Study of the Incidence, Clinicopathological Profile, and Management of Second Primary Tumors in Patients with Index Head and Neck Tumors

Chirag Jain[1] Mansi Jain[2] Ajay Kumar Dewan[3] Pavani Medisetty[4] Ankush Jajodia[5] Dinesh Chandra Doval[6] Venkata Pradeep Babu Koyyala[6]

[1]Department of Cancer Surgery, Safdarjung Hospital and Vardhman Mahavir Medical College, New Delhi, India
[2]Department of Anaesthesia, Safdarjung Hospital and Vardhman Mahavir Medical College, New Delhi, India
[3]Department of Surgical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India
[4]Department of Anesthesia, Dr. Baba Saheb Ambedkar Medical College and Hospital, New Delhi, India
[5]Department of Radiology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India
[6]Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

Address for correspondence Venkata Pradeep Babu Koyyala, MD, DNB, Rajiv Gandhi Cancer Institute and Research Centre, Room 3162, 1st Floor, D Block, Sector 5, Rohini, New Delhi 110085, India (e-mail: pradeepbabu.koyyala@gmail.com).

Asian J Oncol 2020;6:53–60

Abstract

Introduction This study was performed to study the incidence and clinicopathological profile of second primary tumors (SPTs) in patients with squamous cell carcinoma of head and neck at our institute.

Materials and Methods In this study, we included the data of 120 patients who developed an SPT of the upper aerodigestive tract following treatment of their index tumor (IT). Since the online data of cancer patients in our cancer registry was available from January 2005, we started the study retrospectively from that time. At our institute, Rajiv Gandhi Cancer Institute and Research Centre, the incidence was found to be 8.4%. Warren and Gates criteria were followed for defining a second tumor.

Results Our study results showed an incidence of 8.4% of SPTs among patients of head and neck squamous cell carcinoma (HNSCC). The mean age of the patients was 56.47 ± 10.42 years with a male predominance. The mean period of addiction in patients was 18.48 ± 4.63 years. It was found that patients with SPT had significant history of tobacco and alcohol use. The most common location for ITs and SPT was tongue and buccal mucosa. The main modality of treatment was surgery in all patient groups. Patients were followed up at three-month intervals for the first 2 years. The SPT was diagnosed with a confirmation biopsy. Majority of patients with SPT again underwent surgery with reconstruction with either free flaps or local flaps. Recurrence after SPT treatment was seen in 16.67% cases, and primarily, it was a locoregional recurrence. Only patients with at least 6 months follow-up posttreatment of SPT were included in this study. At the end of the study, 62.5% patients were disease free, 20.83% patients were alive with disease, and 16.67% patients were dead. Some of the patients who are alive with disease developed a third primary tumor which was managed as per guidelines.

Keywords
- second primary tumors
- head and neck squamous cell carcinoma
- field cancerization

published online
June 17, 2020

DOI https://doi.org/10.1055/s-0040-1713961
ISSN 2454-6798.

Conclusion The incidence of SPTs is 8.4% in our institute. This study adds to the theory of field cancerization proposed by Slaughter et al. We found a significant history of tobacco chewing in our patients who developed SPT. The clinical significance of this study is identifying the features of SPT in patients with HNSCC and allowing for a rational follow-up schedule. The most important part of treatment although still lies with the patient by quitting use of alcohol and tobacco.

Introduction

Head and neck squamous cell carcinomas (HNSCCs) are one of the most common causes of cancer-related morbidity in India. HNSCC develops in the mucosal linings of the oral cavity, pharynx, larynx, and the cervical esophagus. The prognosis of the HNSCC is significantly worsened by the development of second primary tumors (SPTs). The concept of SPT has frequently been explained by field cancerization. Studies differ widely in their estimated risk of SPT development, in part due to inconsistencies in patient selection or diagnostic criteria and inadequate follow-up. SPT develops in 2 to 30% of patients who have HNSCC as the index tumor (IT), based on different studies.[1,2] In 1953, Slaughter et al used the term field cancerization for the first time and proposed the concept of field cancerization also known as field defect or field effect in cancer.[3] The investigators examined pathology slides from 783 patients with head and neck cancers in an effort to understand the gross changes found in epithelia surrounding these tumors and explain their clinical behavior. It was discovered that all of the epithelium beyond the boundaries of tumor possessed histologic changes, and 88/783 (11%) of patients were found to have more than one independent area of malignancy. They hypothesized that the entire epithelium of the upper aerodigestive tract (UADT) has an increased risk of development of premalignant lesions due to the multiple genetic alterations.[3] It is now well established that the accumulation of genetic alterations forms the basis of progression of normal cell to a malignant cell referred to as multistep carcinogenesis.

