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# Clinical and Prognostic Analysis of Hypopharyngeal Squamous Cell Carcinoma with Synchronous and Metachronous Multiple Malignancies

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**Abstract.** *Background/Aim: To analyze the clinical features and prevalence of synchronous and metachronous second primary malignancies (SPMs) in patients with hypopharyngeal squamous cell carcinoma (HSCC), their associated risk factors, and cause-specific mortality. Patients and Methods: We retrospectively reviewed 136 patients treated with curative intent at our hospital. Statistical analyses were performed to determine factors predictive of SPM and cause-specific mortality. Results: Sixty-three of 136 patients (46.3%) developed SPM; of these, 41 (30.1%) and 42 (30.9%) had synchronous and metachronous SPMs, respectively, with patient overlap. The most common site of synchronous and metachronous SPMs was the oesophagus (65.8% and 24.4%, respectively); the corresponding overall survival rates were 34.1% and 66.5%, respectively. Furthermore, heavy drinking was significantly correlated with synchronous SPM (p<0.001). Conclusion: Oesophageal cancer surveillance is recommended for patients with HSCC, especially heavy drinkers. Our findings may help identify and properly manage HSCC patients at high risk of SPMs.*

Hypopharyngeal squamous cell carcinoma (HSCC) exhibits clinical manifestations that are different from other head and neck cancers. While it is less prevalent than other head and neck SCCs, accounting for 3-5% of all such malignancies, it carries a very poor prognosis (1-3). High mortality due to HSCC is caused not only by the high rates of nodal and early systemic metastases at presentation or during follow-up, but also the occurrence of second primary malignancies (SPMs) that are identified either simultaneously with the primary lesion (synchronous) or a period of time thereafter (metachronous). A recent study found that 17% of 2,063 patients with head and neck cancer involved SPMs, and that the overall survival rates of these patients were significantly lower than in those without SPMs (4). The head and neck, lung, and oesophagus are the most frequent areas of SPM development after an index head and neck cancer (4, 5). Many of the common risk factors for head and neck cancer, such as smoking, alcohol, aging, and poor oral hygiene, can increase the risk for SPM elsewhere in the body. Patients with HSCC in particular develop SPMs more frequently than those with other primary regions of head and neck cancer (5, 6); therefore, identifying the critical risk factors for this phenomenon is important for the earlier detection and prevention of multiple primary cancers. However, there have been few studies that focused on SPM in patients with HSCC. Hence, the present study aimed to analyse the clinical features and prevalence of synchronous and metachronous SPM in patients with HSCC, as well as to identify the risk factors associated with SPM occurrence and determine the cause-specific mortality.

## Patients and Methods

*Patients*. A total of 136 patients (121 men and 15 women) with HSCC were diagnosed and treated between 2006 and 2015 at the Department of Otolaryngology, Sapporo Medical University, Japan. The patients' median age was 67 years (range=33-84 years). Primary HSCC was diagnosed by otolaryngologists following clinical examinations and imaging. Pathological diagnosis was confirmed by the Department of Surgical Pathology at Sapporo Medical University. HSCC stage was classified according to the 7th edition of the International Union against Cancer tumour-node-metastasis system. Inclusion criteria were primary biopsy-proven SCC (but not recurrent or multiple primary tumours), eligibility for curative radiotherapy, and availability for long-term follow-up data of at least 2 years. Exclusion criteria were previous malignancy before HSCC, previous chemotherapy, and/or previous radiotherapy



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*Key Words:* Hypopharyngeal cancer, synchronous cancer, squamous cell carcinoma, oesophageal cancer.

treatment for non-cancer ailments. SPM arising from other organs were defined according to the criteria of Warren and Gates (7) as follows: 1) the tumors must be clearly malignant on histological examination, 2) the tumors must be separated by normal mucosa, and 3) the possibility that the second tumor represents metastasis must be excluded. We confirmed SPMs using biopsies; a synchronous SPM was defined as that which developed within 6 months of the index tumor diagnosis, while a metachronous SPM developed more than 6 months after initiating radiotherapy.

