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Survival following surgery for oral cancer – A 30 year experience.

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Abstract:

Oral squamous cell carcinoma is the most common intraoral malignancy. Our unit has advocated radical primary surgery with adjuvant treatment where indicated. The main aims of this work are to identify the overall survival of a consecutive series of patients and to relate survival to clinical and pathological factors.

Methods

Kaplan-Meier curves were produced for site, gender, TNM status, and post-operative radiotherapy. Statistical significance was set at $p<0.05$. The data were analysed using the software IBM SPSS Statistics version 23.

Results

A total of 921 patients were recorded in the database with a diagnosis of oral squamous cell carcinoma out of a total of 1958 (43.1%). The earliest date of diagnosis was 1973. The data were censored at 31 March 2016. The database comprised 340 women (36.92%) and 581 men (63.08%). A total of 339 deaths were recorded (34.51%): 117 women (33.7%) and 222 men (65.49%). The mean age at death was 73.37 years (range: 31.38 to 97.51 years) and 68.65 years (range: 33.29 to 95.47 years) for women and men respectively. This difference was statistically significant ($t(337) = 3.28$, $p = 0.001$).

Discussion

Our overall survival is somewhat better than 56% 5-year survival reported for oral cancer in England in 2010. This may be a reflection of the treatment methods. This work supports the view that aggressive management may improve overall survival.

Introduction

Oral squamous cell carcinoma (OSCC) is the most common intraoral malignancy and may have neck node metastases. Even amongst patients with no clinical or radiological evidence of lymph node metastases preoperatively, 20-30% of all specimens reveal positive nodes in pathohistological analysis.[1,2,3,4] OSCC includes tumours of the anterior two thirds of tongue, floor of mouth, buccal mucosa, retromolar area, gingivae and palate. Globally oral and oropharyngeal cancer is the 6th most common cancer and OSCC accounts for the majority of these.[5,6] There has been a significant increase in oral cancer diagnosis in recent decades which may be attributed to increased exposure to risk factors such as tobacco and alcohol.[7] Oral cancer and particularly tongue cancer is also on the increase in young adults under the age of 45 years.[6,8]Our unit has advocated radical primary surgery with free tissue transfer reconstruction where indicated in the management of oral cancer. A selective neck dissection is performed when depth of tumour invasion exceeds 3 mm. Operations are performed with intention to cure by resection of in excess of a 0.5 cm margin of normal tissue. This is the practice of several international units. Cure and survival is of primary concern for patients however there are several problems with basing outcome exclusively on overall survival. Patients are relatively elderly and often have associated co-morbidity associated with their life style and background. Therefore following oral cancer treatment they can die of other causes and have life expectancy of less than five years (5-years survival).[9]The main aims of this work are to evaluate our service and identify the overall survival of a consecutive series of patients presenting with oral cancer and to relate survival to clinical and pathological factors.

Methods

Data was recorded in an Access 97 database. Clinical data and basic socio-demographic details were extracted from the database. These were patients treated by the senior authors, in Leeds General Infirmary and represents more than half of the total number of patients treated by all teams in the unit within this time frame. Independent groups t-test was used to evaluate differences between gender and age at diagnosis as well as age at death. Life tables were used to calculate survival rates at 1, 2, 3, 5 and 10 years' post-diagnosis. Kaplan-Meier curves were produced for site, gender, TNM status, and post-operative radiotherapy. The log-rank

test was used to evaluate differences between factors. Statistical significance was set at $p<0.05$. The data were analysed using the software IBM SPSS Statistics version 23.

Results

Clinical features

A total of 921 patients were recorded in the database with a diagnosis of oral squamous cell carcinoma out of a total of 1958 (43.1%). The most common sites were the tongue (350/921, 38% of cases), followed by floor of mouth (208/921, 22.58%).

The earliest date of diagnosis was 1973. The data were censored at 31 March 2016. The database comprised 340 women (36.92%) and 581 men (63.08%) (Table 1).

The mean age at diagnosis was 63.59 years (range: 20.68 to 96.07 years). Women were on average slightly older at diagnosis compared to men: 66.38 years (range: 26.78 to 96.07 years) and 61.96 years (range: 20.68 to 90.75 years), respectively. This difference was statistically significant ($t(919) = 5.08$, $p<0.0001$). A total of 339 deaths were recorded (34.51%): 117 women (33.7%) and 222 men (65.49%). The mean age at death was 73.37 years (range: 31.38 to 97.51 years) and 68.65 years (range: 33.29 to 95.47 years) for women and men respectively. This difference was statistically significant ($t(337) = 3.28$, $p = 0.001$).

