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Second Primary Tumours of the Head and Neck are not Associated with Adverse Overall Survival in Oral Squamous Cell Carcinomas

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Abstract

Objective: Second primary tumours (SPT) have been implicated in the dismal overall survival (OS) of head and neck Squamous cell carcinomas (HNSCC). The incidence of SPT, the SPT diagnostic time-lag and the impact on OS were assessed.

Subjects and methods: 363 consecutive patients treated for primary oral SCCs (1967-2004) were analyzed retrospectively in this study. 95.1% and 90.5% of patients reached a minimum follow-up period of 3 and 5 years respectively.

Results: Of 363 patients; 68 (18.7%) were diagnosed with metachronous SPT, 49 (13.5%) developed upper aerodigestive tract (UAD)-SPT, 28 (7.7%) were diagnosed with HNSCC-SPT, and 21 (5.8%) developed lung or esophageal carcinoma. Patients with subsequent HNSCC-SPT had a better median survival during follow-up than those not diagnosed with SPTs (p=0.0018). The rate of mortality in these patients showed a substantial increase compared to patients with no subsequent SPT Diagnosis after 144 months. After 200 months the survival experience was no better than those without SPT.

Conclusion: These results suggest a better OS for patients afflicted with HNSCC-SPT. This also reflects that at least some of the noted improved OS of HNSCC-SPT patients is due to temporally cumulated risk associated with developing SPT.

Keywords: Oral squamous cell carcinoma; Second primary tumours; Prognosis; Overall survival

Introduction

Head and neck squamous cell carcinoma (HNSCC) incidence, morbidity and mortality remain a serious public health issue. Despite relatively early diagnosis, treatment and accessible anatomical surveillance, oral squamous cell carcinoma (OSCC) continues to have poor outcomes including poor overall survival (OS) [1]. Second primary tumours (SPT), a well established phenomenon in HNSCC, are universally considered to be a poor prognostic indicator for OS. Reports of SPT incidence vary from 2-30% [2-6]. These involve the upper aerodigestive (UAD) tract as well as remote sites.

The field cancerisation theory first put forward by Slaughter asserts that repeated exposure of the UAD mucosa to carcinogens, chiefly tobacco and alcohol, result in independent neoplastic tissues along the tract that are separated by site and time [7]. Many previous reports have either lacked adequate follow-up or have suffered from inconsistencies in diagnostic criteria and patient selection [8].

The aim of this study was, first to establish the incidence and risk of developing UAD-SPT in patients diagnosed with OSCC and second, to appraise the OS rates of patients with SPT in this cohort.

Materials and Methods

Patients

A single center retrospective analysis of 371 patients treated for primary OSCC at Prince of Wales Hospital Department of Radiation Oncology (1967-2007) was undertaken. To ensure a minimal three-year follow-up, only patients commencing treatment for their primary OSCC between 1967 and 2004 were used in this study. Ethics approval was obtained in accordance with the National Health and Medical Research Council from the South-East Area Health Service Ethics Committee. All regular patient follow-up was undertaken at Prince of Wales Multi-disciplinary Outpatient Radiation Oncology clinics.

Diagnosis of SPTS were based on the Warren and Gates criteria: [9]

1. Each lesion is distinct and separated by normal tissue
2. The possibility of metastasis is excluded
3. Histological documentation of each malignancy at the time of diagnosis

The patient cohort was divided into two broad groups: those with a subsequent diagnosis of SPT and those free from SPT during follow-up. Five patients were diagnosed with synchronous SPT (within 6 months of the primary OSCC), and three patients were missing information on the time of SPT occurrence. After excluding these cases 363 patients remained to be studied. The total patients lost during follow-up were, 18 (5.0%) and 37 (10.2%) at three and five years respectively. Patients diagnosed with SPT were further stratified into those occurring in the UAD-SPT (either HNSCC or lung/oesaphageal), and those that occurred elsewhere (Remote-SPT). Lung lesions were designated SPT only if solitary and histologically distinct from the index tumour.

