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Original Article

A multicentric randomized controlled phase III trial of adaptive and 18F-FDG-PET-guided dose-redistribution in locally advanced head and neck squamous cell carcinoma (ARTFORCE)

Anna Liza M.P. de Leeuw [a,*], Jordi Giralt [b,c], Yungan Tao [d], Sergi Benavente [b,c], Thanh-Vân France Nguyen [d], Frank J.P. Hoebers [e], Ann Hoeben [f], Chris H.J. Terhaard [g], Lip Wai Lee [h], Signe Friesland [i], Roel J.H.M. Steenbakkers [j], Lisa Tans [k], Jolien Heukelom [e], Mutamba T. Kayembe [l], Simon R. van Kranen [a], Harry Bartelink [a], Coen R.N. Rasch [m], Jan-Jakob Sonke [a], Olga Hamming-Vrieze [a,*]

[a] Department of Radiation Oncology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
[b] Department of Radiation Oncology, Hospital General Vall d'Hebron, Barcelona, Spain
[c] Vall d'Hebron Institute of Oncology, Barcelona, Spain
[d] Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France
[e] Department of Radiation Oncology (Maastro), GROW School for Oncology and Reproduction, Maastricht University Medical Centre+, Maastricht, The Netherlands
[f] Division of Medical Oncology, Department of Internal Medicine, GROW-School of Oncology and Developmental Biology Maastricht University Medical Center+, Maastricht, The Netherlands
[g] Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands
[h] Department of Radiation Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom
[i] Department of Radiation Oncology, Karolinska Institute, Stockholm, Sweden
[j] Department of Radiation Oncology, University Medical Center Groningen, Groningen, The Netherlands
[k] Department of Radiation Oncology, Erasmus Medical Center, Rotterdam, The Netherlands
[l] Department of Bioinformatics and Statistics, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
[m] Department of Radiation Oncology, Leiden University Medical Center, Leiden, The Netherlands

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ABSTRACT

Background and purpose: This multicenter randomized phase III trial evaluated whether locoregional control of patients with LAHNSCC could be improved by fluorodeoxyglucose-positron emission tomography (FDG-PET)-guided dose-escalation while minimizing the risk of increasing toxicity using a dose-redistribution and scheduled adaptation strategy.

Materials and methods: Patients with T3-4-N0-3-M0 LAHNSCC were randomly assigned (1:1) to either receive a dose distribution ranging from 64-84 Gy/35 fractions with adaptation at the 10th fraction (rRT) or conventional 70 Gy/35 fractions (cRT). Both arms received concurrent three-cycle 100 mg/m^2 cisplatin. Primary endpoints were 2-year locoregional control (LRC) and toxicity. Primary analysis was based on the intention-to-treat principle.

Results: Due to slow accrual, the study was prematurely closed (at 84 %) after randomizing 221 eligible patients between 2012 and 2019 to receive rRT ($N = 109$) or cRT ($N = 112$). The 2-year LRC estimate difference of 81 % (95 %CI 74–89 %) vs. 74 % (66–83 %) in the rRT and cRT arm, respectively, was not found statistically significant (HR 0.75, 95 %CI 0.43–1.31, P=.31). 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=.05). In post-hoc subgroup analyses, rRT improved LRC for patients with N0-1 disease (HR 0.21, 95 %CI 0.05–0.93) and oropharyngeal cancer (0.31, 0.10–0.95), regardless of HPV.

Conclusion: Adaptive and dose redistributed radiotherapy enabled dose-escalation with similar toxicity rates compared to conventional radiotherapy. While FDG-PET-guided dose-escalation did overall not lead to

* Corresponding authors at: Department of Radiation Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Plesmanlaan, 1211066 CX Amsterdam, The Netherlands.
E-mail addresses: a.d.leeuw@nki.nl (A.L.M.P. de Leeuw), o.vrieze@nki.nl (O. Hamming-Vrieze).

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significant tumor control or survival improvements, post-hoc results showed improved locoregional control for patients with N0-1 disease or oropharyngeal cancer treated with rRT.

Introduction

More than half of the patients with head and neck squamous cell carcinomas (HNSCC) are diagnosed at a locally advanced stage (LA) [1]. The standard of care for LAHNSCC treatment is concurrent chemo-radiation with curative intent. Although this locoregionally targeted therapy is effective in the majority of patients, locoregional recurrences are four-fold more common than metastases [2].

A strategy to improve local control is radiotherapy dose painting. Dose painting is based on the hypothesis that intratumoral cellular heterogeneity leads to heterogeneous radiotherapy sensitivity. Focal increase of radiation dose in radioresistant subvolumes could therefore increase tumor control. However, non-invasive detection of radio-resistant subvolumes remains challenging. 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is an attractive candidate to define these subvolumes by quantifying glucose metabolism, as it is commonly integrated in routine cancer staging and follow-up work-flows. In HNSCC specifically, high FDG uptake values in the primary tumor, such as the maximum standardized uptake value (SUVmax), is associated with poorer survival outcomes [3–6]. Additionally, studies on local recurrence patterns in treated LAHNSCC found that recurrences are mostly located directly inside or inside a 10 mm range of the metabolic volume. This implies that FDG-PET can identify undertreated sub-volumes [7–9].

Building forward on this intratumoral heterogeneity hypothesis, we hypothesized that tissue located outside metabolic subvolumes are less radioresistant and/or have expectedly lower tumor cell density and therefore require a lower radiation dose. This hypothesis was tested in a multicenter, randomized controlled phase III trial, the Adaptive and innovative Radiation Treatment FOR improving Cancer treatment outcomE (ARTFORCE, NCT01504815) trial. The primary aim of this trial was to improve two-year locoregional control for LAHNSCC by FDG-PET-guided dose-escalation without increasing toxicity by implementing both scheduled adaptive radiotherapy and dose-redistribution strategies. This article reports on survival outcome and the primary endpoints of the ARTFORCE trial: locoregional control and two-year toxicity.