*Assessment of smoking and alcohol consumption*. The cumulative cigarette consumption was calculated in pack-years; which is defined as 20 cigarettes smoked every day for 1 year. We evaluated the drinking frequency and volume of alcohol intake according to beverage types. The amount was converted to ethanol (grams), and values for each beverage type were summed. The ethanol estimates for these calculations were as follows: 5% for beer, 15% for Japanese saké, 12% for wine, 35% for shochu (a distilled alcoholic beverage made in Japan), and 43% for whisky. The cumulative amount of alcohol consumption was then expressed as the saké index (weight [g]/22 g of ethanol consumed per day multiplied by years of drinking). The traditional Japanese drinking unit, the gou, corresponds to 22 g of ethanol; thus, this index represents the total gou consumed per day multiplied by years of drinking.

*Statistical analysis*. All statistical analyses were conducted using the SPSS software (version 22.0J for Windows, IBM Corp., Armonk, NY, USA). The Fisher's exact test and Student's *t*-test were used to compare categorical variables and continuous variables, respectively. Survival outcomes were calculated using the Kaplan-Meier method and compared using the log-rank test. All *p*-values were 2-sided, and $p>0.05$ was considered statistically significant.

## Results

*Clinical characteristics of HSCC with or without SPM*. The clinical characteristics of patients in our study are shown in Table I. The patients were predominantly men, with an 8:1 ratio over women. The median follow-up duration of the surviving patients was 30 months (range=3-124 months). The index HSCC was located in the piriform sinus in 76.2% of patients, the posterior wall in 15.8%, and the post-cricoid area in 5.7%. Approximately three-quarters of the patients had nodal metastases at the time of diagnosis, and more than half had stage IV HSCC.

*Distribution and survival outcomes of patients with SPM*. Sixty-three of our patients (46.3%) had SPMs; the most common site was the oesophagus (27.2%), followed by the stomach (10.3%), head and neck region (7%), lung (4.4%), and colon/rectum (4.4%) (Table II). The most common type of oesophageal cancer was thoracic (87.5%) followed by cervical (6.3%). During the follow-up period, the 5-year overall survival rate for patients with HSCC was 54.8%; this rate was lower in patients with SPM than in patients without (60.0%, 95% confidence interval [CI] 0.00-0.00] *vs*. 48.5%), but the difference was not significant (Figure 1).

Table I. *Characteristics of patients in the present study.*

| Characteristics | No. of patients | % |
|---|---|---|
| All cases | 136 | |
| Gender | | |
| Male | 121 | |
| Female | 15 | |
| Median age, years (range) | 67.0 (33-84) | |
| Mean follow-up months (range) | 30 (3-124) | |
| Primary site | | |
| Piriform sinus | 106 | 76.2 |
| Posterial wall | 22 | 15.8 |
| Post-cricoid area | 8 | 5.7 |
| T classification | | |
| T1 | 20 | |
| T2 | 53 | |
| T3 | 32 | |
| T4 | 31 | |
| N classification | | |
| N0 | 36 | |
| N1 | 22 | |
| N2 | 75 | |
| N3 | 4 | |
| Overall TNM stage | | |
| Stage I | 7 | 5 |
| Stage II | 20 | 14.4 |
| Stage III | 25 | 18 |
| Stage IV | 84 | |
| Smoking | | |
| Yes | | |
| No | | |

Table II. *Distribution of second primary malignancies in patients with hypopharyngeal carcinoma.*

| | No. of patients | % |
|---|---|---|
| Second primary malignancies | | |
| Yes | 63 | 46.3 |
| Oesophagus | 37 | 27.2 |
| Stomach | 14 | 10.3 |
| Head & Neck | 10 | 7.4 |
| Lung | 6 | 4.4 |
| Colorectal | 6 | 4.4 |
| Others | 9 | 6.6 |
| No | 73 | 53.7 |

