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Incidence, timing, presentation, treatment, and outcomes of second primary head and neck squamous cell carcinoma after oral cancer

S.N. Rogers [a,b,*], A. Swain [c], C. Carroll [c], D. Lowe [d]

[a] *Evidence-Based Practice Research Centre (EPRC), Faculty of Health and Social Care, Edge Hill University, St Helens Road, Ormskirk, L39 4QP, UK*
[b] *Liverpool Head and Neck Centre, Aintree University Hospital, Liverpool, L9 1AE, UK*
[c] *Medical School, Liverpool University, Cedar House, Ashton Street, Liverpool, L69 3GE, UK*
[d] *Evidence-Based Practice Research Centre (EPRC), Faculty of Health, Edge Hill University, St Helens Road, Ormskirk, L39 4QP, UK*

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Abstract

After their initial presentation of oral squamous cell carcinoma (SCC), patients have a lifelong risk of developing another new SCC of the head and neck. The aim of this study was to establish second primary rates, baseline characteristics (site, clinical or pathological stage, and smoking and alcohol history), timing, presentation, treatment, and outcomes. From the regional unit we analysed records of patients treated with curative intent for their first oral cancer between 2002 and 2007 inclusive. All patients had had at least 10 years of follow up either to death or the end of 2017. A total of 347 patients had been treated with curative intent, and of them, 29 had a second primary at a median (IQR) of 52 (30-79) months after the index operation. The incidence of developing a second primary tumour within two years was 1.7% (95% CI: 0.7% to 3.7%), within five years was 4.9% (95% CI: 2.9% to 7.7%), and within 10 years was 7.8% (95% CI: 5.1% to 11.1%). Early stage of first cancer was the only significant factor ($p = 0.001$) for development of a second primary within 10 years, reflecting survivorship. Most second primaries (21 patients) were staged as early, and by visual inspection. Most ($n = 20$) were within the oral cavity, one of which overlapped the oropharynx; eight others were in the oropharynx, and one in the larynx. Most patients ($n = 22$) were treated by operation with curative intent. Three were treated palliatively. Patients need to be aware of the risk of a second primary and, as most are in the mouth or oropharynx, there is a role for surveillance by primary dental care practitioners.

Keywords: Oral cancer; second primary; metachronous; survival; outcomes; multiple primary tumours

Introduction

After treatment for oral cancer there is a risk of developing a second primary. Reported rates vary: 3% - 7%,[1] 7%,[2] 9%,[3] 11%,[4,5] 13%,[6] and as high as 18.4%.[7] Of the sites in the head and neck, the oral cavity and oropharynx are the most likely to be affected.[8–10] Risk factors include a continuation of smoking and alcohol consumption,[11–13] chewing of areca quid,[5] and the presence of multiple oral dysplastic lesions.[14] The site of the second primary is influenced by

* Corresponding author at: University Hospital Aintree, Liverpool, L9 1AE, UK.
E-mail addresses: simonn.rogers@aintree.nhs.uk (S.N. Rogers), A.Swain2@student.liverpool.ac.uk (A. Swain), C.Carroll@student.liverpool.ac.uk (C. Carroll), astraglobeltd@btconnect.com (D. Lowe).

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causative factors - for example, in patients whose oral cancer was related to betel-nut chewing, an annual incidence of 5% has been reported, with three-quarters occurring in the oral cavity.[15] The clinical significance of a second primary after head and neck cancer has been reflected in poor prognosis,[10] with overall five-year survival as low as 15%.[9] Fujisawa et al[16] reported that a second primary was the second most common cause of death (90 patients) in a group of 966 patients with early-stage (I and II) oral cancer.

The issue of incidence and early detection of second primaries is part of the debate about the frequency and duration of follow up after oral cancer. There is no international consensus,[17] but Kanatas et al have suggested that early discharge into primary care after two or three years might be an appropriate use of health resources.[18] However, depending on the risk, it could be argued that follow up should be lifelong[19,20] because the chance of developing a second primary increases as survival improves. Death is a conflicting variable, as those who die early and are more likely to have advanced oral cancer, have a lower chance of developing a second primary.

Although there is evidence concerning the rates of second primaries from various continents, the aim of this study was to estimate the yearly rates of those that arise in the head and neck in a group of patients in the United Kingdom. Another aim was to find out whether any baseline characteristics (site, clinical or pathological stage, and history of smoking and alcohol consumption) were more likely to be associated. The final aim was to describe the clinical presentation, treatment, and outcome of patients with second primaries. The data might help inform both clinicians and patients about a more individualised approach to follow up based on the perceived risk over time.

