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Disease control and late toxicity in Adaptive Dose Painting by Numbers vs. non-adaptive radiotherapy for head and neck cancer: a randomized controlled phase II trial

Short title: Long term outcome of A-DPBN in head & neck cancer

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Previous presentation(s) about the study

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

Data sharing statement

Trial protocol and statistical analysis plan can be requested or be made available online.

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ABSTRACT

BACKGROUND AND PURPOSE

Local recurrence remains the main cause of death in stage III-IV non-metastatic head-and-neck cancer (HNC) with relapse-prone regions within high ^{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 non-adaptive standard intensity-modulated radiotherapy (S-IMRT).

MATERIALS AND METHODS

This two-center randomized controlled phase II trial assigned (1:1) patients to receive A-DPBN or S-IMRT (+/-chemotherapy). Eligibility: non-metastatic 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 two steps to an absolute dose-volume limit (≤1.75cm^3 can receive >84Gy and normalized isoeffective dose >96Gy) 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 amounts 31 months (IQR: 14-48 months); 29 patients died (17 of cancer progression). A-DPBN results in superior LC compared to S-IMRT with 1- and 2-year LC of 91% and 88% vs. 78% and 75%, respectively (hazard ratio, 3.13; 95% confidence interval, 1.13-8.71; p=0.021). RC and overall survival are comparable between arms, as is overall grade (G) ≥3 late toxicity (36% vs. 20%, p=0.1). More ≥G3 late mucosal ulcers are observed in active smokers (29% vs. 3%, p=0.005) and alcohol users (33% vs. 13%, p=0.02), independent of treatment arm. Similarly, in the A-DPBN arm, significantly more patients that smoked at diagnosis developed ≥G3 (46% vs. 12%, p=0.005) and ≥G4 (29% vs. 8%, p=0.048) mucosal ulcers. One arterial blowout occurred following a G5 mucosal toxicity.

CONCLUSION

A-DPBN resulted in superior 1- and 2-year LC for HNC compared to S-IMRT. This supports further exploration in multicenter phase III trials. It will however be

challenging to recruit a substantial patient sample for such trials as concerns have arisen on the association of late mucosal ulcers when escalating the dose in continuing smokers.

ClinicalTrials.gov identifier: NCT01341535

INTRODUCTION

Local recurrence (LR) 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 radiotherapy with concomitant cisplatin, up to 50% of patients will suffer a LR (1), depending on disease-site and -stage (2). For radiotherapy as a single treatment modality, altered fractionation has demonstrated to result 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 nor 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 due to intratumoral subvolumes of radioresistance (5-8). Tumor response to radiation depends on different tumor-specific factors e.g. 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 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 radiotherapy. We previously demonstrated technical and clinical feasibility of adaptive ^{18}F-FDG-PET-based dose-painting performed in two phase I 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 II randomized controlled trial comparing adaptive ^{18}F-FDG-PET-voxel intensity-based radiotherapy, being adaptive dose-painting-by-numbers (A-DPBN), with non-adaptive standard intensity-modulated radiotherapy (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 being local control, regional control (RC), and survival, as well as long term toxicity, are discussed. For the dosimetry analysis and acute toxicity, we refer to our second manuscript by Vercauteren et al.

MATERIALS AND METHODS

Study design and patients

We performed a prospective, randomized controlled phase II trial in two Belgian healthcare centers, designed to demonstrate superior LC using A-DPBN compared to 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). 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 non-melanoma 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 HNSCC patients were randomly assigned (1:1) to receive either experimental A-DPBN or standard non-adaptive 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-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 due to 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 radiotherapy 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 (OARs), 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 & acute toxicity paper by Vercauteren et al. and to our study protocol.

1. Dose prescription in the A-DPBN arm

Supplementary Figure 1 provides the dose prescription protocol (DPP) to the macroscopic and elective targets. Dose painting was performed in targets GTV-P and GTV-N. During the conduct of the trial, the DPP has been adapted in two 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: ≤1.75cm3 can receive >84Gy and normalized isoeffective dose >96Gy (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).

2. 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 PTV. The elective neck received of 56 Gy in 32 fractions using a simultaneously integrated boost technique.

3. 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/m2 every three weeks or 40 mg/m^2 weekly.

Sample size

This study used a randomized phase II 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=0.95). Consequently, the study can be conducted with at least 90 eligible patients (45 patients per arm). Considering a 10 % drop out of patients due to lost to follow-up, a total number of 100 eligible patients were needed.

Statistical analysis

1. Descriptive statistics

Descriptive statistics were used to summarize patient characteristics per treatment arm, using nonparametric tests (Mann–Whitney U and Fischer's Exact or χ^2, for continuous and categorical variables). Tests were performed two-sided using

statistical software SPSS version 25 (IBM, NY, USA) and p-values ≤0.05 were considered significant.

2. Survival analysis

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

3. 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, the elective neck or outside the elective neck.

