

A large number of studies have demonstrated multiple occurrences of squamous cell carcinoma in the upper aerodigestive tract, including the esophagus, head and neck region. The incidence of such multiplicities has been reported to be between 9 and 14 % [6]. In patients with ESCC and HNSCC, routine surveillance and long-term follow-up have resulted in more frequent detection of a second primary cancer [9–13]. However, the management and clinical course of these patients with multiple squamous cell carcinomas have been poorly investigated. The poor prognosis of each carcinoma taken individually, and their anatomic proximity, limit the therapeutic possibilities.

This study presents the experience of the National Kyushu Cancer Center regarding the treatment of synchronous and metachronous ESCC and HNSCC. The aim of this study was to evaluate the treatment outcomes of the patients, focusing on the simultaneous treatment of both cancers.

## Patients and methods

### Patients

A total of 509 patients with ESCC were initially treated from 2003 to 2010 at National Kyushu Cancer Center. We routinely screen HNSCC patients for ESCC, and ESCC patients for HNSCC including ear, nose and throat (ENT) consultations and an esophageal endoscopy at our institution. Among the 509 patients with ESCC, 50 (9.8 %) patients presented with synchronous and metachronous HNSCC. We investigated these 50 patients in this study. On the other hand, a total of 1,885 patients with HNSCC (oral floor: 433 patients, lip: 7 patients, epipharynx: 190 patients, mesopharynx: 310 patients, hypopharynx: 299 patients, larynx: 449 patients, auditory organs: 6 patients, nose and paranasal sinuses: 191 patients) were treated at the Division of Head and Neck Surgery in our institute during the same time interval. Among the 1,885 patients with HNSCC, 46 patients (2.4 %) had ESCC (38 synchronous cancers, 4 ESCC preceding metachronous cancers, and 4 HNSCC preceding metachronous cancers).

Synchronous carcinomas were defined as second neoplasms diagnosed at the same time or within 6 months of finding the primary lesion. Neoplasms diagnosed after this period were classified as metachronous neoplasms. The pretreatment diagnostic evaluations consisted of a barium swallow, endoscopy with Lugol's iodine, cervical and abdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) of the HN area, and bone scintigraphy. Whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning was not routinely performed for all patients. To diagnose primary

multiple ESCC, we used the following criteria: (1) each cancerous lesion showed definite malignant histological features and was located individually with no continuity; (2) concomitant carcinomas accompanied the areas of intraepithelial carcinomas. The staging of the tumor was based on the TNM classification defined by Union for International Cancer Control [14].

### Treatment

The treatment strategy for synchronous and metachronous ESCC and HNSCC was determined by the managing physician considering the tumor staging and the general condition of each patient. When surgical resection was indicated for thoracic ESCC, an esophagectomy with three-field lymphadenectomy was considered as an initial treatment. Chemoradiotherapy (CRT) was also considered as an option for the treatment of thoracic ESCC. The treatment was finally determined after adequate informed consent was obtained from the patients. For mucosal ESCC, endoscopic mucosal resection (EMR) or CRT was generally indicated. Especially when synchronous ESCC and HNSCC were detected, the therapeutic strategy was determined by the more advanced tumor, which was thought to more strongly influence the patient's prognosis. If simultaneous surgical procedures were indicated, the patient underwent a one-staged operation for ESCC and HNSCC.

When simultaneous CRT was indicated for the patients with synchronous ESCC and HNSCC, the daily fractional radiation dose was 1.2–2 Gy (median 1.6 Gy), administered 5 days per week. The total radiation dose was 60 Gy for ESCC and 70 Gy for HNSCC. The initial radiotherapy field included the head and neck, and mediastinal region. Chemotherapy was performed concurrently with radiotherapy. Chemotherapy consisted of cisplatin/5-FU or platinum-based monotherapy (cisplatin alone or carboplatin alone). The initial treatment response was defined as follows [15]; a complete response was defined as the disappearance of the tumor mass on endoscopy, CT, MRI, and/or PET. A partial response was defined as more than 30 % regression based on a one-dimensional measurement by means of endoscopy, CT, or MRI, and no response was defined as <30 % regression or <20 % progression. Acute and late toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The median length of follow-up was 33.2 months (range 1.6–95.5 months).

