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Original Article

# Comparing adaptive and dose redistributed radiotherapy to conventional radiotherapy in head and neck cancer – Quality of life results from the phase III ARTFORCE trial

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ABSTRACT

*Purpose:* This study compared patient-reported quality of life (QoL) between patients with head and neck cancer treated with either FDG/PET-guided dose redistribution with scheduled treatment adaptation (rRT) or conventional radiotherapy (cRT).
*Methods:* QoL outcomes were assessed at baseline, directly after radiotherapy and at 6-month, 1-, 2-, and 5-year follow up using the EORTC QLQ C30, EORTC QLQ HN35 and EQ-5D-5L. Linear mixed-effects models (LMMs) were used for longitudinal analysis including fixed effects for baseline QoL scores, trial arm, time, an interaction term between trial arm and time and random effects for patients.
*Results:* 142 out of 221 patients (64 %) filled out at least one QoL questionnaire and were included for analysis. QoL was overall comparable between trial arms, with exception of a significant increase in sticky saliva complaints at 1 year and decreased global health status at 2 years in cRT compared to rRT. In the majority of the other LMMs, patients' QoL was significantly associated with their baseline QoL values and initial QoL deterioration observed after treatment was followed by improvement throughout follow up.
*Conclusions:* In line with the primary results of the trial (ARTFORCE, NCT01504815), dose redistribution combined with scheduled treatment adaptation showed comparable QoL outcome to conventional radiotherapy. Overall, QoL was mostly determined by patients' individual baseline QoL and improved at 6 months of follow up. These results confirm that this dose redistribution strategy is a safe strategy to increase dose to tumor subregions.

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## Introduction

Late toxicities after radiation therapy for head and neck cancer can be invalidating as they may affect speech, breathing and swallowing domains. Predicting accurately which patients will develop late toxicities is challenging as it depends on various factors including the dose on organs at risk, location of tumor, age, smoking habits and concurrent systemic treatment. [1] Strategies to decrease dose to healthy tissue, such as IMRT, [2] margin reduction [3], dose de-escalation in p16-positive tumors [4] and sentinel node procedures [5] have successfully decreased toxicity. However, dose reduction strategies are limited by the risk of compromising disease control.

In current clinical practice, most head and neck tumors are treated uniformly with a homogeneous dose regardless of radiosensitivity or tumor cell density. Under this approach, the rate of locoregional recurrence in patients with locally advanced head and neck cancer is approximately 40 %. [6] This implies that in conventional treatment, a portion of patients remain inadequately treated, while the majority of patients might currently be subjected to overtreatment. Dose painting is an approach that has emerged as radiotherapy techniques have become more precise in delivering dose. By targetting tumor subvolumes which are more likely to recur, dose painting has the potential to enhance disease control, while maintaining toxicity. Several imaging biomarkers have been investigated to pinpoint high risk tumor subvolumes. To date, FDG-PET is most frequently used in clinical trials evaluating dose painting. [7,8].

A few trials investigated dose painting strategies with varying results in terms of treatment safety and toxicity, compared to conventional treatment [9–13] This appears largely dependent on the maximum dose given. [14] Although the primary objective of these trials was to improve local control by increasing dose at biomarker-defined tumor subvolumes, more recent trials actively incorporated dose painting strategies reducing dose to low-risk target areas to simultaneously limit toxicity. [9,15] These studies were promising in terms of toxicity, but have yet to be confirmed in a non-inferiority setting.

Dose painting trials have mainly reported physician-rated outcomes. However, patient-reported outcomes, such as quality of life (QoL), do not always correspond to physician-scored toxicities as these are also dependant on patients' context. [16] Also, QoL questionnaires evaluate social-economic and emotional domains that are not scored by physicians. Lastly, QoL has shown to provide prognostic information by showing poorer survival outcomes in patients with low QoL scores at baseline or degrading QoL after treatment. [17,18,19] For all these reasons, it is important to evaluate both physician- and patient-reported outcomes.

