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RECURRENCE-FREE SURVIVAL AND PATTERNS OF RECURRENCE IN SQUAMOUS CELL CARCINOMA OF ORAL CAVITY: AN INSTITUTIONAL PERSPECTIVE

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ABSTRACT

Objective: To determine the recurrence-free survival (RFS) in patients with squamous cell carcinoma of oral cavity (OSCC)

Methodology: It was a longitudinal study conducted on oncology patients who were diagnosed as having squamous cell carcinoma of the oral cavity and treated in our tertiary care hospital in the department of medical oncology. Patients were followed for the evaluation of disease recurrence. The Chi-square test was used to see the association between outcomes and clinicopathological features of the tumor.

Results: Of 97 patients, 85(87.62%) patients had no disease, however, 12(12.37%) patients had residual/recurrent disease in the first post-treatment follow-up scans performed three months after the completion of curative treatment. Subsequent follow-up scans showed disease recurrence in 87(89.69%) patients, out of which 52(59.77%) had loco-regional disease recurrence while 35(40.22%) patients had combined loco-regional and systemic disease recurrence with lung(n=18) being the most common site of distant metastasis. The mean RFS was 15 months (IQR= 8, 26). Patients with lymph vascular invasion (LVI), perineural invasion (PNI), positive margin, and extranodal extension(ENE) had a significantly higher risk of progressive disease after primary treatment, on follow up scans. The relationships between treatment outcomes and LVI, PNI, positive margin and ENE were statistically significant ($p<0.05$).

Conclusion: Our study shows that there is a higher frequency of recurrence in patients with OSCC among patients with extra nodal extension, lymph vascular and perineural-invasion, and positive margins. Clinical trials are required to identify other poor prognostic factors and the need of developing a prognostic model for risk-stratification of such patients.

Keywords: Squamous Cell Carcinoma; Oral Cavity; Outcome; Recurrence Head and Neck.

INTRODUCTION

Oral cancer is a deadly illness with rising incidence and low survival rates.¹ Oral Squamous Cell Carcinoma is the most prevalent head-and-neck cancer. It affects the lips, retromolar region, buccal and labial mucosa, gingiva, palate, and floor of the mouth.^{2,3}

Oral cancer incidence varies globally. Western and Eastern nations had 3-6 and 30% incidence, respectively.^{4,5} In Pakistan, it is the second most prevalent malignancy if both genders are combined and the first in men, comprising 15.9% of anticipated new cancer cases compared to 6% and 2.3% in males and females globally and using tobacco and betel quid is a risk factor for oral cancer in underdeveloped nations like Pakistan.^{6,7}

Surgical resection is the only mode of therapy while combined modality therapy, which consists of surgery followed by adjuvant radiation therapy or adjuvant chemoradiation therapy, is generally recommended for 60% of patients with locally advanced disease at diagnosis, it is only recommended for 30% to 40% of patients with early-stage disease (stage I-II).⁸⁻¹⁰ The aggressive local invasion and metastasis, resulting in recurrence, make the prognosis of OSCC dismal despite breakthroughs in chemotherapy, radiation therapy (RT), and targeted treatment in recent years.⁹

Clinicopathologic and follow-up data on patients with oral cavity squamous cell carcinoma who underwent primary surgical resection at our institute and subsequently received standard adjuvant treatments based on histopathological features and TNM (tumor,

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node, metastasis) staging of HNN (head and neck) cancers were collected for this study. Finally, we evaluated the characteristics that increased or decreased the risk of recurrence in these patients, and we recorded their pattern of recurrences (locoregional and systemic) and survival outcomes (full remission vs. residual/recurrent illness). Because there is a dearth of research on head and neck cancer in Asia. This study aims to fill that void by helping doctors pinpoint which HNN cancer patients are at the highest risk and so require the most intensive care.

METHODOLOGY

It was a longitudinal study conducted at the Aga Khan University Hospital, Karachi, Pakistan in the Department of Medical Oncology between January 2015 and December 2017. Non-probability purposive sampling technique was used to calculate the sample size. A total of 97 patients were included in the study analysis. Patient inclusion criteria consist of the following: (1) Primary OSCC which was confirmed by both preoperative and postoperative histopathological examination. (2) All patients underwent definitive surgery followed by either observation or complete adjuvant radiation therapy or adjuvant chemo-radiation therapy and (3) Complete clinicopathologic and follow-up data were available. Exclusion criteria consist of all biopsy-proven squamous cell carcinoma of oral cavity patients who have distant metastasis outside the head and neck region. Patients who have another (secondary) malignancy. Patients with Eastern Cooperative Oncology Group (ECOG) performance status of IV who is not a candidate for primary surgery.