Survival by gender

The mean overall length of survival was 8.11 years (range: 0.0 to 34.08 years). The 1, 3, 5 and 10-year survival rates were as follows: 0.87, 0.80, 0.70 and 0.62, respectively. The mean survival time (Table 2) was longer for men (20.52 years, 95% confidence intervals (CI): 19.10 to 21.94) compared to women (17.76 years, 95%CI: 16.06 to 19.47) (Figure A). This was not statistically significant ($X^2(1) = 1.07$, $p = 0.30$).

Survival by site

There were 5 sites with N>40, namely tongue, floor of mouth, retromolar area (RA), buccal mucosa (BM) and mandibular alveolus (MA). The longest mean survival (Figure B) was registered by the latter group of patients at 20.74 years (95%CI 16.13 to 25.34), whereas the RA group had the lowest mean survival at 15.05 years (95%CI 12.11 to 18.00). There were no statistically significant differences between the sites ($X^2(4) = 5.04$, $p = 0.284$).

Survival by T,N and M status (Table 3)

T-status

The longest mean survival (excluding TX patients) was shown for patients with T1 status (24.48 years, 95%CI 22.45 to 26.50) compared to a mean survival of 13.03 years (95%CI 11.56 to 14.49) for patients with T4 status (Figure C) which was statistically significant ($X^2(4)=39.14$, $p<0.0001$).

N-status

A similar pattern was also observed for N-status with patients (excluding NX) with no regional lymph node involvement demonstrating the longest mean survival (21.23 years, 95%CI 19.34 to 23.19) and patients with N3 involvement the shortest (5.52 years, 95%CI 2.54 to 8.50) (Figure D). This was statistically significant ($X^2(3)=23.74$, $p<0.0001$).

M-status

Finally, patients with metastatic disease (M1) had shorter survival times than those with no metastatic disease: 5.94 years (95%CI 2.51 to 9.38) and 20.55 years (95%CI 19.03 to 22.07) respectively (Figure E). This was also statistically significant ($X^2(2)=4.55$, $p=0.005$) although the number of patients with metastatic disease was small (n=11).

Survival by post-operative radiotherapy

The average length of survival for patients who had undergone post-operative radiotherapy was 17.19 years (95%CI 15.41 to 18.97) compared to 20.50 years (95%CI 18.82 to 22.19) for those who had only undergone surgery (Figure F). This difference was not statistically significant ($X^2(1) = 0.12$, $p = 0.73$).

Discussion

Here we analysed data in our unit from 1973. We were in a position to follow-up patients for at least 5 years. Our overall survival is somewhat better than data presented before and this may be a reflection of the treatment.[1] The data have been recorded prospectively. A comprehensive analysis is presented and includes survival by gender, by cancer site, TNM status, and post-operative radiotherapy. This is a single centre experience and this is a weakness of this study. Also, another weakness is the fact that these are patients of one of the teams in the unit and not the total number treated by all surgeons. Gaps in the data collection are present but in this work we could draw meaningful conclusions. The overall 5-year