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At diagnosis and treatment of primary OSCC, a number of clinical parameters were recorded, including age, tumour stage, nodal stage, clinical stage, and treatment mode. Following treatment of the primary tumour any local or nodal recurrence was noted. Local recurrence was defined as a lesion growing at the primary tumour site, not separated by any normal tissue, with histological findings supporting recurrence. Mortality was recorded to the nearest month and information on HNSCC specific death was also available. Clinical parameters of the patient cohort are presented in Table 1.

Statistical analysis

Stata 10.1 was used for all statistical analysis. Initially patient characteristics were assessed across the SPT subgroups using a Pearson Chi-Squared test. For groups with small expected cell frequencies, the Fisher Exact Test was used but there was little difference from the Chi-squared test and so it is not reported. Due to the small number of oesophageal SPT, this subgroup was combined with the lung SPT subgroup.

Time to SPT occurrence and OS were assessed for different patient groups using log-rank and Wilcoxon tests. Further analysis was carried using Cox's proportional hazard model to compare the survival of HNSCC-SPT against no SPT patients after adjustment for recurrence.

Results

Patient characteristics

Three-hundred and sixty-three patients diagnosed and treated for primary OSCC were included in this study. During a median follow-up period of 44 months (range 0-314 months), 68 (18.7%) developed metachronous SPT. The majority of these (49, 13.5%) were UAD-SPT. The HNSCC-SPT were dominant at 28 (7.7%), followed by lung at 18 (5.0%) and a small number (3 or 0.8%) of oesophageal malignancies.

	Second Primary Tumor Status				
Clinical Parameters	**None**	**HNSCC**	**Lung/ Oesophagus**	**Remote**	**p –value***
Age					
<65	172 (81%)	18 (8%)	9 (4%)	14 (7%)	0.230
≥65	123 (82%)	10 (7%)	12 (8%)	5 (3%)	
Sex					
Male	188 (80%)	22 (9%)	14 (6%)	11 (5%)	0.086
Female	107 (84%)	6 (5%)	7 (5%)	8 (6%)	
Index Tumour Stage†					
1	87 (85%)	5 (5%)	6 (6%)	4 (4%)	0.784
2	123 (79%)	16 (10%)	9 (6%)	7 (5%)	
3	62 (82%)	4 (5%)	4 (5%)	6 (8%)	
4	21 (75%)	3 (11%)	2 (7%)	2 (7%)	
Index Nodal Stage					
0	206 (81%)	22 (9%)	14 (5%)	13 (5%)	0.197
1	47 (80%)	6 (10%)	1 (2%)	5 (8%)	
2	40 (85%)	0 (0%)	6 (13%)	1 (2%)	
3	2 (100%)	0 (0%)	0 (0%)	0 (0%)	
Index Clinical Stage†					
1	76 (85%)	5 (6%)	4 (4%)	4 (4%)	0.799
2	97 (78%)	14 (11%)	8 (6%)	5 (4%)	
3	75 (81%)	6 (6%)	5 (5%)	7 (8%)	
4	45 (82%)	3 (5%)	4 (7%)	3 (5%)	
Recurrence‡					
No Recurrence	147 (74%)	21 (11%)	18 (9%)	14 (7%)	0.001
Local Recurrence Only	78 (89%)	7 (8%)	1 (1%)	2 (2%)	
Nodal Recurrence Only	39 (98%)	0 (0%)	1 (3%)	0 (0%)	
Both Nodal and Local	31 (91%)	0 (0%)	0 (0%)	3 (9%)	
Treatment Modality					
Radiotherapy Alone	69 (85%)	3 (4%)	4 (5%)	5 (6%)	0.775
Surgery Alone	119 (81%)	12 (8%)	8 (5%)	8 (5%)	
Surgery + Radiotherapy	98 (80%)	12 (10%)	7 (6%)	5 (4%)	
Radiotherapy-> Surgery	9 (69%)	1 (8%)	2 (15%)	1 (8%)	
Status					
Non HNSCC death	100 (66%)	20 (13%)	20 (13%)	11 (7%)	0.000
HNSCC death	123 (98%)	1 (1%)	0 (0%)	2 (2%)	
Alive	72 (84%)	7 (8%)	1 (1%)	6 (7%)	
All Cause Death					
Yes	223 (81%)	21 (8%)	20 (7%)	13 (5%)	0.177
No	72 (84%)	7 (8%)	1 (1%)	6 (7%)	

Row percentages shown in braces
*P-value calculated across columns
† 2 patients missing tumor and clinical stage information
‡1 patient missing local recurrence information

Table 1: Patient groups and characteristics.