Methods

Study design

The trial was originally designed in 2012 as a 2x2 phase II randomized trial to compare adaptive and FDG-PET-guided dose-redistribution (rRT) to conventional radiotherapy (cRT) as well as cetuximab to cisplatin. In 2014, the discontinuation of cetuximab supply led to the cessation of the randomized comparison between concomitant cetuximab and cisplatin. The trial therefore transitioned from a four-armed phase II to a two-armed phase III trial solely comparing rRT to cRT. Extensive description of the full protocol of the initial study design was published in the early stage of the trial by Heukelom et al. [10] Supplementary 1 provides an overview of all major protocol changes implemented when the study was altered in 2014. Here, the latest trial protocol will be described.

The study trial was designed in accordance with the Guideline for Good Clinical Practice (GCP) [11]. Nine institutes participated in the accrual of patients for this trial, located in The Netherlands, Spain, France, United Kingdom and Sweden. Medical ethical committees at all participating institutes approved the protocol. Local investigators ensured written informed consent, compliance to protocol and GCP requirements.

Participants and randomization

Patients diagnosed with stage III-IV,T3-T4-N0-3-M0 (6th edition AJCC) HNSCC located in the oral cavity, oropharynx or hypopharynx and scheduled for definitive chemoradiation were eligible for inclusion (Supplementary 2). Patients were randomly assigned in a 1:1 ratio to receive either cRT or rRT. Randomization was stratified by institute, T-stage, tumor site, tumor volume ($<$ or $\geq$ 30 cc) and human papilloma virus (HPV) status for oropharyngeal tumors. Twenty-four patients were randomized before the 2014 protocol amendment, of which eleven to the trial arms receiving concomitant cetuximab instead of cisplatin. These patients remained included in the final analysis considering the early protocol change and equal allocation to the radiation treatment strategies.

Treatment

All patients received a total body FDG-PET/CT in treatment position in the two weeks prior to treatment initiation. In the rRT arm, planning target volume (PTV-PET) was delineated corresponding to 50 % of the maximum standard uptake value (SUV) on FDG-PET (GTV-PET) and its 3 mm expansion. The surrounding macroscopic tumor (GTVp) was expanded by 10 mm to include subclinical disease (CTVp) and an additional 3–5 mm (according to the institute's protocol) resulting in the planning target volume (PTVp). The dose prescription for PTV-PET was a dose gradient ranging between 70–84 Gy (mean 77 Gy), allowing a maximum of 2 % of the PTV-PET volume, preferably located near the maximum SUV, to receive 84 Gy. The PTVp, excluding PTV-PET, received a median dose of 67–69 Gy with a minimum dose of 64 Gy at the edge of the PTVp. In the cRT arm, the PTVp was delineated using the same criteria, but the entire PTVp was prescribed a homogeneous dose of 70 Gy. Overall, this resulted in a higher dose at the edge of the PTVp in the cRT arm, but a higher maximum PTVp dose in the rRT arm (Fig. 1). The prescribed doses to pathological lymph nodes and elective fields were 70 Gy and 54.25 Gy, respectively, and equivalent in both treatment arms. All patients were treated by simultaneous integrated boost technique in 35 fractions over a period of seven weeks. Systemic treatment for both arms of the trial consisted of three concurrent cycles of cisplatin doses (100 mg/m^2) on days 1, 22, and 43 of treatment.

In the rRT arm, replanning was scheduled in the third treatment week, adjusting exclusively for clear anatomical changes on CT. GTV-PET of the primary plan was rigidly adopted and modified for regression to fit within the anatomically adjusted GTVp.

Follow-up

Weekly reviews were scheduled during treatment, which continued for three weeks post-treatment. At ten to twelve weeks post-treatment, response was evaluated using FDG-PET with MRI and/or CT. Thereafter, reviews were required every three months until two years post-treatment. Further clinical evaluations were continued every six months until five years post-treatment. Toxicities were scored according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) and assessed at every moment of evaluation during treatment and follow-up.

Endpoints

The goal of this trial was to improve locoregional control with similar toxicity, compared to the standard of care. Therefore, the primary endpoints of this trial were two-year locoregional control (LRC) and

two-year toxicity. A sample size of 268 patients was calculated to provide 80 % power, at a two-sided 0.05 significance-level, to detect a 15 % increase in LRC at two-years, assuming 65 % LRC in the cRT arm [12]. The trial was not formally powered for the analysis of non-inferiority. Secondary endpoints were overall survival (OS), progression free survival (PFS), quality of life and swallowing preservation.

Statistical analyses

All randomized patients were analyzed, according to the intention-to-treat principle. LRC, OS, PFS and late toxicity incidence rates were estimated by the Kaplan-Meier (KM) method and Cox regression models and measured from randomization. Definitions used for the KM endpoints are stated in Supplementary 3. Trial arms were compared using the two-sided log-rank test. Unadjusted hazard ratios (HR) were calculated using univariable Cox regression models. Explanatory multivariable Cox regression models were built to evaluate causal relationship between trial arm and the clinical endpoints. Stratification factors and relevant covariates with a significance level of < 0.10 were included in these explanatory models. A parsimonious model was built by stepwise backward strategy using the Akaike information criterion. Both models were internally validated by bootstrapping with one thousand samples. Details on the model building process and bootstrap results can be found in Supplementary 4. Toxicity prevalence rates at 2 years were compared between arms using the Fisher's exact test in patients who were alive and free of locoregional recurrence. Freedom from late toxicity was evaluated from three months post-treatment using the KM method. The reverse KM method was used to estimate follow-up time. Per-protocol analyses of LRC, OS, PFS were performed exclusively on patients who completed all 35 radiotherapy fractions and, for the rRT arm, who also had undergone treatment adaptation and dose-redistribution. These analyses were outlined in the protocol and prespecified prior to analysis. Additionally, post-hoc subgroup analyses were performed using univariable Cox regression models to evaluate treatment effect within subgroups. R (v.1.1) was used for analysis.

Patterns of local failure

Of additional interest was the location of local recurrences in relation to the GTV-PET. To evaluate this, the first CT/PET-CT/MRI scan showing the local recurrence was rigidly registered to the planning CT. The location of the center of mass of the recurrent volume was determined against the GTV-PET and the CTVp volumes.

