Second Primary Malignancies in Squamous Cell Carcinomas of the Tongue and Larynx: An Analysis of Incidence, Pattern, and Outcome

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Background: Head and neck cancer patients have a higher risk of developing a second primary malignancy (SPM) than the general population. This study was conducted to identify the characteristics of SPM and its impact on survival in patients with squamous cell carcinoma of the tongue (TSCC) and larynx (LSCC).

Methods: A retrospective study was conducted of 538 patients who were treated by surgery primarily for TSCC ($n = 146$) and LSCC ($n = 392$) from 1990 to 2000. The incidence, site, and overall survival of SPMs were evaluated.

Results: Seventy-seven patients developed SPM during the follow-up period (median, 73 months), including 18 (12%) with TSCC and 59 (15%) with LSCC. Fifty-six percent of SPMs of the TSCC group appeared in the oral cavity. Among the SPMs of LSCC patients, 54% developed in the lung (31%) and larynx (24%). The 5-year overall survival after the diagnosis of SPM in the head and neck was 39%, compared to 29% for SPM in other areas ($p = 0.010$).

Conclusion: SPMs after treatment of TSCC and LSCC are similar in incidence but distinct in pattern. SPMs within the head and neck are associated with a better prognosis than those outside this area. [*J Chin Med Assoc* 2008; 71(2):86–91]

Key Words: head and neck, laryngeal cancer, second primary tumor, tongue cancer

Introduction

The appearance of second primary malignancy (SPM) is a crucial problem in treating patients with head and neck squamous cell carcinoma (HNSCC) and has a negative impact on survival.[1–4] As a result of carcinogen exposure, patients with HNSCC face a significantly higher risk of developing a new malignancy than the general population.[4,5] Depending on the primary site and follow-up duration, the incidence of SPM in HNSCC patients varies between 14% and 47%.[1–5] Nonetheless, the pattern of SPM differs from person to person, and the follow-up program should be adjusted individually.

The purpose of this study was to identify the incidence, patterns, and survival of SPM in patients with squamous cell carcinoma of the tongue (TSCC) and larynx (LSCC), and to explore the potential association between the index tumor and SPM, in order to guide appropriate surveillance protocol, treatment, and outcome prediction.

Methods

We retrospectively reviewed 538 previously untreated patients, including 146 TSCC and 392 LSCC patients, who underwent surgery for curative intent at the Department of Otolaryngology, Taipei Veterans General Hospital, between January 1990 and December 2000. TSCC patients treated at the Department of Dentistry were excluded because of a different management policy.

At the time of data collection, all of the patients had been followed for a minimum of 5 years after surgery. Patient characteristics are listed in Table 1.

The index tumor was defined as the first diagnosed tumor and was re-staged according to the TNM staging system of the 2002 American Joint Committee on Cancer. All of the patients had biopsy-proven SCC and underwent comprehensive tumor surveys. Seventy percent of TSCC and 53% of LSCC were diagnosed at an early stage (stages I and II). Among the 146 patients with TSCC, 134 (92%) underwent partial or hemiglossectomy and 12 (8%) underwent total glossectomy. Of the 359 LSCC patients, 82 (21%) received endoscopic laser excision, 135 (34%) partial laryngectomy, and 175 (45%) total laryngectomy. Moreover, 89 (61%) TSCC and 129 (33%) LSCC patients also underwent cervical lymph node dissection. Postoperative radiation therapy was performed in 29 (20%) TSCC and 55 (14%) LSCC patients with positive surgical margins, multiple cervical lymph node metastases, or extracapsular spread in neck pathology.

The definition of SPM was based on the criteria of Warren and Gates[6] as modified by Hong et al in 1990:[7] both tumors are malignant with histologic confirmation; the 2 tumors are geographically distinct (at least 2 cm of normal mucosa between them) or separated in time by 3 or more years; any new tumor of the lung is solitary and histologically different, unless more than 3 years; and the possibility of metastatic tumor has been excluded. In terms of chronology, SPMs were classified as synchronous if they were diagnosed at the same time or within 6 months of diagnosis of the index tumor. After a 6-month follow-up period, they were defined as metachronous tumors.

All of the patients received a standard follow-up program, including recent medical history and detailed head and neck examination every month during the first year, every 2 months in the second year, every 3 months in the third year, and every 6 months thereafter. Patients also underwent annual chest radiography and necessary investigations, if indicated, by their symptoms and clinical findings.

