INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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CLINICAL INVESTIGATION

Disease Control and Late Toxicity in Adaptive Dose Painting by Numbers Versus Nonadaptive Radiation Therapy for Head and Neck Cancer: A Randomized Controlled Phase 2 Trial

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Received Nov 7, 2022; Accepted for publication Jan 2, 2024

Purpose: Local recurrence remains the main cause of death in stage III-IV nonmetastatic head and neck cancer (HNC), with relapse-prone regions within high ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET)-signal gross tumor volume. We investigated if dose escalation within this subvolume combined with a 3-phase treatment adaptation could increase local (LC) and regional (RC) control at equal or minimized radiation-induced toxicity, by comparing adaptive ^{18}F-FDG-PET voxel intensity−based dose painting by numbers (A-DPBN) with nonadaptive standard intensity modulated radiation therapy (S-IMRT).

Methods and Materials: This 2-center randomized controlled phase 2 trial assigned (1:1) patients to receive A-DPBN or S-IMRT (+/−chemotherapy). Eligibility: nonmetastatic HNC of oral cavity, oro-/hypopharynx, or larynx, needing radio (chemo)therapy; T1-4N0-3 (exception: T1-2N0 glottic); KPS ≥ 70; ≥18 years; and informed consent. Primary outcomes: 1-year LC and RC. The dose prescription for A-DPBN was intercurrently adapted in 2 steps to an absolute dose-volume limit (≤1.75 cm^3 can receive >84 Gy and normalized isoeffective dose >96 Gy) as a safety measure during the study course after 4/7 A-DPBN patients developed ≥G3 mucosal ulcers.

Results: Ninety-five patients were randomized (A-DPBN, 47; S-IMRT, 48). Median follow-up was 31 months (IQR, 14-48 months); 29 patients died (17 of cancer progression). A-DPBN resulted in superior LC compared with S-IMRT, with 1- and

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This protocol is registered with ClinicalTrials.gov and may be viewed online at https://classic.clinicaltrials.gov/ct2/show/NCT01341535.

On April 29, 2019, the study was presented as a late breaking abstract at ESTRO38 (OC-0504).

Disclosures: J.-F.D. has received grants from Kom Op Tegen Kanker and consulting fees/honoraria from Varian Medical Systems and Aquilab. The other authors declare no conflicts of interest. This project was supported by the following grants: Kom op tegen kanker, Stichting Tegen Kanker, Elekta Consortium on adaptive radiation therapy, and Agentschap voor Innovatie door Wetenschap en Technologie. They did not play a role in study design, data collection, analysis, interpretation, or writing of the report. The corresponding authors had full access to all data and final responsibility for the decision to submit for publication.

Data Sharing Statement: The trial protocol and statistical analysis plan can be requested or can be made available online.

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ijrobp.2024.01.012.

Int J Radiation Oncol Biol Phys, Vol. 000, No. 00, pp. 1−12, 2024
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https://doi.org/10.1016/j.ijrobp.2024.01.012

2-year LC of 91% and 88% versus 78% and 75%, respectively (hazard ratio, 3.13; 95% CI, 1.13-8.71; $P = .021$). RC and overall survival were comparable between arms, as was overall grade (G) ≥3 late toxicity (36% vs 20%; $P = .1$). More ≥G3 late mucosal ulcers were observed in active smokers (29% vs 3%; $P = .005$) and alcohol users (33% vs 13%; $P = .02$), independent of treatment arm. Similarly, in the A-DPBN arm, significantly more patients who smoked at diagnosis developed ≥G3 (46% vs 12%; $P = .005$) and ≥G4 (29% vs 8%; $P = .048$) mucosal ulcers. One arterial blowout occurred after a G5 mucosal toxicity.

Conclusions: A-DPBN resulted in superior 1- and 2-year LC for HNC compared with S-IMRT. This supports further exploration in multicenter phase 3 trials. It will, however, be challenging to recruit a substantial patient sample for such trials, as concerns have arisen regarding the association of late mucosal ulcers when escalating the dose in continuing smokers. © 2024 Elsevier Inc. All rights reserved.

Introduction

Local recurrence remains the main cause of relapse and death for patients with stage III-IV head and neck squamous cell carcinoma (HNSCC).[1] Despite an absolute local control (LC) and overall survival (OS) benefit when combining normofractionated radiation therapy with concomitant cisplatin, up to 50% of patients will experience a local recurrence,[1] depending on disease site and stage.[2] For radiation therapy as a single treatment modality, altered fractionation has resulted in better LC and OS.[3] However, standard, hyperfractionated, or accelerated irradiation, with homogeneous, uniform dose distributions and without treatment adaptation over several weeks, does not consider the spatial or temporal heterogeneity and complex dynamic biology of tumors.[4]

Relapse-prone regions have been previously described to be located within the high ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) signal gross tumor volume (GTV) for HNSCC, presumably because of intratumoral subvolumes of radioresistance.[5-8] Tumor response to radiation depends on different tumor-specific factors—for example, varying oxygen supply, tumor cell proliferation, and density,-all of these indicating tumor biology heterogeneity.[9] In addition, tumor shrinkage[10] and weight loss result in changes in dose-deposition in the case of unchanged treatment plans.

We hypothesized that adaptive dose painting using ^{18}F-FDG-PET−guided[11] dose escalation in a shrinking target might tackle these hurdles in HNSCC radiation therapy. We previously demonstrated the technical and clinical feasibility of adaptive ^{18}F-FDG-PET−based dose painting performed in 2 phase 1 clinical trials,[12-15] in which we observed an excellent LC of 90% at 1 year of follow-up, without acute dose-limiting toxicity.[14]

We conducted this phase 2 randomized controlled trial comparing adaptive ^{18}F-FDG-PET voxel intensity−based radiation therapy, adaptive dose painting by numbers (A-DPBN), with nonadaptive standard intensity modulated radiation therapy (S-IMRT), investigating if adaptive dose escalation could result in a higher LC with minimal or reduced radiation-induced toxicity.

