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ExteNT N0 Trial- Extent of **N**eck **T**reatment in clinically **N0** oral cancer: A Randomized Controlled Trial

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STUDY PROTOCOL

Title of the study-

ExteNT N0 Trial- Extent of **N**eck **T**reatment in clinically **N0** oral cancer: A Randomized Controlled Trial

ExteNT N0 Trial- Extent of Neck Treatment in clinically N0 oral cancer: A Randomized Controlled trial

INTRODUCTION

Oral cavity squamous cell carcinoma (OCSCC) is one of the most common head and neck malignancies, particularly in South-East Asia, where tobacco chewing and smoking are major etiological factors [1,2]. Despite advances in diagnosis and treatment, cervical lymph node metastasis remains the single most important prognostic factor influencing survival. Even in clinically node-negative (cN0) necks, the incidence of occult nodal metastasis ranges from 20–40% [2,3]. Management of the cN0 neck in oral cavity cancer has evolved over decades. Elective neck dissection has been shown to improve regional control and survival in early lesions too [4]. Selective neck dissection (SND) involving lymph node levels I-III or I-IV, widely adopted as the preferred elective procedure in cN0 oral cavity cancers. This approach is based on predictable patterns of lymphatic spread, with the majority of metastases occurring in these nodal levels [5,6]. While SND I-III has become the standard approach [7,8], the oncologic significance of level IV nodal involvement remains controversial [5,6]. Level IV dissection increases operative time, surgical morbidity, and functional impairment, particularly related to shoulder function and sensory deficits [9]. Most available evidence comes from retrospective and institutional series, which are prone to selection bias and variability in surgical technique, and lack direct head-to-head comparisons.

Surgical practice varies widely across institutions and surgeons, leading to inconsistency in care. At our institution/country too, the practice amongst different surgeons has not been uniform with all these options being used based on individual preference of the treating physician.A well-designed randomized controlled trial comparing SND I-III and SND I-IV is therefore essential to generate level I evidence that can guide clinical decision-making.

This study aims to compare the survival outcomes, regional control, morbidity, and quality of life between SND I-III and SND I-IV in patients with N0 OSCC. The results of this trial have the potential to provide level I evidence to guide surgical decision-making and optimize the balance between oncologic safety and functional preservation.

RESEARCH QUESTION

Does SND I- IV improve oncologic outcomes without increasing morbidity in clinically N0 OSCC?

HYPOTHESIS

Null hypothesis (H_0): There is no difference in Regional Recurrence-Free Survival (RRFS) disease-free survival, overall survival, or surgical morbidity between SND I-III and SND I-IV in patients with clinically N0 OSCC.

Alternative hypothesis (H_1): SND I-IV provides superior regional control compared to SND I-III in cN0 OSCC.

REVIEW OF LITERATURE

1. Byers RM et al. Frequency and therapeutic implications of "skip metastases" in the neck from squamous carcinoma of the oral tongue. Head Neck.

   1997

   The study analyzed pathological specimens from patients who underwent comprehensive neck dissection to determine the pattern of cervical lymph node spread. The authors reported that approximately 15–16% of patients demonstrated skip metastases, defined as metastatic involvement of lower cervical lymph node levels (particularly level III or IV) without involvement of the preceding nodal levels.

2. Pantvaidya GH, et al. Prospective study of patterns of nodal metastasis in oral tongue cancer. Head Neck

   2013

   In this prospective analysis, occult nodal metastasis was identified in approximately 30–35% of clinically node-negative (cN0) patients. The most commonly involved nodal levels were levels I and II. Level III involvement was less frequent, and isolated level IV metastasis (skip metastasis) was uncommon, reported in a small percentage of cases (around 2–4%). Importantly, level IV involvement rarely occurred without

simultaneous involvement of higher nodal levels.Based on these findings, the authors concluded that supraomohyoid neck dissection (levels I–III) is adequate for most patients with cN0 oral tongue cancer, as routine inclusion of level IV may not be necessary due to the low incidence of isolated level IV metastasis.

