in JCOG0607	No indication, requiring surgery
Undifferentiated (diffuse)	No indication, being evaluated in this study, JCOG1009/1010	No indication, requiring surgery	No indication, requiring surgery	No indication, requiring surgery

Figure 1. Indications for endoscopic resection of early gastric cancer.

5 years) multiple cancers, except intramucosal tumor curable with local therapy; (ii) infectious disease requiring systemic therapy; (iii) body temperature higher than 38°C; (iv) pregnant or breast-feeding woman; (v) psychosis; (vi) use of systemic steroids; (vii) history of myocardial infarction within 6 months or unstable angina pectoris within 3 weeks; (viii) uncontrolled hypertension; (ix) severe respiratory disease requiring continuous oxygen therapy; (x) inability to hold anticoagulant or antiplatelet medications and (xi) uncontrolled diabetes mellitus or administration of insulin.

Registration

Patients are registered into the JCOG1009/1010 trial after confirming the inclusion/exclusion criteria by telephone or fax to the JCOG Data Center. Online website registration is also available.

Quality Control of ESD

Thirty institutions among the GIESG and 21 institutions among the SCSG of the JCOG are participating in this trial (Table 1). All participating endoscopists have agreed to the technical details for ESD. To control the quality of the ESD technique and endoscopic diagnosis, central review of photographs and videotapes in arbitrarily selected patients will be performed at the semi-annual investigators' meeting. All ESD procedures are done or directly supervised endoscopists certified by study chair. The minimum criterion for certification in this study is having experience with 50 or more ESD for gastric cancer.

Treatment Methods

Endoscopic Submucosal Dissection

ESD of EGC is performed within 30 days after patient registration. Tumors should be resected en-bloc with ESD, and ESD should be performed by certified endoscopists or other staff members under the supervision of certified endoscopists. There are no specific criteria regarding devices used for ESD.

Decision Criteria after ESD

After ESD, patients are categorized into two groups: undifferentiated type group and differentiated-type group, according to the dominant histopathology diagnosed in the resected specimens. In both groups, ESD is deemed 'non-curative' if any of the following criteria is met in the histological diagnosis of resected specimens;

(A) undifferentiated type group:
  (i) pT1b (submucosa, SM),
  (ii) with UL,
  (iii) size of tumor >2 cm;
(B) differentiated type group:
  (i) pT1a (M) with UL and size of tumor ≥3 cm,
  (ii) pT1b (SM1; tumor invasion is within 0.5 mm beyond the muscularis mucosae) with a component of undifferentiated type adenocarcinoma in the most advanced area,
  (iii) pT1b (SM1) and size of tumor 3 cm or more,
  (iv) depth of tumor invasion is pT1b (SM2, tumor invasion is 0.5 mm or deeper beyond the muscularis mucosae) or more,
  (v) pT1a (M) without UL and size of undifferentiated type histology component 2 cm or more;
(C) both groups:
  (i) vascular or lymphatic invasion present,
  (ii) histological vertical margin positive or non-evaluable,
  (iii) histological horizontal margin positive or non-evaluable,
  (iv) tumors not treated in en-bloc resection,
  (v) intratumor resection found pathologically,
  (vi) presence of component of muc (mucinous adenocarcinoma).

'Non-curative' cases must undergo gastrectomy according to the Japanese Gastric Cancer Treatment Guidelines.

ESD is deemed 'curative' if none of the above criteria are met. 'Curative' cases receive no additional treatment after ESD.

Table 1. Participating institutions

GIESG (30 institutions)

1. Iwate Prefectural Central Hospital, Iwate
2. Iwate Medical University Hospital, Iwate
3. Yamagata Prefectural Central Hospital, Yamagata
4. Ibaraki Prefectural Central Hospital, Ibaraki
5. Tochigi Cancer Center, Tochigi
6. National Cancer Center Hospital East, Chiba
7. Asahi Hospital, Chiba
8. Chiba Cancer Center, Chiba
9. National Cancer Center Hospital, Tokyo
10. Showa University Hospital, Tokyo
11. Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo
12. Toranomon Hospital, Tokyo
13. Kanagawa Cancer Center, Kanagawa
14. Yokohama Municipal Citizen's Hospital, Kanagawa
15. Kitasato University East Hospital, Kanagawa
16. Yokohama City University Medical Center, Kanagawa
17. Ishikawa Prefectural Central Hospital, Ishikawa
18. Saku Central Hospital, Nagano
19. Shizuoka Cancer Center Hospital, Shizuoka
20. Aichi Cancer Center, Aichi
21. Aichi Cancer Center Aichi Hospital, Aichi
22. Kyoto University Graduate School of Medicine, Kyoto
23. Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka
24. Osaka City General Hospital, Osaka
25. Kobe University Hospital, Hyogo
26. Hyogo Cancer Center, Hyogo
27. Shikoku Cancer Center, Ehime
28. Kochi Health Sciences Center, Kochi
29. Sano Hospital, Hyogo
30. Hiroshima City Hospital, Hiroshima

SCSG (21 institutions)