In this manuscript, long-term outcomes such as LC, regional control (RC), survival, and long-term toxicity, are discussed. For the dosimetry analysis and acute toxicity, we refer to our second manuscript by Vercauteren et al. which is under review.

Methods and Materials

Study design and patients

We performed a prospective, randomized controlled phase 2 trial in 2 Belgian health care centers, designed to demonstrate superior LC using A-DPBN compared with S-IMRT. This study was approved by the Ghent University Hospital (GUH) ethics board (EC2010/567) and the institutional review board at the participating site (Namur), and was registered on ClinicalTrials.gov (NCT01341535).

Eligibility criteria included primary histologically confirmed HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx, which was unresectable or for which the patient refused surgery; TNM Classification of Malignant Tumors 7th Edition clinical categories T1-4 N0-3 (exception: T1-2 N0 glottic cancer); needing primary radio (chemo)therapy; Karnofsky performance status ≥70%; ≥18 years; and willingness to provide informed consent. Patients with prior irradiation to the head and neck region; prior malignancies (exception: cured nonmelanoma skin cancer, curatively treated in situ cervix carcinoma, or other curatively treated cancers without evidence of disease for ≥5 years); M1 disease; pregnancy; creatinine clearance ≤60 mL/min; need for combined brachytherapy; mental condition or unlikely to comply with the protocol or to complete the study, were considered ineligible.

Randomization and masking

Eligible patients with HNSCC were randomly assigned (1:1) to receive either experimental A-DPBN or standard nonadaptive IMRT. Randomization was stratified per treating center, balanced using randomly permuted blocks, and performed at GUH. Random treatment assignment was not masked.

Outcomes

1. The primary outcome measures were LC and RC at 1 year, defined as the time from randomization to local and regional disease relapse or progression, respectively, preferentially confirmed by biopsy.

2. Secondary outcomes included tumor response with ^{18}F-FDG-PET computed tomography (CT) scan at 3 months after treatment; distant disease control (documentation of second primary cancer was mandatory); disease-free survival (DFS; time from randomization to local, regional, or distant disease progression or to death in absence of recurrent disease); distant metastases-free survival (DMFS; time from randomization to distant disease progression); disease-specific survival (DSS; time from randomization to death that can be attributed to the index cancer); OS (time from randomization to death from any cause); acute toxicities (dermatitis, mucositis, dermatitis, necessity of feeding tube, hospitalization, weight loss, fatigue); and late toxicities (xerostomia, dysphagia, and mucosal ulcers).

Physical examination including laryngo-pharyngoscopy and late adverse event scoring, using LENT/SOMA (Late Effects in Normal Tissues-Subjective, Objective, Management, and Analytic Score), were performed every 3 months for 2 years and half-yearly thereafter. Late toxicity assessment was performed at each follow-up visit from 6 months after radiation therapy until the last consultation. The highest toxicity grade during follow-up is reported. Grade grouping for statistical assessment was performed, considering ≥G3 mucosal ulcers, ≥G2 xerostomia, and ≥G2 dysphagia as clinically meaningful.

Procedures

For extensive details on delineation of targets and organs at risk, dose prescription, treatment planning and delivery for both treatment groups, and for the dose painting by numbers strategy from Ghent and Namur, we refer to our secondary dosimetry and acute toxicity paper by Vercauteren et al and to our study protocol.

Dose prescription in the A-DPBN arm

Figure E1 provides the dose prescription protocol (DPP) to the macroscopic and elective targets. Dose painting was performed in targets GTV-P (P = primary tumor) and GTV-N (N = node). During the conduct of the trial, the DPP was adapted in 2 steps: in a first step, as an unexpectedly high number of ≥G3 mucosal ulcerations occurred in the A-DPBN arm (4/7 patients), and in a second step based on the results of an analysis of our group demonstrating an absolute dose-volume limit for dose escalation to limit the risk of mucosal ulcers.[16] This dose-volume limit was defined as follows: ≤1.75 cm^3 can receive >84 Gy and normalized isoeffective dose >96 Gy.[16]

Elective node irradiation sums up to 40 Gy in 20 fractions. This prescription was based on the results of an elective dose de-escalation trial that did not demonstrate increased risk of regional recurrence.[17,18]

Dose prescription in the S-IMRT arm

In the S-IMRT arm, the clinical dose prescription from GUH was applied with 32 fractions of 2.16 Gy in 5 weekly fractions to the high-risk planning target volume. The elective neck received 56 Gy in 32 fractions using a simultaneously integrated boost technique.

Concurrent chemotherapy

Administration of concurrent chemotherapy was decided by the multidisciplinary tumor board and left at the discretion of the treating physician. In general, chemotherapy was indicated in patients with cT3-4 or/and cN+ tumors. The chemotherapy scheme of preference was cisplatin 100 mg/m^2 every 3 weeks or 40 mg/m^2 weekly.

Sample size

This study used a randomized phase 2 design to detect an improvement in LC at 1 year of follow-up using A-DPBN. Based on previous original work from our institution,[12-14] we could determine an expected 90% LC rate using DPBN and considered a 75% rate as unacceptable (α = 0.15; P = .95). Consequently, the study could be conducted with at least 90 eligible patients (45 patients per arm). Considering a 10% drop out of patients lost to follow-up, a total number of 100 eligible patients was needed.

Statistical analysis

Descriptive statistics

Descriptive statistics were used to summarize patient characteristics per treatment arm, using nonparametric tests (Mann-Whitney U and Fisher exact or χ^2, for continuous and categorical variables). Tests were performed using 2-sided using statistical software SPSS version 25 (IBM) and P values ≤.05 were considered significant.