### Statistical analysis

The differences in the distribution frequencies among the groups were evaluated using Fisher's exact test or the unpaired *t* test. The survival curves were plotted according

**Table 1** The clinical backgrounds of the 50 patients with synchronous and metachronous ESCC and HNSCC

Sex (male/female)	46/4
Mean age (range)	64.1 (42–85)
Synchronous	38
Metachronous	12
ESCC → HNSCC	4
HNSCC → ESCC	8
Synchronous and metachronous other cancers	13 <sup>a</sup>
Gastric cancer	9
Colon cancer	4
Lung cancer	2
ESCC	
Solitary/multiple	40/10
Clinical stage: 0/I/II/III/IV/unknown	20/14/7/4/4/1
HNSCC <sup>b</sup>	
Oral floor	9
Mesopharynx	9
Hypopharynx	26
Larynx	8
Clinical stage: I/II/III/IV	10/12/7/21

ESCC esophageal squamous cell carcinoma, HNSCC head and neck squamous cell carcinoma

<sup>a</sup> One case had synchronous gastric cancer and metachronous colon and lung cancer

<sup>b</sup> Two cases had two HNSCCs

to the Kaplan-Meier method, and any differences were analyzed using the log-rank test. Differences were considered to be significant for  $p < 0.05$ . The data were analyzed using the StatView software package (Abacus Concepts, Inc., Berkeley, CA).

## Results

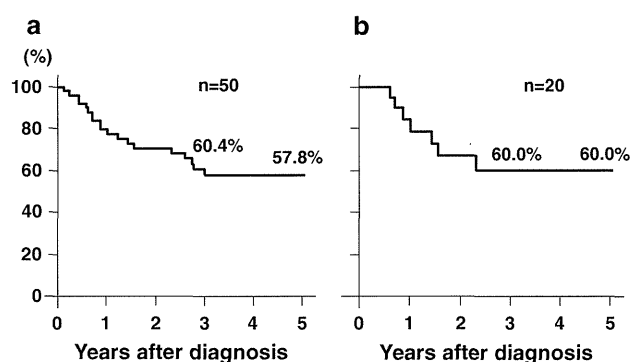
The treatment outcomes of 50 patients with synchronous and metachronous ESCC and HNSCC

The patient characteristics are shown in Table 1. There were 38 patients (76.0 %) with synchronous ESCC and HNSCC, and 12 patients (24.0 %) with metachronous ESCC and HNSCC. In 38 patients with synchronous cancers, 29 patients (76.3 %) first visited the institute with either a diagnosis or suspicion of HNSCC, and thereafter ESCC was diagnosed by a screening examination. Three out of the four patients with ESCC preceding metachronous cancers (75.0 %) and six patients out of the eight patients with HNSCC preceding metachronous cancers (75.0 %) had been treated from the starting point of the treatment for the initial cancer and under the follow-up

**Table 2** The treatments used for the 50 patients with synchronous and metachronous ESCC and HNSCC

ESCC	
EMR	13
Surgery	8
CRT	28
RT	1
HNSCC	
Surgery	10
CRT	35
RT	3
Chemotherapy	1
None	1

ESCC esophageal squamous cell carcinoma, HNSCC head and neck squamous cell carcinoma, EMR endoscopic mucosal resection, CRT chemoradiotherapy, RT radiotherapy



