

Survival Outcomes of Complete Pulmonary Metastasectomy for Head and Neck Squamous Cell Carcinomas

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Purpose: Metastatic head and neck squamous cell carcinoma (HNSCC) is relatively poor; however, depending on the selected cases, pulmonary metastasectomy can be a practical therapeutic option. This study aimed to identify the outcomes of complete metastasectomy based on each primary site and to investigate unfavorable prognostic factors.

Patients and Methods: We used the database from the Metastatic Lung Tumour Study Group of Japan. Between November 1980 and April 2017, 231 patients were deemed eligible. According to anatomy and the current epidemiology of HNSCC, the patients were divided into three groups: nasopharynx, oropharynx, and salivary gland (n = 40, Group 1), oral cavity, tongue, and paranasal sinuses (n = 69, Group 2), and larynx and hypopharynx (n = 122, Group 3).

Results: The 5-year overall survival after complete pulmonary metastasectomy was 58.5%, 25.0%, and 46.9% in G1, 2, and 3, respectively ($p < 0.01$). Multivariate analyses revealed unfavourable prognostic factors to be G2, and pathological maximum diameter was >20 mm. Therefore, on dividing group 1 and 3 with or without diameter, the 5-year overall survival was significantly worse in HNSCC with a diameter >20 mm (n = 74) than that in the remnant (n = 88; 61.9% vs 35.5%; $p < 0.01$).

Conclusion: According to the multi-institutional Japanese data, pulmonary metastasectomy from HNSCC indicates a potential survival benefit. Oral cavity, tongue, and paranasal sinuses cancer, and tumour size (>20 mm) were poor prognostic factors for pulmonary metastasectomy from head and neck cancer.

Keywords: pulmonary metastasectomy, head and neck squamous cell carcinoma, pulmonary metastasis, survival outcomes

Introduction

Head and neck cancers (HNC) are common and have high mortality rates; furthermore, squamous cell carcinomas account for 90% of these cancers.¹ Despite their small-scale and retrospective nature, several studies have proposed that head and neck squamous cell carcinomas (HNSCC), which encompass those in oral cavity, tongue, floor of the mouth, pharynx, larynx, oropharynx, nasopharynx, paranasal sinus, and salivary glands, have biological behaviors different from those of other histological types of HNC and should be separately considered because HNSCC are likely recur within 2 years after metastases resection.^{2,3} Many factors have been reported to show association with a poor prognosis of the patients who underwent PM from HNSCC, including incomplete resection,⁴⁻⁶ disease-free interval (DFI) <12 months,^{3,7} or <24 months,^{4,8} age of >60 ⁹ or >55 ⁴ lymph node metastases in the primary site,^{5,6} male,² and oral cavity involvement.^{6,8} However, these studies had small-scale and retrospective designs.

On the other hand, in 2010, Ang et al first reported that human papillomavirus (HPV) is strongly associated with an independent prognostic factor for oropharyngeal cancer survival.¹⁰ Recently, the American Joint Committee on Cancer, eighth edition, reported an update regarding cancer staging; it suggested that a separate staging algorithm should be used for high-risk HPV in oropharynx cancer.¹¹ Additionally, it suggested that there is a strong relationship between Epstein–Barr virus (EBV) and nasopharynx cancer. HPV-positive oropharyngeal cancers are associated with sexual behavior, occur more often in white men and individuals who do not use tobacco or alcohol, and may occur in a younger population.¹² These cancers differ in terms of cell abnormality, genomic origin, and likelihood to become cancerous. Furthermore, these differences are probably caused by the virus or tobacco use, and the prognosis after pulmonary metastasectomy (PM) indicates that they might be caused by the site of origination (head and neck). However, few studies have assessed the therapeutic efficacy of PM based on each primary site.

The PM for HNSCC with pulmonary metastases has inadequately contributed to an ideal improvement of survival outcomes in the histological and general remarks. Therefore, it is clinically crucial on how to define patients who will benefit for PM. We previously reported that the survival of men with oral cavity cancer that metastasized was significantly worse, but the number of cases at each site in the head and neck is quite small.⁶ With advancements in radiological imaging and the clinical data accumulated in Japan, the diagnosis and management of pulmonary metastases have developed significantly during the past decade. Therefore, we aimed to evaluate a large-scale cohort with HNSCC to retrospectively assess the surgical outcomes based on each primary site and investigate the prognostic factors.