Survival analysis

Kaplan-Meier survival analysis was used to estimate LC, RC, locoregional control (LRC), DMFS, DFS, DSS, and OS; group comparison was carried out using log-rank test, and associated hazard ratios (HR) and 95% CIs were determined. Patients were censored at their last follow−up.

Exploratory analysis

In case of regional recurrence, diagnostic imaging at time of recurrence was analyzed and compared with the treatment plan, whereafter regional recurrences were categorized as being located within the GTV-N, within the elective neck, or outside the elective neck.

Post hoc univariate analysis (using analysis of variance [ANOVA] tests) and subsequent multivariate analysis (using MANOVA tests) for LC, RC, LRC, DFS, and OS were performed for T and N stage, stage grouping, primary tumor site, concurrent chemotherapy, smokers, alcohol users, and treating center.

Results

Baseline characteristics

Between October 6, 2011, and October 31, 2017, 98 eligible patients were enrolled in the trial, of whom 95 were randomly assigned to receive either A-DPBN or S-IMRT +/− concurrent systemic therapy (Fig. 1). Baseline patient and tumor characteristics per treatment arm are listed in Table 1. Median follow-up time for the whole cohort was 31 months (IQR, 14-48 months) and 37 months for surviving patients (IQR, 25-50 months). An unplanned treatment deviation was necessary in 4/47 and 4/48 patients treated with A-DPBN and S-IMRT, respectively, which was due to technical problems, tracheotomy, refusal of PET−CT, or significant anatomic changes (Fig. 1).

Primary and secondary outcomes

Kaplan-Meier survival estimates are shown in Figure 2A and 2B.

Primary outcomes

Kaplan-Meier analysis demonstrates superior LC after A-DPBN compared with S-IMRT with a 1- and 2-year LC of 91% and 88% versus 78% and 75% for A-DPBN and S-IMRT, respectively (HR, 3.13; 95% CI, 1.13-8.71; P = .021), which is depicted in Figure 2A. Kaplan-Meier estimates show comparable RC and LRC (Fig. 2A), with 1- and 2-year RC estimates of 86% and 81% versus 84% and 82% for A-DPBN and S-IMRT, respectively (HR, 1.04; 95% CI, 0.39-2.78; P = .935) and a 1- and 2-year LRC of 82% and 77% versus 73% and 68%, respectively (HR, 1.78; 95% CI, 0.81-3.92; P = .149). Seven and 8 patients in A-DPBN and S-IMRT had a regional recurrence during follow-up, respectively. In A-DPBN, 3/7 were located within the elective neck compared with 2/8 in S-IMRT (P = .608). All other regional recurrences are located within the GTV-N.

Secondary outcomes

DMFS, DSS, and OS were comparable between both arms (Fig. 2B), with a 1- and 2-year DMFS of 89% and 89% versus 87% and 78%, respectively (HR, 1.9; 95% CI, 0.64-5.68; P = .242), 1- and 2-year DSS of 91% and 86% versus 91% and 80%, respectively (HR, 1.3; 95% CI, 0.51-3.67; P = .535), and a 1- and 2-year OS of 85% and 80% versus 88% and 69%, respectively (HR, 1.73; 95% CI, 0.81-3.67; P = .151) for A-DPBN and S-IMRT. There is a numerical difference in DFS in favor of A-DPBN, although not statistically significant (HR, 1.80; 95% CI, 0.96-3.36; P = .062): 1- and 2-year DFS of 72% and 68% versus 62% and 55% for A-DPBN and S-IMRT, respectively.

