



HAL
open science

Weekly Adaptive Radiotherapy vs Standard Intensity-Modulated Radiotherapy for Improving Salivary Function in Patients With Head and Neck Cancer

Joël Castelli, Juliette Thariat, Karen Benezery, Ali Hasbini, Bernard Gery, Antoine Berger, Xavier Liem, Sébastien Guihard, Sophie Chapet, Sébastien Thureau, et al.

► **To cite this version:**

Joël Castelli, Juliette Thariat, Karen Benezery, Ali Hasbini, Bernard Gery, et al.. Weekly Adaptive Radiotherapy vs Standard Intensity-Modulated Radiotherapy for Improving Salivary Function in Patients With Head and Neck Cancer. *JAMA oncology*, 2023, pp.e231352. 10.1001/jamaoncol.2023.1352 . hal-04117942

HAL Id: hal-04117942

<https://hal.science/hal-04117942v1>

Submitted on 5 Jul 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Weekly adaptive radiotherapy *versus* standard IMRT in head and neck cancer: the ARTIX phase III trial

Joël Castelli^{1*} MD, PhD; Juliette Thariat² MD, PhD; Karen Benezery³ MD; Ali Hasbini⁴ MD;
Bernard Gery² MD; Antoine Berger⁵ MD; Xavier Liem⁶ MD; Sébastien Guihard⁷ MD; Sophie
Chapet⁸ MD; Sébastien Thureau⁹ MD PhD; Pierre Auberdiaç¹⁰ MD; Pascal Pommier¹¹ MD PhD;
Amandine Ruffier⁸ MD; Lionel Perrier¹² PhD; Anne Devillers¹³ MD; Boris Campillo-
Gimenez¹ MD; Renaud de Crevoisier¹ MD PhD

1. Univ Rennes, CLCC Eugène Marquis, Inserm, LTSI – UMR 1099, F-35000 Rennes, France
2. Department of Radiation Oncology, Centre François Baclesse, Laboratoire de Physique Corpusculaire, IN2P3/ENISAEN-CNRS, Normandie Université, Caen, France. jthariat@gmail.com
3. Department of radiotherapy, Centre Antoine Lacassagne, Avenue de Valombrose, F06000 Nice, France
4. Radiotherapy, Clinique Pasteur-Lanroze, 32 Rue Auguste Kervern, F29200 Brest, France
5. Department of radiotherapy, CHU Poitiers, 2 Rue de la Milétrie, F86000 Poitiers, France
6. Academic Department of Radiation Oncology and Brachytherapy, Oscar Lambret Center, Lille, France
7. Department of radiotherapy, ICANS, 17 rue Albert Calmette, F67033, Strasbourg, France
8. Department of radiotherapy, CHU Tours, 2 Bd Tonnellé, F37000, Tours, France
9. Department of radiotherapy, Centre Henri Becquerel, 1 Rue d'Amiens, F76038 Rouen, France
10. Radiotherapy, Clinique Claude Bernard, 1 rue du Père Colombier, F81000, Albi, France
11. Department of radiotherapy, Centre Léon Bérard, 28 Prom. Léa et Napoléon Bullukian, F69008, Lyon, France
12. University Lyon, Leon Berard Cancer Centre, GATE UMR 5824, F-69008 Lyon, France
13. Department of nuclear medicine, Centre Eugene Marquis, Avenue Bataille Flandres Dunkerques F35000 Rennes, France

*Corresponding author : j.castelli@rennes.unicancer.fr, +33299253046 ;@JoelCastelli

Running title: Phase 3 of adaptive radiotherapy in head and neck cancer

Results from this study had been partially presented at ESTRO Copenhagen May 22

Date of revision: March 7 2023

Word count: 2996

Key points

Question: The ARTIX trial is a phase III study investigating the benefit of a maximalist strategy of systematic weekly replanning in locally advanced oropharyngeal cancer to improve salivary gland function and decrease xerostomia.

Findings: A total of 132 patients were randomised between ART (n=67) and standard IMRT (n=65) in 11 French centres. Adaptive radiotherapy compared to standard IMRT did not significantly improve salivary flow assessed by paraffin stimulation, PRO scores, or toxicity rates.

Meaning: ART failed to show a benefit to decrease xerostomia. However, a subgroup of patients with large PG overdoses may benefit from this approach.

Tweet: ARTIX study, first randomized study to evaluate adaptive radiotherapy in H&N failed to demonstrate a benefit to decrease xerostomia. A potential benefit was found only in parotid gland function without clinical benefit.

Importance: Xerostomia is major toxicity associated with intensity-modulated radiotherapy (IMRT) for oropharyngeal cancers.

Objective: To demonstrate the benefits of adaptive radiotherapy (ART) in improving salivary function.

Design: Randomised clinical trial. Patients were enrolled between 5th July 2013 and 1st October 2018.

Setting: This study was conducted in 11 French centres.

Participants: Patients aged 18-75 years, with squamous cell cancer stage III-IVB, treated with chemo radiotherapy.

Intervention: The patients were randomly assigned (1:1) to receive standard IMRT (without replanning) or ART (systematic weekly replanning)

Main Outcomes and Measure: The primary endpoint was the frequency of xerostomia, measured by stimulating salivary flow with paraffin. Secondary endpoints included salivary gland excretory function measured using Tc⁹⁹ scintigraphy, patient-reported outcomes (PRO; Eisbruch's xerostomia-specific and MDASI-HN questionnaires), early and late toxicities, disease control, and overall and specific survival.

Results: A total of 132 patients were randomised between ART (n=67) and standard IMRT (n=65) in 11 French centres. The Median follow-up was 26.4 months (1.2 to 31.3 months). The mean salivary flow (paraffin) at 12 months was 630 mg/min in the ART arm and 584 mg/min in the standard arm (P=0.6). The excretory function of the parotid gland at 12 months, measured by scintigraphy, improved in survival rates were not statistically different between the two arms.

Conclusions and Relevance: Our study failed to demonstrate a benefit of ART to decrease xerostomia compared to standard IMRT. No significant difference was found in all secondary endpoints except for parotid gland excretory function, as assessed by scintigraphy, without impacting disease control and survival rates.

Trial Registration: The study was approved by the French Institutional Review Board on 6th June 2012 and was registered on ClinicalTrials.gov (NCT01874587)

<https://clinicaltrials.gov/ct2/show/NCT01874587>

Funding: The French National Cancer Institute (PAIR VADS 2011 grant).

Key words: Adaptive radiotherapy, head and neck cancer, xerostomia, parotid gland

Introduction

Radiotherapy with chemotherapy or cetuximab is the standard of care for patients with locally advanced squamous cell carcinoma of the head and neck.¹⁻³ The recommended radiotherapy technique is intensity-modulated radiotherapy (IMRT)⁴, which has been proven to reduce the dose to the parotid gland (PG) and subsequently decrease xerostomia.⁵⁻⁷ However, xerostomia remains a major issue causing difficulties in swallowing, speaking, loss of taste, and dental caries, with a direct impact on the patient's quality of life. Xerostomia is mainly caused by radiation-induced damage to the PG and, to a lesser extent, to the submandibular glands.⁸ IMRT is classically based on a single initial planning computed tomography (CT) scan, whereas large anatomical variations can be observed during the treatment course.⁹⁻¹² These variations may result in PG overdose, and therefore an increased risk of xerostomia.⁹⁻¹²

By performing one or several replanning sessions, adaptive radiotherapy (ART) aims to correct PG overdose during treatment.^{11,13-16} A dosimetric benefit of ART has been reported in the literature, with a decrease in the mean PG dose up to 10 Gy compared to the dose delivered without ART.^{9,11,13,16-19} Few studies, mostly retrospective, have suggested a potential clinical benefit of ART, with an increase in quality of life and/or in local control of the disease.^{15,16,20-23} However, no phase III study has distinctly demonstrated the benefit of ART in head and neck cancer (HNC) or even in any tumour localisation.

The study hypothesised that ART might decrease the rate of xerostomia in the locally advanced oropharyngeal carcinoma compared to standard CT scan-based single planning IMRT. This study reports the results of the ARTIX phase III trial comparing systematic weekly replanning (ART) with standard IMRT in patients with locally advanced oropharyngeal cancer (LA-OC).

Methods

Study design and Participants

The ARTIX trial is a randomised, parallel-group, multicentre study comparing systematic weekly replanning (ART) with standard IMRT for patients with LA-OC. This study was conducted in 11 French centres. Eligible patients had histologically documented stage III-IVB squamous cell oropharyngeal cancer according to the UICC/AJCC v7 and had to be treated with chemo-radiotherapy. Patients had an Eastern Cooperative Oncology Group (ECOG) score ≤ 2 and were aged 18–75 years. Immunohistochemical staining for p16 was performed. The main exclusion criteria were previous head or neck radiotherapy, surgical resection of the primary tumour and/or lymph node, previous malignancy except non-melanoma skin cancer, pre-existing salivary gland disease, tumour involvement of the two PGs, or previous or concurrent illness that would compromise the completion of treatment or follow-up.

Written informed consent was obtained from all the patients. This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the French Institutional Review Board on 6th June 2012 and was registered on ClinicalTrials.gov (NCT01874587).

