GAVIN PUBLISHERS

Journal of Oncology Research and Therapy

Lubpairee T, et al. J Oncol Res Ther: JONT-132.

Research Article

DOI: 10.29011/2574-710X.000032

Oral Squamous Cell Carcinomas are Associated with Poorer Outcome with Increasing Ages

Tarinee Lubpairee[1,2], Catherine F Poh[1,3,4], Denise M Laronde[1,2,3], Miriam P Rosin[3,4,5], Lewei Zhang[1,2,3*]

[1]Department of Oral Biological and Medical Sciences, Faculty of Dentistry, The University of British Columbia (BC), Vancouver, Canada

[2]BC Oral Cancer Prevention Program, BC Cancer Agency, Vancouver, Canada

[3]BC Oral Biopsy Service, Vancouver General Hospital, Vancouver, Canada

[4]BC Cancer Research Centre, Vancouver, Canada

[5]School of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, Canada

[*]**Corresponding author:** Lewei Zhang, Department of Oral Biological and Medical Sciences, Faculty of Dentistry, University of British Columbia, 2199 Wesbrook Mall, Vancouver BC, Canada. Tel: +16048754318; +17783873885; Email: lzhang@dentistry.ubc.ca

Citation: Lubpairee T, Poh CF, Laronde DM, Rosin MP, Zhang L (2017) Oral Squamous Cell Carcinomas are Associated with Poorer Outcome with Increasing Ages. J Oncol Res Ther: JONT-132. DOI: 10.29011/2574-710X.000032

Received Date: 2 September, 2017; **Accepted Date:** 16 September, 2017; **Published Date:** 25 September, 2017

Abstract

Objectives: Although oral cancers traditionally occur in people between the age of 50 and 70, there are increasing incidences of this disease in younger and very old people. Objectives: to compare the demographics, habits, clinicopathological features, treatment and outcome of oral cancer in three age groups of patients: Young (≤ 45), Traditional (46 to 75), and Old (> 75).

Subjects: Primary oral cancers (393 patients) in a longitudinal study were used.

Results: Significant differences were noted in ethnicity (fewer Caucasian patients in Young), tobacco habit (more non-smokers in Young), location of cancer (more at tongue for Young and more at low-risk sites for Old) and treatment (more surgery for Young). Compared to Young (univariate analysis), Traditional and Old showed a 3- and 4.5-fold increase in local recurrences respectively; 1.9- and 2.7-fold increase in regional metastasis; 3.1- and 5.4-fold increase in death due to disease; and a 3.4- and 6.6-fold decrease in overall survival. Compared to Young (multivariate analysis), Traditional and Old showed a 2.4- and 3.3-fold increase in local recurrence; 2.7- and 5.4-fold increase in disease-specific survival; and 2.8- and 6.5-fold decrease in overall survival.

Conclusion: Oral cancer in different age groups showed differing ethnicity, habit, location, treatment and outcome.

Introduction

Oral Squamous Cell Carcinoma (OSCC) is one of the most common human cancers with poor prognosis. Until recently, OSCCs have been diagnosed mostly in patients in their sixth or seventh decade of life, with the disease often associated with a history of heavy tobacco consumption [1]. However, the incidence of OSCC in younger individuals (≤ 45 years old, hereby called Young) is rising [2-8], including in British Columbia [9]. At the same time, the extension of life expectancy has led to an aging population (> 75 years old, hereby called Old) both globally and in Canada, with an expected increase of Old oral cancer patients [4,10-12].

The age shift has prompted studies of OSCC in Young and Old patients because the understanding of clinicopathological features, treatment response and outcome of these patients would provide knowledge for better cancer control and management. However, results from studies comparing OSCCs among different age groups to date have been inconsistent. For example, prognosis of clinical outcomes among various age groups remains controversial. Kuriakose et al [13], and others [14-16] found that the disease was more aggressive in Young OSCC patients, whereas other stud-

ies reported better prognosis in Young, and still others could not find any significant differences [17-20]. Such inconsistency could be explained by a number of factors, such as the small number of cases in most of these studies, differences in genetic makeup of various ethnic groups and dissimilarities in dietary habits of diverse cultures. This study was aimed to obtain information (habits, clinicopathological features, treatment and outcome) of Young and Old OSCC patients from the greater Vancouver region in a longitudinal study setting.

Materials and Methods

This study involved patients who were prospectively enrolled in a longitudinal study (the Oral Cancer Predictive and Longitudinal, OCPL) in greater Vancouver, British Columbia (BC), Canada between 1997and 2009. Patients were identified primarily through a centralized oral pathology service, the BC Oral Biopsy Service, which receives biopsies from dentists and ENT surgeons across the province. Patients with oral cancer were referred to five Oral Dysplasia Clinics in Greater Vancouver where they were accrued to the study using written informed consent and a study protocol approved by research ethics board at the UBC/BCCA (University of BC/BC Cancer Agency; H98-61224 and H08-00839). A total of 423 OSCC patients were recruited to the OCPL study. Of these. 393 patients met the inclusion criteria for this study:

- A histological diagnosis of OSCC
- No prior history of OSCC
- The cancer was treated with a curative intent, which was defined as complete removal of the cancer or radiotherapy aimed at cure and
- at least a 6-month follow-up time to ensure that each case had received and completed treatment.

Since the recruitment occurred at Oral Dysplasia Clinics from a dental and ENT network, some OSCC, particularly those late stage ones (stage III and IV) were diagnosed by family doctors (biopsies did not go to the BC Oral Biopsy Service), hence were missing from our recruitment. As a result, the OSCC patients in our study had less representation of late-stage OSCC patients.