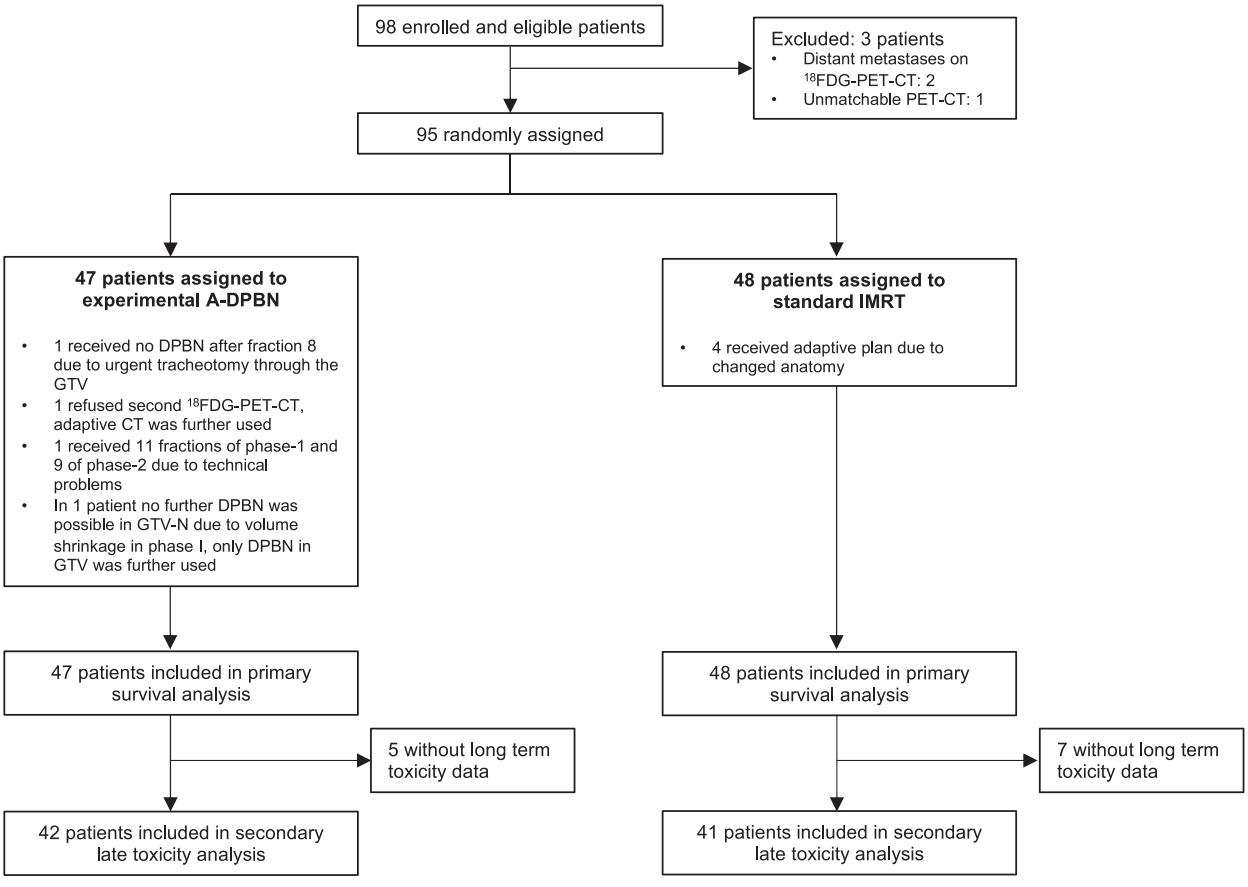


Fig. 1. CONSORT diagram of the randomized phase 2 trial.

Table 1 Baseline patient and tumor characteristics per treatment arm of the eligible cohort

Characteristic	A-DPBN (n = 47)	S-IMRT (n = 48)	*P* value
Age at diagnosis (y)			.25
Median (IQR)	61 (55-67)	58 (53-64)	
Gender			1
Male	40 (85%)	40 (83%)	
Female	7 (15%)	8 (17%)	
Treating center			1
Ghent	39 (83%)	39 (81%)	
Namur	8 (17%)	9 (19%)	
Tumor site			.01
Oropharynx	34 (72%)	19 (40%)	
HPV positive	7 (21%)	4 (21%)	
HPV negative	17 (50%)	10 (53%)	
HPV unknown	10 (29%)	5 (26%)	
Hypopharynx	8 (17%)	18 (38%)	
Larynx	4 (9%)	8 (17%)	
Oral cavity	1 (2%)	3 (6%)	
Stage grouping (TNM 7)			.36
I	1 (2%)	1 (2%)	
II	3 (6%)	3 (6%)	
III	12 (26%)	9 (19%)	
IVa	29 (62%)	27 (56%)	
IVb	2 (4%)	8 (17%)	
Tumor stage			.18
T1	6 (13%)	8 (17%)	
T2	17 (36%)	15 (31%)	
T3	15 (32%)	8 (17%)	
T4a	7 (15%)	9 (19%)	
T4b	2 (4%)	8 (17%)	
Node category			.96
N0	8 (17%)	6 (13%)	
N1	8 (17%)	11 (23%)	
N2a	3 (6%)	3 (6%)	
N2b	11 (23%)	11 (23%)	
N2c	17 (36%)	17 (35%)	
Pre−radiation therapy neck dissection			.09
Yes	7 (15%)	2 (4%)	
No	40 (85%)	46 (96%)	
Concomitant chemotherapy			.53
Yes	31 (66%)	28 (58%)	
Cisplatin	30 (97%)	25 (89%)	
Carboplatin/5FU or cetuximab	1 (3%)	3 (11%)	
No	16 (34%)	20 (42%)	

(*Continued*)

Table 1 (*Continued*)

Characteristic	A-DPBN (n = 47)	S-IMRT (n = 48)	*P* value
Active smoking pretreatment	28 (60%)	26 (54%)	.76
Continued smoking	15 (32%)	20 (42%)	.07
Active alcohol users pretreatment	19 (40%)	14 (29%)	.39
Continued alcohol use	12 (26%)	9 (19%)	.75

Abbreviations: A-DPBN = adaptive dose-painting-by-numbers; 5FU = 5-fluorouracil; HPV = human papillomavirus; S-IMRT = standard intensity modulated radiation therapy.

At a median follow-up of 31 months, 29 out of 95 patients had died (A-DPBN = 11; S-IMRT = 18). Causes of death were cancer progression (17/29, 59%), comorbidities (cardiovascular disease: 5/29, 17%; liver cirrhosis: 1/29, 3%), radio(chemo)therapy-induced toxicity (3/29, 10%; 1 arterial blow out in A-DPBN arm, 1 aspiration pneumonia, and 1 infection), second primary tumor (1/29, 3%), and cause unknown (2/29, 7%).

Exploratory analyses were performed and are depicted in Table 2. In this exploratory univariate analysis, a higher T-stage results in worse LC ($P = .007$), DFS ($P = .027$), and OS ($P = .025$) probability (Table 2). Furthermore, smoking continuation resulted in worse LC ($P = .031$) and a higher N stage in worse DFS ($P = .015$) and OS ($P < .001$) probability. These correlations are confirmed in the subsequent multivariate analysis (Table 2). In the experimental arm, a lower rate of T4 tumors was included without statistical significance. All the previously mentioned variables were comparably distributed between treatment groups (Table 1).

Neither the primary tumor site nor the treating center influenced the outcome measures probability for (L)RC, DFS, or OS in this univariate analysis (Table 2). However, in multivariate analysis, the primary tumor site did influence DFS ($P = .036$) and OS ($P = .038$), with the worst DFS and OS for patients with hypopharyngeal cancer (Table 2).

Tables 3 and 4 and Figure 3 depict late toxicity outcomes. Late toxicity assessment was performed in 83 patients (A-DPBN, 42; S-IMRT, 41) from 6 months after radiation therapy until their last visit, with median follow-up time of 31 months. The other 12 patients either progressed, deceased during or within 3 months after treatment, or failed to maintain compliance. Although a numerical difference can be seen, there was no statistically significant difference in patients suffering any ≥G3 late adverse events: 15/42 (36%) versus 8/41 (20%) in A-DPBN and S-IMRT, respectively ($P = .1$).