3. D'Cruz AK et al. Elective versus therapeutic neck dissection in node-negative oral cancer.

   2015

   A total of 596 patients were randomized to undergo either END at the time of primary surgery or observation with TND performed only upon nodal relapse. At a median follow-up of approximately 39 months, the 3-year overall survival rate was significantly higher in the elective neck dissection group (80.0%) compared with the therapeutic neck dissection group (67.5%). This corresponded to a hazard ratio for death of 0.64 (95% CI, 0.45–0.92; p = 0.01), indicating a 36% reduction in the risk of death in the END group. The 3-year disease-free survival rate was also significantly improved in the END group (69.5% vs. 45.9%; p < 0.001). Regional nodal recurrence occurred more frequently in the therapeutic group.

4. Brazilian Head and Neck Cancer Study Group: Results of a prospective trial on elective modified radical classical versus supraomohyoid neck dissection in the management of oral squamous carcinoma. Am J Surg

   1998

   In this study, patients were prospectively allocated to undergo either classical MRND (levels I–V) or selective supraomohyoid neck dissection (levels I–III). There was no statistically significant difference between the two groups in terms of regional control, disease-free survival, or overall survival. However, the MRND group experienced greater postoperative morbidity, particularly related to shoulder dysfunction due to accessory nerve manipulation. The authors concluded that supraomohyoid neck dissection provides comparable oncologic control to modified radical neck dissection in clinically node-negative oral squamous carcinoma, with reduced morbidity.

5. Guo CB et al: Supraomohyoid neck dissection and modified radical neck dissection for clinically node-negative oral squamous cell carcinoma: A prospective study of prognosis, complications and quality of life. J Craniomaxillofac Surg

   2014

   There was no statistically significant difference between SOHND and MRND in terms of overall survival or disease-free survival during follow-up. Patients undergoing SOHND demonstrated better postoperative shoulder function scores and superior quality-of-life outcomes.

AIM

To compare the survival outcomes, regional control, morbidity, and quality of life between SND I-III and SND I-IV in patients with N0 OSCC.

Primary Objectives

To compare Regional recurrence free survival (RRFS) between SND I-III and SND I-IV in patients with clinically N0 OSCC.

Secondary Objectives

1. To compare overall survival (OS) and Disease free survival between SND I-III and SND I-IV.
2. To determine the incidence and distribution of occult cervical lymph node metastasis, with special emphasis on level IV involvement.
3. To analyze patterns of regional nodal failure following SND I-III and SND I-IV.
4. To evaluate and compare surgical morbidity, particularly: Shoulder dysfunction, chyle leak.
5. To assess postoperative quality of life following SND I-III and SND I-IV.

6. To identify histopathological predictors (depth of invasion, perineural invasion, lymphovascular invasion) associated with level IV nodal metastasis in oral tongue cancer.

METHODOLOGY

Study Setting

This prospective Randomized controlled trial will be conducted in Kolhapur Cancer Centre. Kolhapur Cancer Centre is a tertiary cancer center in western part of Maharashtra. This center is situated in Kolhapur. The center caters around 2000-3000 new cancer patients every year. Oral cancer patients are referred from different centers all over Maharashtra.

Background

- All the information about the study will be informed to the patient & relatives in his/her language that he/she understands
- Helsinki declaration consent (informed written consent) forms will be signed by patients and or/or parents/guardians according to after receiving a detailed explanation about the experimental rationale, surgery, and possible risks associated with the treatment & study in the language (in English, Hindi, Malayalam) that he/she understands.
- All patients will be evaluated with case history, Physical examination, other necessary blood investigations and radiological examination (CECT and/ CEMRI).

Study Design

Prospective, randomized, open-label, parallel-group controlled trial.

Study Period

02 years recruitment + 03 years follow-up, starting from April 2026 to 2031.

Study Population

The sample will be selected in the age group from 21-75 years of age without discriminating on the basis of the gender, socio-economic status, religion and caste.

Inclusion Criteria

1. Patients aged over 21 years will be included.
2. Histologically proven squamous cell carcinoma of oral cavity will be included
3. Clinical stage T1–T4, N0, M0
4. cN0 neck on clinical examination and imaging (CT/MRI)
5. No significant co-morbid conditions - ASA grade II and I.
6. Understands the protocol
7. and is able to give informed consent.

