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Neck Failures in Early Node Negative Carcinoma Tongue (T1 T2 N0): An Emphasis on the Importance of Neck Treatment.

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ABSTRACT

Early node negative carcinoma of the oral tongue (T1T2N0) have excellent local control rates with surgery or radiotherapy. The main area of recurrence is in the neck node which approaches around 15-30%. There is an unanswered question reegarding the management of neck in these subgroup of tumors. We retrospectively reviewed the patients of early carcinoma tongue (T1 T2 N0) from June 2003 to June 2012 treated in our institute. The patterns of local and nodal recurrence were analyzed and the impact of neck treatment was assessed. Total number of patients was 59 with T1 tumors comprising 54.2% and T2 tumors comprising 45.8%. 50 patients underwent biopsy alone and the 9 patients underwent Wide local excision. Neck dissection was done in 6 patients only with 4 patients having SOND and 2 patients having MRND. All patients received brachytherapy (BT) with 40 patients receiving BT alone while 19 patients receiving combination of external beam radiotherapy (EBRT) and BT as boost. In the BT alone group, the 5 year local recurrence free survival (RFS) was 80% and 5 year regional RFS was 70%. In the (EBRT + BT) group, the 5 year local RFS was 77% and 5 year regional RFS was 84%. The total number of patients having neck nodal failures was 15, out of which 10 patients had no previous neck treatment. The 5 year regional RFS in patients without neck treatment was 70% while the 5 year regional RFS in patients with neck treatment was 75% (p = 0.6). Early node negative oral tongue cancers have a good local control rates but have an increased chances of recurrence in neck nodes. Neck failures decreases in patients with neck treatment. Thus, neck should be addressed in the patients with early oral tongue cancers either with neck dissection or neck EBRT, especially in high risk cases.
Keywords: Tongue carcinoma, recurrence, neck, radiotherapy, brachytherapy

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INTRODUCTION

Oral tongue cancers comprise approximately 32% of squamous cell carcinoma of the oral cavity [1]. In patients with early stage disease (T1T2N0), the outcomes are of local treatment (Surgery or Radiotherapy) are excellent, but there is a high incidence of neck nodal recurrence [2–6]. There is always a question whether neck treatment is really necessary in early node negative carcinomas of oral tongue [7–9]. We herein report our institutional experience of early node negative oral tongue cancers treated from 2003 to 2012 and analyze the neck failures after treatment and the impact of the neck treatment.

METHODS

Patient Population and Initial Evaluation

We retrospectively reviewed the patients of early carcinoma tongue (T1 T2 N0) from June 2003 to June 2012 treated in our institute. Total number of patients was 59. We reviewed the records of these patients to extract the following information: age, sex, clinical symptoms, histology, radiology (CT/MRI), TNM stage, tumor extent, extent of surgical resection, surgical margins, radiation (technique, total dose, dose per fraction, number of fractions), toxicity, response, recurrence, progression, metastases and death. Complete blood count, blood chemistry (electrolytes, liver and kidney function tests), chest X ray and CECT of the neck was done in all patients as baseline and staging workup.

Pathological Review and Staging

Operative notes were reviewed to determine intraoperative suspicion of invasion, gross tumor extension into adjoining structures, and completeness of resection. Pathology reports were obtained for all patients. Staging was based on the surgical, radiological and pathological criteria as per TNM Staging system.

Treatment

Surgery, EBRT (External Beam Radiation Therapy) and Brachytherapy (BT) was used in the treatment. Surgical approach consisted of biopsy alone and Wide local excision (WLE) with emphasis on clear margins. Neck dissection was either supra-omohyoid neck dissection (SOND) or Modified radical neck dissection (MRND). Locoregional EBRT was delivered in conventional 2 Gy per fraction. BT was delivered with Ir-192 HDR (high dose rate) source.

Follow-up

The period between the first complaint and diagnosis was registered as symptom duration. Survival, recurrence and progression information were collected through chart review, patient or relative contact. Response evaluation was noted both clinically and radiologically and RECIST (Response Evaluation Criteria in Solid Tumors) criteria were applied [10].

