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# Impact of Age on Prognostic Treatment Outcomes Among Oral Squamous Cell Carcinoma Patients: Evidence from Sri Lanka

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## Abstract

**Introduction:** Disease free survival is the optimum treatment outcome in cancer management. We explored the impact of age on key treatment outcomes among a group of Sri Lankan oral squamous cell carcinoma patients.

**Material & Methods:** We studied clinical records of 44 oral squamous cell carcinoma patients consisted of age- matched two groups (22 in each group) who had close surgical margins and clear surgical margins respectively. Of two groups, the first group completed the post-operative adjuvant radiotherapy but second group did not. The follow–up period was 6-months from the primary cancer ablative surgery. Disease frees survival, recurrence and mortality was assessed as prognostic treatment outcomes.

**Results:** The majority (79.5%) of oral cancer patients survived but 34.1% had recurrences at the end of the follow-up period. The mean ± SD ages of disease-free survivors, survivors with recurrence and non-survivors were 61.6 ± 9.17 years, 56.0 ± 11.08 years and 52.2 ± 9.34 years respectively. The age differences were statistically significant (p=0.04) assessed by ANOVA test.

**Conclusion:** There could be an impact of age on survival of oral cancer patients as indicated by findings of this study. However, findings of the present study should be interpreted and compared with findings of similar studies cautiously as it had a shorter follow up period which was 6-months from primary surgery and a small sample size of 44. Further studies warranted in this regard.

**Keywords:** Disease free survival, Recurrence, Mortality, Oral squamous cell carcinoma, Sri Lanka, Age impact

## Introduction

Improving treatment outcomes for oral cancer patients is underpinned by their disease-free survival and overall survival while ensuring sufficient levels of quality of life [1,2]. There is research evidence to support surgical treatment with or without adjuvant radiotherapy is superior as compared to curative radiotherapy with or without chemotherapy especially for locally advanced stage of oral squamous cell carcinomas (OSCCs) [2-4]. However, pathologic positive margins considered to be a negative prognostic factor for OSCC patients [3]. On the contrary, pathologic safe margins deemed to be a positive prognostic factor in surgical management of oral cancers while there is research evidence to substantiate negative prognostic effects of pathologic close margins [3]. Nevertheless, improving prognostic treatment outcomes for oral cancer patients in developing countries in the Asia-Pacific region where there is high incidence and prevalence is a notable challenge [5]. Despite occurring in one of the

most accessible body sites, oral cancers are presented at late stages that contribute to high recurrences and poor survival rates [6]. Therefore, accomplishing pathologically safe margins has become a serious cause of concern for oral & maxillofacial surgeons in developing countries.

The overarching goal of curative surgery for OSCC patients is to achieve pathologically safe margins (PSM) even among locally advanced cases to ensure better probability of survival. However, the treatment outcome generally becomes poor, for locally advanced cases [3]. Moreover, presence of pathologically adverse features including pathologically positive margin (PPM), extra capsular nodal spread (ECS), perineural invasion (PNI), N2 or N3 nodal disease, and vascular embolism constitute adverse prognostic factors [1,3,7-9] of OSCC thus indicating adjuvant radiotherapy following surgery [3,4]. PPM is known to result in treatment failures that may contribute to patient's death [3]. Hence, overall survival (with or without recurrences) and disease-free survival are considered to be core prognostic outcomes to be assessed in management of OSCC patients [1-5].

Cancers of lip and oral cavity (oral cancer) is the leading cancer type among males in Sri Lanka, a developing middle-income country, while being 8$^{th}$ most common cancer type among females with age standardized rates of 15.6 per 100,000 population and 3.7 per 100,000 populations respectively [10]. Research has proved that older males dominated in the risk profile of oral cancer patients [11,12] and presenting at late stages [13]. Nevertheless, late-stage presentations of oral cancers leading to difficult surgical resections results in close surgical margins more often despite effort. Treatments of such patients are followed by adjuvant radiotherapy within 6 weeks postoperatively to increase better prognostic probability without recurrences [3,4]. However, in developing country context as in Sri Lanka grappling with a high burden of oral cancer there are long waiting lists for surgeries. Moreover, due to poor nutrition of patients leading to delayed wound healing and attempts of re-surgical excisions, the majority of patients receive postoperative adjuvant radiotherapy well after 6-weeks. There is burgeoning research on clinical, histological and molecular prognostic markers of survival, recurrence and age-gender profile of oral cancer patients [1,3,7-9,14]. Previous studies on impact of age on survival rate of oral cancer patients found that survival rate of younger oral cancer patients was better than their older counterpart [15,16]. In this backdrop, the present study, aims to assess impact of age on key treatment outcomes: disease free survival, recurrence and mortality among a group of OSCC patients in Sri Lanka.