Randomisation and masking

Patients were randomly assigned using a central electronic automated system (1:1 ratio) to receive standard IMRT or ART. Computer-generated randomisation with minimisation was used to stratify patients based on tumour stage (AJCC 7th edition), HPV status (based on p16 expression), concomitant chemotherapy (platinum, cetuximab, carboplatin + Fluorouracil (5FU)), and IMRT technique (tomotherapy, VMAT/arcTherapy, and step and shoot technique).

Treatment procedures

All the patients received a total dose of 70 Gy in 35 fractions (2 Gy/fraction/day), with a simultaneous integrated boost technique²⁴ and concomitant chemotherapy. The following chemotherapy regimens were given: cisplatin 100 mg/m² Q3W;²⁵ cetuximab at an initial dose of 400 mg/m² D-7 followed by 250 mg/m² weekly;³ carboplatin (70 mg/m²/d, D1–D4 Q3W) and 5FU (600 mg/m²/d, D1–D4 Q3W).²⁶

The radiation protocol was detailed in eData 1. Contours and dose-volume constraints were set according to the GORTEC recommendations.²⁷ In particular, for the PG, the dose constraints were a mean dose (Dmean) < 30 Gy and a median dose < 26 Gy.²⁸ Treatment parameters were reviewed retrospectively by the Quality Assurance Review Committee (eTable 1 and 2).

For the patients in the ART arm, a weekly CT scan was performed using the same protocol as the initial planning CT (CT0). The dose distribution was computed using the same constraints as those used in the initial planning. A maximum of five days was allowed between each weekly CT scan and the start of the treatment using a new dose distribution. One replanning, based on the radiation oncologist's decision, was allowed in the standard IMRT arm.

In both arms, during the treatment course, daily in-room imaging (2D kV imaging, CBCT, or MVCT) corrected set-up errors >5 mm.

Outcomes

The primary endpoint was the frequency of xerostomia defined by salivary quantification 12 months after the end of radiotherapy. The salivary flow was measured for primary analysis

using stimulation by paraffin wax chewing before radiotherapy (baseline) and at 6, 12, 18, and 24 months after radiotherapy. The patient chewed paraffin wax for 2 min, and while continuing chewing, saliva was collected for 5 min. A salivary flow of ≤ 500 mg/min was used as the threshold for xerostomia.²⁹

The secondary endpoints were salivary gland excretory function measured by scintigraphy, patient-reported outcomes (PRO), early and late toxicities, overall, specific, and progression-free survival, and occurrence of second cancer. Salivary gland excretory function was measured by dynamic image acquisition after injection of ^{99m}Techetium pertechnetate and oral administration of 10 mL of lemon juice to stimulate salivary secretion before treatment and 12 months after the end of radiotherapy.³⁰ All salivary scintigraphy images were centrally reviewed and analysed. PRO was measured using both Eisbruch's xerostomia-specific questionnaire³¹ and the MDASI-HN questionnaire for health-related quality of life,³² collected at 3, 6, 12, 18, and 24 months after the end of radiotherapy. Toxicity was recorded weekly during radiotherapy, monthly for the first 3 months after radiotherapy, and quarterly until the end of follow-up using CTCAE V4.0. Toxicity was defined as 'acute' if it occurred during the first three months following the end of treatment and 'late' if it occurred three months after the end of radiotherapy. Only toxicities occurring at a frequency greater than 1% are reported.

Tumour evolution was assessed by clinical evaluation every three months, and CT and/or PET/CT scans at 3, 15, and 24 months. Locoregional control was defined as the absence of progressive disease according to the RECIST (version 1.1) criteria in the primary tumour and lymph node area. Overall survival (OS) was defined as the time from randomisation to the date of death from any cause or the last follow-up. Cancer-specific survival was defined as the time from randomisation to the date of death related to HNC or last follow-up (deaths related to other causes were censored). Progression-free survival (PFS) was defined as the time from randomisation to the date of cancer recurrence, death from any cause, or last follow-up. Time

to progression was defined as the time from randomisation to the date of cancer recurrence (locoregional and/or metastasis) or the last follow-up (deaths were censored).

Statistical analysis

The study was designed to detect a 25% decrease in xerostomia (assessed by salivary flow after paraffin stimulation) in the ART arm, with an expected xerostomia rate in the standard IMRT arm equal to 60%, with a 5% one-sided Type I error rate and 90% power. The study included 132 patients who were allocated to both arms. An interim analysis by an independent data monitoring committee (IDMC) was planned at 50% inclusion. The IDMC had to decide, in cases of excessive 1-year local disease recurrence, to stop the study early. The stopping guideline was defined using a 1% one-sided type-I error rate.

Quantitative data were described by means and standard deviations (SDs) or medians and interquartile ranges, and qualitative data by absolute and relative frequencies. Survival curves were plotted using Kaplan–Meier estimators and described by median time and 6-, 12-, 18-, and 24-month survival rates. For all the survival and late-toxicity analyses, hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated using Cox regression models. Appropriate non-parametric tests were used to compare the two arms of the study (i.e., Wilcoxon rank-sum test, Fisher’s exact test, and log-rank test). Wilcoxon signed-rank tests were used to compare paired measures such as salivation flow and questionnaire scores from baseline.

Sensitivity analyses concerning the primary endpoint were conducted using logistic regression models considering stratification covariates and possible confounding factors after stepwise multivariable selection. Results were presented as odds ratios (ORs) of xerostomia in the standard arm vs the replanning arm with a two-sided 95% CI. The ORs and CIs were also

presented by subgroups using forest plots. P-value <0.05 was considered as significant. Since a single primary outcome with two treatment groups was defined, no adjustment for multiplicity was required. Thus, findings from secondary outcomes should be considered as exploratory only.

The main analyses were conducted on the modified intent-to-treat population (ITT), defined by the overall subjects receiving at least one dose of chemotherapy and one radiotherapy session, as assigned by the randomisation procedure. In case of missing data related to the primary endpoint, data imputation was also performed with adjacent measurements (*e.g.*, xerostomia diagnosed after 18 months was considered present at 12 months; in the absence of xerostomia, the 12-month value was kept missing). Analyses were also conducted on the per-protocol population (PP), defined as the ITT population without any of the following major protocol violations: non-compliance to written informed consent, failure to meet eligibility criteria, non-compliance with randomisation assignment, and > 30 days between diagnosis CT scan and study treatment start.

Data were analysed using the R software package (R Core Team (2022). R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>) version 4.1.0 (2021-05-18).

Results

From 5th July 2013 to 1st October 2018, 132 patients were recruited and randomly assigned to the ART (n=67) or standard IMRT arms (n=65). Figure 1 shows the flowchart of the study population. The median time between randomisation and the first day of radiotherapy was 9 days. One patient did not receive any treatment and was therefore excluded from the ART arm. Table 1 shows the patient and tumour characteristics at baseline. No significant differences

were found between the two arms. Treatment characteristics are shown in Table 2. Replanning was performed weekly as expected in 62 patients (96%) in the ART arm. In the standard arm, seven (10.8%) patients had one replanning session, based on the physician's decision, at a mean time of 23 days from the start of radiotherapy.

Interim analysis was performed on 87 patients in October 2018. Regarding disease control, no significant difference was found, allowing the study to continue.

No significant differences were found in the initial dosimetry parameters (eTable 1 and 2). eTable 3 and 4 show the dosimetry parameters for each replan in the ART arm. Doses constraints were respected for each replan.

The median follow-up time was 26.4 months (from 1.2 to 31.3 months). At baseline, the mean salivary flow after stimulation with paraffin was 1028 mg/min (SD=729) in the standard arm and 1231 mg/min (SD=855) in the experimental group (P=0.16). At 12 months, the mean stimulated salivary flow was 584 mg/min in the standard arm and 630 mg/min in the ART arm (P=0.6) (Figure 2). Nineteen patients (47.5%) in the ART arm were considered to experience xerostomia (<500 mg/min) compared to 23 patients (47.9%) in the standard arm (P>0.99). Data were missing for 26 (39%) and 17 (26%) patients in the ART and standard arms, respectively. After data imputation based on adjacent measures, no significant difference was found with 20 patients (44.4%) in the ART arm with xerostomia compared to 24 (46.2%) in the standard arm (P>0.99).

At baseline, the mean excretory function of the PG, estimated by salivary scintigraphy, was not different between the two groups (56% and 55% for the ART and standard arms, respectively, P=0.8). The PG excretory function at 12 months showed a significant improvement (P=0.015) in the ART arm (48%) compared to that of the standard arm (41%). No difference in excretory function was observed in the submaxillary glands (eTable 5).

In both groups, PRO scores were significantly worse at three and six months than those at baseline ($P < 0.05$). No differences were found between the two arms at any study time point (eFigure 1 and 2).

No differences in acute toxicities were found between the two arms (eTable 6). The rate of acute xerostomia grade ≥ 2 was 55.4% in the ART arm compared to 55.7% in the standard arm ($P > 0.99$). Regarding late toxicities, the rate of xerostomia grade ≥ 2 at 12 months was 51.8% [95%CI: 37.5%-62.9%] in the ART arm, compared to 53.5% [95%CI: 39.4% - 64.3%] in the standard arm ($P = 0.98$). No significant differences were found in the rates of other late toxicities between the two treatment arms (eTable 7 and eFigure 3).

