ANTICANCER RESEARCH *41*: 477-484 (2021)
doi:10.21873/anticanres.14798

Accelerated Fractionation With Concomitant Boost *vs*. Conventional Radio-chemotherapy for Definitive Treatment of Locally Advanced Squamous Cell Carcinoma of the Head-and-Neck (SCCHN)

CARLOS A. NARVAEZ[1], STEVEN E. SCHILD[2], STEFAN JANSSEN[1,3], URSULA SCHROEDER[4], KARL L. BRUCHHAGE[4], SAMER G. HAKIM[5] and DIRK RADES[1]

Departments of [1]Radiation Oncology, [4]Oto-Rhino-Laryngology and Head and Neck Surgery, and Oral and [5]Maxillofacial Surgery, University of Lübeck, Lübeck, Germany;
[2]Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.;
[3]Private Practice of Radiation Oncology, Hannover, Germany

Abstract. *Background/Aim: Patients with unresectable head-and-neck cancer (SCCHN) unable to tolerate radio-chemotherapy may receive unconventionally fractionated radiotherapy. This retrospective study compared both treatments. Patients and Methods: Eight patients unsuitable for chemotherapy were assigned to accelerated fractionation with concomitant boost (AF-CB, 69.6 Gy/39 fractions) over 5.5 weeks (group A) and 72 patients to cisplatin-based radio-chemotherapy (70 Gy/35 fractions) over 7 weeks (group B). Groups were matched (cancer site, gender, age, performance score, T-/N-stage, histologic grade) and compared for loco-regional control (LRC), metastases-free survival (MFS), overall survival (OS) and toxicities. Results: LRC, MFS, OS and radiation-related toxicities were not significantly different between groups A and B. Improved outcomes were associated with favorable cancer site, better performance score and T3-stage. In group B, toxicity led to reduction/discontinuation of chemotherapy in 38.9% and interruptions of radiotherapy >7 days in 19.3% of patients. Conclusion: AF-CB appeared a reasonable alternative for patients who cannot safely receive radio-chemotherapy for unresectable SCCHN.*

Head-and-neck cancers represented the 7th most common malignancy worldwide in 2018 (1, 2). The vast majority of these cancers were squamous cell carcinomas (SCCHN). Locally advanced tumors may be unresectable and require definitive radiotherapy. The outcomes after definitive radiotherapy were significantly improved with the addition of concurrent (mainly platin-based) chemotherapy. In 2000, a randomized trial compared 66-72 Gy of radiotherapy alone to 66-72 Gy of radiotherapy with concurrent cisplatin and 5-fluorouracil (5-FU) for unresectable locally advanced SCCHN (3). The combined treatment resulted in significantly better loco-regional control (LRC). In 2004, another randomized trial compared 70 Gy in 35 fractions alone to the same regimen plus concurrent carboplatin/5-FU for definitive treatment of locally advanced oropharynx cancer (4). In this trial, concurrent radio-chemotherapy was associated with significantly improved disease-free survival (DFS) and LRC and almost significantly improved overall survival (OS) when compared to radiotherapy alone. These results were confirmed in a large meta-analysis that included 93 randomized trials and demonstrated significantly better OS for concurrent radio-chemotherapy compared to radiation alone (5).

Unfortunately, the addition of chemotherapy to radiotherapy significantly increased grade ≥3 acute toxicities (6, 7). Thus, a considerable number of patients, particularly patients with significant co-morbidities and elderly patients, are unable to withstand concurrent radio-chemotherapy. Moreover, increased toxicity caused by the addition of chemotherapy may require interruptions of the radiotherapy, which can significantly impair the patients' prognoses (8). Patients who are unsuitable for chemotherapy or other systemic agents are treated with radiotherapy alone. Treatment outcomes can be improved with unconventionally fractionated radiotherapy over less treatment time. According to a meta-analysis, unconventional fractionation was significantly superior to conventional fractionation (daily

Correspondence to: Professor Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany. Tel: +49 45150045400, Fax: +49 45150045404, e-mail: rades.dirk@gmx.net

Key Words: Locally advanced head-and-neck cancer, stage IV disease, accelerated fractionation, concomitant boost, conventional radio-chemotherapy.

fractions of 2.0 Gy on five consecutive days per week) with respect to LRC and OS (9).

The term "unconventional fractionation" summarizes several altered dose-fractionation regimens including accelerated fractionation with concomitant boost (AF-CB) (9, 10). According to a randomized trial, AF-CB (72 Gy in 42 fractions over 6 weeks) resulted in more favorable outcomes than conventional fractionation (10). However, in this trial, AF-CB was associated with significantly increased late toxicity. Since the publication of the trial, other AF-CB programs were developed (11-14). One of these programs consisted of 69.9 Gy in 39 fractions given over 5.5 weeks (11). To our knowledge, this AF-CB program has not yet been compared to conventionally fractionated radio-chemotherapy. Therefore, the current study was initiated, which compared AF-CB to conventionally fractionated (70 Gy in 35 fractions) cisplatin-based radio-chemotherapy for definitive treatment of unresectable locally advanced SCCHN.

