ACTA ONCOLOGICA
2019, VOL. 58, NO. 10, 1495–1501
https://doi.org/10.1080/0284186X.2019.1658897

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ORIGINAL ARTICLE

A prospective, multicenter DAHANCA study of hyperfractionated, accelerated radiotherapy for head and neck squamous cell carcinoma

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ABSTRACT

Background: The study aimed to evaluate Hyperfractionated, Accelerated Radiotherapy (HART) with nimorazole for patients with head and neck squamous cell carcinoma (HNSCC) using loco-regional failure (LRF), overall survival (OS), early and late morbidity as endpoints.

Material and methods: From February 2007 to January 2018, 295 patients with unresected HNSCC, T1-T4, N0-N3, M0, were treated with HART prescribed as 76 Gy in 56 fractions (fx), 10 fx weekly. IMRT was used in >90% of patients. No chemotherapy was given. Patients were prospectively registered in the DAHANCA database.

Results: The median age was 64 years, 75% of patients were males. Primary sites were larynx (25%), pharynx (64%) and oral cavity (11%). In total, 59% were stage III-IV (UICC 2002). Of the 150 oropharyngeal cancer (OPC) patients, 42% were p16+. The proportion of patients receiving HART as planned was 97%. The median follow-up time was 66 months. Three-year actuarial LRF was 19% and OS was 66%. LRF was significantly higher for stage III–IV patients compared to stage I–II (25% vs. 11%, HR 2.12 [1.21–3.74]). The site-specific LRF rates were: for larynx 22% [12–32], hypopharynx 30% [16–45], non-p16+ oropharynx 15% [8–23], p16+ oropharynx 7% [1–13] and oral cavity 35% [18–53]. During therapy, 51% reported severe dysphagia and 60% required feeding tubes. The peak incidence of late, severe dysphagia and xerostomia was 21% and 9%, respectively. A comparison to historical data from previous DAHANCA trials showed that tumor control and morbidity are comparable to treatment with acceleration and/or chemo-radiation.

Conclusions: HART represents an attractive approach for patients with HNSCC where treatment intensification is indicated.

ARTICLE HISTORY
Received 26 March 2019
Accepted 15 August 2019

Introduction

DAHANCA, The Danish Head and Neck Cancer Group, has through a series of consecutive, prospective trials improved primary radiotherapy for head and neck squamous cell carcinoma (HNSCC) [1,2]. In the 1980's, loco-regional control was significantly increased by targeting hypoxia and adding the hypoxic radiosensitizer nimorazole to conventionally fractionated radiotherapy of 66–68 Gy in 5 weekly fractions of 2 Gy [3]. In the next decade, the DAHANCA 6&7 trials demonstrated that a further increase in local control was achieved by shortening the overall treatment time with one week, giving 66–68 Gy in 33-34 fractions, but with 6 fractions per week as a moderate acceleration [4]. Inspired by the EORTC and RTOG trials [5–7], the randomized DAHANCA 9 study [8] explored the feasibility of adding dose escalation to 76 Gy through hyperfractionation in addition to the above accelerated treatment. The DAHANCA 9 trial accrued patients during 2000–2007, but was closed prematurely due to low recruitment. The results added to the conclusion of the updated version of the MARCH meta-analysis [9] on altered fractionation: that hyperfractionated radiotherapy improves both local and regional control without a significant increase in late morbidity.

Next, the phase II DAHANCA 18 trial followed which evaluated the addition of weekly concurrent chemotherapy to moderately accelerated normo-fractionated IMRT based radiotherapy with nimorazole for patients with locally advanced HNSCC. This regimen showed encouraging loco-regional outcome, and the treatment became standard of care for locally advanced, node-positive patients fit for chemotherapy [10].

The results and the general practical experience from the DAHANCA 9 trial [8] lead to implementation of an amendment in the DAHANCA guidelines, making accelerated hyperfractionated radiotherapy an optional treatment for patients. As an example, hyperfractionated, moderately accelerated treatment with nimorazole was considered for patients

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with node-positive disease unfit for the concurrent chemotherapy.