For the definition of SPT, most clinicians currently use the criteria of Warren and Gates,[4] which were published in 1932. The criteria are that each of the tumors must present a definite picture of malignancy, each must be distinct, and the probability of one being a metastasis of the other must be excluded. These criteria were further extended by Hong et al in 1990 to exclude the possibility of a local recurrence and added the following criteria. Tumors have to be histologically different, and if they are histologically similar, then they should be separated by 2 cm of normal mucosa or there should be a gap of at least 3 years between the IT and the SPT.

SPTs can be divided into two groups: synchronous SPTs, which develop simultaneously with or within 6 months after the IT, and metachronous SPTs, which develop >6 months after the initial tumor.[5] Most SPTs are metachronous and develop during follow-up of HNSCC patients after curative treatment of the first tumor. Tobacco and alcohol are the major risk factors for most cancers of the head and neck, including the oral cavity. In Asia and the South Pacific, betel nut (*Areca catechu*) chewing is also strongly associated with oral cavity cancers, having both independent and synergistic effects with smoking and alcohol drinking. Oral premalignancies are common in betel nut chewers and 10% of these undergo malignant transformation.[6]

The SPT poses a challenge to the treating team in view of previously operated and/or irradiated area. The diagnosis of an SPT involves keeping the patient on regular follow-up with imaging as and when required and a biopsy of any suspicious lesion found on follow-up. A metastatic workup is required in locally advanced disease. Once the diagnosis is confirmed, the major challenge is the management of the SPT. As these patients have been previously operated for the IT, and majority of them have received radiation, the options for reconstruction and the limitation of dose of radiotherapy (RT) poses the biggest challenge. With advancements in surgical techniques and RT delivery systems such as IMRT and SBRT, management in patients with SPT has gained a new perspective.

The objective of this study is to analyze the incidence of SPT and its location in relation to the location of the IT, chronology of appearance, clinicopathological profile of the patients, and management of patients.

Materials and Methods

The primary objective was to study the incidence of second primary cancers in head and neck cancers, their clinicopathologic characteristics, and management of second primary cancers. The secondary objective was to study the subsite-specific trends in relation to the first primary cancer.

The study population was retrospectively drawn from patients who were diagnosed with HNSCC, diagnosed and treated at Rajiv Gandhi Cancer Institute and Research Centre during the time period between January 2005 and June 2017. Retrieval of data was done from electronic medical records treated for primary head and neck cancer of squamous cell histology exclusively and detected to have a second primary of upper aerodigestive tract. Patient characteristics including demographics, alcohol intake, smoking and tobacco usage, stage of IT, treatment for the IT, follow-up period before onset of SPT, subsite-specific trends, clinicopathologic characteristics, and management of SPT were collected. This included those patients who developed IT between January 2005 and

June 2015 and had a minimum follow-up of 2 years after the IT and who develop an SPT of the UADT. SPTs were then followed up in these patients for a minimum of 6 months after treatment. Patients who did not complete treatment of the IT, who did not come for regular follow-up or lost to follow-up, histology other than squamous cell carcinoma (SCC), and second primary at sites other than head and neck were excluded. Patients were staged based on American Joint Committee on Cancer, seventh edition. Standard treatment protocols as per National Comprehensive Cancer Network guidelines were followed for management of patients in the study.

Definition of Second Primary Cancer

Patients fulfilling Warren and Gates criteria for SPT and with squamous cell histology which are as follows were included in this study. The criteria defined by warren and Gates for SPT are as follows. Tumors have to be malignant and this has to be histologically confirmed. Tumors must be separated from normal tissue, nonneoplastic tissue. It must eliminate the possibility that the SPT is a metastasis of the IT.

Statistical Methods

Categorical variables are presented in number and percentage and continuous variables will be presented as mean ± standard deviation and median. The data are entered in MS Excel spreadsheet and analysis is done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

A total of 1,432 patients diagnosed with head and neck cancer between January 2005 and June 2017 were analyzed. One hundred and twenty patients were eligible for the study.