Table 1. Patient characteristics (n = 538)

	TSCC (n = 146)		LSCC (n = 392)		p
	n	(%)	n	(%)	
Gender					< 0.001
Male	121	(83)	378	(96)	
Female	25	(17)	14	(4)	
Age					< 0.001
Range	25–88		35–90		
Median	51		68		
Risk factors					
Tobacco	106	(72)	283	(72)	0.380
Alcohol	53	(36)	63	(16)	< 0.001
Betel quid	72	(49)	43	(11)	< 0.001
Pathologic T stage					< 0.001
T1	52	(36)	104	(27)	
T2	65	(45)	120	(31)	
T3	20	(14)	85	(22)	
T4	9	(6)	83	(21)	
Pathologic N stage					0.185
N0	112	(77)	328	(84)	
N1	12	(8)	24	(6)	
N2	22	(15)	40	(10)	
N3	0	(0)	0	(0)	
Pathologic TNM stage					0.004
I	49	(34)	102	(26)	
II	52	(36)	105	(27)	
III	16	(11)	83	(21)	
IV	29	(20)	102	(26)	

TSCC = squamous cell carcinoma of the tongue; LSCC = squamous cell carcinoma of the larynx.

Table 2. Characteristics of second primary malignancy in relation to the index tumor
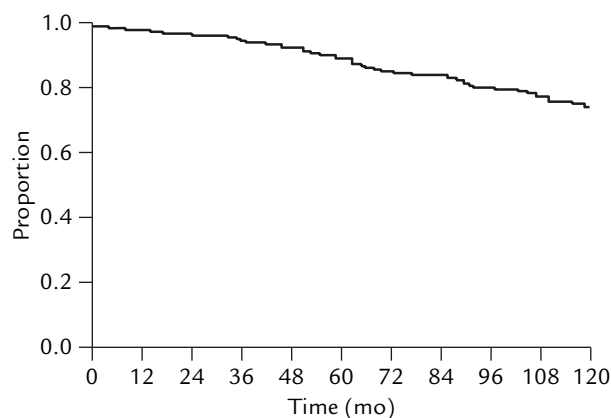
	TSCC	(n = 146)	LSCC	(n = 392)	p
Incidence	12%	(n = 18)	15%	(n = 59)	0.320
5-yr SPM rate	10%		11%		
10-yr SPM rate	31%		25%		
Time interval (mo)					0.436
Median		48		59	
Range		0–128		0–162	
Synchronous (≤ 6 mo)	12%	(n = 2)	10%	(n = 6)	0.539
Metachronous (> 6 mo)	88%	(n = 16)	90%	(n = 53)	
Site of SPM					0.017
Head & neck	72%	(n = 13)	41%	(n = 24)	
Non-head & neck	28%	(n = 5)	59%	(n = 35)	
3-yr overall survival	50%		47%		0.652
5-yr overall survival	30%		44%		

TSCC = squamous cell carcinoma of the tongue; LSCC = squamous cell carcinoma of the larynx; SPM = second primary malignancy.

Statistical analyses were carried out to evaluate the incidence and characteristics of SPMs in relation to the site of the index tumor. The χ^2 test, Fisher's exact test, or Spearman's rank correlation was used for univariate analysis where appropriate. Associations between location and patient survival of SPMs were also analyzed. Survival after SPM development was set as the time interval from SPM diagnosis to the most recent follow-up or the patient's death. Incidence and survival were calculated using the Kaplan-Meier method. All analyses were carried out using JMP version 4.0 (SAS Institute Inc., Cary, NC, USA). A p value of less than 0.05 was considered statistically significant.

Figure 1. Second primary malignancy-free survival for patients with index squamous cell carcinoma of the tongue and larynx.

Results

Among the 538 patients with TSCC and LSCC, there were 499 men (93%) and 39 women (7%). The median age at diagnosis of the index tumor was 51 years (range, 25–88 years) for TSCC and 68 years (range, 35–90 years) for LSCC. The median follow-up time from surgery for the index tumor was 62 months (range, 1–157 months) for TSCC and 79 months (range, 1–188 months) for LSCC. Between the 2 groups, statistical differences were found in sex distribution, and alcohol and betel quid use. A higher proportion of TSCC patients were alcoholic beverage drinkers ($p < 0.001$) and betel quid chewers ($p < 0.001$), while the percentage of smokers was similar in both groups. During the follow-up period, the rate of tumor recurrence was higher in the TSCC group than in the

LSCC group (33% vs. 22%; $p = 0.008$). The 5-year overall survival rates were 66% in TSCC patients and 70% in LSCC patients ($p = 0.246$).