Results

Between September 2012 and November 2019, 226 patients were randomized (Fig. 2). Due to slow accrual, the trial was prematurely closed in 2019 after including 84 % of the intended number of patients. Five patients were considered screening failures, leaving 109 patients in the rRT arm and 112 patients in the cRT arm. No statistical significant differences in baseline characteristics were observed between treatment groups (Table 1). Sixteen patients did not receive cisplatin as systemic treatment, but cetuximab ($N = 15$) or carboplatin ($N = 1$) instead due to randomization to cetuximab treatment arms ($N = 11$) or contra-indications for cisplatin ($N = 5$).

Treatment compliance

Median treatment time was 47 days in both treatment arms (Interquartile range (IQR) rRT 47–49, cRT 46–50, P=.26). Radiotherapy was discontinued in five patients (Fig. 2). All patients in the rRT arm received dose-redistribution. Scheduled adaptation was waived for seven patients as treatment adaptation was deemed unnecessary in these specific cases. Systemic therapy was completed by 54 % of patients in the rRT arm, versus 57 % in the cRT arm (P=.69).

Clinical outcome

Median follow-up time was 5.04(IQR 4.21–5.31) years in the rRT arm and 4.84(4.06–5.26) years in the cRT arm (P=.17). No significant difference in LRC was found between trial arms (P=.31;HR 0.75 95 %CI 0.43–1.31) with a two-year LRC rate of 81.0 % (95 %CI 73.6–89.1 %) in rRT versus 74.3 % (66.4–83.2 %) in cRT (Fig. 3A). Using the acquired 2-year LRC in the cRT arm and total number of included patients, sample size recalculation showed that this study cohort had 80 % power to detect a 14.2 % difference (HR 0.41). To detect a significant 6.7 % difference between trial arms, as observed in this study, a study cohort of 1199 patients would have been required. Univariable analysis revealed that concomitant cetuximab ($P \leq 0.01$;HR 3.22,1.51–6.86), AJCC stage IV (P=.01;HR 2.46,1.20–5.07), larger tumor volumes (P=.02;HR 1.99,1.13–3.47) and oral cavity tumor localization ($P \leq 0.01$;HR 4.43,2.24–8.74) were associated with inferior LRC (Table 2). Improved LRC was observed for HPV-positive oropharynx tumors (P=.01;HR 0.27,0.10–0.77). In the explanatory multivariable analysis, only oral cavity and HPV-positive oropharynx tumors remained significantly associated with LRC (Supplementary 5).

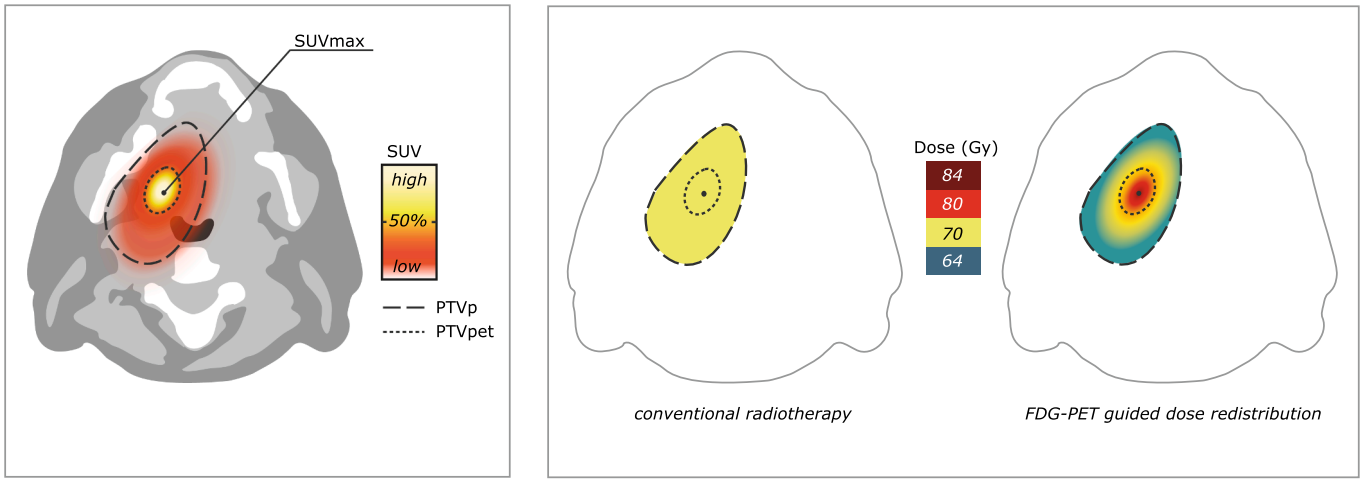

Fig. 1. Comparative illustration of the FDG-PET (A) and the dose distributions (B) of conventional radiotherapy (cRT) versus FDG-PET-guided dose-redistribution (rRT). In cRT, a homogeneous dose of 70 Gy is prescribed to the planning target volume of the primary tumor (PTVp). In rRT, an inhomogeneous dose varying between 70–84 Gy is prescribed to the FDG-PET defined subvolume (PTVpet) and 64–70 Gy to the surrounding PTVp, depending on FDG uptake (50 % SUVmax).