**Fig. 1** **a** The survival curves of the 50 patients with synchronous and metachronous ESCC and HNSCC. The 3- and 5-year overall survival rates were 60.4 and 57.8 %, respectively. **b** The survival curves of the 20 patients with synchronous ESCC and HNSCC who received simultaneous CRT. The 3- and 5-year overall survival rates were both 60.0 %

program at our institute. Notably, there were 13 patients with synchronous and metachronous other cancers, 9 with gastric cancer, 4 with colon cancer, and 2 with lung cancer, including 1 patient with synchronous gastric cancer and metachronous colon and lung cancer. There were 10 patients (20.0 %) with multiple ESCCs among the 50 patients with synchronous and metachronous ESCC and HNSCC. The clinical stage of ESCC was relatively earlier than that of HNSCC; 34 patients (68.0 %) had stage 0–I ESCC, whereas 40 patients (80.0 %) had stage II–IV HNSCC. A total of 13 (26.0 %) ESCCs among the 50 subjects underwent EMR and 28 (56.0 %) received CRT, while 35 (70.0 %) HNSCCs among the 50 subjects received CRT, indicating that the majority of treatments were non-surgical for both cancers (Table 2). The 3- and 5-year overall survival rates of the 50 patients with synchronous and metachronous ESCC and HNSCC were 60.4 and 57.8 %, respectively (Fig. 1a).

The treatment outcomes of 20 patients with synchronous ESCC and HNSCC who received simultaneous CRT

The treatments used for 38 patients with synchronous ESCC and HNSCC are shown in Table 3. Simultaneous surgery for synchronous ESCC and HNSCC was performed in five patients. Among them, four patients are still alive, and one patient died with HNSCC recurrence.

Simultaneous CRT was performed in 20 patients. The clinical backgrounds of those patients are listed in Table 4. Among the 20 patients who received simultaneous CRT, CRT was completed in 19 (95.0 %) patients, excluding 1 patient who refused further therapy halfway through the course of treatment. There were no therapy-related deaths. Grade 3–4 adverse events were observed in five (25.0 %) patients (neutropenia; 3 patients, appetite loss; 2 patients, mucositis; 1 patient). A complete response (CR) and partial response (PR) of the ESCC were observed in 13 (65.0 %)

**Table 3** The treatments used for the 38 patients with synchronous ESCC and HNSCC

ESCC/HNSCC	
Simultaneous surgery	5
Surgery/RT	1
Surgery/chemotherapy	1
Simultaneous CRT	20
CRT/surgery	1
EMR/surgery	1
EMR/CRT	7
EMR/RT	1
Simultaneous RT	1

ESCC esophageal squamous cell carcinoma, HNSCC head and neck squamous cell carcinoma, EMR endoscopic mucosal resection, CRT chemoradiotherapy, RT radiotherapy

**Table 4** The clinical backgrounds of the 20 patients with synchronous ESCC and HNSCC who received simultaneous CRT

Sex (male/female)	19/1
Age (mean)	63.4
ESCC	
Solitary/multiple	15/5
cStage: 0/I/II/III/IV	5/10/3/0/2
HNSCC	
Oral floor	1
Mesopharynx	4
Hypopharynx	13
Larynx	2
cStage: I/II/III/IV	3/6/2/9

ESCC esophageal squamous cell carcinoma, HNSCC head and neck squamous cell carcinoma, CRT chemoradiotherapy

and 5 (25.0 %) patients, respectively. A CR and PR of HNSCC were observed in 11 (55.0 %) and 6 (30.0 %) patients, respectively. CRs of both ESCC and HNSCC were observed in 10 (50.0 %) patients. The 3- and 5-year overall survival rates of the 20 patients was 60.0 and 60.0 %, respectively (Fig. 1b).

In terms of the chemotherapy regimen, cisplatin/5-FU or platinum-based monotherapy (cisplatin alone or carboplatin alone) was administered. Cisplatin/5-FU was administered to 12 patients and platinum-based monotherapy to 8 patients. The effects of simultaneous CRT according to the chemotherapy regimen are shown in Table 5. In the cisplatin/5-FU group, there were six patients whose HNSCC was more advanced than their ESCC, and six patients whose ESCC and HNSCC were in the same stage. In the platinum-based monotherapy group, HNSCC was more advanced than ESCC in all eight patients. In the cisplatin/5-FU group, CRs of the ESCC and HNSCC were observed in eight (66.7 %) and eight (66.7 %) patients, respectively. CRs of both the ESCC and HNSCC were observed in seven (58.3 %) patients. In the platinum-based monotherapy group, CRs of ESCC and HNSCC were observed in five (62.5 %) and three (37.5 %)