1. Sendai Medical Center
2. Miyagi Cancer Center
3. Tokyo Metropolitan Bokutoh Hospital
4. Niigata Cancer Center Hospital
5. Tsubame Rosai Hospital
6. Toyama Prefectural Central Hospital
7. Gifu Municipal Hospital
8. Shizuoka General Hospital
9. Kyoto Medical Center
10. Japanese Red Cross Kyoto Daini Hospital
11. Osaka University
12. Kinki University
13. Osaka National Hospital
14. Osaka Medical College
15. Sakai Municipal Hospital
16. Hyogo College of Medicine, Hyogo
17. Itami City Hospital, Hyogo
18. Tenri Hospital, Nara
19. Wakayama Medical University
20. Hiroshima City Asa Hospital, Hiroshima
21. Oita University Hospital, Oita

Follow-up

All enrolled patients are followed for at least 5 years. Follow-up includes serum tumor markers (CEA and CA19-9), upper GI endoscopy, chest X-ray (or CT) and abdominal CT at least every 6 months for the first 3 years, and then annually.

Central Pathology Review

To reduce the institutional variation in pathological diagnosis, central pathology review of all resected specimens by ESD will be performed. Prior to initiation of this study, pathologists from participating institutions attended the investigators' meeting to share the consensus in pathological assessment for the ESD specimens.

Study Design and Statistical Methods

This trial is designed as a confirmatory trial to determine the efficacy and safety of ESD for cT1a undifferentiated-type early gastric cancer in terms of 5-year OS. Primary analysis will be carried out for the patients with undifferentiated dominant-type diagnosed in ESD specimen (Fig. 2). The sample size for undifferentiated type is planned to be 193 (anticipated total number of registered patients, 276) with 5 years of follow-up and an accrual period of 4 years. This sample size provided 70% power under the hypothesis of primary endpoint as the expected value of 93.2% and threshold value of 88.2% using one-sided testing at 5% significance level. However, because the accrual rate was higher than expected, the sample size was re-evaluated. By the protocol revision, the final sample size based on registered patients was 325 (259 with undifferentiated type), provided 80% power under the hypothesis of primary endpoint as the expected value 94.7% and threshold value of 89.7% using one-sided alpha of 0.025. To test the hypothesis, 5-year OS estimated by the Kaplan–Meier method and its confidence interval based on Greenwood's formula are used.

Interim Analysis and Monitoring

Interim analysis is not planned. If the number of cases with treatment-related death, severe (grade 3 or 4) bleeding or

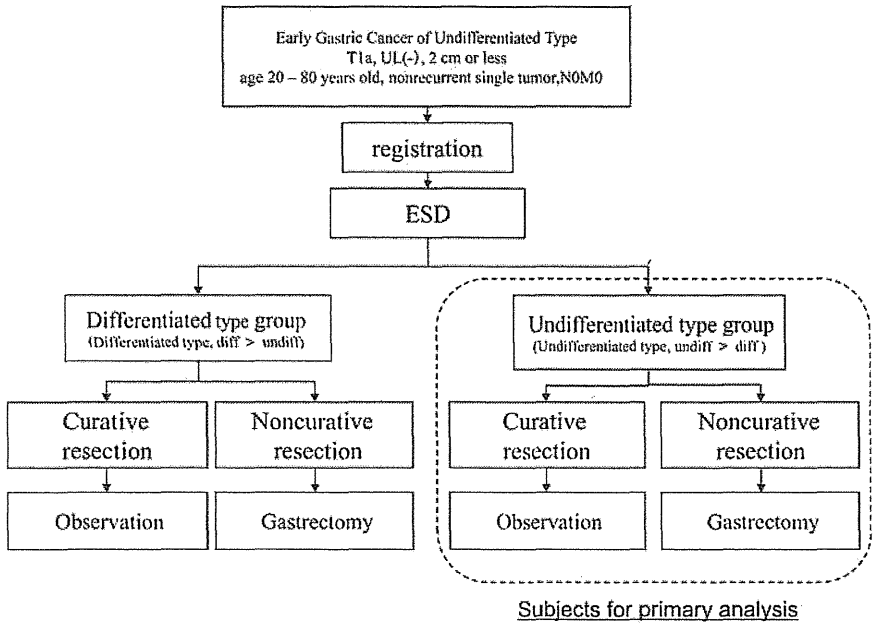

Figure 2. Study schema.

severe (grade 3 or 4) perforation reaches 2, 8 or 19, respectively, the registration will be suspended unless the JCOG Data and Safety Monitoring Committee approves continuation of the trial. The JCOG Data Center is responsible for data management, central monitoring and statistical analysis. JCOG Data Center also provides semi-annual monitoring reports, submitted to and reviewed by the JCOG Data and Safety Monitoring Committee. None of the physicians performing the interventions will be involved in the data analysis. For quality assurance, site-visit audits, not for a specific study basis but for the study group basis, will be performed by the JCOG Audit Committee.

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Conflict of interest statement

None declared.

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Review

Surveillance after endoscopic mucosal resection or endoscopic submucosal dissection for esophageal squamous cell carcinoma

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The objectives of surveillance after endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) for esophageal squamous cell carcinoma are: (i) early detection and treatment of recurrence; and (ii) early detection and treatment of metachronous esophageal squamous cell carcinoma and second primary cancers. Protocols for follow up after EMR or ESD for esophageal squamous cell carcinoma should be based on the risks of lymph node metastasis and distant metastasis as assessed on the basis of tumor staging at initial treatment. Early detection of recurrence or metachronous carcinomas often allows curative or less invasive treatment. Particular attention should be paid to the development of metachronous esophageal squamous cell carcinomas and second primary cancers (in particular, head and neck cancer and gastric cancer because of their high incidence).