## Material and Methods

A hospital-based, retrospective cohort study was conducted comprised of two age-matched groups of OSCC patients with the primary aim of investigating how the timing of commencement of post-operative adjuvant radiotherapy influenced the 6-months survival of oral cancer patients [17]. Patients were selected from the follow-up patient data bases of the Department of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, University of Peradeniya and the Oncology Unit of the National Hospital of Sri Lanka, Kandy for the period from 2015 to 2019. Inclusion criteria consisted of consenting patients with contact information who had surgery as the primary treatment for diagnosed oral cancer and who had close surgical margins (1-5mm) and those who had complete excision with safe margins with contact information. The first group comprised of 22 patients underwent surgery with close surgical margins (1-5mm) as the primary treatment for the histopathologically confirmed OSCC (mean age ± SD =58.55± 10.29 years) [17]. They received adjuvant postoperative radiotherapy after complete recovery from surgery and were followed up [17]. Patients with close margins who did not undergo or failed to complete the full course of radiotherapy were excluded from the study. The timing of commencement of the radiotherapy course was recorded as before 6 weeks or after six weeks from the primary surgery [17]. All patients commenced radiotherapy and completed the full course recommended by the multidisciplinary team. The second group comprised of 22-oral cancer patients who underwent surgery as the primary treatment with complete excisions at the surgical margins considered to be safe. In contrast to former group of patients, the latter group did not receive radiotherapy either because it was not indicated, not consented or defaulted [17].

Socio-demographic and clinical data of the patients were extracted from clinic records and histopathology reports. The data extraction form comprised of age, gender, date of primary surgery, date of commencement of postoperative adjuvant radiotherapy, surgical margin sizes in mm, histological differentiation, staging of the tumour, whether radiotherapy was completed, recurrence and survival outcome. The kith and kin of patients were as well contacted to gather relevant information. The study variables included age, gender, and anatomical sub-site of the oral cavity, stage of the tumour, histological differentiation, and time of commencement of adjuvant therapy after primary cancer resection. Presence of recurrences and survival of the patient were recorded as outcome variables, 6-months from the primary cancer ablative surgery [17]. Tumour staging was performed according to the American Joint Committee on Cancer (AJCC), 6$^{th}$ & 7$^{th}$ edition staging guidelines [18].

Data were entered and analysed using SPSS-21 Statistical Package. As the follow up period was only 6-months and based on the study limitations survival analysis was not used in the present study. Moreover, as the retrospective

data were extracted from the existed data base on patients with complete data the influence of selection and recall biases were minimized. Frequency distributions were used to present data by socio-demographic, clinical and treatment attributes. Age distribution of oral cancer patients was assessed for the distribution by Shapiro-Wilk and Kolmogorov-Smirnov tests of normality which were 0.591 and 0,200 respectively. Hence, independent sample T-test and one-way ANOVA were used to compare group differences in mean age by prognostic treatment outcomes: disease free survival, overall survival and mortality. Moreover, differences in mean ages were compared by gender, stage of oral cancer, sub-site and histopathological differentiation.

The ethical approval for the study was obtained from the Ethics Review Committee, Faculty of Dental Sciences; University of Peradeniya, Sri Lanka.

## Results

Table 1 demonstrates the distribution of OSCC patients by socio-demographic, clinical, surgical & postoperative radiotherapy treatment attributes and prognostic treatment outcomes.

| Attribute | Number | % |
|---|---|---|
| Age group* | | |
| 36-44 years | 2 | 4.6 |
| 45-64 years | 28 | 63.6 |
| ≥ 65 years | 14 | 31.8 |
| Gender | | |
| Male | 37 | 84.1 |
| Female | 7 | 15.9 |
| Sub-Site | | |
| Buccal mucosa | 18 | 40.9 |
| Tongue | 12 | 27.3 |
| All other sub-sites | 14 | 31.8 |
| Staging | | |
| 1 | 2 | 4.6 |
| 2 | 8 | 18.2 |
| 3 | 13 | 29.5 |
| 4 | 21 | 47.7 |
| Histological Differentiation | | |
| Well differentiated SCC | 24 | 54.5 |
| Moderately differentiated SCC | 16 | 36.4 |
| Poorly differentiated SCC | 4 | 9.1 |
| Surgical Margins | | |
| Closed | 22 | 50.0 |
| Clear | 22 | 50.0 |
| Commencement of Postoperative radiotherapy regimen** | | |
| Not commenced | 22 | 50.0 |
| Within 6 weeks | 8 | 18.2 |
| After 6 weeks | 12 | 27.3 |
| Prognostic Treatment outcomes | | |
| Disease free survival | 26 | 59.0 |
| Survival with recurrence | 9 | 20.5 |
| Mortality | 9 | 20.5 |
| * ages ranged from 36-79 years<br>**data missing for 2 patients | | |

**Table 1:** Distribution of OSCC patients by socio-demographic, clinical attributes, radiotherapy regimen and prognostic treatment outcomes.

