

## Articles

## Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial

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### Summary

**Background** Although head and neck cancer can be cured by radiotherapy, the optimum treatment time for locoregional control is unclear. We aimed to find out whether shortening of treatment time by use of six instead of five radiotherapy fractions per week improves the tumour response in squamous-cell carcinoma.

**Methods** We did a multicentre, controlled, randomised trial. Between January, 1992, and December, 1999, of 1485 patients treated with primary radiotherapy alone, 1476 eligible patients were randomly assigned five (n=726) or six (n=750) fractions per week at the same total dose and fraction number (66–68 Gy in 33–34 fractions to all tumour sites except well-differentiated T1 glottic tumours, which were treated with 62 Gy). All patients, except those with glottic cancers, also received the hypoxic radiosensitiser nimorazole. Analysis was by intention to treat.

**Findings** More than 97% of the patients received the planned total dose. Median overall treatment times were 39 days (six-fraction group) and 46 days (five-fraction group). Overall 5-year locoregional control rates were 70% and 60% for the six-fraction and five-fraction groups, respectively (p=0.0005). The whole benefit of shortening of treatment time was seen for primary tumour control (76 vs 64% for six and five fractions, p=0.0001), but was non-significant for neck-node control. Six compared with five fractions per week improved preservation of the voice among patients with laryngeal cancer (80 vs 68%, p=0.007). Disease-specific survival improved (73 vs 66% for six and five fractions, p=0.01) but not overall survival. Acute morbidity was significantly more frequent with six than with five fractions, but was transient.

**Interpretation** The shortening of overall treatment time by increase of the weekly number of fractions is beneficial in patients with head and neck cancer. The six-fractions-weekly regimen has become the standard treatment in Denmark.

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### Introduction

Squamous-cell carcinoma of the head and neck is predominantly a locoregional disease, and the primary treatment methods are surgery and radiotherapy.<sup>1</sup> Head and neck cancer can be cured by radiation, but tumours might be heterogeneous for intrinsic cellular radiosensitivity. This heterogeneity results in variation in the total dose needed to control the tumour, the presence of tumour hypoxia with the consequential hypoxic radioresistance, and tumour-cell proliferation during treatment.<sup>1–4</sup>

In Denmark, there is a long-standing tradition of using primary radiotherapy to treat all laryngeal and pharyngeal carcinomas, and some tumours in the oral cavity, to induce optimum tumour control and to cause minimum normal-tissue complications. The treatment is coordinated by the Danish Head and Neck Cancer Study Group (DAHANCA). So far, DAHANCA has completed two national protocols that used hypoxic radiosensitisers, which significantly improved locoregional tumour control when combined with radiotherapy of pharyngeal and supraglottic laryngeal carcinoma.<sup>5,6</sup> Subsequently, the standard treatment in these groups of patients was selected as the best regimen from the DAHANCA 5 study—ie, conventional fractionation to 66–68 Gy (2 Gy per fraction in five fractions per week) together with the hypoxic radiosensitiser nimorazole.

A cause of treatment resistance could be radiation-induced accelerated proliferation of clonogenic tumour cells. A reduction in the chance of tumour control through the lengthening of treatment time has been clinically and biologically documented.<sup>4,7</sup> Furthermore, in several clinical studies, reduction in the total treatment time has improved tumour control.<sup>8,9</sup> A shorter treatment time may be accomplished by applying a higher dose per fraction, but this change will disproportionately increase the rate of late complications. A shorter treatment time is thus feasible only if the weekly number of radiation fractions is increased.

Repopulation and hypoxia can reasonably be assumed to be independent factors, and, thus, the optimum option is a reduced treatment time with use of concomitant hypoxic modification in relevant tumours. We assessed the suitability of five versus six weekly radiotherapy fractions, given to the same total dose, in unselected patients.

### Patients and methods

#### Protocol design and patients' eligibility

From January, 1992, to December, 1999, we enrolled patients into a randomised controlled trial that comprised of two subprotocols: DAHANCA 6, which included all glottic carcinomas, and DAHANCA 7, which included tumours of the supraglottic larynx, pharynx, and oral cavity. The only difference in the two subprotocols was

that DAHANCA 6 dealt only with the fractionation effect, whereas the DAHANCA 7 also included treatment with the hypoxic radiosensitiser nimorazole.

Pretreatment assessment included clinical examination, endoscopy, radiography of the chest and, if relevant, CT or MRI; no other specific procedures were requested.