Key words: endoscopic mucosal resection, endoscopic submucosal dissection, esophageal squamous cell carcinoma, Japan Esophageal Cohort Study (JEC Study), surveillance

INTRODUCTION

RECENTLY, THE INDICATION range of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for esophageal squamous cell carcinoma has been extended, thereby potentially increasing future risks of local recurrence, nodal recurrence, and distant recurrence.[1] Esophageal squamous cell carcinoma carries an appreciable risk of metachronous esophageal squamous cell carcinoma and second primary cancers such as head and neck cancer and gastric cancer. A previous study reported that a second primary cancer was the most common cause of death in patients who underwent surgery for esophageal cancer without lymph node metastasis.[2] Therefore, regular follow up of the head and neck, esophagus, and stomach by upper gastrointestinal endoscopy is essential.[3,4] Caution is also required for the development of tumors in the colorectum and other organs.[5] However, standardized protocols for follow up after EMR or ESD have yet to be established.

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LOCAL RECURRENCE AFTER EMR OR ESD

BECAUSE LOCAL RECURRENCE after EMR or ESD usually occurs within 1 year after initial treatment and may develop after 2 to 3 years, long-term follow up is required.[6,7] Lugol chromoendoscopy is mainly used to detect local recurrence. Follow-up examinations are usually carried out at 6-month intervals or at 3-month intervals for up to 6 months to 1 year after resection.[6–11] A trend towards a higher risk of local recurrence is associated with piecemeal resection, multiple Lugol-voiding lesions (LVL), and EMR as compared with ESD, necessitating stricter follow-up examination by upper gastrointestinal endoscopy.[6–9]

LYMPH NODE AND DISTANT METASTASIS AFTER EMR OR ESD

ESOPHAGEAL SQUAMOUS CELL carcinoma invading the muscularis mucosae or deeper is associated with increased risks of lymph node metastasis and distant metastasis. Follow-up examinations should therefore include confirmation of the presence or absence of lymph node metastasis and distant metastasis.[12] Lymph node metastasis and distant metastasis are usually detected within 2 years after EMR or ESD, but can occur after 4 years.[1,11] Regular long-term follow up is thus essential. To our knowledge, however, no study has clearly defined an effective protocol for follow up after EMR or ESD in patients with a high risk of lymph node metastasis or distant metastasis. At present, follow-up protocols are decided by individual hospitals. Many hospitals carry out computed tomographic (CT) examinations of the neck, chest, and abdomen at 6–12-month intervals,[1,8,10] and some include ultrasonography (US) of the neck and abdomen or endoscopic ultrasonography (EUS).[13]

Although no study has also defined an effective protocol for follow up after esophagectomy, many institutions carry out CT or US at 3–6-month intervals and modify this schedule as required by evidence of disease progression or the number of years after surgery.[14–16] A phase II study evaluating the efficacy of combined treatment with EMR and chemoradiotherapy is currently ongoing in patients with clinical stage I esophageal carcinoma (JCOG0508 trial). One of the major objectives of this trial is to evaluate the effectiveness of EMR and ESD for esophageal squamous cell carcinoma with submucosal invasion. This trial is registered with the UMIN Clinical Trials Registry, number UMIN553. In this clinical trial, CT of the neck, chest, and abdomen is carried out and tumor markers, such as squamous-cell carcinoma antigen, are measured at 4-month intervals during 3 years of follow up. The clinical practice guidelines for esophageal cancer proposed by the Japan Esophageal Society recommend that CT of the chest and abdomen, US of the neck and abdomen, and EUS are carried out at 6–12-month intervals during routine long-term follow up after EMR or ESD.[17]

INCIDENCE OF METACHRONOUS ESOPHAGEAL SQUAMOUS CELL CARCINOMA AFTER EMR OR ESD

PATIENTS WITH ESOPHAGEAL squamous cell carcinoma tend to have a high incidence of metachronous esophageal squamous cell carcinoma (10–15%), which can develop any time after treatment.[18–20] Long-term follow up is therefore essential. Patients with multiple LVL tend to have a high risk of metachronous esophageal squamous cell carcinoma.[18–20] Strict follow up by upper gastrointestinal endoscopy is thus mandatory.