The following data were collected at study entry and during patient follow-up: habit (tobacco usage), demographics (age at cancer diagnosis, gender and ethnicity), clinicopathological (anatomical site, TNM stage and histopathological grade of the cancer), treatment, and outcome information (local recurrence to carcinoma in situ or invasive SCC, lymph node metastasis, distant metastasis and death). These data were entered into the OSCC database. When the information was not complete for this study, chart review was done.

Among these 393 cases, the average age was 60 years with a standard deviation of 13 years. For the 'Young' group, we used 45 years as the age cut off, which was derived both from previous studies (many used ≤ 45 as the age cut off) [21-27] and from calculation of one standard deviation younger than the average age [average age (60) - 1SD (13) = 47]. For the Old group, we used older than 75 as the cut off, which again came from previous studies [12,28,29] and from calculation [average age (60) + 1SD (13) = 73]. These cutoff values resulted in a separation of the study population (n = 393) into 3 groups, 55 (14%) patients were in the Young group (≤ 45); 295 (75%) were between the ages of 46 and 75, or 'traditional' age group (hereby called Traditional group); and 43 (11%) were in the Old group (> 75).

Statistical Analysis

Differences between two age groups (Young vs Traditional or Young vs Old, or Traditional vs Old) were examined using either Fisher's exact test for categorical variables (gender, ethnicity, smoking habit, tumor size and histological grade) or t-test for continuous variables (age and follow-up time). Time to endpoint was calculated from date of the index biopsy to endpoint date or to last follow-up date before February 2014 if no event occurred. Time-to-outcome curves were estimated using Kaplan–Meier analysis. Hazard ratios (HRs) and the corresponding 95% confidence intervals (95% CI) were determined using Cox proportional hazard regression analysis. Univariate logistic analysis and multiple proportional hazards regression analysis were used for estimating the HR of individual variable and combined effect. All tests were two sided with $P \leq 0.05$ considered to be statistically significant.

Results

Table 1 shows demographics, tobacco habit, clinical features (site and TNM stage), histology, treatment and follow up time for all patients in the current study by age groups. The mean follow up time for the study was 5.1 ± 3.4 years and the median 4.6 years. There were no differences in gender, TNM stage and histological differentiation of the OSCCs among the three age groups. However, differences were noted in ethnicity (less Caucasian in Young), habits (more non-smokers in Young), location (more at tongue for Young and low-risk sites for Old) and treatment (more surgery for Young).

Characteristics	All	Young (Y)	Traditional (T)	Old (O)	P value Y vs. T	P value Y vs. O	P value O vs. T
Case Number	393	55	293	45			
Age (years)							
Mean age ± SD	60.4 ± 13.4	37.3 ± 7.7	61.6 ± 7.6	81.1 ± 4.0			
Gender							
Male	246 (63)	33 (60)	189 (65)	24 (53)	0.54	0.55	0.18
Female	147 (37)	22 (40)	104 (35)	21 (47)			
Ethnicity							
Caucasian	326 (83)	40 (73)	247 (84)	39 (87)	**0.05**	0.14	0.83
Non-Caucasian[a]	67 (17)	15 (27)	46 (16)	6 (13)			
Smoking							
Never smoker[b]	121 (31)	34 (62)	72 (25)	15 (33)	**< 0.0001**	**< 0.0001**	0.21
Ever smoker[c]	272 (69)	21 (38)	221 (75)	30 (67)			
Former-smoker[d]	132 (49)	9 (43)	98 (44)	25 (83)	1	**0.006**	**< 0.0001**
Current-smoker[e]	140 (51)	12 (57)	123 (56)	5 (17)			
Site							
Tongue[f]	204 (52)	47 (85)	136 (46)	21 (47)	**< 0.0001**	**< 0.0001**	**0.04**
FOM (floor of mouth[f]	76 (19)	4 (7)	68 (23)	4 (9)			
Soft Palate[g]	15 (4)	0 (0)	14 (5)	1 (2)			
Low risk sites[h]	98 (25)	4 (7)	75 (26)	19 (42)			
TNM Stage							
Early (stages I and II)	287 (73)	43 (78)	211 (72)	33 (73)	0.41	0.64	1
Late (stages III and IV)	106 (27)	12 (22)	82 (28)	12 (27)			
Histology							
Well-moderate	370 (94)	53 (96)	274 (94)	43 (96)	0.55	0.59	1
Poor	23 (6)	2 (4)	19 (6)	2 (4)			
Treatment							
Surgery	268 (68)	41 (74)	197 (67)	30 (67)	**0.009**	**< 0.0001**	0.13
Surgery & radiation	62 (16)	13 (24)	50 (17)	3 (7)			
Radiation	63 (16)	1 (2)	46 (16)	12 (27)			
Surgery with or without radiation	330 (84)	54 (98)	247 (84)	33 (73)	**0.004**	**0.0004**	0.09
Radiation	63 (16)	1 (2)	46 (16)	12 (27)			
Follow up time (years)							
Mean ± SD	5.1 ± 3.4	6.9 ± 3.3	5.0 ± 3.3	3.3 ± 2.5	**< 0.0001**	**< 0.0001**	**0.002**
Median	4.6	7.4	4.5	2.6			

Significant values, P < 0.05, are bolded.
[a]Non-Caucasian; Asian, First Nation, Hispanic and more than one race.
[b]Never smoker was defined as consumption of less than 100 cigarettes in life time.
[c]Ever Smoker was defined as consumption of more than 100 cigarettes in life time.
[d]Former smoker: Smokers who had stopped smoking after enrolling into the study.
[e]Current smoker: Smokers who continued smoking after enrolling into the study.
[f]Tongue and Floor of Mouth (FOM): are regarded high risk sites where oral premalignant lesions are at high risk of malignant transformation.
[g]Soft palate: is regarded an intermediate risk site where oral premalignant lesions are at an intermediate risk of malignant transformation.
[h]Low-risk sites: Gingiva, vestibule, cheek, lip and hard palate.

