Original Article

Synchronous and metachronous head and neck squamous cell carcinoma in western Australia—a single center experience

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Background: Despite advances in multimodality treatment of head and neck squamous cell carcinoma (HNSCC), survival outcomes have improved minimally. This may be attributable to the increased risk of secondary primary malignancies. We conducted a retrospective analysis of patients treated at Fremantle Hospital, Western Australia with HNSCC to investigate the incidence of second primary malignancy (SPM), the epidemiological risk factors and survival outcome.

Methods: We analyzed 790 patients from our departmental head and neck oncology database with the diagnosis of synchronous and/or metachronous HNSCCs between 1993 and 2011. We analyzed for an association between the risk factors and survival outcomes using the Statistical Package for Social Sciences for statistical analysis.

Results: The commonest HNSCC was lip and oral cavity (37.8%), followed by oropharynx (28.1%) and larynx (26.5%). Of the 790 patients, 55.9% were smokers, 36.8% had a smoking history of over 50 pack-years, and 41.1% had a history of alcohol use. Primary treatment included surgery, surgery/radiotherapy, chemotherapy, surgery/chemotherapy, surgery/chemo-radiotherapy, radiotherapy, chemo-radiotherapy, and palliative, or no treatment. Synchronous tumour occurred in 29 patients (3.7%). Eighteen patients (2.3%) had metachronous tumour: median follow-up period was 25 months; 178 patients (22.5%) were dead at the end of follow-up.

Conclusions: While this study found a lower rate of secondary primary malignancies in patients with HNSCCs than other studies, there was a clear association between patients with significant smoking histories and the development of HNSCCs. Progression to synchronous or metachronous malignancy was associated with a poorer overall survival rate.

Keywords: Head and neck; squamous cell cancer; multimodal; synchronous; metachronous; analysis

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Introduction

Head and neck cancer (HNC) is the sixth most common cancer in the world with squamous cell carcinoma (SCC) being the most common type affecting the head and neck region (1). Recent advances in diagnostic and multimodal management of Head and Neck Squamous Cell Carcinoma (HNSCC) has resulted in better locoregional control and lower recurrence rates. However, survival outcomes have not demonstrated significant improvements (1-4). This may be attributable to patients with HNSCC being at an increased risk of developing a second primary malignancy

Table 1 Primary and secondary head and neck squamous cell carcinoma classifications

Primary site classification
1. Lip & oral cavity
2. Oropharynx
3. Nasopharynx
4. Hypopharynx
5. Pharynx, other
6. Larynx
7. Nasal cavity & paranasal sinuses
8. Major salivary glands
Secondary site classification
1. Lip & oral cavity
2. Oropharynx
3. Nasopharynx
4. Hypopharynx
5. Pharynx, other
6. Larynx
7. Nasal cavity & paranasal sinuses
8. Major salivary glands
9. Lung
10. Other site
11. Unknown/not stated

(SPM) (3-5). Epidemiological risk factors such as tobacco and alcohol use, genetic susceptibility and/or the choice of different treatment modalities may account for SPM (1). Risk factors associated with HNSCC include tobacco and alcohol use, human papilloma virus (HPV) and Epstein-Barr virus (EBV) in oropharyngeal cancer and nasopharyngeal cancer (6-8).

The literature reported that the overall survival rate in this patient population continues to be adversely affected by SPM regardless of its location. The role of panendoscopy as a screening tool is pivotal in the early detection of SPM and subsequent treatment with curative intent. Nevertheless, this clinical entity still portends to poorer overall survival despite the substantial improvement in disease free survival rate (1,3,4).

In this study, we report the incidence of SPM (synchronous and metachronous) in HNSCC patients and association between the epidemiological risk factors and the survival outcomes.

Table 2 The International Statistical Classification of Diseases and Related Health Problems, tenth revision, Australian modification (ICD-10-AM) morphology codes included

Morphology code	Description
M8070/2	Squamous cell carcinoma (SCC) not otherwise specified (NOS), *in situ*
M8070/3	SCC NOS
M8071/2	SCC keratinising NOS, *in situ*
M8071/3	SCC keratinising NOS
M8072/2	SCC large cell nonkeratinising, *in situ*
M8072/3	SCC large cell nonkeratinising
M8073/2	SCC small cell nonkeratinising, *in situ*
M8073/3	SCC small cell nonkeratinising
M8074/2	SCC spindle cell, *in situ*
M8074/3	SCC spindle cell
M8075/2	Adenoid SCC, *in situ*
M8075/3	Adenoid SCC
M8076/2	SCC microinvasive, *in situ*
M8076/3	SCC microinvasive

Methods

We analyzed 790 patients with HNSCCs recorded in the Ear Nose and Throat (ENT) Microsoft Access database at the ENT Department at Fremantle Hospital, Western Australia, between 1993 and May 2011. All patients with cancer who received services through the Department were recorded in this Database, which included the pathology, treatment and follow-up.