INCIDENCE OF SECOND PRIMARY CANCER AFTER EMR OR ESD

PATIENTS WITH ESOPHAGEAL cancer are at high risk for a second primary cancer,[5] attributed to the presence of common risk factors for each cancer in the upper aerodigestive tract. The concept of field cancerization has also been implicated in the pathogenesis of second primary cancers.[21–24]

The incidences and types of second primary cancer differ depending on factors such as years of data collection, follow-up periods, and characteristics of hospitals. A national registry established by the Japan Esophageal Society found that double cancers develop in approximately 20% of patients with esophageal cancer, including 8% with synchronous cancers and 12.2% with metachronous cancers. The most common types of double cancer were, in descending order, gastric cancer, head and neck cancer, colorectal cancer, and lung cancer.[25]

One study reported that head and neck cancer was the most common double cancer.[5] Most studies estimate that double cancers of the head and neck develop in approximately 10% of patients with esophageal cancer. In the head and neck region, pharyngeal cancer is most common.[3,26] Esophageal cancers with a high risk of double cancer of the head and neck are characterized by the presence of multiple esophageal cancers or multiple LVL.[27–29]

Recent progress in endoscopic techniques such as magnifying endoscopy and image-enhanced endoscopy coupled with increased emphasis on screening the head and neck region in patients with esophageal cancer has facilitated the early detection of head and neck cancer on upper gastrointestinal endoscopy.[3,30,31] In response to this phenomenon, an image-enhanced laryngoscope was developed and recently introduced at departments of otolaryngology, facilitating the early detection of cancer on follow-up visits.[32,33]

Double cancers of the esophagus and the stomach have few common risk factors, in contrast to double cancers of the esophagus and the head and neck. Smoking is considered a risk factor for esophageal cancer and gastric cancer.[34] In Japan, however, the high prevalence of gastric cancer may be largely attributed to atrophy of the gastric mucosa due to *Helicobacter pylori* infection.[35,36]

Although standardized protocols for follow up after EMR or ESD have yet to be established to facilitate the early detection of a second primary cancer, regular follow up

of the head and neck, esophagus, and stomach by upper gastrointestinal endoscopy is essential. Moreover, cancer screening should include examination of the head and neck region by an otolaryngologist, examination of the lungs by chest radiography or CT, and colorectal examinations, including fecal occult blood tests or colonoscopy, carried out at suitable intervals.

JAPAN ESOPHAGEAL COHORT STUDY

PREVIOUS STUDIES HAVE reported that multiple LVL of background esophageal mucosa are associated with a very high risk of multiple cancers arising in the esophagus,[18–20] as well as in the head and neck region.[27–29] The ability to use the Lugol-voiding pattern as a biomarker for the risk of second primary cancers in the esophagus and the head and neck region after EMR or ESD in patients with esophageal cancer would facilitate early detection and treatment of metachronous multiple cancers, contribute to improved outcomes of EMR or ESD, and come closer to realizing an optimal surveillance period after EMR or ESD.

A multicenter cohort study (Japan Esophageal Cohort Study: JEC Study) is ongoing to investigate the risk of metachronous multiple cancers and to assess the time required for their development after EMR or ESD, using Lugol-voiding pattern as a biomarker in patients who have esophageal squamous cell carcinoma with invasion limited to the mucosa. This trial is registered in the UMIN Clinical Trials Registry, number UMIN1676.

The primary endpoint is the cumulative incidence of metachronous multiple cancers of the esophagus, as assessed by Lugol-voiding pattern. Secondary endpoints are to estimate: (i) the total annual number of cases of metachronous multiple cancer of the esophagus, as assessed by the Lugol-voiding pattern; and (ii) the cumulative incidence of metachronous multiple cancers of the head and neck region, as assessed by the Lugol-voiding pattern.

The procedure for follow-up observation was established by consensus. Upper gastrointestinal endoscopic examinations of the head and neck, esophagus, and stomach and Lugol chromoendoscopy were carried out at 3-month intervals for up to 6 months after EMR or ESD. Subsequently, these examinations were carried out at 6-month intervals. The head and neck region was examined by an otolaryngologist at the time of EMR or ESD and at 1-year intervals thereafter (Fig. 1).

A total of 331 patients were enrolled and have completed the predetermined follow-up observations. The data are now being analyzed. An optimal protocol for surveillance after EMR or ESD will be proposed on the basis of the study results.

FUTURE DIRECTIONS

THE GUIDELINES OF the National Comprehensive Cancer Network (NCCN) in the USA include a procedure for follow up after EMR in patients with Tis or T1a cancer.[37] These guidelines recommend that upper gastrointestinal endoscopy is carried out at 3-month intervals during the first year after EMR and at 1-year intervals thereafter. However, these recommendations are not supported by references, and their basis and validity remain unclear. The clinical practice guidelines for esophageal cancer proposed by the European Society for Medical Oncology (ESMO) recommend that appropriate action should be taken on the development of symptoms or other abnormalities because evidence showing that regular follow up can improve outcomes is lacking.[38]

Future studies are necessary to produce robust evidence supporting protocols for follow-up observation in patients with esophageal cancer. Patients should be enrolled and followed up in accordance with consensus-based protocols, such as the aforementioned JEC Study. Whether such protocols improve the outcomes and quality of life of patients with