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Statistical Analysis

SPSS v 15 was used for statistical analysis. The Kaplan-meier survival analysis was done for analyzing recurrence free survival (RFS) [11].

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table – 1. Between June 2003 and June 2012, 59 patients of node negative early carcinoma tongue (T1 T2 N0) were registered in our department. The median age was 55.0 years. 38 patients (64.4%) were males and 21 patients (35.6%) were females. The median duration of symptoms was 4 months. Ulceration in tongue was the most common presenting symptom manifesting in all patients followed by local pain and irritation. No patients had neck node metastasis at presentation. T1 was the most common presentation found in 32 patients (54.2%) and the rest 27 patients (45.8%) belonged to T2 stage. The median tumor size was 2.0 cm and ranged from 1 cm to 4 cm.

Table 1: Patient Characteristics

Total number of patients	59
Age (in years)	
Median	55.0
Range	26 – 80
Sex	
Male	38 (64.4%)
Female	21 (35.6%)
Duration of Symptoms	
Median	4 months
Range	1 – 8 months
Primary Tumor	
T 1	32 (54.2%)
T 2	27 (45.8%)
Tumor Size	
Median	2.00 cm
Range	1 – 4 cm

Treatment Details (Table – 2)

Treatment consisted of a combination of surgery in form of wide local excision (WLE), EBRT, and BT. 50 patients underwent biopsy alone and the 9 patients underwent WLE. Of the 9 patients with WLE, 4 patients had clear margins, 4 patients had close margins and one patient had positive margins. Neck dissection was done in 6 patients only with 4 patients having SOND and 2 patients having MRND.

All patients received BT with 40 patients receiving BT alone while 19 patients receiving combination of EBRT and BT as boost. In patients receiving BT alone, the median dose was 42 Gy which ranged from 36 to 52 Gy. 20 patients were treated with 3 Gy per

fraction twice daily 6 hours apart and the other 20 patients were treated with 4 Gy per fraction twice daily 6 hours apart.

Table 2: Treatment details

Surgical Approach	
Biopsy alone	50 (84.7%)
WLE	9 (15.3%)
Surgical Margins	
Negative	4
Close	4
Positive	1
Neck Dissection	6 patients
SOND	4
MRND	2
RT	
Brachytherapy alone	40 patients
EBRT + Brachytherapy	19 patients
Brachytherapy Alone	
3 Gy / #	20 patients
4 Gy/ #	20 patients
Total Dose (median)	42 Gy
Total dose (range)	36 – 52 Gy
Brachytherapy Boost (3 Gy / #)	
Total Dose (median)	24 Gy
Total dose (range)	18 – 24 Gy

In19 patients who received combination of EBRT and BT, the median EBRT dose was 40 Gy and it included the primary and bilateral neck nodal region. The median BT boost dose was 24 Gy which ranged from 18 to 24 Gy at 3 Gy per fraction twice daily 6 hours apart.

Treatment Toxicity and Compliance

There were no surgical complications in form of post-operative deaths or wound complications. EBRT toxicity occurred in all patients in form of grade 1-2 dermatitis and mucositis and there was no grade 3 or higher toxicity. However, BT toxicity was more as compared to EBRT and all patients had grade 3 mucositis, but it was localized to the area of BT and subsided by the 3rd week. All patients completed treatment with no treatment interruption.

Clinical Outcomes

`After treatment completion, patients were assessed for response both clinically and radiologically. Of the 40 patients treated with BT alone, 5 patients had local recurrence while 12 patients had nodal failure in neck (Table – 3). The 5 year local recurrence free survival (RFS) was 80% (Figure – 1) and 5 year regional RFS was 70% (Figure – 2). The mean local RFS was 92.94 months and the mean regional RFS was 77.54 months.

Of the 19 patients treated with combination of EBRT and BT boost, 3 patients had local recurrence while 3 patients had nodal failure in neck (Table – 4). The 5 year local

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recurrence free survival (RFS) was 77% (Figure – 3) and 5 year regional RFS was 84% (Figure – 4). The mean local RFS was 71.54 months and the mean regional RFS was 74.9 months.

