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

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Abstract

Patients following their initial presentation of oral squamous cell carcinoma (SCC) have a lifelong risk of another new head and neck SCC. The present study aimed to establish the rates of second primary (SP), baseline characteristics (site, clinical or pathological stage, smoking and alcohol history), timing, presentation, treatment and outcomes. From the regional unit, records of patients treated with curative intent for their first oral cancer between 2002 and 2007 inclusive were analysed. Patients had at least 10 years of follow-up either to death or to the end of 2017. Of 347 patients treated with curative intent 29 had a SP at a median (IQR) of 52 (30-79) months after index surgery. All patients had at least 10 years of follow-up and the incidence of developing a second primary tumour within 2 years was 1.7% (95% CI: 0.7-3.7%), within 5 years was 4.9% (95% CI: 2.9-7.7% and within 10 years was 7.8% (95% CI: 5.1-11.1%). Early stage of first cancer was the only statistically significant factor (P=0.001) for SP within 10 years reflecting survivorship. SP were mainly (21 patients) staged as early and by visual inspection. Most (20) were located within the oral cavity with one of these overlapping the oropharynx, oropharynx (8) and larynx (1). The majority (22) were treated by surgery with curative intent and 3 were palliative. Patients need to be aware of the risk of SP and as most are in the mouth or oropharynx there is a role for surveillance by primary dental care.

Introduction

Following treatment for oral cancer there is a risk of developing a second primary (SP). The rate is varies in published papers, 3% to 7% [1], 7% [2], 9% [3] 11% [4,5], 13% [6] and as high as 18.4%.[7] Of the head and neck sites, oral cavity and oropharynx are more likely to develop a SP. [8,9,10] Risk factors include continuing smoking and alcohol consumption,[11,12,13] areca quid chewing [5] and the presence of multiple oral dysplastic lesions.[14] The location of the SP is influenced by causative factors for example following betel-nut chewing related oral cancer an annual SP incidence of 5% has been reported with three quarters occurring in the oral cavity. [15] The clinical significance of SP following head and neck cancer has been reflected in poor prognosis [10] with overall survival rates at 5 years as low as 15%. [9] Fujisawa [16] reported that SP was the second most frequent cause of death (90 patients) in a cohort of 966 patients with early-stage (stage I and II) oral cancer.

The issue of incidence and early detection of SP is part of the debate as to the frequency and length of head and neck clinic follow-up following oral cancer. There is no international consensus. [17] It has been suggested that for oral cancer an early discharge into primary care after two or three years might be an appropriate use of health resources. (Kanatas) [18] However, depending on risk of SP it could be argued that follow-up should be lifelong. [19,20] As survival rates improve then so does the chance of developing a SP. Death is a conflicting variable as those who die early, and who are more likely to have advanced oral cancer, have less chance of developing a SP. Although there is evidence concerning SP rates from various continents, the aim of this study was to estimate the yearly rates of second primary (SP) arising in the head and neck region for a United Kingdom based patient group. Another aim was to identify if any baseline characteristics (site, clinical or pathological stage, smoking and alcohol history) were more likely to be associated with SP rates. The final aim was to describe the clinical presentation, treatment and outcome of SP cases. The data might help inform both clinicians and patients as to a more individualised approach to follow-up based on perceived risk of developing SP over time.

Methods

Retrospective records of patients treated surgically and curatively for primary head and neck squamous cell oral carcinoma between 2002 and 2007 inclusive were reviewed. Patient

follow-up was to the end of 2017. Electronic case notes on SIGMA, outpatient clinical letters and MDT forms were used to extract data including age, site and treatment of index cancer, date of death, smoking and drinking status and details about the stage, site and treatment of the second primary tumour. For current smokers the daily consumption was known for all but one patient; however, 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, this being based on the US 2014 Surgeon General's Report stating that nearly 9 out of 10 adult smokers started before age 18 and also on a fact sheet statement from ASH that two-thirds of smokers start before age 18. [21] On the basis of duration and amount consumed an estimate of pack years was obtained. For 4 patients a conversion between amount of tobacco (g, oz) was required in order to put it into cigarette equivalents.