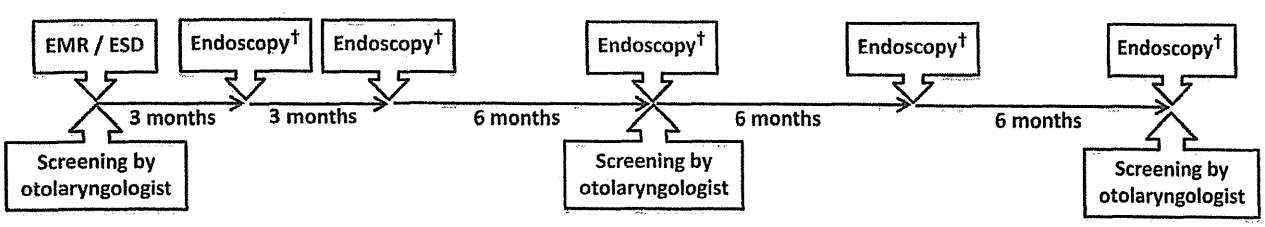

Figure 1 Surveillance after endoscopic mucosal resection or endoscopic mucosal dissection in the Japan Esophageal Cohort Study. †Head and neck region, esophagus, and stomach were examined and Lugol chromoendoscopy was carried out.

esophageal cancer and whether the proposed methods are sound from the viewpoint of medical economics should also be evaluated.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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ORIGINAL ARTICLE

A Dermatitis Control Program (DeCoP) for head and neck cancer patients receiving radiotherapy: a prospective phase II study

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Abstract
Purpose We speculated that a systematic program to manage radiation dermatitis might decrease the incidence of severe or fatal cases in head and neck cancer patients receiving radiotherapy. Here, we conducted a prospective phase II study to clarify the clinical benefit of a Dermatitis Control Program (DeCoP) that did not use corticosteroids.
Patients and methods Head and neck cancer patients scheduled to receive definitive or postoperative radiotherapy were enrolled. Radiation dermatitis was managed with a DeCoP consisting of a three-step ladder: Step 1, gentle washing; Step 2, gentle washing and moistening of the wound-healing environment; Step 3, prevention against infection, gentle washing and moistening of the wound-healing environment. The primary endpoint was the incidence of grade 4 dermatitis.
Results A total of 113 patients were registered between January 2009 and February 2010. Eighty patients received radiotherapy as an initial approach, while the remaining 33 received radiotherapy postoperatively. Grade 3 and 4 dermatitis events occurred in 11 (9.7%) and 0 (0%, 95% confidence interval 0–3.2%) patients, respectively. Median radiation dose at the onset of grade 2 dermatitis was 61.5 Gy (range 36–70 Gy) and median period between onset and recovery was 14 days (range 1–46 days).
Conclusion The Dermatitis Control Program has promising clinical potential. Radiation dermatitis might be manageable if gentle washing and moistening of the wound-healing environment is done.

Keywords Head and neck cancer · Cancer nursing · Dermatitis · Radiotherapy

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Introduction

Chemoradiotherapy is now commonly used in the treatment of head and neck cancer. For example, single-agent cisplatin concurrent with radiotherapy is now the nonsurgical standard care for locally advanced squamous cell carcinoma of the head and neck (SCCHN) patients [1–3], and is also considered the standard adjuvant therapy for high-risk postoperative patients [4–6]. Recently, induction chemotherapy using cisplatin, 5-fluorouracil, and docetaxel followed by chemoradiotherapy has shown promise for locally advanced head and neck cancer patients at high risk of distant metastases [7, 8].

However, as treatment strength increases, so too does the risk of toxicity. Acute skin reactions like radiation dermatitis are common, and not only risk interrupting treatment but can even be fatal. Although various topical medications have been used to manage and treat radiation dermatitis, there remains no agreement on the best treatment plan [9, 10].

Among those being considered, there is strong evidence supporting the efficacy of a simple treatment plan that involves only gentle washing and moistening of the wound-healing environment [11, 12]. Here, we describe a prospective phase II study that uses a Dermatitis Control Program (DeCoP) incorporating a three-step plan, which includes gentle washing and moistening of the would-healing environment but no corticosteroid use, for head and neck patients receiving radiotherapy.

Patients and methods

This single institution prospective phase II study was approved by the institutional review board of the National Cancer Center Hospital before the start of patient enrollment. This trial was registered with UMIN-clinical trials registry (UMIN-CTR: UMIN000001579).

Eligibility

Patients fulfilling the following criteria were enrolled: histologically confirmed SCCHN; 20–75 years of age; Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2; normal organ function; and scheduled to receive definitive or postoperative radiotherapy (>50 Gy). Written informed consent for treatment was obtained from all patients before its initiation.

Treatment

The main protocol was the 'Dermatitis Control Program'. This systematic program consists of a three-step ladder (Table 1).

Supportive treatment for grade 0–1 radiation dermatitis (Step 1)

The basic concept of this step is 'watchful waiting'.

All treatments for radiation dermatitis prevention except gentle washing were avoided. All patients were instructed on how to wash with lukewarm water and mild soap for routine care. Physicians or expert nurses observed each patient for dermatitis at least twice a week.

Table 1 Dermatitis Control Program steps

	Dermatitis grade (CTCAE ver. 3.0)			
	0	1	2	3
Step 1: Gentle wash	○	○	○	○
Step 2: Moistened wound environment		Δ	○	○
Step 3: Infection prevention		Δ	Δ	○

○, Treatment done unconditionally; Δ, treatment done if feasible

Supportive treatment for grade 2 radiation dermatitis (Step 2)

The basic concept of this step is 'minimally required intervention'. The irradiated area was covered with gauze and moistened with either vaseline or dimethyl isopropyl-azulene. All outpatients and their families were instructed on how to cover and moisten the irradiated area. For inpatients, gauze coating was done by the patient or nurse. An example of Step 2 is shown in Fig. 1.