The aim of this study is therefore to investigate differences in patient-reported quality of life (QoL) in patients randomized between treatment with a homogeneous dose distribution and treatment with a FDG-PET-guided dose painting strategy. These investigations will provide further insight on toxicity profiles and tolerability between dose distribution strategies.

**Table 1**
Baseline characteristics of patients with at least one Quality of Life form after treatment compared to patients without forms.

| Characteristics | ≥1 form filled out ($N = 117$) | No forms ($N = 104$) | P-value |
|---|---|---|---|
| **Sex, N (%)** | | | |
| Female | 34 (29 %) | 19 (18 %) | 0.06 |
| Male | 83 (71 %) | 85 (82 %) | |
| **Age (years)** | | | |
| Median (SD) | 58 (± 7.2) | 58 (± 8.0) | 0.50 |
| **BMI (kg/m$^3$)** | | | |
| Median (range) | 25 (± 5.1) | 25 (± 5.3) | 0.44 |
| **WHO, No (%)** | | | |
| 0 | 64 (55 %) | 69 (66 %) | 0.06 |
| 1 | 53 (45 %) | 34 (33 %) | |
| Missing | 0 (0 %) | 1 (1 %) | |
| **Smoking habits, N (%)** | | | |
| non-smoker | 44 (38 %) | 43 (41 %) | 0.72 |
| ex-smoker | 16 (14 %) | 16 (15 %) | |
| smoker | 57 (49 %) | 45 (43 %) | |
| **Tumor site, N (%)** | | | |
| Hypopharynx | 17 (15 %) | 5 (5 %) | ≤0.01 |
| Oral Cavity | 14 (12 %) | 38 (37 %) | |
| Oropharynx, HPV- | 33 (28 %) | 30 (29 %) | |
| Oropharynx, HPV+ | 53 (45 %) | 30 (29 %) | |
| Oropharynx, HPV unknown | 0 (0 %) | 1 (1 %) | |
| **Tumor volume, N (%)** | | | |
| <30 cc | 74 (63 %) | 56 (54 %) | 0.16 |
| ≥30 cc | 43 (37 %) | 48 (46 %) | |
| **AJCC stage, No (%)** | | | |
| III | 40 (34 %) | 32 (31 %) | 0.59 |
| IV | 77 (66 %) | 72 (69 %) | |
| **T-stage, N (%)** | | | |
| T3 | 45 (38 %) | 33 (32 %) | 0.30 |
| T4 | 72 (62 %) | 71 (68 %) | |
| **N-stage, N (%)** | | | |
| N0-1 | 38 (32 %) | 25 (24 %) | 0.17 |
| ≥N2 | 79 (68 %) | 79 (76 %) | |
| **Chemotherapy, N (%)** | | | |
| Cetuximab | 11 (9 %) | 4 (4 %) | 0.16 |
| Cisplatinum | 106 (91 %) | 100 (96 %) | |
| **Institute** | | | |
| Institute 1 | 40 (34 %) | 7 (7 %) | ≤0.01 |
| Institute 2 | 14 (12 %) | 2 (2 %) | |
| Institute 3 | 4 (3 %) | 0 (0 %) | |
| Institute 4 | 3 (3 %) | 3 (3 %) | |
| Institute 5 | 28 (24 %) | 3 (3 %) | |
| Institute 6 | 3 (3 %) | 0 (0 %) | |
| Institute 7 | 14 (12 %) | 4 (4 %) | |
| Institute 8 | 11 (9 %) | 46 (44 %) | |
| Institute 9 | 0 (0 %) | 39 (38 %) | |
| **Trial arm** | | | 0.73 |
| Adaptive & dose redistributed | 59 (50 %) | 50 (48 %) | |
| Conventional radiotherapy | 58 (50 %) | 54 (52 %) | |