All patterns of recurrence including loco-regional and distant systemic metastasis were all defined as recurrence. Time to recurrence was determined by the duration from the surgery to pathologically and/or radiologically confirmed recurrence.

All patients with pathologically proven Oral Squamous Cell Carcinoma (OSCC) who underwent definitive surgery followed by either observation or adjuvant treatment with other concurrent therapies. Depending upon the pathological findings patients were offered surveillance or RT or concurrent chemoradiation (CCRT). Patients who received CCRT, high dose cisplatin with a dose of 100 mg/m²/day given every three weeks for a total of three cycles was used as the preferred standard-chemotherapy regimen if serum creatinine and 24-hour urine creatinine clearance were within normal reference ranges.

If patients were not able to tolerate standard high doses of cisplatin, then they were switched to weekly cisplatin with a dose of 40 mg/m²/day. For patients with poor performance status or the ones who were ineligible for cisplatin treatment (eg: patients with renal insufficiency), weekly carboplatin with an area under curve 02 (AUC2) was used along with RT therapy. External beam radiation was used for radiation.

Patients were followed up for history and physical examination with blood investigations including creatinine, electrolytes and complete blood picture every week by hospital revisits during therapy. They were further followed up after completion of treatment on subsequent visits until disease recurrence. Positron Emission Tomography and Computed Tomography (PET-CT) scans were performed three months after the completion of curative treatment and after that, when clinically indicated.

Data was analyzed using SPSS version 23. Frequency and percentages were calculated for categorical variables including age, sex, addiction, co-morbid, site of the tumor, grade of the tumor, tumor size and nodal status, Lymphovascular and perineural invasions, margin status, extra-nodal extension, and bone involvement. The Chi-square test

was used to see the association between treatment outcomes (complete response v/s residual/recurrent disease) and clinicopathological features of the tumor as well as between loco-regional recurrence and potential effect modifiers. A p-value of ≤0.05 was considered as statistically significant. Graphical representation was used to see the data visually.

RESULTS

A total 97 patients with oral squamous cell carcinoma were included in the study. Most of the patients were of age 41-60 years (55.7%) with a mean age of 47. There was a male (86.6%) predominance in the entire cohort 19 (19.6%) patients were smokers, 8(8.2%) were betel nut consumers and 42(43.3%) were chewing-tobacco consumers. 26.8 % of patients had hypertension and 22.7% of patients had diabetes.

The most frequent site of the tumor was buccal mucosa (79.4%). Moreover, 72 (74.2%) of the patients had grade II (moderately differentiated) carcinoma as per Swiss Society of Pathology, 42 (43.3%) had tumor size as T4 and 36 (37.1%) had nodal status as N2. 36 (37.1%) patients had lymphovascular invasion, 33 (34.0%) had perineural invasion, 9(9.3%) had positive margins, 16 (16.5%) had extra nodal extension present (Table 1).

As shown in table 2, out of 97 patients, 13(13.40%) patients had surgery only as primary treatment, 10 (10.30%) patients received adjuvant radiotherapy, 74 (76.28%) patients received adjuvant chemoradiation therapy. Out of 74 patients who received adjuvant chemoradiation therapy, 41 (55.40%) received Q3 weekly high dose cisplatin with a dose of 100mg/m²/day concurrent with 66Gy of radiation therapy (33 fractions, each with 2 Gy), 15 (20.27%) received Q weekly cisplatin with a dose of 40mg/m²/day concurrent with 66Gy of radiation therapy (33

fractions, each with 2 Gy) and 18 (24.32%) received Q weekly carboplatin AUC 2 concurrent with 66Gy of radiation therapy (33 fractions, each with 2 Gy). Of 10 patients who received adjuvant Radiation therapy, the dose of RT they received was 66 Gy/33 fractions (2 Gy / fr). Of 74 patients who received adjuvant chemoradiation therapy, 67 (90.54%) patients completed planned 33 fractions of RT as mentioned earlier.