Materials and Methods

Study Design and Patients

We established the Metastatic Lung Tumour Study Group of Japan (MLTSG-J), which consists of 25 thoracic facilities in Japan. Our database includes patient data during the period between July 1984 and March 2017, and it is updated annually. The database was queried to find all patients who underwent metastasectomy at each hospital. The indications for metastasectomy were previously published and left to the discretion of the physician at each institution. The specific clinical data for this study were as follows: R0 resection was achieved; complete, registered data; HNSCC metastases histologically proven by pathological experts in a morphological manner; and no residual tumor in extrathoracic lesions or at the primary site. A total of 231 patients who underwent PM were enrolled during this period (Figure 1A). As previously reported, the general indications for surgical resection followed Thomford's criteria. For more information regarding the reliability and registered status, the MLTSG database, which has been described previously, was consulted.⁶

The medical records were reviewed for the following data: patient demographics (age, sex); anatomic site of the primary tumor; treatment for initial HNSCC; disease-free interval (DFI); pathological maximum diameter; the number of

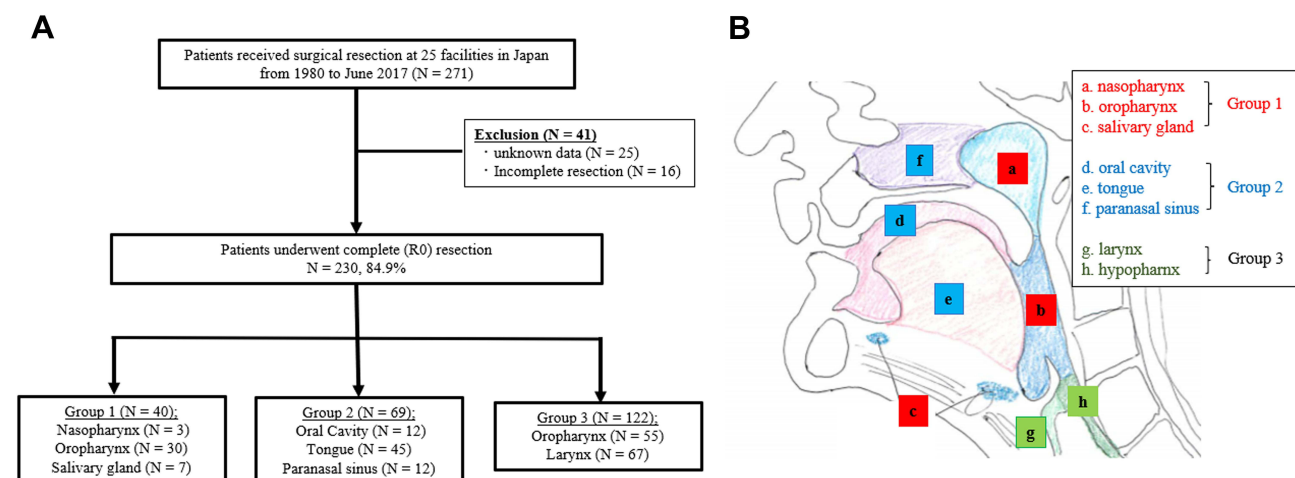


Figure 1 Patient flow (A) and our classification illustrated by head and neck anatomy (B).

metastasized tumors; side; procedures; patient outcomes; duration of follow-up; disease-free survival (DFS); overall survival (OS); and the cause of death. Relapse was defined as the time of radiographic detection. DFI was defined as the time interval between the primary initial treatment and the date of pulmonary relapse.

The study protocol was approved by the Institutional Review Board of Aichi Cancer Center Hospital (2018-1-217). This study was conducted in accordance with the Declaration of Helsinki. Because the anonymity of individual patients was ensured, preoperative informed consent was waived. All patient records and clinical information were anonymized before analysis.