Patients and Methods

Eighty patients with histologically proven locally advanced unresectable SCCHN were included in this retrospective study, which was approved by the Ethics Committee at the University of Lübeck (20-454). Patients had non-metastatic stage IV disease; TNM-stages included T3 N2 M0 (n=25), T4 N0 M0 (n=8), T4 N1 M0 (n=12) and T4 N2 M0 (n=35) (15, 16). Patients with T1- or T2-tumors were not included to increase the homogeneity of the study population. The 7th edition of the American Joint Committee on Cancer staging manual was applied, since the status of human papilloma virus was not available for most patients, but is necessary for the staging of oropharynx cancers in the 8th edition (17).

Eight patients unable to receive radio-chemotherapy due to comorbidity were treated with accelerated radiotherapy including concomitant boost between 2011 and 2019 (group A). Initially, 30 Gy (15 daily fractions of 2.0 Gy over 3 weeks) were given to the primary tumor and regional lymph nodes including low-risk areas. After 30 Gy, the same volumes received additional 21.6 Gy with 1.8 Gy per fraction in the morning for 2.5 weeks (=12 treatment days). After an interval of ≥6 hours, which allowed the normal tissue to recover, 1.5 Gy were administered on the same days. The dose of 1.5 Gy was given to the primary tumor and high/intermediate-risk lymph node areas for 6 days (first concomitant boost, cumulative dose=60.6 Gy), and to the primary tumor and high-risk lymph node areas for another 6 days (second concomitant boost, cumulative dose=69.6 Gy). The treatment time including both concomitant boosts was 5.5 weeks (11, 18).

The other 72 patients (from an existing database) had been assigned to conventionally fractionated radiotherapy with concurrent cisplatin-based chemotherapy between 2000 and 2014 (group B). Initially, 50 Gy (daily fractions of 2.0 Gy over 5 weeks) were given to the primary tumor and regional lymph nodes including low-risk areas. Afterwards, a boost of 10 Gy (2.0 Gy per fraction, once daily) was administered to the primary tumor and high/intermediate-risk lymph node areas (cumulative dose=60 Gy), followed by a second boost of 10 Gy to the primary tumor and high-risk lymph node areas (cumulative dose=70 Gy). Thus, the treatment time in group B was 7 weeks. Concurrent cisplatin-based chemotherapy included either weekly administration of 30 mg/m^2/d of cisplatin (n=15), 100 mg/m^2 of cisplatin every 3 weeks (n=14), 20 mg/m^2/d1-5 of cisplatin every 4 weeks (n=29), 20 mg/m^2/d1-5 of cisplatin plus 600 mg/m^2/d1-5 of 5-fluorouracil (5-FU) every 4 weeks (n=12) or 20 g/m^2/d1-5 of cisplatin plus 1000 mg/m^2/d1-5 of 5-FU every 4 weeks (n=2).

Table I. *Comparison of the two treatment groups A (accelerated fractionation with concomitant boost) and B (conventional radio-chemotherapy) regarding characteristics used for matching. p-Values were calculated with the Fisher's exact test. p-Values <0.05 were considered significant, p-values <0.10 indicated a trend.*

Characteristic	Group A (n=8) N patients (%)	Group B (n=72) N patients (%)	*p*-Value
Tumor site			
Oropharynx	3 (37.5)	29 (40.3)	>0.99*
Hypopharynx	3 (37.5)	24 (33.3)	
Larynx	2 (25.0)	19 (26.4)	
Gender			
Female	2 (25.0)	14 (19.4)	0.66
Male	6 (75.0)	58 (80.6)	
Age at radiotherapy			
≤55 Years	2 (25.0)	20 (27.8)	>0.99
>55 Years	6 (75.0)	52 (72.2)	
Performance status			
KPS 60-70	5 (62.5)	19 (26.4)	**0.049**
KPS 80-100	3 (37.5)	53 (73.6)	
T-stage			
T3	3 (37.5)	22 (30.6)	0.70
T4	5 (62.5)	50 (69.4)	
N-stage			
N0-1	2 (25.0)	18 (25.0)	>0.99
N2	6 (75.0)	54 (75.0)	
Histologic grade			
G1-2	6 (75.0)	53 (73.6)	>0.99
G3	2 (25.0)	19 (26.4)	

KPS: Karnofsky performance score. *For calculation of the *p*-value, hypopharynx and larynx were combined. Statistically significant *p*-values are given in bold.

Both groups were matched for tumor site (oropharynx *vs.* hypopharynx *vs.* larynx), gender, age at radiotherapy (≤55 *vs.* >55 years), primary tumor stage (T3 *vs.* T4), stage of regional lymph nodes (N0-1 *vs.* N2) and histologic grade (G1-2 *vs.* G3). Matching for Karnofsky performance score (KPS 60-70 *vs.* 80-100) was not possible, since the KPS was significantly worse in the AF-CB group. The distributions of the parameters are shown in Table I (comparisons performed with Fisher's exact test).

The groups were compared for LRC, metastases-free survival (MFS) and OS, calculated from the last day of radiotherapy. Univariate analyses for these endpoints were performed with the Kaplan–Meier method and the log-rank test. Characteristics found to be significant ($p<0.05$) or indicated a trend ($p<0.10$) were additionally evaluated for independence using a Cox proportional hazard model (multivariate analysis). Moreover, treatment groups A and B were compared for acute (oral mucositis, radiation dermatitis) and late (regional lymph edema, xerostomia) radiation-related toxicities using the Fisher's exact test. Again, *p*-values <0.05 were considered significant and *p*-values <0.10 indicated a trend.

