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LETTER TO THE EDITOR

DAHANCA 9 – a randomized multicenter study to compare accelerated normo-fractionated radiotherapy with accelerated hyperfractionated radiotherapy in patients with primary squamous cell carcinoma of the head and neck (HNSCC)

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Background and aim

Following the DAHANCA 5 trial [1], which demonstrated the benefit of the hypoxic radiosensitizer Nimorazole, and the DAHANCA 6&7 trial, which demonstrated that accelerated fractionation added significant improvement to the radiotherapy treatment of squamous cell carcinoma of the head and neck (HNSCC) [2,3], the DAHANCA group attempted to further improve the treatment of advanced head and neck cancer by an escalation of the total dose. Thus, the DAHANCA 9 study was designed to evaluate, in a prospective randomized trial, if the use of accelerated, hyperfractionated radiotherapy to a total dose of 76 Gy was feasible and superior to normo-fractionated (2 Gy/fx) accelerated radiotherapy with a total dose of 66–68 Gy. Both regimes being supplemented with the hypoxic radiosensitizer Nimorazole [4–6]. Such dose escalation seems possible by reducing the dose per fraction (fx) while increasing the overall dose. This can be achieved with a hyperfractionated schedule, which gives a dose of 1.35 Gy per fraction given twice daily (10 fx per week) and within the same overall treatment time as normal fractionated accelerated treatment [7].

The trial was initiated in 2000 and included initially only T1–3, N0 (except T1 glottic) cancer patients, because the intention was first to explore the feasibility in patients treated with a relatively small target volume. The study aimed at an inclusion of 1000 patients, but was initiated at a time period where resources for radiotherapy were limited, and thus a trial, which demanded more fractions than the standard treatment, suffered from significant logistic restrictions. The recruitment was consequently low and despite a later modification in 2005 which extended the study to also include patients with node-positive disease, the trial was finally closed in 2006 after an intake of only 77 patients. This was far from enough to secure a conclusive outcome, but there is a scientific and ethical obligation to report the outcome of clinical trials irrespective of whether they are brought to a successful completion. Therefore, we hereby present the results of the incomplete trial.

Furthermore, the data obtained in this incomplete trial has been included into the MARCH meta-analysis of altered fractionation studies [8], and the data thus contribute to the overall evidence generated knowledge related to fractionation of HNSCC.

Protocol design and patient eligibility

The study was activated in February 2000 and recruited patients from the Danish Oncological Centers and from the Norwegian Radium Hospital in Oslo. The patients should be candidates for primary curative radiotherapy and, with the exception of the disease in question, not be in a state or condition which could be expected to influence the compliance to RT or affect the assessment of the treatment. The criteria for eligibility were: untreated histopathologically proven invasive squamous cell carcinoma of the larynx (except stage I glottic tumors), oropharynx, hypopharynx, or oral cavity, T1–3, N0 UICC 1997 classification (later extended to include T4 and N1–3), and without evidence of distant metastases. The patients were stratified according to gender, tumor localization (larynx vs. pharynx vs. oral cavity), tumor classification (T1–2 vs. T3–4; nodal classification (N0 vs. N1–3), and institution (Figure 1(A)).

The study was conducted according to the Helsinki Declaration II and approved by the relevant ethics committees.

Treatment

The trial was performed in the pre-IMRT era using the same RT-technique and guidelines as in the previous DAHANCA 6,7&10 trials [2,3,9]. The experimental arm in the DAHANCA 6&7 trial served as the standard baseline arm in the DAHANCA 9 study. Radiotherapy was initiated within 3 weeks

