

Original Article

Treatment Outcomes of Pulmonary Metastases from Head and Neck Squamous Cell Carcinoma

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Although the lung is the most common site of distant metastases from head and neck squamous cell carcinoma (HNSCC), the number of reports about the effects of pulmonary metastasectomy for the treatment of lung metastasis from HNSCC is limited. Metachronous pulmonary metastases were detected in 45 HNSCC patients at Kumamoto University Hospital from 1998 to 2018. Twenty-two patients underwent an operative resection (Ope group) and 23 underwent chemotherapy (Chemo group). The 3-year overall survival (OS) rate and median OS were evaluated. The effects of adjuvant chemotherapy after pulmonary metastasectomy and of new drugs (cetuximab and nivolumab), in the chemo group were also assessed. The 3-year OS rates and median OS were: Ope, 66.1% and 31.5 months; Chemo, 39.7% and 18 months, respectively. In the Ope group, additional recurrences were significantly fewer in the patients who underwent adjuvant chemotherapy post-surgery versus the patients who underwent surgery alone ($p=0.013$). In the Chemo group, the 3-year OS rate of the patients who received new drugs was significantly better than that of the patients who did not ($p=0.021$). Adjuvant chemotherapy after pulmonary metastasectomy may be a preferable treatment option for preventing recurrences. Cetuximab and nivolumab have a potential to improve OS.

Key words: pulmonary metastasis, head and neck squamous cell carcinoma, pulmonary metastasectomy, adjuvant chemotherapy

The lung is the most common site of distant metastases, accounting for 59-76% of all distant metastases from head and neck carcinoma (HNC) [1-3]. The reported rate of pulmonary metastasis from HNC has ranged from 6.0% to 9.1% [4, 5]. The life expectancy of patients with distant metastasis from HNC has been generally short, and 90% of patients with head and neck squamous cell carcinoma (HNSCC) die within 12 months after the diagnosis of distant metastasis [6, 7]. The recent introduction of new drugs such as molecular targeting agents (*i.e.*, cetuximab) and immune check-

point inhibitors (*i.e.*, nivolumab) has resulted in a statistically significant improvement in the overall survival (OS) of patients with recurrent/metastatic HNC [8, 9], and given this situation, there has been an increase in the application of pulmonary metastasectomy [10-18]. Isolated pulmonary metastases from HNC have long been regarded as potentially curable via surgical resection [4]. At our institution, our basic strategy for treating pulmonary metastases from HNC is to surgically resect the metastatic lesions even in cases with multiple lesions if possible.

We conducted the present study to evaluate and

compare the treatment outcomes and prognoses of patients with metachronous pulmonary metastases from HNSCC after radical treatments with curative intent with those of patients who underwent a pulmonary metastasectomy, patients with unresectable lesions, patients who underwent adjuvant chemotherapy after pulmonary metastasectomy, and patients who did not undergo a pulmonary metastasectomy. The effectiveness of cetuximab and nivolumab treatments was also evaluated.

Patients and Methods

We retrospectively analyzed the cases of 45 HNSCC patients in whom metachronous pulmonary metastases were detected during the 21-year follow-up period from 1998 to 2018 after they had undergone radical treatments with curative intent at Kumamoto University Hospital (Kumamoto, Japan). Patients who also had distant metastases at locations other than the lung and patients who developed pulmonary metastases before the completion of treatment for the primary lesions (with the exception of the consecutive oral administration of S-1) were excluded from the study.

The clinical characteristics of the 45 patients are summarized in Table 1. The patients were 43 men and two women, and the median age at the time of treatment for the primary lesions was 63 years (range 36-82 years). The median follow-up period of the surviving patients after the detection of pulmonary metastasis was 26 months (range 4-146 months). The locations of the primary tumors were the nasal cavity or paranasal sinuses (n=3), oral cavity (n=7), nasopharynx (n=3), oropharynx (n=7), hypopharynx (n=15), and larynx (n=10). The primary tumor classifications were stage I (n=1), stage II (n=4), stage III (n=9), and stage IV (n=31). For treatment of the primary tumor, 29 patients underwent surgical therapy, 15 underwent concurrent chemo (bio-) radiotherapy, and one patient underwent radiotherapy only.

The regimens of concurrent chemo (bio-) radiotherapy for the primary lesions included docetaxel (DTX) + cisplatin (CDDP) + fluorouracil (5-FU) (n=9), CDDP + 5-FU (n=5), and cetuximab (n=1). The surgical therapy regimens included surgery alone (n=14), surgery followed by radiotherapy (n=10), and surgery followed by chemoradiotherapy (n=5).

