

## Special Article - Oral Cancer

# Does Adjuvant Radiation Therapy Improve Outcomes in Pt1-2N0 Oral Tongue Squamous Cell Carcinoma Patients with Isolated Perineural Invasion?

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## Abstract

**Objectives:** To assess the role of adjuvant radiation in pT1-2N0 Oral Tongue Squamous Cell Carcinoma (OTSCC) patients with isolated PNI for Locoregional Control (LRC) and Disease Free Survival (DFS)

**Materials & Methods:** We retrospectively reviewed hospital records from Jan 2012-Sep 2014 for pT1-2N0 OTSCC patients with isolated PNI. 40 patients were found among which 27(67.5%) received adjuvant radiation and 13(32.5%) did not. Univariate analysis was done to find significance between the recurrence and study variables using Fischer's exact test. Kaplan-Meier analysis with log-rank test was used for disease free survival

**Results:** Median follows up was 25 months. LRC for patients who received adjuvant radiation and who did not receive adjuvant radiation was 88.9% (2 local & 1 regional recurrence) and 76.9% (1 local & 2 regional recurrence) respectively. Of the 40 patients studied six (15%) had locoregional recurrence and all the patients who died had recurrence. Thus, in our study the overall mortality rate was equal to the locoregional recurrence rate (15%). There was no significant difference in DFS between two groups ( $p=0.365$ ). Univariate analysis showed no statistical significance with any of the variables (age, gender, pathological grading of cancer, pathological staging of cancer, type of neck dissection and receiving radiation therapy)

**Conclusion:** The study showed no significant difference in locoregional control and disease free survival between patients who received adjuvant radiotherapy and those who did not receive adjuvant radiotherapy

**Keywords:** Radiation therapy; Oral tongue squamous cell carcinoma; Perineural invasion

## Introduction

India contributes up to 7.8% of the global cancer burden and 8.33% of global cancer deaths [1]. Head and neck cancer is a major problem that occurs in Asia, especially in Indian subcontinent. Worldwide more than

200 000 new cases of head and cancers are diagnosed each year. About 40% of the head and neck cancer patients present during advanced stage of disease in developed countries, whereas it is >60% in developing countries like India [2]. This could have a bearing in the nature of treatment provided for these patients including the use of adjuvant radiation therapy. Among the head and neck cancer oral cavity cancer is the most common cancer in India. Overall, oral cavity cancer is the third most common type of cancer and accounts for more than 30% of all cancers in India [3].

In the oral cavity excluding lip, tongue constitutes the most common subsite for squamous cell carcinoma. In carcinoma of tongue, surgery is the preferred mode of treatment in early stage of disease [4]. In advanced stages, surgical resection followed by Radiotherapy (RT) with or without chemotherapy is performed, and it seems to be beneficial [5]. Likewise other head and neck cancers,

Post Operative Radiation Therapy (PORT) is recommended for Oral Tongue Squamous Cell Carcinoma (OTSCC) patients with large primary tumors (T3, T4), with close or positive surgical margins, and evidence of Perineural Invasion (PNI), multiple positive nodes, or Extra Capsular Spread (ECS). Data is limited for high-risk features of recurrence and PORT in early-stage OTSCC. Furthermore, most of the studies reported have studied a mixed patient population with oral cavity cancer [6,7].

Because of the extremely low salvage rate of recurred oral tongue cancer, the proper extent and modality of initial treatment is very important [8]. Pathological stage I and stage II disease with sufficient clear resection margins is generally considered as low-risk and does not require PORT [9]. Perineural Invasion (PNI) has been classified as an intermediate risk factor for recurrence and decreased survival [10,11]. The presence of Lympho Vascular Invasion (LVI) or microscopic tumor foci in muscle increases the risk of recurrence and PORT should be considered. Tumor thickness, or alternative synonyms such as "depth of invasion" or "tumor depth", has been consistently identified as a predictor for cervical lymph node metastasis [12]. Adjuvant therapy is not without risks and selecting the appropriate treatment regimen based on risk assessment,

while maintaining optimal survival outcomes is vital to the overall management of patients with OTSCC. With this background, we tried to assess the role of adjuvant radiation in pT1-2N0 OTSCC patients with isolated PNI for Locoregional Control (LRC) and Disease Free Survival (DFS).

