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Lam, Lisetta Oi Yan; Logan, Richard Martin; Luke, C.  
[Epidemiological analysis of tongue cancer in South Australia for the 24-year period, 1977-2001](#) Australian Dental Journal, 2006; 51(1):16-22

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## Epidemiological analysis of tongue cancer in South Australia for the 24-year period, 1977–2001

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### Abstract

**Background:** Tongue cancer (141 ICD-9) is the most common intra-oral malignancy in Western countries. In recent decades, reported tongue cancer incidence and mortality rates have increased both in Europe and in the United States, whilst survival has not improved. This study aimed to determine the epidemiology and survival trends of tongue cancer in South Australia over the 24-year period from 1977 to 2001.

**Methods:** Population-based data for tongue cancer were provided by the Central Cancer Registry Unit of the Epidemiology Branch of the South Australian Department of Health. Age-standardized incidence and mortality rates for males and females were calculated. Kaplan-Meier survival analysis was conducted according to time periods, age, sex and tongue sub-sites. Cox regression analysis was used to determine factors that influenced survival.

**Results:** During this 24-year period, 611 cases of tongue cancer (398 males, 213 females) were reported, the majority of which were squamous cell carcinomas. The most common age of diagnosis was 65–69 years in males and 60–64 years in females. Fifty cases (8.18 per cent of all tongue cancer cases) occurred in patients 40 years or younger. The most common cancer sub-sites reported were 'unspecified site' (48.45 per cent), lateral border (25.53 per cent) and base (18.49 per cent) of the tongue. The age-standardized incidence and mortality rates for males and females in South Australia were relatively low and stable, and there was no significant improvement in survival of tongue cancer over this period. Significant predictors for survival were sex, age and tongue sub-sites, with male, advanced age and base of tongue associated with poorer survival.

**Conclusions:** Tongue cancer is an important health issue associated with poor survival. Early detection and diagnosis is important in order to improve survival rate for this malignancy.

**Key words:** Tongue cancer, survival, oral cancer, epidemiology.

**Abbreviations and acronyms:** EBV = Epstein-Barr virus; HIV = human immunodeficiency virus; HPV = human papillomavirus; ICD = International Classification of Disease; ICD-O = International Classification of Diseases for Oncology; SCC = squamous cell carcinomas; TNM = tumour, node, metastasis.

(Accepted for publication 13 July 2005.)

### INTRODUCTION

Tongue cancer is the most common intra-oral malignancy in Western countries. It accounts for between 20 to 50 per cent of all malignancies involving the oral cavity.<sup>1</sup> More males than females are affected and the highest incidence occurs in the seventh decade of life.<sup>1,2</sup> The vast majority of tongue malignancies, more than 95 per cent, are squamous cell carcinomas (SCC).<sup>1,2</sup> The lateral border and the base of the tongue are the most commonly involved sub-sites of the tongue. Indeed in some studies, the base of the tongue accounts for up to one-third of all SCC of tongue.<sup>3</sup> The aetiological agents that are considered most important with respect to SCC of the tongue include tobacco (smoking and chewing habits) and alcohol consumption.<sup>1,2</sup>

The incidence and mortality of the disease varies between different geographic areas. There has been a reported increased incidence of tongue SCC and associated mortality over recent decades in Europe and the United States.<sup>2,4,5</sup> Additionally, an increased incidence of SCC of the tongue in young adults has been reported from studies conducted in several countries.<sup>2-6</sup> Approximately 5–10 per cent of cases of tongue cancer occur in younger patients, many of whom do not have the identified risk factors such as smoking and alcohol.<sup>6</sup> Debate continues in the literature regarding the aetiology, tumour biology and prognosis of tongue cancer in young patients.