Diagnosis of Second Primary tumours was based on the Warren and Gates criteria [22] by which each lesion is distinct and separated by normal tissue, or of in a similar locality if greater than 3 years had elapsed.

Patients had at least 10 years of follow-up either to death or to the end of 2017. Fishers exact test was used to compare patient subgroups in regard to mortality and second primary tumour rates within 5 years and within 10 years of the primary tumour. Estimates of cumulative incidence for developing second primaries beyond 10 years were derived from using the STATA software procedure 'stcompet', for use with survival-time type data and with a competing risk (mortality). Kaplan-Meier survival methods were used to estimate overall mortality rates following the diagnosis of a second primary. Statistical significance was taken as $p<0.05$. SPSS v25 and STATA v13 were used for the analyses.

The project received approval by the Clinical Audit and Management System at Aintree University Hospital.

Results

347 patients were treated curatively and surgically for oral cancer at the Regional Maxillofacial Unit between 2002 and 2007 inclusive, comprising 61% (210) male and 39% (137) female. Median (IQR) age was 63 (55-73) years. For 34% (117) the primary index tumour was located in the anterior two-thirds of the tongue, 29% (102) floor of mouth, 18% (63) buccal region, 11% (37) lower gum and 8% (28) other places. Clinical staging was early

(0-2) for 55% (190) and late (3-4) for 45% (157); pathological staging was early for 47% (162), late for 45% (157) and unknown for 8% (28). Index treatment for 63% (220) comprised surgery alone while 37% (127) had surgery and adjuvant radiotherapy. Nearly half (45%, 157) were current smokers, 22% (75) ex-smokers, 26% (91) non-smokers, with no documentation for 7% (24). For current smokers the estimated median (IQR) number of pack years was 35 (24-49). Alcohol intake per week was either 'none/never' for 19% (67), 'low' (<10 units per week, social, occasional) for 24% (84), 'moderate' (10-39 units per week) for 27% (94) or 'high' (40 or more units per week) for 20% (71), and unknown for 9% (31).

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 had at least 10 years of follow-up and the incidence of developing a second primary tumour within 2 years was 1.7% (95% CI: 0.7-3.7%), within 5 years was 4.9% (95% CI: 2.9-7.7% and within 10 years was 7.8% (95% CI: 5.1-11.1%). Beyond 10 years and using cumulative incidence software to analyse variable amounts of follow-up the cumulative incidence within 15 years was estimated as 8.8% (95% CI: 6.0-12.2%), Figure 1. Table 1 details the cumulative incidence over each of the first ten years. It also details the cumulative incidence of mortality and also information for what patients can expect at various survival endpoints. For example, within five years 4.9% had developed a second primary tumour within five years and overall 43.8% had died; some (unknown) of those who died might have developed a second tumour had not death intervened. Of those alive at five years 5.1% had had a second primary tumour. Table 2 indicates several predictors of survival at five and ten years, notably advanced age and staging of the primary tumour, and (if alive) no notable association with having had a second primary. Separate analyses of developing a second primary tumour within ten years yielded no statistically significant association other than with staging of the primary tumour, notably pathological staging (P=0.001) with 22 of 27 patients with second primaries having had early primary index tumours, reflecting survivorship following the impact of primary tumour staging on patient mortality.

Details of presenting symptoms, staging, site and treatment of the second primary tumours are given in Table 3. One patient presented with both pain and swelling, 8 with a white or red patch, 6 with a swelling or lump, 5 with an ulcer, 4 with a sore throat or difficulty swallowing, 4 with pain and 1 with osteoradionecrosis. Tumours were staged mainly (21) as early and by visual inspection and only 2 (both late tumours) had positive neck nodes. Most

(20) were located within the oral cavity with one of these overlapping the oropharynx; 8 others were in the oropharynx and one in the larynx. Fourteen patients were treated curatively by primary closure or laser surgery, 7 by surgery involving free-flap transfer, 4 by radiotherapy/chemotherapy and 1 by laryngectomy. Three patients were referred for palliative care. Kaplan-Meier survival methods estimated overall survival following a SP to be 72% (SE 8%) after 1 year, 58% (SE 9%) after 2 years and 39% (SE 9%) after 5 years.