After treatment of the primary HNSCCs, the patients

Table 1 Characteristics of HNSCC patients with metachronous pulmonary metastasis

Age (median)	36-82 years (63 years)
Sex	
Male	43 (96%)
Female	2 (4%)
Follow up duration (median)	4-146 months (26 months)
Primary lesion	
Nasal cavity/Paranasal sinus	3 (7%)
Oral cavity	7 (16%)
Nasopharynx	3 (7%)
Oropharynx	7 (16%)
Hypopharynx	15 (33%)
Larynx	10 (22%)
Stage	
I	1 (2%)
II	4 (9%)
III	9 (20%)
IV	31 (69%)
Treatment of primary lesion	
Operation	29 (64%)
Chemo (Bio-) radiotherapy	15 (33%)
Radiotherapy	1 (2%)

HNSCC, head and neck squamous cell carcinoma.

were generally followed up via computed tomography (CT) or ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT every 3-6 months during the first 2 years and every 6-12 months thereafter. The date of the diagnosis of pulmonary metastases was defined as the time when radiologists observed one or more suspicious pulmonary lesions on CT or FDG-PET/CT. In some patients, a CT-guided needle biopsy was performed to confirm the diagnosis. Primary lung carcinoma was distinguished from pulmonary metastasis based on radiological findings, pathological diagnostic parameters, and clinical features.

Among the 45 patients, pulmonary metastasis was detected in 15 during the first follow-up year after the completion of the treatment for their primary lesions, 19 during the second year, and 11 after 2 years (range 2-76 months).

In all cases, the treatment policies for metachronous pulmonary metastases were determined during cancer board meetings with otolaryngologists, radiologists, and general surgeons. A pulmonary metastasectomy was performed in patients whose metastatic lesions appeared to have been resected safely and completely. Systemic chemotherapy was performed from the beginning in patients for whom surgery could not be performed. The chemotherapy regimens were also deter-

mined during the aforementioned cancer board meetings. Patients who declined or were not deemed suitable for surgical resection or chemotherapy received only best supportive care.

The metastatic pulmonary lesion treatment strategies used are shown in Table 2. Twenty-two patients underwent a surgical resection (Ope group) and the other 23 underwent chemotherapy (Chemo group). The median ages were 62 years (range 38-75 years) in the Ope group and 65 years (range 36-82 years) in the Chemo group. The number of pulmonary metastatic lesions detected by CT and PET-CT in the Ope group was significantly lower than the numbers in the Chemo group ($p < 0.01$). In the Ope group, the number of metastatic lesions in the resected lung specimens matched the number estimated with the use of CT and/or PET-CT before the surgeries. Though most of the patients in the Ope group had a single metastatic lesion, one patient had 3 lesions and 2 patients each had 2 pulmonary metastatic lesions. These multiple metastatic lesions were resected respectively with a wedge or segmental resection or lobectomy.

The median sizes of the largest pulmonary metastatic lesion in each patient were 13 mm (range 8-27 mm) in the Ope group and 12 mm (range 6-60 mm) in the Chemo group. There were no significant between-group differences in age, clinical stage, or the size of largest pulmonary metastatic lesion, *i.e.*, the parameters other than the number of pulmonary metastatic lesions listed in Table 2.

In the Ope group, some patients received chemo-

therapy as adjuvant therapy after surgical resection, at the discretion of the attending physician. There were 6 patients who received chemotherapy (the adjuvant group) and 16 who did not (the non-adjuvant group). The adjuvant chemotherapy included CDDP + 5-FU + cetuximab, paclitaxel (PTX) + cetuximab, CDDP + 5-FU, PTX, DTX, and S-1.

In Japan, cetuximab was approved for treating HNC in December 2012, and nivolumab was approved in April 2017. Accordingly, the Chemo group included 16 patients who had received one or both of these drugs as of March 2020 (the "recent group") and 7 patients who had not received either of these drugs (the "preceding group").

The OS period was defined as the interval from the date of the patient's diagnosis of pulmonary metastasis to the date of the patient's last follow-up or death. We calculated the OS rate by the Kaplan-Meier method. The log-rank test was used to compare survival between the groups. Statistical analyses of other parameters were performed using the unpaired *t*-test and χ^2 -test (StatView 5.0 for Windows; SAS Institute, Cary, NC, USA). Probability *p* values < 0.05 were accepted as significant.