However, 5 (6.75%) received less than 30 fractions and 2 (2.07%) patients received less than 20 fractions of radiotherapy due to poor tolerance. Of 84 (86.5%) patients who received either radiation or chemoradiation therapy, 11 (13.05%) patients had interruptions in the treatment plan due to toxicities including grade 3-4 mucositis and grade 3-4 dermatitis, however, these patients were replanned and switched to IMRT (intensity modulated radiation therapy) which reduced the toxicity and improved their tolerance to radiation therapy.

Out of 97 patients, 85 (87.62%) patients had no disease, however, 12 (12.37%) patients had residual/recurrent disease in the first post-treatment follow-up scans performed at three months after the completion of curative treatment. Subsequent follow-up scans showed disease recurrence was observed in 87 (89.69%) patients, out of which 52(59.77%) had loco-regional disease recurrence while 35(40.22%) patients had combined loco-regional and systemic disease recurrence. Among the group of patients with loco-regional disease recurrence, 30(57.70%) patients had ipsilateral while combined ipsilateral and contralateral disease recurrence was observed in 22(42.30%) patients.

In our study, Lung (n=18) was the most common site of systemic disease involvement followed by bone, liver, and brain, however, 3 patients had widespread systemic

Table 1: Baseline characteristics of study participants (n=97)

| Variables | | N | % |
|-------------------------|------------------------|----|-------|
| Age Groups (years) | 18-40 | 24 | 24.7 |
| | 41-60 | 54 | 55.7 |
| | 61 & above | 19 | 19.6 |
| Gender | Male | 84 | 86.6 |
| | Female | 13 | 13.4 |
| Addiction | Smoking | 19 | 19.6 |
| | Betel nut | 8 | 8.2 |
| | Chewing tobacco | 42 | 43.3 |
| | Non-addicts | 28 | 28.86 |
| Comorbid | Diabetes | 22 | 22.7 |
| | Hypertension | 26 | 26.8 |
| | Ischemic heart disease | 6 | 6.2 |
| | No comorbidities | 43 | 44.32 |
| Site of Tumor | Buccal Mucosa | 77 | 79.4 |
| | Tongue | 18 | 18.6 |
| | Lips | 2 | 2.1 |
| Grade | G1 | 16 | 16.5 |
| | G2 | 72 | 74.2 |
| | G3 | 9 | 9.3 |
| Tumor Size | T1 | 10 | 10.3 |
| | T2 | 32 | 33.0 |
| | T3 | 13 | 13.4 |
| | T4 | 42 | 43.3 |
| Nodal Status | No | 34 | 35.1 |
| | N1 | 22 | 22.7 |
| | N2 | 36 | 37.1 |
| | N3 | 2 | 2.1 |
| | Nx | 3 | 3.1 |
| Lymphovascular Invasion | Yes | 36 | 37.1 |
| | No | 61 | 62.9 |
| Perineural Invasion | Yes | 33 | 34.0 |
| | No | 64 | 66.0 |
| Margin Positive | Yes | 9 | 9.3 |
| | No | 88 | 90.7 |
| Extra Nodal Extension | Yes | 16 | 16.5 |
| | No | 81 | 83.5 |
| Bone Involved | Yes | 40 | 41.2 |
| | No | 57 | 58.8 |

disease recurrence as well. The mean recurrence-free survival (RFS) was 15 months (IQR= 8, 26) (Fig 1.1). Among patients who had residual/recurrent disease on follow-up scans post completion of curative treatment, 66.67% % had lymphovascular invasion (LVI), 50% % had perineural invasion (PNI),

41.67% patients had extranodal extension (ENE), 25% had positive margins and there was 58.33% with T4 size tumors (Disease recurrence or residual disease was significantly associated with LVI, PNI, ENE and margin status in our study population (Table 02).

