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Original Article

Randomized controlled trial to identify the optimal radiotherapy scheme for palliative treatment of incurable head and neck squamous cell carcinoma

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ABSTRACT

Background: No randomized controlled trials (RCT) have yet identified the optimal palliative radiotherapy scheme in patients with incurable head and neck squamous cell carcinoma (HNSCC). We conducted RCT to compare two radiation schemes in terms of efficacy, toxicity and quality-of-life (QoL).

Materials and methods: Patients with locally-advanced HNSCC who were ineligible for radical treatment and those with limited metastatic disease were randomly assigned in 1:1 ratio to arm 1 (36 Gy in 6 fractions, twice a week) or arm 2 (50 Gy in 16 fractions, four times a week).

Results: The trial was discontinued early because of slow accrual (34 patients enrolled). Objective response rates were 38.9% and 57.1% for arm 1 and 2 respectively ($p = 0.476$). The median time to loco-regional progression was not reached. The loco-regional control rates at 1 year was 57.4% and 69.3% in arm 1 and 2 ($p = 0.450$, HR = 0.56, 95%CI 0.12–2.58). One-year overall survival was 33.3% and 57.1%, with medians of 35.4 and 59.5 weeks, respectively ($p = 0.215$, HR = 0.55, 95%CI 0.21–1.43). Acute grade ≥ 3 toxicity was lower in arm 1 (16.7% versus 57.1%, $p = 0.027$), with the largest difference in grade 3 mucositis (5.6% versus 42.9%, $p = 0.027$). However, no significant deterioration in any of the patient-reported QoL-scales was found.

Conclusion: No solid conclusion could be made on this incomplete study which is closed early. Long-course radiotherapy did not show significantly better oncologic outcomes, but was associated with more acute grade 3 mucositis. No meaningful differences in QoL-scores were found. Therefore, the shorter schedule might be carefully advocated. However, this recommendation should be interpreted with great caution because of the inadequate statistical power.

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A substantial proportion of patients with advanced-stage head and neck squamous cell carcinoma (HNSCC) are unsuitable for radical treatment with surgery or (chemo)radiotherapy [1,2] because of very advanced loco-regional disease, significant comorbidities, poor performance status, distant metastatic disease or any combination of these factors. Patients with untreated advanced HNSCC have a median survival of approximately 100 days [3]. However, this group of patients still requires some form of treatment to control their loco-regional disease and to alleviate their troublesome

symptoms. Although palliative radiotherapy is one of the commonly used options, there is a lack of randomized controlled trials (RCT) or high-level prospective studies on the optimal radiation dose and fractionation schemes in patients with incurable HNSCC. Also the impact of these treatment schedules on quality-of-life (QoL) of these patients with relatively short life expectancy is relatively unknown. Considerations for an optimal palliative radiotherapy schedule are: significant tumor regression and symptom control within as short as possible overall treatment time (OTT) with minimal side-effects and deterioration of QoL. The recently published critical review by Grewal et al. [4] illustrates the lack of high-level of evidence to support one or another radiation scheme. The review included 21 studies (mostly retrospective)

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with a total of 1590 patients treated with 4 different radiation techniques and 15 different radiation schemes with OTT ranging from 1 week to the conventional course of 7 weeks and biological equivalent dose (BED) ranging from 23 to 70 Gy (on average 40 Gy). The overall response rate (ORR) ranges between 45% and 100% and median survival time ranges from 3 to 17 months (on average 6 months). These equivocal results highlight the urgent need for a RCT to identify the optimal radiation scheme for these patients. Therefore, we initiated a multicenter prospective RCT to compare a short-course with a relatively long-course of radiation.