Eligibility criteria were: invasive squamous-cell carcinoma of the larynx, pharynx (including nasopharynx), or oral cavity (stage I–IV, tumour node metastasis [TNM], classification, UICC, Geneva, 1987), and no evidence of distant metastases (primary cancers at other sites were not included); no previous treatment for the cancer; eligibility for primary curative radiotherapy; and, with the exception of the disease in question, being in no state and having no disorder that might affect adherence to treatment, outcome of radiation therapy, or the assessment of treatment. Patients had to have normal liver and renal functions and no neurological disorders expected to interfere with nimorazole treatment before administration of that drug. Otherwise eligible patients who did not meet this last criterion were not excluded, but were given radiotherapy only. All patients gave written informed consent.

Before randomisation we stratified patients according to sex, tumour localisation (glottic larynx, supraglottic larynx, pharynx, or oral cavity), tumour size (T1–2 or T3–4), haemoglobin concentration, and institution. Randomisation was done by telephone at the DAHANCA data centre, where the eligibility criteria were checked. Patients were randomly assigned five or six fractions of radiotherapy per week (figure 1). The study was done according to the Helsinki Declaration II and approved by the local ethics committees.

### Treatment

Radiotherapy was applied according to the DAHANCA 1991 radiotherapy guidelines. The treatment was given with 4–6 MV photons according to standard fields,

including the primary tumour and involved lymph nodes. Electrons were allowed to treat the neck to reduce spinal cord dose, which was less than 50 Gy in all patients. We prescribed a minimum tumour dose of 62–68 Gy (2 Gy per fraction, five fractions per week) dependent on tumour size, with larger tumours receiving the larger dose. Thus, patients who had a primary tumour lymph nodes with a diameter 4 cm or less, or both, were given 66 Gy, and for patients with tumours nodes larger than 4 cm, or both, a minimum dose of 68 Gy was prescribed. Patients with well-differentiated stage I glottic carcinoma could be treated with only 62 Gy. Treatment fields included the first non-involved lymph-node station, but after a maximum of 50 Gy in 5 weeks we reduced the fields to include only the initially macroscopically known tumour lesions with a margin of 1 cm.

In the two treatment groups, patients received fractions of 2 Gy. Patients assigned five fractions per week were given one fraction daily from Monday to Friday. Patients assigned six fractions per week were given one fraction daily, from Monday to Friday, and the sixth fraction was given on Saturday or Sunday, or as an extra fraction on a weekday at least 6 h after the day's first fraction. If any unintended interruption of treatment occurred, we attempted to add any missing fraction as a second daily fraction as soon as possible, preferably within 1 week.

We administered nimorazole orally at a dose of 1200 mg/m<sup>2</sup> body surface with the first 30 radiation treatments. Total dose was planned to be around 36 g/m<sup>2</sup> and was not allowed to exceed 40 g/m<sup>2</sup> or a total of 75 g. A tablet was given 90 min before each radiation treatment as described elsewhere.<sup>6</sup>

As a follow-up to the DAHANCA 5 study, patients being treated under the DAHANCA 7 protocol who had low haemoglobin concentrations before irradiation (women <8 mmol/L, men <9 mmol/L) were randomly assigned blood transfusion or no blood transfusion in addition to one