The aim of the present study was to report on treatment efficacy and peak incidence of acute and late morbidity in Danish patients treated with this optional fractionation schedule after the introduction of IMRT.

Material and methods

Patients

From February 2007 to January 2018, a total of 295 patients received accelerated, hyperfractionated treatment for unresected squamous cell carcinoma of the larynx, hypopharynx, oropharynx or oral cavity, T1–T4, N0–N3, with no signs of distant metastases at the time of diagnosis. Generally, only patients with limited comorbidity and acceptable performance status were eligible for treatment. Patients were included in this analysis regardless of tumor HPV-status [11]. Patient and tumor characteristics are listed in Table 1.

Treatment

All patients were treated according to the Danish national guidelines as established by DAHANCA [12,13]. Five days a week, treatment was given in two daily fractions of 1.36 Gy and with an interval of at least 6 hours. The majority of patients (>90%) were treated with IMRT. A prescribed dose of 76 Gy in 56 fractions with 10 fractions per week were given to the tumor volume and macroscopically involved lymph nodes. Elective nodal areas were treated to 56 Gy and no elective neck dissections were performed. The treatment was accelerated with a planned overall treatment time of $5^1/_2$ weeks. The hypoxic cell sensitizer nimorazole was orally administered 90 mins prior to each fraction, with body surface adjusted dose of 1.2 g/m^2 for the first daily fraction and a fixed dose of 1 g for the following fraction [14]. No patients received concurrent chemotherapy.

Table 1. Patient and tumor characteristics ($n = 295$).

	All patients *n* (%)
Age	
Median	64
Range	(32–81)
Gender	
Male	220 (75)
Female	75 (25)
Performance status	
WHO 0	144 (49)
WHO 1	84 (28)
WHO ≥2	14 (5)
unknown	53 (18)
Tumor site	
Larynx	73 (25)
Oropharynx, p16+	63 (21)
Oropharynx, p16−	68 (23)
Oropharynx, unknown	19 (6)
Hypopharynx	41 (14)
Oral cavity	31 (11)
Tumor classification[a]	
T1	4 (1)
T2	144 (49)
T3	94 (32)
T4	53 (18)
Nodal classification[a]	
N0	236 (80)
N1	17 (6)
N2	42 (14)
Disease stage[a]	
I	1 (<1)
II	121 (41)
III	93 (32)
IV	80 (27)

[a]TNM staging according to UICC 2002 edition.

Endpoints and statistics

Patients were followed according to the DAHANCA guidelines [15,16]. The main outcome measure was loco-regional treatment failure after 3 years of follow up, calculated as the cumulative incidence of loco-regional recurrences (at T- and/or N-site). Data analysis was performed as intention-to-treat, including all non-completing patients in the analysis. Patients with unknown p16-status were grouped with p16-negative, unless otherwise specified. Statistical analyses were performed using Stata Statistical Software Release 15 (StataCorp LLC, College Station, TX, USA). A significance level of 5% was used and 95% confidence intervals are shown in brackets. Competing risk analysis was performed when calculating cumulative failure incidence of loco-regional control, considering distant metastases and death of any cause as competing events. Univariate cox regression was used for comparing hazards between groups for the following endpoints: loco-regional failure, local failure, nodal failure and overall survival. Furthermore, multivariate analysis was performed adjusting for tumor localization, T- and N-classification or stage for hazards of the beforementioned endpoints, and in addition, age-adjustment for overall survival. The probability of overall survival 3 years after treatment was estimated using the Kaplan–Meier method, and defined as death from any cause. All endpoints were calculated from the time of treatment initiation.

Peak incidences of early and late morbidity were established. The peak incidence was defined as the number of patients with a given toxicity grade relative to the total number of evaluable patients. Definition of early morbidity were toxicities arising during treatment and until 6 months after initiation of treatment, and late morbidity as the adverse effects of treatment recorded from 6 months after treatment and until end of follow up. All surviving patients at 6 months follow-up were included in the analysis of late morbidity, regardless if treatment was given as scheduled. Binary endpoints were compared using the Chi^2-test and evaluated by calculation of relative risks using binary logistic regression.