## Methods and materials

### *Patients and treatment*

This study was conducted among 221 patients diagnosed with locally advanced head and neck squamous cell carcinoma (LAHNSCC) who were treated within a prospective phase III clinical trial (NCT01504815) at one of nine participating European institutes. The primary objective of this study was to evaluate if patients who were diagnosed with T3-4, N0-3b, M0 disease and were treated with definitive chemoradiation had comparable QoL regardless of radiation dose distribution strategy. Patients randomized to the experimental arm (rRT) received an FDG-PET-guided dose redistribution to the PTVp, ranging between 64 and 84 Gy, and scheduled adaptation within the third week of treatment. In the conventional arm, a homogeneous dose of 70 Gy was targeted at the PTVp. Pathological lymph nodes and elective fields were treated the same in both arms. Radiotherapy in both arms was delivered in 35 fractions by simultaneous integrated boost over a course of seven weeks. Patients in both arms were treated with 3 cycles of cisplatinum (100 mg/m$^2$ on days 1, 22 and 43 of treatment). An elaborate description of the trial protocol and the primary results of the trial were published previously. [15,20].

### *Quality of life*

QoL questionnaires were prospectively collected at baseline, directly after treatment, at 6 months of follow up and at 1-, 2-, and 5-years of follow up. Local principal investigators were responsible for conducting questionnaires. The questionnaires were collected by paper and digitized by a local data manager at the institute. The validated questionnaires used were the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30),

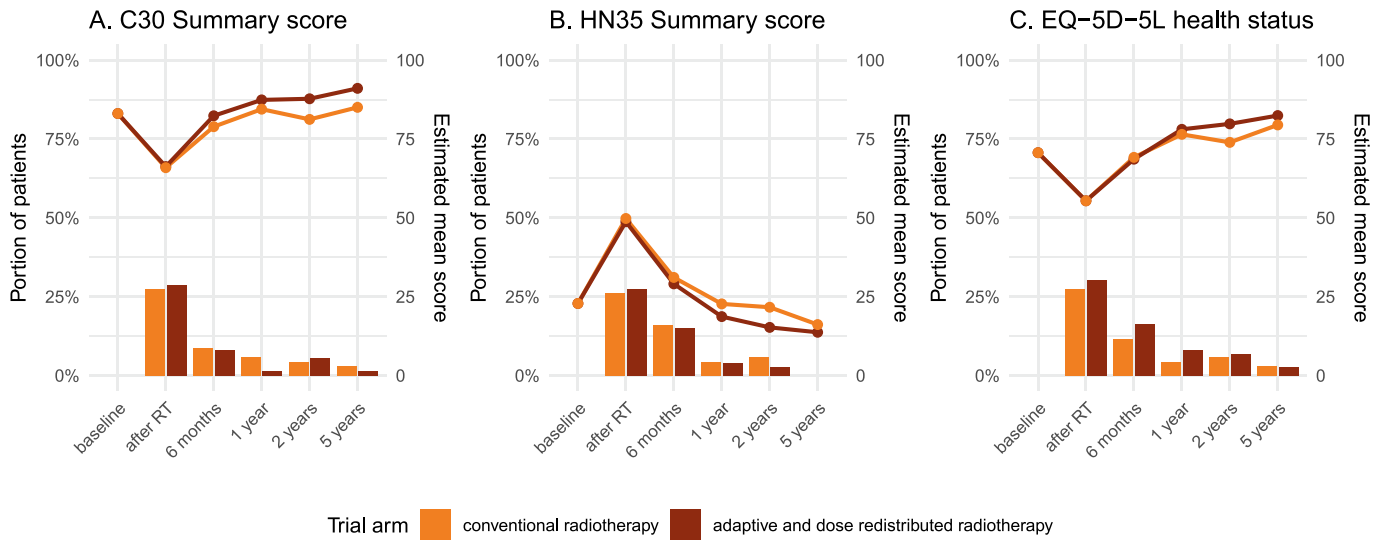


**Fig. 1.** Portion of patients with a ≥ 10 point deterioration (left y-axis, bars) and mean fitted scores (right y-axis, lines) of the Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) Core 30 (C30), mean summary scores of the EORTC QLQ Head and Neck (HN35) and the mean health score of the EuroQoL 5 Dimensions and 5 Levels (EQ-5D-5L).

