表1 ファーストラインにおけるベバシズマブの主な治療成績

試験名	レジメン		RR（%）		PFS（month）		OS（month）	
AVF2192g	5-FU/LV＋BEV	104	26	P=0.055	9.2	HR=0.50, P=0.0002	16.6	HR=0.79, P=0.16
	5-FU/LV	105	15.2		5.5		12.9	
AVF2107g	IFL＋BEV	402	44.8	P=0.004	10.6	HR=0.54, P<0.001	20.3	HR=0.66, P<0.001
	IFL	411	34.8		6.2		15.6	
NO16966	FOLFOX or XELOX ＋ BEV	699	38	P=0.99	9.4	HR=0.83, P=0.0023	21.3	HR=0.89, P=0.077
	FOLFOX or XELOX	701	38		8.0		19.9	

RR: response rate, PFS: progression free survival, OS: overall survival, HR: hazard ratio

る。しかし各々の症例がどのグループであるのかの臨床的判断は難しい。

- 切除不能結腸・直腸がんの治療の目的は，一部の患者では治癒率の向上を目指す場合もあるが，ほとんどの場合，生存期間（OS）の延長，症状の緩和である。症例ごとの状況を考慮してレジメンを選択して治療を進める必要がある。

切除不能結腸・直腸がんに対するベバシズマブのファーストライン治療に関するエビデンス

- ベバシズマブ（BEV）はVEGFに対するキメラ型ヒト化IgG1モノクローナル抗体である。レセプターへのVEGFの結合を阻害して，血管新生を抑制して腫瘍の増大を抑える。また，腫瘍周囲組織の血行が再構築されるため，薬剤の腫瘍への移行や透過性が改善するとも考えられている。
- 表1はファーストライン治療におけるBEV使用のエビデンスである。AVF2192g試験はフルオロウラシル（5-FU）＋ホリナート（LV）療法に対するBEVの上乗せを検討した試験である[2]。Response rate（RR）は5-FU＋LV単独で15.2%，BEV併用群では26%であった。Progression free survival（PFS）のHRも0.5であり顕著な差を認める。
- その後行われたAVF2107g試験はIFL（イリノテカン＋5-FU＋LV）療法との併用で，奏効率，PFS, overall survival（OS）すべてで上乗せが認められている。当時はセカンドライン以降におけるクロスオーバーの症例がなかったとはいえ，OSでハザード比（HR）は0.66と明らかな差を認めた[3]。
- さらにNO16966はFOLFOX4もしくはXELOX療法との併用でBEVの上乗せを検討した試験である。この試験でもプライマリーエンドポイントのPFSにおいてBEVの上乗せが証明された[4]。
- これら臨床試験の結果からファーストライン治療におけるBEV併用の有用性が証明されてきた。つまり切除不能大腸がんのファーストライン治療にはBEVを併用した治療法のエビデンスがある。

ファーストライン治療にBEVを使用しない場合

- 表2は特定使用成績調査時におけるBEVの重篤な副作用である[5]。
- 頻度が低いとはいえ，出血や消化管穿孔などがあり得るため，全周性の原発巣が残存

表2 ベバシズマブの主な有害事象の報告

	G3異常の有害事象		
	特定使用成績調査(%)	First-BEAT(%)[9]	BRiTE(%)[10]
高血圧	0.4	0.5	16.4
出血	1.4	0.8	1.9
タンパク尿	<0.1	—	—
消化管穿孔	0.9	0.7	1.7
動脈血栓塞栓症	0.3	0.6	2.1
静脈血栓塞栓症	1.3	1.0	
創傷治癒遅延	0.3	0.3	1.2

(文献4)より改変)

し，腸閉塞症状や出血を認める場合は，原発巣への対処を行ってからBEVを使用すべきと考えられる。

- BEV使用後には創傷治癒の遅延も経験するため術後早期からのBEVの使用は慎重に考慮すべきである。
- 術後一定期間は分子標的治療薬を併用しないFOLFOX6やFOLFIRI療法を行うか，*KRAS*に変異がなければ抗EGFR抗体を使用することも視野に入れるべきである。