Regarding the efficacy of the treatment at 12 months, the total number of locoregional recurrences was 18 (32%) in the ART arm and 19 (31%) in the standard arm ($P > 0.999$). A total of 30 deaths were reported, with 15 in each group. Twenty deaths were due to oropharyngeal cancer ($n = 10$ in both groups). The OS rates at 12 and 24 months were 81.5% [95%CI: 69.8-89.1] and 76.9% [95%CI: 64.7-85.4] in the ART arm, compared to 86.2% [95%CI: 75.1-92.5] and 76.9% [95% CI: 64.6-85.4] in the standard arm. The OS curves did not differ between the groups ($P = 0.93$) (Figure 3). The 2-year PFS was 61.5% [95% CI: 48.6-72.1] in the ART arm compared to 61.5% [95%CI: 48.6-72.1] in the standard arm ($P = 0.92$). The 2-year locoregional recurrence rate was 23.7% [95%CI: 12-43.7] in the ART arm compared to 22.5% [95%CI: 11.4-32.8] in the standard arm ($P = 0.87$). The 2-year distant metastasis rate was 13.9% [95%CI: 4.4-22.4] in the ART arm compared to 18.4% [95%CI: 7.9-27.7] in the standard arm ($P = 0.5$) (Figure 3).

All analyses were also conducted in the per-protocol (PP) population (eTable 8-10 and eFigure 4-8). The results of the PP analysis were consistent with those of the ITT analysis.

Discussion

To our knowledge, this is the first phase III randomised study of ART in HNC or any other tumour localisation. We tested a systematic maximalist weekly replanning ART³³ approach for LA-OC treated with chemo-radiotherapy. ART appears to be technically feasible and safe and does not decrease local disease control and survival. However, this expensive and intensive process did not translate into a clinical benefit. Indeed, our study failed to demonstrate the clinical benefit of ART.

Regarding clinical outcomes of both arms, the results of this study agree with the data previously published,^{4,34,35} whether for toxicity, with an expected rate of xerostomia of 40–50% or efficacy, with a 2-year overall survival of around 80%.

Although the clinical benefit of ART compared to standard IMRT was reported in a few non-randomised studies, with respect to improvement in quality of life^{16,22,36} and/or in local disease control,^{22,37} this study did not find such a benefit. This can be due to several reasons. First, the study may have overestimated the benefit of ART, assuming a 25% decrease in xerostomia at one year between the two arms³⁸. Second, even if a significant improvement in PG function measured by scintigraphy was found in the ART arm related to PG sparing, no difference in salivary excretion was found for the submandibular gland. This result highlights the importance of a “whole salivary glands sparing” approach and not only the PG to decrease xerostomia. The use of a 3mm PTV margin, thanks to daily CBCT, may allow to reduce the dose to the salivary glands. It must be stressed that the determinants of xerostomia are multifactorial (doses to the oral cavity and all salivary glands, quality of planning...), and it may require to adjusting all these factors to decrease xerostomia. Third, the study results may be related to the complexity of the xerostomia assessment. Even if IMRT had demonstrated better PG sparing, this benefit in salivary function did not translate into an improvement in PRO scores.^{5,6} Finally, dysphagia is another frequent adverse effect, closely related to xerostomia, and has a greater impact on

quality of life than xerostomia, with a potential impact on the patients' responses to the questionnaires.³⁹

It is likely that ART is not necessary for all patients but only for a subset of patients.^{40 23,41} Based on only pre-treatment parameters, the present study could not identify a subgroup of patients with a potential clinical benefit of ART in sensitivity analysis (eFigure 4).

The study had some limitations. The salivary flow after stimulation by paraffin was used as the primary endpoint, and the whole saliva was collected, thus evaluating the whole salivary gland function and not only the PG.³⁰ However, this method is well correlated with PRO in the literature³⁸ and has the advantage of simplicity, even if chewing and spitting may be uncomfortable and unreliable. Another quantitative method involves using scintigraphy to assess the salivary function of each gland. However, scintigraphy is more operator-dependent. To address this limitation, we chose to perform all scintigraphy analyses by an experienced nuclear medicine physician. Finally, PRO questionnaires may be complex for certain patients.

ART could be used to spare another organs at risk, such as pharyngeal constrictors,⁴² which could have improved the quality of life of the patients. Another strategy could have been to propose ART for dose escalation in the tumour to increase local control, as in the ongoing European ARTFORCE study. Moreover, recent software advancements allow real-time adaptive radiotherapy to be performed to adapt the treatment to the daily shape of the patients as viewed by CBCT or onboard MRI.⁴³

In conclusion, our study is the first randomised phase III trial testing the benefits of ART. Despite a maximal and labor-intensive approach, the primary endpoint was not reached, with no benefit of ART to decrease xerostomia, nor in all but one secondary endpoint. A potential benefit of ART was found only in PG function assessed using salivary scintigraphy. ART appears to be feasible and safe, with no unfavourable impact on local disease control and OS.

These findings highlight the need to identify the subset of patients who may benefit from a personalised ART strategy, aided by recent advances in the treatment planning system integrating artificial intelligence and onboard imaging such as MRI.

Acknowledgements:

We thank the patients and the investigators, co-investigators, and study teams at each of the participating centres.

Role of the funding source

This study was sponsored by the Cancer Institute Eugène Marquis, Rennes, France, with funding from the French National Cancer Institute (INCa, grant PAIR VADS 2011). The financiers of our study had no role in the study design, data collection, analysis, interpretation, or writing of the report. The corresponding author had full access to all study data and had the final responsibility for the decision to submit for publication.

Authors' contribution statement:

RdC, BCG and JC designed the study.

RdC was the principal investigator. J.C, J.T, A.H, B.G, A.B, X.L, S.G, S.C, S.T, P.A, P.P, A.R, and RdC recruited and treated patients. AD performed scintigraphy analysis. JC, RdC and BCG performed the statistical analysis. All authors interpreted data and wrote and reviewed the report.

Declaration of interests: We declare no competing interests.

References

1. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet* 2000; **355**(9208): 949-55.
2. Pignon JP, le Maître A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009; **92**(1): 4-14.
3. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006; **354**(6): 567-78.
4. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet* 2019; **393**(10166): 40-50.
5. Kam MK, Leung SF, Zee B, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. *J Clin Oncol* 2007; **25**(31): 4873-9.
6. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011; **12**(2): 127-36.
7. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys* 2006; **66**(4): 981-91.
8. Chambers MS, Rosenthal DI, Weber RS. Radiation-induced xerostomia. *Head Neck* 2007; **29**(1): 58-63.
9. Castelli J, Simon A, Louvel G, et al. Impact of head and neck cancer adaptive radiotherapy to spare the parotid glands and decrease the risk of xerostomia. *Radiat Oncol* 2015; **10**: 6.
10. Ahn PH, Chen CC, Ahn AI, et al. Adaptive planning in intensity-modulated radiation therapy for head and neck cancers: single-institution experience and clinical implications. *Int J Radiat Oncol Biol Phys* 2011; **80**(3): 677-85.
11. Jensen AD, Nill S, Huber PE, Bendl R, Debus J, Münter MW. A clinical concept for interfractional adaptive radiation therapy in the treatment of head and neck cancer. *Int J Radiat Oncol Biol Phys* 2012; **82**(2): 590-6.
12. Castelli J, Simon A, Lafond C, et al. Adaptive radiotherapy for head and neck cancer. *Acta Oncol* 2018; **57**(10): 1284-92.
13. Capelle L, Mackenzie M, Field C, Parliament M, Ghosh S, Scrimger R. Adaptive radiotherapy using helical tomotherapy for head and neck cancer in definitive and postoperative settings: initial results. *Clin Oncol (R Coll Radiol)* 2012; **24**(3): 208-15.

14. Duma MN, Kampfer S, Schuster T, Winkler C, Geinitz H. Adaptive radiotherapy for soft tissue changes during helical tomotherapy for head and neck cancer. *Strahlenther Onkol* 2012; **188**(3): 243-7.
15. Schwartz DL, Garden AS, Thomas J, et al. Adaptive radiotherapy for head-and-neck cancer: initial clinical outcomes from a prospective trial. *Int J Radiat Oncol Biol Phys* 2012; **83**(3): 986-93.
16. Zhao L, Wan Q, Zhou Y, Deng X, Xie C, Wu S. The role of replanning in fractionated intensity modulated radiotherapy for nasopharyngeal carcinoma. *Radiother Oncol* 2011; **98**(1): 23-7.
17. Dewan A, Sharma S, Dewan A, et al. Impact of Adaptive Radiotherapy on Locally Advanced Head and Neck Cancer - A Dosimetric and Volumetric Study. *Asian Pac J Cancer Prev* 2016; **17**(3): 985-92.
18. Olteanu LA, Berwouts D, Madani I, et al. Comparative dosimetry of three-phase adaptive and non-adaptive dose-painting IMRT for head-and-neck cancer. *Radiother Oncol* 2014; **111**(3): 348-53.
19. Schwartz DL, Garden AS, Shah SJ, et al. Adaptive radiotherapy for head and neck cancer--dosimetric results from a prospective clinical trial. *Radiother Oncol* 2013; **106**(1): 80-4.
20. Kataria T, Gupta D, Goyal S, et al. Clinical outcomes of adaptive radiotherapy in head and neck cancers. *Br J Radiol* 2016; **89**(1062): 20160085.
21. Lai YL, Yang SN, Liang JA, et al. Impact of body-mass factors on setup displacement in patients with head and neck cancer treated with radiotherapy using daily on-line image guidance. *Radiat Oncol* 2014; **9**: 19.
22. Yang H, Hu W, Wang W, Chen P, Ding W, Luo W. Replanning during intensity modulated radiation therapy improved quality of life in patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2013; **85**(1): e47-54.
23. Chatterjee S, Maulik S, Prasath S, et al. Xerostomia quality of life and resource requirements following parotid sparing adaptive radiotherapy in head and neck cancers: Results of a prospective cohort study (Study ID CTRI/2017/11/010683). *Radiother Oncol* 2022; **168**: 250-5.
24. Studer G, Huguenin PU, Davis JB, Kunz G, Lütolf UM, Glanzmann C. IMRT using simultaneously integrated boost (SIB) in head and neck cancer patients. *Radiat Oncol* 2006; **1**: 7.
25. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol* 2003; **21**(1): 92-8.
26. Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol* 2012; **13**(2): 145-53.