Methods

We retrospectively reviewed records of patients treated surgically and curatively for primary squamous cell oral carcinoma (SCC) of the head and neck between 2002 and 2007 inclusive. Patients were followed up to the end of 2017. Electronic case notes on SIGMA (System C), outpatient clinical letters, and multidisciplinary forms were used to extract data on age, site, and treatment of the index cancer; date of death; smoking and drinking status; and on stage, site, and treatment of the second primary tumour. For current smokers the daily consumption was known for all but one patient, but the duration of smoking was unknown for almost half, and when known, was often imprecise. In the absence of clear information, a starting age of 18 was assumed, based on the US 2014 Surgeon General's Report, which stated that nearly 9 out of 10 adult smokers started before the age of 18, and also on a fact sheet statement from ASH that two-thirds of smokers start before then.[21] An estimate of pack years was based on the duration and amount consumed. For four patients it was necessary to convert the amount of tobacco (g, oz) into cigarette equivalents.

The diagnosis of a second primary was based on the Warren and Gates criteria[22] that lesions must be distinct and separated by normal tissue or in a similar locality if more than three years has elapsed.

Patients had at least 10 years of follow up either to death or the end of 2017. Fisher's exact test was used to compare subgroups with regard to mortality and second primary tumour rates within 5 and 10 years of the primary tumour. Estimates of cumulative incidence for the development of second primaries beyond 10 years were derived with the help of the StataCorp software procedure "stcompet" for use with survival-time data and data with a competing risk (mortality). Kaplan-Meier survival methods were used to estimate overall mortality after diagnosis of a second primary. Statistical significance was taken as $p < 0.05$. IBM SPSS Statistics for Windows, version 25 (IBM Corp) and Stata release 13 (StataCorp) were used for the analyses.

The project was approved by the Clinical Audit and Management System at Aintree University Hospital.

Results

A total of 347 patients (210 (61%) male and 137 (39%) female) were treated curatively and surgically for oral cancer at the regional maxillofacial unit between 2002 and 2007 inclusive. Median (IQR) age was 63 (55-73) years. The sites of the primary index tumours were the anterior two-thirds of the tongue (n = 117, 34%), floor of the mouth (n = 102, 29%), buccal region (n = 63, 18%), lower gum (n = 37, 11%), and other (n = 28, 8%). Clinical staging was early (0-2) in 190 (55%) and late (3-4) in 157 (45%); pathological staging was early in 162 (47%), late in 157 (45%), and unknown in 28 (8%). Index treatment for 220 (63%) patients comprised operation alone, while 127 (37%) had operation and adjuvant radiotherapy. Nearly half (n = 157, 45%) were current smokers, 75 (22%) were ex-smokers, and 91 (26%) non-smokers. In 24 (7%) it was not known. For current smokers the estimated median (IQR) number of pack years was 35 (24-49). Alcohol intake/week was "none/never" in 67 (19%), "low" (less than 10 units/week, social, or occasional) in 84 (24%), "moderate" (10-39 units/week) in 94 (27%), and "high" (40 or more units/week) in 71 (20%). It was unknown in 31 (9%).

Twenty-nine patients had a second primary tumour at a median (IQR) of 52 (30-79) months after index surgery (range 7.6-151 months). All patients were followed up for at least 10 years. The incidence of development of a second primary within two years was 1.7% (95% CI: 0.7% to 3.7%), within five years 4.9% (95% CI: 2.9% to 7.7%) and within 10 years 7.8% (95% CI: 5.1% to11.1%). Beyond 10 years, and using cumulative incidence software to analyse varying amounts of follow up, the cumulative incidence within 15 years was estimated to be 8.8% (95% CI: 6.0% to 12.2%) (Fig. 1). Table 1 shows the cumulative incidence over each of the first

Table 1
Second primary tumour rates over time. Data are number (%).