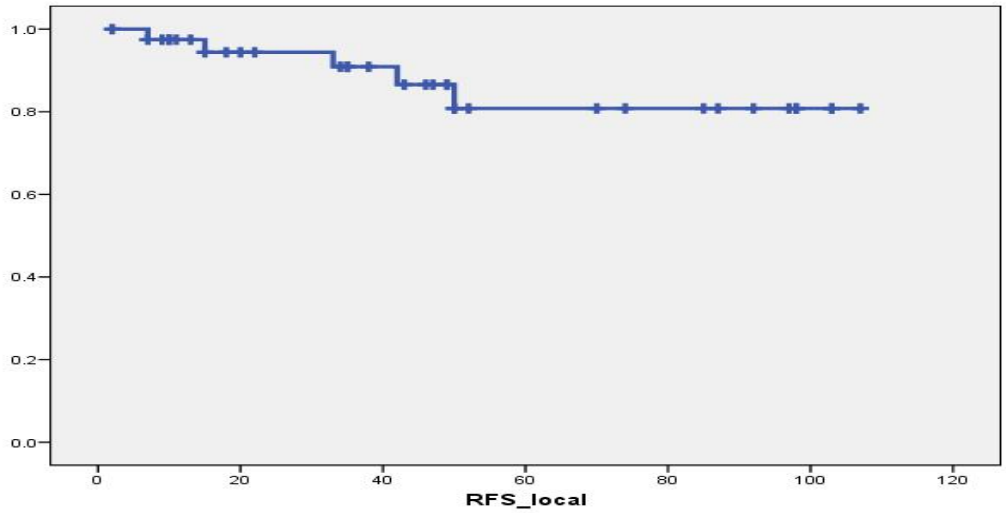

Figure 1: Kaplan Meier curve showing local RFS after brachytherapy alone treatment.

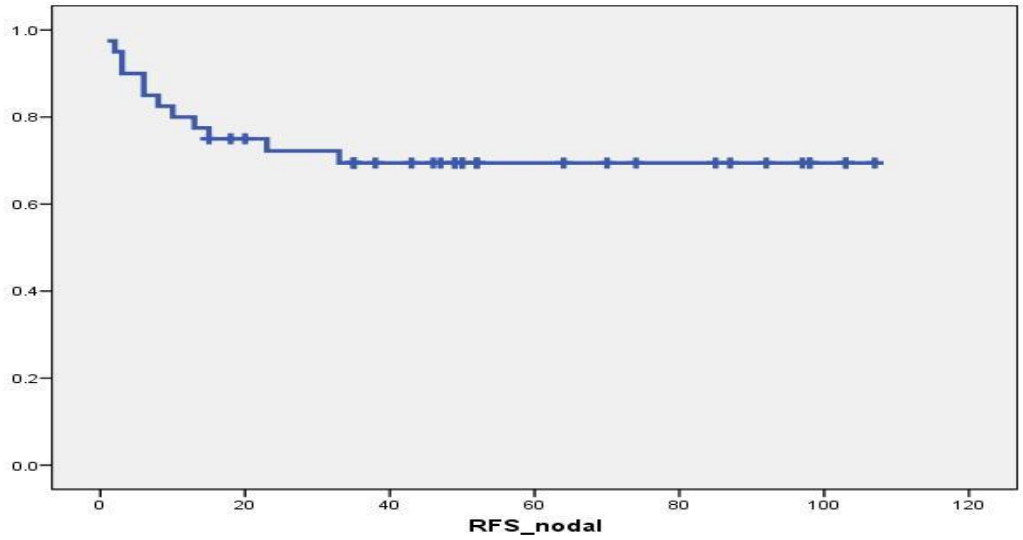

Figure 2: Kaplan Meier curve showing regional (nodal) RFS after brachytherapy alone treatment.