EORTC QLQ Head and Neck (HN35) and EuroQoL 5 Dimensions and 5 Levels (EQ-5D-5L). Questionnaire scores were post-processed according to the questionnaire manuals. Post-processing of the EORTC questionnaires resulted in a score ranging within 0 to 100 per scale. Whereas the HN35 consists of symptom scales only, where an increased score translates into increased complaints, the QLQ-C30 questionnaire consists of both symptom and functional scales. In contrast to symptom scales, a higher functional scores translate to superior functionality. The EQ-5D-5L questionnaire consists of five dimension scales ranging from 1 to 5 where increased scores correlate to poorer functionality. The last question in the EQ-5D-5L contains a visual analogue scale, ranging from 0 to 100, which represents patient-reported perceived health. In this scale, higher scores correspond to better patient-reported health.

*Statistical analysis*

All patients who had at least one QoL form filled out were included in the analyses. Differences in baseline characteristics were evaluated between patients who did and did not have at least one filled out QoL form after treatment in order to evaluate predictors of missing data using chi-square tests. To further assess correlations among characteristics associated with missing data, we conducted Cramer V's and chi-square tests. Locoregional control and late radiation-related toxicity-free interval was compared between patients with and without at least one filled out QoL form to evaluate potential source of missing data. To evaluate the effect of radiotherapy strategy on QoL scores while accounting for missing data, linear mixed effects models (LMMs) were used with fixed effects for baseline QoL, time, radiotherapy and an interaction between time and radiotherapy strategy and with random effects for patients. For patients with missing baseline QoL, but available follow up QoL, simple mean imputation of baseline QoL was performed as mean imputation is an unbiased method for missing baseline values in randomized trials. Akaike Information Criterion (AIC) was used to assess whether incorporating baseline characteristics associated with missingness of QoL data as covariates would improve the LMMs. Differences in QoL between trial arms were evaluated using the P-value from the interaction term between time and radiotherapy strategy. The LMMs were further used to estimate mean QoL scores. Additionally, portions of patients with a ≥ 10 point deterioration compared to baseline were plotted. Benjamini-Hochberg (BH) method was used to account for multiple testing.

## Results

Out of the 221 patients of the study cohort, 142 (64 %) had completed at least one QoL form at baseline and/or after treatment, with 117 (53 %) of them completing forms specifically after treatment. Patients with QoL forms after treatment were evenly split between both arms (50 % both arms, P = 0.73, Table 1), but varied significantly between institutes where patients were treated at (median 85 %, min–max 0–100 %, P≤.01) and between anatomical primary tumor locations. This suggests that missingness of QoL data after treatment was independent of trial arm but dependent of institute and tumor location. Among patients without QoL forms, oral cavity tumors were significantly more common than HPV-positive oropharynx tumors among patients without QoL forms. There was, however, some collinearity between tumor site prevalence and the institute where patients were treated at (Cramer V's 0.30, P ≤ 0.01). Poorer locoregional control (LRC; hazard ratio (HR) 3.14 95 % confidence interval (CI) (1.71–5.75), P ≤ 0.01), late radiation-related toxicity-free interval rates (TFI; 2.38 (1.28–4.42), P = 0.01) and overall survival (OS; 1.74 (1.10–2.76), P = 0.02) were seen in patients without forms after treatment. After correcting for institute, these trends disappeared for TFI (1.70 (0.97–2.98), P = 0.07), LRC (corrected HR 1.76 (0.76–4.06), P = 0.18) and OS (1.39 (0.69–2.77), P = 0.36).

Mean summary scores of the C30 and HN35 questionnaires and the visual analogue scale of the EQ-5D-5L questionnaire are presented in Fig. 1. A clear time pattern can be seen in all three scales as scores were worst after radiotherapy, but improved during follow up. The LMMs showed significant improvement of QoL with time in all three scales, but no significant interaction (Supplement 1–3, unadjusted P ≥ 0.16) was found between time and trial arms. This indicates that trial arm did not influence QoL after treatment. Adding tumor site or institute as covariates did not improve LMMs performance and were therefore excluded in further analyses within the subdomains.