Table II. *Univariate analyses of loco-regional control up to 3 years following radiotherapy for treatment groups A (accelerated fractionation with concomitant boost) and B (conventional radio-chemotherapy) and characteristics used for matching. p-Values were calculated with the log-rank test.*

Characteristic	1 Year	2 Years	3 Years	*p*-Value
Treatment group				
Group A	83	83	56	0.85
Group B	72	64	64	
Tumor site				
Oropharynx	80	71	71	**0.034**
Hypopharynx	53	47	47	
Larynx	85	79	67	
Gender				
Female	87	75	75	0.26
Male	69	63	59	
Age at radiotherapy				
≤55 Years	63	63	63	0.43
>55 Years	76	67	62	
Performance status				
KPS 60-70	62	51	38	0.078
KPS 80-100	77	72	72	
T-stage				
T3	77	67	67	0.64
T4	71	65	60	
N-stage				
N0-1	69	54	54	0.39
N2	74	70	64	
Histologic grade				
G1-2	74	66	62	0.91
G3	69	63	63	

KPS: Karnofsky performance score. Significant *p*-values are given in bold.

Table III. *Univariate analyses of metastases-free survival up to 3 years following radiotherapy for treatment groups A (accelerated fractionation with concomitant boost) and B (conventional radio-chemotherapy) and characteristics used for matching. p-Values were calculated with the log-rank test.*

Characteristic	1 Year	2 Years	3 Years	*p*-Value
Treatment group				
Group A	75	75	75	0.88
Group B	83	75	62	
Tumor site				
Oropharynx	84	80	56	0.23
Hypopharynx	69	63	63	
Larynx	95	81	81	
Gender				
Female	75	75	75	0.82
Male	84	75	64	
Age at radiotherapy				
≤55 Years	79	73	73	0.92
>55 Years	84	76	64	
Performance status				
KPS 60-70	62	49	49	**0.005**
KPS 80-100	92	87	71	
T-stage				
T3	92	85	85	0.070
T4	78	70	56	
N-stage				
N0-1	94	86	74	0.24
N2	79	71	62	
Histologic grade				
G1-2	87	79	65	0.27
G3	69	62	62	

KPS: Karnofsky performance score. Significant *p*-values are given in bold.

Results

Median follow-up periods were 18.5 months (range=0-70 months) in the entire cohort, 21.5 months (range=2-50 months) in group A and 18.5 months (range=0-70 months) in group B, respectively. On univariate analyses, improved LRC was significantly associated with favorable cancer sites (oropharynx or larynx, p=0.034), and a trend was found for KPS 80-100 (p=0.078) (Table II). The difference between group A and group B was not significant (p=0.85, Figure 1). In the subsequent multivariate analysis, KPS showed a trend [hazard ratio (HR)=1.97, 95% confidence interval (CI)=0.89-4.25, p=0.093)]; cancer site was not significant (HR=1.10, 95%CI=0.70-1.71, p=0.68).

Better MFS was significantly associated with KPS 80-100 (p=0.005) on univariate analyses and lower T-stage (T3) showed a trend (p=0.070) (Table III). MFS of treatment groups A and B was not significantly different (p=0.88, Figure 2). In the multivariate analysis of MFS, KPS was significant (HR=3.13, 95%CI=1.29-7.75, p=0.012); a trend was found for T-stage (HR=2.79, 95%CI=0.93-11.99, p=0.068).

Median OS-times were 44 months in the entire cohort, 42.5 months in group A and 50 months in group B, respectively. On univariate analyses (Table IV), improved OS was significantly associated with favorable cancer sites (oropharynx or larynx, p=0.015), and KPS 80-100 showed a trend (p=0.073). No significant association was found for the type of treatment (p=0.47, Figure 3). In the multivariate analysis of OS, KPS showed a trend (HR=1.83, 95%CI=0.91-3.58, p=0.089), cancer site was not significant (HR=1.01, 95%CI=0.67-1.49, p=0.96).

The comparisons of the treatment groups A and B for grade ≥2 and grade ≥3 radiation-related toxicities did not reveal any significant differences (Table V). In group A, one patient did not receive the planned total dose of 69.6 Gy due to acute toxicity. In group B, four patients received less than 70 Gy because of acute treatment-associated toxicity, and in three patients, radiotherapy was limited to 66 Gy due to other reasons.

Data regarding interruptions of radiotherapy >7 days were available for all patients of group A and 57 patients of group B, respectively. Interruptions >7 days were required in 0

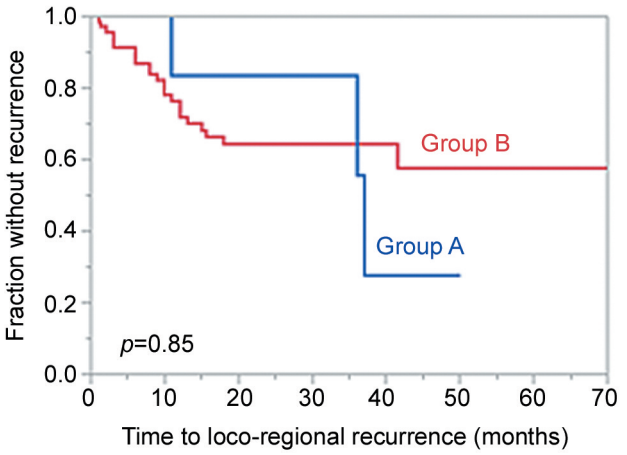

Figure 1. *Kaplan–Meier curves of the patients treated with accelerated fractionation with concomitant boost (group A) and with conventional radio-chemotherapy (group B) with respect to loco-regional control. The p-value was obtained from the log-rank test.*

