ORIGINAL ARTICLE

# AJCC 8th Versus AJCC 7th as a Prognostic Indicator in Buccal Mucosal Squamous Cell Carcinoma

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## Abstract

American Joint Committee for Cancer (AJCC) staging manual has been recently updated with 8th edition which led to an immense shift in the tumor, node, and composite stages, in comparison to the previous staging. This was mainly due to the incorporation of depth of invasion (DOI) and extranodal extension (ENE) in staging. The impact of new staging system is widely studied as combined subsites in oral cancer. This study is to focus on a single subsite of oral cavity which is known for its poor prognosis. We evaluated 109 patients who had buccal mucosal squamous cell carcinomas (BSCC) who underwent treatment, with a curative intend, between 2014 and 2015. Clinical records were reviewed and the tumors were re-staged as per 8th edition of AJCC; disease-free survival (DFS) was also analyzed. Our study population had a mean age of $54.5 \pm 10.35$ years and male to female ratio of 4:1. During a median follow-up of 41 months, 35 patients (32.1%) developed recurrence. There was a statistically significant shift in stages between AJCC 7th edition against AJCC 8th edition leading to 34% upshift in T-stage, 43.1% upshift in N-stage, eventually leading to a 23.9% upshift in the composite stage. Tumors which got upgraded due to upshift in nodal stage had a poor survival ($p = 0.002$). Newer staging system is easy to use in clinical practice. Around a quarter of the BSCC got upstaged with the introduction of the newer staging system. But it was surprising to note that there were no statistically significant differences in DFS between the tumors of the same composite stages with regard to the two staging systems.

**Keywords** Buccal cancer · AJCC · Oral cancer · Squamous cell carcinoma · Disease-free survival · Cancer staging

## Introduction

Staging system plays a crucial part in the cancer management as it directs the treating clinicians for making the right decision and further proceeding with management [1]. American Joint Committee for Cancer (AJCC) staging system is followed for classification of cancers in head and neck region. Though AJCC staging with respect to oral cavity underwent several editorial changes, since its publication in 1977, there was not much modification until the latest 8th edition was published, in 2016 [2]. Especially with the introduction on depth of invasion (DOI) and extranodal extension (ENE), there was a significant upstaging of the disease and this has been widely analyzed in various studies, but the influence of upgrading of staging system on disease-free survival (DFS) and overall survival (OS) is variable, because most studies had included all subsites of oral cavity in the study [3–7].

Head and neck region is the most common site of malignancy that is involved in developing countries like India and it constitutes 25 to 30% of all cancers, as opposed to 3–4% in rest of the world; this is due to the rampant use of tobacco and areca nut. The buccal mucosa is one of the most common subsite involved [8–10]. Different subsite in the oral cavity has a distinct outcome. Among oral malignancies, buccal mucosal squamous cell carcinoma (BSCC) has the poorest outcome, which is possibly related to its tumor biology, surgical expertise, and approach [11].

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Though various articles are available on change in prognosis following the introduction of AJCC 8th edition, most of which had combined all the subsite of the oral cavity or published with respect to tongue alone. Thus, similar study evaluating buccal mucosa is lacking. So, this study is intended to evaluate the impact of change in staging system on a single subsite of the oral cavity which is known for its poor prognosis.

## Materials and Methods

A retrospective analysis was carried out at in Regional Cancer Centre, Trivandrum, between January 2014 and December 2015. The study included patients who underwent primary surgical management of BSCC with a curative intend. The Institutional Ethical Committee clearance was obtained. Patients who underwent salvage surgery, who developed second primary cancer in the buccal mucosa, who received prior radiation in head and neck for any malignancy, patient who did not undergo neck dissection, and patients who expired in immediate perioperative period were excluded from the study. Records of included patients were retrieved and analyzed giving special interest on staging system and disease recurrence.

