possibility of selection bias. From the viewpoint of clinical practice, real-time detection and diagnosis are important. To avoid selection bias and to evaluate the actual diagnostic yield, we recorded the data during the procedure and completely separated the evaluation of white light imaging and narrow band imaging. We also conducted this study according to the Standards for Reporting of Diagnostic Accuracy checklist[29] to obtain high-quality data and to assess the generalizability and applicability of the results. Our data are therefore relevant to daily clinical practice.

Table A1. Rate of Superficial Cancer by Method of Detection in Back-to-Back Fashion

		Primary Examination WLI			Secondary Examination NBI			
Region	No. of Patients	No.	%	95% CI	No.	%	95% CI	*P*
Head and neck	13	1	8	0.2 to 36.0	10	77	46.2 to 95	< .001
Esophagus	105	58	55	45.2 to 65.0	100	95	89.2 to 98.4	< .001
		NBI			WLI			
Head and neck	15	15	100	78.2 to 100	5	33	11.8 to 61.6	< .001
Esophagus	107	104	97	92 to 99.4	85	79	70.5 to 86.6	< .001

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Table A2. Size of Superficial Cancer by Method of Detection

	WLI Positive		NBI Positive		NBI and WLI Positive		Both Negative (false negative)	
Tumor Size (mm)	No.	%	No.	%	No.	%	No.	%
Head and neck region								
< 10	0	0	12	70	5	30	0	0
11-20	0	0	4	40	6	60	0	0
≥ 21	0	0	0	0	1	100	0	0
Total	0	0	16	57	12	43	0	0
Esophagus								
< 10	0	0	14	39	22	58	0	0
11-20	0	0	12	30	28	70	0	0
≥ 21	1	0.7	22	16	113	83	0	0
Total	1	0.5	48	23	163	77	0	0

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Table A3. Median Procedure Time

	Primary WLI (seconds)		Primary NBI (seconds)		
Region	Median	Range	Median	Range	*P*
Head and neck	120	34-275	162	30-525	< .001
Esophagus	95	30-360	135	30-616	< .001
	Secondary WLI		Secondary NBI		
Head and neck	90	10-300	135	30-540	< .001
Esophagus	80	19-776	45	18-700	< .005

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

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Treatment Strategy for Superficial Pharyngeal Squamous Cell Carcinoma Synchronously Combined with Esophageal Cancer

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Key Words
Pharyngeal cancer · Chemotherapy · Esophageal squamous cell carcinoma · Narrow band imaging · Early detection

Abstract
Background: Esophageal squamous cell carcinoma (ESCC) is often synchronously accompanied by pharyngeal squamous cell carcinoma (PSCC). However, treatment strategies for these synchronous cancers have not been established. ***Aim:*** To evaluate retrospectively the effects of both chemoradiotherapy (CRT) targeted for invasive ESCC on synchronous superficial PSCC and additional endoscopic resection (ER) for PSCC. ***Patients and Methods:*** Screening endoscopy in the pharynx was performed in newly diagnosed ESCC patients. CRT combined with 5-fluorouracil (5-FU) and cisplatin (CDDP) was administered to all patients. The effect on superficial PSCC was only evaluated for 5-FU-CDDP chemotherapy that excluded the pharynx from the radiation field. When PSCC was remnant or recurrent in patients evaluated at complete response (CR) of ESCC, ER was performed on the PSCC. ***Results:*** Fourteen cases of superficial PSCC (4.0%) were detected in 348 ESCC patients. Three PSCC reached CR in 8 ESCC-CR patients, while all 3 lesions recurred. No treatment response was found in the remaining 11 PSCC. As a second treatment, ER for 8 PSCC was completed in the 8 ESCC-CR patients, with one complication due to pneumonia. ***Conclusions:*** Standard 5-FU-CDDP CRT targeted for invasive ESCC did not demonstrate a sufficient efficacy for superficial PSCC, while ER even for PSCC after chemotherapy was curative.

Introduction

Esophageal squamous cell carcinoma (ESCC) is often accompanied by pharyngeal squamous cell carcinoma (PSCC) either simultaneously with the primary lesion (synchronously) or after a period of time (metachronously). These findings have been explained by the 'field cancerization' theory that describes how repeated local exposure to carcinogens contributes to the occurrence of multiple cancers in the esophageal and head and neck regions [1]. For more than 5 decades many epidemiological studies have attributed the increased cancer risks associated with alcohol drinking and smoking to this phenomenon

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[2–6]. In 2009, the Working Group of WHO-IARC concluded that acetaldehyde associated with alcoholic beverages was carcinogenic to humans and confirmed the group 1 classification of alcohol consumption [7]. In addition, heterozygous traits found in 40% of Asians, who have an inactive alcohol metabolizing enzyme of aldehyde dehydrogenases 2, accumulate acetaldehyde, with higher relative risks of these cancers [7, 8]. Furthermore, the prevalence of multiple Lugol-unstained lesions (LULs) [9, 10], which are caused by repeated exposure to acetaldehyde, was strongly related to the occurrence of synchronous or metachronous cancers in the esophagus and head and neck regions [11].

In contrast, most patients with PSCC are detected at an advanced stage with a poor prognosis. Even in an operable PSCC case, the extensive surgical resection required may cause a loss of function with respect to swallowing and/or speaking and can lead to cosmetic deformities. Thus it is difficult to determine a final treatment from the viewpoints of both curability and retaining organ function. In cancers combining ESCC and PSCC, the selection of treatment is even more critical. Because of this, the ability to detect pharyngeal lesions at an earlier stage, e.g. as carcinoma in situ, would be of clear benefit to patients. Recently, superficial PSCC has been detected by NBI endoscopy [12].

Systemic 5-fluorouracil-cisplatin (5-FU-CDDP) chemotherapy combined with radiotherapy is the standard treatment for ESCC, and the same treatment is also effective for PSCC patients [13, 14]. The radiation field used in radiotherapy for ESCC does not generally reach the region of the larynx and pharynx, while chemotherapy acts systemically. There have been no reports regarding the efficacy of systemic chemotherapy for patients with superficial PSCC. In this study, we examined the effect on superficial PSCC of chemoradiotherapy (CRT) targeted for invasive ESCC.

Patients and Methods

Patients

Between January 2003 and December 2006, concurrent CRT was performed in 348 patients with invasive ESCC who met the following criteria of this study: (1) newly diagnosed thoracic ESCC; (2) aged between 20 and 75 years; (3) clinical stage I to IVA according to the UICC-TNM classification; (4) absence of previous chemotherapy for malignancy; (5) absence of radiation or surgical treatment for head and neck, and esophageal cancers, and (6) absence of active malignancy except ESCC and PSCC. All patients with invasive ESCC visited our hospital to receive treatment after histological diagnosis of ESCC by endoscopy at another hospital.