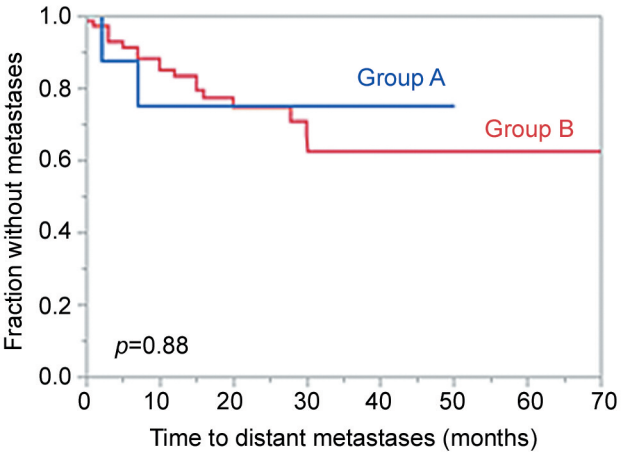

Figure 2. *Kaplan–Meier curves of the patients treated with accelerated fractionation with concomitant boost (group A) and with conventional radio-chemotherapy (group B) with respect to metastases-free survival. The p-value was obtained from the log-rank test.*

patients (0%) of group A and 11 patients (19.3%) of group B, respectively (p=0.33). Chemotherapy could not be given as planned in 28 patients (38.9%) of group B. Toxicities leading to reduction or discontinuation of chemotherapy included impairment in renal function (n=12), severe oral mucositis (n=8), grade 3 nausea/vomiting (n=5), pneumonia (n=3) and other infections (n=2). Chemotherapy was reduced/discontinued in 8/15 patients (53.3%) receiving 30 mg/m^2/d of cisplatin weekly, in 10/14 patients (71.4%) receiving 100 mg/m^2 of cisplatin every 3 weeks, in 6/29 patients (30.7%) receiving 20 mg/m^2/d1-5 of cisplatin every 4 weeks, in 3/12 patients (25.0%) receiving 20 mg/m^2 of cisplatin plus 600 mg/m^2 of 5-FU on days 1-5 every 4 weeks, and in 1/2 patients (50.0%) receiving 20 g/m^2 of cisplatin plus 1000 mg/m^2 of 5-FU on days 1-5 every 4 weeks, respectively.

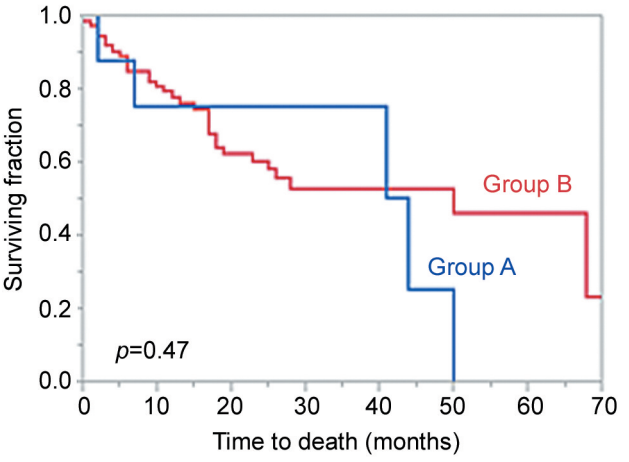

Figure 3. *Kaplan–Meier curves of the patients treated with accelerated fractionation with concomitant boost (group A) and with conventional radio-chemotherapy (group B) with respect to overall survival. The p-value was obtained from the log-rank test.*

Discussion

The prognoses of patients with locally advanced or metastatic SCCHN require improvement. A considerable number of studies were performed during recent years to contribute to this goal (19-24). Patients with locally advanced disease usually receive resection of the primary tumor and dissection of the regional lymph nodes followed by adjuvant radiotherapy or, in case of risk factors, radio-chemotherapy (6, 7, 25). Many patients cannot receive surgery, because the tumor is considered unresectable and/or they have significant co-morbidities. For unresectable SCCHN, cisplatin-based concurrent radio-chemotherapy with conventional fractionation (70 Gy in 35 fractions of 2.0 Gy over 7 weeks) is widely considered the standard treatment (3-5). However, due to co-morbidities including decreased renal function, peripheral neuropathy and hearing loss, a considerable number of patients cannot safely receive standard cisplatin-based chemotherapy. Other potential options of systemic therapy include carboplatin, mitomycin C plus 5-FU and epidermal growth factor receptor (EGFR) antibodies such as cetuximab (26-28). Since also these agents can be associated with significant side effects, the majority of patients unsuitable for cisplatin-based chemotherapy cannot receive other systemic treatments.