Characteristics of Patients

In our study, the mean age of the patients was 56.47 ± 10.42 years. The age distribution of study population is depicted in ►**Table 1**. There were 91 males (75.8%) and 29 females (25.1%).

In our study, 35% of the patients chewed tobacco and were smokers and 34.17% chewed tobacco, smoked, and consumed alcohol, whereas only 18.33% chewed tobacco and consumed alcohol. Around 7.5% consumed alcohol and smoked. The trends of tobacco and alcohol usage are tabulated in ►**Table 2**. In this study population, 52.5% had comorbidities and 47.5% had no comorbidities. Out of all the patients with comorbidities, hypertension was present in 35 patients (29.17%), diabetes mellitus was present in 27 patients (22.5%), hypothyroidism was present in 6 patients (5%), and coronary artery disease and asthma were present in 1 patient each (►**Table 3**).

Table 1 Age distribution of primary head and neck cancers

Age distribution (y)	Frequency	Percentage
31–40	12	10.00%
41–50	17	14.17%
51–60	53	44.17%
61–70	27	22.50%
71–80	11	9.17%
Total	120	100.00%

Characteristics of Index Tumors and Treatment Given

Majority of the ITs were in grade 2 (84.03%). No regional lymph node metastasis was seen in 86 cases. Surgical staging of the ITs of head and neck in our study showed stages I, II, III, IVa, and IVb (22.5, 30, 17.5, 30, and 0%, respectively). Perineural invasion was present in 23.01% cases and lymphovascular invasion was present in 19.64% cases. The pathological stage and grades of ITs of patients are depicted in ►**Table 4**.

Out of 113 cases of ITs who underwent surgery for their tumors, margins of 98.23% cases were free of tumor and only in 1.77% of cases, it was involved. In the ITs, the closest margin was < 5 mm in 37 cases (32.74%) and ≥ 5 mm in 76 cases (67.26%). The depth of invasion (DOI) was ≤ 5 mm in 38.05% cases and > 5 mm in 61.95% cases. The representation of the IT with closest margins and DOI is shown in ►**Table 5**. Extracapsular invasion was seen in 10.17% of ITs and was absent in 89.83% cases. Hypothyroidism was reported in 75 cases (62.5%) after treatment of primary IT.

Characteristics of Second Primary Tumors and Treatment Given

The most common location of the SPT in our study was tongue (27.5%) followed by left lower alveolus (10.0%). Single cases were seen in hard palate and base of tongue. The overall frequency of SPT at various locations is shown in ►**Table 6**. There was no significant association between the four most common locations of IT with all the other locations of SPTs (p-value > 0.05). The comparison is shown in ►**Table 7**.

In our study, surgery was the main mode of management of SPTs. Surgery was done in 100 patients (83.33%). RT, chemoradiotherapy (CRT), and neoadjuvant chemotherapy (CT) were done in 3.33, 10.83, and 2.5% of cases, respectively. Majority of the SPTs were in grade 2 (84.03%). No regional lymph node metastasis was seen in 93 cases (92.08%). Surgical staging of the SPTs of head and neck in our study showed stages I, II, III, IVa, and IVb (10.83, 59.17, 10, 17.5, and 2.5%, respectively). Perineural invasion was present in 38 patients (37.62%) and lymphovascular invasion was present in 18 patients (17.82%). Pathological characteristics of SPTs are depicted in ►**Table 8**. Out of 101 cases of SPTs whose margin status was available, margins of 93.07% cases were free of tumor and only in 6.93% of cases, it was involved. In the SPTs, the DOI was ≤ 5 mm in 40.95% of cases and > 5 mm in 59.41% of cases. The status of margins of the SPTs with margin status and DOI is shown in ►**Table 9**.