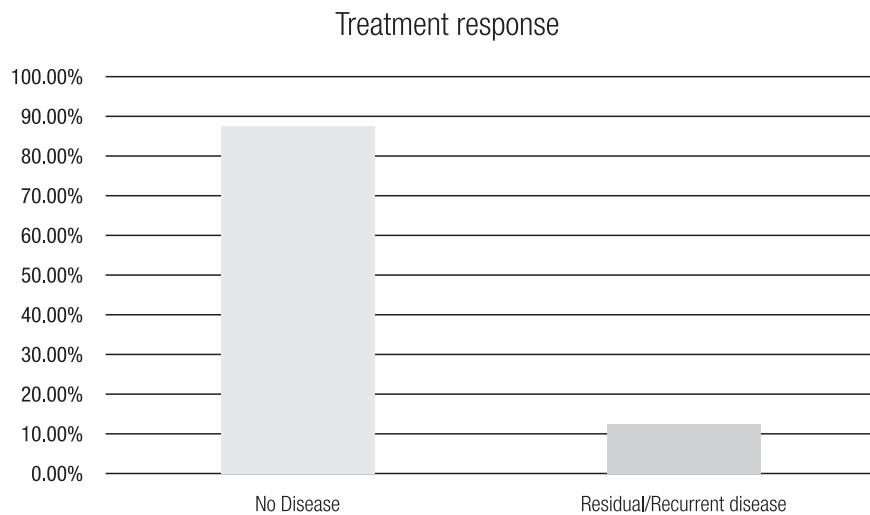


Figure 1: Response after completion of treatment (n=97)

Table 2: Treatment received by the study participants (n=97)

| Primary Treatment Received | Study Participants (n) | Dose of Radiation Therapy (RT) | Dose of chemotherapy | Duration / Interval of chemotherapy |
|------------------------------------|------------------------|--------------------------------|----------------------------|---|
| Surgery | 13 | 66Gy/33fr (2Gy/Fr) | - | - |
| Surgery + RT | 10 | 66Gy/33fr (2Gy/Fr) | - | - |
| Surgery + Chemotherapy + RT (CCRT) | | | | |
| a) High Dose Cisplatin | 41 | 66Gy/33fr (2Gy/Fr) | 100mg/m2/day | Three-weekly for a total of three doses |
| b) Weekly Cisplatin | 15 | 66Gy/33fr (2Gy/Fr) | 40mg/m2/day | Weekly till the completion of RT |
| c) Weekly Carboplatin | 18 | 66Gy/33fr (2Gy/Fr) | Area Under Curve-2 (AUC-2) | Weekly till the completion of RT |

Gy= Gray, Fr= Fractions, RT= Radiation Therapy, CCRT= Concurrent chemoradiation therapy, AUC= Area Under Curve

■ DISCUSSION

Squamous cell carcinoma of the oral cavity is one the most common malignancy in the Asian population, especially in our region of Pakistan due to increased exposure to chewing tobacco. Surgical removal of the tumors with definitive intent or followed by either adjuvant radiation therapy or adjuvant chemoradiation therapy has become the standard management in patients who have no distant metastasis.

However, even with this management, the treatment is not completely successful and accounted for failure in 25-48% of the cases.^{11, 12} The pattern of recurrence can be local at the site of the previous tumor bed or in the region of the ipsilateral neck or the

contralateral neck, or even both.¹¹ Aside from that, distant metastases are not rare.¹² Hence, in our study we have evaluated the patterns of loco-regional and distant metastases and recurrence-free survival in these patients.

In our study, despite definitive surgical resection and adjuvant treatment in patients with OSCC, we observed a mean recurrence-free survival of 15 months. 59.7% had loco-regional recurrence while lungs and bones with the most common sites of distant recurrences in our study. According to recently published data in our country, 66 percent of patients with HNSCC had a 12-month recurrence-free survival rate, with 61.6% percent of patients having a recurrence at the primary site.¹³

In the study by Liu et al. 50% of the patients had a regional recurrence.¹⁴ Same pattern was reported by Lim et al. in their study in which approximately, half of the patients had a regional recurrence and 31% had local recurrence.¹⁵ Singhania et al. also reported that among 13 (26.5%) patients of head and neck cancers who had the disease recurrence, 6 patients had local recurrence, 5 had a regional recurrence and 2 had distant metastasis.¹⁶

A review analysis on head and neck cancer by Denaro N et.al, showed 50-60 % of HNN cancer patients developed loco-regional disease recurrence in less than two years after primary treatment with 30 % of those developing distant disease as well.¹⁷ Similar results have been seen in our study in which