**Table 5** The effects of simultaneous CRT for the 20 patients with synchronous squamous cell carcinoma of the esophagus and head and neck according to the chemotherapy regimen

CDDP/5-FU ( <i>n</i> = 12)	
cStage: 0/I/II/III/IV	
ESCC	1/7/2/0/2
HNSCC	–/3/4/1/4
Response: CR/PR/SD/PD/NA	
ESCC	8/3/0/0/1
HNSCC	8/2/0/1/1
Platinum-based monotherapy ( <i>n</i> = 8)	
cStage: 0/I/II/III/IV	
ESCC	4/3/1/0/0
HNSCC	–/0/2/1/5
Response: CR/PR/SD/PD/NA	
ESCC	5/2/0/0/1
HNSCC	3/4/1/0/0
Total ( <i>n</i> = 20)	
cStage: 0/I/II/III/IV	
ESCC	5/10/3/0/2
HNSCC	–/3/6/2/9
Response: CR/PR/SD/PD/NA	
ESCC	13/5/0/0/2
HNSCC	11/6/1/1/1

ESCC esophageal squamous cell carcinoma, HNSCC head and neck squamous cell carcinoma, CRT chemoradiotherapy, CR complete response, PR partial response, SD stable disease, PD progressive disease, NA not assessed

patients, respectively, while CRs of both the ESCC and HNSCC were observed in three (37.5 %) patients.

The results of the treatments for remnant or recurrent cancer after simultaneous CRT were also investigated. In five patients with remnant ESCC, surgery was applied for one patient, brachytherapy for one patient, chemotherapy for two patients, and best supportive care for one patient. In eight patients with remnant HNSCC (local; 4 patients, lymph node; 4 patients), surgery was applied for five patients, chemotherapy for one patient, and best supportive care for two patients. In four patients with recurrent ESCC (local; 3 patients, lymph node; 1 patient), EMR was applied for one patient, argon-plasma coagulation for one patient, brachytherapy for one patient, and additional CRT for lymph node recurrence was applied for one patient. In five patients with recurrent HNSCC (local; 2 patients, lung metastasis; 3 patients), surgery  $\pm$  chemotherapy was applied for four patients and best supportive care for one patient.

## Discussion

Our routine screening for secondary cancer resulted in finding that 9.8 % of our patients with ESCC presented with synchronous or metachronous HNSCC, and 2.4 % of the patients with HNSCC presented with synchronous or metachronous ESCC. These incidences are moderate compared with those described in previous reports [9–13]. Among our patients, there were 34 (68.0 %) with stage 0–I ESCC and ten (20.0 %) with stage I HNSCC, thus indicating the clinical stages of the original esophageal cancers had been classified as lower stage cases in comparison to the total population of patients with esophageal cancer [16]. This phenomenon can be explained as the effect of routine surveillance, as previously reported [9–13]. There were 13 patients with synchronous and metachronous other cancers, 9 cases of gastric cancer, 4 of colon cancer, and 2 of lung cancer, including 1 patient with synchronous gastric cancer and metachronous colon and lung cancer. There were 10 patients (20.0 %) with multiple ESCCs among the 50 patients with synchronous and metachronous ESCC and HNSCC. One of the unique pathological features of ESCCs is the presence of multiple lesions within the esophagus. Patients with ESCC associated with head and neck cancer have more multiple iodine-unstained lesions and multiple ESCC in comparison to the patients with ESCC alone [17]. Another study found that the presence of numerous irregular-shaped multifocal Lugol-voiding lesions was closely associated with second primary ESCC in patients with HNSCC [18]. These observations may be an indication of “field carcinogenesis.” These findings indicate that meticulous attention to the possible coexistence or

occurrence of secondary cancers is essential not only at the initial diagnosis, but also during the follow-up period for ESCC and HNSCC.