No adjuvant treatment was received by 60.19% cases of SPTs. Among the adjuvant treatments for the SPTs, RT and CRT were done in 41 cases (37.96%) and 2 cases (1.85%), respectively. In our study, recurrence was seen in 20 cases (16.67%) out of 120 SPTs. Recurrence was most common locally (15 cases, 75%) followed by ipsilateral neck (9 cases),

Table 2 Addiction history of tobacco, smoking, and alcohol

Factor	Frequency	Percentage
Smoking + tobacco	42	35.00%
Smoking + alcohol + tobacco	41	34.17%
Tobacco + alcohol	22	18.33%
Smoking + alcohol	9	7.50%
Tobacco	6	5.00%
Total	120	100.00%

Table 3 Location of index tumors of head and neck

Location	Frequency	Percentage
Left buccal mucosa	24	20.00%
Right buccal mucosa	21	17.50%
Left tongue	15	12.50%
Right tongue	21	17.50%
Left retromolar trigone	1	0.83%
Right retromolar trigone	5	4.17%
Left lower gingivobuccal sulcus	3	2.50%
Right lower gingivobuccal sulcus	1	0.83%
Hard palate	2	1.67%
Left lower alveolus	8	6.67%
Right lower alveolus	6	5.00%
Larynx	3	2.50%
Base of tongue	1	0.83%
Left upper alveolus	2	1.67%
Right upper alveolus	4	3.33%
Tonsil	2	1.67%
Maxilla	1	0.83%
Total	120	100.00%

contralateral neck (6 cases), and distant locations (8 cases). Some of these recurrences included recurrences at multiple sites such as three patients had recurrences in both sides of neck and two had nodal recurrence as well as metastatic disease. On comparison between ITs and SPTs on the basis of pathological grading and staging, a significant difference was found between the two as shown in ►**Table 10**.

Follow-up of Second Primary Tumors

In our study, out of 120 patients studied, 75 patients (62.5%) are alive and cured of disease and on regular follow-up. Of the remaining patients, 25 patients (20.83%) are alive with disease and the rest 20 patients (16.67%) have expired.

Discussion

Numerous theories have been laid down for the appearance of the SPT in the HNSCC patients such as field cancerization,

Table 4 Pathological staging and grading

Pathological factor	Frequency	Percentage
Grade (IT) (*n* = 119)		
Grade I	17	14.29%
Grade II	100	84.03%
Grade III	2	1.68%
pT (IT) (*n* = 112)		
TX	0	0.00%
T0	0	0.00%
T1	30	26.79%
T2	47	41.96%
T3	11	9.82%
T4a	24	21.43%%
T4b	0	0.00%
pN (IT) (*n* = 113)		
NX	0	0.00%
N0	86	76.11%
N1	13	11.50%
N2a	1	0.88%
N2b	10	8.85%
N2c	3	2.65%
N3	0	0.00%
Stage (IT) (*n* = 120)		
I	27	22.50%
II	36	30.00%
III	21	17.50%
IVa	36	30.00%
IVb	0	0.00%
PNI (IT) (*n* = 113) present	26	23.01%
LVI (IT) (*n* = 112) present	22	19.64%

Abbreviations: IT, index tumor; LVI, lymphovascular invasion; PNI, perineural invasion.

Table 5 Status of surgical margins for ITs of head and neck

Surgical margin (IT)	Frequency	Percentage
Margin (free/involved) (IT) (*n* = 113)		
Free	111	98.23%
Involved	2	1.77%
Closest (mm) (IT) (*n* = 113)		
<5	37	32.74%
≥5	76	67.26%
DOI (mm) (IT) (*n* = 113)		
≤5	43	38.05%
>5	70	61.95%

Abbreviations: DOI, depth of invasion; IT, index tumor.

Table 6 Location of second primary tumor

Second primary location	Frequency	Percentage
Right buccal mucosa	9	7.5%
Left tongue	11	9.17%
Right tongue	22	18.33%
Left retromolar trigone	6	5.00%
Right retromolar trigone	6	5.00%
Left lower gingivobuccal sulcus	0	0.00%
Right lower gingivobuccal sulcus	2	1.67%
Hard palate	1	0.83%
Left lower alveolus	12	10.00%
Right lower alveolus	4	3.33%
Larynx	3	2.50%
Base of tongue	1	0.83%
Lower lip	5	4.17%
Left upper alveolus	5	4.17%
Right upper alveolus	3	2.50%
Tonsil	9	7.50%
Maxilla	5	4.17%
Total	120	100.00%

condemned mucosa theory, micrometastases, etc. SPT develops in 2 to 30% of patients who have HNSCC as the IT based on different studies.[7-13] Our study results showed an incidence of 8.4% of SPTs among patients of HNSCC. León et al[7] in their study reported an incidence of 15.7% among a data of 2,109 IT patients.