Materials and methods

Study design and participants

We undertook a phase III RCT (ClinicalTrials.gov Identifier NCT02421458) at six radiotherapy centers in the Netherlands (recruitment between February 10, 2016, and December 21, 2017). Eligible patients had histologically confirmed locally-advanced non-metastatic HNSCC located in the oropharynx, larynx (except T1 glottic), and hypopharynx not suitable for radical treatment with surgery or (chemo)radiotherapy. Newly diagnosed patients with primary HNSCC with limited metastatic disease (maximum 3 metastases) in a good general condition were also eligible. Patients had WHO performance status 0–2 and signed written informed consent before inclusion. Exclusion criteria were surgery or chemotherapy for HNSCC before inclusion, previous head or neck radiotherapy, or head and neck malignancies arising from the skin, nose, paranasal sinuses, nasopharynx, salivary glands, thyroid gland or esophagus. The use of other concomitant anti-cancer therapy was not allowed during study treatment. The trial was sponsored by the Dutch Cancer Society. The study was approved by the local research ethics committee (Medical Research Ethics Committee of the Netherlands Cancer Institute/Antoni van Leeuwenhoek: NL 52512.031.15) and endorsed by the other participating centers. Patients were randomly assigned in 1:1 ratio, using a minimization technique as implemented in the registration system TENALEA®, to arm 1 (short-course of radiotherapy, 6 fractions of 6 Gy, twice a week, total dose of 36 Gy during 3 weeks) or arm 2 (long-course of radiotherapy, 16 fractions of 3.125 Gy, four times a week, total dose of 50 Gy in 4 weeks). Stratification factors were M–status (M0 vs. M1), WHO performance status (WHO 0–1 vs. 2), ACE-27 score (0–2 vs. 3), and AJCC stage (I–III vs. IV).

Radiotherapy

Patients were immobilized in supine treatment position in a custom-made head and neck mask. A planning CT-scan, with a maximum of 3-mm slice thickness, was performed. The radiation oncologist delineated the Gross Tumor Volume of the primary tumor and/or lymph nodes (GTV) according to current practice on CT-images, modulated by the findings on clinical examination and the co-registered images of FDG-PET and MRI (when available). No elective neck levels were delineated. Subsequently, 10 mm isotropic margin was added to generate the Clinical Target Volume (CTV) and modified for anatomical structures that were not involved (bone/air). A three to 5 mm margin was then added to the CTV to generate the Planning Target Volume (PTV). Patients were treated with highly-conformal radiation techniques such as intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) in order to minimize the radiation-related toxicities.

Toxicity and follow-up

Treatment side-effects were determined using Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [5]. Toxicity was assessed weekly during treatment, and at each follow-up visit, by the treating radiation oncologist. A distinction was made between acute (onset within 8 weeks after last fraction of radiotherapy) and late (onset ≥ 8 weeks after last fraction of radiotherapy) toxicity. Health-related QOL (HRQOL) was measured at baseline, and 3, 6, 9, 12, 18, and 24 months after treatment, using the European Organization for Research and Treatment of Cancer Quality-of-Life-Questionnaire-C30 (EORTC QLQ-C30) and Quality-of-Life-Questionnaire-Head and Neck 35 (EORTC QLQ-HN35) [6]. HRQOL subscales were calculated according to published EORTC guidelines [7]. The EuroQoL-5 dimensions Questionnaire (EQ-5D-5L) was collected at baseline, weekly during treatment and at 3, 6, 9, 12, 18, and 24 months after treatment.

The response evaluation was done by the head and neck surgeon or the radiation oncologist by clinical examination including flexible endoscopy at 12 weeks. MRI and/or CT scan was only performed if there was any suspicion of disease progression (optional). Hereafter, follow-up visits were scheduled every 3 months during the first 2 years. From the third year onwards, patients were seen according to the Dutch guidelines for follow-up of patients with HNSCC, twice annually until 5 years of follow-up.

Study endpoints

The primary endpoint of this study was the time to loco-regional progression. Secondary endpoints included treatment compliance, incidence of $\geq$ grade 2 acute and late toxicity, HRQOL, the overall response rate (ORR: CR = complete response and PR = partial response), loco-regional control (LRC), progression-free survival (PFS), and overall survival (OS).

Sample size calculation

We assumed that the time to loco-regional progression of the long-course would be at least 10 weeks (2.5 months) longer compared with the short-course radiotherapy (HR = 0.706). With these assumptions, a sample size of 139 patients per treatment arm (number of events required: 258) would achieve a power of 80% at a 5% two-sided significance level. To allow for dropouts because of ineligibility and withdrawal of patients, the total planned sample size was 300 subjects.

Statistical analysis

The analysis was based on a modified intention-to-treat population, comprising all randomized patients who received at least one fraction of radiotherapy. This is because leaving patients without treatment in the analysis would invalidate the interpretation of the results as indicating that there was no difference between the treatment arms.