## Materials and Methods

This was a retrospective cohort study based on review of medical records of OTSCC patients treated at a Tertiary Cancer Center (TCC), South India from January 2012 to September 2014. The study was done after obtaining approval from the institutional review board. Inclusion criteria are pT1-2N0 OTSCC patients with isolated PNI. Exclusion criteria are pT3-4, pathological node positive, margin positive, close margins and positive lympho vascular invasion. 410 patients diagnosed with OTSCC underwent upfront surgery during the study period; 203 patients are diagnosed as stage pT1-2N0; 40 patients of the 203 patients are diagnosed with pT1-2N0 with isolated PNI. All the patients who had a follow up period of at least six months from the time of first visit to the hospital were included in the study.

The patients were followed up post treatment at 6 weeks initially, then every 3 months for first 2 years and every 6 months till 5 years and yearly thereafter, to determine locoregional control and survival. A clinical examination is done at each visit. Imaging and/or biopsy was done if recurrence was clinically suspected.

Tumor staging was based on the pathology findings, according to the American Joint Committee on Cancer Staging System, 7<sup>th</sup> edition. In addition, the following variables were recorded: size, depth of the primary tumor invasion (tumor thickness), and grade of differentiation, status of resection margins, lympho vascular invasion, and peri neural invasion. To determine the status of resection margins, positive margin is defined as carcinoma in situ or as invasive carcinoma at the resection margin, close margin was defined when the distance from invasive tumor front to the resection margin was less than 5 mm, clear margin was defined when the distance from invasive tumor front that is 5 mm or more from the resected margin.

All patients received surgery for the primary site and neck. Resection of the primary site was grouped by the extent of the resection as wide local excision, hemiglossectomy and total glossectomy. The Type of neck dissection used was classified as supraomohyoid or modified radical neck dissection. As this was a retrospective study, the indication for RT was already determined by the individual treating physician after discussing with the patient. A dose of 60Gy in 30 fractions over 6 weeks at 2Gy per fraction and 5 fractions a week is delivered to all patients who received radiation therapy; 14 patients received radiation by conventional technique and the remaining 13 patients by Intensity Modulated Radiation Therapy (IMRT). Data collection and entry was done between January–April 2015 using a structured data capture instrument.

## Data Entry and Statistical Analysis

Data was entered using Microsoft Excel 2010 and analysed using IBM SPSS version 20.0. Continuous variable like age was expressed using mean (SD). Overall mortality rate and recurrence rate was expressed as proportions. Different staging and grading of disease, type of neck dissection done and number receiving radiation therapy were expressed as proportions. Univariate analyses were done to find

**Table 1:** Details of the pathological staging, surgery undergone and treatment received in pT1-2N0 Oral Tongue Squamous Cell Carcinoma patients with isolated perineural invasion (N=40).

| Study Characteristics                                 | Frequency, n (%) |
|---|------------------|
| <b>Surgery details</b>                                |                  |
| <b>Type of surgery</b>                                |                  |
| Wide excision   | 35 (87.5)        |
| Hemi glossectomy                                      | 02 (5.0)         |
| Total glossectomy                                     | 03 (7.5)         |
| <b>Neck dissection</b>                                |                  |
| Unilateral  | 31 (77.5)        |
| Bilateral   | 09 (22.5)        |
| <b>Number of lymph nodes resected, (median (IQR))</b> | 18 (11 to 63)    |
| <b>Pathological grading<sup>#</sup></b>               |                  |
| Well differentiated                                   | 11 (27.5)        |
| Moderately differentiated                             | 27 (67.5)        |
| Poorly differentiated                                 | 02 (5.0)         |
| <b>Pathological staging<sup>#</sup></b>               |                  |
| T <sub>1</sub> N <sub>0</sub>                         | 11 (27.5)        |
| T <sub>2</sub> N <sub>0</sub>                         | 29 (72.5)        |
| <b>Radiation therapy details</b>                      |                  |
| <b>Postoperative radiation therapy (PORT)</b>         |                  |
| Received  | 27 (67.5)        |
| Not received  | 13 (32.5)        |
| <b>Radiation Technique</b>                            |                  |
| Conventional  | 14 (51.8)        |
| Intensity Modulated Radiotherapy(IMRT)                | 13 (48.2)        |

<sup>#</sup>7<sup>th</sup> Edition American Joint Committee on Cancer Staging System.

significance between the recurrence of disease and study variables using Fischer's exact test. Kaplan-Meier analysis with log-rank test was done to check for the difference between disease free survival time between the two treatment groups.