In our study, the mean age of the patients was 56.47 ± 10.42 years and there were 91 males and 29 females, with predominant elderly male population. Tsou et al's study had 102 men with an average age of 50.19 ± 12.1 years in the HNSCC group and in a study by Hsu et al,[16] the median age at diagnosis of the IT was 51 years (range, 25–88 years) for SCC of the tongue and 68 years (range, 35–90 years) for SCC of the larynx. The demographic profile corroborated our study as it also comprised primarily old age male population.

In our study, there was a lower incidence of SPT in females as compared with males. Thirty-five per cent of our study patients chewed tobacco and were smokers. Thirty-four per cent patients chewed tobacco, were smokers, and consumed alcohol, whereas only 18.33% chewed tobacco and consumed alcohol. Around 7.50% consumed alcohol and were smokers and 5% consumed only tobacco. In our society, although the trend is changing, but still, currently males are more prone to addictions such as alcohol, tobacco chewing, and smoking

Table 7 Assessment of SPT locations among most common index tumor locations

Second primary location	Most common location of index tumor				Total	*p*-Value
	LT BM	RT BM	LT tongue	RT tongue		
LT BM	2 (8.33%)	2 (9.52%)	2 (13.33%)	5 (23.81%)	11 (13.58%)	
RT BM	4 (16.67%)	0 (0.00%)	0 (0.00%)	2 (9.52%)	6 (7.41%)	
LT tongue	2 (8.33%)	0 (0.00%)	2 (13.33%)	4 (19.05%)	8 (9.88%)	
RT tongue	4 (16.67%)	6 (28.57%)	5 (33.33%)	1 (4.76%)	16 (19.75%)	
LT RMT	0 (0.00%)	2 (9.52%)	1 (6.67%)	0 (0.00%)	3 (3.70%)	
RT RMT	0 (0.00%)	1 (4.76%)	2 (13.33%)	1 (4.76%)	4 (4.94%)	
RT lower GBS	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (1.23%)	
Hard palate	0 (0.00%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	1 (1.23%)	
LT lower alveolus	2 (8.33%)	3 (14.29%)	1 (6.67%)	3 (14.29%)	9 (11.11%)	0.2
RT lower alveolus	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (1.23%)	27
Larynx	1 (4.17%)	0 (0.00%)	1 (6.67%)	1 (4.76%)	3 (3.70%)	
BOT	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)	1 (1.23%)	
Lower lip	2 (8.33%)	2 (9.52%)	0 (0.00%)	0 (0.00%)	4 (4.94%)	
LT upper alveolus	2 (8.33%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	3 (3.70%)	
RT upper alveolus	2 (8.33%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.47%)	
Tonsil	0 (0.00%)	2 (9.52%)	1 (6.67%)	1 (4.76%)	4 (4.94%)	
Maxilla	3 (12.50%)	1 (4.76%)	0 (0.00%)	0 (0.00%)	4 (4.94%)	
Total	24 (100.00%)	21 (100.00%)	15 (100.00%)	21 (100.00%)	81 (100.00%)	

Abbreviations: BM, buccal mucosa; BOT, base of tongue; GBS, gingivobuccal sulcus; LT, left; RMT, retromolar trigone; RT, right; SPT, second primary tumor.

Table 8 Pathological characteristics of SPTs

Pathological factors (SPT)	Frequency	Percentage
pT (SPT) (*n* = 101)		
TX	0	0.00%
T0	0	0.00%
T1	12	11.88%
T2	73	72.28%
T3	2	1.98%
T4a	14	13.86%
T4b	0	0.00%
pN (SPT) (*n* = 101)		
NX	0	0.00%
N0	93	92.08%
N1	8	7.92%
N2a	0	0.00%
N2b	0	0.00%
N2c	0	0.00%
N3	0	0.00%
Stage (SPT) (*n* = 120)		
I	13	10.83%
II	71	59.17%
III	12	10.00%
IVa	21	17.50%
IVb	3	2.50%
PNI (SPT) (*n* = 101) present	38	37.62%
LVI (SPT) (*n* = 101) present	18	17.82%

Abbreviations: LVI, lymphovascular invasion; PNI, perineural invasion; SPT, second primary tumor.

