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Altered fractionation diminishes importance of tumor volume in oropharyngeal cancer: Subgroup analysis of ARTSCAN-trial

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Abstract

Background: A large tumor volume negatively impacts the outcome of radiation therapy (RT). Altered fractionation (AF) can improve local control (LC) compared with conventional fractionation (CF). The aim of the present study was to investigate if response to AF differs with tumor volume in oropharyngeal cancer.

Methods: Three hundred and twenty four patients with oropharyngeal cancer treated in a randomized, phase III trial comparing CF (2 Gy/d, 5 d/wk, 7 weeks, total dose 68 Gy) to AF (1.1 Gy + 2 Gy/d, 5 d/wk, 4.5 weeks, total dose 68 Gy) were analyzed.

Results: Tumor volume had less impact on LC for patients treated with AF. There was an interaction between tumor volume and fractionation schedule ($P = .039$). This differential response was in favor of CF for small tumors and of AF for large tumors.

Conclusion: AF diminishes the importance of tumor volume for local tumor control in oropharyngeal cancer.

KEYWORDS

altered fractionation, oropharyngeal cancer, radiation therapy, randomized trial, tumor volume

1 | INTRODUCTION

Head and neck cancer is diagnosed in approximately 700 000 people annually, accounting for around 4% of all cancer cases,¹ with the majority consisting of squamous cell carcinomas. These cancers are usually regarded as

predominantly loco-regional diseases and most treatment failures occur at the primary tumor site and/or in regional lymph nodes. Radiation therapy (RT) is a cornerstone to achieve tumor control and cure. Increasing tumor volume is a known negative prognostic factor for tumor control after RT.^{2,3} In the treatment of oropharyngeal cancer, it has been reported that the size of the gross tumor volume (GTV) is the most important factor to predict outcome,⁴ and in another study a volumetric staging

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system, superior to the tumor, nodes, metastasis (TNM)-classification of malignant tumors, was suggested.⁵ The impact of tumor volume in oropharyngeal cancer has mainly been investigated in studies with conventional fractionation (CF) (1.9-2.2 Gy/fraction, 5 fractions per week).^{4,6-8}

An option to improve the outcome of RT is to alter the fractionation schedule. Accelerated RT can potentially achieve this by reducing the overall treatment time. Hereby, it is believed that the repopulation of cancer cells during treatment is reduced, and clinical trials have proven the effectiveness of accelerated RT.^{9,10} Hyperfractionated RT exploits the different radiobiological behavior of tumor compared with surrounding normal tissue. By lowering the fraction dose and irradiating more than once a day, it is possible to reach a higher total absorbed dose without causing more damage to normal tissue, and at the same time enhancing tumor control. Hyperfractionated RT may also profit from shorter overall treatment time (accelerated, hyperfractionated RT). A recent meta-analysis of 11 423 head and neck cancer patients from 33 clinical trials presented an advantage of hyperfractionated RT compared to both accelerated and CF, by improving overall survival (OS) at 5 years with 8.1 percentage points (95% confidence interval [CI] 3.4-12.8).¹¹ There are indications that more advanced tumors (T3-4) benefit more from hyperfractionation.¹²⁻¹⁴ However, the role of actual tumor volume and response to altered fractionated RT is little investigated. The aim of the present study was to evaluate the impact of tumor volume by making an analysis of the patients with oropharyngeal cancer treated in the phase III, randomized ARTSCAN-trial. We have previously reported results of the ARTSCAN-trial, in which moderately altered fractionation (AF; total dose 68 Gy, given with two daily fractions 1.1 Gy + 2 Gy, 5 d/wk for 4.5 weeks) did not improve loco-regional control or OS compared with CF (total dose 68 Gy, 2Gy/d, 5 d/wk for 7 weeks).^{15,16}

2 | METHODS

2.1 | Objectives and endpoints

The primary objective of the present study was to determine if the effect of tumor volume on local control (LC) differs after AF compared with CF in oropharyngeal tumors in the ARTSCAN-trial. Secondary objectives were to investigate the role of tumor volume as predictor of response to AF, to investigate the tumor volume effect in p16-positive tumors and to compare tumor volume and clinically determined T-classifications. The size of the primary GTV-T delineated on the treatment planning CT scan was used as a measure of the primary tumor volume.