Of the patients with SPM, synchronous and metachronous lesions were detected in 41 patients (49.4%) and 42 patients (50.6%), respectively (Table III). In both types of cases, the most common site of SPM was the oesophagus followed by the stomach and head and neck regions. The 5-year overall survival rate of HSCC patients with synchronous SPM was significantly lower than in those with metachronous SPM

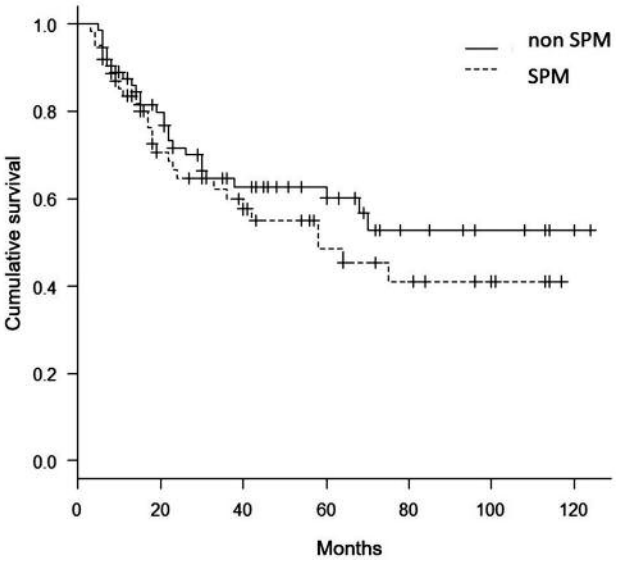


Figure 1. *Comparison of overall survival rates according to the existence of second primary malignancies (log-rank p=0.32).*

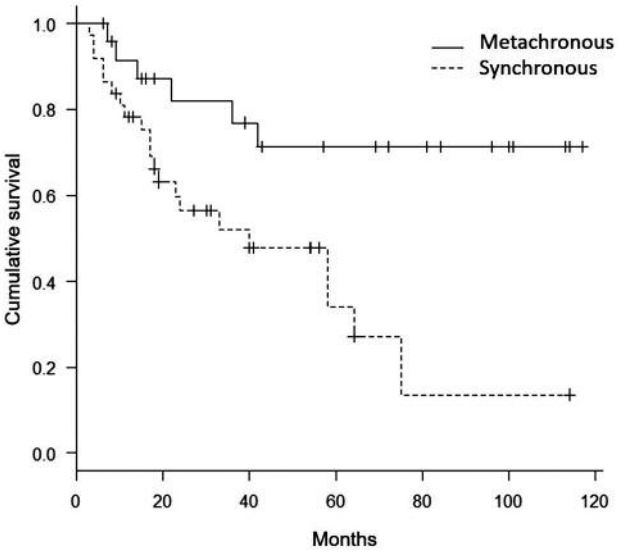


Figure 2. *Comparison of overall survival rates in patients with synchronous versus metachronous second primary malignancies (log-rank p=0.013).*

(34.1% [95%CI=0.15–0.54] *vs*. 65.5% [95%CI=0.42-0.83], log-rank $p$=0.013) (Figure 2). On the other hand, the 5-year overall survival rate of HSCC patients with synchronous and metachronous oesophageal cancer was 40.3% (95%CI=0.17-0.63) and 64.3% (95%CI=0.25-0.87), respectively.

*Comparing the characteristics of synchronous and metachronous SPM*. We investigated the differences in risk factors between synchronous and metachronous SPMs. As shown in Table IV, age ($p$=0.608), sex ($p$=0.385), T and N classification ($p$=0.115 and $p$=0.782, respectively), tumor stage ($p$=0.763), smoking quantity ($p$=0.515), and the Adult Comorbidity Evaluation-27 ($p$=0.237) were not significantly different. Only the amount of alcohol consumption was significantly associated with synchronous SPM development ($p$<0.001).

