Original Article - Retrospective Study

Prognostic Indicators of Oral Squamous Cell Carcinoma

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Abstract

Background: Oral squamous cell carcinoma (OSCC) is the sixth most common malignancy worldwide and is the major public health problem in the Indian subcontinent, where it ranks among the top three types of cancer in the country. Here, we aimed to analyze the clinical and tumor characteristics which impact the survival of OSCC patients. **Methods:** A retrospective analysis of clinical records of all patients who underwent treatment for OSCC at Kidwai Memorial Institute of Oncology, between January 2009 and January 2012 was analyzed. Age, gender, site of the primary lesion, tumor size (T), nodal status (N), stage of the disease, marginal status, and modality of treatment data were collected and analyzed. **Results:** Data of 147 patients with OSCC were included in the study and analyzed. Of the patients analyzed 61% were male, with 56% were <65 years, and 40% presented with buccal mucosa cancer followed by 30% with tongue cancer. Of all patients, 30% of them presented with Stage 1 and rest were Stage 2 and above. In our study, 40% underwent surgery only followed by regular follow-up and 60% needed surgery with postoperative adjuvant treatment based on the marginal status, the lymph node status, and T status of the disease. **Conclusion:** Our data suggest that age <65 years, female patients, alveolus lesion and tongue lesion and the early T Stage and N0 and negative margin had a significant positive impact on disease-free and overall survival of oral cancer patients.

Keywords: Margin status, neck dissection, oral squamous cell carcinoma, patients, T Stage

Introduction

Head and neck cancer, including oral squamous cell carcinoma (OSCC), is the sixth leading cancer worldwide, with an estimated 300,400 cases and 145,400 OSCC-related deaths occurring in 2012.[1] OSCC is one of the most prevalent malignancies in the developing countries and developed countries contributing to the sixth most common cancers in the world[2] and third most common type of cancer in South Central Asia.[3] OSCC is a major public health problem in the Indian subcontinent, where it ranks among the top three types of cancer in the country.[4] Furthermore, OSCC often causes dysfunctions in chewing and swallowing, as well as speech and esthetic disorders, which can worsen patients' quality of life.[5] The majority (90%) of the cases reported of OSCC is attributed to tobacco consumption in various forms, with alcohol and smoking being other attributed factors.[6] Besides, a variety of suspected risk factors such as chronic irritation, poor oral hygiene, viral infection, occupational exposure, malnutrition as well as low fruit and vegetable diets, and genetic factors, have been proposed for the development of oral cancer.[7,8] The relatively high incidence of oral cancer in India is mainly because of extremely popular use of the smokeless tobacco product called gutkha and betel quid chewing (with or without tobacco), which renders its population and especially its youth to a greater risk of developing oral submucous fibrosis, a premalignant condition resulting in increased incidence of oral cancer in younger patients.[9] Apart from tobacco use and alcohol abuse, human papillomavirus (HPV) has recently received special attention. HPV-16 in particular has been indicated as an etiological agent for the development of a subset of OSCC, especially at the base of the tongue and the tonsillar area in the younger individuals compared to the HPV-negative counterpart.[10,11] Patient's age was commonly considered co-variable and was known to influence the outcome of treatment.[12] Gender did not seem to be a significant determinant of survival for

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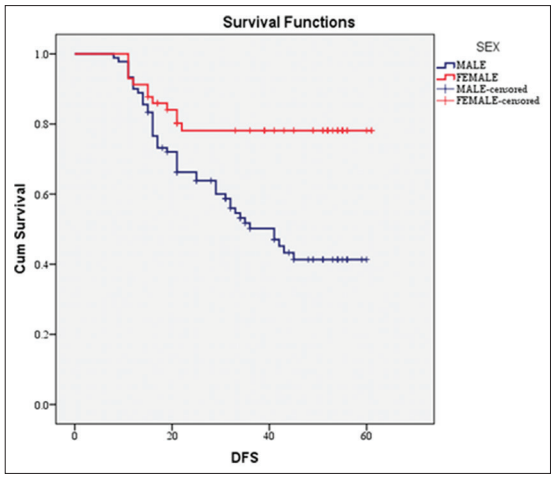