2.2 | Patients, trial design, and RT

In the ARTSCAN-trial, 750 patients with squamous cell carcinoma of the oral cavity, oropharynx, larynx (except T1-2, N0 glottic cancer), and hypopharynx were recruited from 1998 to 2006 and randomized between CF or AF as previously described.^{15,16} The present study cohort consists of all patients with oropharyngeal cancers eligible for evaluation of the primary endpoint with GTV-T volume accessible for analysis. The subgroup of oropharyngeal cancer was chosen since it was the largest subset of patients and constitutes a distinct entity of head and neck cancer. p16-Status was used as a surrogate marker for human papillomavirus (HPV)-associated tumors and determined as earlier described.¹⁶ Target volumes were measured with 3DSlicer, version 4.8.1 (downloaded from www.slicer.org).¹⁷

2.3 | Statistical considerations

Uni- and multivariable Cox regression models were used to analyze effects of tumor volume and AF on outcome. Proportional hazards assumptions in the Cox models were tested by Schoenfeld residuals tests. Interaction between tumor volume and fractionation schedule (AF/CF) were investigated using the likelihood ratio test. Logistic regression was used to estimate dose-response curves. The Kaplan-Meier method was used to illustrate event rates and the log-rank test to compare groups. All statistical calculations were performed in RStudio version 1.0.136 (RStudio Team [2015]. RStudio, Inc., Boston, Massachusetts, URL <http://www.rstudio.com/>). *P*-values $\leq .05$ were considered statistically significant.

3 | RESULTS

3.1 | Patient cohort and tumor volumes

Three hundred and sixty four patients with oropharyngeal cancers were enrolled in the ARTSCAN-trial. Three hundred and fifty seven of these were eligible for evaluation of primary outcome. Treatment planning Computed Tomography (CT)-scans were manually reviewed when available ($n = 272$) to assure correct separation of GTV-T (primary tumor) and GTV-N (nodal regional lymph node metastases). A re-segmentation was performed in 36 patients where GTV-T and GTV-N were originally delineated as a single structure, keeping the total volume unchanged. For 80 patients without accessible CT-scans, tumor volume was acquired from the Quality Assurance documentation of the trial. Among these were GTV-T and GTV-N separated for 52 patients in the original

target segmentation. Thereby, in the final analysis, 324 patients with distinct GTV-T volume were available. All patients had been followed for 5 years after end of RT.¹⁶ Patient characteristics and tumor volumes are described in Table 1.

3.2 | Overall outcome after RT

The current reanalysis confirmed the previously described results,¹⁶ and for the subgroup of oropharyngeal cancer, there was no difference in LC between CF and AF (hazard ratio [HR] 0.97 [95% CI 0.55-1.70], logrank $P = .90$) (Figure 1).

3.3 | Tumor volume and LC

With increasing primary tumor volume, the risk of local failure increased for both trial arms. Using primary tumor

volume as a continuous variable in an univariable Cox regression model, the impact of tumor volume on local failure was less pronounced for AF compared with CF (Figure 2A). A statistically significant interaction was found between tumor volume and trial arms ($P = .039$).

The lack of a difference in LC in the whole group (Figure 1) and a superior efficiency for AF compared to CF with increasing tumor volume (Figure 2A) required further investigation. We therefore estimated the risk of local failure as a function of tumor volume using logistic regression for CF and AF. The analysis indicated that the curves intersect, that is, small tumors seem to respond better to CF and large tumors better to AF (Figure 2B). To further illustrate the interaction between tumor volume and fractionation schedule, patients were dichotomized into having “small” or “large” primary tumors with the cut-off tumor volume chosen at the intersection. This was found at 23 cm³, which was also close to the mean GTV-T volume, and used for illustrations with Kaplan-Meier estimates.