ファーストラインの治療選択とセカンドライン治療でのBEV継続投与

- ML18147試験はファーストラインにBEVを併用した標準的化学療法を行った後に，セカンドラインとしてBEVを継続的に併用する群と，化学療法のみの群を比較した第Ⅲ相試験である[6]。
- BEV併用群のOSは11.2ヵ月，BEV非併用群では9.8ヵ月，HRは0.81（95%信頼区間：0.69-0.94；p=0.0062）であり，有意にBEV併用群でOSの延長が認められた。PFSも，BEV群が5.7ヵ月，化学療法のみ群が4.1ヵ月，HRが0.68（95%信頼区間：0.59-0.78；p<0.0001）でBEV併用群の優越性が証明されている。そのほか，過去に行われたE3200試験でも，大腸がんのセカンドライン治療においてBEVの有用性が証明されている。
- サードライン以降にはセツキシマブ（Cmab）やパニツムマブ（Pmab）などの抗EGFR抗体が単独で効果を発揮することが報告されている。したがって長期の化学療法の継続を考えた場合，ファーストライン，セカンドラインにBEVを使用した治療を行い，サードライン以後に副作用の強い抗EGFR抗体などを行うという考え方もある。
- このようにセカンドライン以降のストラテジーを考えてファーストラインを選択することも大切である。

肝限局型転移に関するエビデンス

- 肝限局転移の治療は，切除を含めた集学的治療を行うことで根治を目指せることも少なくない。肝限局転移の治療方針を決定するうえで必要なのは，ESMOのプラクティスガイドラインでいえばグループ1であるかどうか，最終的に切除が可能かどうかである。
- 切除可能な肝転移症例を対象に行ったEORTC 40983試験では，術前にFOLFOX4療法を

行う群と手術単独群の比較を行っているが，切除可能肝転移に対する術前化学療法によるOSの延長は証明されていない[7]。

- したがって現時点では肝転移の切除が可能と判断されれば，切除を先行させてもよい。
- しかし両葉に多数の転移がある場合や肝内の重要脈管にがんの浸潤がある場合など，明らかに切除不能な場合は長期的に治療を継続する予定でファーストラインの化学療法を選択する。この場合BEVを選択することが合理的である。
- 治療の選択に議論があるのは，切除が最適かどうか判断の難しい病変である。そのような境界領域の病変では縮小効果が高い治療法ほど切除率が向上する。
- これまでのCRYSTAL試験，PRIME試験，OPUS試験などの抗EGFR抗体を使用した臨床試験の結果から勘案すれば，*KRAS*野生型の症例に限るとBEVに比較して抗EGFR抗体の方が縮小率の上乗せ効果が高い傾向にある。したがって，境界領域の病変にはBEVに変えて，抗EGFR抗体を選択してもよいと考えられる。

BEVと抗EGFR抗体の直接比較試験

- 肝限局転移にかかわらず，これまでにファーストライン治療としてBEVと抗EGFR抗体のどちらを使用すべきかについて明らかにした試験結果はない。
- ファーストラインとしてはBEVを使用することを基本としつつも，状況に応じて抗EGFR抗体を使用する場合もある。現在，複数のBEVと抗EGFR抗体を比較する試験が進行中である。
- CALGB/SWOG80405は*KRAS*野生型を対象としたFOLFOX/FOLFIRI＋BEV vs FOLFOX/FOLFIRI＋Cmabの直接比較試験である。
- PEAK試験はFOLFIRI＋BEV vs FOLFIRI＋Pmab，またFIRE-3試験はFOLFIRI＋BEV vs FOLFIRI＋Cmabを比較する試験であるが，この試験においては87例の*KRAS*変異症例に関するサブグループ解析の結果が既に報告されている[8]。
- プライマリーエンドポイントである奏効率はCmab群43.9%，BEV群47.8%（P＝0.83）であり，有意差は認めなかった。また，PFSにも差を認めていない。
- 前述したML18147試験でも*KRAS*変異症例においてはBEVも期待通りの効果を発揮しない可能性が示唆されている。今後の解析結果が大いに期待される。

文　献

1）Van Cutsem E, Nordlinger B, Cervantes A：Advanced colorectal cacner：ESMO Clinical Practice Guidelines for treatment. Ann Oncol 21（Supplement 5）：v93－v97（2010）
2）Kabbinavar FF, Schulz J, McCleod M et al：Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer：results of a randomized phase II trial. J Clin Oncol 23(16)：3697－3705（2005）
3）Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W et al：Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med；350(23)：2335－2342（2004）
4）Saltz LB, Clarke S, Diaz-Rubio E et al：Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer：a randomized phase III study. J Clin Oncol 26(12)：2013－2019（2008）
5）岩崎順子，梁幾　勇，高橋洋一郎ほか：分子標的治療の最前線　臨床研究　アバスチン（ベバシズマブ（BV））結腸直腸癌特定使用成績調査（全例調査）集計結果（第1報）．日本癌治療学会誌（0021－4671）43(2)：259（2008）

