Statistical Analysis Plan

Protocol title:
Quality of Life After Primary TORS vs IMRT for Patients With Early-stage Oropharyngeal Squamous Cell Carcinoma

NCT number: NCT04124198

22/12/2025

Study design

This is a randomized (2:1) phase II trial comparing the experimental arm TORS ±adjuvant therapy to the control arm IMRT±concurrent chemotherapy in the treatment of early stage OPSCC.

Baseline characteristics

Clinical and demographic data including: age, sex, smoking history, alcohol consumption, primary tumor site (palatine tonsil or base of tongue), clinical T and N-stage, p16 status (pos/neg), HPV status (pos/neg) and ECOG status.

Primary endpoint

A Danish validated MDADI questionnaire was utilized [1]. The M. D. Anderson Dysphagia Inventory (MDADI) consists of 4 subdomains (global, emotional, functional and physical) with 20 items in total. The primary endpoint is a composite score of 19 items from the MDADI questionnaire, excluding the global assessment item. The composite score takes values between 20 (extremely low functioning) and 100 (high functioning), evaluated 12 months after treatment.

Secondary endpoints

- Late toxicity (evaluated at 12months after treatment)
    - RTOG/EORTC Late Radiation Morbidity Score graded 0-5 for the following organ tissues: subcutaneous tissue, mucous membrane, salivary glands and larynx (two subcategories).
    - Is dichotomized into two groups 0-2 vs. 3+4.
    - We omit score 5 (death directly related to radiation) as this is not represented by the TORS treatment. This analysis therefore focuses on patients alive after 12 months.
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- Swallowing function (evaluated at baseline, 3 and 12 months follow-up)
    - FEES graded with YALE and PAS scores
    - MBS graded with DIGEST
    - Tube dependency, either nasogastric tube or percutaneous endoscopic
- QoL using MDADI questionnaire (evaluated at 3 months follow-up)
- Long-term nerve impairment (12 months monitoring period)
- Complications short term after staging neck dissection (within 14 days)
- Complications short term TORS or chemoradiation within 1 month
- Serious adverse events or reactions

[1] Sara Fredslund Hajdú et al. Cross-Cultural Translation, Adaptation and Reliability of the Danish M. D. Andeson Dysphagia Inventory (MDADI) in Patients with Head and Neck Cancer. Dysphagia. 2017 Aug;32(4):472-479.

- Delay of treatment for protocolized patients according to the Danish National fast-track Cancer Pathways
- All-cause mortality (time from randomization to death)
- Treatment related death with death from other causes as a competing event
- Risk of recurrence (time from randomization to recurrence endpoint or death as competing event).
- Visualization of MDADI, FEES and MBS scores evaluated at baseline, 3 months and 12 months and descriptive survival and recurrence numbers for sub-treatment arms.
- Radiation Therapy Quality Assurance (RTQA) will be described briefly and include minor and major deviations for the radiation treatment plans. A more detailed analysis of the RTQA will be published in a separate paper.

Analysis principle

The statistical analysis is performed as described below. Changes and additions to the analysis plan are allowed, but results from these analyses are clearly marked as unplanned analyses in the research reports and publications.

Statistical analysis

The level of statistical significance is set at 5% for the primary outcome. The results of the secondary analyses are not adjusted for multiple testing and interpreted as hypothesis-generating.

Primary endpoint: The primary endpoint will be analysed with a linear regression model, which includes additive effects of the treatment group and the baseline value of the composite score. The analysis is performed under the intention-to-treat principle. The primary estimand is the difference in composite MDADI scores under the experimental arm vs. the control arm, conditioned on the survival within the 12 months under both treatment arms. We report the effect of the treatment on the primary outcome for given baseline values with 95% confidence interval and Wald test p-value. In supplementary analyses, we impute missing values under the missing at random assumption.

Secondary endpoints:

Late toxicity

The late toxicity will be analysed at 12 months after treatment. Each domain in late toxicity will be tested using Fisher's exact test and p-values are reported. Point estimates and confidence intervals will be calculated using the binomial exact

method. The distribution of the scores will be shown in a contingency table and stacked proportional barplots.

Swallowing function

The swallowing function is evaluated after baseline, 3 months and 12 months using PAS scores (1-8) and the YALE scores (1-5) for FEES and DIGEST score (0-4) for MBS and a rate of tube dependency, either Nasogastric tube or percutaneous endoscopic, (0,1).
For the PAS, YALE and DIGEST scores, Fisher's exact test for the difference in scores across the months (12-0, 12-3. 3-0) will be performed and contingency tables with p-values are reported.
For the nasogastric tube / percutaneous endoscopic gastrostomy dependency, a Fisher's exact test is performed for (0, 3), (0, 12), (3, 12) months and the contingency tables with p-values are reported.
The PAS, YALE and DIGEST scores are shown in individual trajectories plots.
Stacked proportional barplots are used to summarize changes from baseline at 3 months and at 12 months.

QoL MDADI

Same analysis as for primary endpoint, now evaluated after 3 months (+/- 14 days).

Long-term nerve impairment

Descriptive for the surgical arm including nerves at risk during surgery (spinal accessory, hypoglossal, marginal mandibular branch of the facial nerve, lingual and vagal nerve) within 12 months follow-up.

Complications short term after staging neck dissection (within 14 days)

Report complications as defined per protocol.

Complications short term TORS or chemoradiation within 1 month

Report complications as defined per protocol.