Endoscopic Observation of the Oral Cavity and Pharynx

Since January 2003, endoscopic screening of the oral region has been performed in all ESCC patients in order to detect synchronously superficial PSCC. In the initial endoscopic observation in our hospital, narrow band imaging (NBI) or conventional endoscopy was used because both evaluation of ESCC and gastroduodenal screening including oral cavity and pharynx are performed in all patients. When a mucosal abnormality in the oral cavity or pharynx, or multiple LULs in the esophagus, were found in initially conventional endosopcy, the oral cavity and pharynx were observed again by magnifying NBI endoscopy within 2 weeks. Figure 1 shows the NBI findings of an oral cavity and pharynx using a video endoscope system (EVIS LUCERA CV-260, Olympus Optical Co. Ltd., Tokyo, Japan). When a brownish area and an enhancement of the intraepithelial papillary capillary loop were found in the pharynx (fig. 2), an endoscopic biopsy was performed to histologically confirm the carcinoma.

Lugol chromoendoscopy was performed in all patients for both diagnosis of the correct cancer region and evaluation of LULs in the background esophageal epithelium. After ordinary endoscopic observation, 5–10 ml of 2.0% glycerin-free Lugol iodine solution, which is a brown liquid consisting of 2.0 g potassium iodine and 4.0 g iodine in 100 ml distilled water, was sprayed from the upper thoracic esophagus to the gastroesophageal junction using a plastic spray catheter passed through the biopsy channel of the endoscope. Multiple LULs were defined as described in our previous study [15].

Definition of Superficial Pharyngeal Cancer

According to the Japan Society for Head and Neck Cancer [16], a superficial pharyngeal lesion is defined as one in which the invasion depth is comparatively limited and visual changes do not indicate an advanced cancer. The pharynx has no muscularis mucosa, so this somewhat vague definition suggests that the depth of invasion is limited to the epithelium or just beneath the epithelium, but does not extend to the muscle layer.

Treatment Schedule of CRT for ESCC

Chemotherapy consisted of a protracted infusion of 5-FU at a dose of 1,000 mg/m^2 per day on days 1–5 and 22–26, combined with a 2-hour infusion of CDDP at 75 mg/m^2 on days 1 and 22. A 10-MV radiation treatment was administered for 6 weeks (5 days/week) at 1.8 Gy/day with a total radiation dose of 50.4 Gy, concomitantly with chemotherapy.

Patients who were evaluated for an objective response to this treatment received additional chemotherapy consisting of a continuous infusion of 5-FU at a dose of 1,000 mg/m^2 on days 1–5 and CDDP at a dose of 75 mg/m^2 on day 1. This treatment schedule was administered for 1 week followed by a 3-week break. All patients receiving CRT were monitored by neck, chest and abdominal computed tomography, and by endoscopy to evaluate the efficacy of the treatment on both ESCC and PSCC.

As for response for ESCC, objective responses of measurable metastatic lesions were evaluated according to the response evaluation criteria in solid tumors (RECIST v 1.0) guideline. Response of the primary tumor was evaluated by the criteria of the Japan Esophageal Society [17, 18].

Evaluation of Response for PSCC

All follow-up evaluations after 5-FU-CDDP chemotherapy for PSCC were performed every 2 months for the first year and every 6 months thereafter by magnifying NBI endoscopy, with the same periods of evaluation as for ESCC. For PSCC, complete response (CR) was defined as the disappearance of all visible tumors (brownish areas), including ulceration, for at least 4 weeks, confirmed by normal endoscopic biopsy specimens. The recurrence was defined as the reappearance of a brownish area accompanied by an enhancement of intraepithelial papillary capillary loop by NBI endoscopy, and was confirmed in histological findings by endoscopic biopsy. Non-CR for PSCC was defined as the remnant of brownish areas and was classified into a partial response, stable disease or progressive disease.

In the case of non-CR for PSCC, the second treatment was selected according to the efficacy of CRT for ESCC. When ESCC reached CR with remnant or recurrence of PSCC, endoscopic resection (ER) was performed for PSCC. When the ESCC was evaluated for non-CR, thereafter treatment for ESCC, such as second-line chemotherapy, salvage surgery or palliation was performed.

ER for PSCC after CRT

The ER involved endoscopic mucosal resection using the cup method or an endoscopic subepithelial dissection method with the patient under general anesthesia. An important consideration was that ER for PSCC should be performed with cooperation from the endoscopists and the head and neck surgeons. Some head and neck surgeons participated in the ER to prepare emergency treatment, such as tracheostomy, with evaluation of the degree of laryngeal edema after the procedure.

Statistics

All statistical analyses were performed using IBM SPSS Statistics 18 software (SPSS Inc., Tokyo, Japan). Overall survival data were calculated from the date of commencement of CRT to the date of death or the most recent follow-up visit. Survival curves were plotted according to the Kaplan-Meier method. The significance of differences was assessed using the log-rank test. A p value of <0.05 was considered statistically significant.

Results

Patient Characteristics

Fourteen patients (4.0%) with synchronous superficial PSCC were found among the 348 patients with invasive ESCC (table 1). Of the 14 patients, 13 (93%) were male and the median age was 62 years. The number of patients for ESCC clinical stage I, II, III, and IVA were 5, 2, 6 and 1, respectively. All 14 patients had both daily alcohol consumption and multiple LULs of the esophagus. All PSCC lesions were detected at our institute with no prior detection in other hospitals. Twelve (86%) PSCC lesions were detected using magnifying NBI endoscopy and the other 2 (14%) by conventional endoscopy. The latter 2 lesions were reevaluated with magnifying NBI endoscopy before