In spite of advances in cancer therapy, the worldwide trend in five-year survival rates of tongue SCC since the early 1970s has remained relatively constant,

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approximately 50 per cent in developed countries.<sup>1,2</sup> Many factors related to the patient, tumour and treatment have been identified to predict the survival of patients with tongue cancer.<sup>4,7</sup> Among them, the tumour, node, metastasis (TNM) stage at which the disease is diagnosed is the single most important predictor for survival.<sup>1</sup> The presence of cervical node metastases dramatically reduces the five-year survival rate to 15–30 per cent, as compared to 50 per cent for those without nodal involvement.<sup>1,3</sup> Poorer survival is also related to the male gender, advanced age, posterior location of the tumour and delay in treatment.<sup>2,7</sup>

The aims of this study were twofold: (1) to analyse the epidemiological pattern of tongue cancer in South Australia over the 24-year period, 1977–2001, with respect to the incidence, mortality and five-year survival trends; and (2) to identify statistically significant predictors for survival of tongue cancer which are available on the population-based South Australian Cancer Registry database.

## MATERIALS AND METHODS

The data for the study were provided by the Central Cancer Registry of the Epidemiology Branch of the South Australian Department of Health. This population-based cancer registry processes statutory notifications from all hospitals, pathology laboratories, radiotherapy departments, and the South Australian Registrar of Deaths for all cases of invasive cancer which have occurred in South Australia since 1977. The Cancer Registry also has access to population statistics from the Australian Bureau of Statistics thus allowing calculation of population-based incidence and mortality rates. Cancer cases are coded according to *The International Classification of Disease*, ninth edition (ICD-9). The sub-sites for tongue cancer (141 ICD-9) consist of the following: (1) Base of tongue (141.0 ICD-9); (2) Dorsal surface (141.1 ICD-9); (3) Tip and lateral border (141.2 ICD-9); (4) Ventral surface/anterior two thirds (141.3 ICD-9); (5) Tongue ‘unspecified site’ (141.9 ICD-9). The pathological type or morphology of cancer cases is coded according to *The International Classification of Diseases for Oncology*, second edition (ICD-O).<sup>9</sup>

### Statistical analysis

The total number of cases and the number of cases according to sex, age and sub-site distributions of tongue cancer in South Australia between 1977–2001 were analysed using the Intercooled Stata 8.0 statistical software.<sup>10</sup> The level of statistical significance between various parameters was assessed on PEPI Version 4.0<sup>11</sup> using 95 per cent confidence intervals ( $p < 0.05$ ).

Age-specific incidence and mortality rates for males and females were calculated using the South Australia Census Postcode Population for the years 1981, 1991 and 1996 provided by the Australian Bureau of Statistics. Age-standardized incidence and mortality rates were then calculated for males and females to world population for time periods 1977–1985,

**Table 1. Oral cancer cases reported between 1977–2001 (excluding lip cancer and major salivary gland malignancy)**

Primary cancer site (ICD-9)	Number of cases
Tongue (ICD-9 141)	611 (44.9%)
Gum (ICD-9 143)	84 (6.2%)
Floor of mouth (ICD-9 144)	296 (21.8%)
‘Other mouth’ (ICD-9 145)	369 (27.1%)
Total	1360 (100%)

1986–1993 and 1994–2001 using Microsoft® Excel Software. For analysis of survival trend of tongue cancer, cases were divided according to periods of diagnosis (1977–1985, 1986–1993 and 1994–2001), sex, age groups ( $\leq 59$ , 60–69 and  $\geq 70$  years) and tongue sub-sites (ICD-9). Survival curves were constructed using the method of Kaplan-Meier.<sup>12</sup> Cox proportional hazards analysis was used to identify statistically significant predictors for tongue cancer that were available on the Cancer Registry database, namely time period of diagnosis, sex, age groups and tongue sub-sites. All factors related to survival that had achieved significance levels of 0.05 or less on the univariate regression analysis were incorporated into a multivariable model.