27. Tao Y, Auperin A, Blanchard P, et al. Concurrent cisplatin and dose escalation with intensity-modulated radiotherapy (IMRT) versus conventional radiotherapy for locally advanced head and neck squamous cell carcinomas (HNSCC): GORTEC 2004-01 randomized phase III trial. *Radiother Oncol* 2020; **150**: 18-25.
28. Dirix P, Nuyts S. Evidence-based organ-sparing radiotherapy in head and neck cancer. *Lancet Oncol* 2010; **11**(1): 85-91.
29. Pedersen AM, Bardow A, Jensen SB, Nauntofte B. Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion. *Oral Dis* 2002; **8**(3): 117-29.
30. Wu VWC, Leung KY. A Review on the Assessment of Radiation Induced Salivary Gland Damage After Radiotherapy. *Front Oncol* 2019; **9**.
31. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001; **50**(3): 695-704.
32. Rosenthal DI, Mendoza TR, Chambers MS, et al. Measuring head and neck cancer symptom burden: the development and validation of the M. D. Anderson symptom inventory, head and neck module. *Head Neck* 2007; **29**(10): 923-31.
33. Zhang P, Simon A, Rigaud B, et al. Optimal adaptive IMRT strategy to spare the parotid glands in oropharyngeal cancer. *Radiother Oncol* 2016; **120**(1): 41-7.
34. Lee NY, Ferris RL, Psyrri A, et al. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol* 2021; **22**(4): 450-62.
35. Gebre-Medhin M, Brun E, Engström P, et al. ARTSCAN III: A Randomized Phase III Study Comparing Chemoradiotherapy With Cisplatin Versus Cetuximab in Patients With Locoregionally Advanced Head and Neck Squamous Cell Cancer. *J Clin Oncol* 2021; **39**(1): 38-47.
36. Chen AM, Yoshizaki T, Hsu S, Mikaeilian A, Cao M. Image-guided adaptive radiotherapy improves acute toxicity during intensity-modulated radiation therapy for head and neck cancer. *Journal of Radiation Oncology* 2018; **7**(2): 139-45.
37. Chen AM, Daly ME, Cui J, Mathai M, Benedict S, Purdy JA. Clinical outcomes among patients with head and neck cancer treated by intensity-modulated radiotherapy with and without adaptive replanning. *Head Neck* 2014; **36**(11): 1541-6.
38. Lin A, Helgeson ES, Treister NS, et al. The impact of head and neck radiotherapy on salivary flow and quality of life: Results of the ORARAD study. *Oral Oncol* 2022; **127**: 105783.
39. Ramaekers BL, Joore MA, Grutters JP, et al. The impact of late treatment-toxicity on generic health-related quality of life in head and neck cancer patients after radiotherapy. *Oral Oncol* 2011; **47**(8): 768-74.
40. Brouwer CL, Steenbakkers RJ, Langendijk JA, Sijtsema NM. Identifying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric

changes in head and neck organs at risk during radiotherapy provide information to help?
Radiother Oncol 2015; **115**(3): 285-94.

41. Castelli J, Simon A, Rigaud B, et al. A Nomogram to predict parotid gland overdose in head and neck IMRT. *Radiat Oncol* 2016; **11**: 79.

42. Weppeler S, Quon H, Schinkel C, et al. Patient-Reported Outcomes-Guided Adaptive Radiation Therapy for Head and Neck Cancer. 2021; **11**.

43. Boeke S, Monnich D, van Timmeren JE, Balermipas P. MR-Guided Radiotherapy for Head and Neck Cancer: Current Developments, Perspectives, and Challenges. *Front Oncol* 2021; **11**: 616156.

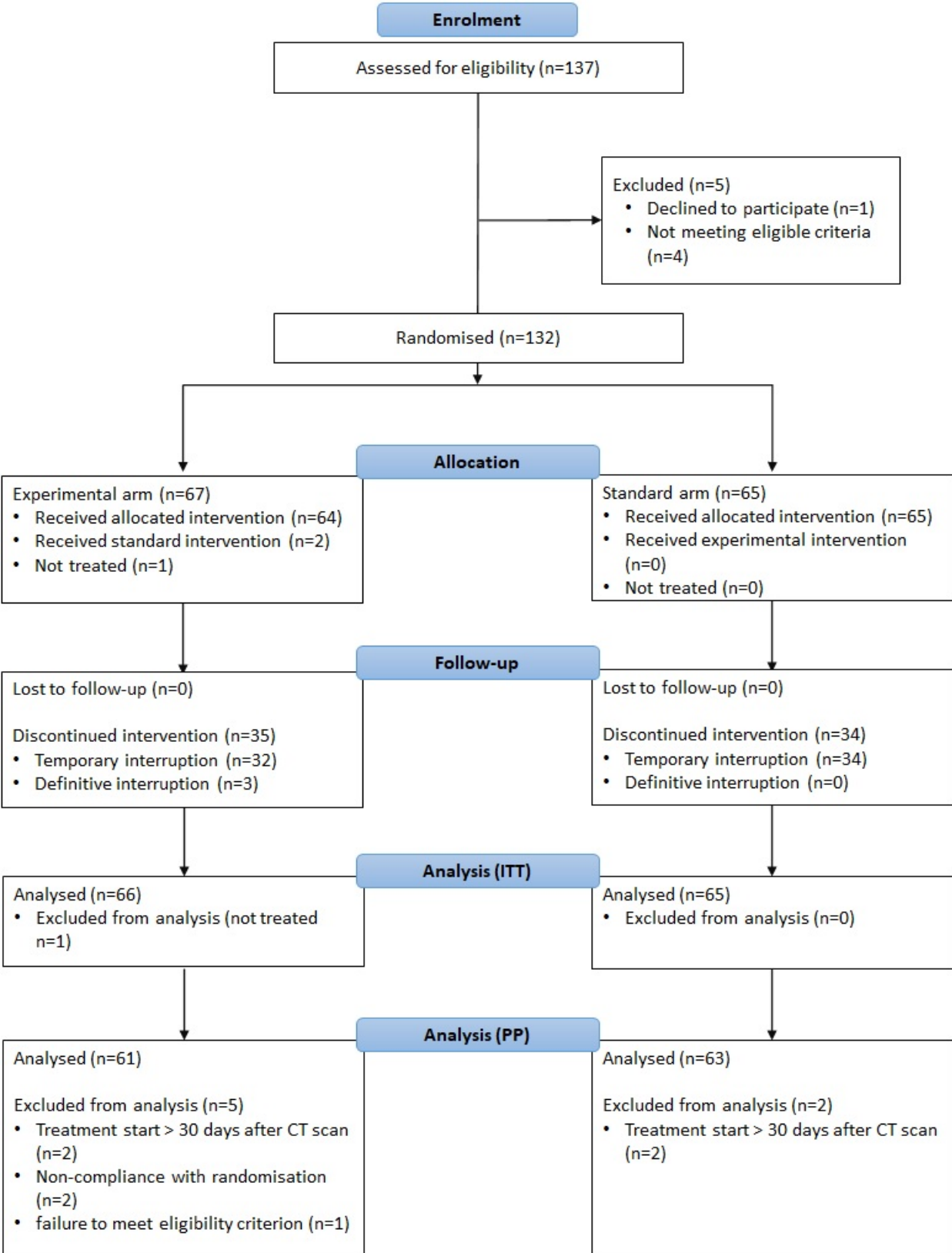
Figure 1: Flowchart of the patient population (Intent-to-Treat and Per Protocol analyses)

Figure 2 : Evolution of the salivary flow after stimulation by paraffin (ITT)