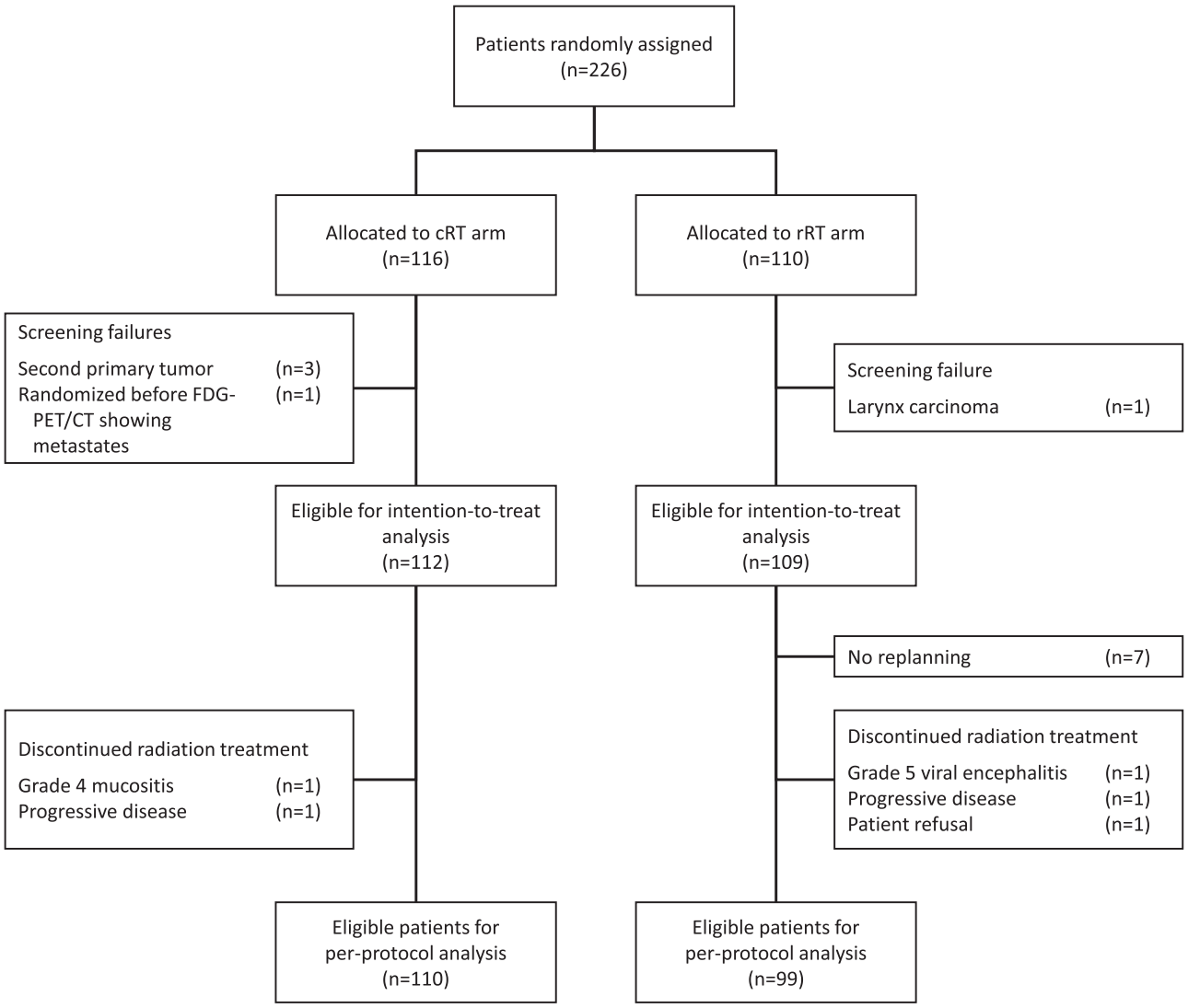

Fig. 2. CONSORT diagram. Patients were randomized to receive conventional radiotherapy (cRT) or adaptive and FDG-PET-guided dose redistributed radiotherapy (rRT). Kaplan-Meier analyses were based on the intention-to-treat principle. Per-protocol analysis was performed to effectiveness of the treatment under ideal conditions.

PFS was not significantly different at 2 years, 68.6 % (95 %CI 60.4–77.9 %) versus 66.9 % (58.8–76.3 %) of patients in rRT and cRT arm, respectively (P=.78, Fig. 3C). OS was similar between trial arms (P=.76, Fig. 3D) with two-year OS of 80.7 % (73.6–88.4 %) in rRT and 79.3 %(72.2–87.2 %) in cRT.

Individual analyses of local, regional and distant control did not show significant differences in control rates between treatment arms either (Supplementary 5). Per-protocol analyses gave similar results as the intention-to-treat analyses (Supplementary 6).

Fig. 3E illustrates a subgroup analysis of the treatment effect on LRC, which revealed improved LRC by rRT for patients with stage N0-1 disease (HR 0.21,0.05–0.93) and patients with tumors situated in the oropharynx (HR 0.31,0.10–0.95). In PFS and OS subgroup analyses, a similar association was seen for the patient subgroup with N0-1 disease (Supplementary 7). Due to small subgroups and the overlap in N0-1 patients having oropharynx tumors (Supplementary 8), it was not possible determine whether rRT specifically benefits N0-1 or oropharyngeal disease.

Patterns of local failure

Local recurrences were diagnosed in fourteen rRT and twenty-two cRT patients. Recurrence mapping could not be performed in two and four rRT and cRT patients, respectfully, as the local recurrence was a sole clinical diagnosis in these cases. Among the remaining local recurrences, two rRT patients had a recurrence outside the CTVp, which were not considered marginal misses. Details of these two patients are described in Supplementary 9. The remaining twenty-eight local recurrences were located within the CTVp. Overall, 75 % (9 out of 12) of the rRT arm and 72 % (13 out of 18) of the cRT had a local recurrence originating from the GTV-PET.

Two-year toxicity

No significant differences in toxicity prevalence were seen two years after treatment (Fig. 4, Supplementary 10. Most common grade $\geq$ 2 toxicities were xerostomia and dysphagia. Grade $\geq$ 2 xerostomia was seen in 10.3 % and 14.1 % of patients in the rRT and cRT arm, respectively (P=.63; OR 0.70, 95 %CI 0.23–2.04). Most common $\geq$ 3 toxicity was dysphagia, which was observed in 6.4 % of rRT and 3.8 % of cRT patients (P=.72; OR 1.71, 0.32–11.39).

Radiation-related toxicity incidence rates between treatment arms were not significantly different (Fig. 3B, Supplementary 11). Pharyngeal stenosis, however, occurred exclusively in the rRT arm, in four patients

Table 1
Baseline characteristics of patients randomly assigned to the adaptive & FDG-PET-guided dose-redistribution or conventional radiotherapy arm.