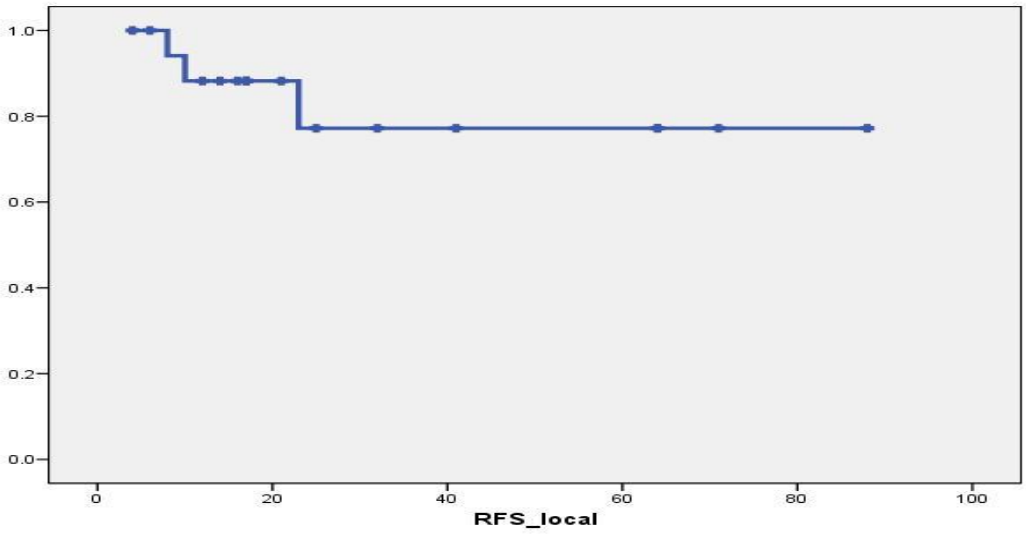

Figure 3: Kaplan Meier curve showing local RFS after (EBRT + brachytherapy) treatment.

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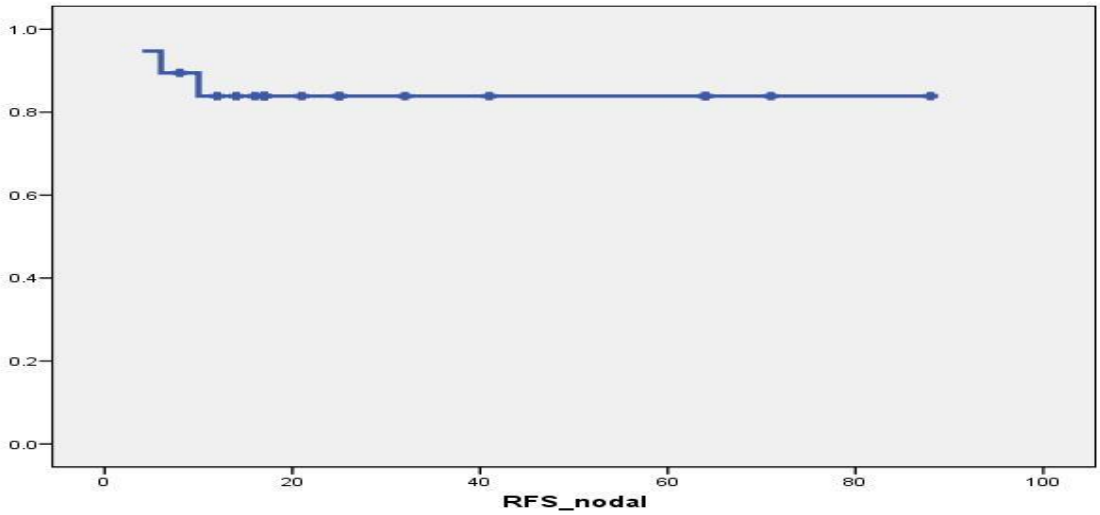

Figure 4: Kaplan Meier curve showing regional (nodal) RFS after (EBRT + brachytherapy) treatment

Table 3: Results of Brachytherapy alone

Total number	40 patients
Local recurrence	5 patiens
Nodal failure	12 patients
Local + Nodal recurrence	2 patients
Local RFS (Mean)	92.94 months
5 yr - Local RFS	80%
Regional RFS (Mean)	77.54 months
5 yr - Regional RFS	70%

Table 4: Results of (EBRT + Brachytherapy)