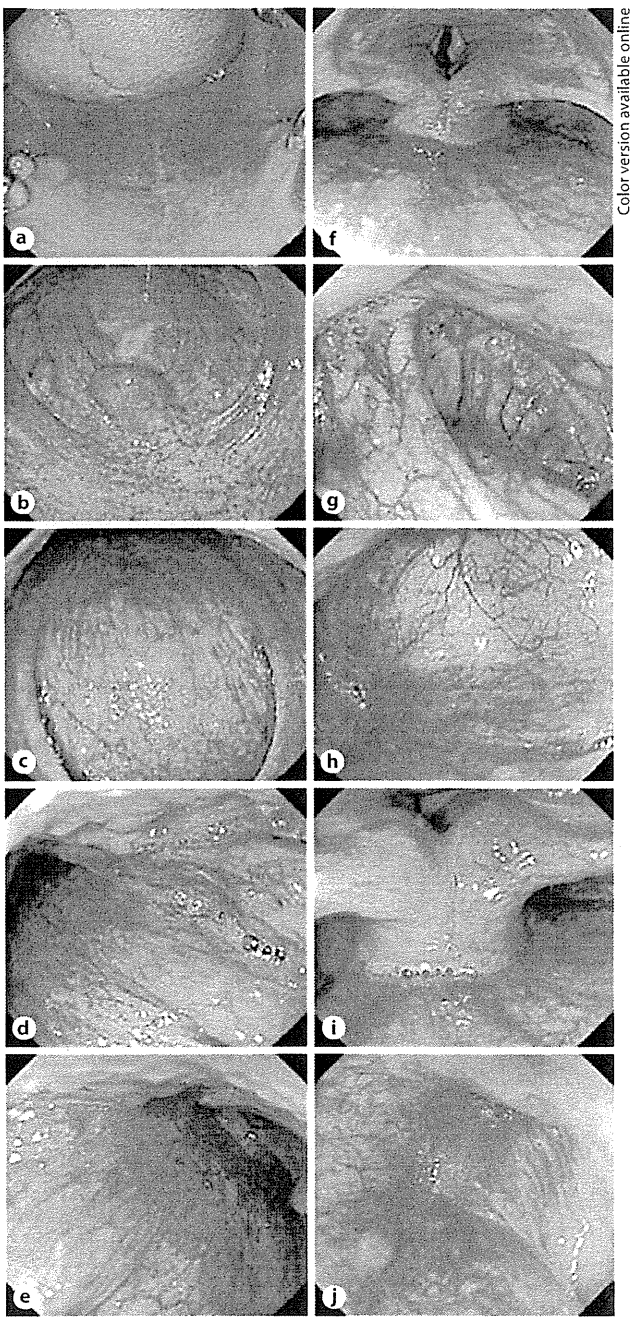

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Fig. 1. Narrow Band Imaging observations in individual regions from the oral cavity to the pharynx. **a** The view seen from the entrance of the oral cavity: dorsal side of tongue, hard palate and soft palate. **b** Uvula, palatoglossal arch and lateral walls of oropharynx. **c** The posterior wall of oropharynx. **d** The right side of base of tongue and lateral wall of oropharynx. **e** The left side of base of tongue and lateral wall of oropharynx. **f** Posterior wall of hypopharynx and larynx. **g** Vallecula of epiglottis, median glossoepiglottic fold. **h** The lateral wall and apex of right piriform sinus. **i** Arytenoids. **j** The lateral wall and apex of left piriform sinus.

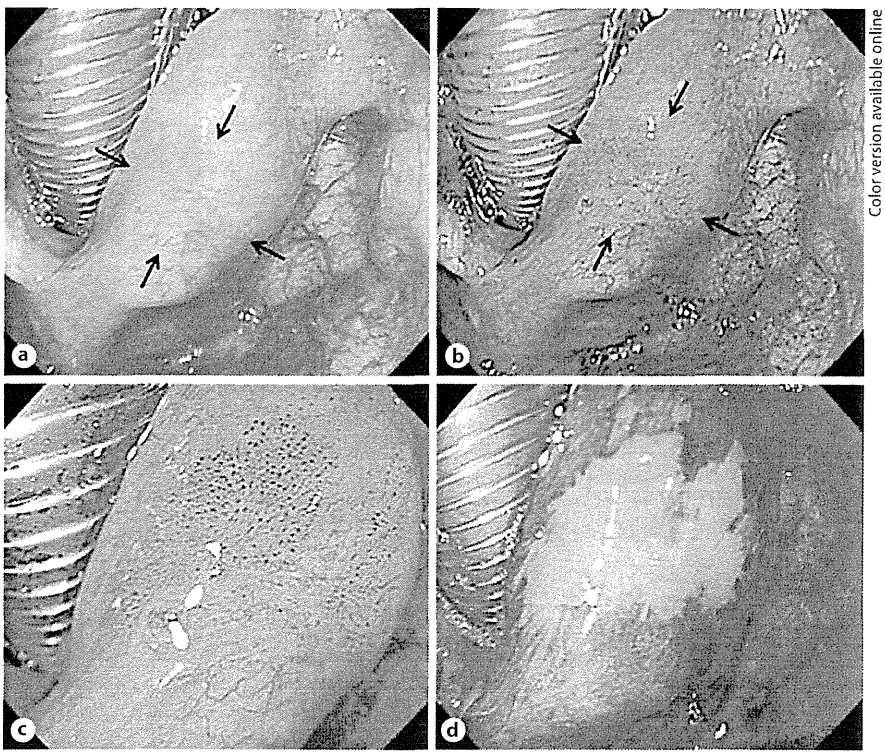

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Fig. 2. Superficial cancer of the right arytenoid. **a** Conventional endoscopic observation. The margin of the cancer is unclear (black arrows). **b** NBI observation. Cancer is shown as a brownish area (black arrows) and the margin is clear. **c** Magnifying NBI observation. The enhanced intraepithelial papillary capillary loop is seen in the cancer area. **d** The view of Lugol staining. Lugol-unstained lesion coincided with the cancer area. Lugol staining method was used to improve lesion visualization during endoscopic treatment. Color refers to the online version only.

Table 1. Patient characteristics

Age, years	Median	62
	Range	47–71
Gender	Male	13
	Female	1
Alcohol consumption	Presence	14
	Absence	0
Cigarette smoking	Presence	12
	Absence	2
Multiple LULs	Presence	14
	Absence	0
PSCC		
Location	Hypopharynx	10
	Oropharynx	4
Size, mm	Median	20
	Range	5–50
Macroscopic findings	Elevated type	5
	Flat type	4
	Depressed type	5
ESCC		
Clinical stage	I	5
	II	2
	III	6
	IVA	1

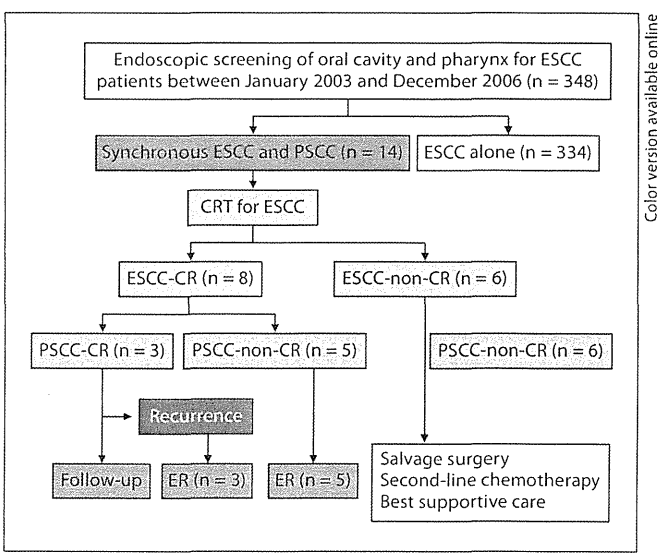

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Fig. 3. Flow chart of this study.