## RESULTS

### Number of tongue cancer cases

The number of cases of tongue cancer reported in South Australia during the 24-year period between 1977 and 2001 are presented in Table 1. Significantly more males (65.14 per cent) than females (34.86 per cent) were diagnosed with tongue cancer with a male:female ratio of 1.9:1 ( $p < 0.001$ ). The tongue was the most common intra-oral site for oral cancer, comprising 44.9 per cent of intra-oral malignancies. Tongue cancers represented 0.41 per cent of all cancers recorded by the Cancer Registry over this period and the majority of tongue cancers were squamous cell carcinomas (97.21 per cent).

### Age of diagnosis of tongue cancer

Figure 1 shows the number of tongue cancer cases according to age at diagnosis. A significant association was found between the number of tongue cancer cases and increasing age for both sexes ( $p > 0.01$ ). Of the total number of tongue cancer cases, there were 50 cases (31 males, 19 females) occurring in patients 40 years or younger, which represented 8.18 per cent of total tongue cancer cases.

### Sub-sites of tongue involved

The total number of cases reported for each tongue sub-site and the number of cases reported according to sex are presented in Table 2. Tongue ‘unspecified site’ (141.9 ICD-9) was the most commonly reported cancer sub-site accounting for 48.45 per cent of the total number of tongue cancer cases in South Australia between 1977–2001.

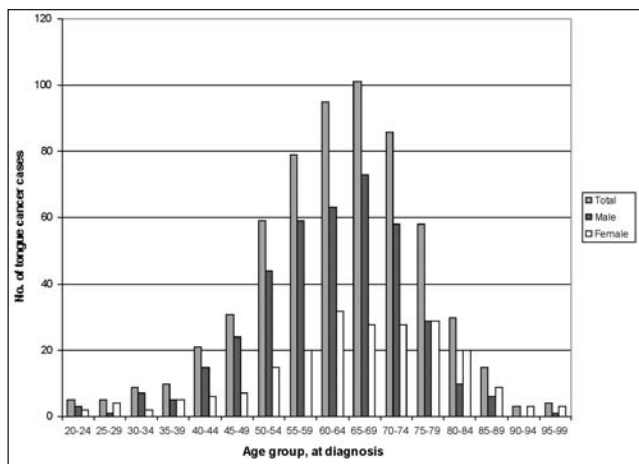


Fig 1. Tongue cancer in South Australia, 1977-2001: age at diagnosis.

Males had significantly more reported tongue cancer occurring at the base, tip and lateral border and at an unspecified site of the tongue, with the male-to-female ratio for base of tongue cancer being 3.35:1 ( $p < 0.001$ ).

The number of reported cases for each tongue sub-site according to the three time periods of diagnosis is presented in Table 3.

#### Incidence and mortality of tongue cancer

Age-standardized incidence and mortality rates for tongue cancer in South Australia for the three diagnostic periods of 1977–1985, 1986–1993 and 1994–2001 are presented in Table 4. Although the age-standardized incidence rate of tongue cancer for males demonstrated an increasing trend over the years 1977–2001, there was no significant difference between the three time periods. Similarly, age-standardized mortality rates for males remained stable over the 24-year period. In females, there was no significant change in the parameters of age-standardized incidence or mortality rates of tongue

cancer over time. Males demonstrated significantly higher incidence and mortality rates than females during all three periods.

#### Analysis of five-year survival trends for tongue cancer

The Kaplan-Meier survival curves by periods of diagnosis, age group, sex and tongue sub-sites are presented in Figs 2–5.

#### Survival by time period of diagnosis

Cox proportional hazards regression analysis revealed no significant difference between periods of diagnosis. However, it can be seen that survival for the two most recent time periods, 1986–1993 and 1994–2001, fall below the survival curve for 1977–1985 (Fig 2). Although not statistically significant, this finding suggests that survival has not improved in recent years.

#### Survival by sex

Males demonstrated a significantly poorer ( $p = 0.025$ ) five-year survival curve than females (Fig 3). The steep decline in the curves during the first two years indicated that mortality is greatest within this period of the disease, after two years there was a continual decline of the male curve.