Table 9 Status of margins and depth of invasion in SPTs of head and neck

Surgical margin (SPT)	Frequency	Percentage
Margins (SPT) (*n* = 101)		
Free	94	93.07%
Involved	7	6.93%
DOI (SPT) (*n* = 101)		
≤5	41	40.59%
>5	60	59.41%

Abbreviations: DOI, depth of invasion; SPT, second primary tumor.

as compared with females and thus the difference. In one such study, the unadjusted survival in women (54.9 ± 3.5%) at 5 years following the diagnosis of the index cancer was significantly better than in men (40.5 ± 2.0%). At 5 years, 8.4% of women and 9.8% of men developed metachronous second primary carcinomas of the respiratory and upper digestive systems. The average annual incidence in women was 15.4/1,000 and in men, l8.2/1,000 which was comparable.[15]

In our study, the mean duration of addiction was 18.48 ± 4.63 years and the mean duration to SPT occurrence after IT treatment was 4.76 ± 1.67 years. In spite of majority of patients quitting alcohol and tobacco postdevelopment of IT, the risk for SPT was present.In a study by Hsu et al,[16] the median time from surgery for the IT to diagnosis of the SPM was 48 months (range, 0–128 months) for SCC of the tongue and 59 months (range, 0–162) for SCC of the larynx. Thus, it was concluded that significant excesses in cancer mortality in men and women were particularly evident between 45 and 64 years of age and were distributed throughout all levels of exposure to tobacco and alcohol. No significant association between the duration and level of addiction could be derived from the previous study and the current study.

Many authors have reported that there is a relationship between the IT and the second malignancy. In the study by Hsu et al,[16] there was an association between the locations of IT and SPT. Patients with index SCC of the tongue had a higher proportion of SPT within the head and neck ($p = 0.017$), with 56% in the oral cavity. On the contrary, the SPT of patients with index SCC of the larynx tended to be in the respiratory axis, including the lung (31%) and larynx (24%). Lin et al[17] stated that patients with oral cavity index cancers had a higher rate of developing SPTs in the head and neck regions and that patients who had been treated for laryngeal index cancers had a higher incidence rate of SPTs in the lung area. In the study by Tsou et al,[13] patients who had been treated for oral cavity index cancers had a higher rate of developing SPTs in the upper aerodigestive tract, especially in the oral cavity and oropharynx; oropharyngeal cancer patients had a higher incidence of SPTs in the oral cavity and hypopharynx; hypopharyngeal cancer patients had a higher incidence of developing SPTs in the larynx and esophagus; and laryngeal cancer patients had a higher incidence of SPTs in the oral cavity and lung.

Given the similar morphologic and histologic appearance, however, it is not always possible to distinguish between SPT, local recurrence, and distant metastasis using routine histology techniques. The distinction of a new tumor from an old one guides subsequent treatment policy and greatly affects prognosis. For example, the emergence of new laryngeal cancer in a patient with previously treated laryngeal SCC will bring up the issue of SPT versus local recurrence. Currently, differential diagnosis primarily relies on clinical parameters, including stage of primary tumor, disease-free interval, and location of SPT. In our study, any tumor with a similar histology developing within 2 cm or 3 years of the IT was defined as a local recurrence, and the median interval between the diagnosis of SPT and surgery for ITs was 4.76 ± 1.67 years. Recent advances in tumor genetics and molecular biology might offer better and more scientific diagnostic methods in the future to differentiate the same.

Half of the ITs were primarily diagnosed in stages I and II, whereas more than half of SPT were diagnosed in stage II with very less in stage I. SPTs are frequently not recognized until they are in a later stage, signifying a more aggressive tumor biology thereby resulting in a poorer prognosis. On comparison between ITs and SPTs on the basis of pathological grading and staging, a significant difference was found between the two (p-value < 0.05) in our study.

Table 10 Comparison of pathological factors among IT and SPT

Pathological factors	IT		SPT		*p*-Value
	Frequency	Percentage	Frequency	Percentage	
pT					
TX	0	0.00%	0	0.00%	0.0001
T0	0	0%	0	0.00%	
T1	30	26.79%	12	11.88%	
T2	47	41.96%	73	72.28%	
T3	11	9.82%	2	1.98%	
T4a	24	21.43%	14	13.86%	
T4b	0	0.00%	0	0.00%	
pN					
NX	0	0.00%	0	0.00%	0.005
N0	86	76.11%	93	92.08%	
N1	13	11.50%	8	7.92%	
N2a	1	0.88%	0	0.00%	
N2b	10	8.85%	0	0.00%	
N2c	3	2.65%	0	0.00%	
N3	0	0.00%	0	0.00%	
Stage					
I	27	22.50%	13	10.83%	<0.0001
II	36	30.00%	71	59.17%	
III	21	17.50%	12	10.00%	
IVa	36	30.00%	21	17.50%	
IVb	0	0.00%	3	2.50%	

Abbreviations: IT, index tumor; SPT, second primary tumor.