The surgical treatment of the patients with synchronous and metachronous ESCC and HNSCC is challenging. A low mortality rate can be achieved with esophagectomy in specialized centers, but the morbidity rates are still high [16, 19–21]. The presence of synchronous or previously treated head and neck cancers may add further difficulties. We investigated the patients with ESCC and HNSCC who were treated at our institute in 8 years by reviewing their medical records. Although surgical resection was considered as an initial treatment, non-surgical therapies were eventually the majority of the therapies that were performed. This suggested that non-surgical therapies, including CRT, tend to be preferred to surgery in practice. However, the usefulness of surgical treatment for the patients with synchronous and metachronous ESCC and HNSCC has been previously reported [22–25]. In this study, simultaneous surgery for synchronous ESCC and HNSCC was performed in five patients. Among them, there was no surgery-related mortality and four patients are still alive, with one patient having died of HNSCC recurrence. Further investigations are needed to evaluate the optimal treatment strategy for these patients.

There have been a few papers that have reported the clinical significance of simultaneous CRT for patients with ESCC and HNSCC. We had previously investigated the efficacy and feasibility of simultaneous CRT for patients with ESCC and HNSCC [26], the subjects of which were partly consistent with those of the current study. In this study, we further analyzed all patients with ESCC and HNSCC who were initially treated from 2003 to 2010 at a single institute. The CRT course was completed by 19 (95.0 %) of the 20 patients, and all adverse events were manageable. CRs of both ESCC and HNSCC were observed in 50.0 % of patients, and the 5-year overall survival rate was 60.0 %. The favorable prognosis after simultaneous CRT for patients with ESCC and HNSCC was reported for the first time in this study. These data demonstrated that simultaneous CRT could therefore be a good choice of treatment.

Based on previous clinical reports, the standard chemotherapy regimen of CRT for ESCC is considered to be cisplatin/5-FU [27–31]. On the other hand, that for HNSCC is controversial, probably because the incidence of HNSCC is too low to establish large-scale clinical trials [32, 33]. In this study, cisplatin/5-FU or platinum-based monotherapy (cisplatin alone or carboplatin alone) was administered. Although there tended to be more advanced patients in the cisplatin/5-FU group than in the platinum-based monotherapy group, the effect of cisplatin/5-FU tended to be better than that of the platinum-based monotherapy not

only for ESCC, but also for HNSCC. Since this comparison was based on a small number of patients and there were no statistically significant differences, we cannot draw any definitive conclusions. However, cisplatin/5-FU might be more active for ESCC and HNSCC when combined with radiation. Further studies with a larger number of patients will be required to evaluate the optimal chemotherapy regimen in simultaneous CRT for patients with ESCC and HNSCC.

Salvage surgery for recurrent or remnant ESCC after CRT has been reported to have high morbidity and mortality rates [34, 35]. On the other hand, salvage surgery for recurrent or remnant HNSCC is often performed in practice. In this study, surgical therapies were chosen more frequently for recurrent or remnant HNSCC than for ESCC. Once simultaneous CRT is chosen as the initial therapy for the patients with ESCC and HNSCC, salvage surgery appears to play an important role in curing both cancers. Taking the high morbidity and mortality rate after salvage surgery for recurrent or remnant ESCC into consideration, cisplatin/5-FU may therefore be more advantageous than platinum-based monotherapy in order to avoid the need for this invasive treatment.

The treatment of the patients with ESCC and HNSCC is very complicated and requires the establishment of a specialized cooperative system involving high volume centers. It is thought to be difficult or impractical to determine the usefulness of surgery or CRT through the use of randomized controlled trials given the relatively small number of patients treated each year. It is therefore necessary to accumulate the findings obtained from retrospective studies at many institutes. We believe that the findings from the present study offer some useful information for determining the optimal treatment strategy for ESCC and HNSCC patients. However, the treatment results obtained from this study should not be generalized, because the patients in this study had been classified as lower stage cases in comparison to the general population because of the surveillance effect. In conclusion, surveillance for double cancer and aggressive treatment contribute to the favorable outcomes of patients with ESCC and HNSCC. The optimal chemotherapy regimen for simultaneous CRT remains to be determined.

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