6) Arnold D, Andre T, Bennouna J et al : Bevacizumab (BEV) plus chemotherapy (CT) continued beyond first progression in patients with metastatic colorectal cancer (mCRC) previously treated with BEV + CT : Results of a randomised phase Ⅲ intergroup study-TML (ML18147). ASCO annual meeting, Vol. 30 (suppl ; abstr CRA3503) (2012)
7) Nordlinger B, Sorbye H, Glimelius B et al : EORTC liver metastases intergroup randomized phase Ⅲ study 40983 : Long-term survival results. ASCO annual meeting, Vol. 30 (suppl ; abstr 3508) (2012)
8) Stintzing S, Fischer von WL, Decker T et al : FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer-subgroup analysis of patients with KRAS : mutated tumours in the randomised German AIO study KRK-0306. Ann Oncol 23(7) : 1693-1699 (2012)
9) Van Cutsem E, Rivera F, Berry S et al : Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer : the BEAT study. Ann Oncol 20(11) : 1842-1847 (2009)
10) Grothey A, Sugrue MM, Purdie DM et al : Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer : results from a large observational cohort study (BRiTE). J Clin Oncol 26(33) : 5326-5334 (2008)

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ORIGINAL ARTICLE

The treatment outcomes of synchronous and metachronous esophageal squamous cell carcinoma and head and neck squamous cell carcinoma

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Abstract
Background The treatment outcomes of patients with esophageal squamous cell carcinoma (ESCC) and head and neck squamous cell carcinoma (HNSCC) have been poorly documented.
Patients and methods We investigated 50 patients with synchronous and metachronous ESCC and HNSCC. We focused on the treatment results of 20 patients with synchronous ESCC and HNSCC who received simultaneous chemoradiotherapy (CRT).
Results There were 34 patients (68.0 %) with stage 0–I ESCC and 40 patients (80.0 %) with stage II–IV HNSCC. A total of 13 (26.0 %) patients underwent endoscopic mucosal resection and 28 (56.0 %) underwent CRT for ESCC, and 35 (70.0 %) of the patients with HNSCC were treated with CRT. The 5-year overall survival rates of the 50 patients with synchronous and metachronous ESCC and HNSCC was 57.8 %. For the 20 patients with synchronous ESCC and HNSCC who received simultaneous CRT, the CRT was completed in 19 (95.0 %) patients. Although grade 3–4 adverse events were observed in five (25.0 %) patients, there were no therapy-related deaths. Complete responses (CRs) of both ESCC and HNSCC were observed in ten (50.0 %) patients. The 5-year overall survival rate of the 20 patients was 60.0 %. CRs of both ESCC and HNSCC were obtained in seven (58.3 %) patients by using a cisplatin/5-FU regimen ($n = 12$), and in the other three (37.5 %) patients by a platinum-based monotherapy regimen ($n = 8$).
Conclusion The surveillance of double cancer and the use of radical treatment contributed to the favorable outcome of the patients with ESCC and HNSCC. The optimal chemotherapy regimen for simultaneous CRT remains to be determined.

Keywords Multiple cancer · Squamous cell carcinoma · Chemoradiotherapy · Surgery · Chemotherapy regimen · Prognosis

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Introduction

The occurrence of multiple primary cancers in the upper aerodigestive tract is a well-known phenomenon that has been ascribed to "field carcinogenesis." Both alcohol consumption and cigarette smoking are well-established risk factors for esophageal squamous cell carcinoma (ESCC), and these two factors have synergistic effects on the development of ESCC and squamous cell carcinoma of the head and neck (HNSCC) [1–8]. Therefore, careful attention should be paid to the diagnosis and during the treatment of ESCC and HNSCC in order to ensure that only one primary tumor is present.