Characteristics of SPMs in relation to the index tumor are summarized in Table 2. In the study population, SPMs were documented in 77 (14%) patients, including 18 (12%) in TSCC and 59 (15%) in LSCC patients. The median time from surgery for the index tumor to diagnosis of the SPM was 48 months (range, 0–128 months) for TSCC and 59 months (range, 0–162 months) for LSCC. Thirty-six SPMs (47%) were diagnosed beyond 5 years after treatment for the index tumor. Figure 1 shows the SPM-free survival for patients with TSCC and LSCC. The incidence of SPM was 3% per year and was constant during the follow-up period

Table 3. Distribution of second primary malignancy by index tumor site

Site of SPM	TSCC (n = 18)		LSCC (n = 59)		Total	
	n	(%)	n	(%)	n	(%)
Head & neck	13	(72)	24	(41)	37	(48)
Oral cavity	10	(56)	3	(5)	13	(17)
Oropharynx	1	(6)	1	(2)	2	(3)
Hypopharynx	0	(0)	0	(0)	0	(0)
Larynx	0	(0)	14	(24)	14	(18)
Others	2	(11)	6	(10)	8	(10)
Non-head & neck	5	(28)	35	(59)	40	(52)
Lung	0	(0)	18	(31)	18	(23)
Esophagus	2	(11)	3	(5)	5	(6)
Others	3	(17)	14	(24)	17	(22)

TSCC = squamous cell carcinoma of the tongue; LSCC = squamous cell carcinoma of the larynx; SPM = second primary malignancy.
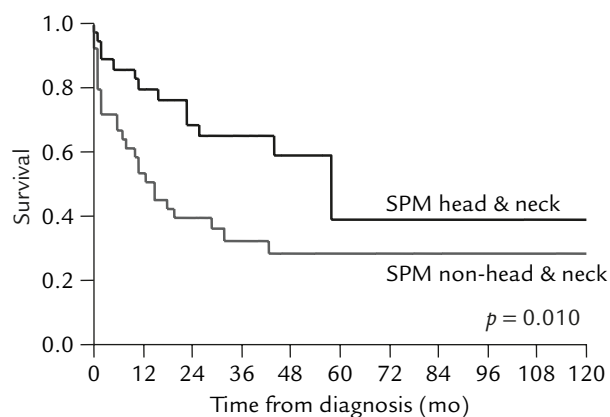
Figure 2. Cumulative survival of patients with squamous cell carcinoma of the tongue and larynx according to location of the second primary malignancy (SPM).

for at least 10 years. There was no statistically significant difference in the incidence of developing SPM between the 2 groups ($p = 0.320$).

Table 3 shows the distribution of SPMs. Thirty-seven SPMs (48%) were carcinomas of the head and neck region, with the most frequent in the larynx (18%) and oral cavity (17%). Forty SPMs (52%) were not head and neck tumors, with the most common sites in the lung (23%) and esophagus (6%). Cumulative survival of patients with TSCC and LSCC according to location of SPMs is shown in Figure 2. The 5-year overall survival rate for patients with SPM of the head and neck was 39%, which was significantly better than that of non-head and neck SPM patients (29%, $p = 0.010$).

There was an association between the locations of index tumor and SPM. Patients with index TSCC had a higher proportion of SPM within the head and neck ($p = 0.017$), with 56% in the oral cavity. On the other hand, the SPM of patients with index LSCC tended

to be in the respiratory axis, including the lung (31%) and larynx (24%). After SPM diagnosis, the 5-year overall survival rates were 30% and 44% in the TSCC and LSCC groups, respectively ($p = 0.651$).

Discussion

Since locoregional control of HNSCC has improved in the past decades, SPM and distant metastasis have become 2 of the main factors that limit survival.[8] More than 80% of distant metastases occur within the first 2 years after diagnosis of the index HNSCC, and the incidence decreases with time.[9] Conversely, the incidence of SPM remains constant for an extended period,[1,10] and its development has a long-term effect on survival. In the present study, SPM increased almost linearly, with an incidence of 3% per year, compared to 2–7% in the literature.[1,10–12] It is important to understand the developing pattern of SPMs and provide appropriate follow-up programs and possible prevention strategies for patients with HNSCC.

The concept of *field cancerization* has frequently been used to explain the relatively high incidence of SPM in patients with HNSCC.[13,14] According to this theory, the respiratory and upper digestive tracts comprise a common field that is exposed to a diversity of carcinogens. The continuous effect of carcinogens on the entire field results in multiple precancerous changes that may progress to malignant transformation. Two or more cancers may develop in the aerodigestive tract.