TABLE 1 Baseline characteristics and tumor volumes (fourth edition of TNM classification of malignant tumors, Union Internationale Contre le Cancer, Geneva, 1987)

	CF No. of patients = 160	%	AF No. of patients = 164	%	P-value
Age at randomization					
Median (range)	58	35-86	59	32-80	.73
Gender					
Male	121	76	118	72	.53
Female	39	24	46	28	
T classification					
T1	27	16.9	29	17.7	.54
T2	70	43.8	62	37.8	
T3	38	23.8	38	23.2	
T4	25	15.6	35	21.3	
Nodal status					
N0	30	18.8	40	24.4	.63
N1	33	20.6	33	20.1	
N2A-N2C	85	53.1	78	47.6	
N3	12	7.5	13	7.9	
P16-status					
P16 positive	69	73.4	74	74.7	.96
P16 negative	25	26.2	25	25.3	
Total	94		99		
Primary tumor volume (GTV-T) (cm ³)					
Mean (SD)	23.7	22.4	25.3	26.0	.55
Median (range)	16.4	0.8-117	17.8	0.15-143	

Abbreviations: AF, altered fractionation; CF, conventional fractionation; GTV, gross tumor volume; TNM- tumor, nodes, metastasis.

For CF there was a statistically significant difference in LC for large ($>23 \text{ cm}^3$) compared to small tumors ($\leq 23 \text{ cm}^3$), (HR 5.6 [2.2-14], $P < .0001$), (Figure 3, solid lines). This difference was reduced and not statistically significant for AF, (HR 1.6 [0.71-3.5], $P = .27$), (Figure 3, dashed lines). For patients with small tumors, the rate of

LC showed an unexpected tendency in favor of CF (HR 2.1 [0.78-5.5], $P = .14$), (Figure 3, grey lines). Conversely, patients with large tumors showed an opposite

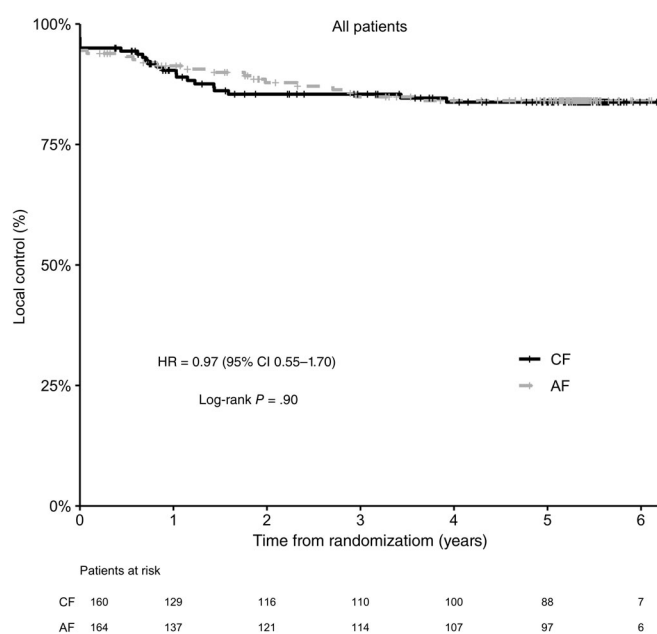


FIGURE 1 Local control (LC) as a function of fractionation schedule. Kaplan-Meier estimates for LC at 5 years were 84% (95% CI 78-90) for CF and 84% (78-90) for AF. AF, altered fractionation; CF, conventional fractionation; CI, confidence interval; HR, hazard ratio