Table III. *Distribution of synchronous and metachronous second primary malignancies in patients with hypopharyngeal carcinoma.*

| Sites | Patients | % |
|---|---|---|
| Synchronous | 41 | 49.4 |
| Metachronous | 42 | 50.6 |

| | Synchronous | | Metachronous | |
|---|---|---|---|---|
| Sites | Patients | % | Patients | % |
| Oesophagus | 27 | 65.8 | 10 | 24.4 |
| Stomach | 7 | 17.0 | 8 | 19.5 |
| Head & Neck | 4 | 9.8 | 6 | 14.6 |
| Lung | 0 | 0 | 4 | 14.6 |
| Colorectal | 2 | 4.9 | 4 | 9.8 |
| Others | 1 | 2.4 | 8 | 20.0 |

## Discussion

Although SPM has been recognized as the leading cause of long-term mortality in patients with head and neck cancer (5-8), to our knowledge, ours is the first study to specifically investigate mortality and risk factors in hypopharyngeal tumor index sites that are associated with the development of SPM. The risk of SPM in head and neck cancer is related to the level of exposure of the upper aerodigestive tract to environmental carcinogens, and is also thought to involve field cancerization (9). Recently, Rennemo *et al*. reported that 17% of patients with head and neck cancer had SPM, and that the overall survival rates of these patients were significantly lower than those in the patients without SPM (4). The early detection and management of SPM are suggested to improve overall survival rates in patients with HSCC (5).

In the present study, oesophageal cancer was the most common SPM in patients with HSCC, which is consistent with previous findings (4-6, 10). Since oesophageal cancer shows a

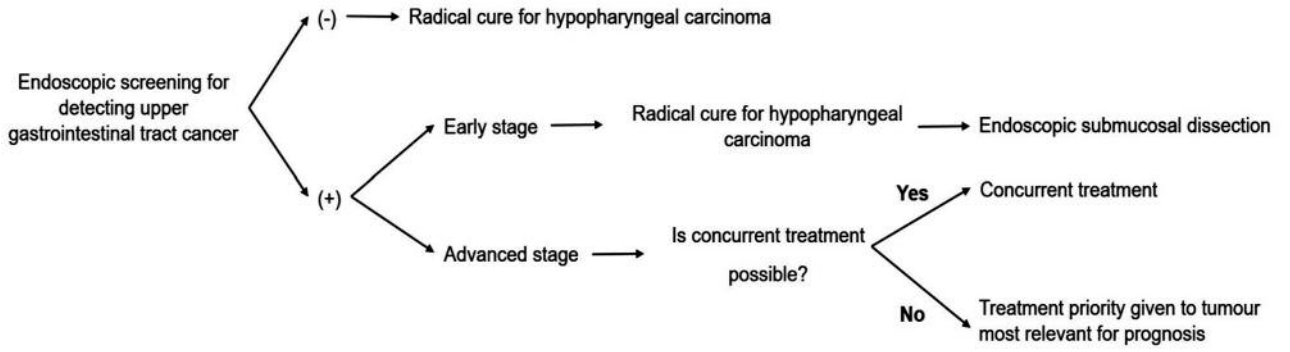


Figure 3. *Our medical chart for oesophageal duplicated cancers in patients with hypopharyngeal cancer. All patients underwent upper endoscopic surveillance; in those with no oesophageal cancer detected by screening, curative treatment of hypopharyngeal carcinoma was performed. In patients with early oesophageal cancer, curative treatment of hypopharyngeal cancer was performed after the endoscopic treatment of oesophageal cancer. In patients with advanced oesophageal cancer, the relevant clinical departments were consulted regarding the availability of concurrent treatment. If concurrent treatment was possible, both the hypopharyngeal and oesophageal cancers were treated. If concurrent treatment proved challenging, treatment priority was administered to treat the tumor that had a greater impact on prognosis.*