Exclusion Criteria

1. Recurrent cases
2. FNAC proven Positive cervical nodes
3. Patients with history of head and neck radiation therapy treatment
4. Previous neck surgery or radiotherapy

Escape Clauses:

A case will be taken off the protocol if:

1. Any indeterminate or suspicious node on clinical or radiological examination will undergo USG-guided FNAC, and only those with positive results will be excluded from trial.
2. Gross node involvement seen at the time of surgery / frozen section that upstages the N0 to N+.
3. The patient dies in the immediate post – operative period due to an unrelated cause viz.

myocardial infarction etc.

Radiological assessment

All imaging scans will be independently reviewed by a senior radiologist. Patients with lymph nodes deemed indeterminate or suspicious on either clinical examination or radiological assessment will subsequently undergo ultrasonography (USG)-guided fine-needle aspiration cytology (FNAC). Only those patients with negative FNAC findings will be considered eligible for inclusion in the trial.

Randomization & Allocation

Participants will be randomized in a 1:1 ratio using a computer-generated stratified permuted block randomization sequence with variable block sizes of 4, 6, and 8. Stratification will be performed according to tumor subsite and T stage. Allocation concealment will be ensured using sequentially numbered, opaque, sealed envelopes prepared by an independent statistician. The operating surgeon will remain unaware of allocation until the time of assignment.

Stratification will be performed based on clinically relevant prognostic factors known to influence cervical nodal metastasis and oncologic outcomes, namely:

primary tumor subsite

- oral tongue
- buccal mucosa / gingivobuccal complex
- other oral cavity subsites

clinical T stage

- early stage (T1–T2)
- advanced stage (T3–T4)

Additional stratification by midline involvement / crossing may be considered because of its potential impact on contralateral neck management.

The randomization sequence will be generated by an independent statistician not involved in patient recruitment, surgery, or outcome assessment.

Allocation concealment will be ensured using sequentially numbered, opaque, sealed envelopes (SNOSE) prepared in advance according to the computer-generated sequence. The envelope will be opened only after patient enrollment and completion of baseline assessment.

Given the nature of the surgical intervention, blinding of the operating surgeon and patient is not feasible; therefore, this will be an open-label trial. However, wherever possible, postoperative functional and quality-of-life assessments will be performed by outcome assessors blinded to treatment allocation.

Operational definition:

Primary tumor management-

Primary tumor resection will be guided by comprehensive clinicoradiological evaluation, with the intent to achieve gross surgical margins of approximately 1 cm. The surgical defect can be closed / reconstructed / left open as per the normal practice of the surgeon.

Neck management-

Selective neck dissection will be done for all patients.

Arm A: SND I-III- Removal of lymph node Levels Ia,Ib, IIa, and III

Arm B: SND I-IV -Removal of lymph node Levels Ia, Ib, IIa, III, and IV

The contralateral neck will be addressed when the lesion reached or crossed the midline, with the extent of dissection determined by the assigned study arm. Any intraoperatively obvious/suspicious lymph nodes will be sent for the frozen section, and if positive, a modified neck dissection will be performed.

At surgery, various nodal levels will be marked at standard anatomical landmarks as follows. Level IA will be separated from level IB at the posterior border of the anterior belly of the digastric muscle. Level IB will be separated from level II at the posterior margin of the submandibular gland and the posterior belly of the digastric muscle. Level II will be separated from level III at the horizontal level of the hyoid bone, and level III will be separated from level IV at the level where the omohyoid muscle crosses the internal jugular

vein. Levels IIA and IIB will be separated by the plane of the spinal accessory nerve. After completion of the neck dissection, the specimen will be placed into separate packets, and sent for histopathological examination.

During histopathological examination, the contents of each packet will be grossly examined, and the number of lymph nodes at each level will be recorded. Sections will be obtained from the paraffin blocks prepared for each node, stained with hematoxylin and eosin, and examined microscopically.

All neck dissections will be performed either by the lead authors (M.W. and P.W.) or under the direct supervision of the lead authors.

Postoperative Management

Postoperatively, all patients will be referred to the Department of Oncophysiotherapy for demonstration of shoulder exercises to be performed at home for at least 6 weeks. The physical treatment will be directed at (1) pain relief, (2) strengthening exercises, and (3) range of motion exercises. The rehabilitation techniques that will be used include gentle shoulder mobilization exercises (pendulum exercises, passive forward flexion and external rotation, and active-assisted range of motion exercises). Before the start of these exercises, the patient will be advised to apply a heat or ice pack to relieve pain.