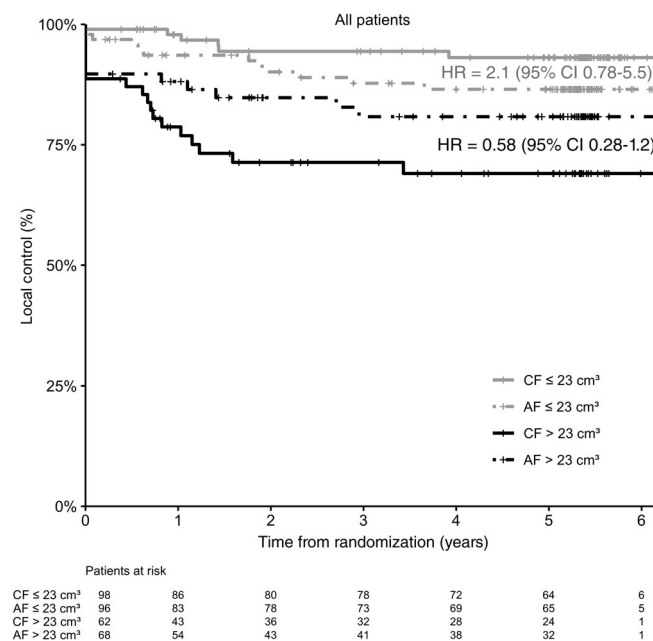


FIGURE 3 Kaplan-Meier estimated local control for small and large tumors for the two fractionation schedules. For conventional fractionation (CF, solid lines), estimated local control at 5 years was 93% (95% CI 88-99) and 68% (57-81) for small and large tumors, respectively. Corresponding estimates for altered fractionation (AF, dashed lines) was 87% (80-94) and 80% (70-90) for small and large tumors, respectively. CI, confidence interval; HR, hazard ratio