Table IV. *Univariate analyses of overall survival up to 3 years following radiotherapy for treatment groups A (accelerated fractionation with concomitant boost) and B (conventional radio-chemotherapy) and characteristics used for matching. p-Values were calculated with the log-rank test.*

Characteristic	1 Year	2 Years	3 Years	*p*-Value
Treatment group				
Group A	75	75	75	0.47
Group B	78	60	53	
Tumor site				
Oropharynx	84	68	56	**0.015**
Hypopharynx	59	37	37	
Larynx	90	84	76	
Gender				
Female	81	74	55	0.69
Male	77	60	55	
Age at radiotherapy				
≤55 Years	73	55	55	0.35
>55 Years	79	64	56	
Performance status				
KPS 60-70	71	46	40	0.073
KPS 80-100	80	67	61	
T-stage				
T3	84	64	64	0.33
T4	75	60	51	
N-stage				
N0-1	80	56	42	0.40
N2	77	63	61	
Histologic grade				
G1-2	83	63	57	0.48
G3	62	56	49	

KPS: Karnofsky performance score. Significant *p*-values are given in bold.

Table V. *Comparison of the two treatment groups A (accelerated fractionation with a concomitant boost) and B (standard fractionation) with respect to radiation-related toxicities. The p-values were obtained from the Fisher's exact test.*

Toxicity	Group A N patients (%)	Group B N patients (%)	*p*-Value
Grade ≥2 oral mucositis	8 (100)	68 (94.4)	>0.99
Grade ≥3 oral mucositis	4 (50.0)	41 (56.9)	0.72
Grade ≥2 radiation dermatitis	5 (62.5)	58 (80.6)	0.36
Grade ≥3 radiation dermatitis	1 (12.5)	21 (29.2)	0.43
Grade ≥2 lymph edema	2 (25.0)	15 (27.3)*	>0.99
Grade ≥3 lymph edema	1 (12.5)	1 (1.8)*	0.24
Grade ≥2 xerostomia	5 (62.5)	46 (63.9)	>0.99
Grade ≥3 xerostomia	1 (12.5)	6 (8.3)	0.54

*Data regarding lymph edema were available only for 55 patients in group B.

Moreover, all systemic treatment increases the toxicity of the mandatory radiotherapy. This may lead to interruptions of the radiation treatment of more than 7 days, which has been shown to have a negative impact on the patients' prognoses. In the multivariate analysis of a study in patients with non-metastatic stage IV SCCHN, lack of interruptions of radiotherapy >7 days was associated with improved LRC (risk ratio=3.32, p=0.015) and OS (risk ratio=2.59, p=0.021) (8).

For these patients, alternative treatment options are required that improve LRC and OS compared to conventionally fractionated radiotherapy alone. Improved outcomes were demonstrated for unconventional fractionated radiotherapy. In a randomized trial, hyper-fractionated radiotherapy (81.6 Gy in 68 fractions, *i.e.* 2×1.2 Gy per day on 5 days per week) and AF-CB (72 Gy in 42 fractions over 6 weeks, *i.e.* 30×1.8 Gy/day to a large field plus a concomitant boost of 1.5 Gy/day given 6 hours after the dose to the large field for the last 12 treatment days) resulted in significantly better LRC and DFS compared to conventional radiotherapy (70 Gy in 35 fractions) (10). The results of this trial were updated in 2014 (29). The absolute reduction in cumulative loco-regional failure at 5 years compared to conventional fractionation was 6.5% for hyper-fractionated radiotherapy and 6.6% for AF-CB, respectively. When considering the patients censored for loco-regional control at 5 years, p-values were 0.05 for hyper-fractionation and 0.11 for AF-CB, respectively. Both hyper-fractionation and AF-CB were significantly superior to conventional fractionation with respect to DFS (29). When considering the patients censored for DFS at 5 years, p-values were 0.01 for hyper-fractionation and 0.05 for AF-CB, respectively. In addition, a meta-analysis of 15 trials demonstrated a benefit with respect to LRC for AF-CB (9). This meta-analysis also observed a survival benefit for unconventionally fractionated radiotherapy. The absolute benefit at 5 years was larger for hyper-fractionated radiotherapy than for AF-CB (8% *vs*. 2%). According to the authors of this meta-analysis, this difference should be interpreted with caution because of variation in patient characteristics between the treatment groups (9). A potential advantage of AF-CB compared to hyper-fractionation is the lower number of fractions (29-42 *vs*. 60-68 fractions). This can be particularly important for institutions with waiting lists due to high patient load or limited capacities at their linear accelerators.

After the trial of Fu *et al*. (10), additional AF-CB programs were reported that achieved promising results (11-14). The AF-CB program used in the current study was presented in a German trial in 2001 (11). The value of AF-CB has not yet been finally clarified. According to two meta-analyses, radiotherapy with accelerated fractionation such as AF-CB alone cannot entirely compensate for the lack of concurrent chemotherapy (30, 31). In a randomized phase III trial of 216 patients with oropharynx cancer, AF-CB (67.5 Gy in 40 fractions over 5 weeks) provided better compliance,

toxicity profile and quality of life with similar disease control when compared to concurrent radio-chemotherapy including 66 Gy in 33 fractions over 6.5 weeks plus cisplatin 100mg/m^2 on days 1, 22 and 43 (32). Moreover, in a recent randomized trial published in 2020, response rates and DFS were not significantly different for AF-CB and concurrent conventionally fractionated radio-chemotherapy (33). Thus, more studies comparing AF-CB and radio-chemotherapy for locally advanced SCCHN are warranted.