Serious adverse events and serious adverse reactions.

Report complications as defined per protocol.

Delay of treatment for protocolized patients

Report number of patients that exceeds the time to treatment according to Danish guidelines (surgery 28 days, chemoradiation 32 days, adjuvant therapy 4 weeks).

All-cause mortality (time from randomization to death)

All-cause mortality is analysed with the Kaplan-Meier method and differences between the treatment groups are tested with the log-rank test.

Treatment-related death

Treatment-related death with death from other causes as a competing risk are analysed with the Aalen-Johansen method. Differences between treatment groups are tested with the Gray test.

Risk of recurrence (time from randomization to recurrence endpoint or death as competing event).

The absolute risks of recurrence with death as a competing event are analysed with the Aalen-Johansen estimator. Differences between treatment groups are tested with the Gray test.

Counts of loco-regional recurrences (in the same T-site or N-site as the initial cancer localization) and distant recurrence are reported in a contingency table.

Visualization of MDADI, FEES and MBS scores evaluated at baseline, 3 months and 12 months and descriptive survival and recurrence numbers for sub-treatment arms.

After randomisation, the patient might not follow the two treatment arms. Post surgery we define the following groups: neck dissection + TORS, neck dissection + IMRT ± chemotherapy, neck dissection + TORS + IMRT ± chemotherapy, IMRT, IMRT ± chemotherapy. Boxplots and trajectories plots are used to illustrate the distribution of the scores across the three time points: baseline, 3 months and 12 months.

Overview of endpoints and analysis:

Endpoint	Type	Analysis Method	Time Point(s)	Report
MDADI 12 months composite score	Continuous	Linear regression (adjusted for treatment and baseline MDADI composite scores)	12 months (±1month)	Effect estimate with 95%CI and Wald test p-value, Individual trajectories plot
Late toxicity subdomains	Categorical /binary 0-2 vs. 3+4	Fisher's exact test binomial exact confidence interval for dichotomous scores	12 months	Contingency tables for all levels, p-value, Stacked barplot for each subdomain.
Swallowing function: Difference in scores for: - PAS scores - Yale scores - DIGEST scores - Tube dependency	Categorical Levels: (1-8), (1-5), (0-4), (0-1)	Fisher's exact test	0, 3 (±14 days), and 12 months (±1 month)	Contingency table, p-value, Stacked proportional barplots and Individual trajectories plot
MDADI 3 months composite score	Continuous	Linear regression (adjusted for treatment and baseline MDADI composite scores)	3 months (±14days)	Effect estimate with 95%CI and Wald test p-value, Individual trajectories plot.
Long-term nerve impairment	Counts	Descriptive	12 months	Contingency table
Complications short term after staging neck dissection	Counts	Descriptive	14 days	Complications as defined per protocol.
Complications short term TORS or chemoradiation	Counts	Descriptive	1 month	Complications as defined per protocol.

Serious adverse events and serious adverse reactions.	Counts	Descriptive	1 month	Complications as defined per protocol.
Delay of treatment for protocolized patients.	Counts	Descriptive		Counts of patients that exceeds the time to treatment according to Danish guidelines (surgery 28 days, chemoradiation 32 days, adjuvant therapy 4 weeks)
All-cause mortality	Time to event	Kaplan-Meier method, log-rank test		Kaplan-Meier plot log-rank test p-value.
Treatment related death; Death from other causes as competing event	Time to event	Aalen-Johansen estimator, Gray test		Aalen-Johansen plot of risk of treatment related death, Gray test p-value.
Recurrence-free survival for local, regional and distant recurrences	Time to event	Kaplan-Meier method, log-rank test		Kaplan-Meier plot of absolute risk of recurrence-free survival, log-rank test, p-value. Two separate plots; one for local and regional and including local, regional and distant recurrences
Risk of recurrence; Death as competing event	Time to event	Aalen-Johansen estimator, Gray test		Aalen-Johansen estimate of absolute risk of recurrence, Gray test p-value;

MDADI, FEES and MBS scores for Sub-treatment arms: neck dissection + TORS, neck dissection + IMRT ± chemotherapy, neck dissection + TORS + IMRT ± chemotherapy, IMRT, IMRT ± chemotherapy.	Categorical	Descriptive	Baseline; 3 months; 12 months	Boxplots and trajectories plots.
Radiotherapy Quality Assurance	Counts	Descriptive		Counts of patients that comply with the per protocol radiotherapy treatment plans including the number of minor and major deviations.

Tables and figures

- Table (Primary): Baseline clinical and demographic characteristics
- Figure (Primary): Composite MDADI quality-of-life scores after 12 months by treatment arm (Individual trajectories plot)
- Figure (Primary): Swallowing outcomes based on MBS and FEES analysis - Individual trajectories plot
- Figure (Primary): Swallowing outcomes based on MBS and FEES analysis - stacked proportional barplots.
- Figure (Primary): All-course mortality (Kaplan-Meier method)
- Figure (Primary): Absolute risk of treatment related death (Aalen-Johansen method)
- Figure (Primary): Recurrence-free survival (Kaplan-Meier method)
- Figure (Supplementary): Absolute risk of recurrence (Aalen-Johansen method) are shown for each treatment arm.
- Figure (Supplementary): Late toxicity - Stacked barplot for each subdomain
- Figure (Supplementary): MDADI, FEES and MBS scores and time (0, 3, 12 months) - For each post-surgery group, boxplots and individual trajectories plots.