The goals of multimodality strategies for patients with advanced head and neck cancer include organ preservation through less radical surgery while improving outcomes. As survival has improved and multimodality organ preservation strategies became more successful, the role of surgery was redefined and has become increasingly more prominent for patients with recurrent disease. Most surgeons hold a general opinion that performing surgery on a patient who has previously undergone RT or CRT can be a challenging task. The salvage surgical approach may be not only technically challenging but also associated with a higher incidence of complications, such as wound-healing problems, fistula, and infection.

Our data present a series of patients who were treated surgically or with RT and CT for HNSCC 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 HNSCC, the most common cancer in the head and neck because diverse tumor biology may exist in different subsites. Second, positive correlation between SPT and RT for the previous tumor has been reported. In addition, potential drawbacks, including the retrospective design and the selection bias in arranging surgery for treating the IT, must also be noted.

In our study, different modes of treatment were used for the IT. Surgery was done in 113 cases (94.17%), CRT was done in 5%, and only RT was done in a single case. Hypothyroidism was the major delayed postoperative complication seen in 62.5% of patients and it has been seen that it negatively affects wound healing. In management of SPT also, surgery was the main mode of treatment (83.33%). RT, CRT, and neoadjuvant CT was done in few cases (3.33, 10.83, and 2.5%, respectively). In managing SPT in our study patients with HNSCC, curative rather than palliative treatment was preferred when the ITs had been diagnosed early, when the SPTs were metachronous, when SPTs were in the head and neck regions, and in patients younger than 70 years. However, if there was a high risk of surgical morbidity, or if patients were in poor general condition, SPTs were treated palliatively by CRT or regional RT.

Tsou et al also found that the patients who developed metachronous SPT in head and neck regions with early index HNSCC and who underwent curative treatment had a better survival rate than patients who developed synchronous SPT in nonhead and neck regions with advanced HNSCC and underwent palliative treatment. Therefore, early-stage HNSCC patients who develop metachronous SPTs will have a better survival rate if the SPT occurs in head and neck regions and are treated surgically. Palliative treatment could be performed on patients developing synchronous SPT in nonhead and neck regions with advanced index HNSCC because there

was no significantly better 3-year survival rate even after surgical management of their SPTs.

Systemic therapy, in general, is considered to be the least effective of all the three treatment modalities used in the management of HNSCC. This is because, as a single treatment modality, CT alone does not have the capability of eliciting curative treatment effects—unlike surgery or RT. In terms of achieving a cure for head and neck cancer, the primary role of systemic therapy is as a sensitizer for RT.

In our study, recurrence was seen in 20 cases (16.67%) out of 120 SPTs. Recurrence was most common locally (15 cases, 75%) followed by ipsilateral neck (9 cases), contralateral neck (6 cases), and distant locations (8 cases). Among the SPTs recurrence, CT was the main mode of management and was done in 15 patients (75%). Surgery, CRT, and immunotherapy were done in few cases (10, 5, and 10%, respectively).

In our study, out of 120 patients studied, 75 patients (62.5%) were disease free at 6 months follow-up, 25 patients (20.83%) were alive with disease, and the rest 20 patients (16.67%) were dead. Staging, grading of SPT, margin status, nodes positive for metastasis, patient's general health condition, remaining treatment choices, and morbidities after previous treatment, all affect outcome of the patient.

HNSCC patients with newly developed SPT may still have a chance of long-term survival. To diagnose at an earlier stage and achieve higher cure rates, continuous surveillance is essential. However, Dhooge et al[18] found that 82% of SPMs were diagnosed because the patient presented with symptoms. Shah and Applebaum[19] also reported that routine annual chest radiography disclosed only 34% of pulmonary SPTs and contributed little to the overall survival of HNSCC patients. Therefore, some authors suggest close follow-up with more frequent chest radiographs, rather than annually.[20]

Conclusion

SPTs in patients with IT of the head and neck are common in patients with history of use of tobacco and alcohol. The incidence of SPTs in the present study is 8.4%. Though surgery was the main modality of treatment for SPT, recurrence rates of 16.67% were seen in our study which was managed mainly by CT. Out of the 120 patients in the study, 83.33% patients were alive at the end of the study. Of the 100 patients who were alive at the end of the study, 75 was disease free and 25 were alive with disease and on treatment. The clinical significance of this study is identifying the features of SPT in patients with HNSCC and allowing for a rational follow-up schedule. The most important part of treatment although still lies with the patient by quitting use of alcohol and tobacco. Thus, to conclude, as an acceptable survival rate can be achieved, SPT should be treated with the appropriate curative therapy. The main limitation is the retrospective nature of study.