## Results

Among the 40 patients studied, the median (IQR) follow up time was 25 (15 to 32) months. The mean (SD) age was 45.1 (10.8) years and 30 (75%) were males. All of them showed an Eastern Cooperative Oncology Group (ECOG) performance status of either "0" or "1". The pathological staging of the disease, details of the surgery undergone and also regarding the radiotherapy treatment are as mentioned in (Table 1).

Of the 40 patients studied six (15%) had locoregional recurrence and all the patients who died had recurrence. Thus, in our study the overall mortality rate was equal to the locoregional recurrence rate (15%). Locoregional control for patients who received adjuvant radiation and who did not receive adjuvant radiation was 88.9% (2 local & 1 regional recurrence) and 76.9% (1 local & 2 regional recurrence) respectively (Table 2). Of the six patients who had locoregional recurrence, five died within three months of recurrence (and one patient survived for 13 months after recurrence). The minimum time to develop recurrence during the follow up period

**Table 2:** Recurrence patterns in patients.

| TREATMENT | Total No | LOCAL RECURRENCE | REGIONAL RECURRENCE | DEATHS   |
|-----------|----------|------------------|---------------------|----------|
| NO RT     | 13       | 1(7.7%)          | 2(15.3%)            | 3(23%)   |
| RT        | 27       | 2(7.4%)          | 1(3.7%)             | 3(11.1%) |
| TOTAL     | 40       | 3                | 3                   | 6        |

**Table 3:** Factors associated with loco-regional recurrence of the disease in pT1-2N0 Oral Tongue Squamous Cell Carcinoma patients with isolated perineural invasion (N=40).

| Study characteristics                         | Total, n | Recurrence present, n (%) | p value* |
|---|----------|---------------------------|----------|
| <b>Age (in years)</b>                         |          |                           |          |
| ≤40   | 17       | 03 (17.6)                 | 1        |
| >40   | 23       | 03 (13.0)                 |          |
| <b>Gender</b>                                 |          |                           |          |
| Male  | 30       | 04 (13.3)                 | 0.629    |
| Female  | 10       | 02 (20.0)                 |          |
| <b>Pathological grading<sup>#</sup></b>       |          |                           |          |
| Well differentiated                           | 11       | 02 (18.2)                 | 1        |
| Moderately/poorly differentiated              | 29       | 04 (13.8)                 |          |
| <b>Pathological staging<sup>#</sup></b>       |          |                           |          |
| T <sub>1</sub> N <sub>0</sub>                 | 11       | 01 (9.1)                  | 1        |
| T <sub>2</sub> N <sub>0</sub>                 | 29       | 05 (17.2)                 |          |
| <b>Neck dissection</b>                        |          |                           |          |
| Unilateral                                    | 31       | 04 (12.9)                 | 0.602    |
| Bilateral                                     | 9        | 02 (22.2)                 |          |
| <b>Postoperative radiation therapy (PORT)</b> |          |                           |          |
| Received                                      | 27       | 03 (11.1)                 | 0.37     |
| Not received                                  | 13       | 03 (23.1)                 |          |

#7<sup>th</sup> Edition American Joint Committee on Cancer Staging System, \*Fischer's Exact test.

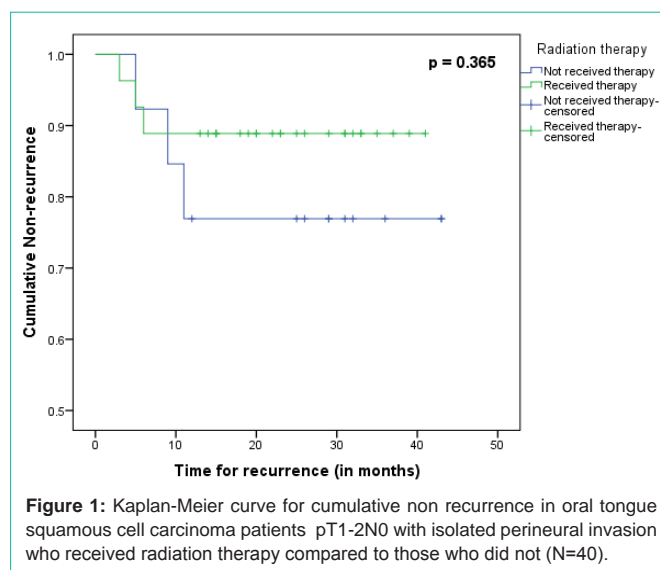
was three months and the maximum was 11 months.