Several noxious substances, such as alcohol and tobacco, have been documented to be associated with a greater risk of SPMs.[5,10] In Asians, betel quid chewing is also a risk factor.[15] However, Wiseman et al found that 25% of head and neck cancer patients without

a history of smoking and alcohol consumption developed SPM.[16] Therefore, factors such as genetic sensitivity and environmental exposure may also play a role in the emergence of SPM.[17]

The distinguishing of a new tumor guides subsequent treatment policy and greatly affects prognosis. Given the similar morphologic appearance, however, it is not always possible to distinguish between SPM, local recurrence and distant metastasis using routine histology techniques. For example, the emergence of new laryngeal cancer in a patient with previously treated LSCC will bring up the issue of SPM versus local recurrence. Currently, differential diagnosis primarily relies on clinical parameters, including stage of primary tumor, disease-free interval, and location of SPM. In this study, any tumor with a similar histology developing within 2 cm or 3 years of the index tumor was defined as a local recurrence, and the median interval between the diagnosis of laryngeal SPM and surgery for LSCC was 67 months (range, 42–155 months). Recent advances in tumor genetics and molecular biology might offer better and more scientific diagnostic methods in the future.[13]

Consistent with some publications,[1,4] the most common site of SPM in this study was the head and neck, followed by the lung and esophagus. The distribution also confirms the theory of field cancerization. Furthermore, the site of the index tumor predicted the development location of SPM, where TSCC patients tended to have oral cavity SPMs, while LSCC patients had SPMs most frequently in the lung and larynx. A higher proportion of TSCC patients were also alcoholic beverage drinkers and/or betel quid chewers, where the main exposed area is the oral cavity. In contrast, the development of LSCC is related to cigarette smoking.[4,10] Although the proportion of smokers was comparable to that in the TSCC group, more than half of SPMs of LSCC patients occurred in the respiratory tract. It can be hypothesized that patients with LSCC might have a higher susceptibility to inhaled carcinogens, which should be further investigated.

As shown previously, the prognosis of SPM mainly depends on its location. SPMs occurring outside the head and neck have a significantly worse prognosis than those developing in the head and neck. In our study, the 5-year overall survival rate of second primary lung cancer was only 20%, and all patients with esophageal SPM died within 18 months of diagnosis. It is of clinical importance to consider the site of SPM when making treatment decisions. Any delay in early and correct diagnosis is also an important factor that influences treatment and survival.[12] SPMs are frequently not recognized until they are in a later stage, thereby resulting in a poorer prognosis. Other factors, including the patient's general health condition, remaining treatment choices, and morbidities after previous treatment, also affect outcome.

Behavioral modification and treatment that can influence the entire aerodigestive tract may be helpful in reducing the high incidence of SPM in patients with HNSCC. Many authors have advocated cessation of cigarette smoking and alcohol consumption in the follow-up period.[10] To prevent transformation from a precancerous change to invasive carcinoma, Sporn et al posited the idea of chemoprevention in 1976.[18] Among the drugs administered for inhibiting carcinogenesis, retinoic acid and its derivatives are the most widely used. Hong et al reported that daily treatment with high doses of isotretinoin was effective in preventing SPMs in patients with HNSCC, except for the drawback of dose-related toxicity.[7] However, Khuri et al found that the occurrence of SPM did not decrease when treating with low-dose isotretinoin.[19] Chemoprevention is still controversial, and further studies are needed to assess the possible benefits in HNSCC patients.

HNSCC patients with newly developed SPM may still have a chance of long-term survival. To diagnose SPMs at an earlier stage and achieve higher cure rates, continuous surveillance is essential.[10] However, Dhooge et al found that 82% of SPMs were diagnosed because the patient presented with symptoms.[2] Shah and Applebaum also reported that routine annual chest radiography disclosed only 34% of pulmonary SPMs and contributed little to the overall survival of HNSCC patients.[20] Therefore, some authors suggest close follow-up with more frequent chest radiographs, rather than annually.[8] As for routine panendoscopy, the benefit is not warranted and is often indicated when the associated symptoms and signs are identified.[8]

Our data presents a series of patients who were treated surgically for TSCC and LSCC in a single medical center. Several strengths and limitations should be noted in this study, and the results should be interpreted with caution. First, this study focused on TSCC, the most common cancer in the oral cavity, because diverse tumor biology may exist in different subsites of the oral cavity. Second, positive correlation between SPM and radiotherapy for the previous tumor has been reported.[3] Investigation of patients primarily treated with surgery may minimize the influence of radiation and better represent the actual incidence of SPM in these patients. In addition, potential drawbacks, including the retrospective design and the selection bias in arranging surgery for treating the index tumor, must also be noted.

The clinical significance of this study is in identifying the features of SPMs in patients with TSCC and LSCC and allowing for a rational follow-up schedule. By understanding the patterns and distributions of SPMs, we suggest that patients with previously treated TSCC and LSCC should receive long-term follow-up. In addition to standard examinations, TSCC patients should undergo regular detailed evaluation of the upper digestive tract, with counseling for frequent oral cavity checking. Patients with LSCC have a higher risk of pulmonary SPM and may require more aggressive chest screening. As an acceptable survival rate can be achieved, SPMs should be treated with the appropriate curative therapy.

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