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

RESULTS

Baseline characteristics

- *Figure 1: Consort diagram of the randomized phase II trial.*
- *Table 1: Baseline patient and tumor characteristics per treatment arm of the eligible cohort.*

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 (Figure 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 (interquartile range [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 anatomical changes (Figure 1).

Primary and secondary outcomes

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

- *Figure 2A: Kaplan-Meier survival analysis on primary outcome measures – local (LC), regional control (RC) and locoregional control (LRC).*
- *Figure 2B: Kaplan-Meier survival analysis on secondary outcome measures – distant metastases free survival (DMFS), disease-free survival (DFS), disease-specific survival (DSS) and overall survival (OS).*

Primary outcomes: Kaplan-Meier analysis demonstrates superior LC following A-DPBN compared to S-IMRT with a 1- and 2-year LC of 91% and 88% vs. 78% and 75% for A-DPBN and S-IMRT, respectively (HR, 3.13; 95% CI, 1.13-8.71; p=0.021), which is depicted in Figure 2A.

Kaplan-Meier estimates show comparable RC and LRC (Figure 2A) with 1- and 2-year RC estimates of 86% and 81% vs. 84% and 82% for A-DPBN and S-IMRT, respectively (HR, 1.04; 95% CI, 0.39-2.78; p=0.935), and a 1- and 2-year LRC of 82% and 77% vs. 73% and 68%, respectively (HR, 1.78; 95% CI, 0.81-3.92; p=0.149). Seven and 8 patients in A-DPBN and S-IMRT were diagnosed with a regional recurrence during follow-up, respectively. In A-DPBN, 3/7 were located within the elective neck compared to 2/8 in S-IMRT (p=0.608). All other regional recurrences are located within the GTV-N.

Secondary outcomes: DMFS, DSS and OS are comparable between both arms (Figure 2B) with a 1- and 2-year DMFS of 89% and 89% vs. 87% and 78%, respectively (HR, 1.9; 95% CI, 0.64-5.68, p=0.242), 1- and 2-year DSS of 91% and 86% vs. 91% and 80%, respectively (HR, 1.3, 95% CI, 0.51-3.67; p=0.535), and a 1- and 2-year OS of 85% and 80% vs. 88% and 69%, respectively (HR, 1.73; 95% CI, 0.81-3.67; p=0.151) 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=0.062): 1- and 2-year DFS of 72% and 68% vs. 62% and 55% for A-DPBN and S-IMRT, respectively.

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%; being 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 depicted in Table 2.

Table 2: Univariate and subsequent multivariate analysis for local (LC), regional (RC), locoregional control (LRC), disease-free (DFS) and overall survival (OS) probability.

In this exploratory univariate analysis, a higher T-stage results in worse LC (p=0.007), DFS (p=0.027) and OS (p=0.025) probability (Table 2). Furthermore, smoking continuation results in worse LC (p=0.031) and a higher N-stage in worse DFS (p=0.015) and OS (p<0.001) probability. These correlations are confirmed in the subsequent multivariate analysis (Table 2). In the experimental arm, a lower rate of T4 tumors were included without statistical significance. All the abovementioned variables are comparably distributed between treatment groups (Table 1).

Neither the primary tumor site nor the treating center influence the outcome measures probability being (L)RC, DFS or OS in this univariate analysis (Table 2). However, in multivariate analysis the primary tumor site does influence DFS (p=0.036) and OS (p=0.038) with the worst DFS and OS for patients with hypopharyngeal cancer (Table 2).

Tables 3-4 and Figure 3 depict late toxicity outcomes.

- *Table 3: Details on all treatment-related late toxicity.*
- *Table 4: Details on treatment-related late mucosal toxicity and its association to active smoking and alcohol consumption.*
- *Figure 3: Details on risk behavior at diagnosis and its association with different grades of late mucosal toxicity.*

Late toxicity assessment was performed in 83 patients (A-DPBN: 42, S-IMRT: 41) from 6 months after radiotherapy 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%) vs. 8/41 (20%) in A-DPBN and S-IMRT, respectively (p=0.1).

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 has been observed. Long-term ≥G2 xerostomia at 36 months of follow-up shows a numerical difference in favor of A-DPBN, although not statistically significant (Table 3).

After adapting the dose prescription in the dose-painting protocol due to G3-4 mucosal ulcers (Supplementary Figure 1; Materials and Methods)(16), still significantly more patients developed G3-4 late mucosal ulcers in the A-DPBN group compared to S-IMRT: G3-4 in 14/42 (33%) vs. 3/41 (7%) (p=0.003; Table 3-4) of which G4 in 8/42 (19%) vs. 2/41 (5%) (p=0.047; Table 3-4). Spontaneous healing was observed in all three 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 due to an arterial blow-out without proof of tumor recurrence, which was therefore considered a G5 radiotherapy-induced mucosal ulcer. The remaining 4 patients needed surgical intervention.