Table 1: Comparison of the Three Age Groups.

Univariate Cox analyses were performed using different outcomes, with local recurrence as outcome shown in Table 2, lymph node metastasis as outcome in Table 3, distant metastasis as outcome in Table 4, disease-specific survival as outcome in Table 5 and overall survival as outcome in Table 6. Increasing ages, location at high-risk sites, and radiation treatment were associated with increased risk of local recurrence; increasing age, Caucasian ethnicity, site (high- or intermediate-risk) and late TNM stages were associated with significantly higher proportion of lymph node metastasis; locations at floor of mouth/soft palate and late TNM stages were associated with significantly higher proportion of distant metastasis; increasing age, location at floor of mouth, late TNM stages and radiation treatment were associated with significantly higher proportion of death due to disease; and increasing age, Caucasian ethnicity, tobacco habit, locations at floor of mouth/soft palate, late TNM stages and radiation treatment were associated with poorer overall survival.

Multivariate analysis was performed using multivariate Cox proportional hazard regression analysis across the different outcomes. Only increasing age and radiation treatment remained associated with local recurrence; increasing age, site (high or intermediate risk) and late stage were associated with lymph node metastasis; site (floor of mouth and soft palate) and late stage were associated with distant metastasis; increasing age, site (floor of mouth/soft palate), late TNM stages and radiation therapy were associated with death due to disease; and increasing age and late stages were associated with poorer overall survival.

Characteristics	All	With outcome	Without outcome	Univariate analysis		Multivariate analysis	
		(% row)	(% row)	HR (95% CI)[a]	P value	HR (95% CI)	P value
Case Number	393	104 (26)	289 (74)				
Age							
Young	55	7 (13)	48 (87)	1		1	
Traditional	293	83 (28)	210 (72)	3.0 (1.4 - 6.6)	**0.01**	2.4 (1.0 – 5.3)	**0.04**
Old	45	14 (31)	31 (69)	4.5 (1.8 - 11.2)	**0.001**	3.3 (1.3 – 8.5)	**0.02**
Gender							
Female	147	41 (28)	106 (72)	1	0.77	1	0.58
Male	246	63 (26)	183 (74)	0.9 (0.6 - 1.4)		0.9 (0.6 – 1.4)	
Ethnicity							
Caucasian	326	81 (25)	245 (75)	1	0.49	1	0.15
Non-Caucasian[b]	67	23 (34)	44 (66)	1.2 (0.7 - 1.9)		1.5 (0.9 – 2.4)	
Smoking							

Never-smoker[c]	121	27 (22)	94 (78)	1	0.12	1	NA
Ever-smoker[d]	272	77 (28)	195 (72)	1.4 (0.9 - 2.2)		NA	
Former-smoker[e]	132	40 (30)	92 (70)	1.5 (0.9 - 2.5)	0.09	1.4 (0.8 – 2.4)	0.25
Current-smoker[f]	140	37 (26)	103 (74)	1.3 (0.8 - 2.1)	0.3	1.1 (0.6 – 2.0)	0.74
Site							
Tongue[g]	204	44 (22)	160 (78)	1		1	
FOM[g]	76	21 (28)	55 (72)	1.6 (1.0 - 2.8)	0.06	1.4 (0.8 – 2.5)	0.25
Soft palate[h]	15	4 (27)	11 (73)	1.8 (0.6 - 4.9)	0.28	1.0 (0.3 – 3.2)	0.94
Low-risk sites[i]	98	35 (36)	63 (64)	1.9 (1.2 - 3.0)	**0.004**	1.3 (0.8 – 2.1)	0.34
TNM Stage							
Early	287	73 (25)	214 (75)	1	0.09	1	0.28
Late	106	31 (29)	75 (71)	1.4 (0.9 - 2.3)		1.3 (0.8 – 2.0)	
Histology							
Well-moderate	371	100 (27)	271 (73)	1	0.32	NA	NA
Poor	22	4 (18)	18 (82)	0.6 (0.2 - 1.6)		NA	
Treatment							
Surgery with or without radiation	330	76 (23)	254 (77)	1	**< 0.0001**	1	**0.02**
Radiation	63	28 (44)	35 (56)	2.4 (1.5 – 3.7)		1.8 (1.1 – 3.1)	

Significant values, $P < 0.05$, are bolded.

[a]HR: indicates a hazard ratio; CI: confidence interval.

[b]Non-Caucasian; Asian, First Nation, Hispanic and more than one race.

[c]Never smoker was defined as consumption of less than 100 cigarettes in life time.

[d]Ever Smoker was defined as consumption of more than 100 cigarettes in life time.

[e]Former smoker: Smokers who had stopped smoking after enrolling into the study.

[f]Current smoker: Smokers who continued smoking after enrolling into the study.