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 patents 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[a]
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[b]	
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

[a] One case had synchronous gastric cancer and metachronous colon and lung cancer

[b] Two cases had two HNSCCs

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

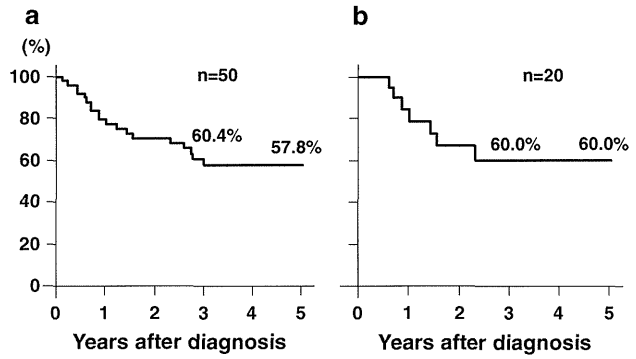

Fig. 1 **a** The survival curves of the 50 patients with synchronous and metachronous ESCC and HNSCC. The 3- and 5-year overall survival rates were 60.4 and 57.8 %, respectively. **b** The survival curves of the 20 patients with synchronous ESCC and HNSCC who received simultaneous CRT. The 3- and 5-year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

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 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 %) 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 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

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 (n = 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 (n = 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 (n = 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 ± 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 multiform 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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References

1. Saeki H, Ohno S, Miyazaki M, Araki K, Egashira A, Kawaguchi H, et al. p53 protein accumulation in multiple oesophageal squamous cell carcinoma: relationship to risk factors. Oncology. 2002;62:175–9.
2. Ito S, Ohga T, Saeki H, Nakamura T, Watanabe M, Tanaka S, et al. p53 mutation profiling of multiple esophageal carcinoma using laser capture microdissection to demonstrate field carcinogenesis. Int J Cancer. 2005;113:22–8.
3. Miyazaki M, Ohno S, Futatsugi M, Saeki H, Ohga T, Watanabe M. The relation of alcohol consumption and cigarette smoking to the multiple occurrence of esophageal dysplasia and squamous cell carcinoma. Surgery. 2002;131:S7–13.
4. Toh Y, Oki E, Ohgaki K, Sakamoto Y, Ito S, Egashira A, et al. Alcohol drinking, cigarette smoking, and the development of squamous cell carcinoma of the esophagus: molecular mechanisms of carcinogenesis. Int J Clin Oncol. 2010;15:135–44.
5. Morita M, Kumashiro R, Kubo N, Nakashima Y, Yoshida R, Yoshinaga K, et al. Alcohol drinking, cigarette smoking, and the development of squamous cell carcinoma of the esophagus: epidemiology, clinical findings, and prevention. Int J Clin Oncol. 2010;15:126–34.
6. Morita M, Saeki H, Mori M, Kuwano H, Sugimachi K. Risk factors for esophageal cancer and the multiple occurrence of carcinoma in the upper aerodigestive tract. Surgery. 2002;131:S1–6.
7. Tachimori Y, Watanabe H, Kato H, Ebihara S, Ono I, Nakatsuka T, et al. Treatment for synchronous and metachronous carcinoma of the head and neck and esophagus. J Surg Oncol. 1990;45:43–5.
8. Morita M, Kuwano H, Ohno S, Sugimachi K, Seo Y, Tomoda H, et al. Multiple occurrence of carcinoma in the upper aerodigestive tract associated with esophageal cancer: reference to smoking, drinking and family history. Int J Cancer. 1994;58:207–10.
9. Murakami S, Hashimoto T, Noguchi T, Hazamada S, Uchida Y, Suzuki M, et al. The utility of endoscopic screening for patients with esophageal or head and neck cancer. Dis Esophagus. 1999; 12:186–90.
10. Scherubl H, von Lampe B, Faiss S, Däubler P, Bohlmann P, Plath T, et al. Screening for oesophageal neoplasia in patients with head and neck cancer. Br J Cancer. 2002;86:239–43.
11. Watanabe A, Hosokawa M, Taniguchi M, Sasaki S. Periodic pharyngolaryngoscopy detects early head and neck cancer and improves survival in esophageal cancer. Ann Thorac Surg. 2003; 76:1699–705.
12. Natsugoe S, Matsumoto M, Okumura H, Ishigami S, Uenosono Y, Owaki T, et al. Multiple primary carcinomas with esophageal squamous cell cancer: clinicopathologic outcome. World J Surg. 2005;29:46–9.
13. Poon RT, Law SY, Chu KM, Branicki FJ, Wong J. Multiple primary cancers in esophageal squamous cell carcinoma: incidence and implications. Ann Thorac Surg. 1998;65:1529–34.
14. UICC International Union Against Cancer. TNM classification of Malignant Tumors, 6th edn.
15. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205–16.
16. Morita M, Yoshida R, Ikeda K, Egashira A, Oki E, Sadanaga N, et al. Advances in esophageal cancer surgery in Japan: an analysis of 1000 consecutive patients treated at a single institute. Surgery. 2008;143:499–508.
17. Matsumoto M, Natsugoe S, Okumura H, Ishigami S, Takatori H, Nakashima H, et al. Clinicopathological and biological characteristics of esophageal squamous cell carcinoma associated with head and neck cancer. Oncology. 2004;67:98–102.
18. Muto M, Hironaka S, Nakane M, Boku N, Ohtsu A, Yoshida S. Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. Gastrointest Endosc. 2002; 56:517–21.