CR was scored in case of complete disappearance of the primary tumor and the involved node(s) by clinical examination and on MRI and/or CT scan (when available). Any response less than CR was scored as PR. Time to loco-regional progression (the primary endpoint) was calculated from randomization to local progression, regional progression, or loco-regional progression. Patients with distant progression or death as first events were censored as well as patients without any event at last follow-up. OS was calculated from the date of randomization to death from any cause, censoring patients who were still alive at last follow-up. PFS was calculated

from the date of randomization to death from any cause or date of first progression (local, regional, loco-regional, or distant), whichever occurred first. Patients who were still alive and did not encounter any progression were censored at last follow-up. The Kaplan-Meier method was used to estimate the time-to-event endpoints (oncological outcomes). For comparing the treatment arms on the time-to-event endpoints, the log-rank test and the Cox model (to estimate hazard ratios (HR)) were used. Both the log-rank test as well as the Cox model were adjusted for the stratification factors at randomization. QoL-scales were analyzed with mixed effects regression models with time in days since randomization as continuous variable, treatment arm and its interaction with time as explanatory variables and a random intercept per patient. Fisher's exact test was used to assess the difference between the two treatment arms on categorical variables (ORR, treatment compliance and toxicity). *P*-values less than 0.05 were considered statistically significant in the analysis of efficacy endpoints. For conducting the analyses, the statistical software SAS 9.4 and R version 3.6.1 were used.

Results

Patients' characteristics are shown in Table 1. In patients with oropharyngeal cancer ($n = 11$), 6 patients were HPV-positive (3 in each arm) and 4 were HPV-negative (2 in each arm) and in one patient HPV-status was not investigated. Of the whole group, only two patient never smoked, 12 patients was stopped smoking (>1 year before diagnosis) and 18 patients were still smoking at presentation. These figures were equally distributed between both arms. Fig. 1 shows the trial flow chart. The trial was discontinued early because of slow accrual. Thirty-four patients were randomized, 18 in arm 1 and 16 in arm 2. Two patients in arm 2 refused the palliative radiotherapy after randomization and were excluded from analysis. Five patients didn't complete the intended course of palliative radiotherapy, 1 in arm 1 (5.5%) and 4 in arm 2 (28.5%) ($p = 0.142$). The reasons were acute grade 3 toxicity ($n = 4$) and patient's request ($n = 1$).

The median follow-up was 24.9 months. LRC at 1 year was 57.4% (95%CI 33.8–97.7) in arm 1 and 69.3% (95%CI 45.3–100) in

Table 1
Patients characteristics at baseline.

	Arm 1 (N = 18)	Arm 2 (N = 14)	Total (N = 32)	<i>p</i> -value
Age in years				0.581
median	73.5	79.5	76.5	
range	52–87	52–88	52–88	
Sex				0.283
male	12 (66.7%)	6 (42.9%)	18 (56.2%)	
Female	6 (33.3%)	8 (57.1%)	14 (43.8%)	
Tumor site				0.733
Oral cavity	7 (38.9%)	4 (28.6%)	11 (34.4%)	
Oropharynx	5 (27.8%)	6 (42.9%)	11 (34.4%)	
Hypopharynx	3 (16.7%)	3 (21.4%)	6 (18.8%)	
Larynx	3 (16.7%)	1 (7.1%)	4 (12.5%)	
T-classification				0.888
T2	4 (22.2%)	3 (21.4%)	7 (21.9%)	
T3	4 (22.2%)	2 (14.3%)	6 (18.8%)	
T4	10 (55.6%)	9 (64.3%)	19 (59.4%)	
N-classification				0.764
N0	2 (11.1%)	2 (14.3%)	4 (12.5%)	
N1 + N2 + N3	16 (88.9%)	12 (85.7%)	28 (87.5%)	
M-classification				0.703
M0	14 (77.8%)	10 (71.4%)	24 (75.0%)	
M1	4 (22.2%)	4 (28.6%)	8 (25.0%)	
AJCC stage				0.613
I–III	3 (16.7%)	1 (7.1%)	4 (12.5%)	
IV	15 (83.3%)	13 (92.9%)	28 (87.5%)	
WHO status				1.000
WHO 0–1	13 (72.2%)	11 (78.6%)	24 (75.0%)	
WHO 2	5 (27.8%)	3 (21.4%)	8 (25.0%)	
ACE-27 score at baseline				1.000
0–2	15 (83.3%)	12 (85.7%)	27 (84.4%)	
3	3 (16.7%)	2 (14.3%)	5 (15.6%)	
G8 scores at baseline				0.688
mean	12	12	12	
range	7–17	6–17	6–17	
VAS at baseline				0.474
mean	4.4	3.8	4.2	
range	7–9	1–9	1–9	
Grade ≥2 dysphagia at baseline				0.465
<2 or not applicable	13 (72.2%)	8 (57.1%)	21 (65.6%)	
≥2	5 (27.8%)	6 (42.9%)	11 (34.4%)	