#### Survival by age groups

Kaplan-Meier survival curves for the three age groups of  $\leq 59$ , 60–69 and  $\geq 70$  years old are presented in Fig 4. The youngest age group accounted for 35.84 per cent ( $n = 219$ ) of cases, the middle age group 32.08 per cent ( $n = 196$ ), and the oldest age group 32.08 per cent ( $n = 196$ ) of cases of tongue cancer. The oldest age group demonstrated the worst survival, followed by the 60–69 years group, with those aged less than 59 years having the best survival. These differences were statistically significant ( $p = 0.041$ ).

Table 2. Tongue cancer in South Australia, 1977–2001: number of cases reported at each sub-site (ICD-9) and male to female distribution and ratio

Primary cancer site (ICD-9)	Number of cases	Male	Female	Male:Female ratio	p
Base of tongue (141.0)	113 (18.49%)	87	26	3.35:1	<0.001
Dorsal surface (141.1)	10 (1.64%)	5	5	1:16	N/S
Tip and lateral border (141.2)	156 (25.53%)	101	55	1.84:1	<0.001
Ventral surface/anterior 2/3 (141.3)	36 (5.89%)	16	20	0.8:1	0.189
Tongue 'unspecified site' (141.9)	296 (48.45%)	189	107	1.73:1	<0.001
Total	611 (100%)	398	213		

Table 3. Tongue cancer in South Australia, 1977–2001: tongue sub-sites (ICD-9) to number of cases diagnosed in the time periods of diagnosis

Tongue sub-sites (ICD-9)	1977-85	1986-93	1994-2001	Sub-site total
Base of tongue (141.0)	17	41	55	113
Dorsal surface (141.1)	1	3	6	10
Tip and lateral border (141.2)	32	53	71	156
Ventral surface/anterior 2/3 (141.3)	8	13	15	36
Tongue 'unspecified site' (141.9)	133	81	82	296
Total for each period	191	191	229	611

**Table 4. Tongue cancer in South Australia, 1977–2001: Age-standardized incidence and mortality rates of tongue cancer per 100 000 standard world population (95 per cent CI) for the three periods of 1977–1985, 1986–1993 and 1994–2001**

Year	Incidence		Mortality	
	Male	Female	Male	Female
1977-1985	0.98 (1.22, 0.74)	0.46 (0.60, 0.31)	0.67 (0.86, 0.47)	0.26 (0.37, 0.15)
1986-1993	1.05 (1.29, 0.81)	0.49 (0.64, 0.34)	0.94 (1.17, 0.72)	0.22 (0.31, 0.13)
1994-2001	1.15 (1.40, 0.90)	0.45 (0.59, 0.32)	0.85 (1.06, 0.65)	0.36 (0.48, 0.24)

**Survival by sub-sites of tongue**

Cancer involving the base of tongue has significantly worse survival than other tongue sub-sites (p=0.033). The Kaplan-Meier survival curve showed a steep decline over the first two years, followed by a slower decline thereafter. Better survival was evident for tongue ‘unspecified site’, tip and lateral border, dorsal surface and ventral surface/anterior two-thirds (Fig 5).

**Predictors for tongue cancer survival**

Univariate analysis using Cox’s proportional hazard regression showed sex, age and sub-site of tongue to be statistically significant for predicting tongue cancer survival (p=0.025, 0.041 and 0.033, respectively). Specifically, male, increasing age and base of tongue sub-site were found to negatively affect survival. Multivariable analysis revealed that the base of tongue sub-site was the most significant factor in predicting tongue cancer survival, even after controlling for sex and age (p=0.002).