Endpoint (years)	Second primary and alive at endpoint	Second primary and died before endpoint	Died before endpoint without second primary	Alive at endpoint without second primary	Died before endpoint	Second primary before endpoint: cumulative incidence	If alive at endpoint how many had had a second primary
1	2 (1)	–	51 (15)	294 (85)	51 (15)	2 (1)	2/296 (1)
2	4 (1)	2 (1)	87 (25)	254 (73)	89 (26)	6 (2)	4/258 (2)
3	5 (1)	3 (1)	110 (32)	229 (66)	113 (33)	8 (2)	5/234 (2)
4	10 (3)	4 (1)	127 (37)	206 (59)	131 (38)	14 (4)	10/216 (5)
5	10 (3)	7 (2)	145 (42)	185 (53)	152 (44)	17 (5)	10/195 (5)
6	10 (3)	8 (2)	158 (46)	171 (49)	166 (48)	18 (5)	10/181 (6)
7	13 (4)	10 (3)	169 (49)	155 (45)	179 (52)	23 (7)	13/168 (8)
8	13 (4)	11 (3)	175 (50)	148 (43)	186 (54)	24 (7)	13/161 (8)
9	15 (4)	12 (4)	179 (52)	141 (41)	191 (55)	27 (8)	15/156 (10)
10	11 (3)	16 (5)	188 (54)	132 (38)	204 (59)	27 (8)	11/143 (8)

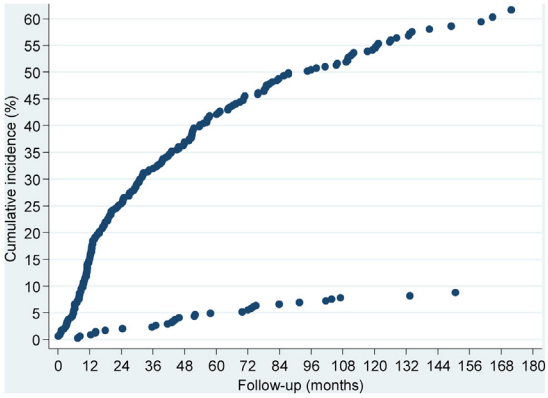

Fig. 1. Cumulative incidence of mortality (upper data) and of developing a second primary tumour (lower data).

10 years, the cumulative incidence of mortality, and information about what patients can expect at various endpoints. For example, 4.9% had developed a second primary tumour within five years, and overall 43.8% had died (some of whom (unknown) might have developed a second tumour had they lived). Of those alive at five years 5.1% had had a second primary tumour.

Table 2 shows several predictors of survival at 5 and 10 years, notably advanced age, staging of the primary tumour, and (if alive) no notable association with having had a second primary. Separate analyses of those who developed a second primary within 10 years showed that staging of the primary tumour (notably pathological staging) was the only significant association ($p = 0.001$). A total of 22 of 27 patients with second primaries had had early-stage primary index tumours, which reflects the fact that those with later-stage primary tumours would be more likely to die before the possibility of a second primary (the impact of the survivorship effect of the staging of the primary tumour on the likelihood of a second primary).

Details of the presenting symptoms, staging, site, and treatment of the second primary tumours are given in Table 3. One patient presented with both pain and swelling, eight with a white or red patch, six with a swelling or lump, five with an ulcer, four with a sore throat or difficulty swallowing, four with pain, and one with osteoradionecrosis. Tumours were staged mainly ($n = 21$) as early and by visual inspection, and only two patients (both with late-stage disease) had positive neck nodes. Most ($n = 20$) tumours were within the oral cavity, one of which overlapped the oropharynx; eight others were in the oropharynx, and one in the larynx. Fourteen patients were treated curatively by primary closure or laser surgery, seven by operation that involved free-flap transfer, four by radiotherapy or chemotherapy, and one by laryngectomy. Three were referred for palliative care. Kaplan-Meier survival methods estimated overall survival after a second primary to be 72% (SE 8%) after one year, 58% (SE 9%) after two years, and 39% (SE 9%) after five.

Discussion

Improved long-term survival after oral cancer raises the likelihood that patients will develop second primaries. Several large population-based studies have reported overall rates after cancer of the head and neck,[9,23–26] but they lack detail on rates/year (factoring in survivorship), presentation, treatment, and outcome. Our study comprised a consecutive group and, because the service is regional, we were able to account for those with second primaries, although a small number might have been lost to follow up - for example, those who moved out of the regional catchment area.

The duration of follow up was appropriate, with the minimum being 10 years, and the date of death allowed for precision in terms of statistical analysis. In the future, with younger patients and an increasing elderly population, it would be helpful to report actual rates of second primaries beyond 20 years. Our rates might have been slightly underestimated because it can sometimes be difficult to discriminate between a recurrence and a second primary, and "recurrence" tends to be recorded if the tumour develops within three years in a similar area of the mouth. We focused on second primaries of the head and neck and did not consider other new primaries such as those of the lung or oesophagus.[9,27]

Table 2
Patients' characteristics at time of primary tumour in relation to mortality and surviving with a second primary tumour.