[g]Tongue and floor of mouth (FOM): are regarded high risk sites where oral premalignant lesions are at high risk of malignant transformation.

[h]Soft palate: is regarded intermediate risk site where oral premalignant lesions are at an intermediate risk of malignant transformation.

[i]Low-risk sites: Gingiva, vestibule, cheek, hard palate and labial mucosa.

Table 2: Univariate and Multivariate Analyses with Local Recurrence as Outcome.

Characteristics	All	With outcome (% row)	Without outcome (% row)	Univariate analysis		Multivariate analysis	
				HR (95% CI)[a]	P value	HR (95% CI)	P value
Case Number	393	82 (21)	311 (79)				
Age							
Young	55	7 (13)	48 (87)	1		1	
Traditional	293	63 (22)	230 (78)	1.9 (0.9 - 4.2)	0.1	2.1 (0.9 – 4.8)	0.07
Old	45	12 (27)	33 (73)	2.7 (1.1 - 6.9)	**0.04**	4.2 (1.6 – 11.4)	**0.004**
Gender							
Female	147	30 (20)	117 (80)	1	0.81	1	0.92
Male	246	52 (21)	194 (79)	1.1 (0.7 - 1.7)		1.0 (0.6 – 1.6)	
Ethnicity							
Caucasian	326	74 (23)	252 (77)	1	**0.04**	1	0.08
Non-Caucasian[b]	67	8 (12)	59 (88)	0.5 (0.2 - 1.0)		0.5 (0.2 – 1.1)	
Smoking							
Never-smoker[c]	121	23 (19)	98 (81)	1	0.52	1	NA
Ever-smoker[d]	272	59 (22)	213 (78)	1.2 (0.7 - 1.9)		NA	
Former-smoker[e]	132	26 (20)	106 (80)	1.0 (0.6 - 1.8)	0.88	0.8 (0.4 – 1.4)	0.43
Current-smoker[f]	140	33 (24)	107 (76)	1.3 (0.8 - 2.2)	0.34	1.1 (0.6 – 2.0)	0.82
Site							
Tongue[g]	204	49 (24)	155 (76)	1		1	
FOM[g]	76	19 (25)	57 (75)	1.1 (0.7 - 1.9)	0.66	1.0 (0.5 – 1.7)	0.87
Soft palate[h]	15	4 (27)	11 (73)	1.2 (0.4 - 3.4)	0.71	1.6 (0.5 – 5.1)	0.44
Low-risk sites[i]	98	10 (10)	88 (90)	0.4 (0.2 - 0.8)	**0.01**	0.4 (0.2 – 0.7)	**0.01**
TNM Stage							
Early	287	54 (19)	233 (81)	1	**0.03**	1	**0.01**
Late	106	28 (26)	78 (74)	1.7 (1.1 - 2.7)		1.8 (1.1 – 2.9)	

Histological							
Well-moderate	371	79 (21)	292 (79)	1	0.46	NA	NA
Poor	22	3 (14)	19 (86)	0.6 (0.2 - 2.1)			
Treatment							
Surgery with or without radiation	330	73 (22)	257 (78)	1	0.26	1	0.16
Radiation	66	9 (14)	54 (86)	0.7 (0.3 - 1.3)		0.6 (0.2 – 1.3)	

Significant values, P < 0.05, are bolded.
[a]HR: indicates a hazard ratio; CI: confidence interval.
[b]Non-Caucasian; Asian, First Nation, Hispanic and more than one race.
[c]Never smoker was defined as consumption of less than 100 cigarettes in life time.
[d]Ever Smoker was defined as consumption of more than 100 cigarettes in life time.
[e]Former smoker: Smokers who had stopped smoking after enrolling into the study.
[f]Current smoker: Smokers who continued smoking after enrolling into the study.
[g]Tongue and Floor of Mouth (FOM): are regarded high risk sites where oral premalignant lesions are at high risk of malignant transformation.
[h]Soft palate: is regarded intermediate risk site where oral premalignant lesions are at an intermediate risk of malignant transformation.
[i]Low-risk sites: Gingiva, vestibule, cheek, hard palate and labial mucosa.

Table 3: Univariate and Multivariate Analyses with Regional Lymph Node Failure as Outcome.

Characteristics	All	With outcome (% row)	Without outcome (% row)	Univariate analysis		Multivariate analysis	
				HR (95% CI)[a]	P value	HR (95% CI)	P value
Case Number	393	29 (7)	364 (93)				
Age							
Young	55	2 (4)	53 (96)	1		1	
Traditional	293	25 (9)	268 (91)	2.9 (0.7 - 12.3)	0.15	2.1 (0.5 – 9.7)	0.32
Old	45	2 (4)	43 (96)	2.0 (0.3 - 14.3)	0.49	1.9 (0.2 – 14.7)	0.56
Gender							
Female	147	12 (8)	135 (92)	1	0.71	1	0.41
Male	246	17 (7)	229 (93)	0.9 (0.4 - 1.8)		0.7 (0.3 – 1.6)	
Ethnicity							
Caucasian	326	26 (8)	300 (92)	1	0.23	1	0.41
Non-Caucasian[b]	67	3 (4)	64 (96)	0.5 (0.1 – 1.6)		0.6 (0.2 – 2.1)	
Smoking							
Never-smoker[c]	121	7 (6)	114 (94)	1	0.36	1	NA
Ever-smoker[d]	272	22 (8)	250 (92)	1.5 (0.6 – 3.5)		NA	