To our knowledge, the AF-CB included in the present study has not yet been compared to standard concurrent radio-chemotherapy with conventional fractionation. To allow better comparability of both treatments, the patients were matched for cancer site, gender, age, primary tumor stage, stage of regional lymph nodes and histologic grade. Matching for KPS was not possible, since KPS was significantly worse in group A. Patients receiving AF-CB were specifically unsuitable for chemotherapy due to significant co-morbidities that also impact KPS.

According to the results of this study, AF-CB was not significantly inferior to conventionally fractionated concurrent radio-chemotherapy with respect to LRC, MFS, OS and radiation-related toxicities. In contrast to the type of treatment, improved outcomes were associated with favorable cancer site (oropharynx or larynx), KPS of 80-100 and T3-stage (compared to T4-stage). These prognostic factors were also identified in previous studies demonstrating consistency of these findings to other studies (34-37). Limitations of this study include its retrospective design, the small sample size in group A, the lack of data regarding the status of the human papilloma virus, and the different treatment periods between the two treatment groups. In 15 patients (20.8%) of group B, chemotherapy consisted of weekly administration of 30 mg/m^2/d of cisplatin. In two previous studies and a meta-analysis, weekly cisplatin appeared less effective than 100 mg/m^2 of cisplatin every 3 weeks and 20 mg/m^2/d1-5 of cisplatin every 4 weeks (38-40). Thus, the results after radio-chemotherapy might have been more favorable without patients receiving weekly cisplatin. Moreover, 38.9% of patients in group B did not receive their chemotherapy as planned due to acute toxicity. This demonstrates the importance of proper selection of patients for concurrent radio-chemotherapy. When patients with unresectable SCCHN undergo a careful selection process prior to treatment, the proportion of patients receiving the complete radio-chemotherapy as planned would likely increase. Concurrent radio-chemotherapy will remain the treatment-of-choice for the majority of patients with unresectable SCCHN.

In summary, given the limitations of this study, AF-CB produced promising results and is a reasonable alternative for the treatment of unresectable SCCHN in patients who cannot receive radio-chemotherapy. Confirmation of the results with a larger prospective trial including the AF-CB program used in the present study is warranted.

Conflicts of Interest

The Authors report no conflicts of interest related to the present study.

Authors' Contributions

The study was designed by all Authors. The data of the new patients were collected by C.A.N. The analyses of the data used for this study were performed by S.E.S. and D.R. The article was drafted by D.R. and S.E.S. and approved by all Authors.

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *68*: 394-424, 2018. PMID: 30207593. DOI: 10.3322/caac.21492

2 Chow LQM: Head and neck cancer. N Engl J Med *382*: 60-72, 2020. PMID: 31893516. DOI: 10.1056/NEJMra1715715

3 Adelstein DJ, Lavertu P, Saxton JP, Secic M, Wood BG, Wanamaker JR, Eliachar I, Strome M and Larto MA: Mature results of a phase III randomized trial comparing concurrent chemoradiotherapy with radiation therapy alone in patients with stage III and IV squamous cell carcinoma of the head and neck. Cancer *88*: 876-883, 2000. PMID: 10679658. DOI: 10.1002/(sici)1097-0142(20000215)88:4<876::aid-cncr19>3.0.co;2-y

4 Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J and Calais G: Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol *22*: 69-76, 2004. PMID: 14657228. DOI: 10.1200/JCO.2004.08.021

5 Pignon JP, le Maître A, Maillard E and Bourhis J; MACH-NC Collaborative Group: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol *92*: 4-14, 2009. PMID: 19446902. DOI: 10.1016/j.radonc.2009.04.014

6 Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A and van Glabbeke M; European Organization for Research and Treatment of Cancer Trial 22931: Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med *350*: 1945-1952, 2004. PMID: 15128894. DOI: 10.1056/NEJMoa032641

7 Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N and Fu KK; Radiation Therapy Oncology Group 9501/Intergroup: Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med *350*: 1937-1944, 2004. PMID: 15128893. DOI: 10.1056/NEJMoa032646

8 Rades D, Stoehr M, Kazic N, Hakim SG, Walz A, Schild SE and Dunst J: Locally advanced stage IV squamous cell carcinoma of the head and neck: Impact of pre-radiotherapy hemoglobin level

and interruptions during radiotherapy. Int J Radiat Oncol Biol Phys *70*: 1108-1114, 2008. PMID: 17905528. DOI: 10.1016/j.ijrobp.2007.07.2380

9 Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, Horiot JC, Le Maître A, Pajak TF, Poulsen MG, O'Sullivan B, Dobrowsky W, Hliniak A, Skladowski K, Hay JH, Pinto LH, Fallai C, Fu KK, Sylvester R and Pignon JP; Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group: Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet *368*: 843-854, 2006. PMID: 16950362. DOI: 10.1016/S0140-6736(06)69121-6

10 Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, Garden AS, Ridge JA, Cooper JS and Ang KK: A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys *48*: 7-16, 2000. PMID: 10924966. DOI: 10.1016/s0360-3016(00)00663-5

11 Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, Flentje M, Eckel HE and Mueller RP: Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy – results of a multicentric randomized German trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys *50*: 1161-1171, 2001. PMID: 11483325. DOI: 10.1016/s0360-3016(01)01544-9

12 Skladowski K, Hutnik M, Wygoda A, Golen M, Pilecki B, Przeorek W, Rutkowski T, Lukaszczyk-Widel B, Heyda A, Suwinski R, Tarnawski R and Maciejewski B: Radiation-free weekend rescued! Continuous accelerated irradiation of 7-days per week is equal to accelerated fractionation with concomitant boost of 7 fractions in 5-days per week: report on phase 3 clinical trial in head-and-neck cancer patients Int J Radiat Oncol Biol Phys *85*: 741-746, 2013. PMID: 22836063. DOI: 10.1016/j.ijrobp.2012.06.037