Among the proposed study population, 109 met our inclusion criteria. All these patients were discussed in the multidisciplinary tumor board (MDT) prior to definitive plan of management. Surgical excision of the primary lesion was done under frozen control, neck dissection was done based on clinical judgment, and suitable reconstruction was done. Following surgery, adjuvant RT was planned based on advanced clinical stage or advanced pathological stage or based on risk factors. MDT discussion was reconsidered and the plan was modified in selected cases, based on histopathology. Data were retrieved, pathological staging was done according to the AJCC 7th edition staging system for cancer of the oral cavity. Pathological staging was also reclassified as per AJCC 8th edition staging system which was updated on 05 June 2018. Stage IVa and IVb diseases are combined as it denotes an advanced stage and ease of statistical analysis.

## Statistical Analysis

Wilcoxon signed rank test was used to find the paired difference between the existing and revised staging system. Kaplan–Meier method was used to estimate the survival probability and log-rank test was used for assessing the significance difference between the survival curves. A $p$ value < 0.05 is considered to be significant.

## Results

One hundred and nine patients with BSCC who underwent surgery in a tertiary care cancer center were retrospectively analyzed in this study. The study population included 88 men and 21 women ($\approx 4{:}1$ ratio). The mean age of patients in the study population was $54.5 \pm 10.35$ years (range 23 to 76 years). With a median follow-up of 41 months, 7 patients (20%) had a recurrence in the primary site, 14 patients (40%) had neck recurrence, 7 patients (20%) developed second primary malignancy, and 7 patients (20%) had distant metastasis, all these accounted to 35 recurrences (32.1%). It was noted that disease recurrence increased with advanced stage of the disease. Among 109 patients 23 (21.1%) succumbed to the disease during the study period.

Hundred and eight patients (99.1%) underwent unilateral neck dissection in the form of supraomohyoid neck dissection/extended supraomohyoid neck dissection/modified radical neck dissection. One patient (0.9%) underwent bilateral neck dissection. Based on institutional protocol and pathological criteria, 89 patients (81.7%) received radiotherapy.

Based on the Wilcoxon signed rank test, there exist significant differences between two staging systems with respect to T-stage, N-stage, and composite stage. To see the actual shift between the two staging systems, contingency tables were plotted. We could note a considerable upgrade in tumor staging, nodal staging, and composite staging, and none of the parameters underwent downstaging.

Thirty-seven of the 109 cases (34%) got upgraded with respect to T-stage ($p = 0.001$) (Fig. 1). This was because of the introduction of the depth of invasion. It was noted that 23 of 77 tumors (29.9%) which were considered early (T1/T2), as per the AJCC 7th staging system [12], got upstaged to an advanced tumor (T3). Majority of tumors which got upgraded to advanced stage belonged to T2 lesion (46.3%). Twenty-four-month DFS in upstaged tumor was 71.1% which was comparable with that of tumors which remained unchanged 71.8% and did not reveal a change in DFS ($p = 0.826$) (Fig. 2).

Significant changes ($p = 0.001$) with respect to the nodal stage was also noted, because of the introduction of ENE in N-staging. Forty-seven of 109 cases (43.1%) had nodal metastasis among which 31 (66%) had ENE; this leads to a gross shift in N-staging in patients with nodal involvement (66%). Seventy-five percent of the N2 tumors got upstaged to N3b and 42.9% of N1 tumors got upstaged to N2a. The new nodal stage N3b included 25 of the 47 node-positive cases (53%). N-stage shift was noted in 28.4% (31 of 109 patients) (Fig. 1). Twenty-four-month DFS in patients who remained in the same N stage was 79.5% which was much better compared to those whose N-stage was upstaged, 51.6%, which was statistically significant ($p = 0.002$) (Fig. 3).