Supportive treatment for grade 3–4 radiation dermatitis (Step 3)

The basic concept for this step is similar to that of Step 2 except for the use of preventative action against infection. Physicians or experts including wound, ostomy, and continence nurses observed for dermatitis every business day. If no infection was noted, antibiotic drugs were not administered.

Toxicity

Adverse events related to acute toxicity by radiotherapy or chemoradiotherapy were coded according to the common terminology criteria of adverse events, version 3 (CTCAE ver. 3.0). According to these criteria, grade 2 radiation dermatitis includes moderate to brisk erythema, patchy moist desquamation mostly confined to skin folds and creases, and moderate edema. Grade 3 radiation dermatitis consists of moist desquamation other than skin folds or creases and bleeding induced by minor trauma or abrasion.

Radiation dermatitis was evaluated by physicians or nurses based on dermatitis grading according to the CTCAE ver. 3.0, followed by DeCoP performed according to the grading. The investigators' gradings were subsequently evaluated by a central review committee using photographs.

Irradiation methods

Irradiation dose and modality (conventional radiotherapy, intensity-modulated radiotherapy or proton beam therapy) varied according to primary site and tumor stage. Full-face immobilization (thickness 2 mm) was used for all patients to minimize set-up error. Target volumes were defined in accordance with International Commission on Radiation Units and Measurements Reports 50 and 62.

Treatment evaluation and statistical analysis

The primary endpoint of this study was the incidence of grade 4 dermatitis. Skin breakdown has the potential for

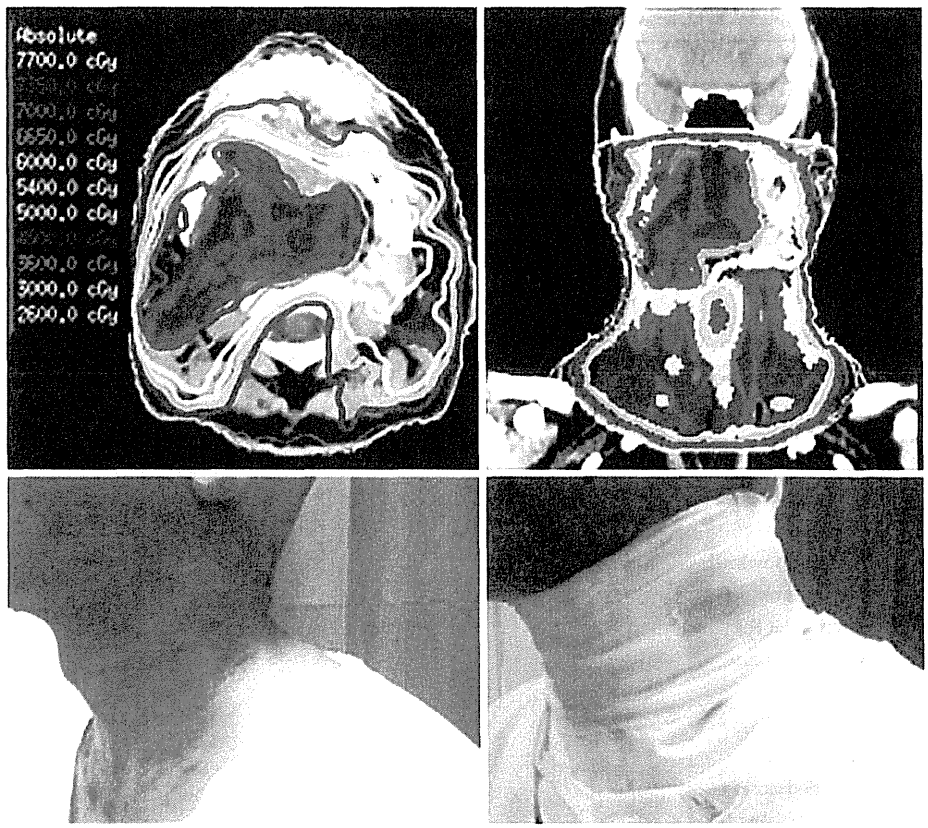

Fig. 1 Dermatitis Control Program Step 2. The case was a 44-year-old-male with T4N2cM0 oro-pharyngeal cancer. He was treated with induction chemotherapy followed by chemoradiotherapy. The irradiated area was covered with gauze and moistened with dimethyl isopropylazulene. It is very important that not only the physicians but also the co-medical staff understand where the radiation field is

infection, which risks disrupting radiotherapy treatment. Unplanned disruption was defined as one or more days of interruption, excluding weekends or days for planned machine maintenance.

If the true rate of grade 4 dermatitis was 7% or less and the true rate of disruption was less than 16%, the DeCoP was applied. To conduct statistical analysis with 90% power and a one-sided type-I error of 5%, a minimum of 104 patients were needed. However, we assumed that 15% of our patients would ultimately be excluded from analysis due to violation of the protocol or other reasons, and thus estimated that 120 patients were needed.

Descriptive statistics, including mean, standard deviation, median, range, and percentage, were used to describe patient demographics, and pathological and clinical characteristics.