Abbreviations: AJCC: American Joint Committee on Cancer; WHO: World Health Organization; ACE: Acute Comorbidity Evaluation; VAS: Visual Analogue Scale

Note: *P*-values for continuous variables (age, G8 score and VAS) were derived using the Kruskal-Wallis test and *p*-values for categorical variables were derived using Fisher's exact test.

Stratification variables were M-status, WHO performance status, ACE-27 score and AJCC stage.

Fig. 1. The trial profile.

arm 2 ($p = 0.450$, HR = 0.56, 95%CI 0.12–2.58) (Fig. 2A). The median time to loco-regional progression was not reached. Within the patient group with loco-regional progression, the median time to loco-regional progression was 17.9 weeks for arm 1 ($n = 5$) and 30.1 weeks for arm 2 ($n = 3$). The PFS at 1 year was 16.7% (95%CI 5.7–46.8) in arm 1 and 28.6% (95%CI 12.5–65.4) in arm 2, with medians of 20.3 and 32.3 weeks for arm 1 and 2, respectively ($p = 0.342$, HR = 0.56, 95%CI 0.26–1.59) (Fig. 2B). The OS at 1 year was 33.3% (95%CI 17.3–64.1) and 57.1% (95%CI 36.3–89.9) and the OS at 2 years was 14.8% (95%CI 4.6–48.1) and 34.3% (95%CI 16.2–72.4) for arm 1 and 2, respectively. The median OS were 35.4 and 59.5 weeks for arm 1 and 2, respectively ($p = 0.215$, HR = 0.55, 95%CI 0.21–1.43) (Fig. 2C).

The ORR (CR + PR) were 38.9% and 57.1% for arm 1 and 2 respectively ($p = 0.476$, odds ratio = 0.49, 95%CI 0.09–2.44). The rates of CR were 27.8% and 35.7% ($p = 0.712$, odds ratio = 0.70, 95%CI = 0.12–4.06) and for PR were 11.1% and 21.4% ($p = 0.631$, odds ratio = 0.47, 95%CI = 0.03–4.83), respectively.

Table 2 illustrates the acute and late radiation-related toxicities. The only significant difference between the two arms was observed for overall acute grade ≥ 3 toxicity; 16.7% and 57.1% for arm 1 and 2, respectively ($p = 0.027$), mostly because patients treated with the long-course radiation had significantly higher grade 3 mucositis, compared to the short-course radiation (5.6% and 42.9%, respectively, $p = 0.027$). With regard to late toxicity, the largest difference between the arms was observed for the rate of grade ≥ 2 late xerostomia (0% and 21.4%, respectively), but this difference was not statistically significant ($p = 0.073$). Supplementary Table 1 showed the effectiveness of symptom palliation after radiotherapy. In only 5 patients (15.6%) no any symptom relief was achieved after the palliative radiotherapy, compared to baseline. In three patients de neck mass progressed 3 months after radiotherapy. In two patients there was increased throat pain as result of local tumor progression, one of them had also repeated aspiration pneumonia and died 3.4 months after radiotherapy.