survival for our study population was 70% which is comparable to or better than international standards.[1,9,10,11] The 1,3,5 and 10-year survival rates were as follows: 0.87, 0.80, 0.70 and 0.62. In terms of gender the mean survival for men was longer (20.52 years, 95% confidence interval (CI):19.10 to 21.94) in comparison to women (17.76 years, 95%CI: 16.06 to 19.47). This difference was not statistically significant. These results are similar to those by (Honorato et al, 2015)[12] who found no difference in survival outcomes for OSCC between males and females. In terms of difference between genders, past tobacco use is an independent prognostic factor for worse survival among males.[12]The most common sites of presentation of OSCC with N>40 were tongue, floor of mouth, retromolar area, buccal mucosa and mandibular alveolus. The longest mean survival was for the mandibular alveolus group at 20.74 years and the lowest for the retromolar area at 15.05 years. There were no statistically significant differences between the sites. This is consistent with other reports highlighting tongue and floor of mouth as the most common sites.[10,13] The site of presentation does not appear to be a significant factor in prognosis, tongue cancer does not appear to have a worse prognosis, the main prognostic factors affecting survival are the stage and grade of cancer.[13]The stage of OSCC had a significant impact on survival in our study. The longest mean survival was shown for patients with T1 status (24.48 years) compared to a mean survival of 13.03 years for patients with T4 status. The N-status also showed a significant difference in survival for N0 and N1 involvement at 21.27 and 16.67 years respectively, in comparison to N3 status with shortest survival (5.52 years). The clinical nodal stage has been reported as a significant prognostic factor in survival for OSCC.[14]The prognosis for patients treated for OSCC depends mainly on tumour factors, treatment and patient factors. The TNM classification system relates well to overall survival rate. The prognosis is best for early detected tumours which are well differentiated with no evidence of regional nodal or distant metastasis.[15] There are a number of histopathological factors which are of important prognostic importance, these are tumour thickness, positive margins, extracapsular spread of nodal metastasis.[16,17] The current UK National guidelines also advocate that elective neck treatment should be offered for all oral cancers.[17] Recent evidence suggests that selective elective neck dissection offers improved overall and disease free survival compared with therapeutic neck dissections for all oral cancers.[18] This evidence also advocates use of neck dissection for smaller tumours less than 4mm thickness. The National Institute for Health and Care Excellence (NICE) guidelines for T1 and T2 N0 oral cancers suggest that patients be offered elective neck dissection or sentinel lymph node biopsy instead of elective neck dissection. This approach avoids the morbidity of neck dissection and may be considered

unless cervical access is required for free flap reconstruction.[19] Although currently advocated by NICE there are substantial logistical issues nationally which have not been addressed and robust studies into patient acceptance, survival, morbidity and quality of life are awaited. The mean length of survival for patients in this study who underwent postoperative radiotherapy was 17.19 years compared to 20.50 years for those who had surgery only. This difference was not statistically significant. This may also represent the fact that radiotherapy in our unit is given to patients with adverse clinical and histopathological features that may include close margins, significant nodal involvement, extracapsular spread and neurovascular invasion. The indications for postoperative radiotherapy are not clearly defined for patients in the group commonly referred to as 'an intermediate risk group' in the UK. Although the results for this patient group have not been presented in this work, in our practice we advocate radiotherapy more often than not. Radiotherapy as primary treatment is less commonly used in oral cavity cancers than other head and neck sites.[16,20] Our unit advocates the use of surgery and adjuvant radiotherapy to improve outcomes for locally advanced disease which is operable. Recent evidence suggests improved survival for locally advanced T3 and T4a OSCCs when treated with surgery and postoperative radiotherapy compared with chemoradiotherapy.[21]The management of oral cancer in our unit is currently to perform primary surgery and adjuvant therapy where indicated. The current United Kingdom National Multidisciplinary Guidelines for head and neck cancer advocate surgery as the primary treatment strategy for oral cancers. Curative surgery involves tumour resection with clinical clearance of 1 cm vital structures permitting.[17] Where close margins of less than 5 mm occur, further treatment with further resection or adjuvant therapy is considered although robust data suggests no significant difference between clear margins of 5 mm and 2 mm.[22] Following resection, the use of free tissue transfer where indicated with tailored tissues has lead to improved functional and cosmetic outcomes.[15] The use of vascularised composite flaps allows more aggressive ablative surgery and restoration of soft tissues and jaw continuity. These reconstructions also help to withstand post-operative radiotherapy and hence improve survival.[23,24]

Conclusion

This work is comparable with or better than data from other UK and international units. It is one of the largest studies involving patients with oral cancer in the UK. This works supports the view that aggressive primary surgical management may improve overall survival.

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Table 1. Basic clinical features

Site	Female	Male	Total	Overall %
Tongue	134	216	350	38.00
FOM	65	143	208	22.58
Retromolar area	16	51	67	7.27
Buccal mucosa	27	27	54	5.86
Mandibular alveolus	16	35	51	5.53
Soft palate	12	24	36	3.91
Mandibular gingivae	18	13	31	3.36
Soft and hard palate	9	14	23	2.50
Maxillary alveolus	7	15	22	2.39
Buccal and labial sulcus	7	9	16	1.74
Labial sulcus	3	7	10	1.09
Hard palate	4	4	8	0.87
Lower lip mucosa	2	6	8	0.87
Unclassified	2	4	6	0.65
FOM with mandibular invasion	5	1	6	0.65
Upper & Lower Buccal/Labial Sulcus	4	1	5	0.54
Maxillary gingivae	2	2	4	0.43
Soft palate and maxillary alveolus	3	1	4	0.43
Buccal sulcus	0	2	2	0.22
FOM and mandible	1	1	2	0.22
Buccal mucosa and hard palate	0	1	1	0.11
Buccal mucosa and labial sulcus	1	0	1	0.11
FOM and gingivae	0	1	1	0.11
FOM and tongue	0	1	1	0.11
Labial and buccal mucosa	0	1	1	0.11
Lateral tongue	0	1	1	0.11
Retromolar trigone	1	0	1	0.11
Retromolar trigone, soft palate, FOM	1	0	1	0.11
Total:	340	581	921	