Composite stage shift was noted in 26 of the 109 patients (23.9%) (Fig. 1) which was statistically significant ($p =$
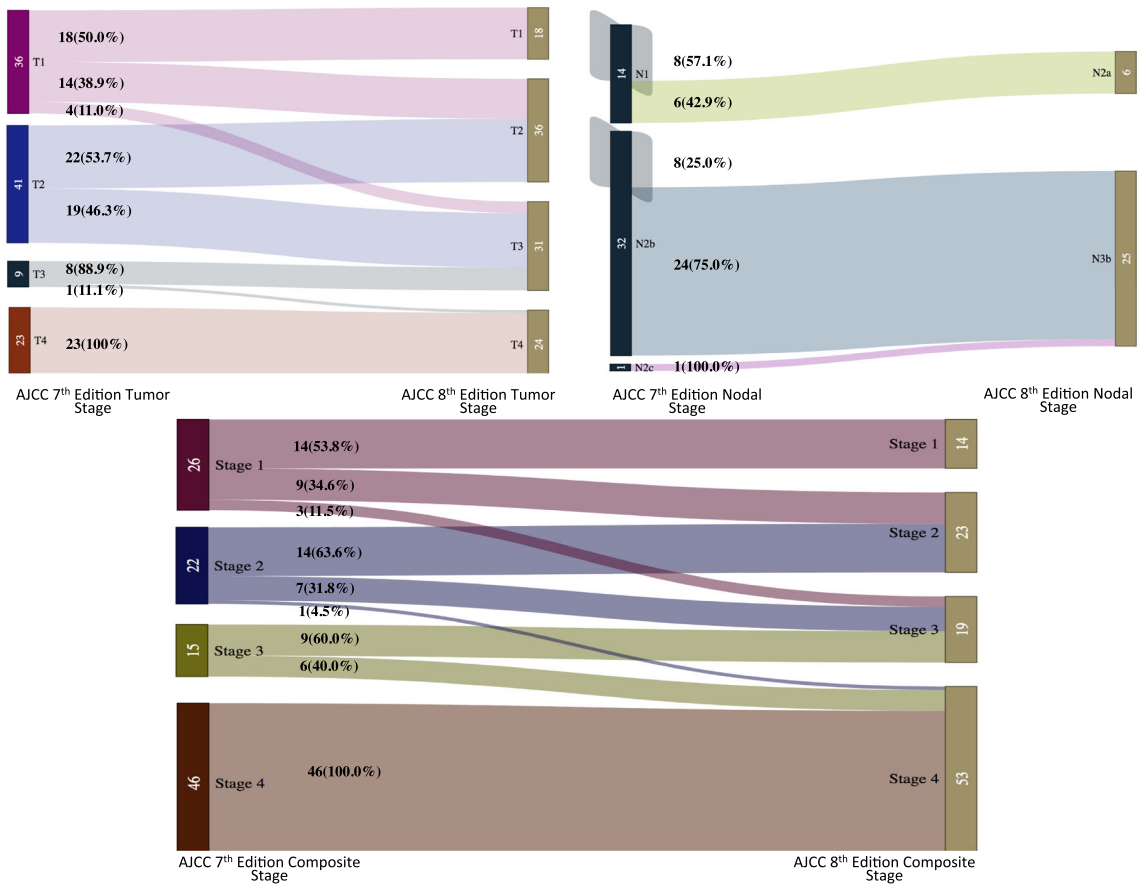
**Fig. 1** Alluvial diagrams representing changes in overall stage, T and N classification between American Joint Committee on Cancer (AJCC) 7th and 8th editions

0.001). Twelve of 26 (46.2%), 8 of 22 (36.4%), and 6 of 15 (40%) tumors belonging to the stage I/II/III, respectively, had a stage upshift, in contemplation with AJCC 8th staging system. Twenty of the 48 tumors (41.7%) which belonged to early stage (stage I/II) got upstaged. Forty-eight (44.0%) and 61 (56%) cases belonged to early and advanced stage as per AJCC 7th edition. With the newer staging system, 37(34%) belonged to early stage and 72 (66%) were in advanced stage. It was noted that 22.9% of tumors belonging to early stage as per AJCC 7th edition got upstaged to advanced stage with newer staging system.
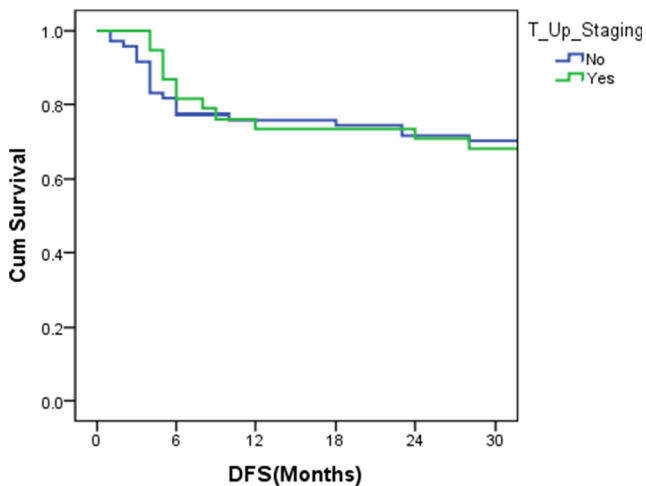