Kaplan-Meier analysis with log-rank test showed that there was statistically no significant difference in the disease free survival time among patients who received PORT and those who did not receive (p = 0.365). The mean survival time was noted to be 35 months and 37 months in patients who did not receive PORT and who received PORT respectively (Figure 1).

Univariate analysis done to find any association between loco-regional recurrence of the disease and independent variables like age, gender, pathological grading of cancer, pathological staging of cancer, type of neck dissection done and receiving radiation therapy showed no statistical significance with any of the variables under study (Table 3).

## Discussion

It is well recognized that postoperative adjuvant RT in Oral Cavity Squamous Cell Carcinoma (OCSCC) patients may increase morbidity, chiefly arising from osteoradionecrosis, mucositis, and xerostomia. In addition, it is still unclear whether patients with pT1-2N0 disease benefit from adjuvant radiation in the presence of free margins and perineural invasion. Accordingly, perineural spread in head-and-



**Figure 1:** Kaplan-Meier curve for cumulative non recurrence in oral tongue squamous cell carcinoma patients pT1-2N0 with isolated perineural invasion who received radiation therapy compared to those who did not (N=40).

neck cancer is an infrequent but possibly aggressive manifestation of the disease [13-16]. Optimal management of postoperative RT for OCSCC patients with pT1-2N0 disease, perineural invasion, and tumor-free margins remains controversial [17-19]. This study was conducted to establish whether this group with isolated PNI would benefit from adjuvant radiation therapy in terms of local control and overall survival rate. In the present report, we deliberately excluded OCSCC patients with positive nodes, pT3 disease, or positive/close margins as these variables are all well-recognized independent prognosticators in subjects with head-and-neck cancer.

Several studies have sought to analyze the effect of PNI in OCSCC patients with N0 neck disease. Liao et al. analyzed 460 patients with clinical T1-3 and N0 neck disease; however 15% of their patients did not undergo neck dissections [20]. They found a significantly increased regional recurrence rate in the PNI+ group and found no benefit for their PNI+ patients undergoing adjuvant radiation treatment, similarly to our study.

In another study by Chinn et al, 88 OCSCC patients treated surgically with pN0 necks were studied. Overall 23% (20/88) were pN0/PNI+ and of those with PNI, 70% (14/20) underwent adjuvant radiotherapy. They concluded that PNI is an independent adverse risk factor in the absence of nodal metastasis and extracapsular spread. They observed a statistically significantly longer DFI and LRC when patients were treated with adjuvant radiation [21].

Our current findings clearly show that there is no significant differences in locoregional recurrence rate among patients with perineural invasion with the addition of adjuvant RT compared to patients with no adjuvant RT. Locoregional control for patients who received adjuvant radiation and who did not receive adjuvant radiation was 88.88% (2 local & 1 regional recurrence) and 76.92% (1 local & 2 regional recurrence) respectively. Independent variables like age, gender, pathological grading of cancer, pathological staging of cancer, type of neck dissection done and receiving radiation therapy showed no statistical significance for locoregional recurrence of the disease.

In our analysis altogether, our retrospective data supports the

contention that surgical resection alone is sufficient treatment even for patients with perineural invasion if there is no other criteria to receive adjuvant therapy. In the interpretation of our findings, however, several limitations must be considered. First, our patient material is limited. Secondly the study is retrospective study and the discretion to use adjuvant radiotherapy has been in the hands of treating physician after discussing with the patient. Although we acknowledge the small sample size, this is one of the largest reviews of PNI as an isolated risk factor. Given the controversy in the literature regarding PNI as an absolute indication for adjuvant radiation, a larger randomized prospective trial would better answer the question of the role of adjuvant radiation for the pN0/PNI+ patient. In addition, better understanding of the molecular mechanisms for PNI is imperative when trying to identify high risk groups and to better understand the mechanism of perineural spread in HNSCC.

## Conclusion

The study showed no significant difference in locoregional control and disease free survival between patients with PNI who received adjuvant radiotherapy and those who did not.

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