Results

At the time of data analysis on 1 May 2019, 159 patients were still alive. The median observation time for survivors was 66 months (range 15–138 months), and 31 patients were followed less than 36 months. Overall, 136 patients had died, of which 60 died either with or from the primary cancer.

Treatment compliance and tolerability

The proportion of patients, who received the scheduled radiotherapy was 97%. The median treatment time was 40 days (range 19–48). Ten patients stopped treatment prematurely (Supplementary Table 1), and of these six patients discontinued before 60 Gy was given. Five patients (2%) died during or shortly after therapy, but no deaths were directly treatment related. Nimorazole was discontinued during treatment in 82 patients (28%), mainly due to gastrointestinal adverse effects [14].

Treatment outcome

The pattern of failures within the first 36 months of follow-up is shown in Figure 1. Of 52 local failures, 50 were listed as in-field recurrences. Eighteen patients presented with disseminated disease at the time of recurrence, without evidence of loco-regional disease (6%). Among patients with distant failure only, there were 11 with an initial primary tumor originating from the oropharynx, of which four were p16+.

A total of 56 patients were diagnosed with loco-regional failure. The 3-year actuarial cumulative incidence was 19% [15–24%], graphed in Figure 2(A). Median time to loco-regional failure was seven months (range 0.6–34.5). Fourteen patients never achieved tumor control, of which five had received less than 60 Gy. Nine of these had received full dose, but in two cases, the failure was in patients, who died before first evaluation (administratively set to failures).

Uni- and multivariate analysis for the risk of loco-regional failure is shown in Table 2. Patients with locally advanced, stage III–IV disease had a significantly higher risk of loco-regional failure, when compared to patients with early stage carcinomas (25% vs. 11%, site-adjusted HR 2.12 [1.21–3.74, $p = .009$, Figure 2(A)) The site-specific failure rates were (Figure 2(B)): for oral cavity cancer 35% [18–53%], hypopharynx 30% [16–45%], larynx 22% [12–32%], non-p16+ oropharynx 15% [8–23%] and p16+ oropharynx 7% [1–13%]. Among the oropharynx tumors with known p16-status, no statistically significant difference between p16+ and p16− tumors was seen (HR 2.06 [0.82–5.20], $p = .125$, Supplementary Figure 1(A)).

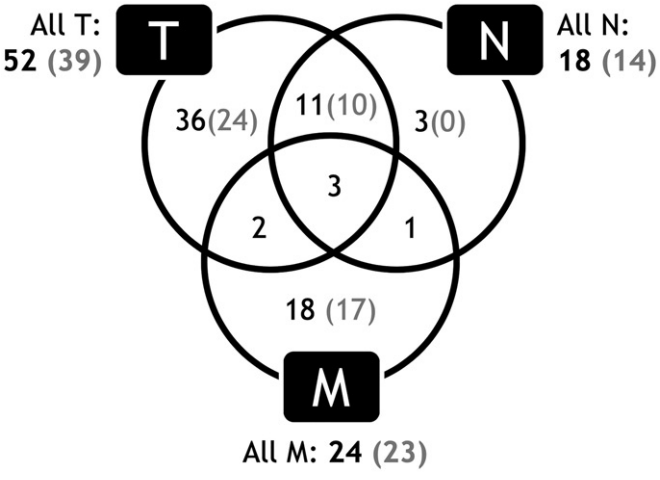

Figure 1. The pattern of failure. Numbers shown in circles represent patients. Numbers outside represent failures. Grey numbers in brackets have been corrected for successful surgical salvage procedures. T-site failures were salvaged in 13 cases, N-site in four cases and M-site in one case. Overall, there were 40 patients with persistent loco-regional failure, of which six had metastatic spread also.

T-classification proved in both uni- and multivariate analysis to be the most important factor for local recurrence (T3–T4 vs. T1–T2; HR 2.5 [1.42–4.42], $p = .002$). Accordingly, the most important factor for nodal control was n-classification (N+ vs N0; HR 5.22 [2.04–13.34], $p = .001$), Supplementary Figures 1(B,C).