Discussion

Improved long-term survival following oral cancer leads to a higher likelihood of developing a SP. There are several large population-based studies reporting overall SP rates following HNC, [9, 23,24,25,26] however these lack detail on rates per year factoring in survivorship, also presentation, treatment and outcome. This study comprises a consecutive cohort and due to the regional service, it has been possible to carefully account for those with SP. A very small number of patients with SP might have been lost to follow-up, for example those who subsequently move out of the regional catchment area. The length of follow up is appropriate with the minimum being 10 years and the date of death has allowed for precision in terms of statistical methodology. In the future, with younger patients and increasing elderly population, it would be helpful to report actual SP rates beyond 20 years. The SP rates might be slightly underestimated because for some patients it can be difficult to discriminate between recurrence or SP, and recurrence tends to be allocated if the tumour occurs in a similar area of the mouth within 3 years. In this study the focus has been on head and neck SP and other new cancer primaries such as lung or oesophageal were not considered. [9,27] Due to the historical case note review there was unfortunately an inadequate record of subsequent alcohol intake or smoking history at clinic reviews. This would potentially have been helpful as these habits would be expected to increase the risk of SP.

Although this data reflects the experience of only one regional unit in the UK, and caution needs to be applied when extrapolating the finding to other institutions, the two key finding are the survivorship effect and the presentation of SP. Overall, the ten-year SP rate was 8% with the incidence increasing year on year, at nearly 2% after two years and nearly 5% after five years. The overall rate is in keeping with other publications Patients with more advanced disease at presentation had less time to develop a SP as they tended to demise sooner than those with earlier oral cancer. In addition, survival is affected by age, so the elderly who

demise have less time to develop a SP. [26] In our cohort most SP occurred in the mouth or oropharynx. Preventive strategies aimed at reducing SP occurrence such as life style advice related to alcohol and smoking are important elements. The symptoms of SP are those that could possibly be recognised in primary care thus minimising delay to referral, for example pain, swelling or lump, a white or red patch, ulcer, sore throat or difficulty swallowing. It is appropriate to inform patients of the rate, presenting symptoms and likely site of SP following oral cancer, so that they might reduce patient delay prior to seeking professional advice. They should be encouraged to keep regular surveillance with a dentist even if edentulous, for example every 6 months. If they were to experience symptoms they should be encouraged not to wait until their scheduled appointment but get checked out early. Some patients might be reluctant to seek urgent opinion as they might feel that they are worrying needlessly and would feel embarrassed about this. Also, they might feel that they are wasting a clinic that a consultant could use for another patient.

Early detection of a SP is a key factor in reducing further treatment burden, dysfunction and optimising disease specific survival. [6] Patients should be reassured by the evidence that if a SP is detected early most are treatable with primary closure, laser, or resection and free tissue reconstruction. With increasing time intervals between follow-up appointments at hospital or and ultimately discharge, [18] patients should have an easy mechanism to allow rapid assessment back into clinic if new symptoms of concern are raised. Appropriate patient information material needs to be developed as part of a discharge information sheet and close collaboration between primary and secondary care fostered.

Conflict of interest statement

We have no conflicts of interest.

Ethics statement/confirmation of patient's 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.