Total number	19 patients
Local recurrence	3 patients
Nodal failure	3 patients
Local + Nodal recurrence	1 patient
Local RFS (Mean)	71.54 months
5 yr - Local RFS	77%
Regional RFS (Mean)	74.9 months
5 yr - Regional RFS	84%

Impact of neck treatment

Of the total 59 patients, neck was addressed in 25 patients only, with 6 patients having neck dissection and 19 patients receiving EBRT to neck. The total number of patients having neck nodal failures was 15, out of which 10 patients had no previous neck treatment. Of the rest 5 patients, 2 had previous neck dissection while 3 had previous neck RT. Thus, nodal failures in previously untreated patients were (10/34) 29% and nodal failures in patients with previous neck treatment patients were (5/25) 20% only. The 5 year regional RFS in patients without neck treatment was 70% while the 5 year regional RFS in patients with neck treatment was 75% (p = 0.6) (Figure – 5). Thus, there was a trend towards benefit of addressing the neck in preventing nodal failures in early node negative carcinoma of tongue.

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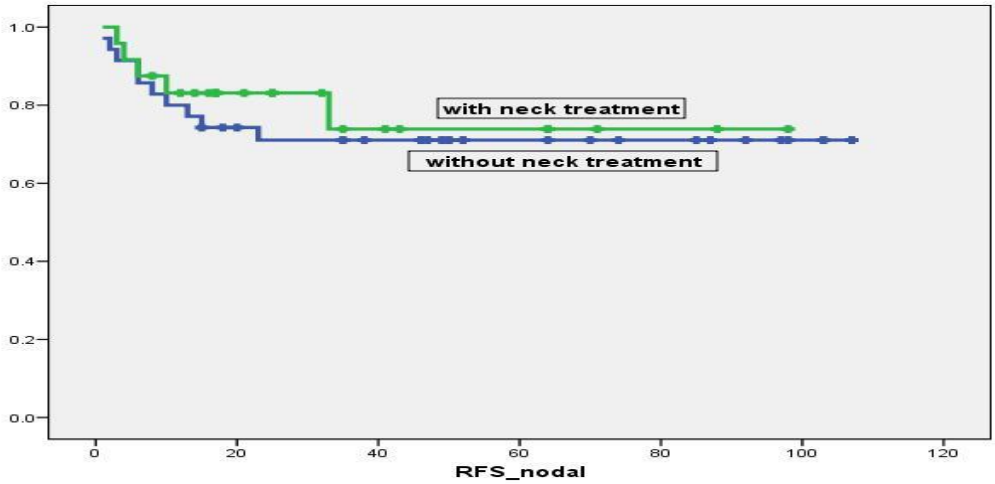

Figure 5: Kaplan Meier curve comparing regional (nodal) RFS with neck treatment

Table 5: Neck Nodal failures

Neck treatment	25 patients
Neck Dissection	6
Neck RT	19
Total nodal failures	15 patients
No Previous Neck Treatment	10
Previous Neck Dissection	2
Previous Neck RT	3

DISCUSSION

Cancer of the oral cavity comprises approximately 30% of head and neck tumors [1]. The most common subsite is the oral tongue comprising approximately 32% of squamous cell carcinoma of the oral cavity (excluding lip). In patients with early stage disease (T1T2N0), the outcomes are generally good, and the reported 5-year survival rates range between 75% and 89% [2–5]. Surgery and radiotherapy (RT) are the important treatment modalities in the management of early oral tongue cancers.

RT, especially interstitial brachytherapy (BT), provides a high local control rate in the treatment of early tongue cancer comparable to surgery [12–14]. It also makes it possible to preserve the shape and functions of the oral tongue. The most common site of failure is in neck nodes in these cases which range from 14% to 30% [15–18]. Because of the high risk of nodal metastases, the question arises whether the neck should be addressed either with surgery or radiation in all but the earliest tumors of the oral tongue.