Table 3: Comparison of treatment outcomes and clinico-pathological features of tumors after curative treatment of SCC oral cavity (n=97)

| Characteristics | | Treatment outcomes (n%) | | p-value |
|-------------------------|---------------|-------------------------|-----------------------------------|---------|
| | | Complete Response n (%) | Residual/Recurrence disease n (%) | |
| Site of Tumor | Buccal Mucosa | 69 (81.18%) | 8 (66.67%) | 0.13 |
| | Tongue | 14 (16.47%) | 2 (16.67%) | |
| | Lips | 2 (2.35%) | 2 (16.67%) | |
| Grade of Tumor | G1 | 15 (17.65%) | 1 (8.33%) | 0.34 |
| | G2 | 62 (72.94%) | 10 (83.33%) | |
| | G3 | 8 (9.41%) | 1 (8.33%) | |
| Tumor Size | T1 | 8 (9.41%) | 2 (16.67%) | 0.08 |
| | T2 | 29 (34.12%) | 3 (25.00%) | |
| | T3 | 13 (15.29%) | 0 (0.00%) | |
| | T4 | 35 (41.18%) | 7 (58.33%) | |
| Nodal Status | No | 30 (35.29%) | 4 (33.33%) | 0.27 |
| | N1 | 19 (22.35%) | 3 (25.00%) | |
| | N2 | 33 (38.82%) | 3 (25.00%) | |
| | N3 | 1 (1.18%) | 1 (8.33%) | |
| | NX | 2 (2.35%) | 1 (8.33%) | |
| Lymphovascular Invasion | Yes | 28 (32.94%) | 28 (32.94%) | 0.03 |
| | No | 57 (67.06%) | 57 (67.06%) | |
| Perineural Invasion | Yes | 27 (31.76%) | 6 (50.00%) | 0.017 |
| | No | 58 (68.24%) | 6 (50.00%) | |
| Extra Nodal Extension | Yes | 11 (12.94%) | 5 (41.67%) | 0.039 |
| | No | 74 (87.06%) | 7 (58.33%) | |
| Margin Positive | Yes | 6 (7.05%) | 3 (25%) | 0.025 |
| | No | 79 (92.94%) | 9 (75%) | |

disease recurrence was seen within two years after primary treatment with a mean RFS of 15 months.

According to Sagheb K et al, 50% of HNSCC patients relapse after 12 months of treatment with cervical nodal metastasis was shown to be strongly related to tumor size and grading.¹⁸ Lin et al. found a 57% loco-regional recurrence rate with 79.7% cases had primary site recurrence alone. They also found out that patients with locally advanced disease who were treated with resection followed by adjuvant treatment had higher overall survival rates than those who were treated with resection alone.¹⁹

In another study by Lubek et al. most of the patients of head and neck cancers, who had the recurrence disease were squa-

mous cell cancers of the buccal mucosa origin.²⁰ Hence, with recent advancement in cancer diagnosis and treatment strategies, the five-year overall disease free survival in HNSCC is still up to 60%, which also differs with respect to age, stage, ethnicity, comorbid conditions and site in the oral cavity.²¹

In our study we found that 87.62% (n=85) of the patients (had no disease after completion of the initial definitive treatment. However, few patients who had the residual/recurrence disease at the end of treatment were significantly associated with the presence of poor prognostic features, including lymphovascular invasion, perineural invasion, positive margins and extranodal extension ($p<0.05$). Cassidy et al. also found that presence of lymphovascular invasion was associated with poor prognosis. There

are multiple factors associated with the recurrence of disease among patients of OSCC apart from the extranodal extension, positive margins, LVI and PNI.e. In a study by Hashmi et al. it has been observed that in addition to the extranodal extension, depth of invasion (DOI) and size of tumor, was strongly associated with recurrence in patients with HNSCC.¹³

Thus, with effective adjuvant treatment, recurrence free survival can be increased but still we need more data to modify the treatment and to limit the negative impact of high-risk factors on the treatment outcomes of OSCC patients. As this is a single-centered institutional study, this research is susceptible to selection bias. Another limitation of our study was limited sample size and non-probability sampling, hence there is a

lack of generalizability of the results. In the future, greater sample size should be considered, and patients should be followed over an extended period of time to determine long-term effects on outcomes as well as the quality of life.

CONCLUSION

Our study shows that there is a higher frequency of recurrence in patients with OSCC among patients with extranodal extension, lymphovascular and perineural invasion and positive margins with recurrence free survival of less than two years clinical trials are required to identify other poor prognostic factors and the need of developing a prognostic model that should allow stratification of high-risk patients and then modifying the current treatment as per risk-adapted approach.

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Author's Contribution

MT, SRK conceived the idea, collected the data and write up of the manuscript. SS, SS, helped in the analysis of data. SJ, YAR, MNZ, AAJ, MM helped in the final write up of the manuscript. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

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None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.