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Table(s)

Table 1. Second primary tumour rates over time

Endpoint	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	
	%	n	%	n	%	n	%	n	%	n	%	n	%	n
1 year	0.6	2	-	-	14.7	51	84.7	294	14.7	51	0.6	2	0.7	2/296
2 years	1.2	4	0.6	2	25.1	87	73.2	254	25.6	89	1.7	6	1.6	4/258
3 years	1.4	5	0.9	3	31.7	110	66.0	229	32.6	113	2.3	8	2.1	5/234
4 years	2.9	10	1.2	4	36.6	127	59.4	206	37.8	131	4.0	14	4.6	10/216
5 years	2.9	10	2.0	7	41.8	145	53.3	185	43.8	152	4.9	17	5.1	10/195
6 years	2.9	10	2.3	8	45.5	158	49.3	171	47.8	166	5.2	18	5.5	10/181
7 years	3.7	13	2.9	10	48.7	169	44.5	155	51.6	179	6.6	23	7.7	13/168
8 years	3.7	13	3.2	11	50.4	175	42.7	148	53.6	186	6.9	24	8.1	13/161
9 years	4.3	15	3.5	12	51.6	179	40.6	141	55.0	191	7.8	27	9.6	15/156
10 years	3.2	11	4.6	16	54.2	188	38.0	132	58.9	204	7.8	27	7.7	11/143

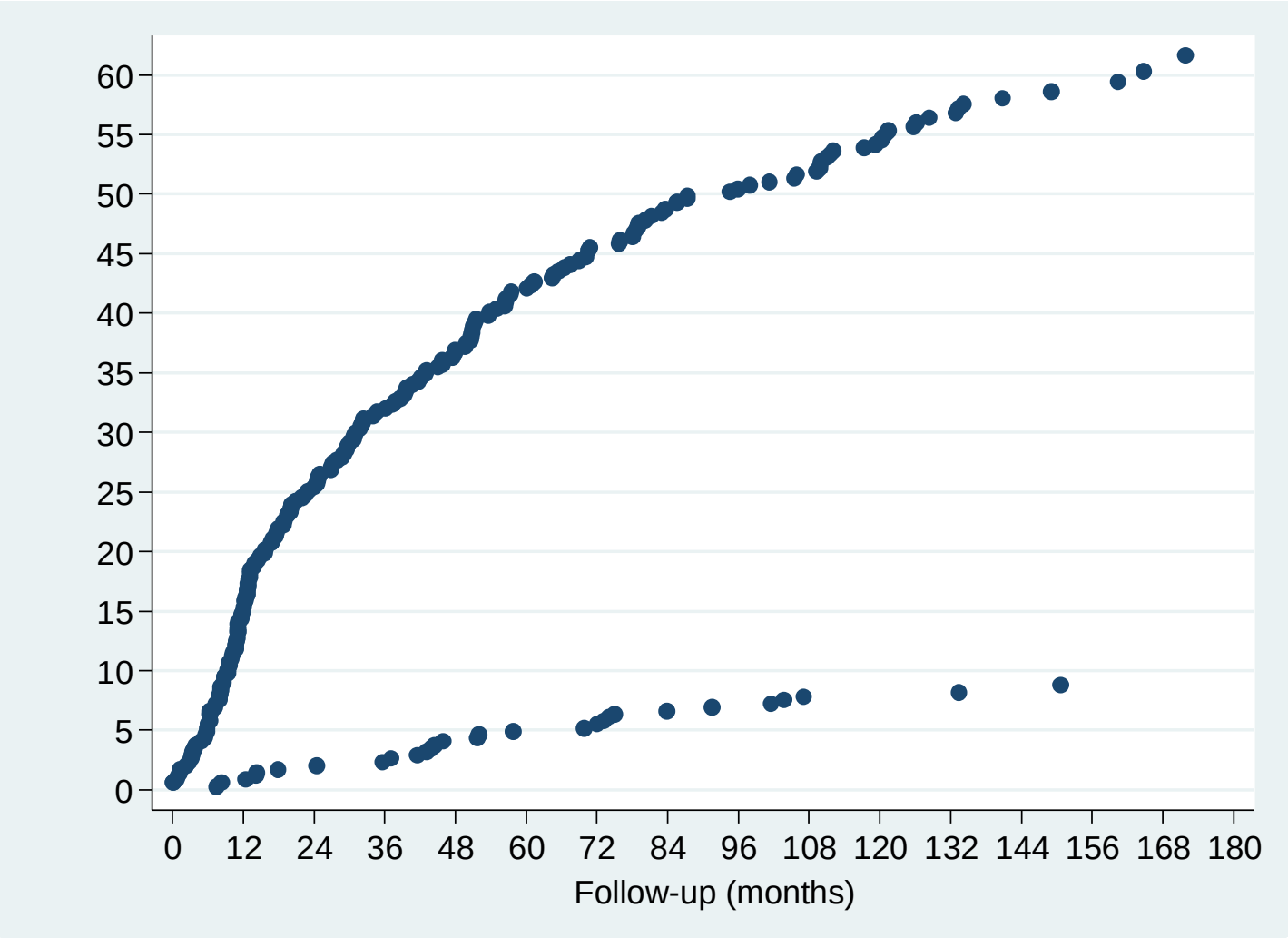
Table 2. Patient characteristics at time of primary tumour in relation to mortality and to surviving with a second primary tumour