A p-value of < 0.02 was considered statistically significant after applying the Benjamini-Hochberg correction. Within the QoL questionnaire subdomains, significant increase in sticky saliva complaints at 1 year and decreased global health status at 2 years was seen in patients treated with cRT compared to rRT. The estimated mean scores are presented in Figs. 2-4 and Supplement 1–3. The LMMs further revealed that baseline scores were generally strong predictors of follow up scores for the individual scales. The only scales without any association with either baseline scores or time were C30 insomnia and HN35 weight gain. Scales that only showed significant association with baseline values, but


**Fig. 2.** Portion of patients with a ≥ 10 point deterioration (left y-axis, bars) and mean scores (right y-axis, lines) of the Treatment of Cancer Quality of Life Questionnaire Core 30 symptom scales (A) and functional scales (B).

did not significantly change over time included C30 financial difficulties and emotional functioning, HN35 dental health, and EQ-5D-5L mobility and anxiety. All scales that showed significant deterioration directly after treatment improved during follow up. In case of a symptom scale, this meant a negative trend, whereas in functional scales, this trend was positive.

The highest EORTC symptom scales (Figs. 2-3, Supplement 1–2) were observed immediately after completing radiotherapy. Pain killer use, use of nutritional supplements, and sticky saliva were scored worst. The estimated mean of the use of painkillers and nutritional supplements was 89.5 (95 %CI 77.7–100.0) and 66.9 (54.6–79.1), respectively, in the experimental arm and 92.3 (80.3–100.0) and 72.5 (60.0–85.0) in the control arm (adjusted P = 0.85, P = 0.70, resp.). Estimated mean scores for sticky saliva were 74.9 (66.3–83.6) in the experimental arm and 67.3 (58.5–76.0) in the control arm (P = 0.39).