Late dysphagia and xerostomia occurred similarly in both arms (Table 3). One patient with primary hypopharyngeal carcinoma infiltrating into the upper esophagus in the S-IMRT group encountered G4 dysphagia at long-term follow-up, due to stricture of the esophageal inlet; no other G4 dysphagia was observed. Long-term ≥G2 xerostomia at 36 months of follow-up showed a numerical difference in favor of A-DPBN, although not statistically significant (Table 3).

After adapting the dose prescription in the dose-painting protocol because of G3-4 mucosal ulcers (Fig. E1; Methods and Materials),[16] still significantly more patients developed G3-4 late mucosal ulcers in the A-DPBN group compared with S-IMRT: G3-4 in 14/42 (33%) versus 3/41 (7%) ($P = .003$; Tables 3 and 4), of which there were G4 ulcers in 8/42 (19%) versus 2/41 (5%) ($P = .047$; Tables 3 and 4). Spontaneous healing was observed in all 3 patients with G3-4 late mucosal ulcers treated with S-IMRT and in 9/14 A-DPBN patients. One patient treated with A-DPBN deceased because of an arterial blow-out without proof of tumor recurrence, which was therefore considered a G5 radiation therapy–induced mucosal ulcer. The remaining 4 patients needed surgical intervention.

Risk behavior at diagnosis associated significantly with ≥G3 late mucosal ulcers in the whole study population. Figure 3 shows that significantly more ≥G3 late mucosal ulcers were observed in active smokers (16/54 [29%] vs 1/29 [3%]; $P = .005$) and alcohol users (11/33 [33%] vs 6/48 [13%]; $P = .024$) compared with nonsmokers/alcohol users at diagnosis. For ≥G4 late mucosal ulcers, comparable results were observed in active smokers at diagnosis (10/54 [19%] vs 0/29 [0%]; $P = .013$), but no association was found with active alcohol use at diagnosis (Fig. 3). Table 4 further depicts that active smoking habits were also significantly linked with the development of ≥G3 (13/28 [46%] vs 3/26 [12%]; $P = .005$) or ≥G4 (8/28 [29%] vs 2/26 [8%]; $P = .048$) mucosal ulcers in the A-DPBN-group specifically.

Discussion

This is the first randomized phase 2 trial that head-to-head compares an adaptive dose-escalation radiation therapy strategy, using ^{18}F-FDG-PET-voxel-intensity-based optimization (dose-painting-by-numbers), to standard nonadaptive IMRT for the primary treatment of HNSCC. We report on L(R)C, D(M)FS, DSS, OS, and late toxicity at a median follow-up of 31 months. Patients treated with A-DPBN experienced superior LC, with an absolute increase of 13% at 1 year of follow-up in comparison to S-IMRT. No RC benefit of the A-DPBN strategy is observed.

Despite relatively good LC with S-IMRT compared with historical data,[1-3] which could be attributed to a relatively large portion of patients with T1-2 stages (48% in S-IMRT; 49% in A-DPBN), superior LC is achieved by increasing the radiation dose to relapse-prone regions, which are