		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		
		%	n		%	n		%	n		%	n	
All patients		44	152/347	P value	5.1	10/195	P value	59	204/347	P value	7.7	11/143	P value
Gender	Male	46	97/210	0.27	6.2	7/113	0.52	59	123/210	>0.99	8.0	7/87	>0.99
	Female	40	55/137		3.7	3/82		59	81/137		7.1	4/56	
Age	<55	31	26/84	<0.001	6.9	4/58	0.67	44	37/84	<0.001	10.6	5/47	0.16
	55-64	43	51/118		4.5	3/67		55	65/118		1.9	1/53	
	65-74	39	29/75		6.5	3/46		56	42/75		12.1	4/33	
	75+	66	46/70		0.0	0/24		86	60/70		10.0	1/10	
Site	Buccal	46	29/63	0.009	14.7	5/34	0.16	68	43/63	<0.001	20.0	4/20	0.19
	Lower gum	49	18/37		0.0	0/19		57	21/37		0.0	0/16	
	Tongue (ant 2/3)	32	37/117		3.8	3/80		41	48/117		8.7	6/69	
	FOM	49	50/102		3.8	2/52		67	68/102		2.9	1/34	
	Other	64	18/28		0.0	0/10		86	24/28		0.0	0/4	
Clinical stage	Early 0,1,2	34	64/190	<0.001	7.1	9/126	0.10	48	91/190	<0.001	11.1	11/99	0.02
	Late 3,4	56	88/157		1.4	1/69		72	113/157		0.0	0/44	
Pathology Stage)	Early 0,1,2	27	43/162	<0.001	6.7	8/119	0.50	46	74/162	<0.001	10.2	9/88	0.33
	Late 3,4	58	91/157		3.0	2/66		69	109/157		4.2	2/48	
Primary Treatment	Surgery only	36	80/220	<0.001	5.0	7/140	>0.99	52	115/220	0.001	8.6	9/105	0.73
	Surgery+ RT	57	72/127		5.5	3/55		70	89/127		5.3	2/38	
Smoking	Current (≥35 pack years)	56	44/79	0.05	8.6	3/35	0.71	67	53/79	0.16	7.7	2/26	0.12
	Current (<35 pack years)	36	28/78		4.0	2/50		59	46/78		0.0	0/32	
	Ex	37	28/75		6.4	3/47		49	37/75		7.9	3/38	
	Never	41	37/91		3.7	2/54		56	51/91		15.0	6/40	
Alcohol	Never/None	43	29/67	0.06	2.6	1/38	0.87	63	42/67	0.02	4.0	1/25	0.75
	>0-<10 units / wk	35	29/84		5.5	3/55		46	39/84		8.9	4/45	
	10-39 units / wk	38	36/94		6.9	4/58		55	52/94		11.9	5/42	
	40+ units / wk	55	39/71		6.3	2/32		70	50/71		4.8	1/21	