Risk behavior at diagnosis associates significantly with ≥G3 late mucosal ulcers in the whole study population. Figure 3 shows that significantly more ≥G3 late mucosal ulcers are observed in active smokers (16/54 (29%) vs. 1/29 (3%), p=0.005) and

alcohol users (11/33 (33%) vs. 6/48 (13%), p=0.024) compared to non-smokers/-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=0.013) but no association was found with active alcohol use at diagnosis (Figure 3). Table 4 further depicts that active smoking habits are also significantly linked with the development of ≥G3 (13/28 (46%) vs. 3/26 (12%), p=0.005) or ≥G4 (8/28 (29%) vs. 2/26 (8%), p=0.048) mucosal ulcers in the A-DPBN-group specifically.

DISCUSSION

This is the first randomized phase II trial that head-to-head compares an adaptive dose-escalation radiotherapy strategy, using ^{18}F-FDG-PET-voxel-intensity-based optimization (dose-painting-by-numbers), to standard non-adaptive 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 to 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 presumably located within ^{18}F-FDG-avid subvolumes (5-8, 19). This has previously been suggested in our matched case-control study on three-phases 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 II trial are consistent with these data.

In contrast, the A-DPBN strategy does not lead to a benefit in RC with 7 recurrences compared to 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 to S-IMRT (with standard prescription on D50). This especially leads to lower doses in necrotic, non-avid pathological 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 are mostly non-necrotic 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 Material and Methods), there are no strong arguments leading to the hypothesis that this difference has influenced regional control, although the trial was not designed to detect differences in regional control 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 remain underpowered to undoubtfully prove non-inferiority in terms of regional control (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: while 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 has been derived from the maximally tolerated dose from our phase I trial (12). Early in the trial, we adapted the levels of dose-escalation in our experimental arm in two 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 sub-volume 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 to S-IMRT (14/42, 33% vs. 3/41, 7%). Concordant findings were described in other phase I trials, with 32% (6/19) of patients with G3 mucosal toxicity in a two-phases study using a simultaneous integrated boost strategy (19) and 13% (9/72) with G4 mucosal toxicity in a three-phases trial (20). Recently, the FiGaRO phase I non-randomized trial investigated a non-adaptive dose-painting strategy (23). They report ≥G3 late mucosal toxicity in up to 19% of the 24 included patients, compared to 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 compares low 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 II 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 that continued smoking developed ≥G3 mucosal ulcers in S-IMRT and A-DPBN arm, respectively (p=0.005). One patient that ceased smoking, developed a G3 ulcer in the A-DPBN arm, none in the S-IMRT arm. Our trial was not designed to detect a difference in developing mucosal ulcers between smokers and non-smokers nor in identifying 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 that 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 oropharyngeal carcinoma patients 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 HPV etiology was low and strictly identical when documented (30% unknown due to 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 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, however not statistically significant, a lower rate of T4 tumors is observed in the experimental treatment arm, which might also attribute to the higher LC. No statistically significant correlations are seen for (loco)regional control probability. The tumor site on the other hand, does influence DFS and OS in multivariate analysis. All these results must be interpreted with caution due to 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 III clinical trials with a sufficient sample size.

With these limitations in mind, our trial demonstrates that better LC in HNSCC patients can be achieved using A-DPBN at the cost of increased late mucosal ulcers in a non-selected 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 III trials will be negatively impacted by this safety limitation.

Future perspectives

LRC has been established as a validated surrogate endpoint for OS concerning evaluation of radiotherapy treatment effects in a meta-analysis by MARCH and MACH-NC research groups (29). Currently active prospective non-randomized phase I/II 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 non-nasopharyngeal head- and neck cancers, 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 II trial of HNSCC patients demonstrated superior 1- and 2-year LC using A-DPBN, without RC benefit. This suggests the need for further exploration in multicenter phase III 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 relation between continuation of smoking and late mucosal ulcers, the observed association let us to conclude that complete smoke cessation, as well as an additional absolute dose-volume limit, seem necessary to minimize the risk of late mucosal ulcers when escalating the radiotherapy 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 III trials extremely challenging.