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

Efficacy of 5-FU-CDDP Chemotherapy for PSCC

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

ER for PSCC and Complications

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

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

Survival

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

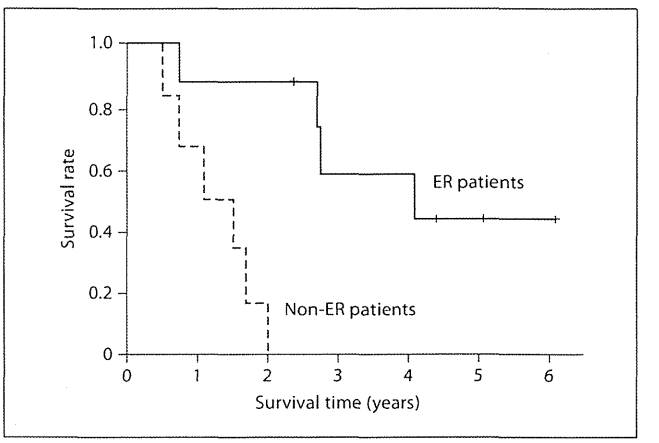

Fig. 4. Overall survival. Median survivals of ER and non-ER patients were 51 and 14 months, respectively (p = 0.002; log-rank test).

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

Discussion

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

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

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

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

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

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

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

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

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

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Disclosure Statement

The authors declare no conflict of interest.

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Treatment Strategy for Superficial Pharyngeal Squamous Cell Carcinoma Synchronously Combined with Esophageal Cancer

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Key Words
Pharyngeal cancer · Chemotherapy · Esophageal squamous cell carcinoma · Narrow band imaging · Early detection

Abstract
Background: Esophageal squamous cell carcinoma (ESCC) is often synchronously accompanied by pharyngeal squamous cell carcinoma (PSCC). However, treatment strategies for these synchronous cancers have not been established. ***Aim:*** To evaluate retrospectively the effects of both chemoradiotherapy (CRT) targeted for invasive ESCC on synchronous superficial PSCC and additional endoscopic resection (ER) for PSCC. ***Patients and Methods:*** Screening endoscopy in the pharynx was performed in newly diagnosed ESCC patients. CRT combined with 5-fluorouracil (5-FU) and cisplatin (CDDP) was administered to all patients. The effect on superficial PSCC was only evaluated for 5-FU-CDDP chemotherapy that excluded the pharynx from the radiation field. When PSCC was remnant or recurrent in patients evaluated at complete response (CR) of ESCC, ER was performed on the PSCC. ***Results:*** Fourteen cases of superficial PSCC (4.0%) were detected in 348 ESCC patients. Three PSCC reached CR in 8 ESCC-CR patients, while all 3 lesions recurred. No treatment response was found in the remaining 11 PSCC. As a second treatment, ER for 8 PSCC was completed in the 8 ESCC-CR patients, with one complication due to pneumonia. ***Conclusions:*** Standard 5-FU-CDDP CRT targeted for invasive ESCC did not demonstrate a sufficient efficacy for superficial PSCC, while ER even for PSCC after chemotherapy was curative.

Introduction

Esophageal squamous cell carcinoma (ESCC) is often accompanied by pharyngeal squamous cell carcinoma (PSCC) either simultaneously with the primary lesion (synchronously) or after a period of time (metachronously). These findings have been explained by the 'field cancerization' theory that describes how repeated local exposure to carcinogens contributes to the occurrence of multiple cancers in the esophageal and head and neck regions [1]. For more than 5 decades many epidemiological studies have attributed the increased cancer risks associated with alcohol drinking and smoking to this phenomenon

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[2–6]. In 2009, the Working Group of WHO-IARC concluded that acetaldehyde associated with alcoholic beverages was carcinogenic to humans and confirmed the group 1 classification of alcohol consumption [7]. In addition, heterozygous traits found in 40% of Asians, who have an inactive alcohol metabolizing enzyme of aldehyde dehydrogenases 2, accumulate acetaldehyde, with higher relative risks of these cancers [7, 8]. Furthermore, the prevalence of multiple Lugol-unstained lesions (LULs) [9, 10], which are caused by repeated exposure to acetaldehyde, was strongly related to the occurrence of synchronous or metachronous cancers in the esophagus and head and neck regions [11].

In contrast, most patients with PSCC are detected at an advanced stage with a poor prognosis. Even in an operable PSCC case, the extensive surgical resection required may cause a loss of function with respect to swallowing and/or speaking and can lead to cosmetic deformities. Thus it is difficult to determine a final treatment from the viewpoints of both curability and retaining organ function. In cancers combining ESCC and PSCC, the selection of treatment is even more critical. Because of this, the ability to detect pharyngeal lesions at an earlier stage, e.g. as carcinoma in situ, would be of clear benefit to patients. Recently, superficial PSCC has been detected by NBI endoscopy [12].

Systemic 5-fluorouracil-cisplatin (5-FU-CDDP) chemotherapy combined with radiotherapy is the standard treatment for ESCC, and the same treatment is also effective for PSCC patients [13, 14]. The radiation field used in radiotherapy for ESCC does not generally reach the region of the larynx and pharynx, while chemotherapy acts systemically. There have been no reports regarding the efficacy of systemic chemotherapy for patients with superficial PSCC. In this study, we examined the effect on superficial PSCC of chemoradiotherapy (CRT) targeted for invasive ESCC.

Patients and Methods

Patients

Between January 2003 and December 2006, concurrent CRT was performed in 348 patients with invasive ESCC who met the following criteria of this study: (1) newly diagnosed thoracic ESCC; (2) aged between 20 and 75 years; (3) clinical stage I to IVA according to the UICC-TNM classification; (4) absence of previous chemotherapy for malignancy; (5) absence of radiation or surgical treatment for head and neck, and esophageal cancers, and (6) absence of active malignancy except ESCC and PSCC. All patients with invasive ESCC visited our hospital to receive treatment after histological diagnosis of ESCC by endoscopy at another hospital.