Surgical salvage

Overall, 74 patients had recurrent disease and surgical salvage was attempted in 24 patients, of which 17 (23%) had radical surgery, Figure 1. The T-site was successfully salvaged in 13 cases (two laryngectomies, four pharyngeal resections, four resections of the floor of mouth including mandibular resections, one tongue resection and two unspecified surgical procedures), the N-site in four cases (neck dissections). One patient with an oligometastatic distant spread had a wedge resection of the lung. The 3-year cumulative incidence of ultimate loco-regional failure was 14% [10–18%], Supplementary Figure 1(D).

Survival

From the time of treatment initiation and within the following 3 years, 99 patients had died and 31 was censored from the study. Fifty-one patients died either with or from the primary disease and 48 patients died without, mainly from other cancers ($n = 22$) and non-cancer diseases ($n = 19$). The cumulative 3-year incidence of disease-specific mortality was 18% [13–22%], and corresponding estimate of overall survival probability was 67% [60–71%], Figure 2(C). The site-specific survival rates were (Figure 2(D)): for oral cavity cancer 48% [30–64%], hypopharynx 56% [39–64%], larynx 56% [43–66%], non-p16+ oropharynx 70% [59–79%] and p16+ oropharynx 87% [75–93%].

Separation of the patients according to disease stage, demonstrates a significantly worse survival probability in patients with locally advanced, stage III–IV disease compared to earlier disease stages (57% [49–64%] vs. 78% [69–84%], site-adjusted HR 2.22 [1.51–3.26], $p < .001$), Figure 2(C). Tumor site, T-classification and N-classification were all important prognostic factors for overall survival in a multivariate regression model (Table 2).

Of the 17 patients salvaged by surgery, 12 were still alive at the time of data analysis, and the remaining five had died from other causes. The probability of being alive and without evidence of the primary disease was 64% [58–69%] at 3 years after radiotherapy allowing for surgical salvage.

Early and late treatment toxicity

Early radiation-induced morbidity was recorded among 288 of the treated patients (97%), Table 3. At the end of the