This study was approved by the Bioethics Committee of Kumamoto University (approval no. 2338), and written informed consent to use clinical data obtained during the course of their diagnosis and treatment was obtained from all patients. This study was performed in accordance with the principles of the Declaration of Helsinki.

Table 2 Clinical characteristics by treatment modality for metastatic pulmonary lesion of HNSCC patients

	Ope group	Chemo group
Number of patients	22	23
Age (median)	38-75 years (62 years)	36-82 years (65 years)
Stage		
I	1 (5%)	0
II	0	4 (17%)
III	6 (27%)	3 (13%)
IV	15 (68%)	16 (70%)
Number of pulmonary metastasis*		
1	18 (82%)	6 (26%)
2	2 (9%)	3 (13%)
≥ 3	1 (5%)	14 (61%)
Size of pulmonary metastasis	8-27 mm (13 mm)	6-60 mm (12 mm)

HNSCC, head and neck squamous cell carcinoma; Ope, operation; Chemo, chemotherapy

*: There is a significant difference between 2 groups.

Results

The median OS periods and the 3-year OS rates were as follows. All patients: 26 months (range 4-146 months) and 53.1%; Ope group: 31.5 months (range 6-146 months) and 66.1%; Chemo group: 18 months (range 4-54 months) and 39.7%. The OS of the Ope patients was significantly better than that of the Chemo patients ($p=0.042$, Fig. 1).

In the Ope group, the median OS periods were 25.5 months (range 6-64 months) in the adjuvant group ($n=6$) and 31.5 months (range 7-146 months) in the non-adjuvant group ($n=16$). There were no significant differences in the 3-year OS rates between the adjuvant (83.3%) and non-adjuvant groups (62.5%) ($p=0.386$, Fig. 2).

Thirteen of the 22 patients in the Ope group showed recurrent metastases in the lung or other lesions after pulmonary metastasectomy (1 of the 6 patients in the adjuvant group and 12 of the 16 in the non-adjuvant group). There was a significant difference in the recurrence rate between the adjuvant and non-adjuvant groups ($p=0.013$).

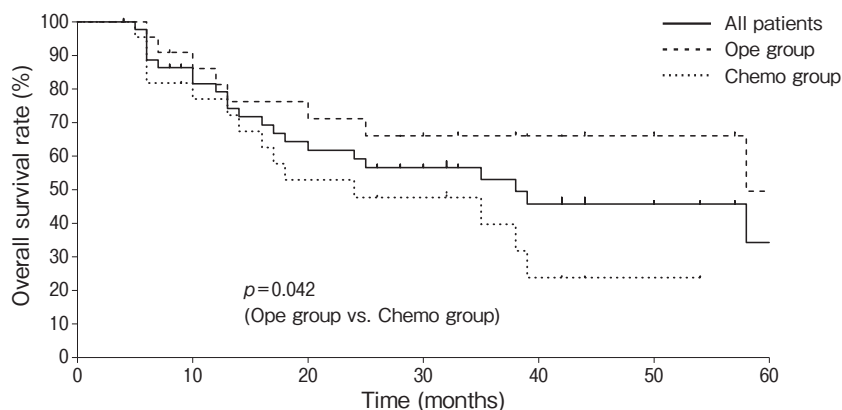
In the Chemo group, the median OS periods were 17 months (range 5-38 months) in the patients who were not treated with cetuximab or nivolumab (the preceding group) ($n=7$) and 22 months (range 4-54 months) in the patients who were treated with cetuximab or nivolumab or both (the recent group) ($n=16$).

The 3-year OS rate was significantly better in the recent group (52.0%) than in the preceding group (14.3%) ($p=0.021$, Fig. 3).

Discussion

Pulmonary metastasectomy is a recognized treatment option for a number of different cancers including colorectal cancers, sarcoma, melanoma, and renal cell carcinoma [19]. In cases of HNC, the number of reports on the usefulness of pulmonary metastasectomy has been increasing [10-18]. The reported 5-year OS rate after pulmonary metastasectomy has ranged from 35.7% to 59.4% for all histopathological carcinomas [10-15] and from 19.4% to 28.6% for squamous cell carcinomas (Table 3) [11, 16-18]. Although the follow-up period in our present patient series was relatively short, the 3-year OS rate after pulmonary metastasectomy was excellent (66.1%). This result suggests that pulmonary metastasectomy should be considered as a treatment option in appropriate cases.