**Fig. 2** Kaplan–Meier analysis, showing the association between disease-specific survival for upstaged and non-upstaged pT
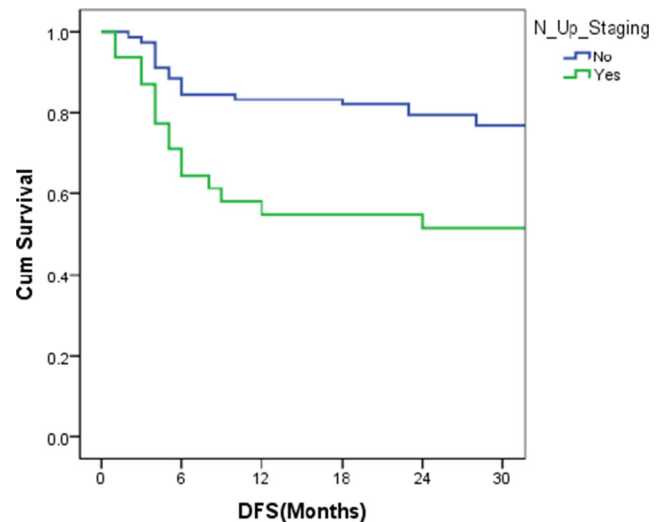


**Fig. 3** Kaplan–Meier analysis, showing the association between disease-specific survival for upstaged and non-upstaged pN

Looking at the recurrences as per the previous staging, it was noted that 9 of 48 (18.8%) patients who belonged to early stage had recurrence which on comparison with the newer staging, 7 of 37 (18.9%) patients had recurrences. Similarly, 26 of 61 (42.6%) patients in advanced tumor stage, as per AJCC 7th staging system, had tumor recurrence (Table 1). However, when the newer staging system was applied, the recurrence in advanced tumor stage was 28 of 72 (38.9%) patients. As noted in Table 1, DFS was nearly comparable in all stages. It was noted that 2-year DFS in the upstaged group was 75.9%, while in those where there was no shift was 66.0%. Kaplan–Meier method did not reveal any significant change in survival ($p = 0.280$) (Fig. 4).

Among 31 patients who had ENE, 19 had recurrence (61.3%). ENE was present in 57.1% with distant metastasis, 42.9% with neck recurrence, 28.6% with second primary, and 71.4% of those with recurrence in primary site. Among the seven patients who had recurrence in primary site, six (85.7%) had a depth which was more than 1.0 cm.

The 2-year DFS of the previously N1-classified patients who were upstaged to N2a was 16.7% compared with 50% in patients who remained in N1 as per newer staging. The 2-year DFS of the previously N2b/N2c classified upstaged to N3b was 60% compared with 50% in patients who remained in N2b in the 8th edition of AJCC.