Former-smoker[e]	132	10 (8)	122 (92)	1.4 (0.5 - 3.6)	0.52	1.0 (0.3 – 2.8)	0.94
Current-smoker[f]	140	12 (9)	128 (91)	1.6 (0.6 - 4.1)	0.32	0.9 (0.3 – 2.7)	0.87
Site							
Tongue[g]	204	11 (5)	193 (95)	1		1	
FOM[g]	76	9 (12)	67 (88)	2.7 (1.1 - 6.5)	**0.03**	2.3 (0.9 – 6.2)	0.09
Soft palate[h]	15	3 (20)	12 (80)	4.6 (1.3 - 16.4)	**0.02**	4.9 (1.0 – 23.4)	**0.04**
Low-risk sites[i]	98	6 (6)	92 (94)	1.2 (0.4 - 3.2)	0.73	1.1 (0.4 – 3.1)	0.92
TNM Stage							
Early	287	17 (6)	270 (94)	1	**0.01**	1	**0.02**
Late	106	12 (11)	94 (89)	2.6 (1.2 - 5.5)		2.6 (1.2 – 5.7)	
Histological							
Well-moderate	371	27 (7)	344 (93)	1	0.67	NA	NA
Poor	22	2 (9)	20 (91)	1.4 (0.3 - 5.8)			
Treatment							
Surgery with or without radiation	330	23 (7)	307 (93)	1	0.31	1	0.78
Radiation	63	6 (10)	57 (90)	1.6 (0.7 – 3.9)		0.9 (0.3 – 2.6)	

Significant values, P < 0.05, are bolded.
[a]HR: indicates a hazard ratio; CI: confidence interval.
[b]Non-Caucasian; Asian, First Nation, Hispanic and more than one race.
[c]Never smoker was defined as consumption of less than 100 cigarettes in life time.
[d]Ever Smoker was defined as consumption of more than 100 cigarettes in life time.
[e]Former smoker: Smokers who had stopped smoking after enrolling into the study.
[f]Current smoker: smokers who continued smoking after enrolling into the study.
[g]Tongue and Floor of Mouth (FOM): are regarded high risk sites where oral premalignant lesions are at high risk of malignant transformation.
[h]Soft palate: is regarded intermediate risk site where oral premalignant lesions are at an intermediate risk of malignant transformation.
[i]Low-risk sites: Gingiva, vestibule, cheek, hard palate and labial mucosa.

Table 4: Univariate and Multivariate Analyses with Distant Metastasis as Outcome

Characteristics	All	With outcome	Without outcome	Univariate analysis		Multivariate analysis	
		(% row)	(% row)	HR (95% CI)[a]	P value	HR (95% CI)	P value
Case Number	393	86 (22)	307 (78)				
Age							
Young	55	5 (9)	50 (91)	1		1	
Traditional	293	67 (23)	226 (77)	3.1 (1.3 – 7.7)	**0.01**	2.7 (1.1 – 7.0)	**0.04**
Old	45	14 (31)	31 (69)	5.4 (1.9 – 15.1)	**0.001**	5.4 (1.8 – 16.1)	**0.003**
Gender							

Female	147	29 (20)	118 (80)	1	0.43	1	0.67
Male	246	57 (23)	189 (77)	1.2 (0.8 – 1.9)		1.1 (0.7 – 1.8)	
Ethnicity							
Caucasian	326	79 (24)	247 (76)	1	**0.01**	1	0.08
Non-Caucasian[b]	67	7 (10)	60 (90)	0.4 (0.2 – 0.8)		0.5 (0.2 – 1.1)	
Smoking							
Never-smoker[c]	121	22 (18)	99 (82)	1	0.25	1	NA
Ever-smoker[d]	272	64 (24)	208 (76)	1.3 (0.8 – 2.2)		NA	
Former-smoker[e]	132	33 (25)	99 (75)	1.4 (0.8 – 2.4)	0.22	0.8 (0.5 – 1.5)	0.53
Current-smoker[f]	140	31 (22)	109 (78)	1.3 (0.7 – 2.2)	0.4	0.7 (0.4 – 1.3)	0.31
Site							
Tongue[g]	204	38 (19)	166 (81)	1		1	
FOM[g]	76	22 (29)	54 (71)	1.8 (1.1 – 3.1)	**0.02**	1.4 (0.8 – 2.5)	0.25
Soft palate[h]	15	6 (40)	9 (60)	2.6 (1.1 – 6.1)	**0.03**	2.8 (1.0 – 7.5)	**0.05**
Low-risk sites[i]	98	20 (20)	78 (80)	1.1 (0.7 – 1.9)	0.65	0.8 (0.4 – 1.5)	0.47
TNM Stage							
Early	287	41 (14)	246 (86)	1	**< 0.0001**	1	**< 0.0001**
Late	106	45 (42)	61 (58)	3.9 (2.5 – 5.9)		3.6 (2.3 – 5.6)	
Histology							
Well-Moderate	371	80 (22)	291 (78)	1	0.62	NA	NA
Poorly	22	6 (27)	16 (73)	1.2 (0.5 – 2.8)			
Treatment							
Surgery with or without radiation	330	65 (20)	265 (80)	1	**0.01**	1	0.94
Radiation	63	21 (33)	42 (67)	1.9 (1.2 – 3.1)		1.0 (0.6 – 1.9)	

Significant values, $P < 0.05$, are bolded.

[a]HR: indicates a hazard ratio; CI: confidence interval.

[b]Non-Caucasian; Asian, First Nation, Hispanic and more than one race.