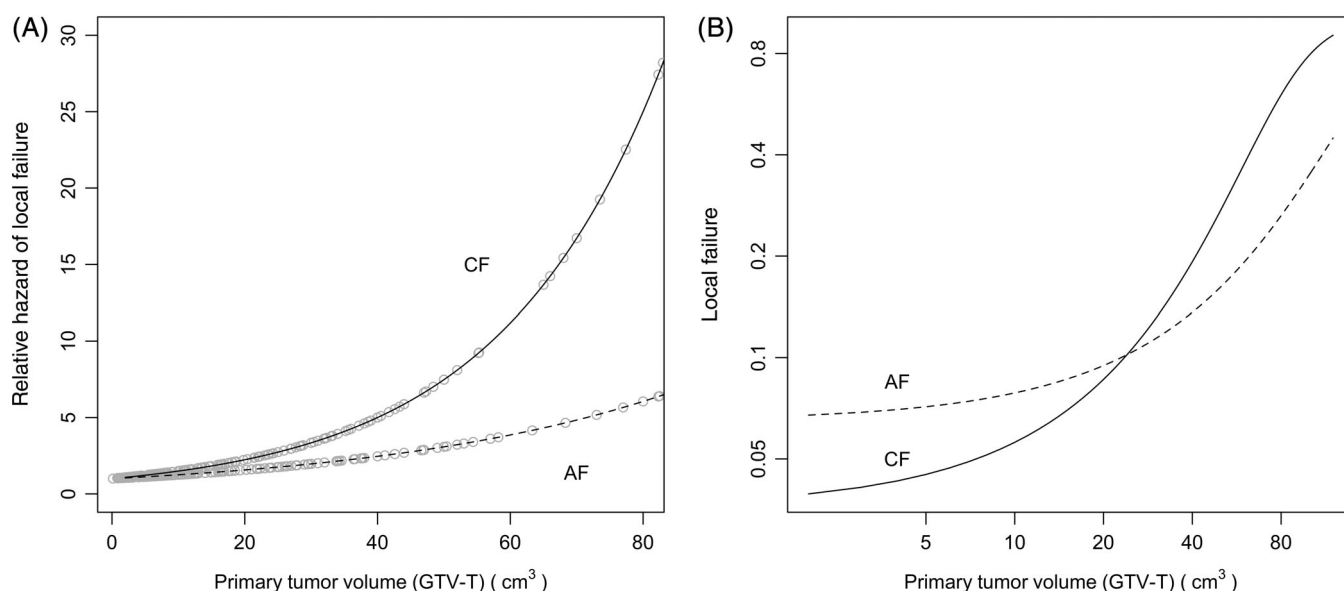


FIGURE 2 A, Univariable Cox regression of relative risk of local failure as a function of primary gross tumor volume (GTV-T) for conventional fractionation (CF, solid line) and altered fractionation (AF, dashed line). Circles denote patients' individual tumor volumes. B, Risk of local failure within 2 years (accounts for ~90% of all failures during the follow-time) as a function of tumor volume estimated with logistic regression for CF (solid line) and AF (dashed line)

tendency in favor of AF (HR 0.58 [0.28-1.2], $P = .12$), (Figure 3, black lines). The lack of a difference in the whole group (Figure 1) could therefore be a consequence of a differential response to AF, where patients with larger tumors do benefit while patients with smaller tumors might have a better response with CF compared with AF.

3.4 | p16-Status

p16-Status was available for 193 patients and, as earlier reported, the general outcome for p16-positive tumors ($n = 143$) was more favorable.¹⁶ Similar to the whole study group, tumor volume had less impact on LC for patients treated with AF in univariable Cox regression models. The Kaplan-Meier estimates also indicate a differential response to the two treatment schedules depending on the tumor volume. For CF, LC at 5 years was 98% (94-100) and 78% (63-97) for small and large tumors, respectively. Corresponding estimates for AF was 89% (81-99) and 86% (72-100).

3.5 | T-classification and tumor volume

The contoured tumor volume (GTV-T) showed a considerable overlap between T-classifications (Figure 4). HR between the trial arms for earlier tumors (T1-2) and advanced tumors (T3-4) was 1.05 (0.30-3.6, $P = .94$) and 0.85 (0.45-1.6, $P = .62$), respectively. No statistically significant interaction was found ($P = .78$), and hence

clinical T-classification was not as accurate as tumor volume to differentiate responders to AF.

4 | DISCUSSION

In this subgroup analysis of 324 patients with oropharyngeal cancer in the randomized ARTSCAN-trial, we showed that the negative impact of increasing tumor volume for LC could be reduced by AF. Further, a statistically significant interaction between tumor volume and fractionation schedule was found; small tumors may benefit from CF, whereas large tumors may have improved outcome with AF.

A weakness of the current analysis was the available imaging information. Contouring was performed on non-contrast-enhanced CT-slices with a slice thickness of typically 5 mm. Compared with current clinical practice, positron emission tomography and/or magnetic resonance imaging was lacking. The absolute volumes should therefore be interpreted with great caution, and the volume used for dichotomization would probably not be equivalent if modern imaging standards were employed. However, the relative volumes in the trial arms are not affected by these uncertainties and the described volume phenomenon should be generalizable. Noteworthy, the current findings are applicable for patients treated with RT alone. The presence of a similar volume effect for patients who undergo concurrent chemotherapy remains yet to be studied.