The data was extracted into Microsoft Excel for screening and preliminary analysis, and subsequently imported into Statistical Package for Social Sciences (SPSS) version 14 (IBM Corporation, New York, USA) for analysis. Descriptive statistics and Kaplan Meier survival analysis were used as appropriate, and a P value of 0.05 was considered statistically significant. Sites were classified according to *Table 1* using free text descriptions and The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) codes entered into the Head

Table 3 Demographic, tobacco and alcohol use

Factor	Number (n)	Percentage (%)
Sex		
Male	600	75.9
Female	190	24.1
Tobacco use		
Yes	442	55.9
Never	73	9.2
Unknown/not stated	275	34.8
Smoking (pack-years)		
≤10	9	1.1
11–20	13	1.6
21–30	13	1.6
31–40	17	2.2
41–50	6	0.8
51–60	4	0.5
61–70	281	35.6
71–80	1	0.1
81 pack years or more	5	0.6
Unknown/not stated	441	55.8
Alcohol use		
Yes	325	41.1
Never	58	7.3
Unknown/not stated	407	51.5
Alcohol consumption		
Seldom	19	2.4
Social	164	20.8
Heavy	111	14.1
Unknown/not stated	496	62.8
Tobacco plus		
No tobacco plus no alcohol	14	1.8
Tobacco only	44	5.6
Alcohol only	30	3.8
Tobacco plus alcohol	294	37.2
Unknown/not stated	408	51.6

and Neck Oncology Database (see *Table 2* for Morphology Codes included) (9). Cases were deemed as synchronous, metachronous or metastases based on the Warren and Gates (10) criteria, which was modified by Hong *et al.* (11,12). Classification for synchronous, i.e., multiple primary HNSCC required (I) each neoplasm to be geographically distinct (separated by normal tissue), and (II) the possibility that the second primary represents a metastasis, or a local relapse must be excluded. A second primary must be separated by at least 2 cm of normal epithelium or occur at least 3 years after the first diagnosis. Any new lung tumor must be solitary and histologically distinct from the first, unless it occurred 3 or more years later. Synchronous carcinomas are second neoplasms occurring at the same time or within a 6-month period of the primary lesion. After this period, they are considered metachronous neoplasms.

For those whose inclusion criteria were met, the demographic data was analyzed, including smoking history (pack-years), smoking status, alcohol consumption (classified by the clinician as never/seldom/social/heavy/not stated), tumor sites, metastases, Tumor, Node, Metastasis (TNM) classification, treatment type (surgical/chemotherapy/radiotherapy/combination/palliative/none), follow-up period and death.

Results

There were a total of 790 patients, with the age ranging from 15 to 111 (median =67) years old. There were 600 (75.9%) males and 190 (24.1%) females. Morphology codes M8070/2, M8070/3, M8071/3 and M8075/3 were the cancer types within the population selected (see *Table 2*).

Of the 790 patients, 442 (55.9%) were smokers, and 281 (35.6%) had a 61–70 pack-year smoking history (see *Table 3*). There were 291 (36.8%) patients who had a smoking history of over 50 pack-years. Additionally, 334 (42.3%) quit smoking for 5 years or less and 72 (9.1%) quit smoking for more than 10 years, while 5 patients (0.6%) quit smoking after their diagnosis. There were 325 (41.1%) patients who had a history of alcohol use: 20.8% (n=164) were social drinkers and 14.1% (n=111) were heavy drinkers (see *Table 3*).

Lip and oral cavity primaries comprised the majority (n=299, 37.8%), followed by oropharynx (n=222, 28.1%), larynx (n=209, 26.5%), major salivary glands (n=26, 3.3%), nasal cavity and paranasal sinuses (n=11, 1.4%), nasopharynx (n=9, 1.1%), pharynx (n=8, 1.0%) and hypopharynx (n=6, 0.8%)—see *Table 4*.