REFERENCES

1. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92(1):4-14.
2. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, Pignon JP. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol. 2011;100(1):33-40.
3. Lacas B, Bourhis J, Overgaard J, Zhang Q, Gregoire V, Nankivell M, et al. Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. Lancet Oncol. 2017;18(9):1221-37.
4. Bando R, Ikushima H, Kawanaka T, Kudo T, Sasaki M, Tominaga M, et al. Changes of tumor and normal structures of the neck during radiation therapy for head and neck cancer requires adaptive strategy. J Med Invest. 2013;60(1-2):46-51.
5. Madani I, Duthoy W, Derie C, De Gersem W, Boterberg T, Saerens M, et al. Positron emission tomography-guided, focal-dose escalation using intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2007;68(1):126-35.
6. Dirix P, Vandecaveye V, De Keyzer F, Stroobants S, Hermans R, Nuyts S. Dose painting in radiotherapy for head and neck squamous cell carcinoma: value of repeated functional imaging with (18)F-FDG PET, (18)F-fluoromisonidazole PET, diffusion-weighted MRI, and dynamic contrast-enhanced MRI. J Nucl Med. 2009;50(7):1020-7.
7. Soto DE, Kessler ML, Piert M, Eisbruch A. Correlation between pretreatment FDG-PET biological target volume and anatomical location of failure after radiation therapy for head and neck cancers. Radiother Oncol. 2008;89(1):13-8.
8. Due AK, Vogelius IR, Aznar MC, Bentzen SM, Berthelsen AK, Korreman SS, et al. Recurrences after intensity modulated radiotherapy for head and neck squamous cell carcinoma more likely to originate from regions with high baseline [18F]-FDG uptake. Radiother Oncol. 2014;111(3):360-5.
9. Gago-Arias A, Sanchez-Nieto B, Espinoza I, Karger CP, Pardo-Montero J. Impact of different biologically-adapted radiotherapy strategies on tumor control evaluated with a tumor response model. PLoS One. 2018;13(4):e0196310.
10. Castadot P, Geets X, Lee JA, Christian N, Gregoire V. Assessment by a deformable registration method of the volumetric and positional changes of target volumes and organs at risk in pharyngo-laryngeal tumors treated with concomitant chemo-radiation. Radiother Oncol. 2010;95(2):209-17.
11. Bentzen SM. Theragnostic imaging for radiation oncology: dose-painting by numbers. Lancet Oncol. 2005;6(2):112-7.
12. Duprez F, De Neve W, De Gersem W, Coghe M, Madani I. Adaptive dose painting by numbers for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2011;80(4):1045-55.
13. Madani I, Duprez F, Boterberg T, Van de Wiele C, Bonte K, Deron P, et al. Maximum tolerated dose in a phase I trial on adaptive dose painting by numbers for head and neck cancer. Radiother Oncol. 2011;101(3):351-5.
14. Berwouts D, Olteanu LA, Duprez F, Vercauteren T, De Gersem W, De Neve W, et al. Three-phase adaptive dose-painting-by-numbers for head-and-neck cancer: initial results of the phase I clinical trial. Radiother Oncol. 2013;107(3):310-6.
15. Vanderstraeten B, Duthoy W, De Gersem W, De Neve W, Thierens H. [18F]fluoro-deoxy-glucose positron emission tomography ([18F]FDG-PET) voxel intensity-based intensity-modulated radiation therapy (IMRT) for head and neck cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2006;79(3):249-58.
16. Olteanu LAM, Duprez F, De Neve W, Berwouts D, Vercauteren T, Bauters W, et al. Late mucosal ulcers in dose-escalated adaptive dose-painting treatments for head-and-neck cancer. Acta Oncol. 2018;57(2):262-8.
17. Nevens D, Duprez F, Daisne JF, Dok R, Belmans A, Voordeckers M, et al. Reduction of the dose of radiotherapy to the elective neck in head and neck squamous cell carcinoma; a randomized clinical trial. Effect on late toxicity and tumor control. Radiotherapy and

oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2017;122(2):171-7.
18. Sher DJ, Pham NL, Shah JL, Sen N, Williams KA, Subramaniam RM, et al. Prospective Phase 2 Study of Radiation Therapy Dose and Volume De-escalation for Elective Neck Treatment of Oropharyngeal and Laryngeal Cancer. International journal of radiation oncology, biology, physics. 2021;109(4):932-40.
19. Leclerc M, Maingon P, Hamoir M, Dalban C, Calais G, Nuyts S, et al. A dose escalation study with intensity modulated radiation therapy (IMRT) in T2N0, T2N1, T3N0 squamous cell carcinomas (SCC) of the oropharynx, larynx and hypopharynx using a simultaneous integrated boost (SIB) approach. Radiother Oncol. 2013;106(3):333-40.
20. Berwouts D, Madani I, Duprez F, Olteanu AL, Vercauteren T, Boterberg T, et al. Long-term outcome of (18) F-fluorodeoxyglucose-positron emission tomography-guided dose painting for head and neck cancer: Matched case-control study. Head Neck. 2017;39(11):2264-75.
21. Deschuymer S, Nevens D, Duprez F, Daisne JF, Dok R, Laenen A, et al. Randomized clinical trial on reduction of radiotherapy dose to the elective neck in head and neck squamous cell carcinoma; update of the long-term tumor outcome. Radiother Oncol. 2020;143:24-9.
22. Deschuymer S, Nevens D, Duprez F, Daisne JF, Voordeckers M, De Neve W, Nuyts S. Randomized Clinical Trial on Reduction of Radiotherapy Dose to the Elective Neck in Head and Neck Squamous Cell Carcinoma: Results on the Quality of Life. Qual Life Res. 2021;30(1):117-27.
23. Michaelidou A, Adjogatse D, Suh Y, Pike L, Thomas C, Woodley O, et al. 18F-FDG-PET in guided dose-painting with intensity modulated radiotherapy in oropharyngeal tumours: A phase I study (FiGaRO). Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2021;155:261-8.
24. Lee NY, O'Meara W, Chan K, Della-Bianca C, Mechalakos JG, Zhung J, et al. Concurrent chemotherapy and intensity-modulated radiotherapy for locoregionally advanced laryngeal and hypopharyngeal cancers. International journal of radiation oncology, biology, physics. 2007;69(2):459-68.
25. Givens DJ, Karnell LH, Gupta AK, Clamon GH, Pagedar NA, Chang KE, et al. Adverse events associated with concurrent chemoradiation therapy in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg. 2009;135(12):1209-17.
26. Vlacich G, Spratt DE, Diaz R, Phillips JG, Crass J, Li CI, et al. Dose to the inferior pharyngeal constrictor predicts prolonged gastrostomy tube dependence with concurrent intensity-modulated radiation therapy and chemotherapy for locally-advanced head and neck cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2014;110(3):435-40.
27. Caudell JJ, Schaner PE, Meredith RF, Locher JL, Nabell LM, Carroll WR, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. International journal of radiation oncology, biology, physics. 2009;73(2):410-5.
28. Smith J, Nastasi D, Tso R, Vangaveti V, Renison B, Chilkuri M. The effects of continued smoking in head and neck cancer patients treated with radiotherapy: A systematic review and meta-analysis. Radiother Oncol. 2019;135:51-7.
29. Michiels S, Le Maitre A, Buyse M, Burzykowski T, Maillard E, Bogaerts J, et al. Surrogate endpoints for overall survival in locally advanced head and neck cancer: meta-analyses of individual patient data. The Lancet Oncology. 2009;10(4):341-50.