Characteristics	Radiotherapy			
	Adaptive dose-redistribution (*N* = 109)	Conventional (*N* = 112)	Overall (*N* = 221)	p-value
Sex, N (%)				0.97
Female	26 (24 %)	27 (24 %)	53 (24 %)	
Male	83 (76 %)	85 (76 %)	168 (76 %)	
Age (years)				
Median (range)	59 (27–69)	58 (29–71)	58 (27–71)	0.68
BMI (kg/m^3)				
Median (range)	25 (14–47)	25 (15–36)	25 (14–47)	0.22
WHO, N (%)				0.98
0	66 (61 %)	67 (60 %)	133 (60 %)	
1	43 (39 %)	44 (39 %)	87 (39 %)	
Missing	0 (0 %)	1 (1 %)	1 (1 %)	
Smoking habits, N (%)				0.53
non-smoker	15 (14 %)	17 (15 %)	32 (15 %)	
ex-smoker	47 (43 %)	40 (36 %)	87 (39 %)	
smoker	47 (43 %)	55 (49 %)	102 (46 %)	
Packyears, N (%) [a]				
Median (range)	40 (1–120)	39 (2–600)	40 (1–600)	0.26
Missing	3 (3.2 %)	4 (4.2 %)	7 (3.7 %)	
Tumor site, N (%)				0.52
Hypopharynx	13 (12 %)	9 (8 %)	22 (10 %)	
Oral Cavity	27 (25 %)	25 (22 %)	52 (24 %)	
Oropharynx	69 (63 %)	78 (70 %)	147 (66 %)	
Tumor volume, N (%)				0.81
<30 cc	65 (60 %)	65 (58 %)	130 (59 %)	
≥30 cc	44 (40 %)	47 (42 %)	91 (41 %)	
AJCC stage, N (%)				0.47
III	33 (30 %)	39 (35 %)	72 (33 %)	
IV	76 (70 %)	73 (64 %)	149 (67 %)	
T-stage, N (%)				0.90
T3	38 (35 %)	40 (36 %)	78 (35 %)	
T4	71 (65 %)	72 (64 %)	143 (65 %)	
N-stage, N (%)				0.41
N0	15 (14 %)	19 (17 %)	34 (15 %)	
N1	10 (9 %)	19 (17 %)	29 (13 %)	
N2a	1 (1 %)	2 (2 %)	3 (1 %)	
N2b	49 (45 %)	38 (34 %)	87 (39 %)	
N2c	28 (26 %)	27 (24 %)	55 (25 %)	
N3	6 (6 %)	7 (6 %)	14 (6 %)	
HPV status, N (%) [b]				1.00
Negative	29 (42 %)	33 (43 %)	62 (42 %)	
Positive	40 (58 %)	44 (56 %)	84 (57 %)	
Missing		1 (1 %)	1 (1 %)	
Chemotherapy, N (%)				0.59
Carboplatinum	0 (0 %)	1 (1 %)	1 (<1%)	
Cetuximab	8 (7 %)	7 (6 %)	15 (7 %)	
Cisplatinum	101 (93 %)	104 (93 %)	205 (93 %)	

[a] Packyears of patients with a history of smoking tobacco (ex-smokers) or patients who smoked at date of diagnosis (smokers).
[b] Human papillomavirus testing result of patients with an oropharyngeal primary tumor.

(4 %, *P*=.05). Of these four patients, three patients had an hypopharynx tumor and one had an oropharynx tumor extending to the hypopharynx. Observed differences in incidence of grade ≥ 2 (*P*=.14; HR 1.63, 0.85–3.12) and ≥ 3 mucosal toxicities (*P*=.08; HR 1.78, 0.93–3.39) as well as grade ≥ 2 (*P*=.58; HR 1.16, 0.70–1.92) and ≥ 3 dysphagia (*P*=.07; HR 1.96, 0.94–4.08) were non-significant. Grade 4 adverse events were reported in two and four patients in the cRT and rRT arm, respectfully, while grade 5 adverse events occurred in three and two (Supplementary 12). Of all five radiation-related grade ≥ 4 toxicities, three occurred in patients with hypopharyngeal cancer, and two in oropharyngeal cancer.

Discussion

This randomized phase 3 trial compared adaptive and FDG-PET-guided dose-redistribution (rRT) with conventional radiation (cRT) in 221 patients diagnosed with LAHNSCC of the oropharynx, hypopharynx and oral cavity. Although no significant improvement in two-year LRC (6.7 % absolute benefit, *P*=.31) was achieved, dose-escalation up to 84 Gy was delivered with similar two-year toxicity compared to conventional 70 Gy homogeneous distribution. This was achieved by de-escalating dose down to 64 Gy to the PTV surrounding the dose-escalation volume and scheduled adaptive radiotherapy.

FDG-PET-guided dose-escalation in similar patient populations has previously been investigated in multiple phase 1 trials [13–16]. A pooled matched-pair analyses of three of these trials compared 72 patients to those treated with standard treatment [17]. In general, tumor control did not significantly improve (8.7 % 5-year absolute benefit, *P*=.36), but a trend towards improved LC and OS (5-year LC 85.9 %; OS 78.7 %) was observed with implementation of two FDG-PET-guided treatment adaptations and a dose range of 65–85 Gy. It is noteworthy that our control arm showed comparable outcome to their dose-escalation arms. This may be attributed to advancement in patient care, improved technology, and a significant portion of our cohort having HPV-positive oropharynx tumors, which is associated with a better prognosis [2,18,19].

While our study confirmed variations in prognosis between LAHNSCC subgroups, we also observed differences in response to dose-redistribution. Notably, LRC improved in patients with N0-1 disease and oropharynx tumors treated with rRT. This was the case for both HPV-positive and −negative tumors. However, we anticipate future dose-escalation studies focusing on HPV-negative tumors are most likely to provide benefit, given their poorer prognosis. The LRC benefit in oropharyngeal tumors could be explained by heterogeneous radiosensitivity among anatomic subsites, as supported by gene expression studies [20,21] and the genome-based model for adjusting radiotherapy dose [22]. Current trend in HPV-positive oropharyngeal cancer research is, however, leaning towards dose de-escalation due to the high toxicity burden and the favorable prognosis compared to HPV-negative disease. Promising results were published by multiple feasibility trials, predominantly in T1-2 disease, showing higher survival rates compared to historic rates [23–30]. Given the lack of a control arm in these studies, and our findings suggesting the potential benefit in T3-4 oropharyngeal cancer, de-escalation is not advised for T3-4 oropharyngeal cancer. To improve the understanding of therapy sensitivity variations between disease stages and anatomical subsites, future studies should explicitly report on differences in clinical outcome among them.