## Discussion

Unpredictable behavior of cancers was better understood by the staging system. AJCC staging system played a significant role in treatment selection, assessment of prognosis, and research in oral malignancies. Previously, AJCC staging was basically related to the size of the lesion, involvement of adjacent structure, and nodal involvement. From the time of its introduction, various authors had highlighted limitations in staging system and it underwent various modifications from time to time. The latest updated edition of AJCC 8th edition had a major shift in paradigm with consideration of two major well evident histological features, the first being the
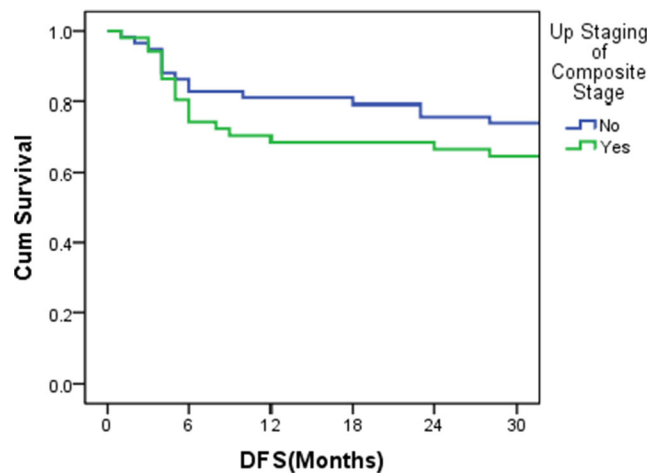


**Fig. 4** Kaplan–Meier analysis, showing the association between disease-specific survival for upstaged and non-upstaged composite stage

introduction of DOI in T-staging and second being ENE in N-staging [3]. This leads to a noticeable upgrade in staging in all the major parameters. There was 34%, 43.1%, and 23.9% upshift noted with respect to T-stage, N-stage, and composite stage, respectively.

Concept of DOI in head and neck malignancies was stated in 1992 by Bryne et al. when they studied the invasive margins of the tumor [13]. Following this, many studies had been published, but there was no definitive consensus regarding DOI, as it was used as a term interchangeable with tumor thickness. It was well noted by various studies that DOI is a good prognostic indicator compared to tumor thickness [14]. DOI is now defined pathologically and is measured from the level of the basement membrane of the closest adjacent normal mucosa. A "plumb line" is dropped from this plane to the deepest point of tumor invasion. As per newer staging system, other than size criteria, for every 5 mm increment in depth, the stage increases by 1; thus, pT1 has a DOI of 5 mm or less; pT2 has DOI between 5 to 10 mm and pT3 disease has a depth which is more than 10 mm [3, 12, 15]. Thus, the introduction of DOI had a massive shift of 29.9% of early tumors to an advanced tumor stage. DOI measurement has its own challenges [16]. The precise measurement of DOI is difficult clinically in BSCC, especially in those patients who have trismus

**Table 1** Representing changes overall stage change and its impact on recurrence and DFS between American Joint Committee on Cancer (AJCC) 7th and 8th editions

| AJCC 7th Edition Composite Stage | Number of cases | Recurrences | Disease-free survival | AJCC 8th Edition Composite Stage | Number of cases | Recurrences | Disease-free survival |
|---|---|---|---|---|---|---|---|
| 1 | 26 | 6 (23.1%) | 76.9% | 1 | 14 | 3 (21.4%) | 78.6% |
| 2 | 22 | 3 (13.6%) | 86.4% | 2 | 23 | 4 (17.4%) | 82.6% |
| 3 | 15 | 7 (28%) | 72% | 3 | 19 | 5 (26.3%) | 73.7% |
| 4 | 46 | 19 (41.3%) | 58.7% | 4 | 53 | 23 (43.4%) | 56.6% |
| Total | 109 | 35 (32.1%) | 67.9% | | 109 | 35 (32.1%) | 67.9% |

due to disease. Further, pathologist will find it difficult to stage a large tumor as muscle invasion is difficult to make out, DOI in tumors close to bony margin is again difficul, and all these might jeopardize the result. Imaging can provide details on DOI, preoperatively.