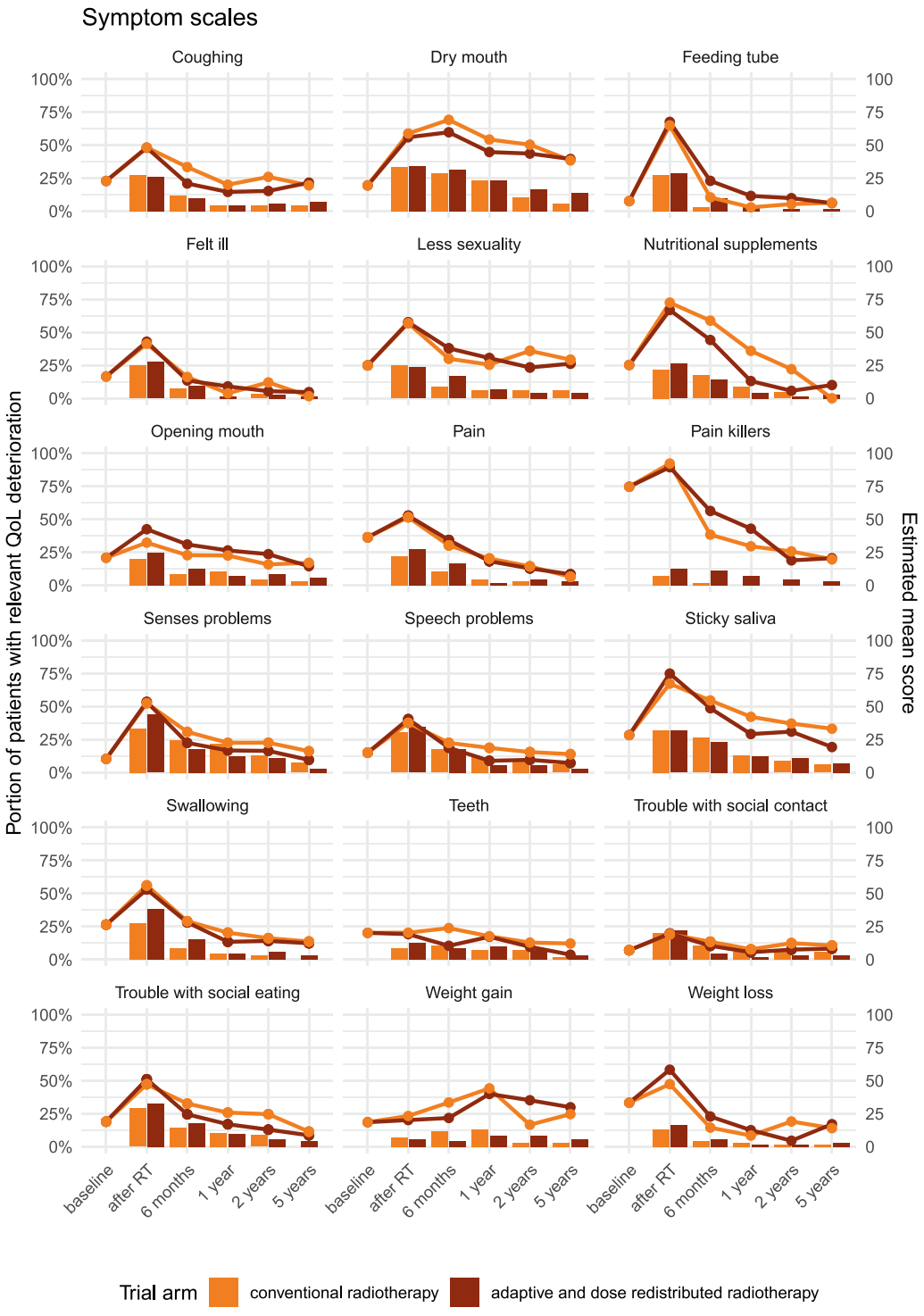


**Fig. 3.** Portion of patients with a ≥ 10 point deterioration (left y-axis, bars) and mean symptom scores (right y-axis, lines) of the Treatment of Cancer Quality of Life Questionnaire Head and Neck (HN35) symptom scales.

## Discussion

This study presents the quality of life (QoL) results of a randomized phase III trial comparing adaptive and dose redistributed radiotherapy techniques (rRT) to conventional radiotherapy (cRT) in patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC). QoL scores were very comparable between radiotherapy techniques, except for an increase in sticky saliva complaints at 1 year and decreased global health status at 2 years with cRT compared to rRT. These results are in line with previously reported primary results of the trial, as toxicity prevalence and incidence rates were similar between trial arms, with exception for a significant increased grade ≥ 3 pharyngolaryngeal stenoses incidence rate in the rRT arm (0 versus 4 %, P = 0.05). [15] Although small toxicity differences are not likely to translate in QOL differences, we believe that this QOL analysis supports the further development of rRT as a strategy to increase dose to tumor subregions of interest.