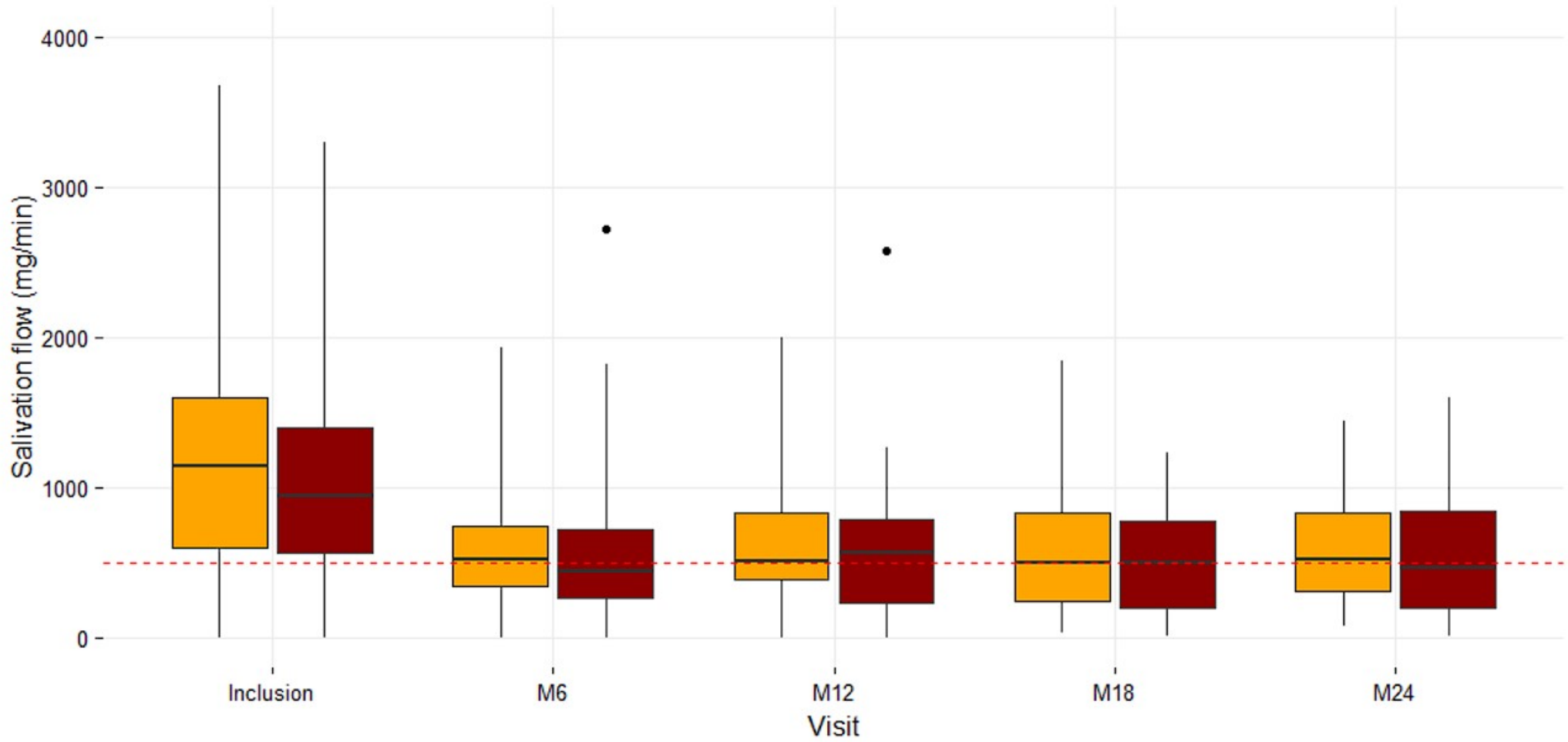
Salivary flow was measured using the formula: weight of the saliva sample/sample collection time in minutes (mg/min). Xerostomia was defined as the salivary flow of < 500 mg/min (red dotted line).²⁹ The salivary flow was significantly decreased at all time points compared to inclusion in both arms (Wilcoxon signed-rank test). No significant difference in salivary flow was found between the two arms at any given time (Wilcoxon signed-rank test).

Figure 3: Survival curves of the study (ITT).

(A) Overall survival, (B) Cancer-specific survival, (C) Progression-free survival, and (D) Time to progression curves. No significant differences were found between the two treatment arms for all endpoints of treatment efficacy.



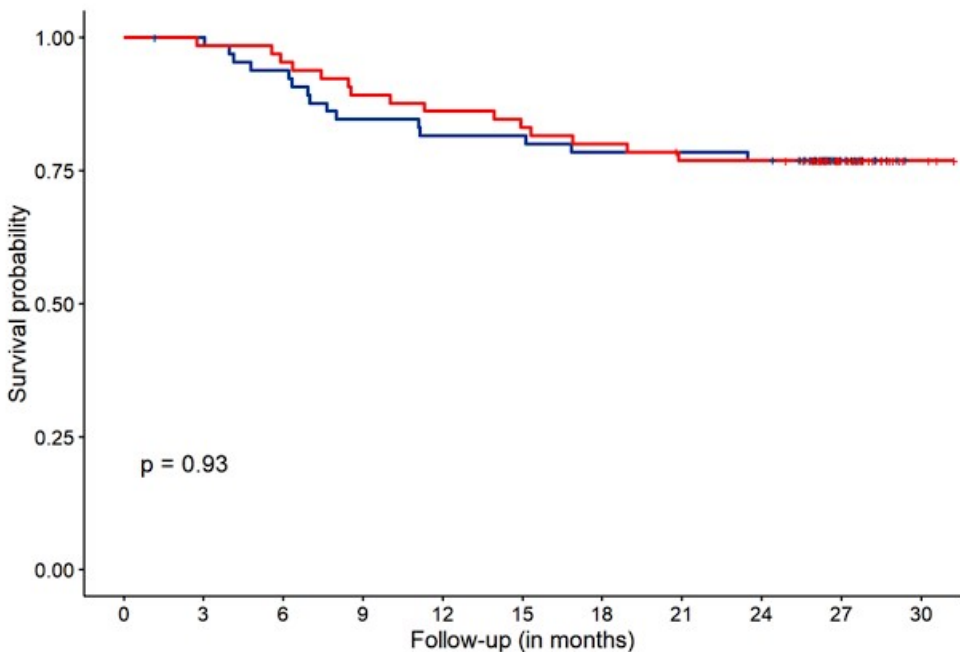
■ Replanning arm
 ■ Standard arm
 - - - Threshold for xerostomia (< 500 mg/min)



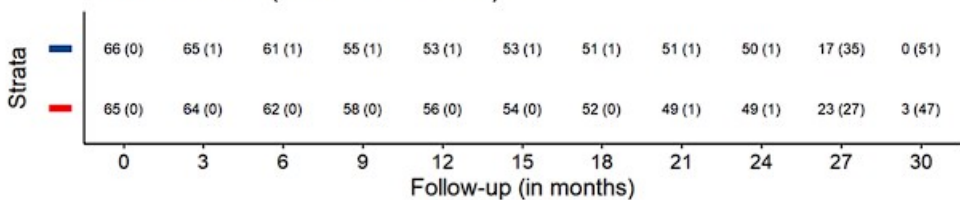
	Inclusion	M6	M12	M18	M24
Number of data					
Standard arm	64	45	48	33	28
Replanning arm	61	44	40	31	27
% xerostomia					
Standard arm	23.44%	55.56%	47.92%	48.48%	53.57%
Replanning arm	19.67%	47.73%	47.50%	51.61%	44.44%

A : Overall survival

Strata — Replanning arm — Standard arm

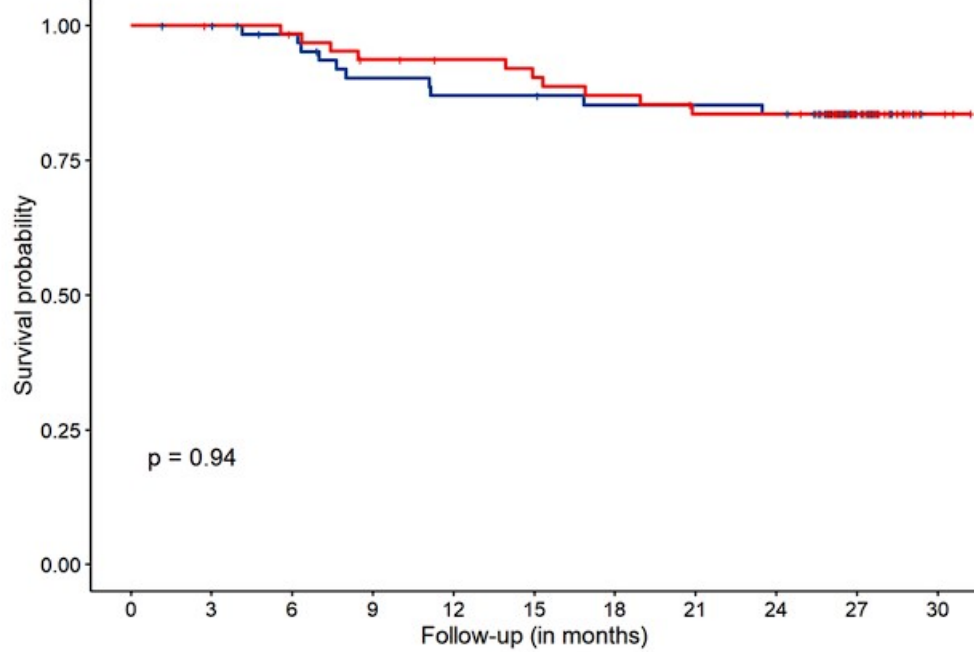


Number at risk (number censored)