	Mortality within 5 years		Of those alive at 5 years how many had had a second primary		Mortality within 10 years		Of those alive at 10 years how many had had a second primary	
	No. (%)	p value	No. (%)	p value	No. (%)	p value	No. (%)	p value
All patients	152/347 (44)		10/195 (5)		204/347 (59)		11/143 (8)	
Sex:								
Male	97/210 (46)	0.27	7/113 (6)	0.52	123/210 (59)	>0.99	7/87 (8)	>0.99
Female	55/137 (40)		3/82 (4)		81/137 (59)		4/56 (7)	
Age (years):								
<55	26/84 (31)		4/58 (7)		37/84 (44)		5/47 (11)	
55-64	51/118 (43)	<0.001	3/67 (4)	0.67	65/118 (55)	<0.001	1/53 (2)	0.16
65-74	29/75 (39)		3/46 (7)		42/75 (56)		4/33 (12)	
75+	46/70 (66)		0/24		60/70 (86)		1/10 (10)	
Site:								
Buccal	29/63 (46)		5/34 (15)		43/63 (68)		4/20 (20)	
Lower gum	18/37 (49)		0/19		21/37 (57)		0/16	
Tongue (ant 2/3)	37/117 (32)	0.009	3/80 (4)	0.16	48/117 (41)	<0.001	6/69 (9)	0.19
FOM	50/102 (49)		2/52 (4)		68/102 (67)		1/34 (3)	
Other	18/28 (64)		0/10		24/28 (86)		0/4	
Clinical stage:								
Early (0,1,2)	64/190 (34)	<0.001	9/126 (7)	0.10	91/190 (48)	<0.001	11/99 (11)	0.02
Late (3,4)	88/157 (56)		1/69 (1)		113/157 (72)		0/44	
Pathological stage:								
Early (0,1,2)	43/162 (27)	<0.001	8/119 (7)	0.50	74/162 (46)	<0.001	9/88 (10)	0.33
Late (3,4)	91/157 (58)		2/66 (3)		109/157 (69)		2/48 (4)	
Primary treatment:								
Surgery only	80/220 (36)	<0.001	7/140 (5)	>0.99	115/220 (52)	0.001	9/105 (9)	0.73
Surgery + radiotherapy	72/127 (57)		3/55 (5)		89/127 (70)		2/38 (5)	
Smoking:								
Current (≥35 pack years)	44/79 (56)		3/35 (9)		53/79 (67)		2/26 (8)	
Current (<35 pack years)	28/78 (36)	0.05	2/50 (4)	0.71	46/78(59)	0.16	0/32	0.12
Ex	28/75 (37)		3/47 (6)		37/75 (49)		3/38 (8)	
Never	37/91 (41)		2/54 (4)		51/91 (56)		6/40 (15)	
Alcohol:								
Never/none	29/67 (43)		1/38 (3)		42/67 (63)		1/25 (4)	
>0-<10 units/week	29/84 (35)		3/55 (5)		39/84 (46)		4/45 (9)	
10-39 units/week	36/94 (38)	0.06	4/58 (7)	0.87	52/94 (55)	0.02	5/42 (12)	0.75
40+ units/week	39/71 (55)		2/32 (6)		50/71 (70)		1/21 (5)	

Table 3
Details of the 29 patients diagnosed with second primary tumours.