There are two potential explanations for why dose-escalation strategies in LAHNSCC have not been able to significantly improve outcomes. One plausible factor is that a sufficiently high dose level has not been reached in the FDG-PET-defined subvolume. The main concern of dose-escalation is, however, the risk of increased toxicity, particularly late dysphagia and mucosal ulcers [17]. We did not score ulcers separately, but we did evaluate late mucositis. Equivalent two-year toxicity prevalence was seen between trial arms and although dysphagia and mucositis incidence rates were higher in the rRT arm, they were not

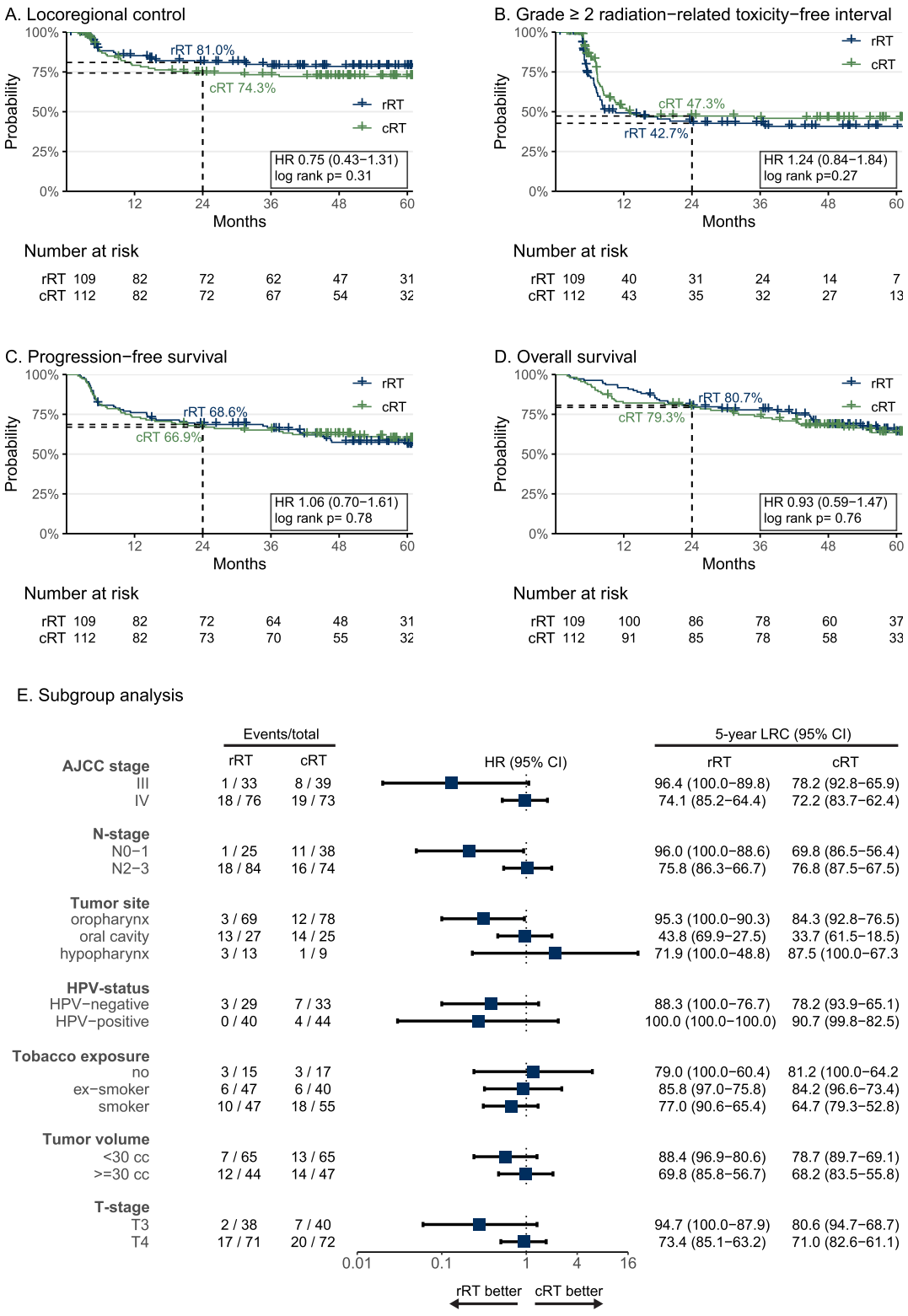

Fig. 3. Kaplan Meier estimates of locoregional control (A), grade ≥ 2 radiation-related toxicity-free interval (B), progression-free survival (C) and overall survival (D) of patients treated by adaptive dose-redistribution (rRT, blue) or conventional radiotherapy (cRT, green). E, LRC subgroup analysis forrest plot. HR; the unadjusted hazard ratio of rRT in comparison to cRT.CI; confidence interval.

statistically different. This might indicate that redistribution strategies cause a temporary increase in toxicities or an extended recovery time. In our study group, grade ≥ 3 laryngopharyngeal stenosis rates were significantly higher with rRT (0 % vs. 4 %, *P*=.05). The majority of these patients and patients with radiation-related grade ≥ 4 toxicities had a hypopharynx tumor, emphasizing the need for cautious exploration of dose-escalation strategies in hypopharyngeal and laryngeal structures. Optimizing adaptive workflow to minimize margins and improving subvolume selection to enhance delivery precision of dose-redistributed radiation treatment might further decrease toxicity.

Table 2
Univariable and multivariable regression analyses investigating the impact of (possible) prognostic factors on locoregional failure.