**DISCUSSION**

This study investigated various epidemiological parameters related to tongue cancer in South Australia reported over the 24-year period 1977–2001. Cancer of the tongue accounted for the majority of oral cancers (excluding lip cancer and major salivary gland

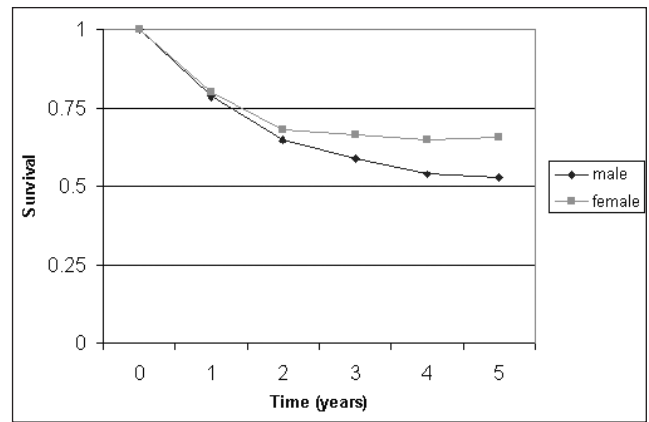


Fig 3. Kaplan-Meier survival curves for tongue cancer by sex.

malignancies) and was most common in males and in the seventh decade of life. The vast majority of tongue cancers were squamous cell carcinomas and this was in accordance with findings of studies conducted in Europe, the United States, as well as other states of Australia.<sup>2,5,6,13</sup> The most commonly reported sub-sites were ‘unspecified site’, tip and lateral border and base of the tongue. Interestingly, almost 45 per cent of the cases reported to occur on an ‘unspecified site’ were reported during the earliest time period, 1977–1985 (Table 3), which could reflect less specific documentation of cancer site in earlier years.

Compared with other Australian states, the incidence of tongue cancer in males in South Australia is low.<sup>2,13</sup> For example, the incidence is 2.1 per 100 000 per annum in Victoria and 2.8 per annum in Western Australia.<sup>2</sup> Roder and Wilson<sup>14</sup> reported a male incidence rate of 1.8 per 100 000 per annum in South Australia between 1977–1980 and the same rate was reported between the years 1988–1992.<sup>2,15</sup> The reason for regional difference in the incident rates is not clear. Previous authors have suggested regional differences in carcinogen exposure or diet along with potential differences in regional awareness of oral lesions that might represent premalignancy or oral cancer.<sup>1</sup> Further detailed investigation is required in order to confirm these hypotheses.

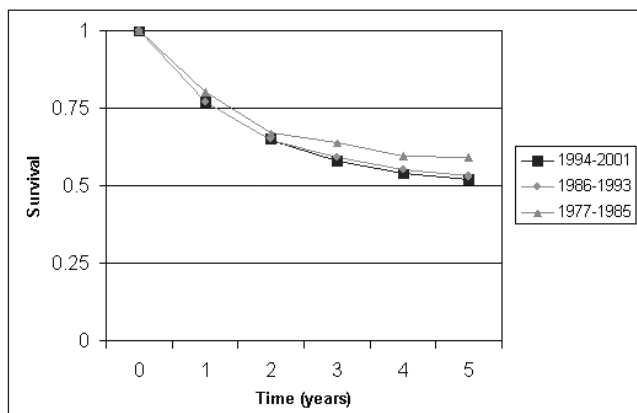


Fig 2. Kaplan-Meier survival curves for tongue cancer by periods of diagnosis: 1977-1985, 1986-1993 and 1994-2001.

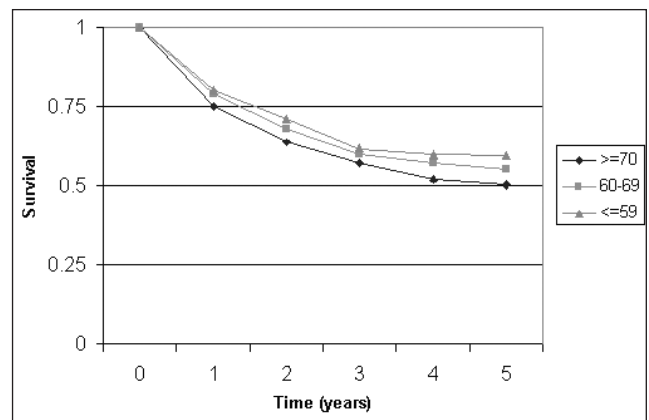


Fig 4. Kaplan-Meier survival curves for tongue cancer by age groups.