Bennet et al. in 1971 evaluated the prognostic significance of nodes which had extracapsular spread in laryngeal and hypopharyngeal malignancies. Since then, a lot of studies had shown the association of ENE with increased locoregional recurrence and distant metastasis [17]. Pathological ENE is defined as an extension of metastatic carcinoma from within a lymph node through the fibrous capsule and into the surrounding connective tissue, regardless of the presence of stromal reaction [14]. Randomized studies have pointed out the poor prognosis when ENE is present and have described the need for concurrent chemo-radiotherapy [18–20]. Sixty-six percent of our study population who had nodal disease had ENE, which portrays the poor prognosis of BSCC. A total of 57.1% of patients who had distant metastasis had ENE; similarly, 42.9% patient who had neck recurrence had ENE. The 2-year DFS of the previously N1-classified patients who were upstaged to N2a was 16.7% compared with 50% in patients who remained in N1 as per 8th edition AJCC. However, the DFS of patients with N3b disease was 60% and those with N2a disease as per AJCC 8th edition was 50%, which means that presence of a single node with ENE was undertreated.

A study by the same author, with 16 factors influencing locoregional recurrence and DFS in BSCC, found that only nodal involvement and margin of clearance played a statistically significant role in locoregional recurrence (LRR). The study showed that single nodal involvement had 6.8 times increased risk for LRR compared to 1.8 times increased risk when multiple nodes are involved [14]. So, BSCC which had more than one node was treated more aggressively compared to disease which had a single nodal metastasis which eventually leads to a better outcome in advanced diseases. With the newer staging system, we would be able to give a proper treatment by upstaging this selected category of patients. We should be aggressive in treating those nodal diseases with ENE with at least modified radical neck dissection and adjuvant chemoradiotherapy [20]. Being said, it is difficult to find a pN1 neck node with ENE in a clinically node-negative neck.

As we can see in Fig. 1, though there was more than a quarter shift in tumor stage, nodal stage, and a near quarter shift in composite stage, the DFS seems to be the same (Table 1). Kalplan-Meier graph plot shows that though there was a difference in survival in those patients who had a shift in N-stage, similar finding was not reflected in composite stage. Thus, in BSCC, ENE had significantly upstaged the disease and decreased DFS, but when it comes to overall staging, DFS tends to remain the same, even with significant upstage of

disease as per AJCC 8th edition. This might be due to the judicial use of adjuvant therapy in the form of radiotherapy or chemotherapy after MDT discussion.

Though there are similar studies conducted with combined oral subsets or tongue as a unique subsite, this study stand separate as it is a single institutional study which studied the poor prognostic single subsite in oral cavity. The disadvantage of the study is it is a retrospective study.

## Conclusion

The system is easy to follow. We could note a definitive shift in stages especially in early stage malignancies. More than one-third of the BSCC underwent a significant shift in tumor and neck staging with introduction of newer staging system and a near quarter shift with respect to composite stage. However, there was no significant change in DFS of BSCC patients after upstaging in accordance with AJCC 8th edition staging system; this might be due to the effective usage of combined modality of treatment in the management of BSCC.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

## References

1. Pan JJ, Ng WT, Zong JF, Chan LL, O'sullivan B, Lin SJ, Sze HC, Chen YB, Choi HC, Guo QJ, Kan WK (2016 Feb 15) Proposal for the 8th edition of the AJCC/UICC staging system for nasopharyngeal cancer in the era of intensity-modulated radiotherapy. Cancer. 122(4):546–558

2. Murthy S, Low TH, Subramaniam N, Balasubramanian D, Sivakumaran V, Anand A, Vijayan SN, Nambiar A, Thankappan K, Iyer S (2019 Mar) Validation of the eighth edition AJCC staging system in early T1 to T2 oral squamous cell carcinoma. J Surg Oncol 119(4):449–454

3. Tirelli G, Gatto A, Nata FB, Bussani R, Piccinato A, Marcuzzo AV, Tofanelli M (2018 Jan 1) Prognosis of oral cancer: a comparison of the staging systems given in the 7th and 8th editions of the American Joint Committee on Cancer Staging Manual. Brit J Oral and Max Surg 56(1):8–13