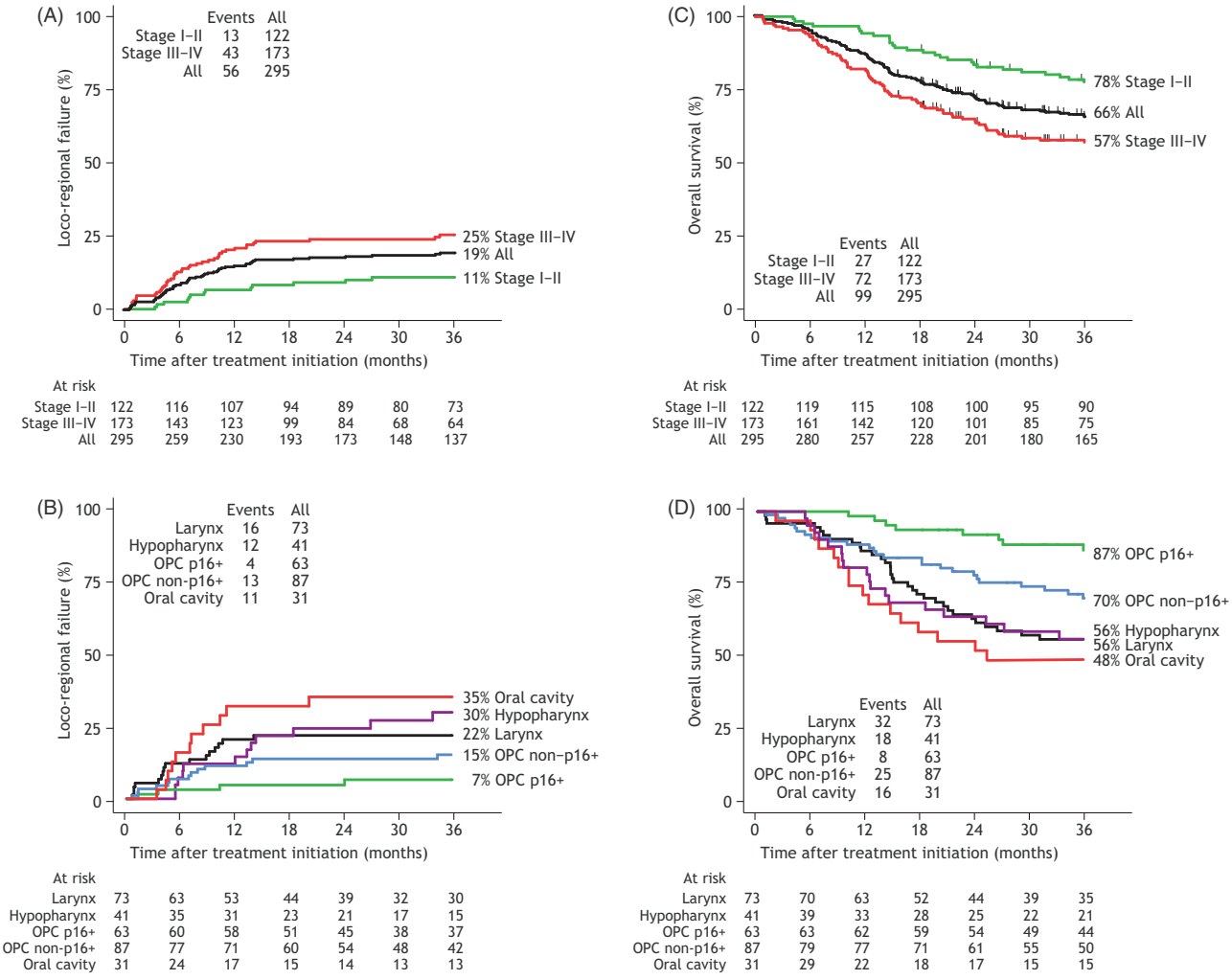

Figure 2. Loco-regional failure in 295 patients treated with dose escalated, hyperfractionated and accelerated radiotherapy with concomitant nimorazole from 2007 to 2017 according to disease stage (A) and tumor site (B) and corresponding overall survival according to disease stage (C) and tumor site (D). In oropharynx patients, tumors with unknown p-16 status are grouped with p16-negative.

treatment, half of the patients (51%) were suffering from severe dysphagia, and confluent or ulcerative mucositis was observed in 55% of patients. Nasogastric- or G-tubes were used in 60% of patients during therapy. The dependency of tube feeding decreased to 7% at 6 months after therapy.

Late radiation-related morbidity was registered in 257 patients among the 280 patients alive at 6 months of follow-up (92%). Here, peak incidence of severe dysphagia was 21%, with 11% of patients complaining of severe xerostomia. At 12 months, 5% were using feeding tubes. Osteoradionecrosis was recorded in 6% of patients (Table 3).

An important factor associated with the risk of developing severe late dysphagia was the disease stage, which stayed significant when correcting for the irradiated tumor site (stage III–IV vs. stage I–II, RR 2.23 [1.27–3.92], $p = .006$).

Discussion

In this prospective multicenter cohort study of patients treated with hyperfractionated dose escalation, the proportion of non-completing patients were 3% and the risk of treatment loco-regional failure less than 20% within the first three years after treatment. The risk of death of the primary disease was equivalent.

The tumor site and T- as well as N-classification were significant factors in a both univariate and multivariate analysis for locoregional recurrence. It has previously been shown that hyperfractionation is effective for tumor control both at T- and N-site [9], indicating that accelerated, dose escalated radiotherapy using hyperfractionation could be an effective treatment option to target both patients with larger T-sites and/or patients with node-positive disease unfit for concurrent cisplatin. In the present analysis, we demonstrate a loco-regional failure rate of 25% and a survival probability of 57% among the 173 stage III–IV patients within 36 months of follow-up. The site-specific loco-regional control among these patients is very similar to the rates in the DAHANCA 18 study (see Supplementary Figure 2 for comparison to historical data). Thus, the hyperfractionated dose escalated regimen provide evidence that the treatment efficacy is favorable for HNSCC patients in early stages, and for patients in advanced stages comparable to that of accelerated, chemo-radiotherapy with standard 2 Gy-fractionation.

