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ExteNT N1 Trial- Extent of **N**eck **T**reatment in clinically **N1** oral cancer: A Randomized Controlled Trial

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STUDY PROTOCOL

Title of the study-

ExteNT N1 Trial- Extent of **N**eck **T**reatment in clinically **N1** oral cancer: A Randomized Controlled Trial

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ExteNT N1 Trial- Extent of Neck Treatment in clinically N1 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.

A recent large-scale study indicates that 91% of LNM in OSCC occur in levels I, II and III, while metastasis rates in levels IV and V are relatively low at 4.7% and 3.3%, respectively [3]. Traditionally, modified radical neck dissection (MRND) has been considered the standard treatment for N+ neck disease. MRND involves clearance of lymph node levels I–V while preserving one or more non-lymphatic structures such as the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle. This approach provides comprehensive oncological clearance, especially in patients with multiple nodes, bulky nodal disease (N2/N3), fixed nodes, or suspected extranodal extension (ENE). Level IV dissection increases operative time, surgical morbidity, and functional impairment, particularly related to shoulder function and sensory deficits [5]. 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-IV and MRND I-V with preserving all non-lymphatic structures is therefore essential to generate level I evidence that can guide clinical decision-making.

This study aims to compare the quality of life, survival outcomes, regional control, and morbidity between SND I-IV and MND I-V in patients with N1 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 N1 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-IV and MND I-V in patients with clinically N1 OSCC.

Alternative hypothesis (H_1): SND I-IV provides equal regional control compared to MND I-V in cN1 OSCC.

REVIEW OF LITERATURE

1. Traynor, S. J., Cohen, J. I., Gray, J., Andersen, P. E., & Everts, E. C. (1996). Selective neck dissection and the management of the node-positive neck.

   1996

   The study by S J Traynor et al. evaluated the oncologic effectiveness of selective neck dissection (SND) in patients with node-positive neck disease from upper aerodigestive tract squamous cell carcinoma. In this 4-year retrospective review of 29 patients (36 SND procedures), most patients had advanced nodal disease (N1–N2), and many received adjuvant radiotherapy. At a minimum 2-year follow-up, the 4-year disease-specific survival was 47% overall, with better outcomes in N1 (67%) compared to N2 disease (41%). Regional control was excellent, with only one neck recurrence (4% failure rate), although local recurrence and distant metastasis rates were relatively high (36% each). The authors concluded that, in carefully selected patients, SND provides effective regional control and can be an oncologically sound alternative to more extensive neck dissections in node-positive disease.

2. Pantvaidya GH, et al. Prospective study of patterns of nodal metastasis in oral tongue cancer. Head Neck [4]

   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. Shin, Y. S., Koh, Y. W., Kim, S. H., & Choi, E. C. (2013). Selective neck dissection for clinically node-positive oral cavity squamous cell carcinoma. [6]

   In this retrospective study, Yoo Seob Shin and colleagues evaluated whether selective neck dissection (SND) is adequate for clinically node-positive oral cavity squamous cell carcinoma (OSCC). A total of 92 patients with cN+ OSCC who underwent either comprehensive or selective neck dissection were reviewed. Metastasis to level IV or V nodes was found in 22% of ipsilateral neck dissections, while occult metastasis in these levels occurred in 16% of clinically unsuspected cases. The risk of level IV/V involvement was significantly higher in nodal stages above N2b. Importantly, in patients with cN1 and cN2a disease, SND involving levels I–III combined with appropriate adjuvant therapy achieved regional control and survival outcomes comparable to comprehensive neck dissection. The authors concluded that for carefully selected patients with cN2a or lower nodal stage, levels IV and V may be safely omitted, thereby reducing surgical morbidity without compromising oncologic outcomes.

4. Hashmi, S. S., Abbas, A., Bukhari, A., Saeed, J., Shafqat, A., Siddique, A. H., Buksh, A. R., & Murtaza, G. (2022). Selective Neck Dissection for Node-Positive Oral Cavity Squamous Cell Carcinoma: A Retrospective Cohort Study. [7]

   This retrospective cohort study evaluated the oncologic safety of selective neck dissection (SND) in patients with node-positive oral cavity squamous cell carcinoma (OSCC) and compared outcomes with node-negative cases. A total of 111 patients underwent SND, including 40 clinically node-positive and 71 node-negative patients. The study demonstrated comparable regional control rates between the two groups (96% in node-positive vs 95% in node-negative cases) and similar disease-specific survival (82.5% vs 84.5%, respectively), with no statistically significant difference. The authors concluded that SND can provide effective regional control and survival outcomes even in clinically node-positive OSCC, supporting its use as a less morbid alternative to comprehensive neck dissection in selected patients.

AIM

To compare the survival outcomes, regional control, morbidity, and quality of life between SND I-IV and MND I-V in patients with N1 OSCC.

Primary Objectives

To compare Regional recurrence free survival (RRFS) and quality of life between SND I-IV and MND I-V in patients with N1 OSCC.

Secondary Objectives

1. To compare overall survival (OS) and Disease free survival between SND I-IV and MND I-V.
2. To determine the incidence and distribution of cervical lymph node metastasis.
3. To analyze patterns of regional nodal failure following SND I-IV and MND I-V.
4. To evaluate and compare surgical morbidity, particularly: Shoulder dysfunction, chyle leak.

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

03 years recruitment + 03 years follow-up, starting from March 2026 to 2032.

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, N1, M0
4. cN1 neck on clinical examination and imaging (CT/MRI)
5. Single node which is FNAC proven without any other significant nodes.
6. No significant co-morbid conditions - ASA grade II and I.
7. Understands the protocol and able to give informed consent.

Exclusion Criteria

1. Recurrent cases
2. Multiple significant nodes
3. Nodes clinical/radiological with ENE
4. Single metastatic node at level III/IV/V
5. Single metastatic node with other suspicious nodes
6. Patients with history of head and neck radiation therapy treatment
7. Previous history of any malignancy

Escape Clauses:

A case will be taken off the protocol if:

1. Gross extranodal extension seen at the time of surgery / frozen section that upstages the N1 to N3.
2. The patient dies in the immediate post – operative period due to an unrelated cause viz. myocardial infarction etc.

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 and modified neck dissection will be performed for intraoperative frozen positive nodes.

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

Arm B: MND I-V -Removal of lymph node Levels Ia, Ib, IIa, IIb, III, IV and V preserving nonlymphatic structures like SCM/SAN/IJV.

The contralateral neck was addressed when the lesion reached or crossed the midline, with the extent of dissection- SND will be performed if it is cN0.

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. Level V will be separated from posterior to SCM and anterior to trapezius. 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 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 at 6-month intervals.

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.
   Quality of life- Neck Dissection Impairment Index (NDII) questionnaire 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

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. Level-wise nodal involvement

e. Shoulder function -

   - Shoulder function will be assessed using the Constant–Murley shoulder score[9], 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[10]- Preoperatively, 1 week postop, 1 month, 3 months, 6 months, 1 year and 2 year
   - Arm abduction test/score (AAS)[11]

f. Chyle leak rate-

g. Prevalence of Other surgical morbidity- Chyle leak, Hematoma, any other deficit.

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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