Figure 1: Disease-free survival of sex

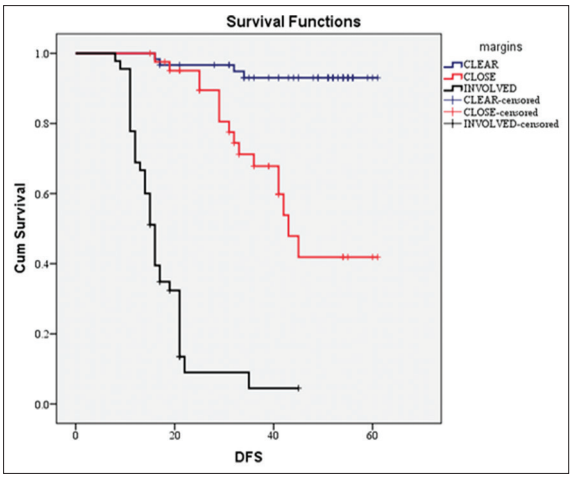

Figure 2: Disease-free survival of margin

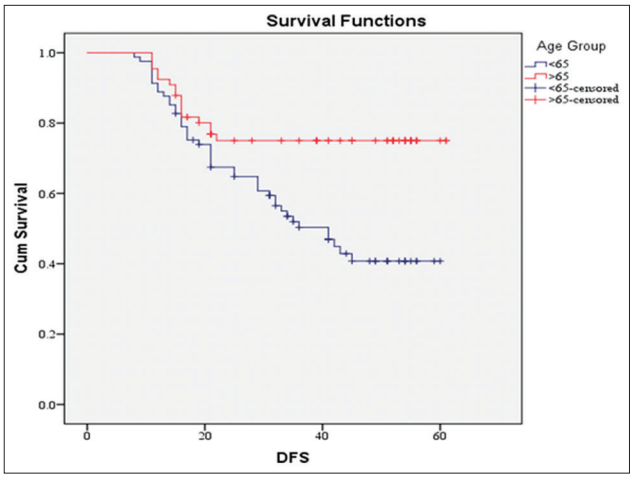

Figure 3: Disease-free survival of age

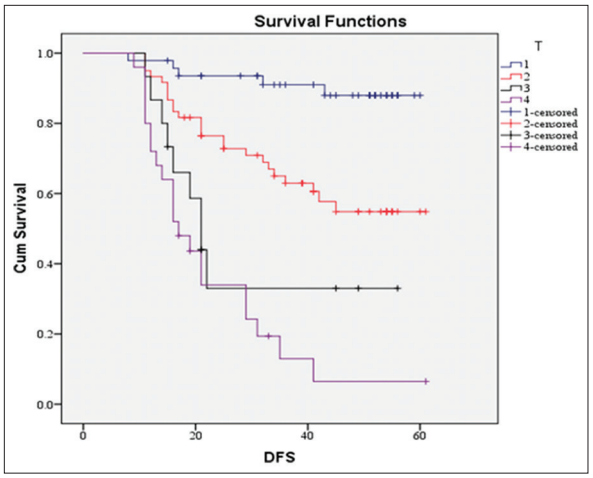

Figure 4: Disease-free survival of T stage

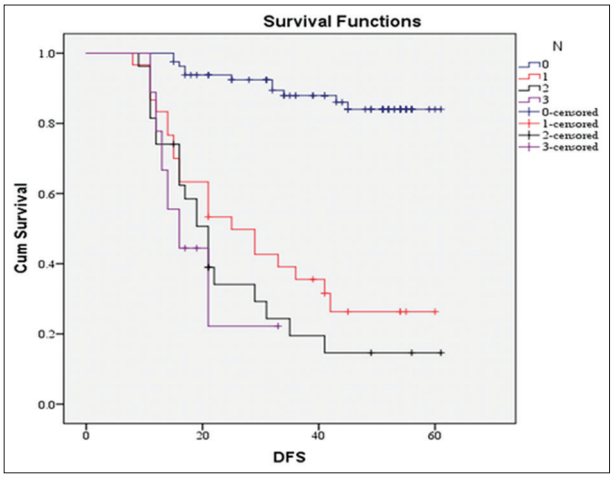

Figure 5: Disease-free survival of N stage

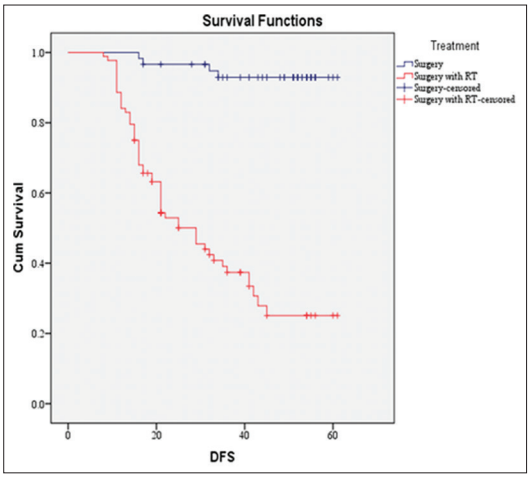

Figure 6: Disease-free survival of treatment

a patient with OSCC.[13] Moore *et al*. stated that 84% of patients with tumor diameter <2 cm survived a disease-free period of 3 years as compared to 52% of patients with a tumor larger than 2 cm in diameter.[14] Woolgar showed tumor depth exceeded 5 mm; the metastatic rate was 64.7%.[15] The presence of residual carcinoma at the margins of surgical resection is an important risk factor for local recurrence in OSCC.[16] The presence of perineural invasion in the primary tumor is a predictor for cervical metastasis, locoregional recurrence.[17] Vascular invasion correlates with the presence