The mean ages of three key treatment outcomes are shown in Table 2. Accordingly, the mean ages ± SD of disease-free survival group, overall survival and mortality cases were 61.6±9.17 years, 56.0±11.08 years and 52.2 ± 9.34 years respectively. These differences were statistically significant ($p<0.05$). Hence, disease free survivors were older OSCC patients in early sixties compared to survivors with recurrences and non survivors whom were in their mid-fifties and early fifties respectively. Hence, non survivors appeared to be relatively younger OSCC patients compared to survivors with recurrences and disease-free survivors (Table 2).

Table 3, below illustrates the mean differences of age of oral squamous cell carcinoma patients by gender and selected clinical attributes such as sub-site, staging and histological differentiation. Accordingly, males and who had the cancer involving buccal mucosa were relatively older than females and those who had tongue and other oral sites involved cancers i.e., retro-molar area. Moreover, the mean age of patients with poorly differentiated squamous cell carcinomas emerged to be younger than those who had moderately differentiated and well differentiated squamous cell carcinomas. In contrast, stage 1 oral cancer patients were older than those who presented in stages 2, 3 and 4. However, t mean age differences among those groups were not statistically significant ($p>0.05$).

As shown in Table 4, the mean ages of 3 postoperative adjuvant radiotherapy treatment groups were almost the same without statistical significance ($p>0.05$) (Table 3).

| Prognostic Treatment Outcome | Mean age ± SD | F-vale* | p-value |
|---|---|---|---|
| Disease free survival | 61.6 ± 9.17 | | |
| Overall survival (Survival with recurrences) | 56.0 ± 11.08 | | |
| Recurrence | 52.2 ± 9.34 | 3.953 | 0.036 |
| *one-way ANOVA | | | |

**Table 2:** Comparison of age differences of oral cancer patients by prognostic treatment outcomes.

| Attribute | Mean age ± SD | t-value/F-value* | p-value |
|---|---|---|---|
| Gender | | | |
| Male | 59.00 ± 10.08 | | |
| Female | 56.14 ± 11.13 | 0.677 | 0.502 |
| Clinical attributes | | | |
| Sub-site | | | |
| Buccal mucosa | 59.61 ± 10.68 | | |
| Tongue | 57.83 ± 8.16 | | |
| All other surfaces | 57.79 ± 11.57 | 0.773 | 0.516 |
| Staging | | | |
| Stage 1 | 65.00 ± 14.14 | | |
| Stage 2 | 59.00 ± 7.13 | | |
| Stage 3 | 55.38 ± 12.23 | | |
| Stage 4 | 59.71 ± 9.62 | 0.773 | 0.516 |
| Histological Differentiation | | | |
| Well-differentiated SCC | 58.71 ± 11.66 | | |
| Moderately differentiated SCC | 59.06 ± 8.92 | | |
| Poorly differentiated SCC | 55.50 ± 5.26 | 0.196 | 0.823 |
| *two groups t-value, >2 groups F-value | | | |

**Table 3:** Comparison of age differences of oral cancer patients by gender and clinical attributes.

| Commencement of treatment | Mean age ± SD | F-value | p-value |
|---|---|---|---|
| Not commenced | 58.55 ± 10.29 | | |
| Commenced within 6-weeks postoperatively | 58.13± 12.87 | | |
| Commenced after 6-weeks postoperatively | 58.00 ± 9.29 | 0.012 | 0.988 |

**Table 4:** Comparison of age differences by commencement of post-operative adjuvant radiotherapy treatment.

## Discussion

Ensuring favourable prognostic outcomes for oral cancer patients in developing countries carrying a high burden of the disease is a challenge. As corroborated by the findings of present study, older adults especially males dominate the well-established global risk profile of oral cancer patients however, substantial proportions of younger patients as well present with the disease [12,19]. The heavy and frequent indulgence on well-established life-style-related-risk habits such as betel chewing with or without tobacco, smoking and alcohol consumption over prolonged periods, poor oral hygiene and periodontal disease burden add to the risk profile of older OSCC patients [12,20]. Cumulative harmful effect of such habits resulting in several genetic aberrations compounded by age-related diminished immune surveillance could increase the risk for oral cancer in old age [19]. Moreover, there is emerging research evidence for pro-inflammatory bacteriome and dysbiotic mycobiome within OSCC tumour-microenvironments of Sri Lankan OSCC patients that are capable of synergizing harmful effects of well established, life-style related risk habits in progression of oral cancer [20,21]. Present study provides new insights on impact of age on prognostic outcomes of a group of Sri Lankan oral cancer patients in this backdrop,