Preclinical studies indicate that the higher number of clonogenic cancer cells in larger tumors contribute to poorer outcome.¹⁸ It has also been suggested that the tumor microenvironment may differ with tumor volume, and negative factors such as hypoxia may be more predominant in larger tumors.^{19,20} The negative impact of tumor volume on treatment outcome for oropharyngeal cancer has been shown in several studies,^{4,7,21-23} although some contradictory results exist.^{8,24-26} To our knowledge, the importance of tumor volume and response to AF has not previously been exclusively addressed. Our analysis shows that large, but not small, primary tumors respond better to AF compared with CF. This is in agreement with earlier findings where hyperfractionation is increasingly efficient with higher T-classification.¹²⁻¹⁴ Similar to our current findings for oropharyngeal cancer, hyperfractionated accelerated RT has also been shown to diminish the negative impact of larger tumor volumes for non-small cell lung cancer.²⁷

In the present study, tumor volume provided a more accurate discrimination of responders to AF compared to clinical T-classification. Others have shown tumor volume to be superior to T-classification in discriminating outcome after RT.^{4,6} The prognostic impact of HPV in

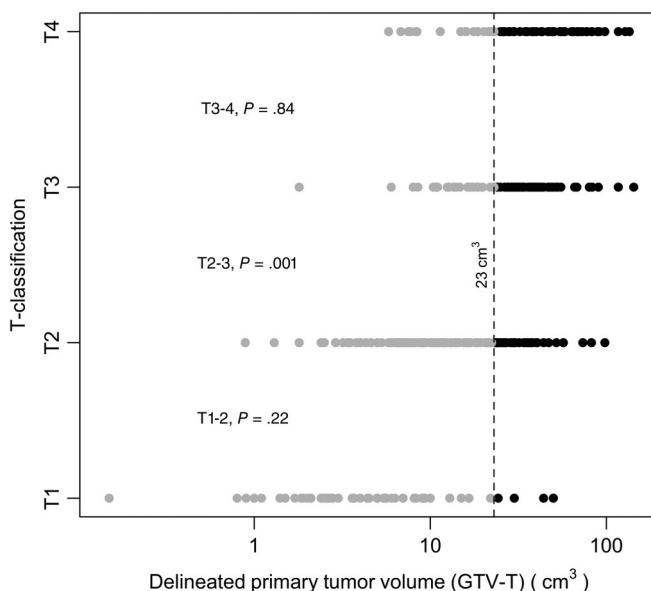


FIGURE 4 Clinically determined T-classification and delineated primary tumor volume (GTV-T)

oropharyngeal cancers is well established.²⁸ Recently, a meta-analysis showed that HPV status could not predict response to AF.²⁹ For p16-positive cases in the current study, the relationship between tumor volume and response to different fractionation schedules was similar to the whole cohort.

Our findings for small tumors oppose the findings of DAHANCA for purely accelerated RT (2 Gy/fraction, 6 fractions/wk) where the benefit of accelerated RT is higher for earlier T-classifications.^{10,30} In the ARTSCAN-trial, AF was delivered with two fractions per day (1.1 Gy + 2 Gy), which also exploits benefits of hyperfractionation.³¹ In animal studies with radiation given twice a day, small tumors were shown to be more efficient in repairing sublethal damage compared with large tumors.^{32,33} Since the AF-schedule was delivered with two fractions per day, a more efficient sublethal damage repair in small tumors would decrease the radiation effect for AF compared with CF. Thereby, a speculative reason for the unexpected trend for small tumors toward higher efficiency for CF could be due to improved sublethal damage repair. Theoretically, according to the linear quadratic-model,³⁴ the lower fraction doses in the AF schedule result in a lower biologically effective dose (BED) (BED 79.6 Gy [AF] vs 81.6 Gy [CF], $\alpha/\beta = 10$ Gy, assuming full sublethal damage repair between the intradaily fractions and omitting overall treatment time). Thus, the results suggest that two fractions a day, with lower fraction doses, might be less efficient in small tumors.

In conclusion, this study indicates that AF can diminish the impact of increasing primary tumor volume for oropharyngeal cancer, including p16-positive tumors. A statistically significant interaction between tumor volume and fractionation schedule was found. For large primary tumors, there was a consistent trend toward higher LC for patients treated with AF in comparison with CF. A meta-analysis of randomized controlled trials comparing AF vs CF with stratification of tumor volume would be desirable in order to validate our findings.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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