much poorer outcome than head and neck cancer, oesophageal cancer stage was found to be a crucial prognostic factor, including for HSCC patients with SPM. Therefore, it is critical to accurately diagnose SPMs in patients with HSCC. We routinely performed endoscopic screening for upper gastrointestinal tract cancer in all patients with HSCC (Figure 3). It has been demonstrated that routine endoscopic screening is effective for the early detection of oesophageal cancer, which in turn results in less invasive treatments such as endoscopic submucosal dissection (ESD) (11). Recent advances in narrow band imaging (NBI) and Lugol chromoendoscopy (LCE) have been particularly useful for the early detection of oesophageal cancer, which can then be treated by ESD (12). NBI and LCE, along with conventional endoscopy, are recommended for the diagnosis of early oesophageal cancer and to evaluate the potential of developing SPM in patients with HSCC. On the other hand, several studies have reported the usefulness of fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) for the detection of SPM (13, 14). Although FDG-PET/CT is useful for detecting multiple SPMs, the reliability of this modality's ability to identify early oesophageal cancer is unclear; moreover, the sensitivity of FDG-PET/CT for detecting synchronous oesophageal cancer is reported to be relatively low (15, 16).

Synchronous and metachronous oesophageal cancer were found in 65.8% and 24.4% of patients with HSCC in our study, respectively. In other words, oesophageal cancer was the most frequent synchronous SPM in our patients. On the other hand, metachronous SPM sites in our patients tended to be systemic. Heavy alcohol consumption was the only variable that predicted a greater probability of synchronous SPM in patients with HSCC compared to metachronous SPM. This may be characteristic of patients in East Asian countries due to the slower metabolism of alcohol than in Western patients, which increases the toxic accumulation of acetaldehyde (17-19). Previous studies in Japan indicated that *ALDH2* inactivation plays a crucial role in the susceptibility of the upper aerodigestive tract to multiple cancers (20, 21). Since drinking and smoking are known to show synergistic adverse effects, it is difficult to analyze each separately. However, a previous study that investigated patients who either drink or

Table IV. *Risk factors for the development of second primary malignancies in patients with hypopharyngeal carcinoma.*

| | | Synchronous | Metachronous | *p*-Value |
|---|---|---|---|---|
| Gender | Male | 35 | 22 | 0.385 |
| | Female | 2 | 3 | |
| Age | ≥70 | 9 | 16 | 0.608 |
| | <70 | 16 | 21 | |
| T | T1-2 | 18 | 17 | 0.115 |
| | T3-4 | 19 | 7 | |
| N | N0 | 11 | 9 | 0.782 |
| | N1-3 | 26 | 16 | |
| Stage | I-II | 8 | 7 | 0.763 |
| | III-IV | 29 | 18 | |
| Pack-year | <50 | 25 | 13 | 0.515 |
| | ≥50 | 7 | 6 | |
| Sake index | <50 | 1 | 9 | <0.001 |
| | ≥50 | 26 | 8 | |
| ACE-27 | 0-1 | 25 | 21 | 0.237 |
| | 2-3 | 12 | 4 | |

ACE: Adult comorbidity evaluation.

smoke, but not both, showed that smoking produces a risk of developing head and neck cancer in a volume-dependent manner. In contrast, alcohol produces a risk of head and neck cancers (in the oropharynx/hypopharynx and larynx) only when consumed heavily (22).

## Conclusion

Physicians should be aware of the possible coexistence of SPMs in patients with HSCC, as these secondary malignancies were found in 46.3% of our patients. The survival rate of patients with HSCC who had synchronous SPM was significantly poorer than that in patients with metachronous SPM. Early detection of HSCC and proper intervention may lead to reduction of serious adverse events and mortality related to this disease. Endoscopic surveillance of the head and neck region is recommended in patients with HSCC to improve the early detection rates and treatments of both synchronous and metachronous SPMs, particularly in the oesophagus among heavy drinkers.

## Conflicts of Interest

None.

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