13 Kubes J, Cvek J, Vondracek V, Pala M and Feltl D: Accelerated radiotherapy with concomitant boost technique (69.5 Gy/5 weeks): an alternative in the treatment of locally advanced head and neck cancer. Strahlenther Onkol *187*: 651-655, 2011. PMID: 21947124. DOI: 10.1007/s00066-011-2246-2

14 Ghoshal S, Goda JS, Mallick I, Kehwar TS and Sharma SC: Concomitant boost radiotherapy compared with conventional radiotherapy in squamous cell carcinoma of the head and neck--a phase III trial from a single institution in India. Clin Oncol (R Coll Radiol) *20*: 212-220, 2008. PMID: 18343310. DOI: 10.1016/j.clon.2008.01.011

15 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A (eds.): AJCC cancer staging manual (7th ed). New York, NY, Springer, 2010.

16 Edge SB and Compton CC: The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol *17*: 1471-1474, 2010. PMID: 20180029. DOI: 10.1245/s10434-010-0985-4

17 Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds.): AJCC cancer staging manual (8th ed.). New York, NY, Springer, 2017.

18 Semrau R, Mueller RP, Stuetzer H, Staar S, Schroeder U, Guntinas-Lichius O, Kocher M, Eich HT, Dietz A, Flentje M, Rudat V, Volling P, Schroeder M and Eckel HE: Efficacy of intensified hyperfractionated and accelerated radiotherapy and concurrent chemotherapy with carboplatin and 5-fluorouracil: updated results of a randomized multicentric trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys *64*: 1308-1316, 2006. PMID: 16464538. DOI: 10.1016/j.ijrobp.2005.10.039

19 Loganadane G, Kann BH, Park HS, Johnson SB, Mehra S, Judson BL, Bhatia A, Belkacemi Y, Yarbrough WG, Burtness B and Husain ZA: Clinical outcomes of head and neck cancer patients who undergo resection, but forgo adjuvant therapy. Anticancer Res *39*: 4885-4890, 2019. PMID: 31519591. DOI: 10.21873/anticanres.13674

20 Rades D, Staackmann C and Janssen S: Predicting the ambulatory status of patients irradiated for metastatic spinal cord compression (MSCC) from head-and-neck cancer. Anticancer Res *38*: 4833-4837, 2018. PMID: 30061256. DOI: 10.21873/anticanres.12794

21 Staackmann C, Janssen S, Schild SE and Rades D: A tool to predict the probability of intracerebral recurrence or new cerebral metastases after whole-brain irradiation in patients with head-and-neck cancer. Anticancer Res *38*: 4199-4202. PMID: 29970550. DOI: 10.21873/anticanres.12714

22 Morimoto M, Bijl HP, van der Schaaf A, Xu CJ, Steenbakkers RJHM, Chouvalova O, Yoshioka Y, Teshima T and Langendijk JA: Development of normal tissue complication probability model for trismus in head and neck cancer patients treated with radiotherapy: The role of dosimetric and clinical factors. Anticancer Res *39*: 6787-6798, 2019. PMID: 31810944. DOI: 10.21873/anticanres.13894

23 Grehn M, Stille M, Ziemann C, Cremers F, Rades D and Buzug TM: A new phantom for individual verification of the dose distribution in precision radiotherapy for head-and-neck cancer. Anticancer Res *39*: 6931-6938, 2019. PMID: 31810964. DOI: 10.21873/anticanres.13914

24 Iijima Y, Bandow K, Sano M, Hino S, Kaneko T, Horie N and Sakagami H: *In vitro* assessment of antitumor potential and combination effect of classical and molecular-targeted anticancer drugs. Anticancer Res *39*: 6673-6684, 2019. PMID: 31810932. DOI: 10.21873/anticanres.13882

25 Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, Ozsahin EM, Jacobs JR, Jassem J, Ang KK and Lefèbvre JL: Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck *27*: 843-850, 2005. PMID: 16161069. DOI: 10.1002/hed.20279

26 Budach V, Stromberger C, Poettgen C, Baumann M, Budach W, Grabenbauer G, Marnitz S, Olze H, Wernecke KD and Ghadjar P: Hyperfractionated accelerated radiation therapy (HART) of 70.6 Gy with concurrent 5-FU/Mitomycin C is superior to HART of 77.6 Gy alone in locally advanced head and neck cancer: long-term results of the ARO 95-06 randomized phase III trial. Int J Radiat Oncol Biol Phys *91*: 916-924, 2015. PMID: 25670541. DOI: 10.1016/j.ijrobp.2014.12.034

27 Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, Raben D, Baselga J, Spencer SA, Zhu J, Youssoufian H, Rowinsky EK and Ang KK: Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival

data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol *11*: 21-28, 2010. PMID: 19897418. DOI: 10.1016/S1470-2045(09)70311-0

28 Guan J, Li Q, Zhang Y, Xiao N, Chen M, Zhang Y, Li L and Chen L: A meta-analysis comparing cisplatin-based to carboplatin-based chemotherapy in moderate to advanced squamous cell carcinoma of head and neck (SCCHN). Oncotarget *7*: 7110-7119, 2016. PMID: 26755647. DOI: 10.18632/oncotarget.6858