Endoscopic Observation of the Oral Cavity and Pharynx

Since January 2003, endoscopic screening of the oral region has been performed in all ESCC patients in order to detect synchronously superficial PSCC. In the initial endoscopic observation in our hospital, narrow band imaging (NBI) or conventional endoscopy was used because both evaluation of ESCC and gastroduodenal screening including oral cavity and pharynx are performed in all patients. When a mucosal abnormality in the oral cavity or pharynx, or multiple LULs in the esophagus, were found in initially conventional endosopcy, the oral cavity and pharynx were observed again by magnifying NBI endoscopy within 2 weeks. Figure 1 shows the NBI findings of an oral cavity and pharynx using a video endoscope system (EVIS LUCERA CV-260, Olympus Optical Co. Ltd., Tokyo, Japan). When a brownish area and an enhancement of the intraepithelial papillary capillary loop were found in the pharynx (fig. 2), an endoscopic biopsy was performed to histologically confirm the carcinoma.

Lugol chromoendoscopy was performed in all patients for both diagnosis of the correct cancer region and evaluation of LULs in the background esophageal epithelium. After ordinary endoscopic observation, 5–10 ml of 2.0% glycerin-free Lugol iodine solution, which is a brown liquid consisting of 2.0 g potassium iodine and 4.0 g iodine in 100 ml distilled water, was sprayed from the upper thoracic esophagus to the gastroesophageal junction using a plastic spray catheter passed through the biopsy channel of the endoscope. Multiple LULs were defined as described in our previous study [15].

Definition of Superficial Pharyngeal Cancer

According to the Japan Society for Head and Neck Cancer [16], a superficial pharyngeal lesion is defined as one in which the invasion depth is comparatively limited and visual changes do not indicate an advanced cancer. The pharynx has no muscularis mucosa, so this somewhat vague definition suggests that the depth of invasion is limited to the epithelium or just beneath the epithelium, but does not extend to the muscle layer.

Treatment Schedule of CRT for ESCC

Chemotherapy consisted of a protracted infusion of 5-FU at a dose of 1,000 mg/m^2 per day on days 1–5 and 22–26, combined with a 2-hour infusion of CDDP at 75 mg/m^2 on days 1 and 22. A 10-MV radiation treatment was administered for 6 weeks (5 days/week) at 1.8 Gy/day with a total radiation dose of 50.4 Gy, concomitantly with chemotherapy.

Patients who were evaluated for an objective response to this treatment received additional chemotherapy consisting of a continuous infusion of 5-FU at a dose of 1,000 mg/m^2 on days 1–5 and CDDP at a dose of 75 mg/m^2 on day 1. This treatment schedule was administered for 1 week followed by a 3-week break. All patients receiving CRT were monitored by neck, chest and abdominal computed tomography, and by endoscopy to evaluate the efficacy of the treatment on both ESCC and PSCC.

As for response for ESCC, objective responses of measurable metastatic lesions were evaluated according to the response evaluation criteria in solid tumors (RECIST v 1.0) guideline. Response of the primary tumor was evaluated by the criteria of the Japan Esophageal Society [17, 18].

Evaluation of Response for PSCC

All follow-up evaluations after 5-FU-CDDP chemotherapy for PSCC were performed every 2 months for the first year and every 6 months thereafter by magnifying NBI endoscopy, with the same periods of evaluation as for ESCC. For PSCC, complete response (CR) was defined as the disappearance of all visible tumors (brownish areas), including ulceration, for at least 4 weeks, confirmed by normal endoscopic biopsy specimens. The recurrence was defined as the reappearance of a brownish area accompanied by an enhancement of intraepithelial papillary capillary loop by NBI endoscopy, and was confirmed in histological findings by endoscopic biopsy. Non-CR for PSCC was defined as the remnant of brownish areas and was classified into a partial response, stable disease or progressive disease.

In the case of non-CR for PSCC, the second treatment was selected according to the efficacy of CRT for ESCC. When ESCC reached CR with remnant or recurrence of PSCC, endoscopic resection (ER) was performed for PSCC. When the ESCC was evaluated for non-CR, thereafter treatment for ESCC, such as second-line chemotherapy, salvage surgery or palliation was performed.

ER for PSCC after CRT

The ER involved endoscopic mucosal resection using the cup method or an endoscopic subepithelial dissection method with the patient under general anesthesia. An important consideration was that ER for PSCC should be performed with cooperation from the endoscopists and the head and neck surgeons. Some head and neck surgeons participated in the ER to prepare emergency treatment, such as tracheostomy, with evaluation of the degree of laryngeal edema after the procedure.

Statistics

All statistical analyses were performed using IBM SPSS Statistics 18 software (SPSS Inc., Tokyo, Japan). Overall survival data were calculated from the date of commencement of CRT to the date of death or the most recent follow-up visit. Survival curves were plotted according to the Kaplan-Meier method. The significance of differences was assessed using the log-rank test. A p value of <0.05 was considered statistically significant.

Results

Patient Characteristics

Fourteen patients (4.0%) with synchronous superficial PSCC were found among the 348 patients with invasive ESCC (table 1). Of the 14 patients, 13 (93%) were male and the median age was 62 years. The number of patients for ESCC clinical stage I, II, III, and IVA were 5, 2, 6 and 1, respectively. All 14 patients had both daily alcohol consumption and multiple LULs of the esophagus. All PSCC lesions were detected at our institute with no prior detection in other hospitals. Twelve (86%) PSCC lesions were detected using magnifying NBI endoscopy and the other 2 (14%) by conventional endoscopy. The latter 2 lesions were reevaluated with magnifying NBI endoscopy before