Study Population

The most frequent primary site of HNSCC was larynx ($n = 67$, 29.0%), followed by hypopharynx ($n = 55$, 23.8%), tongue ($n = 45$, 19.5%), oropharynx ($n = 30$, 13.0%), paranasal sinus ($n = 12$, 5.2%), oral cavity ($n = 12$, 5.2%), salivary gland ($n = 7$, 3.0%), and nasopharynx ($n = 3$, 1.3%). Then, we visually divided the patients into three groups according to the anatomy, epidemiology, and functional characteristics, namely, Group 1: Nasopharynx, Oropharynx, and Salivary gland ($n = 40$); Group 2: Oral cavity, tongue, and paranasal sinus ($n = 69$); Group 3: hypopharynx and larynx ($n = 122$) (Figure 1B).

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS; version 25.0; SPSS Institute Inc., Chicago, IL, USA). Categorical variables were compared using the chi-square test. Differences among the three groups were calculated using the Kruskal–Wallis test. Survival rates were analyzed using the Kaplan–Meier method, and survival among the patient groups was compared using a Log rank test. A cox proportional hazards regression analysis was performed to investigate the factors related to survival. Hazard ratios were also derived. Covariates with $p < 0.10$ in the univariable analysis were included in the multivariable model; $p < 0.05$ was considered statistically significant.

Results

Patient Characteristics

Patient characteristics of the 231 patients are summarized in Table 1. The median pathological maximum diameter and DFI from initial treatment to PM was 20.0 mm (range; 0.2 to 270), and 20.2 months (range; 1 to 144), respectively. The proportion of male patients in G1 (90.0%) was as high as that in G2 (90.0%), and significantly higher than that in G3 (69.6%) ($p < 0.01$). The most common initial treatment of primary sites was surgery, and these distributions were 65.0% in G1, 87.0% in G2, and 83.8% in G3, respectively, but a significant difference was not found ($p = 0.11$). A significant

Table 1 Characteristics of Patients

Variables	Group 1 (n = 40)	Group 2 (n = 69)	Group 3 (n = 122)	p
Age (years)	63	60	65	0.15
(mean, range)	31–78	23–83	42–91	
Male sex (number, %)	36, 90.0%	48, 69.6%	114, 93.4%	< 0.01*
Treatment for primary site				0.11
Surgery (number, %)	26, 65.0%	60, 87.0%	110, 83.8%	
Chemotherapy	8, 20.0%	4, 5.8%	12, 9.8%	
Radiotherapy or ablation	1, 2.5%	1, 1.4%	2, 1.6%	
Unknown	5, 12.5%	4, 5.8%	7, 5.8%	
Disease-free interval (month)	33.6 ± 28.8	20.5 ± 14.7	27.1 ± 20.2	0.02*
Pathological maximum diameter (mm)	24.2 ± 28.9	30.8 ± 37.3	27.8 ± 24.3	0.09
Procedures (number, percent)				0.21
Sublobar	28, 70.0%	41, 59.4%	64, 52.5%	
Lobectomy or more	12, 30.0%	28, 40.6%	58, 47.5%	

Note: * $p < 0.05$ indicates significant values.

difference was observed in DFI between three groups, but not in age, initial treatment, and pathological maximum diameter (Table 1). In therapeutic management for pulmonary metastases, sublobar resection was more frequent in G1 (70%), followed by in G2 (59.4%), and in G3 (52.5%). There was no significant difference for PM between three groups ($p = 0.21$).

Survival Outcomes After Pulmonary Metastasectomy

One-hundred three patients (44.6%) died during the study period. The 2-year and 5-year OS were 67.6% and 42.5%, respectively. According to our categories, those were 58.5% in G1, 25.0% in G2, and 46.9% in G3, respectively. A significant difference was obtained between G1 and G2 ($p < 0.01$), G2 and G3 ($p < 0.01$), but not between G1 and G3 ($p = 0.16$) (Figure 2A). The survival outcomes according to each primary site are presented in Table 2.

The 5-year OS after treatments of primary HNSCC were 84.3% in G1, 42.1% in G2, and 60.9% in G3. A significant difference was obtained between G1 and G2 ($p < 0.01$), G2 and G3 ($p < 0.01$), but not between G1 and G3 ($p = 0.15$) (Figure 2B).