[c]Never smoker was defined as consumption of less than 100 cigarettes in life time.

[d]Ever Smoker was defined as consumption of more than 100 cigarettes in life time.

[e]Former smoker: Smokers who had stopped smoking after enrolling into the study.

[f]Current smoker: Smokers who continued smoking after enrolling into the study.

[g]Tongue and Floor of Mouth (FOM): are regarded high risk sites where oral premalignant lesions are at high risk of malignant transformation.

[h]Soft palate: is regarded intermediate risk site where oral premalignant lesions are at an intermediate risk of malignant transformation.

[i]Low-risk sites: Gingiva, vestibule, cheek, hard palate and labial mucosa.

Table 5: Univariate and Multivariate Analyses with Disease-Specific Survival (Death Due to Disease) as Outcome.

Characteristics	All	With outcome (% row)	Without outcome (% row)	Univariate analysis		Multivariate analysis	
				HR (95% CI)[a]	P value	HR (95% CI)	P value
Case Number	393	143 (36)	250 (64)				
Age							
Young	55	8 (15)	47 (85)	1		1	
Traditional	293	111 (38)	182 (62)	3.4 (1.7 - 7.1)	**0.001**	2.8 (1.3 – 5.9)	**0.01**
Old	45	24 (53)	21 (47)	6.6 (3.0 - 14.8)	**< 0.0001**	6.5 (2.7 – 15.3)	**< 0.0001**
Gender							
Female	246	45 (31)	102 (69)	1	0.11	1	0.45
Male	147	98 (40)	148 (60)	1.3 (0.9 - 1.9)		1.2 (0.8 – 1.7)	
Ethnicity							
Caucasian	326	130 (40)	196 (60)	1	**0.001**	1	0.06
Non-Caucasian[b]	67	13 (19)	54 (81)	0.4 (0.2 - 0.7)		0.6 (0.3 – 1.0)	
Smoking							
Never-smoker[c]	121	27 (22)	94 (78)	1	**0.001**	1	NA
Ever-smoker[d]	272	116 (43)	156 (57)	2.0 (1.3 - 3.1)		NA	
Former-smoker[e]	132	50 (38)	82 (62)	1.8 (1.1 - 2.8)	**0.02**	1.0 (0.6 – 1.7)	0.9
Current-smoker[f]	140	66 (47)	74 (53)	2.2 (1.4 - 3.5)	**< 0.0001**	1.4 (0.8 – 2.3)	0.24
Site							
Tongue[g]	204	62 (30)	142 (70)	1		1	
FOM[g]	76	37 (49)	39 (51)	2.0 (1.3 - 3.1)	**0.001**	1.3 (0.8 – 2.1)	0.22
Soft palate[h]	98	35 (36)	63 (64)	1.2 (0.8 - 1.8)	0.36	0.7 (0.5 – 1.2)	0.2
Low-risk sites[i]	15	9 (60)	6 (40)	2.5 (1.3 - 5.1)	**0.01**	1.7 (0.8 – 3.9)	0.18
TNM stage							
Early	287	83 (29)	204 (71)	1	**< 0.0001**	1	**< 0.0001**
Late	106	60 (57)	46 (43)	2.7 (1.9 - 3.8)		2.4 (1.7 – 3.4)	
Histology							
Well-moderate	371	131 (35)	240 (65)	1	0.24	NA	NA
Poor	22	12 (55)	10 (46)	1.4 (0.8 - 2.6)			
Treatment							
Surgery with or without radiation	330	104 (32)	226 (68)	1	**< 0.0001**	1	0.23
Radiation	63	39 (62)	24 (38)	2.2 (1.5 – 3.2)		1.3 (0.8 – 2.1)	

Significant values, $P < 0.05$, are bolded.
[a]HR: indicates a hazard ratio; CI: confidence interval.
[b]Non-Caucasian; Asian, First Nation, Hispanic and more than one race.
[c]Never smoker was defined as consumption of less than 100 cigarettes in life time.
[d]Ever Smoker was defined as consumption of more than 100 cigarettes in life time.
[e]Former smoker: Smokers who had stopped smoking after enrolling into the study.
[f]Current smoker: Smokers who continued smoking after enrolling into the study.
[g]Tongue and Floor of Mouth (FOM): are regarded high risk sites where oral premalignant lesions are at high risk of malignant transformation.
[h]Soft palate: is regarded intermediate risk site where oral premalignant lesions are at an intermediate risk of malignant transformation.
[i]Low-risk sites: Gingiva, vestibule, cheek, hard palate and labial mucosa.

Table 6: Univariate and Multivariate Analyses with Overall Survival as Outcome.

Discussion

Our study results showed that oral SCC in the three age groups differed in many parameters, notably the habit of the patients, site, treatment and outcome of the SCCs.

Similar to previous studies, Young OSCC patients were more likely to be nonsmokers as compared to Traditional and Old groups. IARC working group has concluded that 'in the oral cavity, there was sufficient evidence for the carcinogenicity of HPV 16 and limited evidence for the carcinogenicity of HPV 18' (IARC, 2012, 2007). It is reasonable to hypothesize that HPV plays a more important role in the pathogenesis of oral SCC in younger people. However, there is a lack of study to show increased HPV infection in the oral cavity SCC from younger people. One study from the United States did show increased incidence of HPV-related oral SCC in younger patients [30].