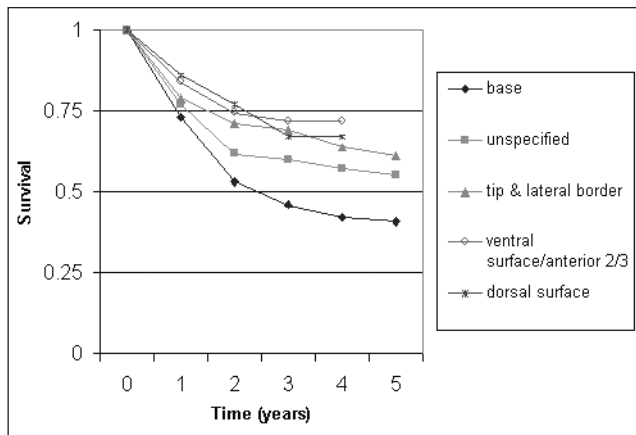


Fig 5. Kaplan-Meier survival curves for tongue cancers by sub-sites.

The results of the present study indicate that there was no significant difference in male incidence or mortality in South Australia over the three time periods. This is consistent with other reports which indicate the rates of tongue cancer in Australia have remained stable over the years with the exception of New South Wales where both incidence and mortality rates are increasing.<sup>2,13,16</sup> Macfarlane *et al.*<sup>16</sup> believe this pattern is consistent with Australian trends in per capita decline in consumption of tobacco and alcohol, and increased consumption of fruit and vegetables, which is considered to have a protective role against oral cancer. The incidence and mortality of tongue cancer in females in South Australia are low and have remained stable, similar to that reported in other regions of Australia and United States.<sup>2,17</sup> In contrast, there is an increasing incidence and mortality for tongue cancer in Europe and the United States, particularly amongst young adult males and some female populations.<sup>2,17</sup>

The five-year survival rate for tongue cancer has not improved over the 24-year period. This is a common finding in many reports on oral cancer, despite significant advances in surgical resection techniques, reconstruction, radiation therapy and chemotherapy.<sup>16,18</sup> The most important clinical prognostic predictor for survival is the TNM stage at the time of diagnosis.<sup>4</sup> Cure rates decrease by approximately 50 per cent when lymph node metastasis occurs.<sup>19</sup> The lack of improvement in survival rates of tongue cancer indicates that these cancers are not being diagnosed at an early stage. Delays in diagnosis, particularly for base of tongue cancers, subsequently lead to delays in treatment, which in turn allows local extension of the lesion and an increased risk for metastatic spread. This ultimately translates to a poorer outcome for the patient.<sup>4,7,20</sup>

Of the variables available on the South Australian Cancer Registry population-based database, univariate analysis revealed that sex, age and sub-site of tongue were significant predictors for tongue cancer survival. The poorer five-year survival for males compared with females can be explained partly by sub-site distribution.

Male cases had a significantly higher proportion of lesions involving the base of the tongue (Table 2). Kantola *et al.*<sup>4</sup> also noted the inter-relationships between various prognostic factors in tongue cancer and demonstrated that several demographic factors significantly related to clinical TNM stage. It was found that male patients had significantly more neck lymph node involvement and that older age is significantly related to carcinoma spread outside the tongue.<sup>6</sup>