Figure A. Survival by gender

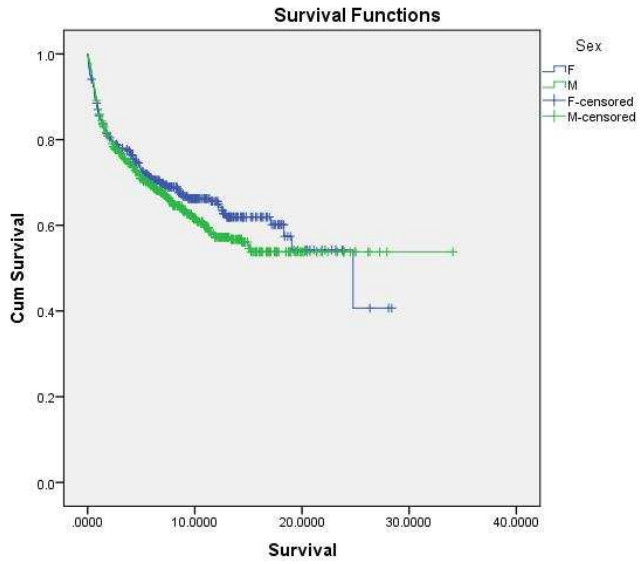

Table 2: Mean survival time

Sex	Female		Male		Total	
	Mean	Min-Max	Mean	Min-Max	Mean	Min-Max
Age at diagnosis	66.38	26.78 - 96.07	61.96	20.68 - 90.75	63.59	20.68 - 96.07
Age at death	73.37	31.38 - 97.51	68.65	33.29 - 95.47	70.28	31.38 - 97.51
Survival	8.29	0.025 - 28.38	8.01	0 - 34.08	8.11	0 - 34.08