Nineteen (5.2%) developed remote-SPT. Comparison of clinico-pathologic criteria of patients did not indicate any important differences across the SPT categories except for local and nodal recurrence (Table 1).

SPT timing, location and effect on survival

Comparison of median survival amongst patients indicated a superior OS of those diagnosed with a UAD-SPT (112 months from the diagnosis of the primary tumor) when compared to patients without SPT (40 months). Further analysis confirmed this to be confined to the HNSCC-SPT subset (Table 2, Figure 1). A further analysis comparing OS in patients with recurrence showed that the superior survival in HNSCC-SPT patients is not as strong in patients without a recurrence (Table 3). Cox proportional hazard regression analysis (Table 4) showed that patients with HNSCC-SPT have a mortality rate 51% less than those patients without SPT after adjustment for local and nodal recurrence. To explore the possibility that this is a selection bias the same Cox analysis was conducted on subjects that had survived for at least 24 months (Table 5). This showed that the rate of death for the HNSCC-SPT groups is still lower than the 'No SPT' group but no longer statistically significant. The median diagnostic time delay from the onset of the index tumor to UAD-SPT was the longest for the HNSCC type. Head and neck specific survival could not be analyzed across SPT subgroups, due to lack of events in patients with SPT.

Discussion

The adverse survival prognostic effect of HNSCC-SPTs has long been accepted [3,6,10]. An increased incidence of other malignancies including bladder, pancreas and colorectal cancers has also been reported, but pathogenic theories have focused on UAD malignancies. [10] 'Condemned' mucosa or field cancerisation theory has been proposed as the basis of SPT development. Consistent with this overall theory, recent investigations examining the molecular basis of SPTs claim that at least a proportion of these originate from a single contiguous pre-malignant epithelial field, the so called second field tumours [11,12]. Studies differ widely (2-30%) in their estimated risk of SPT development in part due to inconsistencies in patient selection or diagnostic criteria as well as generally inadequate follow up (Table

Patient Groups Overall Survival Comparisons	Median follow up	Survival (months)		95% Confidence Interval for the Median Survival		Wilcoxon	Log-Rank
		Median	Std. Error	Lower	Upper		
no SPT	31	40	5.40	30	54	<0.001	0.011
UAD SPT	91	112	10.85	60	140		
no SPT	31	40	5.40	30	54	<0.001	0.002
HNSCC SPT	134	151	4.55	78	188		
no SPT	31	40	5.40	30	54	0.159	0.974
lung/oesophagus SPT	60	60	2.66	33	116		
no SPT	31	40	5.40	30	54	0.017	0.047
remote SPT	94	94	6.92	46	171		

Table 2: Comparative overall survival of patient groups.

Survival Comparisons		Survival (months)		95% Confidence Interval for the Median survival		Wilcoxon	Log-Rank
SPT	**Recurrence (local and/or nodal)**	**Median**	**Std. Error**	**Lower**	**Upper**		
no SPT	**Yes**	16	0.93	14	22	0.006	0.013
HNSCC SPT	**Yes**	110	7.49	41	*		
no SPT	**No**	109	6.74	77	119	0.062	0.274
HNSCC- PT	**No**	152	5.67	78	197		

* not estimable (beyond the range of the data)

Table 3: Overall survival comparison for HNSCC-SPT and no SPT within all recurrence strata.

Variable	Hazard Ratio	95% Confidence Interval		p-value
		Lower	Upper	
Developed HNSCC-SPT	0.49	0.31	0.78	0.002
Local Recurrence	3.23	2.45	4.25	<0.001
Nodal Recurrence	1.31	0.97	1.77	0.074

Table 4: Cox proportional hazard model for overall survival comparing patients that developed HNSCC-SPT with those that did not develop SPT.