In terms of TNM classification, 155 (19.7%) were T1, 190 (24%) were T2, 115 (14.6%) were T3, and 107 (13.5%) were T4. Of the N staging, 297 (37.6%) were

Table 4 Primary tumor site, whether synchronous and metachronous head and neck squamous cell carcinoma was present

Primary site	Primary site		Synchronous tumor								Metachronous tumor							
			Not present		Present		Unable to determine		Uncertain		Not present		Present		Unable to determine		Uncertain	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Lip & oral cavity	299	37.8	283	35.8	13	1.6	3	0.4	0	0.0	290	36.7	6	0.8	3	0.4	0	0.0
Oropharynx	222	28.1	211	26.7	6	0.8	5	0.6	0	0.0	211	26.7	6	0.8	5	0.6	0	0.0
Nasopharynx	9	1.1	9	1.1	0	0.0	0	0.0	0	0.0	9	1.1	0	0.0	0	0.0	0	0.0
Hypopharynx	6	0.8	5	0.6	1	0.1	0	0.0	0	0.0	6	0.8	0	0.0	0	0.0	0	0.0
Pharynx, other	8	1.0	8	1.0	0	0.0	0	0.0	0	0.0	8	1.0		0.0	0	0.0	0	0.0
Larynx	209	26.5	195	24.7	8	1.0	6	0.8	0	0.0	198	25.1	5	0.6	6	0.8	0	0.0
Nasal cavity & paranasal sinuses	11	1.4	10	1.3	1	0.1	0	0.0	0	0.0	10	1.3	1	0.1	0	0.0	0	0.0
Major salivary glands	26	3.3	23	2.9	0	0.0	2	0.3	1	0.1	23	2.9		0.0	2	0.3	1	0.1
Total	790	100.0	744	94.2	29	3.7	16	2.0	1	0.1	755	95.6	18	2.3	16	2.0	1	0.1

n: total number of patients. %: percentage. Not Present: not present or tumor is a local relapse (i.e., same histology in a site within 2 cm). Present: as per definitions of synchronous and metachronous in introduction. Unable to determine: database had missing fields for date of diagnosis, deceased date (if deceased) or last contact. Uncertain: inadequate information in database.

N0, 91 (11.5%) were N1, 162 (20.5%) were N2, and 19 (2.4%) were N3. Only 23 (2.9%) had metastatic disease at diagnosis, with chest being the most common site (n=10, 1.3%), followed by liver (n=4, 0.5%) and skeletal system (n=2, 0.3%). Eight patients had a second metastatic site: chest (n=3, 0.4%), skeletal system (n=2, 0.3%), liver (n=1, 0.1%), spine (n=1) and other (n=1).

Primary treatment comprised of: surgery (n=244, 30.9%), surgery plus radiotherapy (n=150, 19.0%), chemotherapy only (n=77, 9.7%), surgery plus chemotherapy (n=59, 7.5%), surgery plus chemo-radiotherapy (n=59), radiotherapy only (n=58, 7.3%), chemo-radiotherapy (n=51, 6.5%) and palliative treatment (n=17, 2.2%). Seventy-five (9.5%) patients declined to receive any of the treatment modalities.

Synchronous tumor was found in 29 (3.7%) patients: lung (n=9, 1.1%), larynx (n=5, 0.6%), lip and oral cavity (n=5, 0.6%), oropharynx (n=2, 0.3%), and other sites (n=7, 0.9%)—see *Table 5*. One was not stated. The TNM staging was: T1 (n=2), T2 (n=5), and T3 (n=1); N0 (n=5), N1 (n=1), and N2 (n=1) (N staging was not documented in one). Of the patients with synchronous tumor, 18 (62.1%) were deceased at the end of the follow-up period (see *Table 6*).

Fifteen patients (2.3%) had documented metachronous tumor: oropharynx (n=5, 0.6%), lip and oral cavity (n=4, 0.5%), larynx (n=3, 0.4%), lung (n=2, 0.3%), and other sites (n=4, 0.5%)—see *Table 5*. The recorded T staging was T2 (n=6) and T3 (n=2). Of the patients with metachronous tumor, six patients (33.3%) had deceased tumors at the end of the follow-up period (see *Table 6*).