On univariate analyses, pathological maximum diameter (>20 mm) and G2 had a statistically significant impact on a poor OS (both $p < 0.01$) (Table 2). Multivariable analysis of potential prognostic factors also revealed that pathological maximum diameter (>20 mm) and G2 had a statistically significant impact on a poor OS (both $p < 0.01$) (Table 3).

Actual Survival Outcomes

Among them, patients who had a pathological maximum diameter (>20 mm) in G2 corresponded to 36 patients (48.0%). The OS was significantly poorer in those enrolled patients than other HNSCC (45.8% vs 23.5%, $p < 0.01$) (Figure 3A). From G1 and G3, there were 74 patients (45.7%) who had a pathological maximum diameter (>20 mm). In G1 and G3, the 5-year OS was significantly higher in the selected patients than in the others ($n = 88$) (61.9% vs 35.5%, $p < 0.01$), and equivalent to that in G2 ($p = 0.11$) (Figure 3B).

Discussion

We aimed to provide additional information regarding PM for HNSCC by performing a retrospective multi-institutional study to assess survival outcomes. It has been 10 years since the last publication regarding PM for HNSCC as assessed by our group.⁶ Our data demonstrated that outcomes based on each primary site could be differentiated; this was attributed to our further accumulation of clinical data.

The present study revealed that a pathological maximum diameter of >20 mm, and HNSCC in oral cavity, tongue, and paranasal sinus were the poorer prognostic factors. The patients who were associated with those factors comprised 15.6% among all HNSCC cases, and 5-year OS in those patients was significantly poorer than the other cases ($p < 0.01$). In

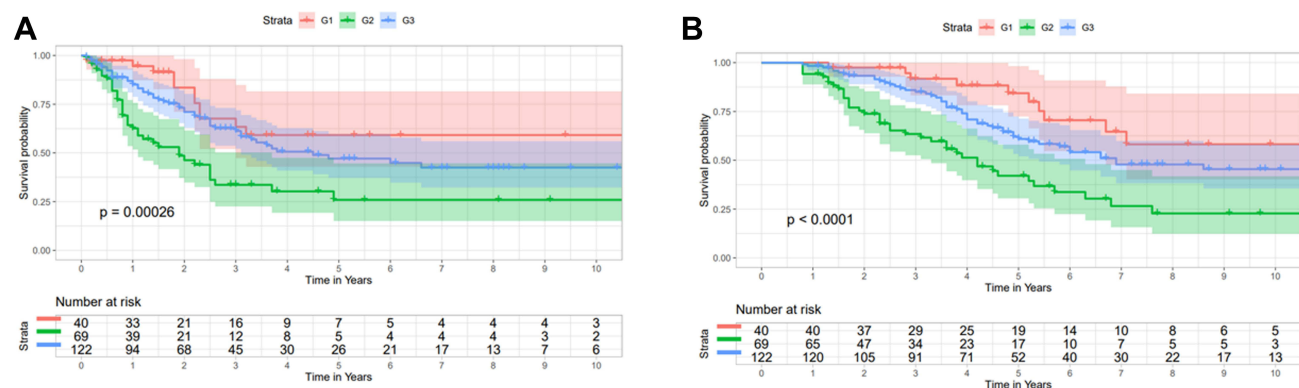


Figure 2 Kaplan-Meier survival curve with 95% confidence interval. **(A)** Overall survival of patients with head and neck squamous cell carcinomas patients after pulmonary metastasectomy. Red line: nasopharynx, oropharynx, and salivary gland (G1, $n = 40$); green line: Oral cavity, tongue, and paranasal sinus (G2, $n = 69$); and blue line: hypopharynx and larynx (G3, $n = 122$). **(B)** Overall survival of patients with head and neck squamous cell carcinomas patients after the date of treatment of primary cancers. Red line: nasopharynx, oropharynx, and salivary gland (G1, $n = 40$); green line: Oral cavity, tongue, and paranasal sinus (G2, $n = 69$); and blue line: hypopharynx and larynx (G3, $n = 122$).