Results

Patient characteristics

One hundred and twenty patients were registered between January 2009 and February 2010. Seven patients were excluded from analysis due to a change in treatment strategy (surgery for three patients, palliation for three patients) and refusal to participate after registration (one patient). The remaining 113 patients are characterized in Table 2.

With regard to treatment strategy, 80 patients (71%) received radiotherapy as an initial approach, and the remaining 33 (29%) in a postoperative setting. The major combination chemotherapy regimen was cisplatin alone (53/113, 47%).

Treatment compliance

All patients received the planned radiotherapy without any dose reduction. The rate of unplanned breaks in radiotherapy was 10.6% (12/113) owing to acute toxicity (two patients), PEG trouble (one patient), emergency tracheostomy (one patient), infection (three patients), unplanned machine trouble (one patient), patient discretion (two patients), and other reasons (two patients). Of these, the median interval of radiation interruption was 4 days (range 1–5 days), and no unplanned break of more than 1 week occurred.

Toxicity

The toxicity profile during radiotherapy/chemoradiotherapy is shown in Table 3. No fatal hematological events occurred.

Table 2 Patient characteristics

Characteristics	*n*
No. of patients	113
Age, years	
Median (range)	63 (22–87)
Gender	
Male/female	93/20
Performance status	
0–1/2	99/14
Primary site	
Naospharynx	13
Oropharynx	23
Hypopharynx	18
Larynx	33
Tongue, oral cavity	12
Unknown	14
Radiotherapy setting	
Postoperative RT	33
Definitive RT	80
Treatment strategy	
IC → CRT	25
CRT	43
RT alone	45
Radiation dose, Gy	
Median (range)	70 (54–70)
Combination	
Cisplatin alone	53
Chemotherapy	
Cisplatin and 5-FU	11
Cisplatin and S-1	2
Other platinum	1

CRT Chemoradiotherapy, *IC* induction chemotherapy, *RT* radiotherapy, *5-FU* 5-fluorouracil

Mucositis and dermatitis were the most common non-hematological toxicities.

Grade 2 and 3 dermatitis events were seen in 63 (56%) and 11 (9.7%) patients, respectively. No grade 4 dermatitis events were seen (0%, 95% confidence interval 0–3.2%). Median time until the onset of grade 2 dermatitis was 43.5 days (range 23–60 days) and the median radiation dose at onset was 61.5 Gy (range 36–70 Gy). Median period between onset and recovery was 14 days (range 1–46 days) and the median time until recovery from the initiation of radiotherapy was 57 days (range 39–91 days) (Fig. 2).

Grade 3 mucositis events in the categories 'clinical exam' and 'functional/symptomatic' occurred in about half of the patients for each. Weight loss was recorded in 22 grade 2 patients, but not in any grade 3 patients. No treatment-related deaths occurred.

Table 3 Toxicity

	Dermatitis grade (CTCAE ver. 3.0)				
	1	2	3	4	% 3 and 4
Leucopenia	23	34	4	1	4.4
Neutropenia	71	20	1	1	1.8
Anemia	13	30	1	2	2.7
Thromobocytopenia	16	6	3	0	2.7
Nausea	23	26	5	0	4.4
Mucositis					
CE	11	56	42	1	38.1
FS	15	44	47	0	41.6
Xerostomia	14	60	2	0	1.8
Dermatitis	39	63	11	0	9.7
Febrile neutropenia	–	–	1	0	0.9
Weight loss	19	22	0	0	0

CE Clinical exam, *FS* functional/symptomatic

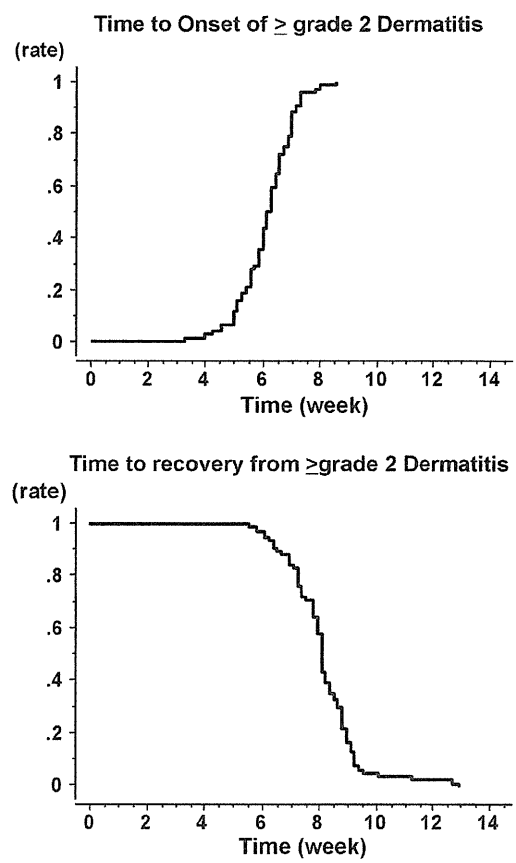

Fig. 2 Time to onset (upper) and recovery (lower) of > grade 2 dermatitis. Median time to onset of grade 2 dermatitis from the initiation of radiotherapy was 43.5 days (range 23–60 days), and median radiation dose at onset was 61.5 Gy (range 36–70 Gy). In several cases, dermatitis became worse after the end of treatment. Median time to recovery from grade 2 dermatitis from the initiation of radiotherapy was 57 days (range 39–91 days). Recovery did not take more than 6 weeks in any case

DeCoP data

All 113 patients received the planned dose of radiotherapy. The median radiation dose was 70 Gy (range 60–70 Gy) and the median duration of radiotherapy treatment was 49 days (range 33–63 days).