Overall, no significant differences were seen on the most clinically relevant health-related QoL-scales. Fig. 3 shows the observed values of selected items of QoL-scales and the random effects model results on QoL-scales are presented in Table 3. The interaction effects are the effects of interest and indicate the difference between the treatment groups over time (difference of the slope per group). For the EORTC QLQ-C30 scales, significant differences between the treatment arms at baseline were found for social func-

tioning ($p = 0.007$) and diarrhea scale ($p = 0.026$) where arm 2 scored worse compared to arm 1 on both scales. A significant main effect of time was found on emotional functioning ($p = 0.046$) and significant interaction effects between time and treatment arm were found on cognitive functioning ($p = 0.041$) in favor of arm 2, dyspnea ($p = 0.047$) and diarrhea scale ($p = 0.035$), both in favor of arm 1. For the EORTC QLQ-HN35 scales, no significant differences between the treatment arms at baseline were observed, but a significant main effect of time was found on pain ($p = 0.045$) and opening mouth ($p = 0.02$) and significant interaction effects were found on opening mouth ($p = 0.037$) in favor of arm 2 and weight loss ($p = 0.034$) in favor of arm 1. No significant effects were found on the EQ-5D-5L VAS (visual analogue scale) score.

Discussion

This is the first RCT to date reporting on the outcome of two radiation schemes for patients with HNSCC in a disease stage beyond cure. Unfortunately, the study was discontinued early because of the slow accrual after enrollment of 34 patients. First of all, we would like to stress that the statistical power of the results from the current study is inadequate to draw firm conclusion from our trial. However, the principal investigators feel obliged to share the results of the treated patients and try to identify the reasons for failure to complete a RCT investigating an important and pressing question in a group of patients with significant disease burden.

With small sample sizes, randomization cannot always successfully mitigate all baseline differences between arms. In the current study however, no substantial imbalances of baseline characteristics between arms were observed (even for characteristics that were not stratified for in the randomization process), except for some QoL-scales. With the limits of a sample far smaller than planned, no statistically significant differences were seen in terms of oncologic outcomes. However, it could be noted that the Kaplan-Meier curves for LRC, PFS, and OS (Fig. 2) maintained a consistent separation in favor of the long-course of radiotherapy. These patients have also slightly better response rates, longer time to develop loco-regional progression, longer median survival and longer median PFS. However, all these differences did not reach statistical significance. Moreover, it should be noted that these results were achieved at the cost of longer treatment time, more

Fig. 2. Kaplan Meier curves for loco-regional control, disease-free survival and overall survival of both treatment arms. *P*-values are based on the stratified log-rank test.

hospital visits because of more fractions and higher incidence of overall acute grade ≥ 3 toxicity, specifically acute grade 3 mucositis. In view of the relatively short survival of these patients, the importance of length of radiation course and the number of hospital visits could not be overstated and must be balanced against symptomatic relief and loco-regional tumor control. For most QoL-scales, no significant effects were found for the main effect of time and for the difference over time between the treatment arms (interaction effects). This was the case for relevant QoL-scales as global health, social functioning (QLQ-C30), swallowing, dry mouth (QLQ-HN35) and EQ-5D-5L VAS. Although there were significant interaction effects for QoL-scales cognitive functioning, dyspnea, diarrhea (QLQ-C30), opening mouth and weight loss (QLQ-HN35), these effects are not considered clinically relevant

Table 2

Toxicity summary of all adverse events (related and unrelated).

	Arm 1 (n = 18)	Arm 2 (n = 14)	<i>p</i> - value
Overall grade ≥ 2 acute toxicity	17 (94.4%)	13 (92.9%)	1
Grade ≥ 2 acute dermatitis	1 (5.6%)	4 (28.6%)	0.142
Grade ≥ 2 acute mucositis	13 (72.2%)	13 (92.9%)	0.196
Grade ≥ 2 acute dysphagia	9 (50%)	6 (42.9%)	0.735
Overall grade ≥ 3 acute toxicity	3 (16.7%)	8 (57.1%)	0.027
Grade ≥ 3 acute dermatitis	0 (0%)	0 (0%)	NA
Grade ≥ 3 acute mucositis	1 (5.6%)	6 (42.9%)	0.027
Grade ≥ 3 acute dysphagia	1 (5.6%)	5 (35.7%)	0.064
Overall grade ≥ 2 late toxicity	8 (44.4%)	7 (50%)	1
Grade ≥ 2 late xerostomia, dry mouth	0%	3 (21.4%)	0.073
Grade ≥ 2 late dysphagia	1 (5.6%)	0 (0%)	1
Overall grade ≥ 3 late toxicity	6 (33.3%)	3 (21.4%)	0.694
Grade ≥ 3 late dysphagia	1 (5.6%)	0 (0%)	1