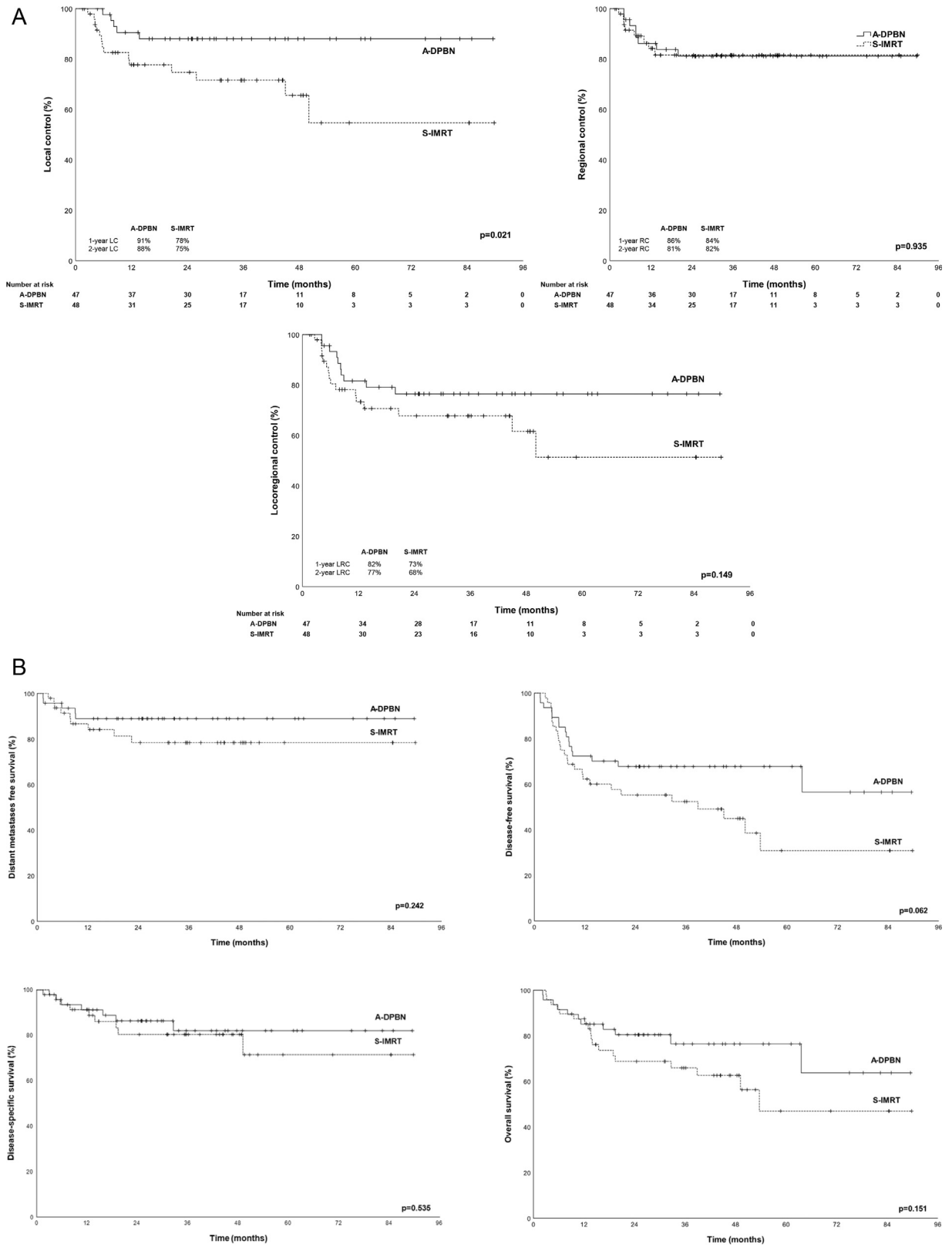


Fig. 2. (A) Kaplan-Meier survival analysis on primary outcome measures — local, regional, and locoregional control. (B) Kaplan-Meier survival analysis on secondary outcome measures: distant metastases-free, disease-free, disease-specific, and overall survival.

Table 2 Univariate and subsequent multivariate analysis for LC, RC, LRC, DFS, and OS probability

		Univariate analysis (*P* values)					Multivariate analysis (*P* values)		
		LC	RC	LRC	DFS	OS	LC	DFS	OS
Factor	n								
T stage		**.007**	.686	.1	**.027**	**.025**	**<.001**	**.027**	**.025**
T1-2	46	**42 (86%)**	39 (85%)	37 (80%)	**31 (67%)**	**37 (80%)**			
T3-4	49	**34 (69%)**	40 (82%)	32 (65%)	**22 (45%)**	**29 (59%)**			
N stage		.750	.375	.623	**.015**	**<.001**		**.015**	**<.001**
N0-1	33	27 (82%)	29 (88%)	25 (76%)	**24 (73%)**	**30 (91%)**			
N2	62	49 (79%)	50 (81%)	44 (71%)	**29 (47%)**	**36 (58%)**			
Stage grouping (TNM 7)	.715	.524	.507	.693	.051				
I-II	8	6 (75%)	6 (75%)	5 (62%)	5 (62%)	8 (100%)			
III-IV	87	70 (80%)	73 (84%)	64 (74%)	48 (55%)	58 (67%)			
Tumor site		.127	.420	.464	.077*	.083*	.393	**.036**	**.038**
Oral cavity	4	2 (50%)	3 (75%)	2 (50%)	2 (50%)	3 (75%)			
Oropharynx	53	46 (87%)	43 (81%)	40 (75%)	34 (64%)	40 (75%)			
Larynx	12	10 (83%)	12 (100%)	10 (83%)	8 (67%)	10 (83%)			
Hypopharynx	26	18 (69%)	21 (81%)	17 (65%)	9 (35%)	13 (50%)			
Smoking		**.031**	.194	.134	.600	.325	**.031**		
Never/stopped	39	**28 (72%)**	30 (77%)	25 (64%)	21 (54%)	26 (67%)			
Continued	35	**11 (31%)**	31 (89%)	28 (80%)	21 (60%)	27 (77%)			
Alcohol use		.441	.208	.467	.604	.326			
Never/stopped	49	38 (78%)	38 (78%)	33 (67%)	27 (55%)	34 (69%)			
Continued	21	18 (86%)	19 (90%)	16 (76%)	13 (62%)	17 (81%)			
Concurrent chemotherapy	.531	.972	.690	.219	.173				
No	36	30 (83%)	30 (83%)	27 (75%)	23 (64%)	28 (78%)			
Yes	59	46 (78%)	49 (83%)	42 (71%)	30 (51%)	38 (64%)			
Treating center		.692	.542	.837	.784	.207			
Ghent	78	63 (81%)	34 (44%)	57 (73%)	43 (55%)	52 (67%)			
Namur	17	13 (76%)	15 (88%)	12 (71%)	10 (59%)	14 (82%)			

Significant outcomes are in boldface. Percentages are provided at median follow-up of 31 months.

Abbreviations: DFS = disease-free survival; LC = local control; LRC = locoregional control; OS = overall survival; RC = regional control.

* *P* values with a trend toward significance, which were also evaluated in multivariate analysis.

presumably located within ^{18}F-FDG-avid subvolumes.[5-8,19] This has previously been suggested in our matched case-control study on 3-phase A-DPBN,[20] which showed an absolute benefit in LC of 8.7% at 5 years, due to dose escalation up to 24% in function of FDG-avidity.[20] Our findings in this randomized phase 2 trial are consistent with these data.