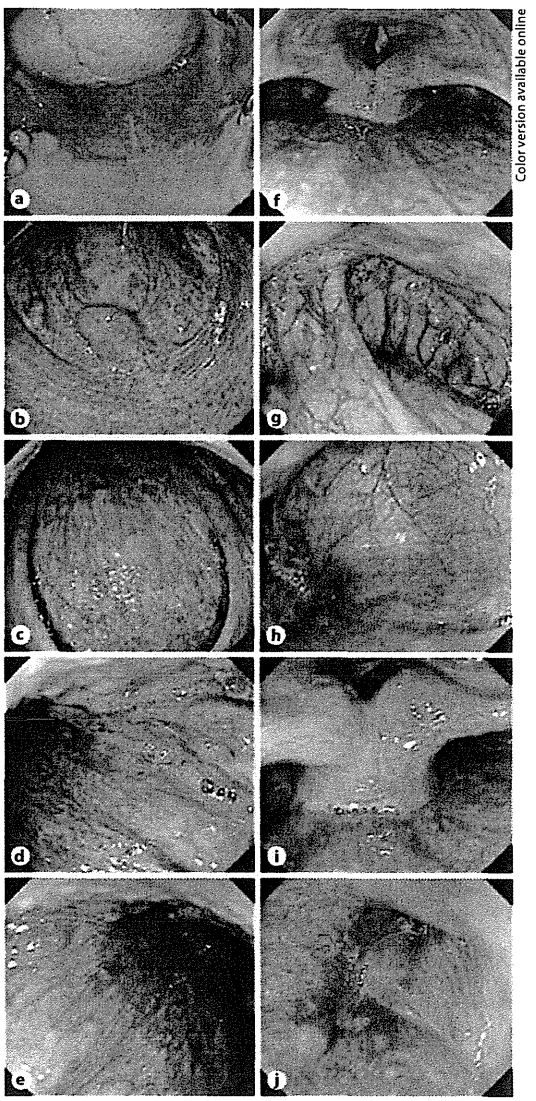

Fig. 1. Narrow Band Imaging observations in individual regions from the oral cavity to the pharynx. **a** The view seen from the entrance of the oral cavity: dorsal side of tongue, hard palate and soft palate. **b** Uvula, palatoglossal arch and lateral walls of oropharynx. **c** The posterior wall of oropharynx. **d** The right side of base of tongue and lateral wall of oropharynx. **e** The left side of base of tongue and lateral wall of oropharynx. **f** Posterior wall of hypopharynx and larynx. **g** Vallecula of epiglottis, median glossoepiglottic fold. **h** The lateral wall and apex of right piriform sinus. **i** Arytenoids. **j** The lateral wall and apex of left piriform sinus.

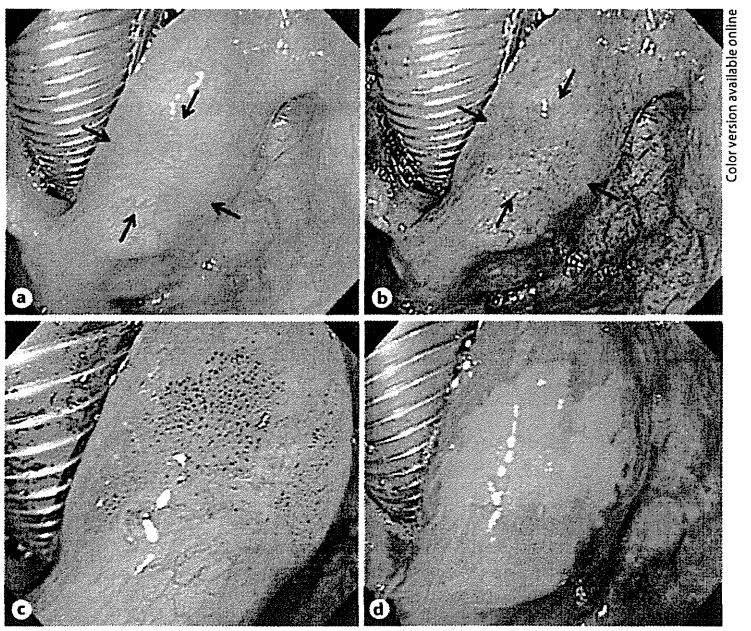

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Fig. 2. Superficial cancer of the right arytenoid. **a** Conventional endoscopic observation. The margin of the cancer is unclear (black arrows). **b** NBI observation. Cancer is shown as a brownish area (black arrows) and the margin is clear. **c** Magnifying NBI observation. The enhanced intraepithelial papillary capillary loop is seen in the cancer area. **d** The view of Lugol staining. Lugol-unstained lesion coincided with the cancer area. Lugol staining method was used to improve lesion visualization during endoscopic treatment. Color refers to the online version only.

Table 1. Patient characteristics

Age, years	Median	62
	Range	47–71
Gender	Male	13
	Female	1
Alcohol consumption	Presence	14
	Absence	0
Cigarette smoking	Presence	12
	Absence	2
Multiple LULs	Presence	14
	Absence	0
PSCC		
Location	Hypopharynx	10
	Oropharynx	4
Size, mm	Median	20
	Range	5–50
Macroscopic findings	Elevated type	5
	Flat type	4
	Depressed type	5
ESCC		
Clinical stage	I	5
	II	2
	III	6
	IVA	1

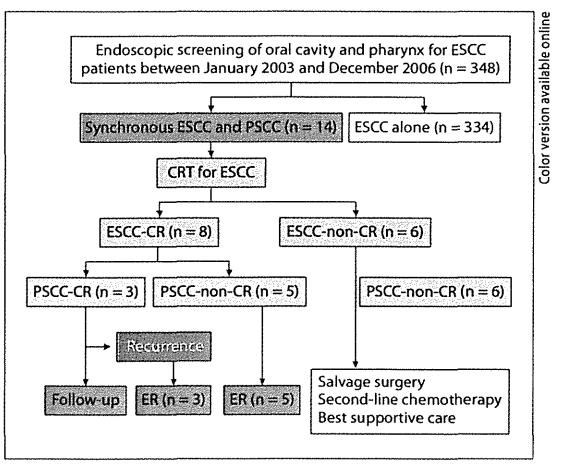

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Fig. 3. Flow chart of this study.

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

Efficacy of 5-FU-CDDP Chemotherapy for PSCC

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

ER for PSCC and Complications

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

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

Survival

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

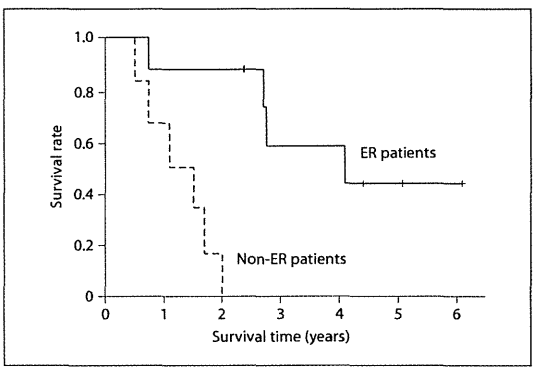

Fig. 4. Overall survival. Median survivals of ER and non-ER patients were 51 and 14 months, respectively (p = 0.002; log-rank test).

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

Discussion

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

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

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

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

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

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

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

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

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

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Disclosure Statement

The authors declare no conflict of interest.