Figure B: Survival by site

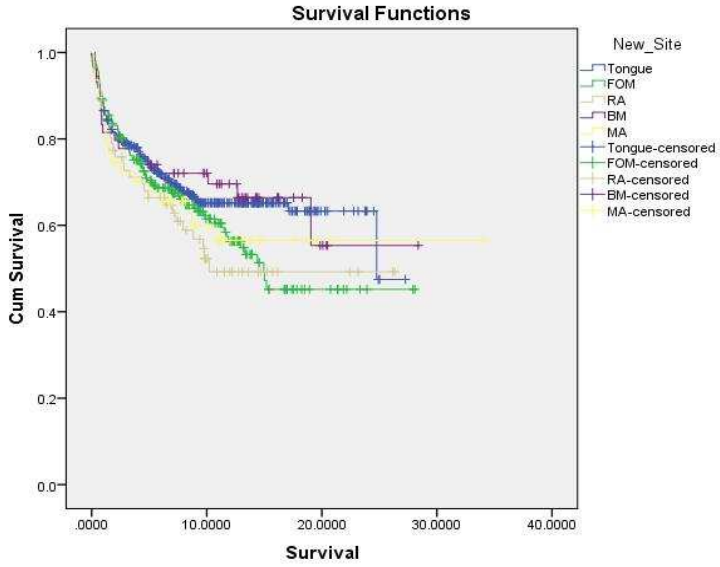

Figure C. Survival by T-status

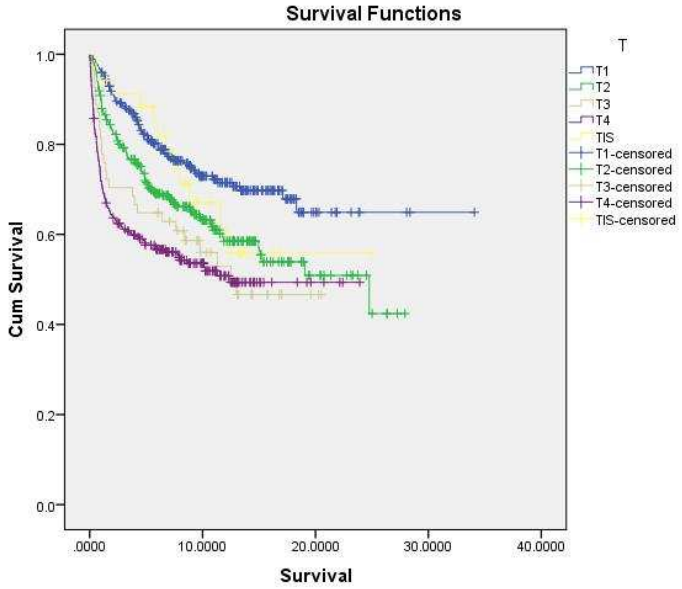

Figure D. Survival by N-status

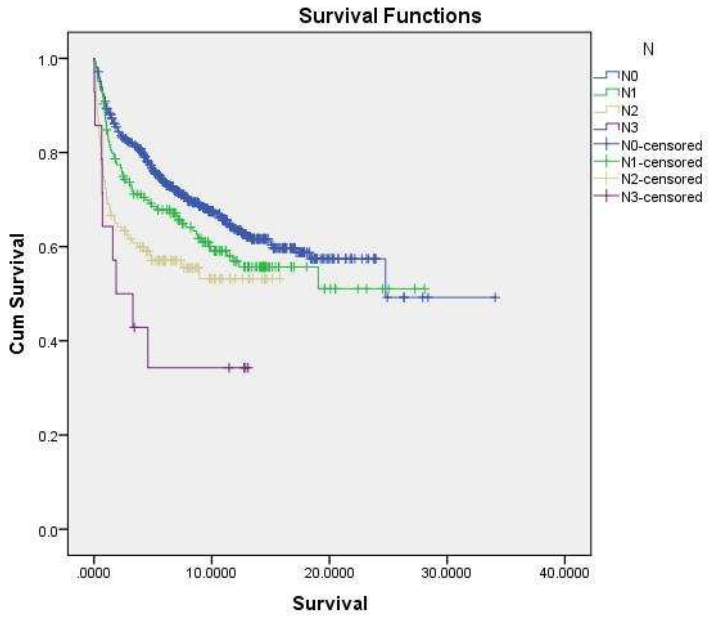

Figure E. Survival by M-status

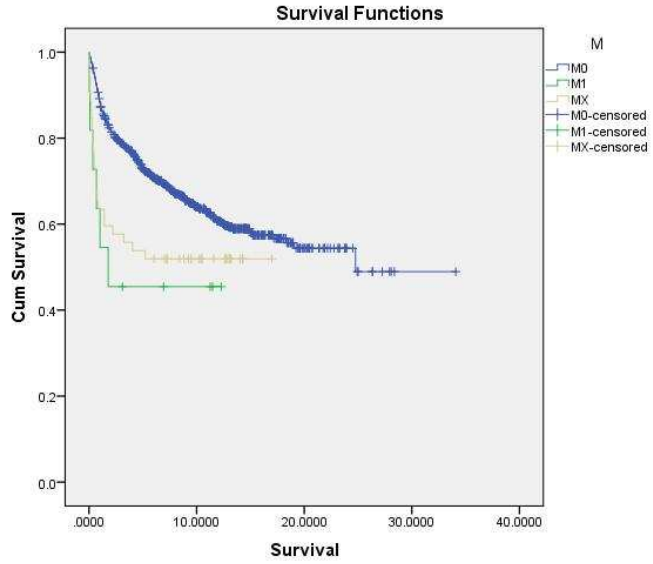

Table 3. Summary of survival by factors

		Female	Male	Total	%
Survival	**Alive**	223	359	582	63.19
	Deceased	117	222	339	36.81
Post-operative Radiotherapy	**No**	278	438	716	77.74
	Yes	62	143	205	22.26
T-status	**T1**	117	154	271	29.42
	T2	97	186	283	30.73
	T3	12	42	54	5.86
	T4	85	161	246	26.71
	TIS	16	19	35	3.80
	TX	2	3	5	0.54
	Missing	11	16	27	2.93
N-status	**N0**	235	359	594	64.50
	N1	54	111	165	17.92
	N2	36	87	123	13.36
	N3	5	9	14	1.52
	NX	1	1	2	0.22
	Missing	9	14	23	2.50
M-status	**M0**	304	530	834	90.55
	M1	4	7	11	1.19
	MX	22	30	52	5.65
	Missing	10	14	24	2.61

Figure F. Survival by post-operative radiotherapy