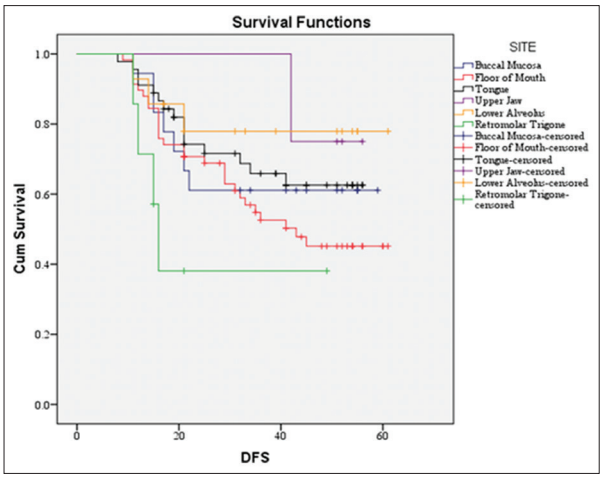

Figure 7: Disease-free survival of site

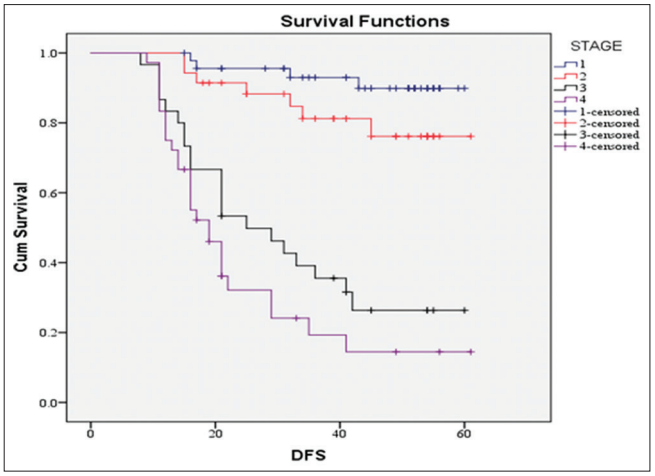

Figure 8: Disease-free survival of stage

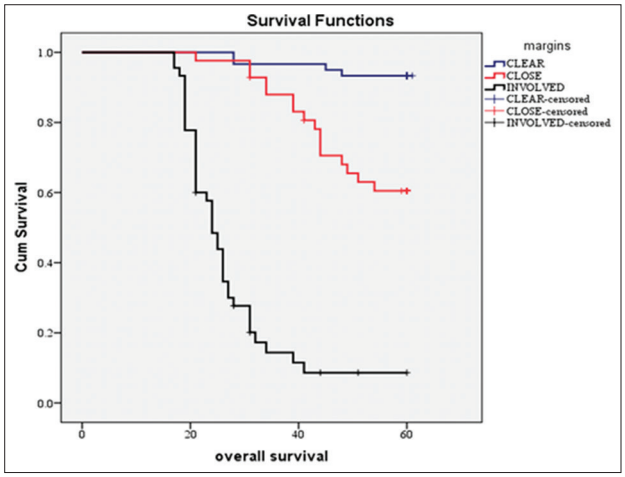

Figure 9: Overall survival of margin

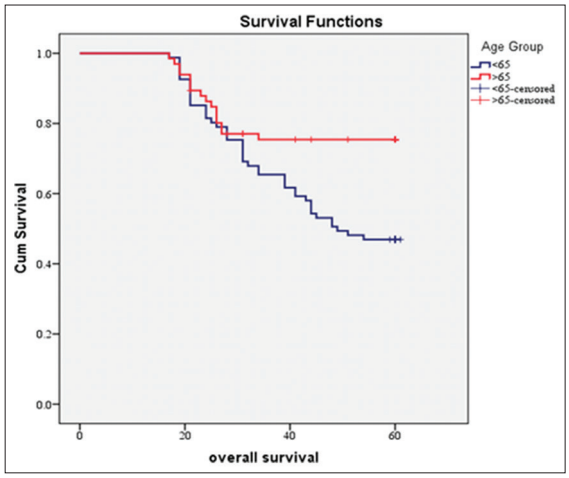

Figure 10: Overall survival of age

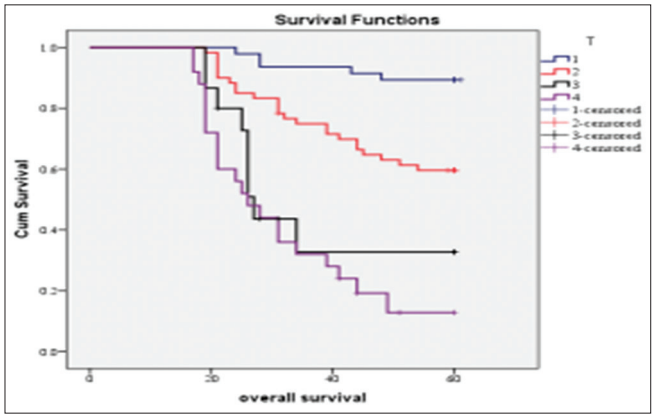

Figure 11: Overall survival of T stage

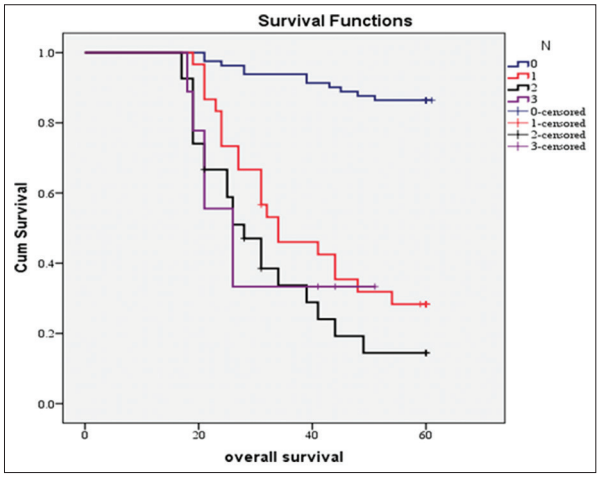

Figure 12: Overall survival of N stage

of concomitant cervical metastases and showed an increased risk of distant metastatic disease.[18] Lymph node number exhibited a strong dose-response correlation with distant metastasis and survival. It also indicated the risk for regional recurrence and distant metastasis. The relative importance of extracapsular extension versus the number of positive nodes remains somewhat controversial. Standard of treatment of any OSCC is surgical resection with adequate margins with postoperative adjuvant therapy as indicated. Inadequate

