A Phase III Randomized Controlled Trial Evaluating the Non-Inferiority of Adjuvant RTvs CTRT in Borderline Resectable Oral Cancers Following Neoadjuvant Chemotherapy and Surgery

Introduction

Borderline resectable oral cancers often require multimodal therapy, including neoadjuvant chemotherapy (NACT) to improve resectability, followed by surgery. For high-risk pathological features such as extranodal extension (ENE) or positive margins, adjuvant chemoradiotherapy (CTRT) is the standard of care. However, for patients with intermediate-risk features likedepth of invasion (DoI ≥ 10 mm), perineural invasion (PNI), close margins (<5 mm), Worst Pattern of Invasion (WPOI) of 5, lymphovascular invasion (LVI), or nodal involvement without ENE, the choice of adjuvant treatment remains unclear.

The use of NACT has not shown significant improvements in overall survival (OS) or disease-free survival (DFS) compared to standard treatment arms. While adjuvant CTRT may enhance DFS, it is associated with increased toxicity and a reduction in quality of life (QoL). This study hypothesizes that adjuvant RT alone is non-inferior to CTRT in achieving DFS, with the added benefit of significantly reducing toxicity and improving QoL. The trial aims to provide robust evidence to potentially redefine treatment protocols for this intermediate-risk patient subgroup.

Objectives

Primary Objective

To determine whether adjuvant RT alone is non-inferior to CTRT in achieving 3-year DFS in patients with intermediate-risk oral cancers.

Secondary Objectives

To compare overall survival at 3 and 5 years.

To evaluate locoregional recurrence-free survival (LRRFS) and distant metastasis-free survival (DMFS).

To assess acute and late toxicities using CTCAE v5.0.

To measure QoL outcomes

Methodology

Study Design

Type: Phase III Randomized Controlled Trial

Randomization: 1:1 allocation to either Adjuvant RT alone or Adjuvant CTRT

Blinding: Open-label.

Population

Inclusion Criteria:

-Age between 18 to 70 years

-KPS Score of 70 and above

-Histologically confirmed squamous cell carcinoma of the oral cavity.

-Borderline resectable disease who received ≥2 cycles of NACT and surgery.

All patients except those with positive or close margins, pre NACT ENE at nodes (iENE) or ypENE

Exclusion Criteria

-Incomplete HPR information

-Distant metastases

Arms

Arm A: Adjuvant RT alone (60-64Gy in 30-32 fractions).

Arm B: Adjuvant RT with concurrent weekly cisplatin (40 mg/m²)

Endpoints

Primary: 3-year DFS

Secondary: OS, LRFS, DMFS, acute and late toxicity, QoL.

Statistical Analysis

The primary endpoint is 3-year disease-free survival (DFS), with a non-inferiority margin of 12%, corresponding to a hazard ratio (HR) upper limit of 1.44. The study is powered at 80%, with a one-sided significance level of 0.05, requiring a total of 402 patients (201 in each arm). A 10% attrition rate and 10% lost-to-follow-up have been accounted for in our calculations.

Follow-Up

Patients will undergo clinical follow-up every 3 months during the first 2 years, transitioning to biannual assessments thereafter, for a total follow-up period of up to 5 years. As part of the surveillance protocol, a contrast-enhanced CT or MRI of the head and neck will be performed at one year, accompanied by a CT scan of the thorax to monitor for any disease recurrence or progression

Anticipated Outcomes

Primary Outcome

Demonstrate non-inferiority of RT alone compared to CTRT for 3-year DFS.

Secondary Outcomes

Establish reduced acute and late toxicity in the RT-alone arm.

Identify QoL benefits in the RT-alone arm without compromising locoregional or distant control.

Timelines

Months 1-3:Protocol finalisation, IEC approval

After 3 months: Patient accrual

Till 3-4 years: Patient recruitment

Follow-up: 2 years till after last patient accrued