Variable	Hazard Ratio	95% Confidence Interval		p-value
		Lower	Upper	
Developed HNSCC-SPT	0.67	0.40	1.10	0.113
Local Recurrence	2.77	1.82	4.18	<0.001
Nodal Recurrence	1.13	0.71	1.79	0.621

Table 5: Cox proportional hazard model for overall survival comparing patients that developed HNSCC-SPT with those that did not develop SPT (for patients surviving a minimum of 24 months).

Author	Patient (n)	Index Site	Time delay to SPT (Yrs)	Incidence of SPT		Site of SPT							
						HNSCC-SPT		Lung-SPT		Oesophagus-SPT		Remote-SPT	
				No	%	No	%	No	%	No	%	No	%
Berg[13]	1651	HNSCC	-	167	10.1	30	1.8	39	2.4	11	0.7	-	-
Boice[14]	4139	Larynx	1-4	541	13.1	40	1.0	178	4.3	19	0.5	139	3.4
Brown[15]	1600	HNSCC	5	61	3.8	16	1	18	1.1	-	-	17	1.1
Cohn[16]	267	Larynx	-	44	17	16	6.0	10	3.7	12	4.5	10	3.7
De Viri[18]	1660	Larynx	5.5	84	5	5	0.3	25	1.5	4	0.2	52	3.1
DeVries[29]	748	Larynx	4	104	14	9	1.2	64	8.6	0	0	31	4.1
Gluckman[19]	5337	HNSCC	-	548	11.2	246	5.0	181	3.7	120	2.5	-	-
Haughey[20]	3706	HNSCC	-	475	12.8	246	6.6	106	2.9	17	0.5	159	4.3
Larson[10]	875	HNSCC	1.5	207	23.7	126	14.4	54	6.2	13	1.5	-	-
Leon[6]	1074	Larynx	-	169	15.7	48	4.5	66	6.1	13	1.2	39	3.9
Lin[5]	662	Larynx	-	51	7.7	6	0.9	31	4.7	2	0.3	-	-
Lundgren[21]	295	Larynx	6.3	32	10.8	10	3.4	12	4.1	2	0.7	-	-
Masaki[22]	3162	HNSCC	-	182	5.8	66	2.1	34	1.1	-	-	18	0.6
McDonald[23]	235	Larynx	4	50	21	9	3.8	22	9.4	-	-	16	6.8
Miyahara[24]	1389	Larynx	0-23	138	9.95	43	3.1	23	1.7	3	0.2	68	4.9
Olsen[25]	3847	HNSCC	1-4	368	9.6	16	0.4	131	3.4	-	-	100	2.6
Tsou[4]	1477	HNSCC	1.9	108	7.3	63	4.2	5	0.3	14	0.9	39	2.6
Vaamonde[3]	636	HNSCC	-	48	7.5	34	5.3	7	1.1	4	0.6	3	0.5
Wagenfeld[30]	740	Larynx	-	48	6.5	16	48	25	52	-	-	-	-
Farhadieh[8]	987	Larynx	3.5	143	14.5	83	8.4	56	5.7	4	0.41	65	6.6

Table 6: Retrospective patient series examining the incidence of SPT.

6) [3-6,8,10,13-26]. It is generally accepted that diagnosis of the index tumour in concert with the premise of field cancerisation imparts a subsequent permanent risk of developing SPT [2-6,20,27].

In a recent series of 1257 patients (595 Oral SCCs and 662 Larynngeal SCCs) Lin et al. [5] reported a significantly better disease-specific survival, disease-free survival and a better 3-year survival trend for patients with UAD-SPTs. Further evidence from recent investigations into UAD-SPT confirms that patients afflicted with HNSCC-SPT fare better than those with SPT of other origins (pulmonary or oesophageal) [3-6]. Most recently we analysed the effects of radiotherapy in larynngeal SCCs. In a study of 987 cases we were unable to demonstrate any difference in the incidence of SPT amongst patients receiving radiotherapy or those treated with surgery alone [28]. Our analysis of incidence of SPT during follow-up broadly reflected similar outcomes reported here. There was no evidence that the HNSCC-SPT had an adverse effect on OS [8].