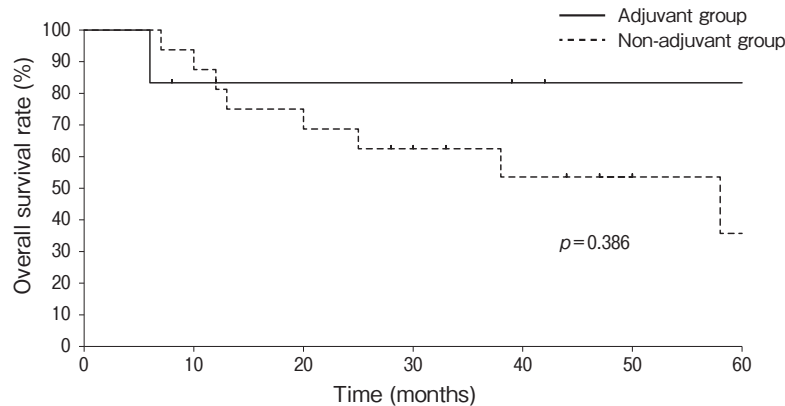
The usefulness of adjuvant chemotherapy after pulmonary metastasectomy in cases of colorectal carcinoma has been described [20,21]. With regard to HNC, only one published study investigated the effects of adjuvant chemotherapy after pulmonary metastasectomy [14]. In that study, the 5-year OS rate in the adjuvant chemotherapy group ($n=20$) did not differ significantly from that in the surgery-alone group ($n=38$). In



	Number of patients	OS period (median)	3-year OS rate
All patients	45	4-146 months (26 months)	53.1%
Ope group	22	6-146 months (31.5 months)	66.1%
Chemo group	23	4-54 months (18 months)	39.7%

Ope, operation; Chemo, chemotherapy; OS, overall survival.

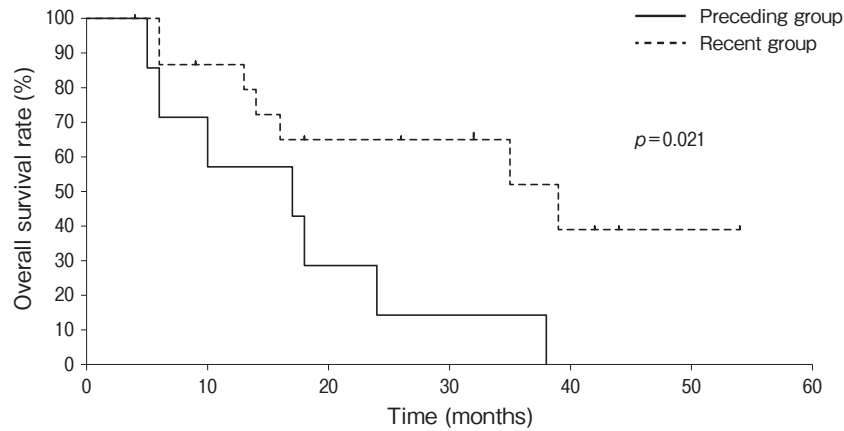
Fig. 1 Overall survival (OS) curves for all patients, those in the Ope (operation) group, and those in the Chemo (chemotherapy) group.



	Number of patients	OS period (median)	3-year OS rate
Adjuvant group	6	6-64 months (25.5 months)	83.3%
Non-adjuvant group	16	7-146 months (31.5 months)	62.5%

OS, overall survival.
 Adjuvant group: patients who received chemotherapy after pulmonary metastasectomy;
 Non-adjuvant group: patients who did not received chemotherapy after pulmonary metastasectomy

Fig. 2 OS curves for the adjuvant and non-adjuvant subgroups of the Ope group. Adjuvant group: patients treated with chemotherapy after pulmonary metastasectomy; Non-adjuvant group: patients who were not treated with chemotherapy after pulmonary metastasectomy.