Table 2. Uni- and multivariate analysis for outcome endpoints.

	Overall survival[a]							Loco-regional failure[b]						
	Univariate				Multivariate			Univariate				Multivariate		
Covariate	Events/all	HR	[95%CI]	*p*-value	HR	[95%CI]	*p*-value	Events/all	HR	[95%CI]	*p*-value	HR	[95%CI]	*p*-value
Age														
<65 yrs	45/163	1	–		1	–		29/163	1	–				
≥65 yrs	53/132	1.46	[1.04–2.04]	**.03**	1.36	[0.96–1.92]	.081	27/132	1.31	[0.80–2.13]	.281			
Gender														
Male	73/220	1	–					46/220	1	–				
Female	26/75	1.06	[0.72–1.56]	.767				10/75	0.60	[0.31–1.14]	.116			
Performance status														
WHO 0	33/144	1	–					17/144	1	–				
WHO ≥1	49/98	2.74	[1.87–4.00]	**<.001**				29/98	2.54	[1.45–4.46]	**.001**			
Tumor site														
Larynx	32/73	1	–		1	–		16/73	1	–		1	–	
Hypopharynx	18/41	1.37	[0.83–2.27]	.222	1.21	[0.71–2.07]	.488	12/41	1.29	[0.62–2.68]	.5	1.04	[0.48–2.25]	.92
Oropharynx, p16+	8/63	0.26	[0.13–0.51]	**<.001**	0.31	[0.16–0.60]	**.001**	4/63	0.39	[0.16–0.93]	**.034**	0.47	[0.19–1.13]	.093
Oropharynx, non-p16+	25/87	0.74	[0.47–1.17]	.196	0.92	[0.58–1.46]	.714	13/87	0.70	[0.36–1.37]	.296	0.78	[0.39–1.56]	.492
Oral cavity	16/31	1.68	[1.01–2.80]	**.045**	1.56	[0.92–2.64]	.096	11/31	1.79	[0.86–3.72]	.12	1.53	[0.72–3.24]	.265
Tumor classification														
T1–T2	33/148	1	–		1	–		16/148	1	–		1	–	
T3–T4	66/147	2.56	[1.80–3.65]	**<.001**	2.30	[1.60–3.31]	**<.001**	40/147	2.65	[1.57–4.47]	**<.001**	2.33	[1.37–3.99]	**.002**
Nodal involvement														
N0	70/236	1	–		1	–		35/236	1	–		1	–	
N+	29/59	2.23	[1.53–3.25]	**<.001**	1.79	[1.19–2.68]	**.005**	21/59	2.56	[1.53–4.29]	**<.001**	2.16	[1.25–3.73]	**.006**
Disease stage														
Stage I–II	27/122	1	–					13/122	1	–				
Stage III–IV	72/173	2.53	[1.74–3.68]	**<.001**				43/173	2.43	[1.39–4.22]	**.002**			
Nimorazole														
≥50 doses	37/130	1	–					17/130	1	–				
<50 doses	33/82	1.52	[1.02–2.27]	**.042**				21/82	1.94	[1.06–3.55]	**.033**			

All patients included ($n = 295$). *p*-Values reaching the significance level in bold.
HR: Hazard Ratio; WHO: World Health Organization's classification of performance status.
Oropharynx non-p16+: includes both p16− and tumors with unknown p16 status.
[a]Adjustment for age, tumor site, T classification and N classification.
[b]Adjustment for tumor site, T classification and N classification.

Table 3. Acute toxicity at the end of therapy among 288 patients with follow-up and late morbidity among the 257 patients with late scoring followed for at least 6 months. Peak incidences. Historical data from previous DAHANCA trials as comparators.