The median follow-up period was 25 (range, 0–177) months: 178 (22.5%) were deceased at the end of the follow up period, leading the possibility of attrition bias. Of the 746 patients without synchronous or metachronous HNSCC, 154 (19.5%) were deceased at the end of the follow up period (see *Table 6*). The overall survival was much poorer in the synchronous group than the metachronous and HNSCC without SPM groups (P<0.05) but there was no significant difference between the metachronous and HNSCC with SPM groups (P<0.2).

Discussion

In the era of rapid advancements in diagnostic and therapeutic management for HNSCC, and with better detection and locoregional control rates, the overall survival rate has not experienced significant improvement (1,13). Similar studies have shown that the incidence of synchronous and metachronous carcinoma ranges from

Table 5 Location of synchronous and metachronous tumor in relation to primary site of head and neck squamous cell carcinoma

Primary site	Lip & oral cavity				Oropharynx				Larynx				Lung				Other*^				Not stated				Total			
	Sync		Meta		Sync		Meta		Sync		Meta		Sync		Meta		Sync		Meta		Sync		Meta		Sync		Meta	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Lip & oral cavity	4	0.5	2	0.3	0	0.0	1	0.1	1	0.1	1	0.1	2	0.3	0	0.0	5	0.6	2	0.3	1	0.1	0	0.0	13	1.6	6	0.8
Oropharynx	0	0.0	0	0.0	1	0.1	3	0.4	1	0.1	1	0.1	4	0.5	2	0.3	0	0.0	0	0.0	0	0.0	0	0.0	6	0.8	6	0.8
Hypopharynx	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0
Larynx	1	0.1	1	0.1	1	0.1	1	0.1	2	0.3	1	0.1	3	0.4	0	0.0	1	0.1	2	0.3	0	0.0	0	0.0	8	1.0	5	0.6
Nasal cavity & paranasal sinuses	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1
Total	5	0.6	4	0.5	2	0.3	5	0.6	5	0.6	3	0.4	9	1.1	2	0.3	7	0.9	4	0.5	1	0.1	0	0.0	29	3.7	18	2.3

Syncr, synchronous tumor; Meta, metachronous tumor; n, total number of patients. %, percentage. *, other synchronous site: neck [3], rectum [2], scalp [1], submandibular [1], chest [1], lymph nodes [1], and cerebral [1]. ^, other metachronous site: rectum [2], esophagus [1], mandible [1], lymph nodes [1], post-auricular [1], and cerebral [1].

Table 6 Treatment provided and deceased at end of follow-up for patients with synchronous and metachronous head and neck squamous cell carcinoma

Primary treatment	Total				Without synchronous or metachronous				Synchronous tumor				Metachronous tumor			
	n	%	DCD	%	n	%	DCD	%	n	%**	DCD	%**	n	%**	DCD	%**
Surgical	244	30.9	35	4.4	240	30.4	30	3.8	0	0.0	4	13.8	4	22.2	1	5.6
Chemotherapy only	77	9.7	18	2.3	76	9.6	17	2.2	1	3.4	1	3.4	0	0.0	0	0.0
Radiation only	58	7.3	14	1.8	56	7.1	13	1.6	2	6.9	1	3.4	0	0.0	0	0.0
Chemo-radiotherapy	51	6.5	7	0.9	51	6.5	7	0.9	0	0.0	0	0.0	0	0.0	0	0.0
Surgery plus radiotherapy*	150	19.0	47	5.9	133	16.8	37	4.7	10	34.5	7	24.1	7	38.9	3	16.7
Surgery plus chemotherapy*	59	7.5	15	1.9	56	7.1	12	1.5	2	6.9	2	6.9	1	5.6	1	5.6
Surgery plus chemo-radiotherapy*	59	7.5	14	1.8	51	6.5	13	1.6	2	6.9	0	0.0	6	33.3	1	5.6
Palliative	17	2.2	11	1.4	15	1.9	10	1.3	2	6.9	1	3.4	0	0.0	0	0.0
No treatment	75	9.5	17	2.2	72	9.1	15	1.9	3	10.3	2	6.9	0	0.0	0	0.0
Total	790	100.0	178	22.5	750	94.9	154	19.5	22	75.8	18	61.9	18	100.0	6	33.3

*, includes pre-operative and post-operative, but excludes palliative; **, percentage relating to the total number of patients in that sub-category. n, total number of patients; DCD, deceased. Without synchronous or metachronous: includes not confirmed as synchronous or metachronous.