	Number of patients	OS period (median)	3-year OS rate
Preceding group	7	5-38 months (17 months)	14.3%
Recent group	16	4-54 months (22 months)	52.0%

OS, overall survival.
 Preceding group: patients who did not use cetuximab or nivolumab;
 Recent group: patients who used cetuximab or nivolumab or both drugs

Fig. 3 OA curves for the preceding and recent subgroups of the Chemo group. Preceding group: patients who were not treated with cetuximab or nivolumab. Recent group: patients who were treated with cetuximab or nivolumab or both drugs.

the present investigation, although there was no significant difference in the 3-year OS rate between the adjuvant and non-adjuvant groups, the recurrence rate was significantly better in the adjuvant group than in the non-adjuvant group. These results suggest that adjuvant

chemotherapy after pulmonary metastasectomy may prevent additional metastases. Because the number of patients in the present study was relatively small (n = 45), further studies including more patients are necessary.

The OS rate of the Chemo group was significantly

Table 3A Treatment outcomes of pulmonary metastasis from HNC

Author	Year	Number of patients	5-year OS rate
Chen F ¹⁰	2008	20 (SCC 10)	59.4%
Haro A ¹¹	2010	25	50%
Yotsukura M ¹²	2015	34 (SCC 19)	57.9%
Hosokawa S ¹³	2016	16 (SCC 7)	46%
Nakajima Y ¹⁴	2017	58 (SCC 49)	35.7%
Oki T ¹⁵	2018	77 (SCC 58)	54%

HNC, head and neck carcinoma; OS, overall survival

Table 3B Treatment outcomes of pulmonary metastasis from HNSCC

Author	Year	Number of patients	5-year OS rate
Winter H ¹⁶	2008	55	19.4%
Shiono S ¹⁷	2009	114	26.5%
Daiko H ¹⁸	2010	33	43% (3-year)
Haro A ¹¹	2010	15	28.6%
Miyamaru S	2020	22	66.1% (3-year)

HNSCC, head and neck squamous cell carcinoma; OS, overall survival

worse than that of the Ope group in this study. Although this result may be due mainly to the large number of lung metastatic lesions in the Chemo group, the existence of distant metastatic lesions in sites other than the lung and the general condition of the patient should also be considered in decisions regarding whether surgery should be performed. Patient selection bias in addition to the number of metastatic lesions in the lung might thus have affected the difference in the OS rate that we observed between the present Ope and Chemo groups.

With regard to HNSCC recurrence or metastasis, median OS periods ranging from 7.4 to 10.1 months have been reported in patients who underwent chemotherapy after the detection of recurrence [8]. In the present study the median OS period after the detection of pulmonary metastasis in the Chemo group was 18 months. This relatively good OS may have been due to the use of cetuximab or nivolumab or both in 16 of the 23 Chemo group cases. In the patients treated with cetuximab or nivolumab or both, the median OS period after the detection of pulmonary metastasis was 22 months. In addition, the 3-year OS rate in the recent group was significantly better than that in the preceding group. These results indicate that cetuximab and nivolumab were effective in cases of pulmonary

metastasis of HNSCC.

A study limitation was the difficulty in distinguishing pulmonary metastases of HNSCC from primary lung squamous cell carcinoma, which was due to similarities in their histopathological and radiographical presentations and a lack of useful markers. Many patients with HNSCC have a history of heavy smoking, which is also a risk factor for lung cancer. One report revealed that the incidence of lung cancer in HNC patients was 3-6 times higher than that in the normal population [22].

Recent studies indicate that the expression of epidermal growth factor receptor mutation in squamous cell carcinoma is 90% in HNC patients, whereas in lung cancer patients, it is only 0-13%; this expression may therefore be a useful marker for distinguishing between HNC and lung cancer [8, 23, 24]. In addition, analyses of the loss of heterozygosity [25] and immunostaining patterns [26] have been used to distinguish between pulmonary metastasis from HNC and primary lung cancer. The prognoses after the pulmonary resection of both metastasis from HNC and primary lung cancer were studied [27]; the median OS periods after the resection of molecularly defined primary lung cancer (23.1 months) and pulmonary metastasis from HNSCC (25.1 months) did not differ significantly. That result suggests that differences between pulmonary metastasis of HNSCC and primary lung squamous cell carcinoma were unlikely to have influenced our present findings.

In conclusion, the surgical resection of metachronous pulmonary metastases from HNSCC is a reliable treatment option in appropriate patients. Adjuvant chemotherapy after pulmonary metastasectomy may be preferable for preventing recurrences. Cetuximab and nivolumab may have improved the overall survival of the patients with metachronous pulmonary metastases from HNSCC in this study. It may be necessary to determine the optimal combination and order of administration of 'old' and 'new' drugs for the treatment of metachronous pulmonary metastases from HNSCC.

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