FIGURES

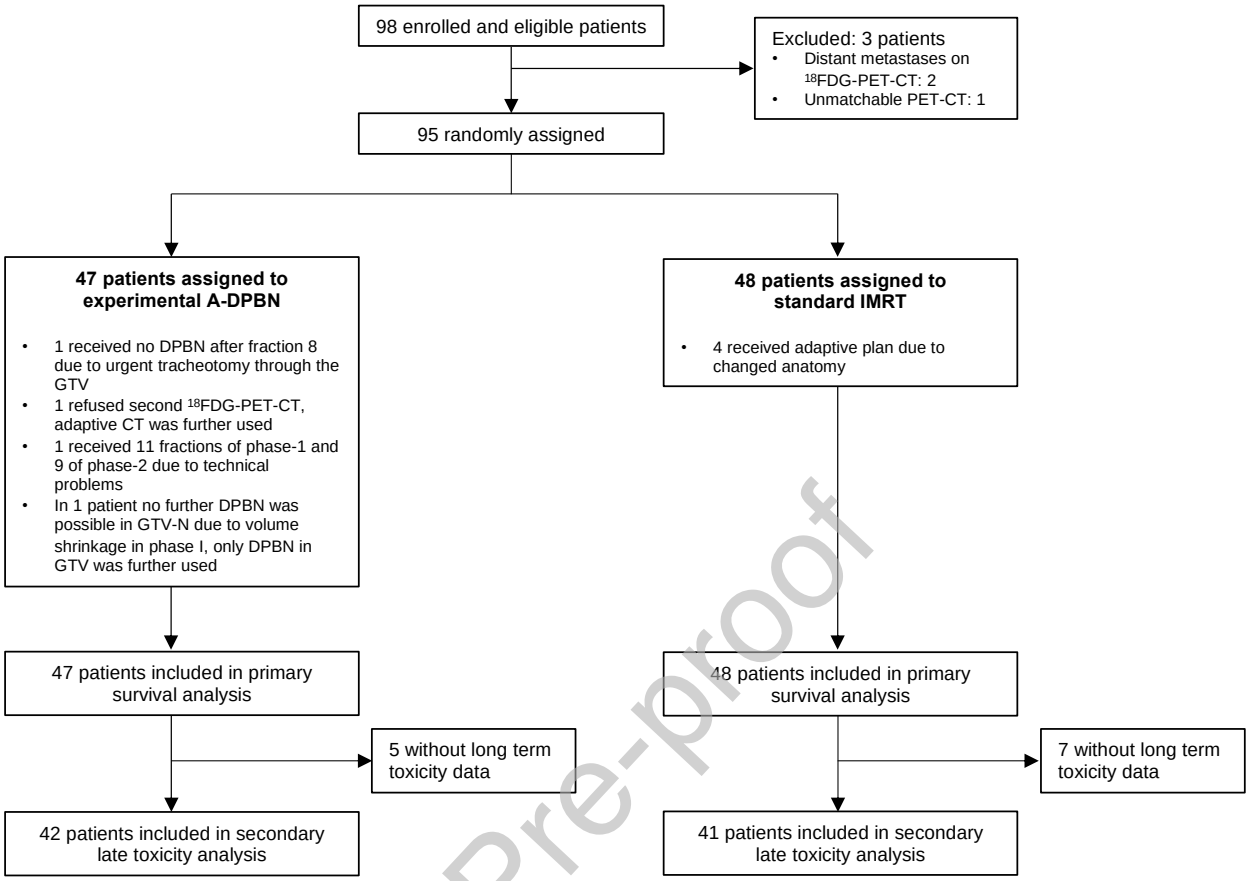


Figure 1: Consort diagram of the randomized phase II trial.