for several reasons. First, the actual effects are very small when taking into account that all QoL scales are measured on a 0–100 scale. Second, the overall sample size is small (low power) and the sample size further decreases over time resulting in wide confidence intervals (see Fig. 3) and thus more uncertainty. The small sample size is also likely the cause of the observed difference in some QoL scores at baseline and our failure to detect any deterioration over time for most QoL scales. Third, the large number of tests performed for the QoL endpoint increases the likelihood of making erroneous inferences due to a multiple testing problem and when correcting for multiple testing, the statistically significant interaction effects would not hold.

As the response evaluation is only clinical (including flexible endoscopy), and imaging is only optional (only if possible), the assessment of the primary endpoint would be, to a certain extent, patient- and clinician-dependent, thereby introducing variability and unreliability in the determination of time without progression. This could vary by 3–4 weeks from when a patient presents with new symptoms or when the physician clinically detects new signs – so a potential 40% variability on the primary endpoint. However, in a RCT this potential variability is applicable to both arms and when taking the general condition of these patients into account the addition of obligatory imaging for the response evaluation was, in our opinion, a bridge too far for this vulnerable group of patients.

Also from radiobiological, economical and logistical points of view and for the comfort of patients and their families, short-course of radiation might be advocated especially in patients with major comorbidities and poor general condition with competing risk of death from these comorbidities, as late toxicity in these patients is a less relevant issue. On the other hand, long-course of palliative radiotherapy should, in our opinion, be offered only to patients with relatively good general condition without major comorbidity who might survive longer. In these cases, late toxicity of the hypofractionated scheme might count more and lower fraction dose (as in arm 2 of the current study) might be warranted.

Historically, physicians indiscriminately enrolled patients with HNSCC in trials while nowadays different issues have resulted in generally lower accrual rates in studies and that might have resulted in early discontinuation of this trial. Despite the availability of different nomograms [8–10], the pre-treatment prognostication of patients with locally-advanced HNSCC is extremely difficult and the decision not to offer these patients radical treatment options might be a selection bias during the screening for enrollment in such RCT. Furthermore, physicians usually overestimate survival of these patients by factor of 3 [11]. The physician prefer-

Fig. 3. Mean scores by arm at planned times with 95% confidence intervals (no CI given for single observations) and p-values of the arm-by-time interaction from mixed effects regression for a selected set of quality of life scales.

ence might be another factor, as radiation oncologists would select the most suitable regimen based on holistic judgment of the patient characteristics (age, comorbidity score, performance status, the tumor load, the type of symptoms to be palliated) and patient's wishes and choices. The logistics of treatment delivery such as the travel distance to the hospital and the institutional preference might have influenced the shared decision making and offered these patients another schemes outside the framework of the current study. Last, the choice for two schemes with major differences in treatment time and frequency of travelling to the radiation department could have discouraged physicians and patients to participate. However, the choice to compare these two schemes with large differences in the number of fractions was done because these two schemes for palliative radiotherapy for HNSCC are the most commonly used in the Netherlands. Moreover, it is quite reasonable to investigate whether a relatively longer course of radiotherapy with slightly higher BED would be better than a short-course of radiotherapy with limited number of visits to the clinic in terms of outcome, potential toxicity and QoL. This delicate balance between outcomes, possible toxicity, deterioration of QoL

and patient's comfort has justified the choice for these two treatment arms. Perhaps choosing two regimens with a greater biological difference would have been more relevant.

In conclusion, from this incomplete study which is closed early no solid conclusions could be made. Long-course palliative radiotherapy did not show significantly better oncologic outcomes but was associated with significantly higher incidence of overall acute grade ≥ 3 toxicity, specifically acute grade 3 mucositis. No meaningful differences in QoL-scores were found. Therefore, the short-course radiotherapy might be carefully advocated during the shared decision making especially in patients with poor general condition and/or major comorbidities, also because of the limited number of hospital visits. However, this recommendation should be interpreted with great caution because of the inadequate statistical power.

Conflict of interest

All authors declare no conflict of interest.

Table 3

Results of mixed effects regression models comparing treatment arms on QoL scales.