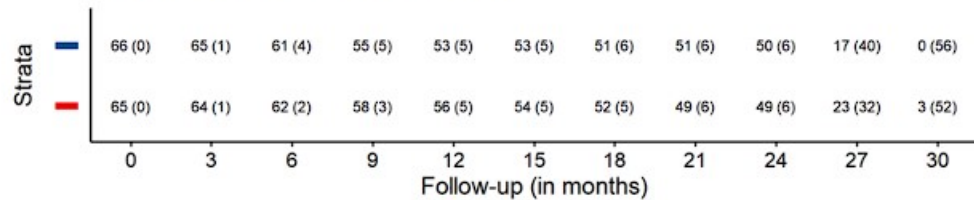


B : Cancer specific survival

Strata — Replanning arm — Standard arm

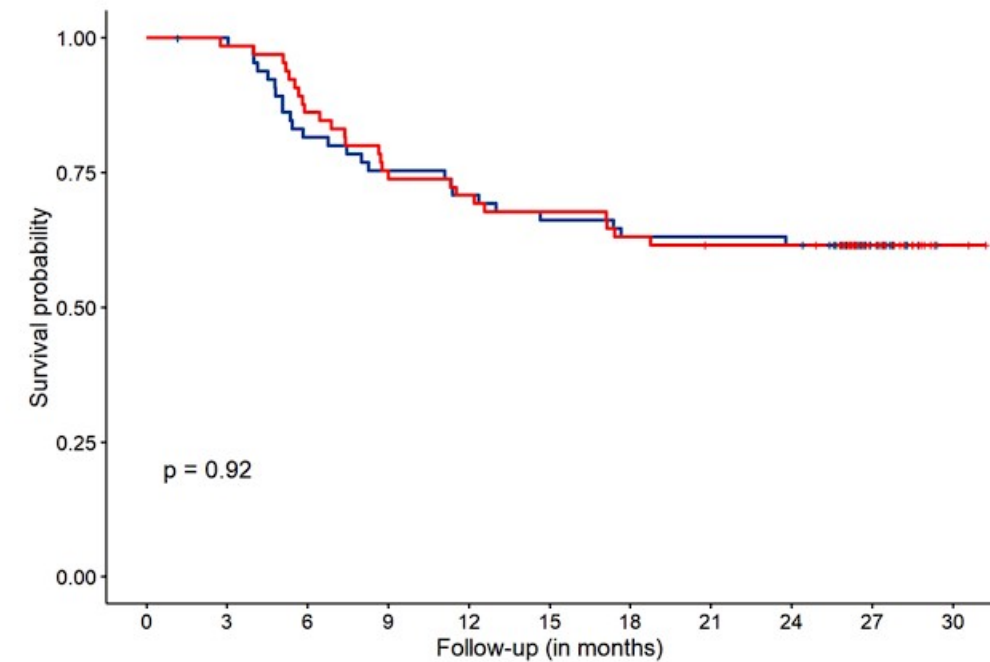


Number at risk (number censored)

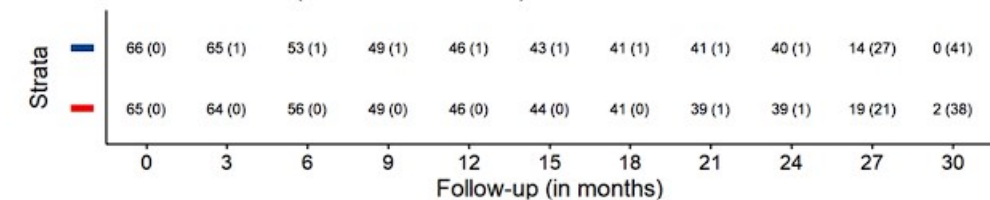


C : Progression free survival

Strata — Replanning arm — Standard arm

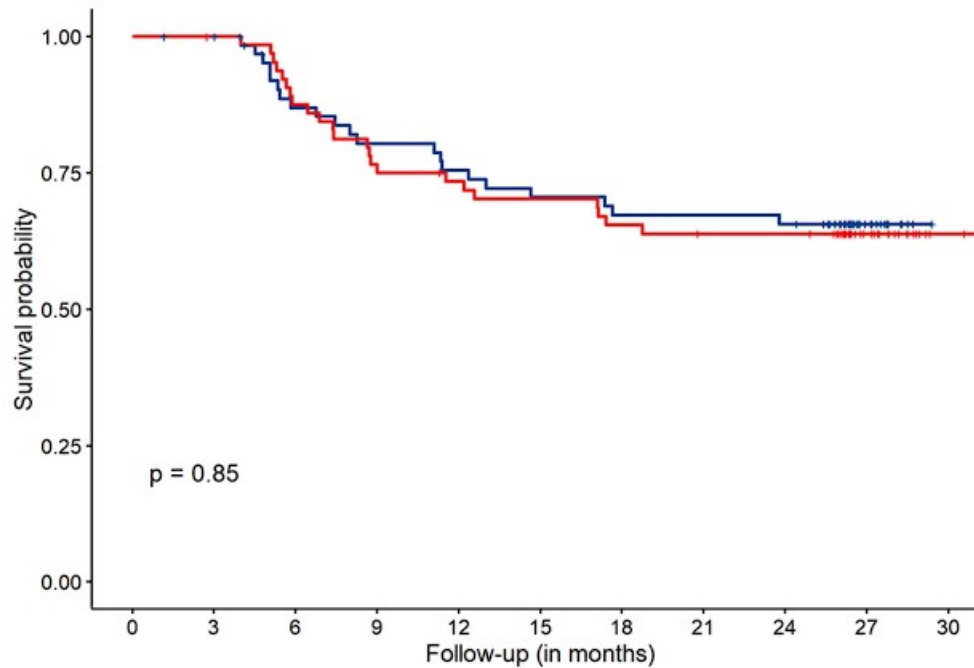


Number at risk (number censored)