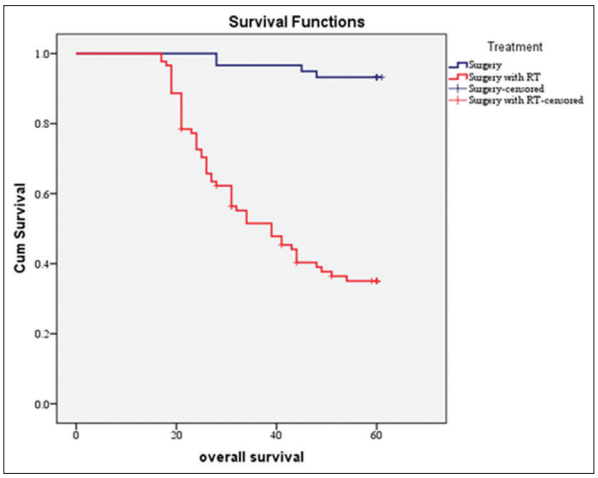

Figure 13: Overall survival of treatment

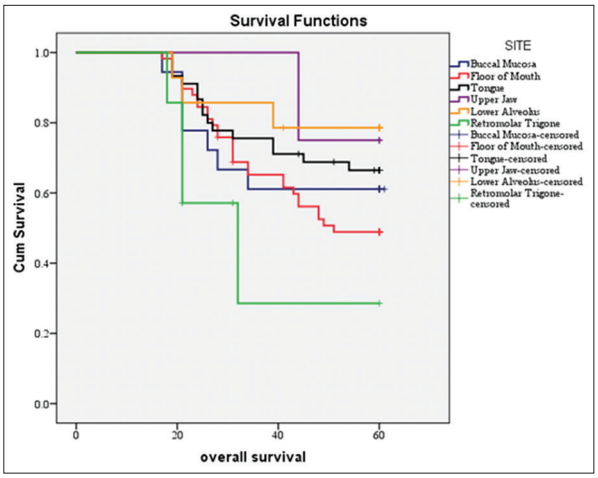

Figure 14: Overall survival of site

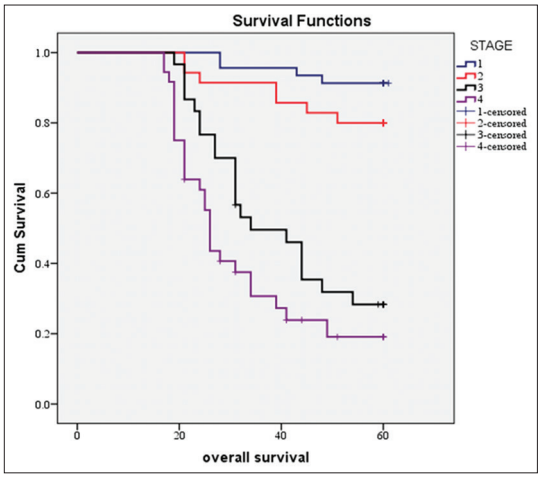

Figure 15: Overall survival of stage

clearance of tumor results in increased local recurrence and decreased long-term prognosis.[19] Postoperative adjuvant treatment has improved the survival statistics.[20,21] Many prognostic factors have been found which are known to influence the oncological outcomes in the form of 5-year survival and overall survival (OS). The literature on the management and survival of cancers in the west is widely available, but data in the Indian context is sparse. Therefore, the present study was conducted to provide a holistic picture of oral cancer survival and to evaluate and validate the predictors of survival in the Indian population.