The questionnaires were collected before, shortly after radiotherapy

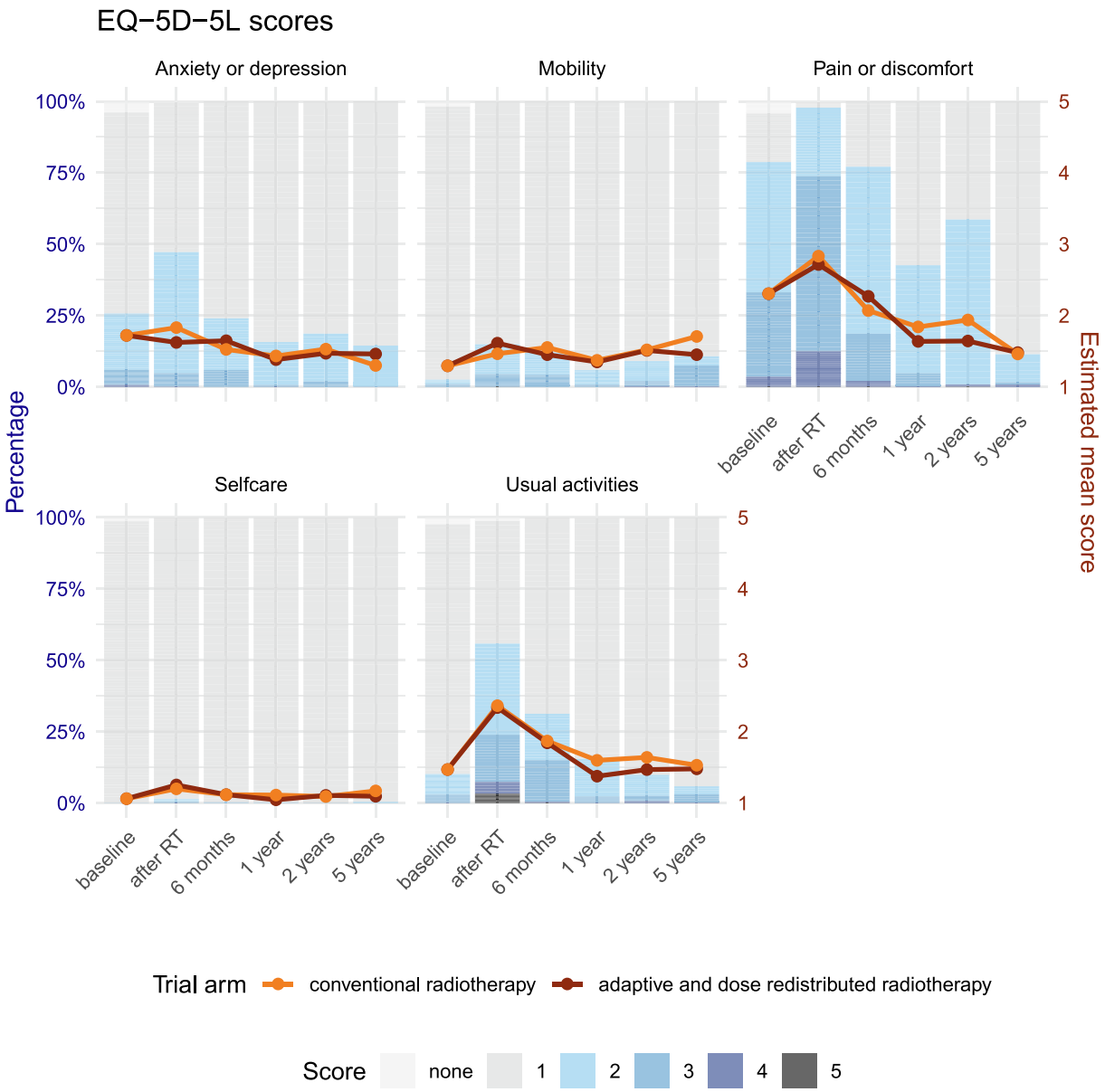


**Fig. 4.** Portion of patients with the individual EuroQoL 5 Dimensions and 5 Levels (EQ-5D-5L) scores (left y-axis, blue bars) and mean EQ-5D-5L scores between trial arms (right y-axis, red and orange lines). A score of 1 represents no complaints, whereas a score of 5 represents complete disability or extreme complaints.

and on multiple occasions during follow up. Similar to previously reported studies on quality of life in patients treated with radiotherapy, a significant deterioration of QoL shortly after treatment was found in the majority of the QoL scales that corresponds to the development of toxicities caused by treatment. [21,22] This deterioration is reflected in both a decrease in functionality and an increase in symptom QoL scales. Comparing these early QoL results with other QoL studies is challenging, not only due to confounding socio-economic and comorbidity factors [23,24], but also due to differences in disease characteristics. [22,24,25] Also, since this study was primarily designed to evaluate QoL after treatment, no QoL forms were gathered during treatment, which complicates the evaluation of QoL differences between trial arms during treatment.