Decroix and Ghossein reported outcomes in 602 patients with cancer of oral tongue treated with BT or BT plus external RT.[19] In this series, recurrence at primary site or primary site and neck was 14% and 22% for T1 and T2 lesions, respectively. Pernot et al reported local control rates of 96% for T1 and 85% for T2 lesions treated with BT and neck dissection [17]. In this series, the locoregional control rates were 83% and 70% respectively. Yuen et al reported that 11 of 35 patients of early node negative tongue cancer developed neck nodal recurrence after local treatment only [9]. This result corresponds to an occult

metastases rate of 30%. In our series, the neck nodal failure rate was 25.4%, which is similar to other studies.

Because of the high risk of nodal metastases the neck should be addressed either with surgery or radiation in all but the earliest tumors of the oral tongue. Treatment of the clinically negative neck can be accomplished by neck dissection or EBRT. Elective neck dissection (END) appears to result in better overall cancer outcome than observation. There are many studies in the literature reporting on the therapeutic benefit of END but there are no standard guidelines [20–23]. END has the extra advantage of enabling the accurate staging of patients, which then allows for better patient counseling with regard to prognosis as well as allowing the clinician to identify patients who are at high risk of a poor outcome and selecting patients who need PORT.

Neck EBRT is an effective non-surgical method for addressing the neck in high risk cases [24, 25]. The results of neck EBRT in early node negative oral tongue cancer is appealing and is routinely recommended in cases with high risk of occult nodal metastasis. In our series also, there was a trend towards better neck control rates in patients with neck EBRT or neck dissection.

Thus, neck observation can be justified only in some patients who have small, superficial tumors. Now, there are many reports that have identified factors that predict for the presence of occult metastases in neck [26–34]. Tumor thickness and depth of invasion have been shown to confer a higher risk of regional metastases. A recent meta-analysis by Huang et al concluded that a primary tumor thickness 4 mm was the most predictive tumor thickness for occult metastases [30]. Other studies also have reported that poor histologic grade was predictive of occult metastases.

Assessment of the depth of invasion by clinical examination or at the time of surgery is difficult. Frozen section analysis may be helpful, but this may be restricted to centers where it is readily available with experienced head and neck pathologists. Preoperative ultrasonography and intraoperative ultrasonography is currently being investigated by several groups for tumor depth assessment [35,36]. It has demonstrated a high correlation between ultrasound measurement and pathologic measurement of tumor thickness with an accuracy of > 90%.

Sentinel lymph node biopsy (SLNB) has also been used to detect of occult metastases in early tongue cancers. Ross et al investigated 57 SLNBs in 48 patients with clinically N0 neck status and reported that 15 patients (35%) were upstaged by SLNB [37]. The overall sensitivity of the technique was 94%. Civantos et al reported on 140 patients with T1T2 oral cancer, SLNB correctly predicted a pathologically negative neck in 96% of patients [38]. However, this technique does require experience and currently is recommended only for centers with the necessary expertise and the appropriate volume of patients.

Positron Emission Tomography (PET) scan is now widely used in cancer staging. Rodrigues et al showed superiority of PET-CT as compared to CECT for assessment of small nodes in neck in early cancers of head and neck. Nq et al in a study of 134 patients of clinically node negative early oral cancers showed that PET had two fold higher sensitivity

than CT/MRI in detecting occult neck metastasis [39]. Thus, PET can be a useful investigation in assessing the occult nodal disease in neck in high risk cases.

In view of very good local control rates and a higher incidence of occult neck nodal metastasis, all the patients with early stage oral tongue cancers should undergo a detailed evaluation of neck and neck should be addressed in all cases except the very early superficial tumors. The poor prognostic features that signals increased chances of neck nodal metastases should be carefully looked into in the management and they serve as a guide to neck treatment. There is a significant decrease in nodal failure rates after neck treatment and this reflects in increased survival rates and improved quality of life of the patients.

The management of early tongue cancer is a paradigm of cooperation between clinicians, surgeons and pathologists from establishing diagnosis to organizing the therapeutic strategy. With new techniques, there is a significant improvement of therapeutic standard and early tongue cancer represent a model of therapeutic implementation and achievement in oncology. Novel strategies including combined CCT with RT and/or dose escalation with advanced RT techniques such as IMRT and proton therapy should be prospectively investigated.

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