Methods

Patient

Around 1248 South Indian patient who had symptoms of oral cancer had reported to the Department of Oral Oncology, Kidwai Cancer Institute tertiary care center from January 2009 to January 2012, out of which 432 patients were admitted to oral oncology department after staging workup and 147 patients with OSCC were included in our study after retrospectively analyzing the data considering inclusion and exclusion criteria.

Inclusion criteria

Patients with biopsy proven OSCC who were fit for surgery and gave consent for the study were included. Exclusion criteria: patient who had other than squamous cell carcinoma, a patient who was planned for definitive radiotherapy, or chemoradiation, and who did not give informed consent or who was lost to follow-up were excluded from the study.

After the routine collection of the patient details, a detailed history was elucidated to recognize the predisposing factors and the predominant symptoms in the patients followed by physical examination. Further evaluation included routine blood tests, chest X-ray, and computerized tomography (CT) scan of the head and neck was done followed by biopsy of the lesion. Surgery was considered for medically fit patients after routine preanesthesia checks up. Of 432 patients, 198 were planned for surgery after thorough preoperative work 147 patients underwent surgery (22 did not give consent for surgery, 20 lost to follow-up, and 9 did not complete treatment). Informed consent was taken from all patients before the surgery. All patients were advised regarding oral hygiene along with removal or treatment of loose dentures was done as appropriate. All intraoperative details, immediate postoperative period complications, and in-hospital mortality were noted.

Surgical technique

Medically fit patients were planned for surgery after thorough preoperative workup, Primary lesion was addressed with wide excision to the negative margin with primary closure or leaving wound to heal by secondary intention or with local advancement flap. Tumors with mandibular invasion were managed by marginal or segmental or hemimandibulectomy with pectoralis major myocutaneous flap. The neck was addressed in the form of ipsilateral SOND for N0 with primary in high-risk sites (tongue, the floor of mouth) and contralateral neck. If the tumor is crossing midline and N0 with low risk, it was left for observation.

Table 1: Survival analysis of the oral squamous cell carcinoma patients

	DFS (months)	*P**	HR	95.0% CI for Exp(*B*)		OS (months)	*P**	HR	95.0% CI for Exp(*B*)	
				Lower	Upper				Lower	Upper
Age group										
>65 (*n*=66)	38.74	0.003**	0.41	0.232	0.733	45.51	0.004**	2.303	1.297	4.091
<65 (*n*=81)	49.66					51.01				
T										
T1 (*n*=47)	55.77	<0.001**	0.057	0.021	0.152	58.14	<0.001**	0.057	0.021	0.153
T2 (*n*=60)	44.71	<0.001**	0.256	0.141	0.468	40.03	<0.001*	0.255	0.141	0.464
T3 (*n*=15)	30.01	0.175	0.581	0.265	1.273	36.73	0.303	0.663	0.303	1.45
T4 (*n*=25)	22.79					31.782				
N										
0 (*n*=81)	55.774	<0.001**	0.072	0.026	0.2	57.49	<0.001**	0.087	0.032	0.238
1 (*n*=30)	31.906	0.233	0.57	0.57	1.437	39.53	0.435	0.696	0.28	1.73
2 (*n*=27)	25.942	0.648	0.808	0.808	2.017	32.7	0.796	1.127	0.454	2.796
3 (*n*=9)	19.333					31.55				
Margins										
Clear (*n*=60)	58.495	<0.001**	0.015	0.005	0.043	59.41	<0.001**	0.19	0.006	0.055
Close (*n*=42)	45.661	<0.001**	0.118	0.062	0.226	52.33	<0.001**	0.126	0.067	0.237
Involved (*n*=45)	17.625					27.75				
Treatment										
Surgery (*n*=59)	58.451	<0.001**	0.058	0.021	0.163	59.39	<0.001**	0.067	0.024	0.187
Surgery + adjuvant (*n*=88)	32.498					40.14				
Gender										
Male (*n*=90)	38.67	0.001**	2.88	1.529	5.424	45.55	0.003**	2.629	1.394	4.958
Female (*n*=57)	51.07					51.96				
Site										
Buccal mucosa (*n*=58)	40.608	0.195	0.498	0.174	1.428	46.61	0.136	0.391	0.114	1.343
Floor of mouth (*n*=18)	46.61	0.136	0.391	0.114	1.343	4507	0.189	0.494	0.173	1.416
Tongue (*n*=45)	43.053	0.047**	0.324	0.107	0.984	49.69	0.036**	0.305	0.1	0.928
Upper Jaw (*n*=4)	52.5	0.119	0.174	0.019	1.568	56	0.143	0.193	0.021	1.739
Lower alveolus (*n*=14)	50.955	0.037**	0.202	0.045	0.907	52.78	0.03*	0.188	0.042	0.848
Retro molar trigone (*n*=7)	27.143					34.85				
Stage										
1 (*n*=46)	56.817	<0.001**	0.051	0.18	0.148	58.89	<0.001**	0.048	0.016	0.138
2 (*n*=35)	53.19	<0.001**	0.129	0.056	0.3	54.85	<0.001**	0.117	0.05	0.272
3 (*n*=30)	32.21	0.138	0.646	0.363	1.151	40.11	0.08	0.598	0.337	1.063
4 (*n*=36)	25.209					32.75				