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

Age at primary diagnosis	Months from index surgery to second primary diagnosis date	Presenting features	Tumour staging	Tumour location	Treatment	Months after second primary to death or to survival at 31-12-2017
66	7.56	Leukoplakia	T1N0	R lateral tongue	Surgery (Primary closure/laser)	116 (alive)
45	8.34	Soreness L throat	T2N0	L Tonsil	Surgery (Free-flap)	8 (died)
80	12.39	Swelling	T1N0	R lip (oral)	Surgery (Laser)	11 (died)
72	14.06	Leukoplakia	T1N0	Contralateral oropharynx	Surgery (Primary closure/laser)	18 (died)
52	14.26	Pain / swelling / R earache	T4N0	R Oropharynx	Chemo-radiotherapy	32 (died)
70	17.91	Leukoplakia	T1N0	L buccal mucosa	Surgery (Primary closure/laser)	122 (alive)
38	24.44	Osteoradionecrosis	T2N0	L mandible	Surgery (Free-flap)	125 (alive)
55	35.68	Sore throat, difficulty swallowing	T3N0	R piriform	Surgery (Laryngectomy)	14 (died)
53	37.16	Increasing swelling over R cheek	T4N0	R mandible	Surgery (Free-flap)	87 (alive)
71	41.46	Ulcer	T1N0	L buccal mucosa	Surgery (Primary closure/laser)	94 (alive)
45	43.07	R buccal swelling and R neck tenderness	T4N2b	Oropharynx	Surgery (Free-flap)	7 (died)
64	43.93	Difficulty swallowing	T2N0	L oropharynx	Surgery (Free-flap)	14 (died)
55	44.48	Leukoplakia	T2N0	R anterior floor of mouth	Surgery (Primary closure/laser)	82 (alive)
58	45.83	Swelling in cheek/back of throat	T2N0	R lateral tongue/oropharynx	Surgery (Free-flap)	48 (died)
53	51.68	Bleeding soft palate	T2N0	Soft palate	Palliative, nursing home, cognitive impairment	9 (died)
63	51.94	Punched out ulcer R soft palate	T1N0	R soft palate	Surgery (Primary closure/laser)	89 (alive)
63	57.76	Rough patch	T1N0	R anterior floor of mouth	Surgery (Primary closure/laser)	51 (died)
80	69.88	Leukoplakia	T1N0	R maxillary alveolus	Surgery (Primary closure/laser)	107 (died)
84	72.05	Leukoplakia	T1N0	Anterior maxillary alveolus	Palliative, cardio-respiratory comorbidity	12 (died)
70	73.20	Difficulty swallowing	T1N0	Border of tongue	Surgery (Primary closure/laser)	4 (died)
50	74.05	Lump L neck	T3N1	L tonsil	Chemo-radiotherapy	99 (alive)
59	74.94	Mass R posterior tongue	T2N0	R tongue	Surgery (Primary closure/laser)	34 (died)
73	83.84	Sore patch/speckled leukoplakia	T1N0	L buccal mucosa	Surgery (Primary closure/laser)	53 (died)
84	91.47	Necrotic ulcer	T4N0	L mandible alveolus	Palliative radiotherapy	10 (died)
66	101.59	Sore tongue	T3N0	Tongue tip	Radiotherapy	12 (died)
41	103.66	Sore tongue	T1N0	R tongue	Surgery (Primary closure/laser)	77 (alive)
72	107.10	Pain	T2N0	R tongue	Radiotherapy	10 (died)
50	133.49	Pain	T2N0	R tongue	Surgery (Primary closure/laser)	12 (alive)
58	150.67	Ulcer	T4N0	R mandible	Surgery (Free-flap)	22 (alive)

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



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

Simon N Rogers, Aoife Swain, Conor Carrol, Derek Lowe

Conflict of interest statement

We have no conflicts of interest.

Ethics statement/confirmation of patient's permission

The project received approval by the Clinical Audit and Management System at Aintree University Hospital.

Confirmation of Authorship

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CONFIRMATION OF AUTHORSHIP

TITLE: INCIDENCE, TIMING, PRESENTATION, TREATMENT AND OUTCOMES OF SECOND HEAD AND NECK SQUAMOUS CELL CARCINOMA FOLLOWING ORAL CANCER.

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