QoL scale	Difference at baseline*		Main effect of time		Interaction effect time × treatment arm*	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
<i>Functional scales QLQ-C30 (higher is better)</i>						
Physical functioning	−4.825	0.594	0.008	0.584	−0.007	0.685
Role functioning	−2.686	0.792	−0.006	0.78	−0.012	0.644
Emotional functioning	6.041	0.437	0.036	0.046	−0.026	0.231
Cognitive functioning	−14.13	0.131	−0.019	0.138	0.032	0.041
Social functioning	−19.11	0.007	−0.005	0.798	0.016	0.474
Global health status/QoL	−0.85	0.906	0.006	0.705	0.003	0.896
<i>Symptom scales/items QLQ-C30 (higher is worse)</i>						
Fatigue	−1.099	0.903	0.011	0.604	−0.007	0.788
Nausea/Vomiting	6.749	0.344	−0.001	0.932	−0.001	0.926
Pain	−5.419	0.571	−0.009	0.718	0.015	0.604
Dyspnea	1.947	0.846	0.037	0.09	−0.052	0.047
Insomnia	−5.81	0.542	−0.013	0.628	−0.006	0.845
Appetite loss	2.067	0.85	0.041	0.103	−0.039	0.199
Constipation	−8.144	0.277	−0.012	0.566	0.021	0.406
Diarrhea	17.15	0.026	0.009	0.598	−0.046	0.035
Financial problems	1.534	0.81	−0.01	0.516	0.002	0.929
<i>Symptom scales/items QLQ-HN35 (higher is worse):</i>						
HN pain	−6.67	0.485	−0.034	0.045	0.022	0.273
HN swallowing	0.586	0.944	0.01	0.612	−0.01	0.655
HN senses problems	11.227	0.185	−0.005	0.796	−0.01	0.665
HN speech problems	1.401	0.865	−0.026	0.161	0.018	0.416
HN trouble with social eating	0.57	0.947	0.008	0.682	−0.026	0.281
HN trouble with social contact	−2.278	0.527	−0.007	0.386	0.01	0.318
HN less sexuality	−1.294	0.93	−0.005	0.843	−0.019	0.496
HN teeth	3.552	0.787	0.009	0.655	−0.013	0.596
HN opening mouth	−9.591	0.285	−0.046	0.02	0.05	0.037
HN dry mouth	8.616	0.393	−0.024	0.345	0.012	0.689
HN sticky saliva	−3.922	0.752	−0.021	0.437	0.013	0.692
HN coughed	5.106	0.581	−0.005	0.836	−0.016	0.582
HN felt ill	−1.32	0.893	−0.006	0.765	0.01	0.705
HN pain killers	−10.448	0.494	−0.045	0.278	0.058	0.242
HN nutritional supplements	13.527	0.361	−0.011	0.798	−0.064	0.244
HN feeding tube	2.697	0.759	−0.002	0.864	0.015	0.354
HN weight loss	0.569	0.971	0.069	0.102	−0.109	0.034
HN weight gain	16.032	0.091	−0.012	0.662	0	0.993
<i>EQ-5D-5L VAS (higher is better)</i>						
VAS score	1.507	0.794	0	0.996	0.008	0.636

Abbreviations: QoL/QLQ = Quality of Life Questionnaire; HN = Head & Neck Module; VAS = Visual Analogue Scale.

* Arm 1 (short-course radiotherapy) is the reference category in the mixed effects regression models. This means a positive value is in favor of arm 2 (long-course radiotherapy).

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Author's contributions

AA was principal investigator and conceived and designed the study with the other principal investigators of the participating centers (all co-authors). RK, EW, and AA contributed to data collection, analyzed and interpreted the data. AA drafted the manuscript, in cooperation with all co-authors. All authors revised the manuscript and approved the submission.

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Ethics committee approval

The study (ClinicalTrials.gov Identifier NCT02421458) was conducted in accordance with the Declaration of Helsinki. The study was approved by the local research ethics committee (Medical Research Ethics Committee of the Netherlands Cancer Institute/Antoni van Leeuwenhoek, protocol ID: NL 52512.031.15). All patients were given oral and written information about the study, and were given sufficient time to consider participating. Written informed consent was obtained from each patient before inclusion.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2020.05.020>.

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