Table 2 Univariate Analysis for Overall Survival and 5-Year Overall Survival

	Overall Survival		
	N = 231	5 Years (%)	P value
Age			0.08
> 60	123	50.3	
≤ 60	108	36.4	
Sex			0.56
Male	198	42.5	
Female	33	40.9	
Primary site			< 0.01*
Group 1	40		
Nasopharynx	3	NA	
Oropharynx	30	51.9	
Salivary gland	7	55.6	
Group 2	69		
Oral Cavity	12	36.7	
Tongue	45	24.9	
Paranasal sinus	12	14.3	
Group 3	122		
Hypopharynx	55	34.6	
Larynx	67	57.2	
DFI (months)			0.09
≤ 24	131	37.1	
> 24	100	50.0	
Pathological maximum diameter (mm)			< 0.01*
≤ 20	121	52.6	
> 20	110	31.6	
Procedures			0.17
Sublobar	134	44.8	
Lobectomy or more	95	40.3	
Unknown	2		
Side			0.63
Either	212	42.1	
Bilateral	19	44.9	
Number			0.58
Solitary	181	42.4	
Multiple	50	42.6	

Note: * $p < 0.05$; indicates significant values.

Abbreviations: DFI, disease-free interval; NA, not available.

addition, when the patients in G1 and G3 were divided into the patients with pathological maximum diameter of >20 mm and others, the 5-year OS was significantly poorer in those patients ($p = 0.01$). Furthermore, this was equivalent to that in the oral cavity, tongue, and paranasal sinus cancers ($p = 0.11$). These results indicated that patient selection could lead to

Table 3 Multivariate Analysis for Overall Survival

Variables	HR	95% CI	P
Age (≤ 60)	1.38	0.93–2.05	0.10
Maximum tumour diameter (> 20 mm)	1.97	1.32–2.94	< 0.01*
Group 2	2.03	1.35–3.03	< 0.01*
Disease free survival (≤ 24 months)	1.43	0.95–2.14	0.61

Note: * $p < 0.05$ indicates significant values.

Abbreviations: HR, hazard ratio; CI, confidence intervals.

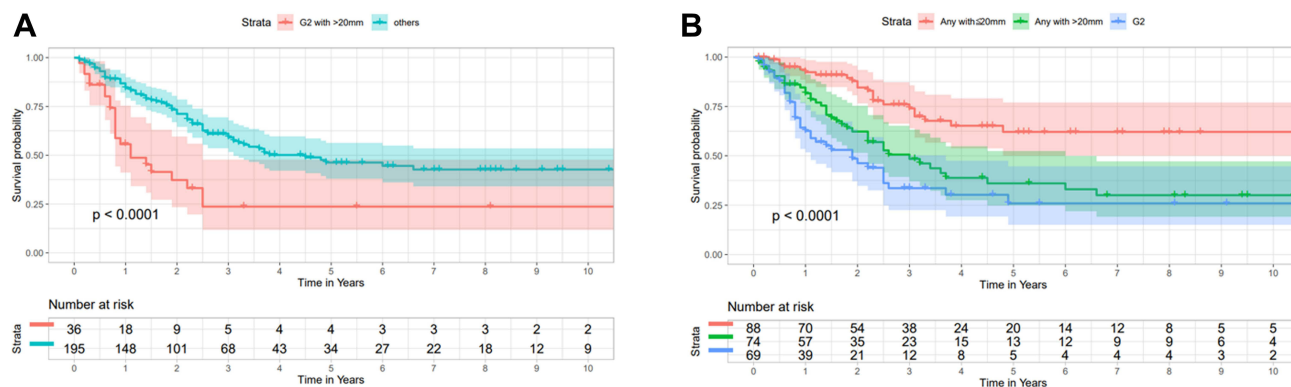


Figure 3 Kaplan–Meier survival curve with 95% confidence interval. **(A)** Overall survival of patients with head and neck squamous cell carcinomas patients after pulmonary metastasectomy. Red line: oral cavity, tongue, and paranasal sinus with pathological maximum diameter (> 20 mm) (n = 36); green line; others (n = 195). **(B)** Overall survival of patients with head and neck squamous cell carcinomas patients after pulmonary metastasectomy. Red line: any head and neck sites excluding oral cavity, tongue, and paranasal sinus with a pathological maximum diameter (≤ 20 mm) (n = 88); green line: any head and neck sites excluding oral cavity, tongue, and paranasal sinus with a pathological maximum diameter (> 20 mm) (n = 74); blue line: oral cavity, tongue, and paranasal sinus (n = 69).

improve survival outcomes after PM even in G1 and G3. In addition, the overall survival of pulmonary resection for pulmonary metastases was similar to those from the date of treatment for primary HNSCC, which was able to prove that it had a much influence of Primary site. Thus, it was revealed that the degree of malignancy of primary site for HNSCC was compatible with the surgical outcomes of pulmonary metastasectomy.