29 Beitler JJ, Zhang Q, Fu KK, Trotti A, Spencer SA, Jones CU, Garden AS, Shenouda G, Harris J and Ang KK: Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. Int J Radiat Oncol Biol Phys *89*: 13-20, 2014. PMID: 24613816. DOI: 10.1016/j.ijrobp.2013.12.027

30 Gupta T, Kannan S, Ghosh-Laskar S and Agarwal JP: Systematic review and meta-analysis of conventionally fractionated concurrent chemoradiotherapy *versus* altered fractionation radiotherapy alone in the definitive management of locoregionally advanced head and neck squamous cell carcinoma. Clin Oncol (R Coll Radiol) *28*: 50-61, 2016. PMID: 26454839. DOI: 10.1016/j.clon.2015.09.002

31 Lacas B, Bourhis J, Overgaard J, Zhang Q, Grégoire V, Nankivell M, Zackrisson B, Szutkowski Z, Suwiński R, Poulsen M, O'Sullivan B, Corvò R, Laskar SG, Fallai C, Yamazaki H, Dobrowsky W, Cho KH, Beadle B, Langendijk JA, Viegas CMP, Hay J, Lotayef M, Parmar MKB, Aupérin A, van Herpen C, Maingon P, Trotti AM, Grau C, Pignon JP and Blanchard P; MARCH Collaborative Group: Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis Lancet Oncol *18*: 1221-1237, 2017. PMID: 28757375. DOI: 10.1016/S1470-2045(17)30458-8

32 Gupta P, Dhull AK and Kaushal V: A comparative study of concomitant boost radiation *versus* concomitant boost with concurrent chemoradiation *versus* standard fractionation chemoradiation in locally advanced head-and-neck cancer. J Cancer Res Ther *16*: 478-484, 2020. PMID: 32719254. DOI: 10.4103/jcrt.JCRT_475_18

33 Rishi A, Ghoshal S, Verma R, Oinam AS, Patil VM, Mohinder R and Sharma SC: Comparison of concomitant boost radiotherapy against concurrent chemoradiation in locally advanced oropharyngeal cancers: a phase III randomised trial. Radiother Oncol *107*: 317-324, 2013. PMID: 23746674. DOI: 10.1016/j.radonc.2013.05.016

34 Huttenlocher S, Seibold ND, Gebhard MP, Noack F, Thorns C, Hasselbacher K, Wollenberg B, Schild SE and Rades D: Evaluation of the prognostic role of tumor cell podoplanin expression in locally advanced squamous cell carcinoma of the head and neck. Strahlenther Onkol *190*: 1021-1027, 2014. PMID: 24928249. DOI: 10.1007/s00066-014-0694-1

35 Seibold ND, Schild SE, Bruchhage KL, Gebhard MP, Noack F and Rades D: Prognostic impact of VEGF and FLT-1 receptor expression in patients with locally advanced squamous cell carcinoma of the head and neck. Strahlenther Onkol *189*: 639-646, 2013. PMID: 23748230. DOI: 10.1007/s00066-013-0341-2

36 Seidl D, Janssen S, Strojan P, Bajrovic A, Schild SE and Rades D: Prognostic factors after definitive radio(chemo)therapy of locally advanced head and neck cancer. Anticancer Res *36*: 2523-2526, 2016. PMID: 27127167.

37 Fakhry C, Zhang Q, Nguyen-Tân PF, Rosenthal DI, Weber RS, Lambert L, Trotti AM 3rd, Barrett WL, Thorstad WL, Jones CU, Yom SS, Wong SJ, Ridge JA, Rao SSD, Bonner JA, Vigneault E, Raben D, Kudrimoti MR, Harris J, Le QT and Gillison ML: Development and validation of nomograms predictive of overall and progression-free survival in patients with oropharyngeal cancer. J Clin Oncol *35*: 4057-4065, 2017. PMID: 28777690. DOI: 10.1200/JCO.2016.72.0748

38 Rades D, Seidl D, Janssen S, Bajrovic A, Karner K, Strojan P and Schild SE: Comparison of weekly administration of cisplatin *versus* three courses of cisplatin 100 mg/m(2) for definitive radiochemotherapy of locally advanced head-and-neck cancers. BMC Cancer *16*: 437, 2016. PMID: 27391309. DOI: 10.1186/s12885-016-2478-8

39 Rades D, Seidl D, Janssen S, Strojan P, Karner K, Bajrovic A, Hakim SG, Wollenberg B and Schild SE: Comparing two lower-dose cisplatin programs for radio-chemotherapy of locally advanced head-and-neck cancers. Eur Arch Otorhinolaryngol *274*: 1021-1027, 2017. PMID: 27687678. DOI: 10.1007/s00405-016-4326-5

40 Guan J, Zhang Y, Li Q, Zhang Y, Li L, Chen M, Xiao N and Chen L: A meta-analysis of weekly cisplatin *versus* three weekly cisplatin chemotherapy plus concurrent radiotherapy (CRT) for advanced head and neck cancer (HNC). Oncotarget *7*: 70185-70193, 2016. PMID: 27602493. DOI: 10.18632/oncotarget.11824

Received November 26, 2020
Revised December 3, 2020
Accepted December 4, 2020