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Trial arm				
conventional radiotherapy	1.00 (reference)		1.00 (reference)	
adaptive dose-redistribution	0.75 (0.43–1.31)	0.31	0.71 (0.4–1.26)	0.25
Sex				
Male	1.00 (reference)			
Female	1.04 (0.54–1.99)	0.91		
Age (years)	0.98 (0.95–1.02)	0.29		
BMI (kg/m^3)	0.95 (0.90–1.01)	0.09		
T-stage				
T3	1.00 (reference)		1.00 (reference)	
T4	2.66 (1.29–5.47)	0.01	1.30 (0.53–3.23)	0.57
N-stage				
N0-1	1.00 (reference)			
N2-3	1.18 (0.63–2.18)	0.61		
AJCC stage				
III	1.00 (reference)		1.00 (reference)	
IV	2.46 (1.20–5.07)	0.01	1.04 (0.43–2.48)	0.93
Tumor site				
oropharynx HPV-negative	1.00 (reference)		1.00 (reference)	
oropharynx HPV-positive	0.27 (0.10–0.77)	0.01	0.29 (0.1–0.81)	0.02
oral cavity	4.43 (2.24–8.74)	≤0.01	4.06 (1.95–8.46)	≤0.01
Hypopharynx	1.02 (0.33–3.16)	0.97	1.35 (0.42–4.4)	0.62
Tumor volume, N (%)				
<30 cc	1.00 (reference)		1.00 (reference)	
≥30 cc	1.99 (1.13–3.47)	0.02	1.78 (0.97–3.28)	0.06
Performance scale				
WHO 0	1.00 (reference)			
WHO 1	1.16 (0.66–2.05)	0.60		
Tobacco exposure				
No	1.00 (reference)			
ex-smoker	0.84 (0.32–2.17)	0.71		
Smoker	1.76 (0.73–4.22)	0.21		
Systemic treatment				
Cisplatin	1.00 (reference)		1.00 (reference)	
Cetuximab	3.22 (1.51–6.86)	≤0.01	1.86 (0.85–4.07)	0.12

Another explanation for the lack of clinical benefit observed with rRT could be the inadequacy of pre-treatment FDG-PET to accurately identify radioresistant areas. Although 75 % local recurrences seemed to originate from within FDG-PET-defined subvolume (PTV-PET), this explanation remains relevant given that the 70–84 Gy dose range within the PTV-PET was guided by FDG uptake. In fact, the maximum 84 Gy dose was restricted to 2 % of the PTV-PET showing the highest FDG uptake values (SUVmax). ^{18}F-misonidazole(FMISO), ^{18}F-fluoroazomycin *arabino*-side or ^{18}F-flortanidazole(HX4)-PET-tracers are other promising imaging biomarkers which show hypoxic instead of metabolic activity. Two studies investigating spatial overlap between FDG-PET and hypoxia-PET in laryngo-pharyngeal tumors revealed a partial overlap, suggesting these tracers provide distinct information [31,32]. Results of a patient selection and dose-escalation trial using FMISO-PET were promising, as they found a 5-year LC of 100 % in patients with non-hypoxic tumors who received conventional 70 Gy/35fx treatment [33]. However, the complex study setup eventually led to premature trial closure without reaching a sufficient sample size to evaluate the clinical benefit of hypoxia-guided dose-escalation. A key challenge is that these unconventional imaging modalities remain less accessible and less integrable in standard healthcare compared to FDG-PET. Hypoxia-guided dose-escalation currently under further investigation (NCT01212354) [34].

Similar to the FDG-PET, magnetic resonance imaging (MRI) has become indispensable in the LAHNSCC treatment workflow. Recent developments in MR(−Linac) have shown to be capable of visualizing hypoxic tumor subvolumes [35]. Such technology could enable a more convenient approach for hypoxia-guided dose painting that does not require additional imaging. However, the observed two-year LRC of 74 % in the overall conventional treatment arm and 91 % in the HPV-positive subgroup indicate that the majority of patients do not require further treatment intensification. Considering the high toxicity burden in this patient population, future studies should investigate selection strategies using accessible and predictive biomarkers. Even though post-hoc results showed that our rRT strategy was possibly effective in patients with oropharyngeal cancer, patients with oral cavity and hypopharyngeal cancer exhibit worse prognosis which necessitates further research for improved treatment options. Investigating differences in recurrence patterns and radiosensitivity between anatomical subsites may provide insights into the differences in treatment effectiveness among them.

A limitation of this study was premature closure after reaching 84 % of the sample size during a 7-year accrual period. Nevertheless, it is unlikely that the conclusion of this trial would have been altered with a complete study cohort since the observed increase in two-year LRC for rRT would have required a study cohort of 1199 patients to reach statistical significance. Secondly, discontinuation of the cetuximab arms most likely had a minimal effect, because the trial was modified after including only twenty-four patients and all patients were evenly distributed between the radiotherapy arms. Furthermore, it is important to mention that this trial was not designed for post-hoc analyses or to evaluate non-inferiority.

This randomized phase III study comparing conventional radiotherapy to adaptive and FDG-PET-guided dose-redistribution in LAHNSCC failed to show a locoregional control improvement, but successfully delivered dose-escalation with similar two-year toxicity rates. In post-hoc subgroup analyses, patients with oropharyngeal and stage N0-1 cancer treated with adaptive and FDG-PET-guided dose-redistribution showed improved locoregional control compared to the control groups. This warrants further investigation into treatment efficacy differences across tumor sites and stages and accessible selection methods.

Anna Liza M.P. de Leeuw; PhD-student at the Antoni van Leeuwenhoek hospital.

Jordi Giralt; Radiation oncologist at the Vall d'Hebron Unniversity Hospital.

Yungan Tao; Radiation oncologist at the Institut Gustave roussy.

Sergi Benavente; Radiation oncologist at the Vall d'Hebron Unniversity Hospital.

Thanh-Vân France Nguyen; Radiation oncologist at the Institut Gustave roussy.

Frank J.P. Hoebers; Radiation oncologist at the Maastro Center.

Ann Hoeben; Clinical oncologist at the Maastro Center.

Chris H.J. Terhaard; retired radiation oncologist at the University Medical Center Utrecht.