The 5-year OS in this study was 40.9% for all patients with HNSCC, which is relatively prolonged compared with the rates reported previously (4.0–57.6%).^{13,14} Notably, we provided better outcomes in our new series than our previous results (26.5%) by a larger multi-centre retrospective study encompassing an accumulated 231 HNSCC cases after complete PM and could be quite robust of observed benefit of PM.⁶ The relatively improved survival of the present cohort in comparison with the prior cohort and those from Japanese data might be due to improvements in the frequent chest high-resolution CT follow-up after initial treatment and the management of advanced cancers, which has led to greater detection rates of even small lesions and provided a benefit of PM by patient selection.

However, local treatment of the metastasized organs including lung is not plausible because such metastases indicate systemic disease. Winter et al examined the clinical course after treatment of primary sites of HNSCC for 5135 patients with HNC and reported that the salivary gland had the highest distribution rate of pulmonary metastases (13.0%), followed by the hypopharynx (10.8%), oropharynx (6.5%), larynx (5.5%), nasopharynx (4.8%), and oral cavity (4.6%); however, only a few cases (range, 0.4–3.3%) were eligible to receive PM at various primary sites.¹⁵ Of note, ‘surgeons’ experiences tend to assume that very few selected patients with metastases could survive if they could be removed.¹⁶ Therefore, PM intended to cure have to reverse a lethal component of disease. Further investigation should be needed to dissolve the questions.

Clinical diagnosis and management of potential pulmonary metastatic nodules after curative treatment of HNSCC can be challenging because overdiagnosis and misdiagnosis have always been problems. During the initial staging workup or subsequent follow-up observation for HNSCC, pulmonary nodules should be evaluated to determine whether they are benign, represent metastasis, or represent synchronous or metachronous second primary lung cancer. Kwon et al reported that the cumulative incidence rates of pulmonary malignancy development at 2 years after treatment of HNSCC were equivalent regardless of whether non-specific pulmonary nodules were present during the initial staging workup.¹⁷ Advanced primary stage and primary cervical lymph node (LN) involvement were independent factors for pulmonary malignancy development, and they led to the hypothesis that the lower cervical LN near the thoracic space would be at significant risk for lung metastases based on the “cascade theory”, which infers that some adjacent sites are seeded first and that further metastases proceed in sites other than the primary site.¹⁷ Additionally, primary cervical LN involvement was demonstrated to be a poor prognostic factor after PM for HNSCC.^{5,6,18} These data suggest that primary site cervical LN involvement might have a significant effect on pulmonary metastases and might be associated with a poor prognosis.

Particularly, this HNSCC cases involved 12 paranasal sinus cancers, which have relatively unknown survival outcomes after PM. There were no significant differences in the survival outcomes of those with HNSCC in the paranasal sinus and oral cavity, including the tongue ($p = 0.53$). A study performed in Japan by Nakajima et al indicated that the primary lesion was most often confirmed in the hypopharynx (29.3%), followed by the larynx (25.9%), oral cavity (15.5%), oropharynx (13.8%), salivary gland (6.9%), nasopharynx (5.2%), and nasal cavity and paranasal sinus (3.4%). The 5-year OS rates were 38.7%, 27.7%, 20.8%, 58.3%, 66.6%, 33.3%, and 0%, respectively.¹⁹ When their data corresponded to our subclassification (33.3% to 58.3% in group 1; 0% to 20.8% in group 2; and 27.7% to 38.7% in group 3), we found that the survival outcomes were comparable. Although further data are needed, it is crucial to investigate the clinicopathological findings and survival outcomes after PM of each primary site.