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手技の解説

上部消化管内視鏡検査における頭頸部腫瘍の早期診断法

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要 旨

多くの内視鏡医は，これまで，上部消化管内視鏡検査において，頭頸部領域を詳細に観察し，「頭頸部癌の早期診断する」と言う概念を持っていなかった．しかしながら，頭頸部癌は患者背景やリスクファクターが食道癌に類似しており，臨床上頭頸部・食道重複癌が問題になることも少なくない．さらに，近年開発された狭帯域内視鏡（Narrow Band Imaging：NBI）を用いることで，いままで発見が困難だった中下咽頭の上皮内癌を見つけられることが報告されている．中下咽頭癌を早期診断できれば，内視鏡治療も可能であり，失声や嚥下障害を伴う咽喉頭全摘術を回避することができ，臓器温存や患者のQOL向上の観点から，極めて重要である．

実際の上部消化管内視鏡検査の際には，消化管での観察同様，見落としの無いよう口腔内から食道入口部かけて系統だった観察が必要である．さらに，容易に嚥下反射が誘発され，観察が困難になるため，愛護的な操作が必要である．頭頸部表在癌の診断には，NBIが有用であり，NBIを用いた頭頸部表在癌の現時点での診断基準は，境界明瞭なbrownish area及び病変内の拡大観察で拡張した異型血管の増生を認めることである．

本稿では，消化器内視鏡医が知っておくべき上部消化管内視鏡検査における，頭頸部領域観察手技の実際と癌の早期診断を中心に解説する．

Key words 頭頸部癌／早期診断／NBI

I はじめに

頭頸部は，耳鼻科医の診療領域とされ，多くの消化器内視鏡医は日々の検査で目にする，この領域を観察することに興味を抱いてこなかった．さらに，上部消化管内視鏡検査において，消化管の入り口である咽頭は，詳細に観察すると反射を引き起こし，患者が苦痛を自覚することが多いため，スムーズに通過することが推奨されてきた．そのため，消化器内視鏡医には，頭頸部腫瘍を早期診断するという概念はなかった．さらに，同じ扁平上皮領域である食道で早期癌の指摘診断に極めて有用なルゴール染色は，刺激が強く誤嚥のリスクがあり，咽頭領域には使用できないため，早期診断する方法もなかった．しかしながら，頭頸部癌は，患者背景やリスクファクターが食道癌に類似しており，臨床的には頭頸部・食道重複癌が問題になることも少なくない．また，近年開発され，オリンパス社から市販されている狭帯域内視鏡（Narrow Band Imaging：NBI）は，粘膜表面の微細構造や毛細血管構造の明瞭な描出を可能にした内視鏡システムであり，このNBI内視鏡を用いることで，いままで発見が困難だった中下咽頭の上皮内癌を見つけられることが報告されてい

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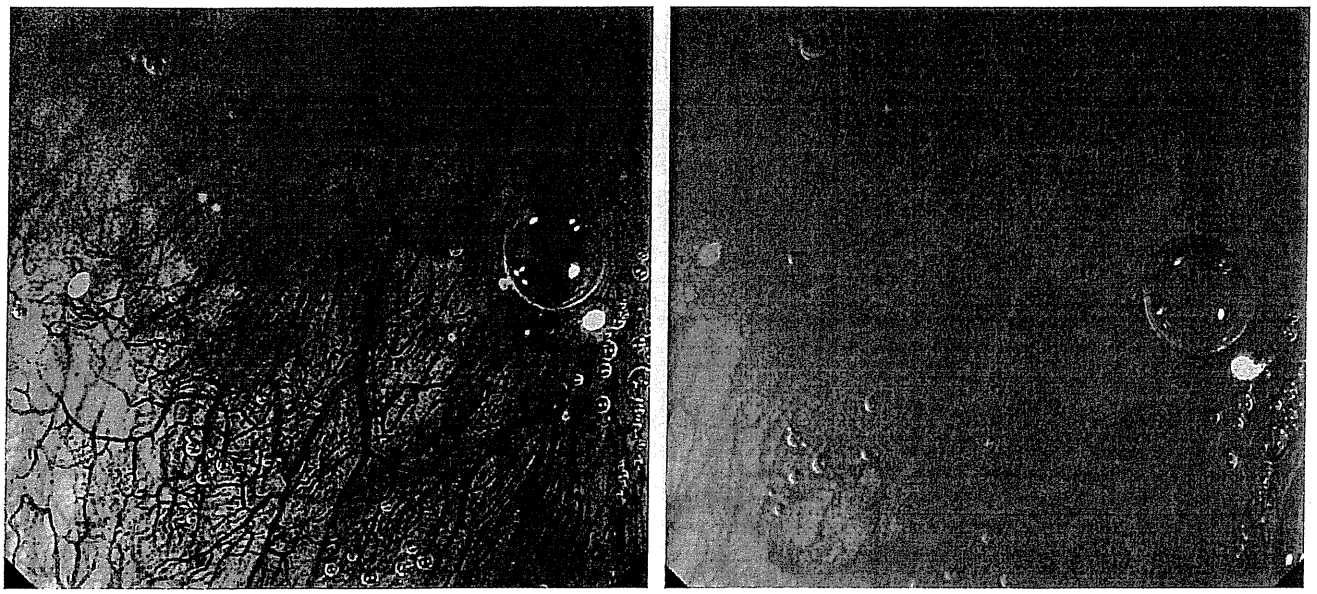

a　　b

Figure 1　中咽頭後壁の粘膜．NBI 画像(a) は白色光観察(b) と比較すると，より微細な血管網が観察可能であることが分かる．

る[1]．さらに，頭頸部領域の早期癌は，早期消化管癌に対する内視鏡的粘膜切除術（endoscopic mucosal resection：EMR）を応用して治療が行われ始めている．中下咽頭癌は，進行癌で発見されれば，根治手術が可能であっても失声や嚥下障害を伴う咽喉頭全摘術が必要とされることも多い．頭頸部癌の早期診断は，臓器温存や患者の QOL 向上の観点で極めて重要であり，頭頸部領域も上部消化管内視鏡検査の際に観察すべき領域の一つと認識され始めている．本稿では，消化器内視鏡医が知っておくべき上部消化管内視鏡検査における，頭頸部領域観察手技の実際と癌の早期診断を中心に解説する．また，本稿における頭頸部は，消化器内視鏡での観察が可能な口腔内の一部と中・下咽頭領域とし，表在癌は，頭頸部表在癌研究会で提唱されている「癌進展が上皮下層までにとどまる癌で，リンパ節転移の有無を問わない」病変とする．