Genetic susceptibility of young OSCC patients is another commonly held thesis as the etiology for OSCC in younger people. The lack of HPV infection and tobacco usage history in most young OSCC patients would support the hypothesis that the young oral SCC patients were genetically susceptible to oral cancer formation [31,32]. In a parallel thesis, old oral SCC patients could be less genetically susceptible than the traditional group since it took longer for oral SCCs to develop in the old group as compared to the traditional group. Interestingly, among the smokers, less than half of the smokers in Young and Traditional groups in our study quite smoking after the diagnosis of OSCC; whereas the majority of smokers in Old group quit smoking after the diagnosis.

Our results also showed that the three age groups showed significant differences in the location of the cancer: a significantly higher percentage of oral SCCs in the Young group were located on the tongue (85% in Young vs 46% and 47% in Traditional and Old groups), a significantly higher percentage of oral SCCs in the Traditional group were located in the floor of mouth (23% in Traditional vs 7% and 9% in Young and Old groups); and a significantly higher percentage of Oral SCCs in the Old group were located low-risk sites (42% in Old vs 7% and 26% in Young and Traditional groups).

The site predilection of cancer in the tongue is not only seen in young oral cancer patients, but also in non-smoker oral cancer patients, another population that possibly have genetic susceptibility to oral cancer. The basis for such site predilection remains unknown. The site predilection of oral cancer in the floor of mouth in the Traditional group could reflect the thesis that epithelium in the floor of mouth is thinner than the rest of the oral cavity, hence easier to penetrate to the basal epithelial cells, the target of the carcinogens, and the thesis that tobacco dissolved in saliva could expose the floor of mouth to carcinogens longer than the rest of the oral cavity. It is therefore surprising that there is such a low occurrence of oral SCC in the floor of mouth in the Old group, considering that most of oral SCCs in this group is smoking related. The site predilection of cancer in the low-risk sites in the Old group could be attributed to irritation from mastication/biting trauma in the cheek and labial mucosa or denture to the alveolar ridge and vestibular mucosa or periodontitis since inflammation and trauma would promote cancer development. This information is important for our screening of high-risk oral lesions for older patients, and we need to be vigilant not only for the floor of mouth and tongue areas, but also low-risk sites.

Oral SCCs in the Young group were more likely to be treated with surgery with or without radiation; whereas oral SCCs in the Old group were more likely to be treated with radiation alone, possibly owing to the general health of the patients. Compared to radiation therapy, surgery with or without radiation showed significantly lower rate of local recurrence and no statistical differences in the regional or distant metastasis. However, patients with radiation therapy seemed to have significantly higher mortality, either from the oral cancer or from other causes. Young oral SCC patients fared consistently better than Traditional and Old age groups as judged by most outcomes (Tables 2, 3, 5 and 6). Traditional group fared better than Old age groups in mortality rate, either from the oral cancer or from other causes. It is quite possible that the better outcome from Young to Traditional to Old reflects the general health of the patients, with Young patients in the best health and Old patients the worst.

Conclusion

In conclusion, there are significant differences in OSCCs among the three age groups in various clinicopathological parameters, treatment and outcome. Understanding these differences should help the clinicians in the management of the disease.

Acknowledgement: The authors want to thank Dr. Huijun Jiang for her assistance in data collection and statistical analysis. This work was supported by grants R01 DE13124 and R01 DE17013 from the National Institute of Dental and Craniofacial Research.

Conflict of Interest: None to declare.

Author Contributions: Drs Poh, Laronde and Rosin have contributed in conception and design, in revising and in approval of the paper. Drs Lubpairee and Zhang have contributed in conception and design, acquisition, analysis and interpretation of data; in drafting the paper, and in the final approval of the paper.