4. Moeckelmann N, Ebrahimi A, Tou YK, Gupta R, Low TH, Ashford B, Ch'ng S, Palme CE, Clark JR (2018 Oct 1) Prognostic implications of the 8th edition American Joint Committee on Cancer (AJCC) staging system in oral cavity squamous cell carcinoma. Oral Oncol 85:82–86

5. Kowalski LP, Köhler HF (2019 Mar) Relevant changes in the AJCC 8th edition staging manual for oral cavity cancer and future implications. Chin Clin Oncol 20

6. Koyfman S, Joshi NP, Lamarre E, Tsai CJ, Schymick MA, Liu H, Tam L, Rybicki L, Dunlap NE, Porceddu S, Ghanem AI (2018 Nov 1) Validating the AJCC 8th edition of the oral cavity cancer staging system: a multi-institutional collaborative study. Int J Radiat Oncol 102(3):S22

7.  Awadallah MW (2018 Oct 1) Staging and treatment implications of the 7th Vs. 8th AJCC Staging System for Oral Cancer. J Oral Maxillofac Surg 76(10):e27

8.  Singhania V, Jayade BV, Anehosur V, Gopalkrishnan K, Kumar N (2015 Oct 1) Carcinoma of buccal mucosa: a site specific clinical audit. Indian J Cancer 52(4):605–610

9.  Dandekar M, Tuljapurkar V, Dhar H, Panwar A, DCruz AK (2017 Apr) Head and neck cancers in India. J Surg Oncol 115(5):555–563

10. Riju J, George NA, Krishna J (2018 Aug) Salvage surgery versus primary surgery for buccal mucosal squamous cell carcinoma and the need for neck dissection. J Med Sci Clin Res 6(8):218–225

11. Anderson CR, Sisson K, Moncrieff M (2015 May 1) A meta-analysis of margin size and local recurrence in oral squamous cell carcinoma. Oral Oncol 51(5):464–469

12. Amit M, Tam S, Takahashi H, Choi KY, Zafereo M, Bell D, Weber RS (2019 May) Prognostic performance of the American Joint Committee on Cancer 8th edition of the TNM staging system in patients with early oral tongue cancer. Head Neck 41(5):1270–1276

13. Bryne M, Koppang HS, Lilleng R, Kjærheim Å (1992 Apr) Malignancy grading of the deep invasive margins of oral squamous cell carcinomas has high prognostic value. J Pathol 166(4):375–381

14. Riju J, George NA (2019) Factors influencing locoregional recurrence and disease-free survival in buccal mucosal squamous cell carcinoma. Indian J Surg:1–5

15. Mascitti M, Rubini C, Michele F, Balercia P, Girotto R, Troiano G, Muzio L, Santarelli A (2018) 7th vs 8th edition of AJCC staging system: any improvement for patients with squamous cell carcinoma of the tongue? Oral Surg. Oral Med. Oral Pathol, Oral Radiol **in press**

16. Subramaniam N, Thankappan K, Anand A, Balasubramanian D, Iyer S (2018 Jan 1) Implementing American Joint Committee on Cancer 8th edition for head-and-neck cancer in India: context, feasibility, and practicality. Indian J Cancer 55(1):4–8

17. Bennett SH, Futrell JW, Roth JA, Hoye RC, Ketcham AS (1971) Prognostic significance of histologic host response in cancer of the larynx or hypopharynx. Cancer. 28(5):1255–1265

18. Puri SK, Fan CY, Hanna E (2003 Apr 1) Significance of extracapsular lymph node metastases in patients with head and neck squamous cell carcinoma. Curr Opin otolaryngo 11(2):119–123

19. Wreesmann VB, Katabi N, Palmer FL, Montero PH, Migliacci JC, Gönen M, Carlson D, Ganly I, Shah JP, Ghossein R, Patel SG (2016 Apr) Influence of extracapsular nodal spread extent on prognosis of oral squamous cell carcinoma. Head Neck 38(S1):E1192–E1199

20. Mermod M, Tolstonog G, Simon C, Monnier Y (2016 Nov 1) Extracapsular spread in head and neck squamous cell carcinoma: a systematic review and meta-analysis. Oral Oncol 62:60–71