PET-CT: Positron Emission Tomography – Computed Tomography; A-DPBN: Adaptive Dose-Painting-by-Numbers; IMRT: Intensity-Modulated Radiotherapy; GTV: Gross Tumor Volume; GTV-N: Gross Tumor Volume Nodes; IMRT: intensity modulated radiotherapy.

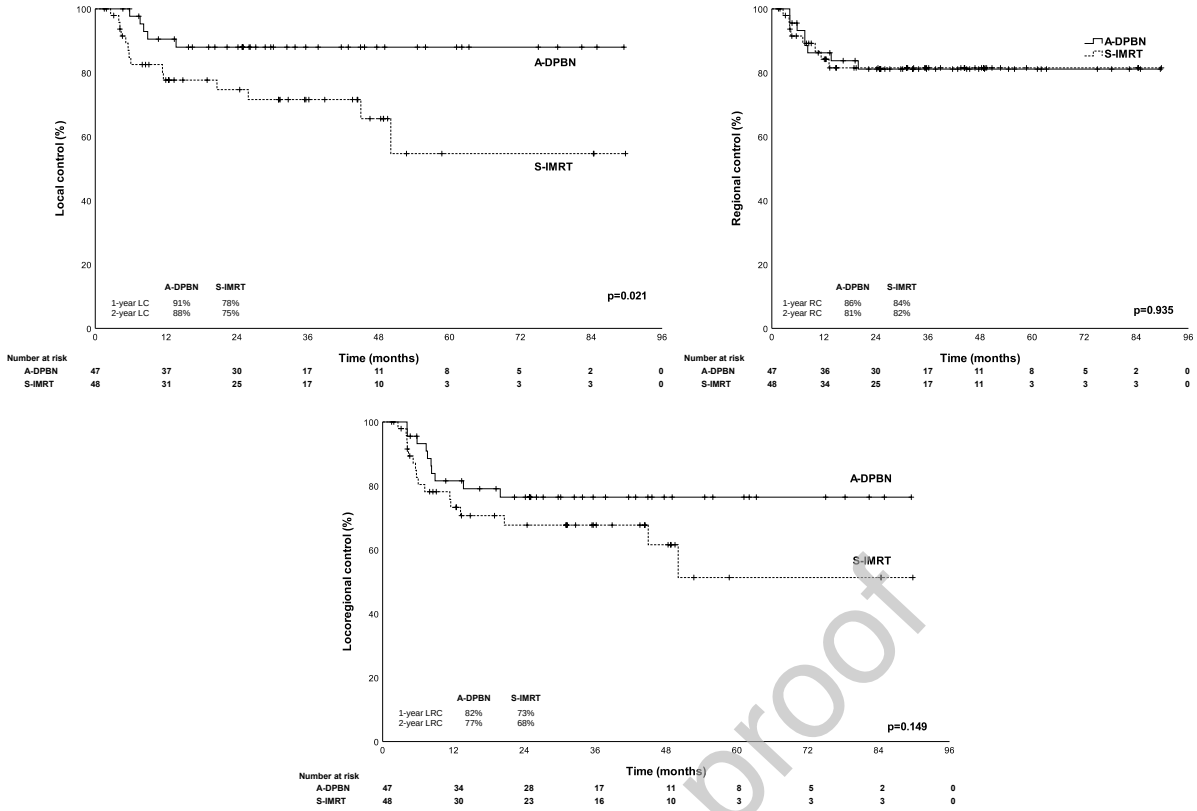


Figure 2A: Kaplan-Meier survival analysis on primary outcome measures – local (LC), regional control (RC) and locoregional control (LRC).

Treatment group comparison was carried out using a log-rank test (two-sided) with associated p-values depicted in the figures with p-values <0.05 considered significant. Patients were censored at their last follow-up. A-DPBN: adaptive dose-painting-by-numbers; S-IMRT: standard intensity-modulated radiotherapy.