CI: Confidence interval, OS: Overall survival, HR: Hazard ratio, DFS: Disease-free survival. **Statistically significant

For any N + ipsilateral RND, modified radical dissection according to the nodal status was done. Wound was closed following placement of drains. Extubation was done at the end of the procedure, and the patient was kept in the intensive care unit for a day. Flaps were tested for viability before discharge by examination and visual inspection. Ryles tube feed was started after 24 h. Based on the histopathological report, the patient was referred for adjuvant treatment as per T, N, and marginal status indicated. Fourteen patients were upstaged from Stage 1 to 2 and 11 from Stage 2 to 3 after radiological (CT scan) workup. The postoperative report collected of age, gender, T, N, Stage (AJCC 7th edition), marginal status, site and treatment given was analyzed, and disease-free survival (DFS) and OS were analyzed. Patients were followed in OPD every three monthly in first year and six monthly at second year and annually thereafter with history and physical examination. At every visit, physical examination is done to rule out locoregional recurrence and second primary. Biopsy and imaging were done if recurrence was detected.

Statistical analysis

Data were entered into Microsoft Excel datasheet and were analyzed using SPSS 22 version software. Categorical data were represented in the form of frequencies and proportions. Continuous data were represented as a mean and standard deviation. OS of patient is denoted as the duration from the time of diagnosis until the death due to the disease. DFS was defined as the time from the treatment of the diagnosed disease to the first relapse of the disease. OS and DFS of the subjects were analyzed by Kaplan–Meier survival analysis and Cox regression model. Kaplan–Meier survival curve was used to depict the *P* value (probability that the result is true) and <0.05

was considered as statistically significant after assuming all the rules of statistical tests. Statistical software: MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) were used to analyze data.[22]

Results

In the present study, majority (55%) of patients were < 65 years, 61% were male and 40% presented with buccal mucosa cancer followed by 30% with tongue cancer and 30% of them presented with Stage 1 and rest were Stage 2 and above. In our study, [Table 1] 40% underwent surgery followed by regular follow-up and 60% needed surgery with postoperative adjuvant treatment based on the T, N status and margin status. Patient with age <65 compared to age more than 65 years had better DFS of 50 months compared to 38.7 months, OS was observed to be 51 months versus 45 months, respectively ($P = 0.003$; 0.004).

Patients with T 1 lesion had better DFS with 55.7 months and OS of 58.1 months compared to T2 and above lesions which had DFS of 22.7 and OS of 3.7 months which was statistically significant ($P \leq 0.001$; <0.001).

Even nodal status with node-negative had better DFS with 55.7 months and OS of 57.4 months compared to node-positive which had DFS (median) of 25.9 and OS of 32 months which was statistically significant ($P \leq 0.001$; <0.001).