Adjuvant radiotherapy/chemoradiotherapy as per final histopathology and standard guidelines. Adjuvant radiotherapy will be given to pathologically advanced stages (Stage III and IV) and in early lesions where depth of invasion is more than 7mm. Adjuvant chemoradiotherapy will be offered to patients with positive margins and or extranodal extension.

Follow-up strategy

Postoperative patients will be advised to attend regular follow-up visits at intervals of 2 months in the first year, 3 months in the second year, 4 months in the third and 6 months in the fourth, and fifth years, and every 6 months to 1 year thereafter. In cases of non-compliance with the scheduled follow-up protocol, telephone interviews will be

conducted as and when required. A contrast enhanced CT scan of the neck is to be done at the completion of one year and again at the completion of

two years.

STUDY TOOLS

1. Primary Outcome- Regional recurrence-free survival (RRFS) at 3 years.
   Regional recurrence-free survival is defined as the interval from the date of surgery to the date of first documented regional recurrence in the cervical lymph nodes (neck) or death from any cause, whichever occurs earlier.

2. Secondary Outcomes

a. Overall survival (OS)- The time interval from the date of definitive surgery to death from any cause or last follow-up, whichever occurs first.
b. Disease-free survival (DFS)- The time interval from the date of definitive surgery to the first documented evidence of local recurrence at the primary site, or regional recurrence in cervical lymph nodes, or distant metastasis, or death from any cause, whichever occurs first.
c. Nodal yield-
d. Occult nodal metastasis rate- the proportion of patients with histopathologically proven metastatic disease in cervical lymph nodes on final postoperative pathology despite a clinically and radiologically node-negative (cN0) neck preoperatively.
e. Level-wise nodal involvement
f. Shoulder function -
    - Shoulder function will be assessed using the Constant–Murley shoulder score[10], a validated 100-point scoring system at preoperative, postoperative at 1 week, 1 month, 3 months, 6 months, 1 year and 2 year
    - Shoulder pain and disability index[11]- Preoperatively, 1 week postop, 1 month, 3 months, 6 months, 1 year and 2 year
    - Arm abduction test/score (AAS)[12]
g. Chyle leak rate-
h. Prevalence of Other surgical morbidity- Chyle leak, Hematoma, any other deficit.

i. Quality of life- Neck Dissection Impairment Index (NDII) questionnaire[13] will be used as a quality-of-life measure and measure at 1 week, 1 month, 3 months, 6 months, 1 year and 2 year

STATISTICAL ANALYSIS

- Data will be entered into Microsoft excel data sheet and will be analyzed using SPSS version 21.0.
- The primary analysis will follow the intention-to-treat principle, including all randomized participants according to the assigned treatment arm.
- The variables for univariate analysis will be selected based on their clinical relevance as well as those previously described in literature
- Univariate analysis will be done using chi-square test (2-sided significance).
- All significant ($p<0.05$) variables will be subsequently tested using multivariate analysis by using binary logistic regression.
- The odds ratio (OR) and hazard ratio will be calculated whenever necessary.
- Kaplan-Meier statistics were used to describe overall survival and the Log-Rank test will be used for comparing survival proportions in two arms.
- p value <0.05 will be considered as statistically significant after assuming all the rules of statistical tests.

ETHICS CONSIDERATIONS

- The permission from the institutional review board/institutional scientific committee will be obtained for the study.
- The process of data collection will not pose any risk or harm to the subjects.
- Data confidentiality: The names of the patients will not be entered anywhere in the study

TRIAL REGISTRATION

This study will be prospectively registered with the Clinical Trials Registry – India (CTRI) before enrollment of the first participant, in accordance with the ICMR National Ethical Guidelines and CONSORT recommendations for randomized controlled trials.

The trial will be registered as:

- Registry: Clinical Trials Registry – India (CTRI)
- Registration Number: to be added after registration
- Registration Date: dd/mm/yyyy

All protocol amendments, if any, will be updated in the trial registry.

DISSEMINATION OF RESULTS:

The results will be published in peer reviewed national and international journals and conferences, increasing the body of knowledge and informing the larger scientific/medical body.

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