Toxicity	Events	%	*DAHANCA 6&7* [17]	*DAHANCA 18* [10]
Early				
Dysphagia (severe, liquids only)	147	51%	45%	74%
Confluent mucositis	158	55%	63%	76%
Tube feeding (G-tube or nasogastric)	174	60%	–	64%
Moist skin desquamation	38	13%	23%	12%
Late				
Dysphagia (severe, liquids only)	53	21%	16%	19%
Xerostomia (grade 3, severe)	27	11%	21%	19%
Neck fibrosis (grade 3, severe)	16	6%	13%	14%
Mucosa atrophy (grade 3, severe)	29	11%	7%	12%
Tardive edema (grade 3, severe)	23	9%	12%	8%
Tube dependency, 6 months	18	7%	–	10%
Tube dependency, 12 months	14	5%	–	6%
Osteoradionecrosis	16	6%	10%	7%

DAHANCA 6&7 randomized trial on acceleration of treatment: numbers from the acceleration arms.
DAHANCA 18 phase II trial: accelerated treatment with nimorazole + concurrent weekly cisplatin.

The toxicity profile during and immediately after treatment was dominated by more than half of patients experiencing confluent or ulcerative mucositis and severe dysphagia, and with a peak incidence of G-tube dependency in 60% of the cases. This accentuation of toxicity is much in line with our expectations given that the treatment was both accelerated and dose escalated. In the DAHANCA 18 phase II trial on conventionally fractionated chemo-radiotherapy, the acute toxicity was even more pronounced [10].

The extent of the late effects after the therapy was also at comparable levels with historical data, both when comparing to the acceleration arms of the DAHANCA 6&7 trials [17] and to the results of DAHANCA18 trial, where acceleration was combined with cisplatin (Table 3). Furthermore, experiences from the randomized DAHANCA 9 trial [8] showed that there was no increase in late toxicity despite the increase in total dose in the hyperfractionation arm vs. the arm with acceleration alone. Overall, the present data supports the understanding that hyperfractionation does not cause added late toxicity [5–8], even when combined with moderate acceleration and dose escalation as in this study.

Contrary to previously published literature on hyperfractionation [5–8], our study presents data from patients treated almost exclusively with intensity modulated radiotherapy (IMRT). Another study strength is the relatively large data set of prospectively collected data. However, included in this analysis were node-positive patients unfit for concurrent cisplatin due to health issues excluding them from chemotherapy. Such fragile condition may possibly affect outcomes negatively, especially the overall survival.

The standard of care for node-positive and locally advanced patients remains to be chemo-radiation in Denmark, since the benefits of this approach is established in the MACH-NC meta-analysis [18,19] and a direct comparison between standard chemo-radiation and dose escalated hyperfractionation alone remains to be undertaken. A large randomized trial investigating this matter is unlikely to ever be performed and thus, the present study is among the best available evidence at the moment.

Besides confirming the efficacy and lack of excess late toxicity of hyperfractionated radiotherapy, the present study shows that a dose escalation can be safely combined with a moderate acceleration of treatment with 10 weekly fractions over $5^1/_2$ weeks treatment time. The results of a feasibility trial on further treatment intensification (the DAHANCA 28 study, NCT01733823), adding concurrent chemotherapy to the accelerated, dose-escalated hyperfractionation, shows that this combination, although more toxic, is manageable and possibly even more effective that dose escalation alone [20]. This type of treatment, which is considered to be the optimal treatment for locally advanced HNSCC [21], is now being investigated in a phase II trial on dose escalation for patients with PET-visualized pretreatment hypoxic, locally advanced HNSCC (the DAHANCA 33 trial, NCT02976051).

Conclusions

The present prospective study on patients treated with moderately accelerated, dose escalated hyperfractionation within the IMRT era demonstrate that the approach is both a tolerable and effective way of improving chances of loco-regional control, and suitable and safe option for HNSCC patients where therapy intensification seems indicated.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This study was funded by Aarhus University and Danish Cancer Society.

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