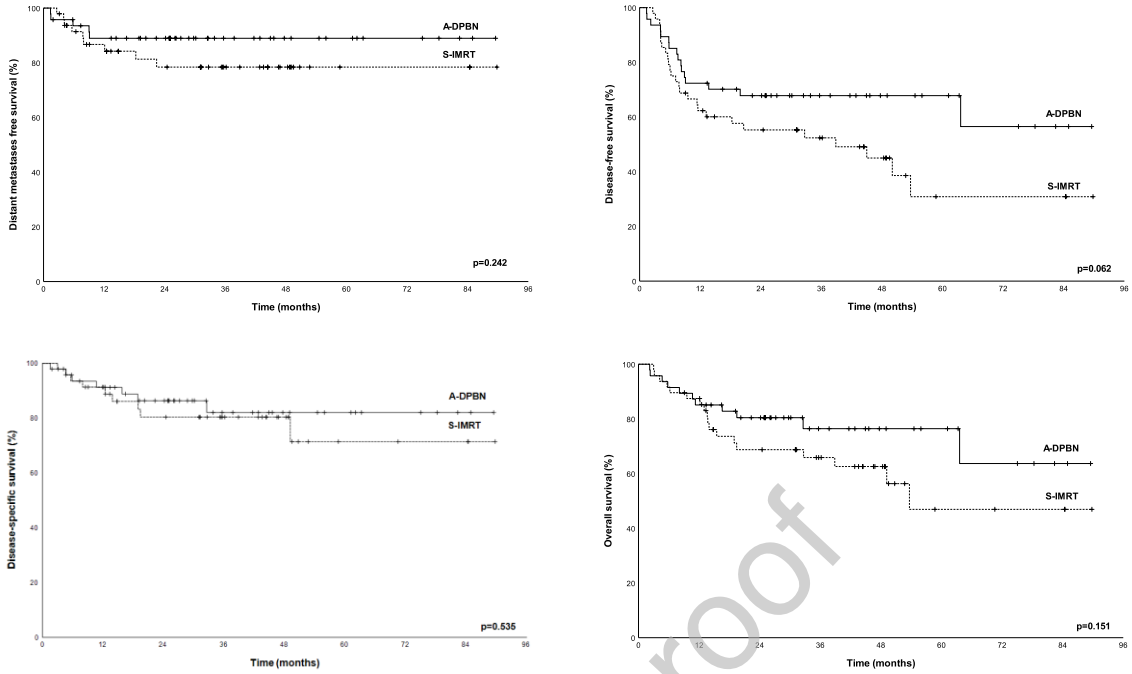
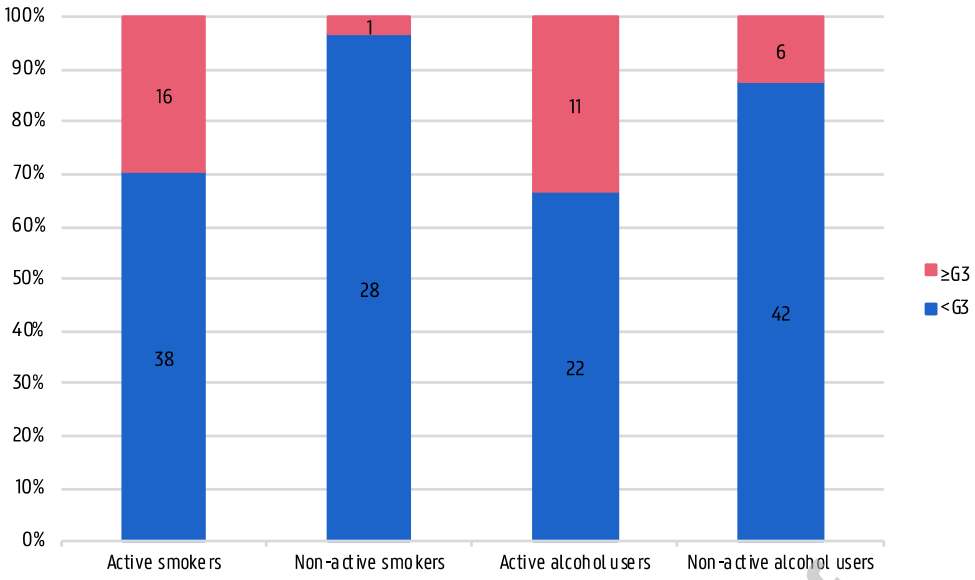


Figure 2B: Kaplan-Meier survival analysis on secondary outcome measures – distant metastases free survival (DMFS), disease-free survival (DFS), disease-specific survival (DSS) and overall survival (OS).

Treatment group comparison was carried out using a log-rank test (two-sided) with associated p-values depicted in the figures above with p-values <0.05 considered significant. Patients were censored at their last follow-up. A-DPBN: adaptive dose-painting-by-numbers; S-IMRT: standard intensity-modulated radiotherapy.



		<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*	

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

P-values were calculated using non-parametric tests. G3: grade 3 toxicity; G4: grade 4 toxicity.

TABLES

TABLE 1: BASELINE CHARACTERISTICS			
CHARACTERISTIC	**A-DPBN (n=47)**	**S-IMRT (n=48)**	**p-value**
Age at diagnosis (years)			0.25
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			**0.01**
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)			0.36
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			0.18
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			0.96
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-radiotherapy neck dissection			0.09
Yes	7 (15%)	2 (4%)	
No	40 (85%)	46 (96%)	
Concomitant chemotherapy			0.53
Yes	31 (66%)	28 (58%)	
Cisplatin	*30 (97%)*	*25 (89%)*	
Carboplatin/5FU or cetuximab	*1 (3%)*	*3 (11%)*	
No	16 (34%)	20 (42%)	
Active smoking pretreatment	28 (60%)	26 (54%)	0.76
Continued smoking	15 (32%)	20 (42%)	0.07
Active alcohol users pretreatment	19 (40%)	14 (29%)	0.39
Continued alcohol use	12 (26%)	9 (19%)	0.75

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

A-DPBN: adaptive dose-painting-by-numbers; S-IMRT: standard intensity modulated radiotherapy; IQR: interquartile range; HPV: Human Papillomavirus; 5FU: 5-Fluorouracil.