II　頭頸部領域を観察すべき対象

日本人の口腔・咽頭癌の粗罹患率は，人口 10 万人あたり男性 12.6，女性 4.9 であり，それぞれ胃癌の約 10 分の 1 程度の頻度である．男女ともに 40 歳代後半から増加し，特に男性では，年齢とともに頻度が増えていき，65 歳以上では人口 10 万人あたり 30 を超える[2]．疾患頻度を鑑みると，上部消化管内視鏡検査を行う際に，すべての患者で頭頸部の詳細な観察を行う必要はなく，頭頸部癌の高危険群を設定し，効率よくスクリーニングすることが肝要である．中下咽頭癌の危険因子は，食道癌同様，飲酒，喫煙とされているため，飲酒喫煙歴がある中高年男性では，上部消化管内視鏡検査の際に頭頸部を観察することが望ましい．更に，Muto らは，頭頸部・食道癌の重複症例では食道内に大小不同の多発ヨード不染帯（multiple lugol-voiding lesions；multiple LVL）を高頻度に認めること，その原因はアルコールの代謝産物であるアセトアルデヒドの蓄積による可能性があることを報告している[3)~5)]．問診にて，フラッシング現象（少量の飲酒でも顔面が紅潮する）があるにも関わらず飲酒を継続している場合は，アセトアルデヒドが蓄積している可能性があり，更に高危険群と考え検査に臨む必要がある．当院では，特に食道癌の治療前スクリーニングや治療後経過観察の時には，頭頸部領域を必ず観察するようにしている．

III　NBI システム

NBI システムは，当センターに在職していた佐野（現，佐野病院院長），オリンパス株式会社の後野らによって共同開発された内視鏡システムである．NBI は，ヘモグロビンに吸収されやすい 415 nm，540nm に狭帯域化された光を照射することによって，粘膜表面の微細な血管構造を顕在化す

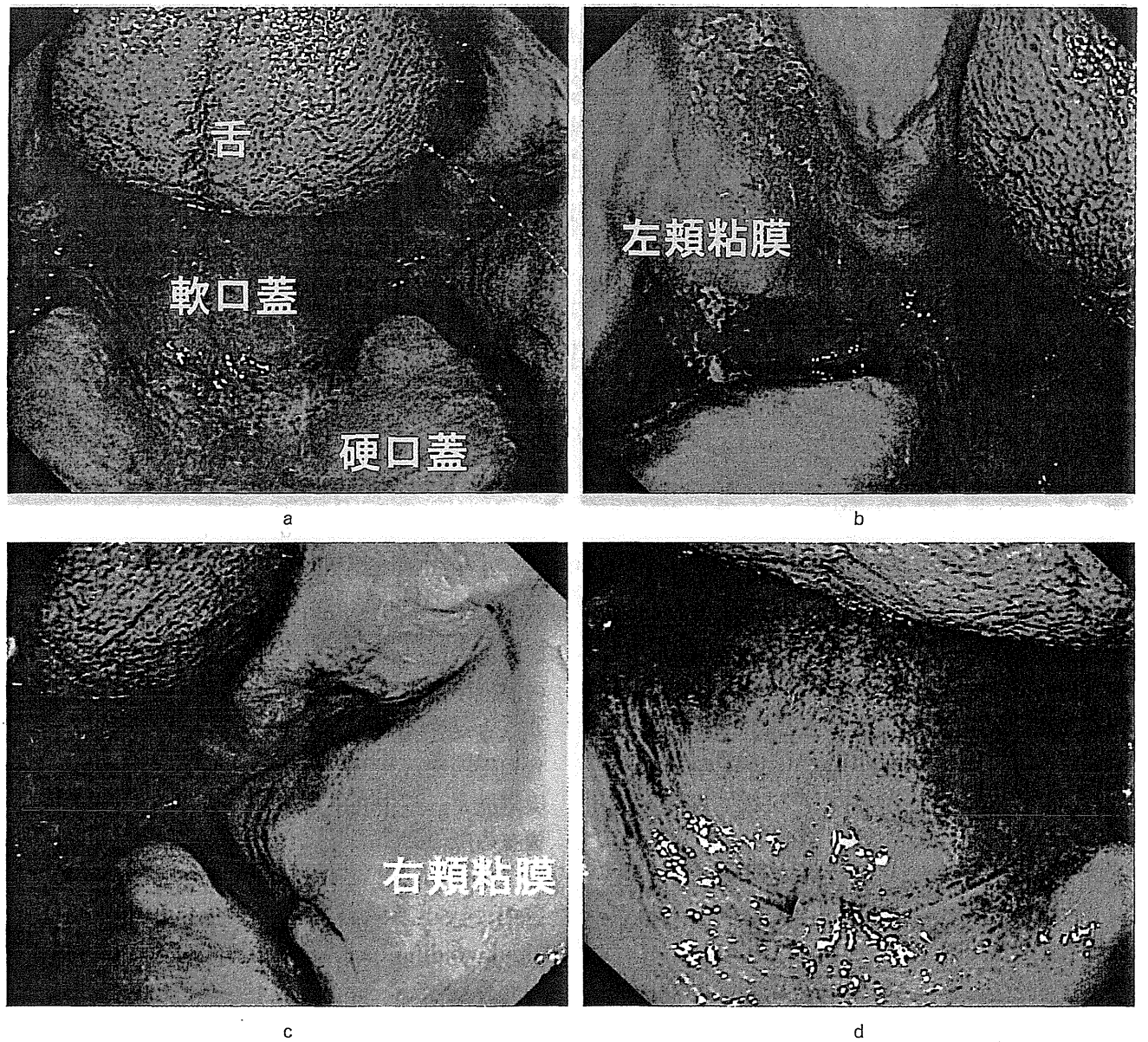

Figure 2 口腔内の観察．dが硬口蓋と軟口蓋の境界部，この境界部より肛門側が中咽頭になる．

ることを可能にしたイメージング方法である．NBIが，特に拡大観察を併用することによって，消化管の各領域において，粘膜内病変の質的診断や癌の範囲診断に有用であると言う報告がなされ，現在本邦のみならず世界中で急速に普及しつつある[6)~8)]．

頭頸部領域の正常粘膜でも，通常白色光観察と比較すると，NBIでは粘膜表面の血管構造が顕在化することが可能になる．さらに拡大観察することにより，白色光観察では視認できないような，より微細な血管まで視認可能になる（Figure 1）．頭頸部領域では，前述のように食道と違ってルゴール染色を使った癌の早期診断が不可能であり，NBIを用いた粘膜表面の血管構造の変化を礎にした癌の早期診断が色素内視鏡に代わる強力な診断ツールとなり得ると考えられる．

Ⅳ 内視鏡的な中下咽頭亜部位と観察手技の実際

1．前処置

前投薬は，咽頭観察のみを行う場合には，唾液分泌抑制を目的として，硫酸アトロピン0.5mgを筋肉注射しているが，上部消化管内視鏡検査で咽頭領域を詳細に観察する場合には，ブチルスコポラミン10～20mg及び軽い鎮静を目的とした塩酸ペチジン35mgを静注している．頭頸部領域は，唾