8% to 21%, showing that its presence is a poor prognostic factor with a subsequently poor overall survival rate (1,4,13,14).

In 2009, over 3,800 new cases of HNC were diagnosed in Australia, comprising approximately 3.3% of Australia's 114,137 total new cancer diagnoses that year (15,16). In Australia, lip, oral cavity and pharynx cancers resulted in 763 deaths in 2010 (15). This is comparable to a projected total of 35,540 new oral cavity and pharynx cases and 1,529,560 total new cancer cases (approximately 2.3%) in the United States in 2010 (17). Oral cavity and pharynx related deaths in the United States were predicted to be approximately 1.4% of all cancer related deaths in 2010 (17), with SCC arising from oral mucosal lining accounting for over 90% of tumors (18-20).

Over an 18-year period, 790 new cases of HNSCC were identified at our institution or approximately 44 new cases per year. Annual Australian incidence of new HNC is over 3,800 per year (3.3%) (15,16).

Excluding skin cancers, world-wide, cancer of the mouth and pharynx have been ranked between fifth and sixth overall in the world (behind lung, stomach, breast, colon and rectum, and cervix/corpus uteri), and is the sixth leading cause of cancer mortality (21-23). In developed countries, men are affected two to three times as often as women, possibly due to higher use of alcohol and tobacco.

Our study revealed 5.9% (44 patients) patients developed SPM (29 with synchronous, and 15 with metachronous tumor) within a median follow-up period of 25 months.

Researchers looking at risk of SPM following HNC (24,25) have reported 1.3% of patients (1,294) developing a SPM within a mean 4.9-year follow-up period. This exceeded their expected number of 115.75, and cumulative risk was 36%. However, meta-analysis (26) has found an overall SPM prevalence of 14.2%, with the majority being metachronous and oral cavity. Our findings fall within expected limits for SPM occurrence. Our results revealed a higher occurrence of synchronous (3.7%), rather than metachronous (2.3%) malignancy. Time to diagnosis (early or late) and TNM classification, may impact on the synchronous and metachronous proportions.

Warren and Gates [1932] looked at 1,259 cases of multiple primary tumors arising from unrelated sites (of which 40 were their own cases), and calculated multiple malignancy to be 3.9% of all cancer cases (10). These figures have remained stable over time.

Pooled studies have looked at the risk of SPM following a primary HNC (oral cavity, pharynx and larynx) and the risk of HNC as a SPM. A review of 13 cancer registries from Europe, Canada, Australia and Singapore between 1943 and 2000 noted a total of 99,257 patients (74,988 men and 24,269 women; median age 63) had a first primary HNC (15,985 tongue, 22,378 mouth, 20,758 pharyngeal and 40,190 laryngeal cancer) who contributed 489,855 person-years of follow-up (mean follow-up time: 4.9 years) (24). During the follow-up period, 1,294 of these patients (1.3%) were diagnosed with second HNC at a different site (342 tongue, 345 mouth, 418 pharynx and 189 larynx) compared to an expected 115.75 (24,25). The 20-year cumulative risk was 36% (25).

Furthermore, a meta-analysis of the Washington University Department of Otolaryngology Head and Neck Tumor Registry and 24 studies reported an overall SPM prevalence of 14.2% in 40,287 patients (26). Most tumors were metachronous, with oral cavity tumors having the highest rate of SPM.

The risk of developing synchronous and metachronous HNSCC is well correlated with tobacco and alcohol use (2,15,16,27), and this relationship is dose-dependent (28-31). Leon *et al.* found that the risk of developing a SPM was doubled in patients who used tobacco and alcohol, compared to non-users (2). In patients with tumors related to tobacco and alcohol use (oral cavity, oropharynx and larynx), 80% of SPM occurred in the oral cavity, oropharynx and larynx (2,28). This was less than 50% for non-alcohol or tobacco users.

Leon reported that (2,28) among never alcohol-users, cigarette smoking was associated with an increased risk of HNC and this was dose and exposure dependent (pack-years). Furthermore, in never tobacco-users, high-frequency alcohol consumption was associated with increased risks of cancers of the oropharynx, hypopharynx and larynx only.