In contrast, the A-DPBN strategy does not lead to a benefit in RC, with 7 recurrences compared with 8 in S-IMRT. Regardless of dose escalation, most regional recurrences in both arms were located within the initial GTV-N: 4 patients in the A-DPBN arm had an in-field regional recurrence, which is statistically comparable to the 6 in-field recurrences in the S-IMRT group. However, the A-DPBN dose prescription in this trial was designed to deliver a somewhat lower D98 to the non-FDG-avid subregions within the GTV-N compared with S-IMRT (with standard prescription on D50). This especially leads to lower doses in necrotic, nonavid pathologic lymph nodes. We cannot rule out that this might have hampered with obtaining a comparable benefit in control as in the escalated primary tumors, which were mostly nonnecrotic and more FDG-avid in larger relative parts. Furthermore, 3/7 regional recurrences were located in the electively treated neck up to 40 Gy in 20 fractions in the A-DPBN arm and 2/8 in the electively treated neck up to 56 Gy in 32 fractions in the S-IMRT arm. Notwithstanding such different dose prescriptions for the elective neck (see Methods and Materials), there are no strong

Table 3 Details on all treatment-related late toxicity

G	A-DPBN	S-IMRT	*P* value
Late toxicity in general			.1
<G3	27 (64%)	33 (80%)	
≥G3	15 (36%)	8 (20%)	
Mucosal ulcers			
≥G3	14 (33%)	3 (7%)	**.003**
≥G4	8 (19%)	2 (5%)	**.047**
Xerostomia			.15
G0-1	30 (83%)	19 (68%)	
G2-3	6 (17%)	9 (32%)	
Xerostomia (at 36 mo)			.07
G0-1	15 (94%)	9 (64%)	
G2-3	1 (6%)	5 (36%)	
Dysphagia			.31
G0-1	35 (97%)	24 (89%)	
G2-4	1 (3%)	3 (11%)	
Dysphagia (at 36 mo)			1
G0-1	15 (94%)	16 (100%)	
G2-4	1 (6%)	0 (0%)	
Other G3 toxicities			
Atrophy	0	1	
Denture use	1	1	
Difficulty breathing	0	1	
Fibrosis	0	1	
Hoarseness	3	1	
Mastication dysfunction	1	1	
Sensation	1	0	
Taste alteration	2	2	
Trismus	2	0	
Other G4 toxicities			
Stridor or dyspnea	1	1	
Taste alteration	0	1	

Significant outcomes are in boldface. The highest toxicity grade during follow-up is reported. Assessment was performed at median follow-up time of 31 months. Fisher exact tests were used to calculate *P* values for the comparison of the adverse events between treatment arms.

Abbreviations: A-DPBN = adaptive dose painting by numbers; G = grade; S-IMRT = standard intensity modulated radiation therapy.

arguments leading to the hypothesis that this difference influenced RC, although the trial was not designed to detect differences in RC in the purely elective neck. Within the research arena, however, we used the elective neck dose of 40 Gy to limit toxicity, as previous multicenter studies illustrated the potential benefit of this type of de-escalation, although also in a recent update the results remained underpowered to undoubtfully prove noninferiority in terms of RC.[21,22]

The equal occurrence of regional recurrences in both treatment arms mitigates the beneficial effect of A-DPBN on combined LRC. However, it could be argued that the superior LC associated with A-DPBN remains clinically relevant: although salvage neck dissection can mostly be offered with curative intent in case of regional failure, most patients with local recurrent disease show a poor prognosis.

The first DPP of the current trial was derived from the maximally tolerated dose from our phase 1 trial.[12] Early in the trial, we adapted the levels of dose escalation in our experimental arm in 2 steps after 4/7 cases of ≥G3 mucosal ulcers. We hypothesized that the occurrence of these ulcers could be strongly reduced by restricting the mathematical dose and normalized isoeffective dose exceeding 84 and 96 Gy, respectively, to a subvolume of ≤1.75 cm^3. This was described in our previous published paper during the trial.[16] Unfortunately, even after adapting the dose prescription, patients treated with A-DPBN still developed significantly more ≥G3 late mucosal ulcers compared with S-IMRT (14/42, 33% vs 3/41, 7%). Concordant findings were described in other phase 1 trials, with 32% (6/19) of patients with G3 mucosal toxicity in a 2-phase study using a simultaneous integrated boost strategy[19] and 13% (9/72) with G4 mucosal toxicity in a 3-phase trial.[20] Recently, the FiGaRO phase 1 nonrandomized trial investigated a nonadaptive dose-painting strategy.[23] They reported ≥G3 late mucosal toxicity in up to 19% of the 24 included patients, compared with 33% in our A-DPBN group.[23] This percentage, however, correlates more similarly to the ≥G3 late mucosal toxicity rate in standard IMRT series, with rates up to 24.6%.[24-27] The 7% toxicity rate in our S-IMRT is low compared to the ones in these large series.[24-27]

Other historical identified risk factors contributing to late mucosal ulcers are age, vascular disease, concurrent cisplatin, continued smoking,[28] alcohol abuse, and several more. In our phase 2 trial, like others, we observed a significant association between active smoking, but not with continuation of alcohol use, and the development of mucosal ulcers: 3/26 (12%) and 13/28 (46%) of patients who continued smoking developed ≥G3 mucosal ulcers in S-IMRT and A-DPBN arms, respectively (P = .005). One patient who ceased smoking developed a G3 ulcer in the A-DPBN arm, and there were none in the S-IMRT arm. Our trial was not designed to detect a difference in developing mucosal ulcers between smokers and nonsmokers or to identify a causal correlation between smoking continuation and DPBN. However, these findings allowed us to confirm an association between smoking and late mucosal ulcers and let us cautiously conclude that this dose escalation might not be safely delivered to patients who possibly will continue to smoke.