Whether a larger metastasized diameter is an independent prognostic factor is currently controversial. A few studies have investigated the survival outcomes according to tumor diameters after PM for HNC. The cutoff values for tumor size can vary, with studies using metastasized diameters of 10 mm⁴, 25 mm², and 30 mm;^{15,19} however, no significant differences were found among these studies. We previously reported that patients whose recurrent sites extending downstream from the lung via hematogenous colorectal cancer spread had significantly larger pulmonary tumor sizes than those with recurrent sites confined to the lung and regions upstream of the lung.²⁰ Because all these studies were small-scale, a large-scale study is required to determine whether the difference in histological type or biological aggressiveness has an influence on such results. Therefore, we believe that our proposals in this study may lead to new knowledge.

Many recent reports investigating younger age focused more on the connection with carcinogenesis or the metastasis form.²¹ Young et al reported that 70–90% of new oropharyngeal cancers have evidence of HPV; these cancers have different demographic patterns and are more likely to occur in younger adults in their 40s and 50s.¹⁸ Additionally, the outcomes of HPV-positive HNC are significantly better than those of HPV-negative cancers, likely due to HPV-positive cancers being more responsive to treatment.²² In Japan and Korea, the rate of HPV oropharyngeal cancer is as high as 67%.²³ HPV-positive HNSCC is well-known to be more aggressive and to have a higher tendency to metastasize to distant organs.^{21,22} Age at diagnosis of the index HNC (younger than 65 years), histological type (squamous cell carcinoma), and lesion location (hypopharynx) were found to be significant predictors of the metachronous esophageal cancer incidence.²¹

This is the largest study of PM for HNSCC at multiple institutions in Japan. However, the retrospective nature of this report and the relatively low frequency resulted in several limitations. Shiono et al previously reported that selection bias affects PM outcome results, and this report is no exception.⁶ The verification in effective PM in more common colorectal cancer is based on an assumption that there would be zero survival without PM.¹⁶ The difficulty distinguishing the diagnosis of second primary lung cancer, which occurs in 3.3% to 5.5%, is well-known.^{24,25} Many authors have discussed this issue,^{19,26} but no reliable distinguishing strategy has been found. Winter et al reported that a solitary node of the lung after radical HNSCC treatment is a good candidate for surgical treatment, regardless of whether the nodule is primary lung cancer or metastasis.² Thomas et al reported that differentiation between second primary lung cancer and metastasis of HNSCC is not important to the prognosis.²⁷ Lung squamous cell carcinoma and HNSCC have common clinicopathological characteristics, including histology, epithelial cells of origin, and an association with tobacco, and there is no gold standard to validate therapeutic approaches, potentially introducing selection bias when addressing the role of PM.¹⁶ Furthermore, tobacco-related diseases that are not ranked high as a cause of death for Japanese people accounted for a much higher proportion of deaths attributable to other diseases. However, patient information regarding comorbidity, morbidity, mortality, and the cause of death are not included in the MLTSG-J. Therefore, we cannot calculate HNSCC-specific deaths and collect the recurrence information of the old decades and analyzed using 85.7% of DFS data. Additionally, we could not obtain data regarding smoking, HPV status, or EBV status because of the use of the registered database. Furthermore, we used the maximum pathological diameter instead of the radiological diameter. Because the duration of our database spanned four decades, we considered that the use of a maximum pathological diameter would be useful for decreasing selection bias and measurement errors because of the progress of radiological modalities. Finally, chemotherapy before and after metastasectomy, which might affect curability, did not appear to be a significant prognostic factor affecting survival outcomes.

Conclusion

Pulmonary metastasectomy from head and neck squamous cell carcinomas indicates a potential survival benefit. However, pulmonary metastasectomy for metastasized tumours from the oral cavity, tongue, and paranasal sinus and those from the other sites with a diameter of >20 mm should be considered in surgical indication and selected patients because this might improve the survival outcomes as well as help uncover an opportunity for a cure.

Abbreviations

HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; DFI, disease-free interval; HPV, human papillomavirus; DFI, disease-free interval; OS, overall survival.

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Disclosure

The authors report no conflicts of interest in this work.

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