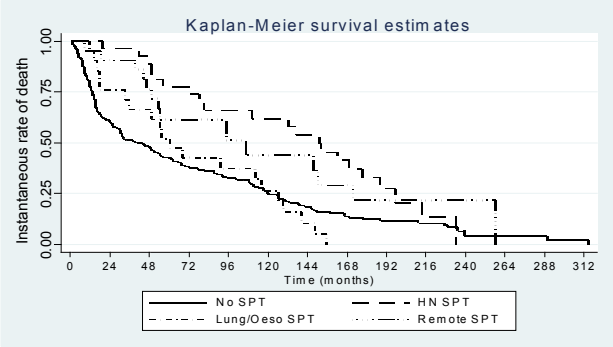

Figure 1: Kaplan-Meier all-cause survival curves for Head & Neck SPT, Lung & Oesophagus SPT, Remote SPT, and no SPT patient groups.

In our series we were able to show a better OS for patients diagnosed with HNSCC-SPT during follow-up when compared to patients not diagnosed with SPTs or those diagnosed with lung/oesophageal SPT. This latter comparison marks the clearly well established poor survival prognosis of these (lung/oesophageal SPTs) malignancies and our results are consistent with those of other series [6,10]. The apparent survival superiority of HNSCC-SPT patients is at odds with most previous studies.

Any longitudinal investigation of this nature is inevitably tainted to some degree by survivorship bias e.g. patients with 'worst' primary tumours will succumb to these and will be inadvertently overlooked because of their lack of visibility. Specifically in this study, median follow-up for patients with no SPT was short (31 months), and given the risk of SPTs is assumed constant, many of these patients would have developed an SPT later on (after 31 months).

This concept can explain why the patients that did not develop SPT had markedly higher rates of recurrence (local and/or nodal) as compared with the HNSCC-SPT group. Added to this, autopsy was not performed in every patient who died, therefore there will be even more SPT in this group that could be overlooked. Only with adequate and substantial follow-up, can the constant and accumulating development of SPT be appreciated.

Nevertheless, a separate analysis conducted for subjects with no recurrence shows that this superior survival of HNSCC-SPT patients persists. However, there may potentially be other unmeasured confounding variables that act to elevate the rate of death in patients who do not develop SPT. The less significant impact of HNSCC-SPT on OS is related to the relatively innocuous prognosis of HNSCCs when compared with lung or esophageal malignancies. The initial better survival shown by patients who develop HNSCC-SPT is tempered by an increase in mortality rate beyond 96 months. Figure 2 show

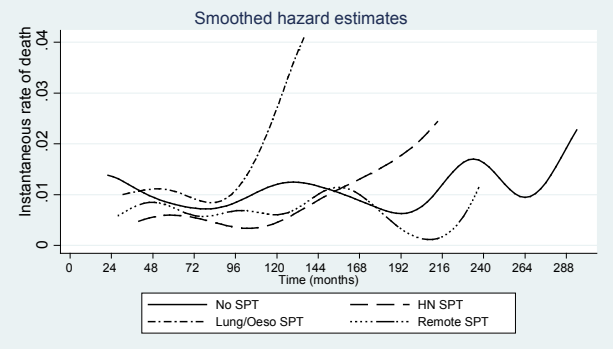

Figure 2: The rate of death with time for Head and Neck SPT, Lung and Oesophagus SPT, and Remote SPT groups and the no-SPT group.

that after 200 months, there are little differences in survival between HNSCC-SPT patients and patients without SPT (however few patients remain at risk to infer a clear conclusion). An area with huge potential for development and research is the molecular study of second field tumors and single contiguous pre-malignant epithelial fields and how these influence local recurrences, SPTs and prognosis.

Conclusion

In light of this series, we believe that UAD-SPT should be clinically divided into the HNSCC-SPT and non-HN subsets for classification purposes. This would have a significant bearing on the perceived overall prognosis of patients.

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