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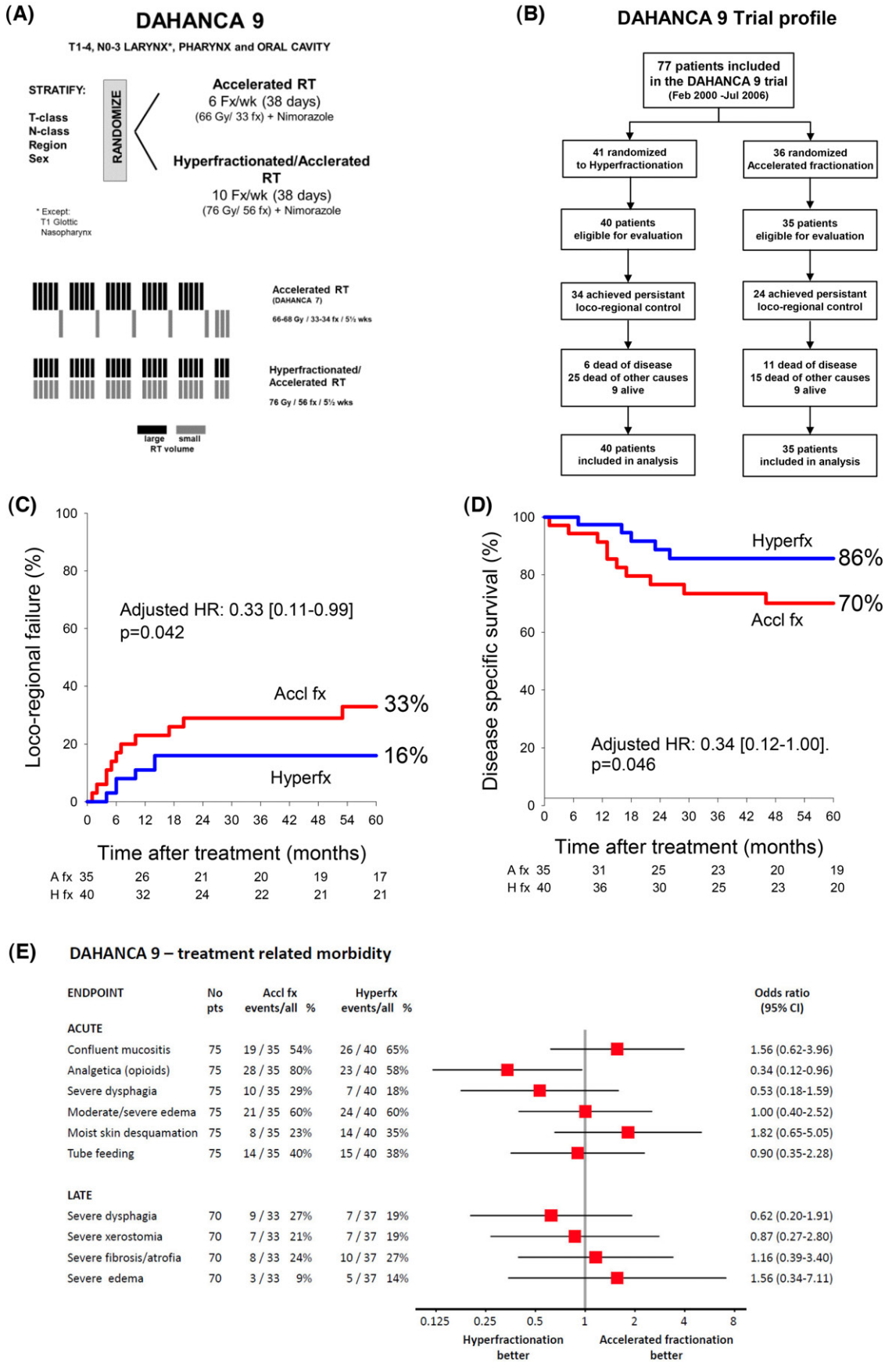

Figure 1. DAHANCA 9 trial design (A); trial profile (B); ultimate loco-regional tumor control (C); disease-specific survival (D); and acute and late radiation-related morbidity (E) as a function of stratification group in eligible patients.

of randomization and applied according to the DAHANCA guidelines [10]. Patients were treated with accelerated fractionation with 66–68 Gy in 33–34 fractions given with 6 fx of 2 Gy per week as previously described [2,3,9]. Patients were given 1 fraction per day, Monday through Friday with the sixth fraction given either during the weekend or as an additional fraction on one of the weekdays, but allowing at least a 6-h inter-fraction interval. Macroscopically involved tumor area with a margin of 1 cm was given a minimum dose of 66–68 Gy with 2 Gy per fraction, 6 fx per week. The total dose depended on the tumor size, with primary tumors or nodes larger than 4 cm receiving a minimum dose of 68 Gy. Uninvolved nodal areas were treated with 50 Gy, and no elective neck dissection was allowed.

Hyperfractionated radiotherapy was given with 2 daily fractions of 1.35 Gy five days a week. The interval between fractions being at least 6 h. The macroscopically involved tumor area was given a 76 Gy in 56 fx with 10 fx per week. The elective nodal areas were treated with 33 fx. With exception of the first week, the second daily fraction was limited to the small boost field (Figure 1(A)). The treatment was accelerated with a planned overall treatment time of $5^1/_2$ weeks in both arms.

Nimorazole was administered in doses of 1, 2 g/m^2 body surface in connection with the first daily fraction. If 2 fx were applied on the same day, the second dose was limited to 1 g (irrespective of body surface). Total dose was planned to be ~36 g/m^2 and not allowed to exceed 40 g/m^2 or a total of 75 g. The drug was given 90 min prior to each radiation treatment as described elsewhere [5].

Results

A total of 77 eligible patients were randomized between 2000 and 2006 (Figure 1(B)). The median follow-up time was 79 months (range: 1–198). Two patients were excluded, one in each arm. One patient withdraw consent, and the other was treated at an outside department with a non-protocol regime. Seventy-five patients were eligible for analysis; 40 patients were randomized to accelerated hyperfractionated radiotherapy and 35 patients to accelerated fractionation. The patients were evenly distributed according to the stratification parameters (gender, T and N stage, tumor site) (Table 1).