Conflict of Interest
None declared.

References

1 Hong WK, Lippman SM, Itri LM, et al. Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. N Engl J Med 1990;323(12):795–801
2 Farhadieh RD, Petr O,, Taghavi K, et al. Second primary tumours of the head and neck are not associated with adverse overall survival in oral squamous cell carcinomas. J Cancer Sci Ther 2011;3:2
3 Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953;6(5):963–968
4 Warren S, Gates O. Multiple primary malignant tumors. A survey of the literature and a statistical study. Am J Cancer 1932;16:1358–1414
5 Heroiu Cataloiu A-D, Danciu CE, Popescu CR. Multiple cancers of the head and neck. Maedica (Buchar) 2013;8(1):80–85
6 Chiba I. Prevention of betel quid chewers' oral cancer in the Asian-Pacific area. Asian Pac J Cancer Prev 2001;2(4):263–269
7 León X, Quer M, Diez S, Orús C, López-Pousa A, Burgués J. Second neoplasm in patients with head and neck cancer. Head Neck 1999;21(3):204–210
8 Berg JW, Schottenfeld D, Ritter F. Incidence of multiple primary cancers. III. Cancers of the respiratory and upper digestive system as multiple primary cancers. J Natl Cancer Inst 1970;44(2):263–274
9 Gluckman JL, Crissman JD. Survival rates in 548 patients with multiple neoplasms of the upper aerodigestive tract. Laryngoscope 1983;93(1):71–74
10 Haughey BH, Gates GA, Arfken CL, Harvey J. Meta-analysis of second malignant tumors in head and neck cancer: the case for an endoscopic screening protocol. Ann Otol Rhinol Laryngol 1992;101(2 Pt 1) :105–112
11 Olsen JH. Second cancer following cancer of the respiratory system in Denmark, 1943-80. Natl Cancer Inst Monogr 1985;68:309–324
12 Vaamonde P, Martín C, del Río M, LaBella T. Second primary malignancies in patients with cancer of the head and neck. Otolaryngol Head Neck Surg 2003;129(1):65–70
13 Tsou YA, Hua CH, Tseng HC, Lin MH, Tsai MH. Survival study and treatment strategy for second primary malignancies in patients with head and neck squamous cell carcinoma and nasopharyngeal carcinoma. Acta Otolaryngol 2007;127(6):651–657
14 Waridel F, Estreicher A, Bron L, et al. Field cancerisation and polyclonal p53 mutation in the upper aero-digestive tract. Oncogene 1997;14(2):163–169
15 Schottenfeld D, Gantt RC, Wyner EL. The role of alcohol and tobacco in multiple primary cancers of the upper digestive system, larynx and lung: a prospective study. Prev Med 1974;3(2):277–293
16 Hsu YB, Chang SY, Lan MC, Huang JL, Tai SK, Chu PY. Second primary malignancies in squamous cell carcinomas of the tongue and larynx: an analysis of incidence, pattern, and outcome. J Chin Med Assoc 2008;71(2):86–91
17 Lin K, Patel SG, Chu PY, et al. Second primary malignancy of the aerodigestive tract in patients treated for cancer of the oral cavity and larynx. Head & Neck 2005;27(12):1042–1048
18 Dhooge IJ, De Vos M, Van Cauwenberge PB. Multiple primary malignant tumors in patients with head and neck cancer: results of a prospective study and future perspectives. Laryngoscope 1998;108(2):250–256
19 Shah SI, Applebaum EL. Lung cancer after head and neck cancer: role of chest radiography. Laryngoscope 2000;110(12):2033–2036
20 León X, Ferlito A, Myer CM III, et al. Second primary tumors in head and neck cancer patients. Acta Otolaryngol 2002;122(7):765–778