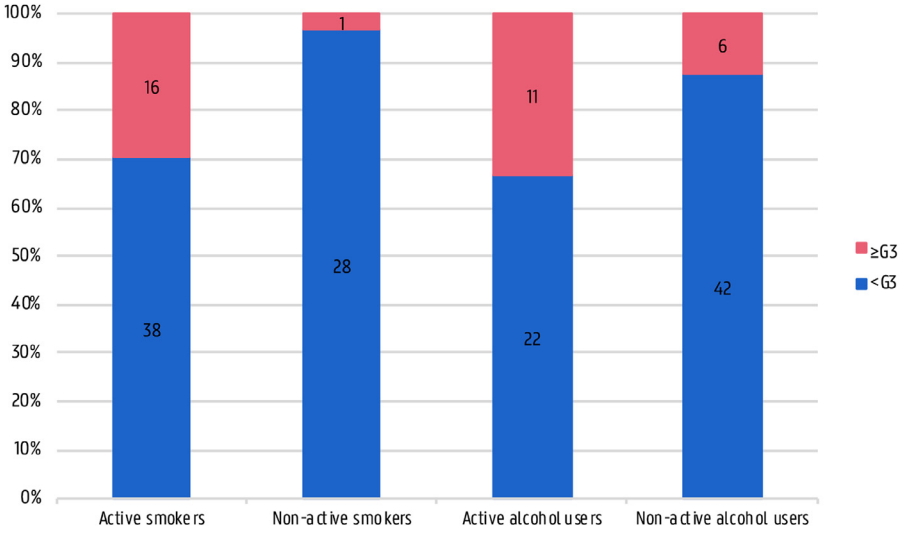
The most important limitation to our randomized trial is the unfortunate, statistically significant, imbalance in distribution of the primary tumor site, as randomization was stratified by treating center only. There were more patients

Table 4 Details on treatment-related late mucosal toxicity and its association with active smoking and alcohol consumption

Subgroups	Mucosal toxicity	A-DPBN	S-IMRT	*P* value
All patients	Total	42 (100%)	41 (100%)	
	≥G3	14 (33%)	3 (7%)	**.003**
	≥G4	8 (19%)	2 (5%)	**.047**
Active smokers	Total	28 (100%)	26 (100%)	
	≥G3	13 (46%)	3 (12%)	**.005**
	≥G4	8 (29%)	2 (8%)	**.048**
Nonactive smokers	Total	14 (100%)	15 (100%)	
	≥G3	1 (7%)	0 (0%)	.483
	≥G4	0 (0%)	0 (0%)	-
Active alcohol users	Total	19 (100%)	14 (100%)	
	≥G3	8 (42%)	3 (21%)	.278
	≥G4	4 (21%)	2 (14%)	.618
Nonactive alcohol users	Total	23 (100%)	25 (100%)	
	≥G3	6 (26%)	0 (0%)	**.006**
	≥G4	4 (17%)	0 (0%)	**.029**

Significant outcomes are in boldface. *P* values were calculated using nonparametric Fisher exact tests.
Abbreviations: A-DPBN = adaptive dose painting by numbers; G = grade; S-IMRT = standard intensity modulated radiation therapy.

with oropharyngeal carcinoma in the A-DPBN group and more hypopharyngeal tumors in the S-IMRT group. Superior LC using A-DPBN might be attributed to this imbalance, although the percentage of human papillomavirus (HPV) etiology was low and strictly identical when documented (30% unknown because of the absence of routinely assessing the HPV/p16-status in the first years of recruitment). We tried to adjust for this imbalance by a post hoc



		<G3	≥G3	≥G4	Total
Smoking (n=83)	Active	38 (46%)	16 (19%)	10 (12%)	54 (65%)
	Not active	28 (34%)	1 (1%)	0 (0%)	29 (35%)
p-value			*0.005*	*0.013*	
Alchol use (n=81)	Active	22 (27%)	11 (14%)	6 (7%)	33 (41%)
	Not active	42 (52%)	6 (7%)	4 (5%)	48 (59%)
p-value			*0.024*	*0.186*	

Fig. 3. Details on risk behavior at diagnosis and its association with different grades of late mucosal toxicity.

uni- and multivariate analysis. This could only show that T stage and continuation of smoking, but not primary tumor site, influence the LC probability (Table 2). Numerically, although not statistically significant, a lower rate of T4 tumors was observed in the experimental treatment arm, which might also attribute to the higher LC. No statistically significant correlations were seen for (L)RC probability. The tumor site, on the other hand, did influence DFS and OS in multivariate analysis. All these results must be interpreted with caution because of the very small numbers in this exploratory subgroup analysis. Stratification for the primary tumor site (and T stage) will be obligatory in future, better-powered phase 3 clinical trials with a sufficient sample size.

With these limitations in mind, our trial demonstrates that better LC in patients with HNSCC can be achieved using A-DPBN at the cost of increased late mucosal ulcers in a nonselected population. Critical selection of patients, ideally non- or absolutely ceased smokers, will be key in the A-DPBN approach. Unfortunately, conduction of any consecutive phase 3 trials will be negatively affected by this safety limitation.

Future perspectives

LRC has been established as a validated surrogate endpoint for OS concerning evaluation of radiation therapy treatment effects in a meta-analysis by MARCH and MACH-NC research groups.[29] Currently, active prospective nonrandomized phase 1/2 clinical trials on dose painting for HNSCC are recruiting patients and will provide more knowledge on clinical outcomes. RADPAINT and RADPAINT-2 include patients with nonnasopharyngeal HNC, and for oropharyngeal tumors in particular, only HPV-negative patients are eligible. This trial will focus on acute and late toxicities as primary endpoints in an estimated group of 15 and 10 patients, respectively (NCT03847480, NCT04910308). Smoking cessation is not defined as an exclusion variable in these trials.

Conclusion

This randomized clinical phase 2 trial of patients with HNSCC demonstrated superior 1- and 2-year LC using A-DPBN, without RC benefit. This suggests the need for further exploration in multicenter phase 3 trials. We believe that critical selection of patients is paramount to safely deliver A-DPBN. Even though the trial was not designed to detect a causal relationship between continuation of smoking and late mucosal ulcers, the observed association led us to conclude that complete smoking cessation, as well as an additional absolute dose-volume limit, seem necessary to minimize the risk of late mucosal ulcers when escalating the radiation therapy dose with A-DPBN. This, however, will hamper inclusion of patients to whom voxel intensity −based dose escalation could be of benefit and will make the accrual in large multicenter phase 3 trials challenging.

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