The frequency of using either Steps 2 or 3 to control dermatitis during radiotherapy was 63% (71/113), while at 2 weeks and 1 month after the end of radiotherapy it was 19% (21/113) and 2% (2/113), respectively.

Discussion

The primary endpoint of this study was the incidence of grade 4 dermatitis, which did not occur in any patient (0%, 95% confidence interval 0–3.2%). Grade 2 and 3 dermatitis events were seen in 63 (56%) and 11 (9.7%) patients, respectively. Given that radiotherapy is contraindicated in the presence of grade 4 dermatitis, these findings suggest that our DeCoP has good clinical potential.

To date, two randomized trials [11, 13] have assessed the effectiveness of washing. Roy et al. [13] conducted trials with 99 patients randomized to washing with soap and water or no washing, and found a significantly higher incidence of moist desquamation in the non-washing group; while Campell et al. [11] randomized 99 women receiving adjuvant radiotherapy for breast cancer into one of three groups with different washing practices, and found a significant reduction in itching score at the end of treatment and a reduction in erythema and desquamation scores at 6 or 8 weeks after treatment in patients who washed with soap and water independent of bolus dose.

Based on these results, we established Step 1 in our DeCoP as washing only.

Patients received elaborate instructions on how to wash properly. The median time to the onset of grade 2 dermatitis was 43.5 days (range 23–60 days). The frequency of Steps 2 or 3 at 2 weeks and 1 month after the end of radiotherapy was 19 and 2%, respectively. These results show that radiation dermatitis in head and neck lesions can be managed with minimal intervention.

This report has two major limitations. One is that, in our trial, we could not mention the prevention of dermatitis. Another is that it is not enough to mention whether corticosteroids are useful or not for the management of dermatitis because this trial is not a randomized study.

Given this minimal invasiveness, the DeCoP used here appears to be not only useful for clinical practice, but also effective as a control measure for large-scale randomized control trials investigating topical corticosteroids and other medications for dermatitis. Such studies are necessary because although corticosteroids remain frequently prescribed for the management of radiation dermatitis in clinical practice, the evidence for their effectiveness has been inconclusive [9, 12, 14–16].

To change our clinical practice, a further large-scale and qualified phase III study may play a great role.

In conclusion, the results above suggest that radiation dermatitis in head and neck lesions may be manageable if only gentle washing and moistening of the wound-healing environment is done during radiotherapy.

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Conflict of interest There is no conflict of interest.

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ORIGINAL ARTICLE

Strontium-89 (Sr-89) chloride in the treatment of various cancer patients with multiple bone metastases

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Abstract
Background Although the use of Sr-89 chloride in the treatment of patients with prostate and breast cancer has been widely reported, little information is available about its use for other malignancies. Here, we retrospectively analyzed the clinical profile of Sr-89 chloride in various patients with painful bone metastases.
Methods Entry criteria were a pathologically proven malignancy, clinically diagnosed multiple bone metastases, and adequate organ function. Sr-89 chloride (Metastron) was given by single intravenous infusion at 2 MBq/kg over 2 min. Self-reported outcome measures were used as a response index, including pain diary data on a 0–10 numeric rating scale (NRS).
Results Fifty-four consecutive patients with painful bone metastases were treated with Sr-89 chloride at the National Cancer Center Hospital East between March 2009 and July 2011, consisting of 26 with breast/prostate cancer and 28 with other malignancies (lung 8, head and neck 6, colorectal 6, others 8). Thirteen (24 %) patients experienced a transient increase in pain, which was categorized as a flare-up response. Grade 3–4 anemia was observed in 6 patients, 3 of whom required blood transfusion. Regarding efficacy, response rates and complete response rates were 71.2 % and 34.6 %, respectively, and time to response from the initiation of treatment was 36 days (range, 13–217). No significant difference in response rates was seen between patients with breast/prostate cancer and other cancers (breast/prostate 69.2 %, other 73.1 %; $p = 0.76$).
Conclusions As in patients with breast and prostate cancer, Sr-89 chloride is a promising agent for the treatment of painful bone metastases in patients with various other malignancies.

Keywords Palliative care · Radiation oncology · Radiation therapy · Radionuclide · Pain control

Background

The prevalence of painful osseous metastases varies among different types of cancer. Approximately 65 % of patients with prostate or breast cancer and 35 % of those with advanced cancers of the lung, thyroid, and kidney develop symptomatic skeletal metastases. The management of bone pain in these patients remains challenging, and no standardized procedures have yet been adopted. In patients with multifocal osteoblastic metastases, systemic administration of radiopharmaceuticals is the preferred adjunctive therapy for pain palliation.

Similar to calcium, strontium is a divalent cation that is incorporated into hydroxyapatite in bone after intravenous injection [1]. Sr-89 chloride (Metastron) is the first U.S.

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