19. Jamieson GG, Mathew G, Ludemann R, Wayman J, Myers JC, Devitt PG. Postoperative mortality following oesophagectomy and problem in reporting its rate. Br J Surg. 2004;9:943–7.
20. Saeki H, Masuda T, Okada S, Ando K, Sugiyama M, Yoshinaga K, et al. Impact of perioperative peripheral blood values on postoperative complications after esophageal surgery. Surg Today. 2010;40:626–31.
21. Saeki H, Ishimura H, Higashi H, Kitagawa D, Tanaka J, Maruyama R, et al. Postoperative management using intensive patient-controlled epidural analgesia and early rehabilitation after an esophagectomy. Surg Today. 2009;39:476–80.
22. Sun K, Matsubara T, Ueda M. Surgical treatment for primary esophageal cancer developing after pharyngolaryngectomy for head and neck cancer. Surgery. 1997;122:15–9.
23. Wind P, Roullet MH, Quinaux D, Laccoureye O, Brasnu D, Cugnenc PH. Long-term results after esophagectomy for squamous cell carcinoma of the esophagus associated with head and neck cancer. Am J Surg. 1999;178:251–5.
24. Wind P, Roullet MH, Douard R, Laccoureye O, Brasnu D, Cugnenc PH. Experience in the treatment of synchronous and metachronous carcinoma of the oesophagus and the head and neck. J Surg Oncol. 2000;73:138–42.
25. Lo OS, Law S, Wei WI, Ng WM, Wong KH, Tong KH, et al. Esophageal cancers with synchronous or antecedent head and neck cancers: a more formidable challenge? Ann Surg Oncol. 2008;15:1750–6.
26. Shinoto M, Shioyama Y, Sasaki T, Nakamura K, Ohura H, Toh Y, et al. Clinical results of definitive chemoradiotherapy for patients with synchronous head and neck squamous cell carcinoma and esophageal cancer. Am J Clin Oncol. 2010;34:362–6.
27. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (radiation therapy oncology group 94–05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol. 2002;20:1167–74.
28. Kato H, Sato A, Fukuda H, Kagami Y, Udagawa H, Togo A, et al. A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCOG9708). Jpn J Clin Oncol. 2009;39:638–43.
29. Nakajima TE, Ura T, Ito Y, Kato K, Minashi K, Nihei K, et al. A phase I trial of 5-fluorouracil with cisplatin and concurrent standard-dose radiotherapy in Japanese patients with stage II/III esophageal cancer. Jpn J Clin Oncol. 2009;39:37–42.
30. Saeki H, Morita M, Nakashima Y, Sonoda H, Hashimoto K, Egashira A, et al. Neoadjuvant chemoradiotherapy for clinical Stage II–III esophageal squamous cell carcinoma. Anticancer Res. 2011;31:3073–8.
31. Saeki H, Kawaguchi H, Kitamura K, Ohno S, Sugimachi K. Recent advances in preoperative hyperthermochemoradiotherapy for patients with esophageal cancer. J Surg Oncol. 1998;69:224–9.
32. Browman GP, Cripps C, Hodson DI, Eapen L, Sathya J, Levine MN. Placebo-controlled randomized trial of infusional fluorouracil during standard radiotherapy in locally advanced head and neck cancer. J Clin Oncol. 1994;12:2648–53.
33. Pfister DG, Laurie SA, Weinstein GS, Mendenhall WM, Adelstein DJ, Ang KK, et al. American Society of Clinical Oncology clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. J Clin Oncol. 2006;24:3693–704.
34. Morita M, Kumashiro R, Hisamatsu Y, Nakanishi R, Egashira A, Saeki H, et al. Clinical significance of salvage esophagectomy for remnant or recurrent cancer following definitive chemoradiotherapy. J Gastroenterol. 2011;46:1284–91.
35. Yoshida R, Morita M, Ando K, Masuda T, Saeki H, Oki E, et al. Salvage esophagectomy after definitive chemoradiotherapy for synchronous double cancers of the esophagus and head-and-neck. Dis Esophagus. 2010;23:59–63.