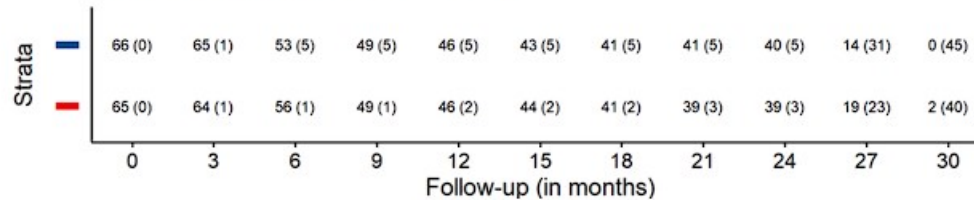


D : Time to progression

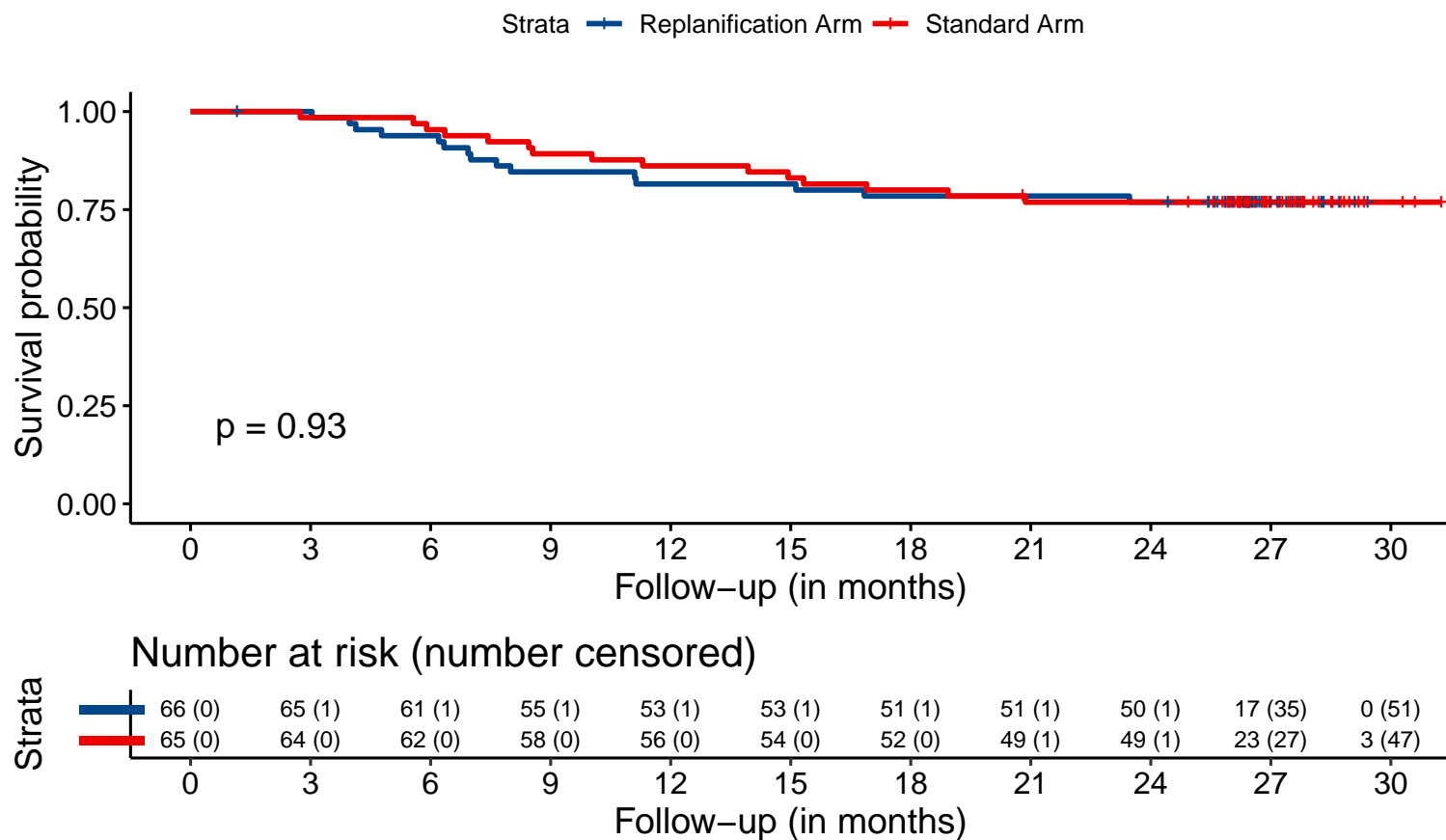
Strata — Replanning arm — Standard arm



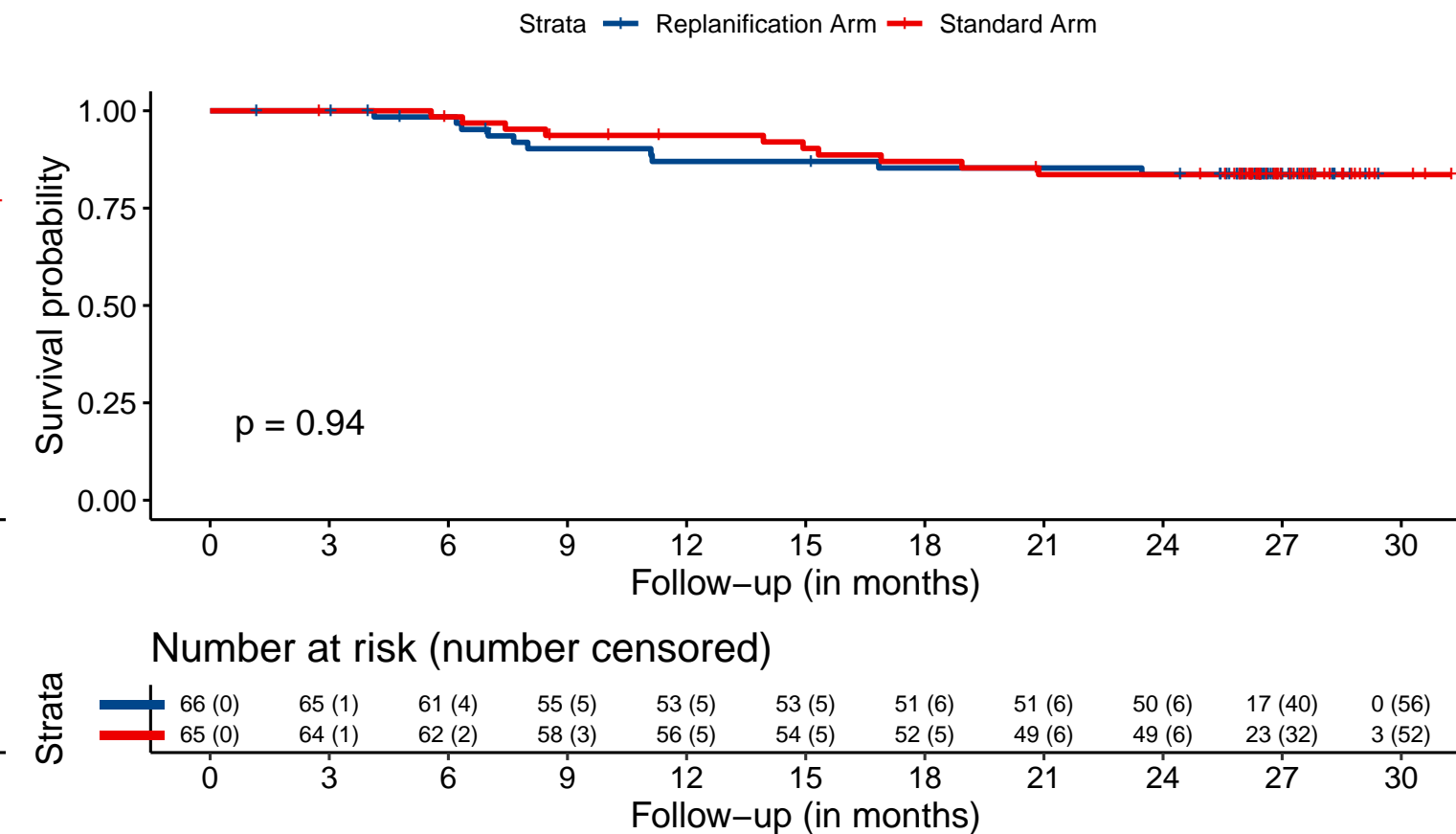
Number at risk (number censored)