		TABLE 2: UNI- AND MULTIVARIATE ANALYSIS ON LOCO(REGIONAL) CONTROL AND SURVIVAL OUTCOME MEASURES							
		Univariate analysis (p-values)					Multivariate analysis (p-values)		
		LC	RC	LRC	DFS	OS	LC	DFS	OS
Factor	**n**								
T-stage		**0.007**	0.686	0.1	**0.027**	**0.025**	**<0.001**	**0.027**	**0.025**
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		0.750	0.375	0.623	**0.015**	**<0.001**		**0.015**	**<0.001**
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)		0.715	0.524	0.507	0.693	0.051			
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		0.127	0.420	0.464	0.077*	0.083*	0.393	**0.036**	**0.038**
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		**0.031**	0.194	0.134	0.600	0.325	**0.031**		
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		0.441	0.208	0.467	0.604	0.326			
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		0.531	0.972	0.690	0.219	0.173			
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		0.692	0.542	0.837	0.784	0.207			
Ghent	78	*63 (81%)*	*34 (44%)*	*57 (73%)*	*43 (55%)*	*52 (67%)*			
Namur	17	*13 (76%)*	*15 (88%)*	*12 (71%)*	*10 (59%)*	*14 (82%)*			

Table 2: Univariate and subsequent multivariate analysis for local (LC), regional (RC), locoregional control (LRC), disease-free (DFS) and overall survival (OS) probability.

Significant outcomes are marked in bold. P-values with a trend towards significance are marked with '*', which were also evaluated in multivariate analysis. Percentages are provided at median follow-up of 31 months. T: tumour; N: node; n: number.

TABLE 3: LATE TREATMENT-INDUCED TOXICITY			
GRADE	**A-DPBN**	**S-IMRT**	**P-VALUE**
Late toxicity in general			0.1
<G3	27 (64%)	33 (80%)	
≥G3	15 (36%)	8 (20%)	
Mucosal ulcers			
≥G3	14 (33%)	3 (7%)	**0.003**
≥G4	8 (19%)	2 (5%)	**0.047**
Xerostomia			0.15
G0-1	30 (83%)	19 (68%)	
G2-3	6 (17%)	9 (32%)	
Xerostomia (at 36 months)			0.07
G0-1	15 (94%)	9 (64%)	
G2-3	1 (6%)	5 (36%)	
Dysphagia			0.31
G0-1	35 (97%)	24 (89%)	
G2-4	1 (3%)	3 (11%)	
Dysphagia (at 36 months)			1
G0-1	15 (94%)	16 (100%)	
G2-4	1 (6%)	0 (0%)	
Other grade 3 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 grade 4 toxicities			
Stridor or dyspnea	1	1	
Taste alteration	0	1	

Table 3: Details on all treatment-related late toxicity.

The highest toxicity grade during follow-up is reported. Assessment was performed at median follow-up time of 31 months. Fisher's exact tests were used to calculate p-values for the comparison of the adverse events between treatment arms. A-DPBN: adaptive dose-painting-by-numbers; S-IMRT: standard intensity modulated radiotherapy; G: grade.

TABLE 4: DETAILS ON LATE MUCOSAL ULCERS				
SUBGROUPS	**MUCOSAL TOXICITY**	**A-DPBN**	**S-IMRT**	**P-VALUE**
ALL PATIENTS	Total	42 (100%)	41 (100%)	
	≥G3	14 (33%)	3 (7%)	**0.003**
	≥G4	8 (19%)	2 (5%)	**0.047**
ACTIVE SMOKERS	Total	28 (100%)	26 (100%)	
	≥G3	13 (46%)	3 (12%)	**0.005**
	≥G4	8 (29%)	2 (8%)	**0.048**
NON-ACTIVE SMOKERS	Total	14 (100%)	15 (100%)	
	≥G3	1 (7%)	0 (0%)	0.483
	≥G4	0 (0%)	0 (0%)	-
ACTIVE ALCOHOL USERS	Total	19 (100%)	14 (100%)	
	≥G3	8 (42%)	3 (21%)	0.278
	≥G4	4 (21%)	2 (14%)	0.618
NON-ACTIVE ALCOHOL USERS	Total	23 (100%)	25 (100%)	
	≥G3	6 (26%)	0 (0%)	**0.006**
	≥G4	4 (17%)	0 (0%)	**0.029**

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

P-values were calculated using non-parametric Fisher's Exact tests. A-DPBN: adaptive dose-painting-by-numbers; S-IMRT: standard intensity modulated radiotherapy; G3: grade 3 toxicity; G4: grade 4 toxicity.

Conflicts of Interests

J-F Daisne 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.