References

1. Wyss A, Hashibe M, Chuang SC, Lee YC, Zhang ZF, et al. (2013) Cigarette, cigar, and pipe smoking and the risk of head and neck cancers: Pooled analysis in the international head and neck cancer epidemiology consortium. Am J Epidemiol 178: 679-690.
2. Annertz K, Anderson H, Biorklund A, Möller T, Kantola S, et al (2002) Incidence and survival of squamous cell carcinoma of the tongue in Scandinavia, with special reference to young adults. Int J Cancer 101: 95-99.
3. Atula S, Grénman R, Laippala P, Syrjänen S (1996) Cancer of the tongue in patients younger than 40 years: A distinct entity? Arch Otolaryngol Neck Surg 122: 1313-1319.
4. Chen K, Song F, He M, Li H, Qian B, et al. (2009) Trends in head and neck cancer incidence in Tianjin, China, between 1981 and 2002. Head Neck 31: 175-182.
5. Conway DI, Stockton DL, Warnakulasuriya KAAS, Ogden G, Macpherson LM (2006) Incidence of oral and oropharyngeal cancer in United Kingdom (1990-1999) -- recent trends and regional variation. Oral Oncol 42: 586-592.
6. Elango JK, Gangadharan P, Sumithra S, Kuriakose M a (2006) Trends of head and neck cancers in urban and rural India. Asian Pac J Cancer Prev 7: 108-12.
7. Shiboski CH, Schmidt BL, Jordan RCK (2005) Tongue and tonsil carcinoma: Increasing trends in the U.S. population ages 20-44 years. Cancer 103: 1843-1849.
8. Patel SC, Carpenter WR, Tyree S, Couch ME, Weissler M, et al (2011) Increasing Incidence of Oral Tongue Squamous Cell Carcinoma in Young White Women, Age 18 to 44 Years. J Clin Oncol 29: 1488-1494.
9. BC Cancer Agency (2009) Oral Cancer Incidence Trend. http://www.bccancer.bc.ca/statistics-and-reports-site/Documents/IncidenceOral.pdf. Accessed 13 Mar 2016
10. Morse DE, Pendrys DG, Neely AL, Psoter WJ (1999) Trends in the incidence of lip, oral, and pharyngeal cancer: Connecticut, 1935-94. Oral Oncol 35: 1-8.
11. Hakulinen T, Tryggvadóttir L, Gislum M, Storm HH, Bray F, et al. (2010) Trends in the survival of patients diagnosed with cancers of the lip, oral cavity, and pharynx in the Nordic countries 1964-2003 followed up to the end of 2006. Acta Oncol 49: 561-577.
12. Hasegawa Y, Fukuhara T, Fujiwara K, Takeuchi E, Kitano H (2015) Treatment Outcomes of Head and Neck Squamous Cell Carcinoma in the Elderly: A Retrospective Study over 7 Years (2003 - 2009). Yonago Acta Med 58: 9-13.
13. Kuriakose M, Sankaranarayanan M, Nair MK, Cherian T, Sugar AW, et al. (1992) Comparison of oral squamous cell carcinoma in younger and older patients in India. Eur J Cancer Part B Oral Oncol 28: 113-120.
14. Garavello W, Spreafico R, Gaini RM (2007) Oral tongue cancer in young patients: A matched analysis. Oral Oncol 43: 894-897.
15. Liao CT, Wang HM, Hsieh LL, Chang JTC, Ng S, et al. (2006) Higher distant failure in young age tongue cancer patients. Oral Oncol 42: 718-725.
16. Cavalcanti LG, Araújo RLF, Bon C, Torres-pereira CC (2015) Biology of Blood and Marrow Transplantation Oral Manifestations Compatible with Chronic Graft-versus-Host Disease in Patients with Fanconi Anemia. 21: 275-280.
17. Friedlander PL, Schantz SP, Shaha a R, et al (1998) Squamous cell carcinoma of the tongue in young patients: a matched-pair analysis. Head Neck 20: 363-368.
18. Kaminagakura E, Vartanian JG, da Silva SD, dos Santos CR, Kowalski LP (2010) Case-control study on prognostic factors in oral squamous cell carcinoma in young patients. Head Neck 32: 1460-1466.
19. van Monsjou HS, Lopez–Yurda MI, Hauptmann M, van den Brekel MW, Balm AJ, et al. (2013) Oral and oropharyngeal squamous cell carcinoma in young patients: The Netherlands Cancer Institute experience. Head Neck 35: 94-102.
20. Siegelmann-Danieli N, Hanlon A, Ridge JA, Padmore R, Fein DA, et al. (1998) Oral tongue cancer in patients less than 45 years old: institutional experience and comparison with older patients. J Clin Oncol 16: 745-753.
21. Braakhuis BJM, Visser O, René Leemans C (2009) Oral and oropharyngeal cancer in The Netherlands between 1989 and 2006: Increasing incidence, but not in young adults. Oral Oncol 45: e85-e89.
22. Brägelmann J, Dagogo-Jack I, El Dinali M, et al. (2013) Oral cavity tumors in younger patients show a poor prognosis and do not contain viral RNA. Oral Oncol 49: 525-533.
23. Chang T-S, Chang C-M, Ho H-C, Su YC, Chen LF, et al. (2013) Impact of Young Age on the Prognosis for Oral Cancer: A Population-Based Study in Taiwan. PLoS One 8: e75855.
24. Ho H-C, Lee M-S, Hsiao S-H, Hwang JH, Hung SK, et al. (2008) Squamous cell carcinoma of the oral cavity in young patients: a matched-pair analysis. Eur Arch Otorhinolaryngol 265 Suppl: S57-S61.
25. Kantola S, Parikka M, Jokinen K, K Hyrynkangs, Y Soini, et al. (2000) Prognostic factors in tongue cancer - relative importance of demographic, clinical and histopathological factors. Br J Cancer 83: 614-619.

26. Kostrzewska-Poczekaj M, Gawecki W, Illmer J, Rydzanicz M, et al (2013) Polymorphisms of DNA repair genes and risk of squamous cell carcinoma of the head and neck in young adults. Eur Arch Otorhinolaryngol 270: 271-276.

27. Llewellyn CD, Linklater K, Bell J, et al. (2003) Squamous cell carcinoma of the oral cavity in patients aged 45 years and under: A descriptive analysis of 116 cases diagnosed in the South East of England from 1990 to 1997. Oral Oncol 39: 106-114.

28. Sarini J, Fournier C, Lefebvre J-L, Bonafos G, Van JT, et al. (2001) Head and Neck Squamous Cell Carcinoma in Elderly Patients. Arch Otolaryngol Neck Surg 127: 1089.

29. Huang SH, O'Sullivan B, Waldron J, Lockwood G, Bayley A, et al. (2011) Patterns of care in elderly head-and-neck cancer radiation oncology patients: a single-center cohort study. Int J Radiat Oncol Biol Phys 79: 46-51.

30. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML (2008) Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 26: 612-619.

31. Li R, Faden DL, Fakhry C, Langelier C, Jiao Y, et al. (2015) Clinical, genomic, and metagenomic characterization of oral tongue squamous cell carcinoma in patients who do not smoke. Head Neck 37: 1642-1649.

32. Lingen MW, Xiao W, Schmitt A, Jiang B, Pickard R, et al. (2013) Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. Oral Oncol 49: 1-8.