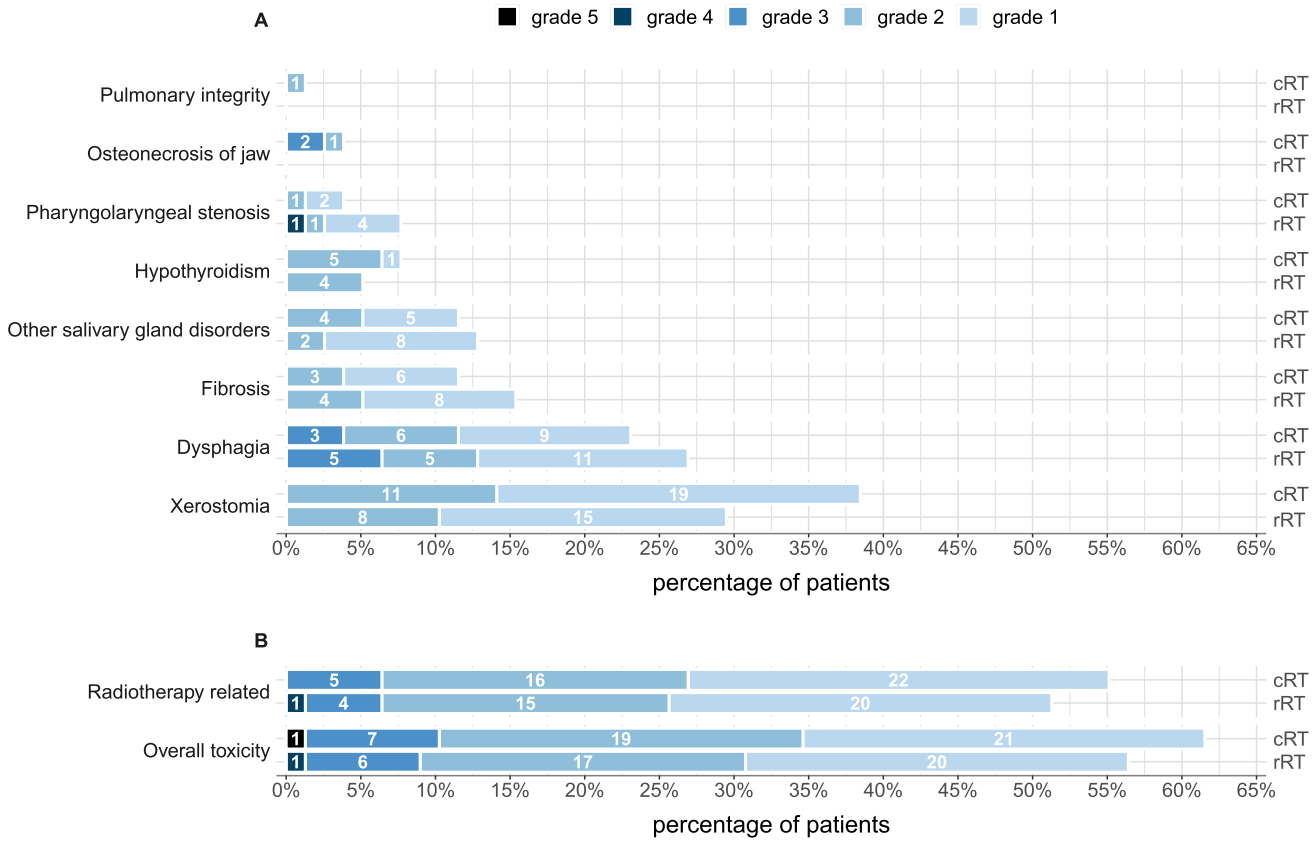

Fig. 4. Individual (A) and cumulative (B) two-year toxicity prevalence for patients treated by conventional radiotherapy (cRT) or adaptive dose-redistribution (rRT) with corresponding number of patients with toxicity (white).

Lip Wai Lee; Radiation oncologist at the Christie NHS Foundation Trust.

Signe Friesland; Radiation oncologist at the Karolinska Comprehensive Cancer Center.

Roel J.H.M. Steenbakkers; Radiation oncologist at the University Medical Center Groningen.

Lisa Tans; Radiation oncologist at the Erasmus Medical Center.

Jolien Heukelom; Radiation oncologist at the Maastro Center; former PhD-student on ARTFORCE trial/FP7 project.

Mutamba T. Kayembe; Statistician at the Antoni van Leeuwenhoek hospital.

Simon R. van Kranen; Postdoc at the Antoni van Leeuwenhoek hospital.

Harry Bartelink; retired radiation oncologist at the Antoni van Leeuwenhoek hospital.

Coen R.N. Rasch; Professor at Leiden University; Radiation oncologist at the Leiden University Medical Center.

Jan-Jakob Sonke; Professor by special appointment at University of Amsterdam; senior group leader at Antoni van Leeuwenhoek hospital; ownership of patent/license fees/copyright at Elekta AB; member of the international advisory board at Physics, medicine and biology; editorial board member of Physics & Imaging in Radiation Oncology.

Olga Hamming-Vrieze; Radiation oncologist at Antoni van Leeuwenhoek hospital.

CRediT authorship contribution statement

Anna Liza M.P. de Leeuw: Formal analysis, Investigation, Methodology, Visualization. **Jordi Giralt:** Investigation, Methodology, Resources, Writing – review & editing. **Yungan Tao:** Conceptualization, Investigation, Methodology, Resources, Writing – review & editing. **Sergi Benavente:** Investigation, Resources, Writing – review & editing. **Thanh-Vân France Nguyen:** Investigation, Resources, Writing – review & editing. **Frank J.P. Hoebers:** Conceptualization, Investigation, Methodology, Resources, Writing – review & editing. **Ann Hoeben:** Resources, Writing – review & editing. **Chris H.J. Terhaard:** Investigation, Resources, Writing – review & editing. **Lip Wai Lee:** Investigation, Resources, Writing – review & editing. **Signe Friesland:** Investigation, Resources, Writing – review & editing. **Roel J.H.M. Steenbakkers:** Investigation, Resources, Writing – review & editing. **Lisa Tans:** Investigation, Resources, Writing – review & editing. **Jolien Heukelom:** Investigation, Resources, Writing – review & editing. **Mutamba T. Kayembe:** Formal analysis, Validation, Writing – review & editing. **Simon R. van Kranen:** Resources, Software, Supervision, Writing – review & editing. **Harry Bartelink:** Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing. **Coen R.N. Rasch:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. **Jan-Jakob Sonke:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Olga Hamming-Vrieze:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110281.

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