Patients who had clear and close margin had better DFS and OS (58.4; 59.41 months respectively) compared to an involved margin of DFS and OS (17.6;27.7 months, respectively) which was statistically significant ($P \leq 0.001$; <0.001).

Tongue and lower alveolus showed DFS and OS as (43; 49.6 months) and (52.5; 56 months), respectively, which was statistically significant ($P = 0.047$; 0.037).

Moreover, Stage 1 had DFS and OS (56.8 and 59) compared to Stage 4 (25.2 and 32.7 respectively) which was statistically significant ($P \leq 0.001$; <0.001). (DFS Figures 1-8; OS Figures 9-15).

Recurrence was noted in the 11 patients. Seven nodal recurrence who were treated with radiotherapy (as initially not given as per staging) four patients had a primary recurrence (three had re-excision and two were given radiotherapy as per staging, one patient was followed up), and 2 death was found due to postoperative pneumonia.

Discussion

In our study, the gender distribution of OSCC patients about 1.6:1 ratio (92 males and 56 females), the proportion of men was higher which may be due to the prevailing and predisposing factors such as smoking and alcohol consumption and most of the male patients presented with higher T status. The result was similar to the gender distribution of the literature researched in Korea.[2,3] There was no significant difference in the disease-specific 5-year survival rate by gender (male 82.5% and female 84.6%) as other reports Liu *et al*. and Rogers *et al*.[23,24] but in our study, there was a statistically significant difference probably due to the prevailing risk factors and presenting with advanced lesions in the male gender.

In this study, survival rate was slightly higher in the patients who were <65 years, with log-rank test showing significant difference which is similar to Rogers *et al*. who reported that as the age of the patient increase, disease-specific 5-year survival rate decreases but Liu *et al*. reported that there were no significant differences statistically. The effect that the age of OSCC patients with surgical treatment has on prognosis has been controversial.

Shah and Gil reported that OSCC showed another biological aspect according to the primary site.[25] On the other hand, carcinomas on mucosal lip showed a good prognosis; carcinomas on anterior two-third of the tongue, the floor of the mouth, and the lower alveolar ridge have a high risk of metastasis to adjacent lymph nodes and showed relatively poor prognosis. Rogers *et al*.[23] reported that the disease-specific 5-year survival rate depending on the primary site was 64%–44%, which was not statistically significant in the 489 oral cancer patients. In this study, the disease-specific 5-year survival rate depending on primary site varied from 34.85 months to 56 months and tongue and lower alveolar lesion showed significant difference in survival as most of the tongue lesion presented in early T Stage; however, buccal mucosa also showed near statistically significant and retromolar trigone showed lowest DFS and OS of 27.1 and 34.8, respectively, which was similar to another study.

Rajapakshe *et al*. and Geum *et al*. reported that TNM stage is the factor that has a significant influence on the prognosis of OSCC patients.[26,27] In this study, as the stage increases, the OS rate decreased ($P < 0.001$).

Rogers *et al*. reported that the OS 5-year survival rate (87%) of the case without cervical lymph node metastasis was significantly higher than that of the case (54%) with cervical lymph node metastasis. OS 5-year survival rate of N0, N1, and N2-3 stage was 87%, 68%, and 40%, respectively.[23] In this study, the OS rate 57.49 months without cervical lymph node metastasis, which was significantly higher than that of the case with cervical lymph node metastasis, which accorded with previous researches. In this study, the OS rate according to cervical lymph node stage was 57.49 for the N0 (111 patients), 39.53% for the N1 (20 patients), 32.70 for N2 (14 patients), 31.55 for N3 (3 patients) and by the log-rank test results, cervical lymph node stage had significant effects on OSCC prognosis ($P < 0.001$).

Conclusion

Oral cavity carcinoma is one of the most common in the Indian subcontinent. Our study presents a comprehensive evaluation of prognostic factors and demonstrates that apart from

conventional TNM system other factors namely, age <65 years, male patients, positive margins, and retromolar trigone have a negative prognostic impact on survival.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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