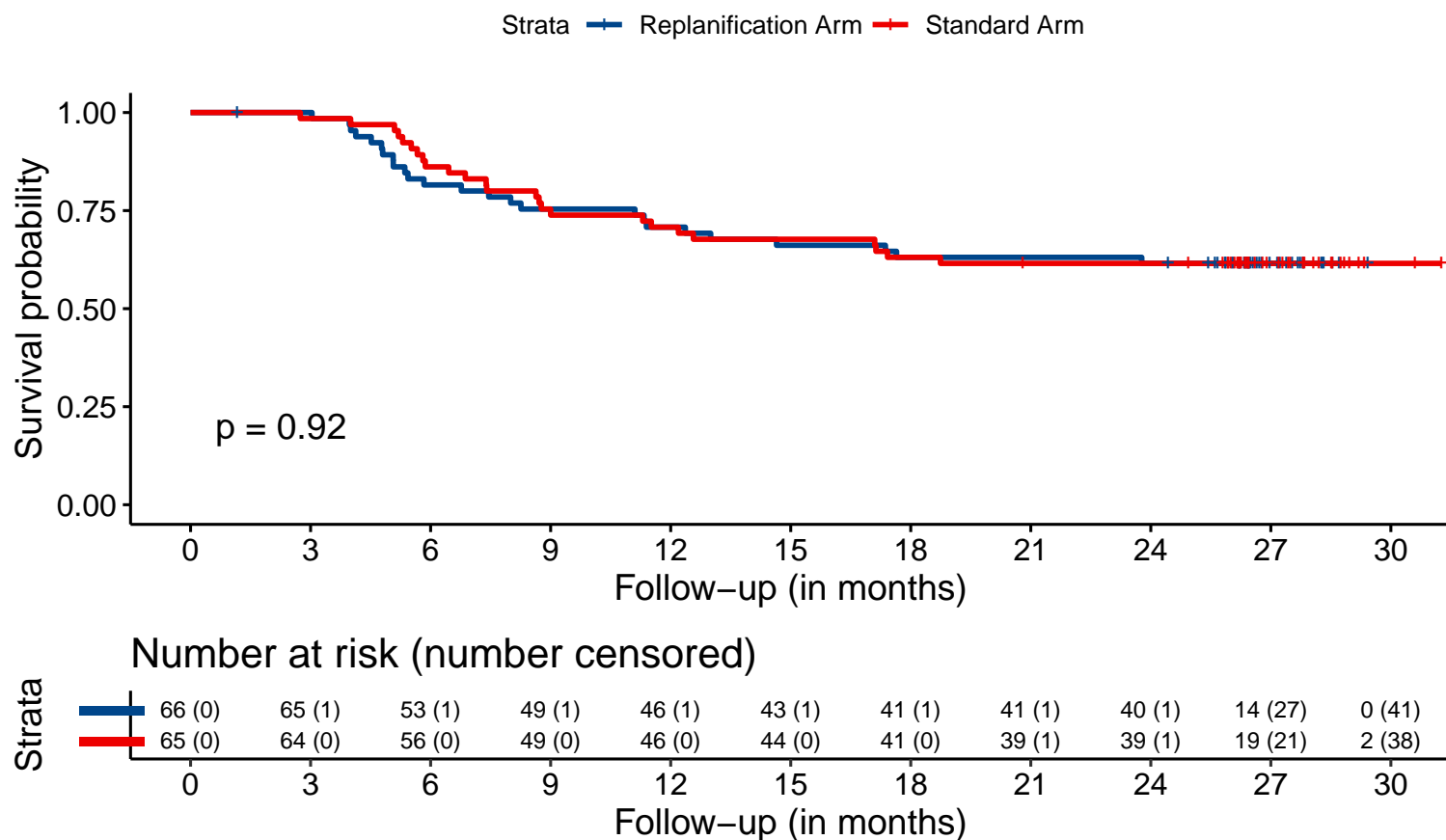
A: Overall survival



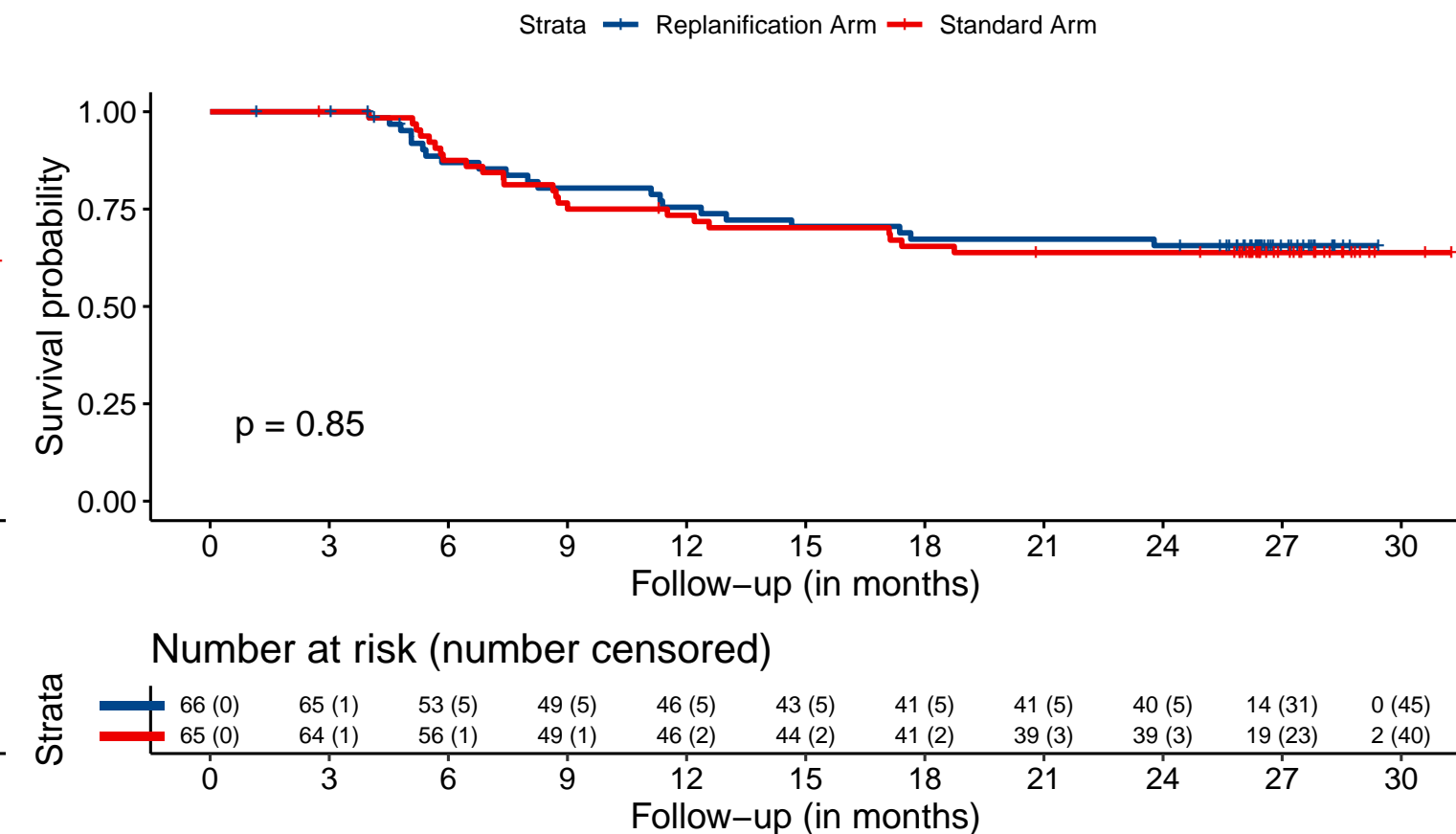
B: Cancer specific survival



C: Progression-free survival



D: Time to progression



Enrolment

Assessed for eligibility (n=137)

Excluded (n=5)

- Declined to participate (n=1)
- Not meeting eligible criteria (n=4)

Randomized (n=132)

Allocation

Experimental arm (n=67)

- Received allocated intervention (n=64)
- Received standard intervention (n=2)
- Not treated (n=1)

Standard arm (n=65)

- Received allocated intervention (n=65)
- Received experimental intervention (n=0)
- Not treated (n=0)

Follow-up

Lost to follow-up (n=0)

Discontinued intervention (n=35)

- Temporary interruption (n=32)
- Definitive interruption (n=3)

Lost to follow-up (n=0)

Discontinued intervention (n=34)

- Temporary interruption (n=34)
- Definitive interruption (n=0)

Analysis (ITT)

Analysed (n=66)

- Excluded from analysis (not treated n=1)

Analysed (n=65)

- Excluded from analysis (n=0)

Analysis (PP)

Analysed (n=61)

Excluded from analysis (n=5)

- Treatment start > 30 days after CT scan (n=2)
- Non-compliance with randomization (n=2)
- failure to meet eligibility criterion (n=1)

Analysed (n=63)

Excluded from analysis (n=2)

- Treatment start > 30 days after CT scan (n=2)

Table 1: Demographic and clinical data of the study population (ITT)

Characteristics	Replanning arm, N = 66¹	Standard arm, N = 65¹	p-value²
Patients			
Gender, male	57 (86.4%)	57 (87.7%)	>0.999
Age at inclusion (years)	60 (8) ³	60 (8) ³	0.825
OMS performance status			0.572
OMS = 0	27 (40.9%)	26 (40.0%)	
OMS = 1	34 (51.5%)	37 (56.9%)	
OMS = 2	5 (7.6%)	2 (3.1%)	
Tobacco smoking			0.755
Active smoker	23 (34.8%)	19 (29.2%)	
Former smoker	34 (51.5%)	38 (58.5%)	
Non smoker	9 (13.6%)	8 (12.3%)	
Number of pack-year	40 (23) ³	38 (21) ³	0.960
Ethylism			0.592
Yes	21 (31.8%)	20 (30.8%)	
Weaned	20 (30.3%)	25 (38.5%)	
No/Occasional	25 (37.9%)	20 (30.8%)	
Diabetes Mellitus			0.850
Insulino-dependent diabetes	2 (3.0%)	3 (4.6%)	
Non-insulin dependent diabetes	7 (10.6%)	5 (7.7%)	
No diabetes	57 (86.4%)	57 (87.7%)	
Clear Fair skin phototype, yes	21 (31.8%)	18 (27.7%)	0.703
Tumors			
Tumor histology			0.839
squamous cell carcinoma poorly differentiated	17 (27.0%)	15 (24.6%)	
squamous cell carcinoma well-differentiated	46 (73.0%)	46 (75.4%)	
p16 gene expression, positive	28 (43.1%)	27 (41.5%)	>0.999
Primary tumor localization			0.813
Base of the tongue (anterior wall)	15 (22.7%)	17 (26.2%)	
Pharynx (posterior wall)	1 (1.5%)	1 (1.5%)	
Several regions	38 (57.6%)	32 (49.2%)	
Tonsillar region (lateral wall)	12 (18.2%)	15 (23.1%)	
Tumor laterality			0.835
Bilateral	5 (7.6%)	3 (4.6%)	
Left	27 (40.9%)	29 (44.6%)	
Medial	7 (10.6%)	5 (7.7%)	
Right	27 (40.9%)	28 (43.1%)	
Largest diameter of the primary tumor (mm)	41 (13) ³	41 (15) ³	0.947
Lymph Nodes			0.064
Yes, homolateral	34 (51.5%)	36 (55.4%)	
Yes, contralateral	0 (0.0%)	4 (6.2%)	
Yes, bilateral	23 (34.8%)	13 (20.0%)	
No	9 (13.6%)	12 (18.5%)	
Conglomerate of lymph nodes, yes	17 (30.9%)	14 (26.9%)	0.676
Number of lymph nodes involved (if no conglomerate)	2.97 (1.78) ³	2.39 (1.05) ³	0.227
N Stage			0.931
N0	9 (13.6%)	12 (18.5%)	
N1	5 (7.6%)	5 (7.7%)	
N2a	1 (1.5%)	0 (0.0%)	
N2b	28 (42.4%)	29 (44.6%)	
N2c	20 (30.3%)	17 (26.2%)	
N3	3 (4.5%)	2 (3.1%)	
AJCC tumor staging			0.630
Stage III	17 (25.8%)	19 (29.2%)	
Stage IVa	43 (65.2%)	43 (66.2%)	
Stage IVb	6 (9.1%)	3 (4.6%)	

¹n (%); ²Fisher's exact test; Wilcoxon rank sum test; ³Mean (SD)

Table 2: Treatment characteristics of the patient groups (ITT)

Characteristics	Replanning arm, N = 66 ¹	Standard arm, N = 65 ¹	P-value ²
Type of chemotherapy			0.430
ARCORO (5Fu carboplatin)	9 (13.6%)	9 (13.8%)	
CDDP	42 (63.6%)	47 (72.3%)	
Cetuximab	15 (22.7%)	9 (13.8%)	
IMRT Modality, by tomotherapy (vs arc therapy)	17 (25.8%)	16 (24.6%)	>0.999
Number of CT scans (including initial planning - CT0)			<0.001
1	2 (3.0%)	58 (89.2%)	
2	2 (3.0%)	7 (10.8%)	
6	51 (77.3%)	0 (0.0%)	
7	11 (16.7%)	0 (0.0%)	
Patients with at least 35 cycles of radiotherapy	63 (95.5%)	65 (100.0%)	0.244
Interruption of treatment			0.295
No	33 (50.0%)	32 (49.2%)	
Yes, definitive	3 (4.5%)	0 (0.0%)	
Yes, temporary	30 (45.5%)	33 (50.8%)	
Overall time of radiotherapy (in days)	50.4 (8.6)	51.6 (4.3)	0.808
Reason of interruptions			0.362
Not related to toxicity	22 (33.3%)	27 (41.5%)	
Toxicity	11 (16.7%)	6 (9.2%)	
No interruption	33 (50.0%)	32 (49.2%)	

¹n (%); Mean (SD)²Fisher's exact test; Wilcoxon rank sum test

Interruption is defined as at least one day