After treatment, QoL generally slowly recovered during follow up and sometimes even seemed to exceed their initial baseline value. This pattern of recovery, where QoL scores exceed baseline values, is a common phenomenon in QoL research and is called the response shift effect. This effect is often explained by the change in patient's standards, values and definition of QoL during their diagnosis and treatment. [26] However, it is also important to consider survivorship bias influencing these findings. We found no significant association between missing data and survival or disease control after adjusting for treating institute (the main source of missing data). Nonetheless, these outcomes are likely to have contributed to missing data and may have influenced the results. Moreover, the trend of increased physician-rated toxicity in patients with missing QoL could have led to an overestimation of QoL estimates. Even so, given the consistently similar outcome [15], missing data and QoL patterns between trial arms, we presume minimal differences in QoL between trial arms.

This study prospectively collected QoL data to evaluate differences between trial arms. Although minor differences between trial arms were observed, we did find a consistent correlation between QoL scores after treatment and patients' baseline QoL scores for the majority of scores. These results are in line with previous studies showing the prognostic value of baseline QoL scores. [22,24] The prognostic value of QoL scores has prompted multiple investigations into applications of patient-reported outcomes. Studies investigating active patient-reported symptom monitoring concluded that active monitoring improved survival

with a hazard ratio of 0.48–0.83 [27,28] In follow up of these studies, the randomized trial (NCT03086629) is currently investigating whether integrating QoL scoring in the shared decision making and disease monitoring processes using guidance tools will improve QoL in head and neck cancer patients. [29] Furthermore, recent radiation dose–effect models have incorporated baseline symptom values as prognostic factors to guide treatment planning by toxicity risk profiling. [30] All in all, these studies further signify the potential of personalized treatment and shared decision making with use of QoL evaluations.

The main limitation of this study was the high rate of missing data, which appeared to be institute specific. Paper questionnaires and limited centralization across participating institutes in different countries made consistent data collection challenging. Future trials could benefit from electronic and centralized data collection. We also observed a difference in anatomical subtypes between patients with and without QoL forms, which may be related to variations in subtype prevalence across institutes. There is an underrepresentation of patients with oral cavity tumors and overrepresentation of patients with HPV-positive oropharynx tumors in this study compared to the total study cohort. However, since both missing and observed data were equally distributed between trial arms at baseline and after treatment, we believe that the impact of this potential confounder on the conclusion of this study is minimal and that the significant amount of missing data is the main limitation of this study.

In conclusion, similar QoL trends were observed between LAHNSCC patients treated with conventional and adaptive dose redistributed radiotherapy. QoL after treatment was mostly determined by baseline QoL and improved in time. Although previous research mainly focussed on evaluating QoL after completing treatment and follow up, future studies should focus on using QoL evaluations prospectively for shared decision making and disease monitoring to ultimately improve QoL.

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## CRediT authorship contribution statement

**Anna Liza M.P. de Leeuw:** Writing – original draft, Methodology, Formal analysis. **Frank J.P. Hoebers:** Writing – review & editing, Investigation. **MD Jordi Giralt:** Writing – review & editing, Investigation. **Yungan Tao:** Writing – review & editing, Investigation. **Chris H.J. Terhaard:** Writing – review & editing, Funding acquisition. **Lip Wai Lee:** Writing – review & editing, Investigation. **Signe Friesland:** Writing – review & editing, Investigation. **Roel J.H.M. Steenbakkers:** Writing – review & editing, Investigation. **Lisa Tans:** Writing – review & editing, Investigation. **Mutamba T. Kayembe:** Writing – review & editing, Methodology. **Simon R van Kranen:** Writing – review & editing, Supervision. **Harry Bartelink:** Writing – review & editing, Supervision. **Coen R.N Rasch:** Writing – review & editing, Supervision. **Jan-Jakob Sonke:** Writing – review & editing, Supervision. **Olga Hamming-Vrieze:** Writing – review & editing, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.111044.

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