Table 1. Patient and tumor characteristics for eligible patients as a function of randomization group.

Parameter	Hyperfx ($N=40$)		Accl fx ($N=35$)	
Median age (year) (range)	63	(42–83)	61	(42–80)
Gender				
Male	36	90%	24	69%
Female	4	10%	11	31%
Primary site				
Larynx	26	65%	26	74%
Pharynx	10	25%	9	26%
Oral cavity	4	10%	0	0%
TNM classification				
T1–2	34	85%	31	89%
T3–4	6	15%	4	11%
N0	37	92%	32	91%
N1–3	3	8%	3	9%
Performance status				
WHO 0	23	57%	18	49%
WHO 1–2	17	43%	18	51%

The majority of the patients achieved a persistent tumor control after treatment, but 20 patients developed loco-regional failure, which in three cases were successfully salvaged by surgery. The five-year cumulative incidents of the ultimate loco-regional failure are seen in Figure 1(C), which shows a non-significant better outcome after hyperfractionated treatment than after accelerated fractionation (16% vs. 33%, $p=.11$) and with a univariate Hazard Ratio (HR) of 0.48 [0.18–1.29]. This was also seen for the endpoint of 5-year disease-specific survival (86% vs. 71%, $p=.12$ for hyperfractionation vs. normo-fractionation, respectively, HR: 0.45 [0.15–1.30]) (Figure 1(D)), whereas the overall survival in the two arms were indistinguishable (HR: 1.01 [0.51–1.98]), reflecting the high risk of dying from another smoking-related disease.

Adjusting the outcome according to the stratification parameters resulted in a more pronounced and statistically significant benefit of the hyperfractionated treatment with HR of 0.33 [0.11–0.99]) and 0.34 [0.12–1.00]), for the endpoints of loco-regional failure and dead of disease, respectively.

The compliance to the treatment was good, but two patients did not complete treatment due to non-treatment related early death (one in each arm). Radiation-related side-effects were recorded using the DAHANCA morbidity scoring system as applied in the DAHANCA 6&7 protocol [3]. There were no significant differences between the acute morbidity seen in the two schedules (Figure 1(E)), although a slightly more (not significant) amount of confluent mucositis and moist skin reaction occurred in the hyperfractionated schedule. The late morbidity was limited, and again without any significant difference between the two schedules.

Discussion

The DAHANCA 9 trial was ceased prematurely and without a clear answer to the potential benefits of accelerated hyperfractionation. However, the study indicated that such a regime could be given without excess morbidity when compared to conventional accelerated fractionation. It also suggested that the outcome was likely better when the total dose was increased. This observation is in line with previous (non accelerated) studies where dose escalation in head and neck cancer had been performed with the aim to improve the total tumor dose, without increasing the (late) morbidity [11–16]. Consequently, it also adds to the conclusion from the large MARCH meta-analysis which clearly showed that hyperfractionation may be the most beneficial among the altered fractionation regimes [8,17].

In contrast to previous studies which compared conventional normo-fractionated (2 Gy/fx) therapy (5 fx/week) with a higher total dose achieved by hyperfractionation given in the same overall treatment time, we also attempted to combine the benefit of accelerated fractionation (6 fx/week) and compare it with a hyperfractionated schedule to at total dose 76 Gy given in the same accelerated treatment time.

Dose-escalated hyperfractionation may cause a slightly more pronounced acute morbidity, but if given without too extensive acceleration (no more than a week's reduction), is the extend of the acute morbidity not significantly different from that seen after accelerated fractionation alone [3], and without any enhanced late morbidity. In fact, the treated volume is of greater influence than the fractionation schedule.

Since the treatment principle appears to be useful and well tolerated, it was reintroduced into the DAHANCA guidelines as an option to patients who had advanced disease, but were non-eligible to receive chemoradiotherapy (as e.g., in the DAHANCA 19 trial). More recently we explored the feasibility of accelerated hyperfractioned chemoradiotherapy with weekly cisplatin and nimorazole to patients with advanced HPV/p16 neg HNSCC, and found it to be a tolerable regimen (DAHANCA 28) which consequently now are being explored as a treatment option to patients with expected resistant tumors (DAHANCA 33). Such treatment has also shown to be feasible, and further underline that we must constantly strive for the biologically most optimal way to deliver radiotherapy.

The trial was conducted in Denmark and Norway as a part of the long-term clinical collaboration which exists within head and neck oncology in the Nordic countries [18–20].

Conclusion

Dose-escalated hyperfractionated, accelerated radiotherapy to HNSCC was a feasible treatment which indicated a better outcome than conventional fractionated accelerated radiotherapy. However, the study was closed prematurely due to lack of sufficient radiotherapy resources. In order to secure that the data were available for the evidence-generating literature, all information from this incomplete study was subsequently included into the MARCH meta-analysis of altered fractionation in HNSCC.

Disclosure statement

No potential conflict of interest was reported by the authors.

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