Our findings also support the phenomenon that patients with HNSCC are at increased risk for the development of SPM. Although, the patterns were consistent with malignancies related to smoking and alcohol, our statistical analysis was limited and dependent on the accuracy of the patient records. In terms of tobacco use, 55.9% of patients reported tobacco use, 9.2% did not, while 34.8% was undeterminable. Similarly, for alcohol, 41.1% reported alcohol use, 7.3% did not, while 51.1% was undeterminable. Of determinable use, 37.2% reported both and 1.8% reported neither. These results support the phenomenon that patients with HNSCC are at an increased risk for developing a SPM. However, due to the retrospective nature of the study, the missing data may affect the final

results.

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Primary tumors of the lip and oral cavity were most common (37.8%) and these most commonly recurred as synchronous and metachronous tumors again in the lip and oral cavity. While only 1.8% of patients reported neither tobacco nor alcohol use, our findings support previous research that HNC relating to tobacco and alcohol use have SPM pertaining to the oral cavity (2,28). This is due to the chronic and accumulative toxic insult to the oral mucosa by the tobacco and alcohol use. Those patients who continued to smoke after the diagnosis of the HNSCC with SPM had poorer overall survival rates.

Due to both the rate of SPC and the majority of synchronous and metachronous tumors occurring in the oral cavity, oropharynx, larynx and lung, clinical attention must focus on prevention. Once malignancy is established, the focus must shift to regular surveillance. Patient education on smoking and alcohol cessation may reduce incidence of multiple primaries.

Limitations of this study include that being a retrospective analysis, while data was screened; there were limitations on information captured. The data was dependent on the accuracy of personnel entering the data, which resulted in incomplete and omitted fields. Patients with multiple or important omissions were excluded from analysis. The ENT Database may not include all patients that presented to our institution. Unfortunately, there was missing data for tobacco and alcohol use which reduced the strength of association and the deductions that could be made. Some fields were predetermined. For example, pack years could be calculated, however alcohol use was recorded subjectively (e.g., socially *vs.* heavily), which depends on the honesty of the patient and interpretation of the clinician collecting the data.

While this study found a lower rate of SPM in patients with HNSCC than some other studies, there is a clear association between smoking and the development of HNSCCs. Fatality in patient with HNSCC is high and the development of a SPM has a higher fatality than without. Once malignancy is established, the focus must shift to regular surveillance. Given the anatomical location of HNSCC and SPC, prevention and early treatment of SPC will impact on a patient's quality of life. Patient education on smoking and alcohol cessation may reduce incidence of multiple primaries. While this study did not look at the role of viruses (such as HPV and EBV) in the development of HNSCC, growing research supports this association, and future data collection could include DNA testing for such viruses.

Conclusions

This retrospective study demonstrates that the SPM occurred at the rate of 5.9% and that there is a clear association between tobacco and alcohol use with the development of HNSCC with SPM. In our patient population, 3.7% developed synchronous and 2.3% metachronous malignancy. Metachronous malignancy was associated with much poorer overall survival rate. This study contributes to the literature in that it strengthens the notion that public health efforts should target alcohol and smoking cessation in Australia, and that our study specifies specific malignancies that patients are at risk for.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ajo.2019.03.03). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was exempt from the Fremantle Hospital ethical review board