Case No.	Age at primary diagnosis (years)	Months from index surgery to second primary diagnosis date	Presenting features	Tumour staging	Tumour site	Treatment	Months after second primary to death or to survival at 31-12-2017
1	66	7.56	Leukoplakia	T1N0	R lateral tongue	Surgery (primary closure/laser)	116 (alive)
2	45	8.34	Soreness L throat	T2N0	L tonsil	Surgery (free-flap)	8 (died)
3	80	12.39	Swelling	T1N0	R lip (oral)	Surgery (laser)	11 (died)
4	72	14.06	Leukoplakia	T1N0	Contralateral oropharynx	Surgery (primary closure/laser)	18 (died)
5	52	14.26	Pain / swelling / R earache	T4N0	R oropharynx	Chemoradiotherapy	32 (died)
6	70	17.91	Leukoplakia	T1N0	L buccal mucosa	Surgery (primary closure/laser)	122 (alive)
7	38	24.44	Osteoradionecrosis	T2N0	L mandible	Surgery (free-flap)	125 (alive)
8	55	35.68	Sore throat, difficulty swallowing	T3N0	R piriform	Surgery (laryngectomy)	14 (died)
9	53	37.16	Increasing swelling over R cheek	T4N0	R mandible	Surgery (free-flap)	87 (alive)
10	71	41.46	Ulcer	T1N0	L buccal mucosa	Surgery (primary closure/laser)	94 (alive)
11	45	43.07	R buccal swelling and R neck tenderness	T4N2b	Oropharynx	Surgery (free-flap)	7 (died)
12	64	43.93	Difficulty swallowing	T2N0	L oropharynx	Surgery (free-flap)	14 (died)
13	55	44.48	Leukoplakia	T2N0	R anterior floor of mouth	Surgery (primary closure/laser)	82 (alive)
14	58	45.83	Swelling in cheek/back of throat	T2N0	R lateral tongue/oropharynx	Surgery (free-flap)	48(died)
15	53	51.68	Bleeding soft palate	T2N0	Soft palate	Palliative, nursing home, cognitive impairment	9 (died)
16	63	51.94	Punched out ulcer R soft palate	T1N0	R soft palate	Surgery (primary closure/laser)	89 (alive)
17	63	57.76	Rough patch	T1N0	R anterior floor of mouth	Surgery (primary closure/laser)	51 (died)
18	80	69.88	Leukoplakia	T1N0	R maxillary alveolus	Surgery (primary closure/laser)	107 (died)
19	84	72.05	Leukoplakia	T1N0	Anterior maxillary alveolus	Palliative, cardiorespiratory comorbidity	12 (died)
20	70	73.20	Difficulty swallowing	T1N0	Border of tongue	Surgery (primary closure/laser)	4 (died)
21	50	74.05	Lump L neck	T3N1	L tonsil	Chemoradiotherapy	99 (alive)
22	59	74.94	Mass R posterior tongue	T2N0	R tongue	Surgery (primary closure/laser)	34 (died)
23	73	83.84	Sore patch/speckled leukoplakia	T1N0	L buccal mucosa	Surgery (primary closure/laser)	53 (died)
24	84	91.47	Necrotic ulcer	T4N0	L mandible alveolus	Palliative radiotherapy	10 (died)
25	66	101.59	Sore tongue	T3N0	Tongue tip	Radiotherapy	12 (died)
26	41	103.66	Sore tongue	T1N0	R tongue	Surgery (primary closure/laser)	77 (alive)
27	72	107.10	Pain	T2N0	R tongue	Radiotherapy	10 (died)
28	50	133.49	Pain	T2N0	R tongue	Surgery (primary closure/laser)	12 (alive)
29	58	150.67	Ulcer	T4N0	R mandible	Surgery (free-flap)	22 (alive)

Because of the historical case-note review, records of subsequent alcohol intake or smoking history at clinic reviews were inadequate. This could have been helpful, as we would expect these habits to increase the risk of a second primary.

Although our data reflect the experience of only one regional unit in the UK, and caution needs to be applied when extrapolating them to other institutions, the two key findings are the effect of survival, and the presentation of second primaries. Overall, the 10-year rate of development of a second primary was 8% and the incidence increased year on year (nearly 2% after two, and nearly 5% after five). The overall rate is in keeping with other publications. Patients with more advanced disease at presentation had less time to develop a second primary, as they tended to die sooner than those with earlier disease. Survival was also affected by age, so the elderly who died had less time to develop a second primary.[26] In our group most cases occurred in the mouth or oropharynx.

Preventive strategies aimed at reducing the occurrence of second primaries, such as life-style advice about alcohol and smoking, are important. To minimise delay to referral, symptoms - for example, pain, swelling or lump, a white or red patch, ulcer, sore throat, or difficulty swallowing, could be identified in primary care. It is also appropriate to inform patients about the rate, presenting symptoms, and likely site of a second primary, to reduce delay before they seek professional advice. They should be encouraged to attend regular appointments for surveillance by a dentist even if edentulous, for example, every six months, and told not to wait until their scheduled appointment if they notice any symptoms. Some patients might be reluctant to seek urgent opinion as they might feel that they are worrying needlessly and would be embarrassed about this. They might also feel that they are wasting an appointment that could be given to another patient.

To optimise disease-specific survival and reduce the burden of further treatment and dysfunction, early detection of a second primary is key.[6] Patients should be reassured by the evidence that most second primaries that are detected early can be treated by primary closure, laser, or resection and free-tissue reconstruction. With increasing intervals of time between follow-up appointments at hospital or discharge, or both,[18] mechanisms that allow for a rapid referral back into clinic should be easy for patients to access when they are concerned. Appropriate information sheets need to be developed to give to patients at discharge, and close collaboration between primary and secondary care fostered.

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Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

The data, which had been collected as part of a service audit rather than for research, met the criteria of the local clinical governance department for service evaluation. Patients' permission not required for this analysis and data presentation.

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