The findings of the present study should be interpreted and compared with findings of similar studies cautiously as it had a shorter follow up period which was 6-months from primary surgery and a small sample size of 44. However, the present study included age-matched two groups of patients managed by surgery with close margins and clear margins and the former group having had adjuvant post-operative radiotherapy. However, it was not possible to match the two groups by socio-economic variables such as level of education. Moreover, heterogeneity of study populations, data bases, health systems, follow –up periods, aggregating oral and oro-pharyngeal cancers together and country specific management protocols make difficulties in comparability of findings. Nevertheless, as emerged from the salient findings of the present study, there was significant difference in mean age of patients for disease-free survival favouring the relatively older age group compared to their younger counterpart. This finding contradicted many studies that reported older age group having elevated risk of more unfavourable treatment outcomes for OSCC [6,15,16,22-25]. A research conducted among Taiwanese population has revealed that increasing age among those older than 69-years was a significant poor prognostic factor for some ethnic communities with OSCC [22]. Poor treatment tolerance and advanced stages of diagnosis associated with advancing age have being incriminated for such findings. Another study conducted using Surveillance Epidemiology and End Results and -Medicare data base in USA involving 7,023 66-year –olds diagnosed with primary oral cavity and oro-pharyngeal cancers [26]. The authors concluded that age, stage and site were the crucial determinants of treatment selection for oral and oro-pharyngeal cancer patients while increasing age and stage had increasingly driven treatment towards non-surgical options and non-treatment at all [26]. Such findings reflect prioritization of treatment options for oral cancer patients accessing health services in different country contexts. Hence, it could be reasonably argued that lack of such polarizations for treatment prioritization and options in Sri Lankan context could have influenced present findings.

Moreover, the present study did not show any significant differences in mean ages with regard to gender, sub-site, staging and histological differentiation of OSCC. However, the OSCC patients who had tongue involvement and poorly differentiated histological type were relatively younger in age compared to those with buccal mucosa involvement and well differentiated histological type. The latter considered having better prognosis in general in contrast to the former [2]. On contrary to present findings, among Taiwanese cancer patients, gender differences were strongly correlated with survival rates in some indigenous communities but slightly among Taiwanese aborigines [22]. Moreover, males had poorer survival compared to females [22] and this finding was supported by another study [6]. Possible reasons could be the gender differences in incidence of oral cancer and expression of clinically relevant poor prognostic markers where males are more disadvantageous compared to females. Interestingly, a research reported a possible explanation in this regard as among male OSCC patients, high interleukin –IL-6 expression in tumour cells was significantly associated

with poor prognosis (p = 0.025) and a 1.5-fold higher death risk compared to female OSCC patients [25].

A retrospective study from rural Kerala, India reported that node involvement was the single crucial factor for recurrence and survival while the overall survival and disease-free survival were better in patients without lymph node involvement and those with early stage of cancer compared to the counterpart with lymph node involvement and late stages [27]. Moreover, histological prediction models that estimated the probability of developing nodal metastatic deposits demonstrate more consistent findings irrespective of study population [9,14,27,28]. Accordingly, tongue cancers, pattern of invasion, tumour size and depth in one study [9] and pattern of invasion, histological differentiation and stage in another study [29] were the independent predictors of nodal metastasis among Sri Lankan cohorts of OSCC patients. However, the present study did not assess age differences in nodal metastasis due to short follow-up period.

Better disease-free survival for Sri Lankan oral cancer patients in their early sixties compared to those in their 5$^{th}$ decade in the 6-months follow up period after primary surgery merits further investigations. If those patients were followed up for 5-years there could have been different findings or even similar findings. Interestingly as reported by Kim et al., [7], the disease specific 5-year survival rate of 130 South Korean oral cancer patients was not associated with their age, gender, primary site and histological differentiation. The present study did not attempt to compare prognostic treatment outcomes i.e., disease free survival rate and recurrence rate with local studies or studies conducted in other countries as the follow-up period was just 6-months from primary surgery. Nevertheless, post treatment surveillance in short term and long term pertaining to prognostic treatment outcomes among cohorts of OSCC patients becomes crucial. Short term surveillance will focus on detecting tumour recurrence at an early stage aimed at providing reclaim procedures, despite limited global consensus on actual timing of follow ups [29]. However, the present study has the main limitation of 6-months follow up period which should be addressed by a larger sample size longer follow-up period with survival analysis.

In conclusion, age significantly impacted on disease free survival of oral cancer patients in Sri Lanka followed up for 6-months post surgically. Nevertheless, further studies warranted in this regard with refined methodology.

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