due to the negligible risk on collections of non-identifiable data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Jung YS, Lim J, Jung KW, et al. Metachronous Second Primary Malignancies after Head and Neck Cancer in a Korean Cohort (1993-2010). PLoS One 2015;10:e0134160.
2. León X, Ferlito A, Myer CM 3rd, et al. Second primary tumors in head and neck cancer patients. Acta Otolaryngol 2002;122:765-78.
3. Larson JT, Adams GL, Fattah HA. Survival statistics for multiple primaries in head and neck cancer. Otolaryngol Head Neck Surg 1990;103:14-24.
4. Erkal HS, Mendenhall WM, Amdur RJ, et al. Synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites. J Clin Oncol 2001;19:1358-62.
5. Jones AS, Moorar P, Phillips DE, et al. Second Primary Tunours in Patients with Head and Neck Squamous Cell Carcinoma. Cancer 1995;75:1343-53.
6. Wittekindt C, Wagner S, Mayer CS, et al. Basics of tumor development and importance of human papilloma virus (HPV) for head and neck cancer. GMS Curr Top Otorhinolaryngol Head Neck Surg 2012;11:Doc09.
7. Alibek K, Kakpenova A, Baiken Y. Role of infectious agents in the carcinogenesis of brain and head and neck cancers. Infect Agent Cancer 2013;8:7.
8. Hocking JS, Stein A, Conway EL, et al. Head and neck cancer in Australia between 1982 and 2005 show increasing incidence of potentially HPV-associated oropharyngeal cancers. Br J Cancer 2011;104:886-91.
9. ICD-10 Mapping Tables. Available online: https://www.accd.net.au/Downloads.aspx?type=Archive
10. Warren S, Gates O. Multiple primary malignant tumors: A survey of the literature and a statistical study. Am J Cancer 1932;16:1358-414.
11. Schwartz LH, Ozsahin M, Zhang GN, et al. Synchronous and Metachronous Head and Neck Carcinomas. Cancer 1994;74:1933-8.
12. 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;323:795-801.
13. Schwartz LH, Ozsahin M, Zhang GN, et al. Synchronous and metachronous head and neck carcinomas. Cancer 1994;74:1933-8.
14. Parker RG, Enstrom JE. Second primary cancers of the head and neck following treatment of initial primary head and neck cancers. Int J Radiat Oncol Biol Phys 1988;14:561-4.
15. Cancer in Australia: an overview, 2012. Available online: https://www.aihw.gov.au/getmedia/efaa639f-d6b8-4e19-8d38-bcba7646360e/14757.pdf.aspx?inline=true
16. Head and Neck Cancer. Retrieved 25 February 2013. Available online: http://www.cancer.org.au/about-cancer/types-of-cancer/head-and-neck-cancer.html
17. Jemal A, Siegel R, Xu J, et al. Cancer Statistics, 2010. CA Cancer J Clin 2010;60:277-300.
18. Neville BW, Day TA. Oral Cancer and Precancerous Lesions. CA Cancer J Clin 2002;52:195-215.
19. Silverman S Jr. Demographics and occurrence of oral and pharyngeal cancers. The outcomes, the trends, the challenge. J Am Dent Assoc 2001;132 Suppl:7S-11S.
20. Ogbureke KU, Bingham C. Overview of Oral Cancer. InTech, 2012. Available online: https://www.intechopen.com/books/oral-cancer/overview-of-oral-cancer
21. Johnson N. Tobacco Use and Oral Cancer: A Global Perspective. J Dent Educ 2001;65:328-39.
22. Parkin DM, Pisani P, Ferlay J. Global Cancer Statistics. CA Cancer J Clin 1999;49:33-64, 1.
23. Goon PK, Stanley MA, Ebmeyer J, et al. HPV & head and neck cancer: a descriptive update. Head Neck Oncol 2009;1:36.
24. Bosetti C, Scelo G, Chuang SC, et al. High constant incidence rates of second primary cancers of the head and neck: A pooled analysis of 13 cancer registries. Int J Cancer 2011;129:173-9.
25. Chuang SC, Scelo G, Tonita JM, et al. Risk of second primary cancer among patients with head and neck cancers: A pooled analysis of 13 cancer registries. Int J Cancer 2008;123:2390-6.
26. Haughey BH, Gates GA, Arfken CL, et al. Meta-analysis of second malignant tumors in head and neck cancer: the case for an endoscopic screening protocol. Ann Otol

Rhinol Laryngol 1992;101:105-12.
27. León X, del Prado Venegas M, Orus C, et al. Influence of the persistence of tobacco and alcohol use in the appearance of second neoplasm in patients with a head and neck cancer. A case-control study. Cancer Causes Control 2009;20:645-52.
28. León X, Quer M, Diez S, et al. Second neoplasm in patients with head and neck cancer. Head Neck 1999;21:204-10.
29. Cianfriglia F, Di Gregorio DA, Manieri A. Multiple primary tumours in patients with oral squamous cell carcinoma. Oral Oncol 1999;35:157-63.
30. Hashibe M, Brennan P, Benhamou S, et al. Alcohol Drinking in Never Users of Tobacco, Cigarette Smoking in Never Drinkers, and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst 2007;99:777-89.
31. Hashibe M, Brennan P, Chuang SC, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the INHANCE consortium. Cancer Epidemiol Biomarkers Prev 2009;18:541-50.

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