The fact that older people had significantly poorer five-year survival from tongue cancer may be due to a number of factors including delay in diagnosis, poorer nutritional and immunological status and reduced ability to withstand aggressive treatment modalities such as radiotherapy or surgery.<sup>21,22</sup> Many studies have specifically addressed the relationship between age and prognosis for tongue SCC and offered conflicting conclusions. Some studies have reported that younger age was associated with poor prognosis;<sup>22,23</sup> others have found it to be a positive prognostic influence,<sup>24,25</sup> or to have no influence at all.<sup>26,27</sup> Some authors have proposed that the patient population regarded as 'young' patients with oral SCC (generally defined as less than 35 or 40 years of age) may be composed of several subsets of patients with variable clinical course.<sup>24,28</sup> In this study, there were 50 cases (8.18 per cent) reported in persons 40 years or younger. Many studies have addressed the issue of oral SCC in younger patients. Younger patients consistently make up less than five per cent of head and neck SCC patients in reported series.<sup>14</sup> The tongue is the most frequently involved site and the involvement of this site is increasing in incidence.<sup>6,24,29</sup> Knowledge of the aetiology, clinical behaviour and effective management of oral SCC in young adults is limited (primarily by the small sample size) and is sometimes contradictory between studies. Tobacco and alcohol are not always implicated in the aetiology of oral SCC of young adults, and the pathogenic role of other recreational drugs, such as marijuana, remain unclear.<sup>6,30</sup> This suggests that other external or internal factors play a role in the development of the disease in young adults. A genetic basis for oral SCC in young adults has been proposed,<sup>31</sup> but any causative role for infective agents such as Epstein-Barr virus (EBV), human papillomavirus (HPV), hepatitis C, hepatitis G viruses or human immunodeficiency virus (HIV) remains to be established.<sup>32,33</sup> More recent studies have suggested that age alone is not predictive of disease-free survival and that traditional predictors of survival outcome such as stage, status of surgical margins, and presence of nodal metastasis are more important than age.<sup>25-28,34</sup>

Sub-site distribution of tongue cancer also influences survival. The more posterior the tumour, the poorer the survival is likely to be.<sup>4,35</sup> In particular, base of tongue cancer has significantly worse survival than other sub-sites and is the most significant indicator of poor survival, even after controlling for age and sex in the multivariate analysis. This finding is consistent with

other reports.<sup>35,36</sup> Nason *et al.*<sup>35</sup> reported that disease-specific survival at five years for the tongue base was 26 per cent, compared with 64 per cent for the anterior tongue. Cancers of the anterior two-thirds of the tongue tend to be better differentiated and are usually detected earlier than those of the posterior one-third.<sup>37</sup> Base of tongue cancers are typically asymptomatic in the early stages and are not easily detectable clinically, as a result, presentation is often late. It has been reported that 71 per cent of patients with tongue base tumours had advanced stages of disease at presentation compared with 32 per cent for the anterior tongue.<sup>21</sup> In addition, there is a high incidence of cervical node metastases associated with SCC of the base of tongue, with 60 per cent or more of patients having ipsilateral nodal disease at the time of initial presentation.<sup>3,7</sup> Due to the relatively rich lymphatic network supplying the tongue and the tendency of these lymphatic channels to drain to both sides of the neck, delays in the detection of inconspicuous tumours will increase the chance for nodal metastasis and significantly reduce survival rate.<sup>3,4,7</sup>

## CONCLUSION

This study analysed the epidemiology of tongue cancer in South Australia between the years 1977–2001. The finding that the incidence and survival of tongue cancer has not improved reflects a need for increasing patient and general public awareness of this disease and its risk factors. Regular professional oral cancer examination needs to be emphasized. Clinicians should be aware of the potential for tongue cancer to occur in younger patients who may not have obvious risk factors, such as tobacco and alcohol use. The most important message is that early detection and diagnosis of tongue cancers will greatly improve not only the survival rates of tongue cancer but also patients' quality of life as a consequence of less radical and therefore debilitating treatment.

## ACKNOWLEDGEMENTS

This study was generously supported by the Australian Dental Research Foundation Undergraduate Summer Vacation Research Scholarship. Our thanks go to Dr Simon Moore for his advice and support throughout this project, Ms Lesley Milliken for her administrative support at the Cancer Registry, and Ms Sandie Hughes for her computer technical advice.

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