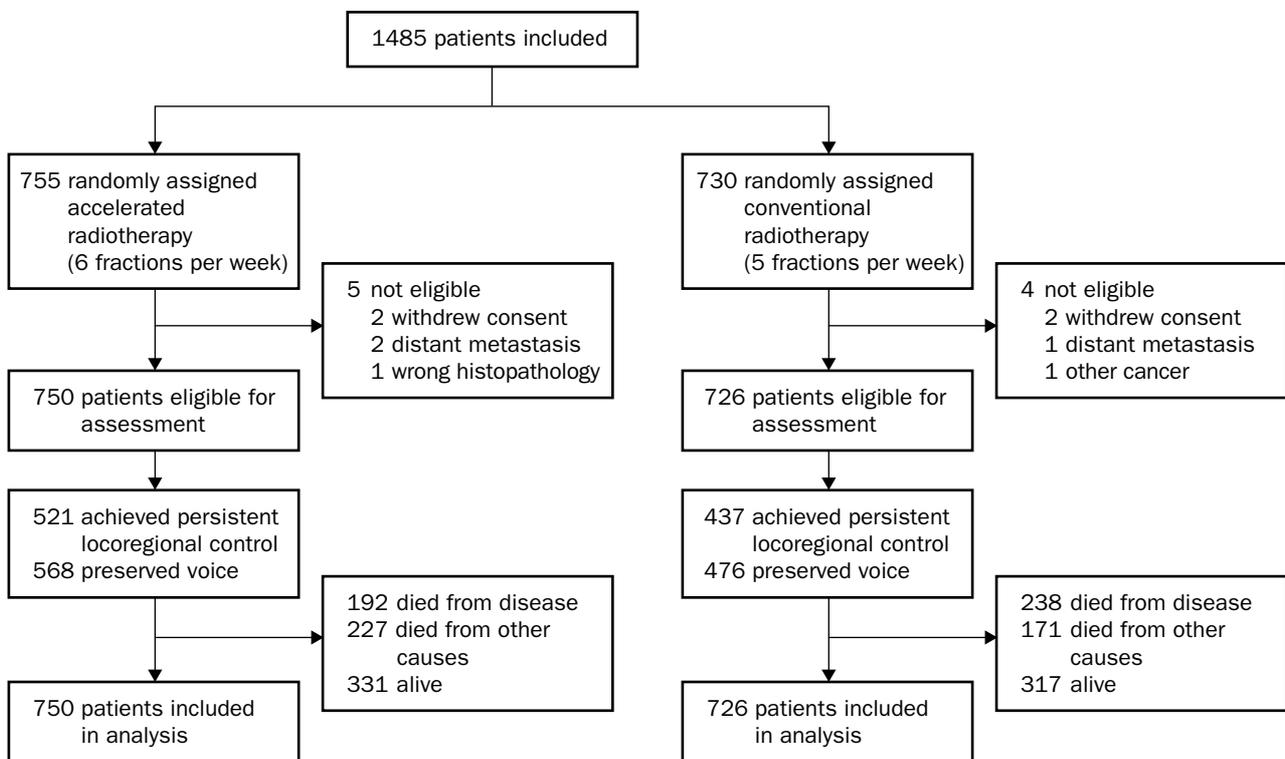


Figure 1: Trial profile

of the fractionation schedules.<sup>6</sup> The outcome of this transfusion policy will be analysed separately elsewhere, but as reported in the DAHANCA 5 trial, did not affect the tumour or survival outcome.

Patients were followed up at the oncological centres for at least 5 years or until death. We assessed patients by clinical examination weekly during treatment, 2 months after treatment, and thereafter every 3 months in the first year, every 4 months in the second year, and then every 6 months for up to 5 years after randomisation. Further examinations were done only if patients had symptoms or signs of recurrent disease. Additionally, we recorded treatment-related morbidity in the DAHANCA morbidity recording scheme. Only patients with recurrence or other physical disorders underwent follow-up longer than 5 years.

If patients had residual tumour, disease recurrence, or progression, salvage surgery or palliative treatment was used dependent on the status of the individual patient, their symptoms, and previous treatment. All recurrences were histopathologically verified unless obvious by clinical examination.

The primary endpoint was locoregional control after radiotherapy. We defined this endpoint as complete and persistent disappearance of disease in the primary tumour (T site) and regional lymph nodes (N site) after radiotherapy. Failure was recorded in the event of recurrent tumour, or if the primary tumour never completely disappeared. In the latter situation, the tumour was assumed to have failed at the time of randomisation. Since some uncertainty might exist about time to early recurrence, we did not graphically represent this endpoint for findings within the first 4 months after randomisation. The primary endpoint did not include the effect of a successful procedure with salvage surgery.

Secondary endpoints included: local T site and regional N site control, with and without salvage procedures; voice preservation; disease-specific survival; overall survival; and early and late treatment-related morbidity. For disease-specific survival we used the endpoint death from or with the actual cancer. All time estimates were done with the date of randomisation as initial value.

### Statistical analysis

All diagnostic, therapeutic, and follow-up data were validated and processed by the DAHANCA data centre. To maintain the optimum data quality, we cross checked recorded events with patients' records to assure a correct registration of site or sites of failure and cause of death.

We designed the trial as a stratified, balanced, randomised phase III study, and planned to include a total of 1000 assessable patients, which we estimated entailed a 4-year recruitment period. If we assumed a true improvement of locoregional tumour control from 55% to 65%, the probability that such a gain would be detected at a significance level of 5% was more than 90%. When the recruitment number was reached in October, 1997, it became apparent that the number of patients with glottic tumours would not express enough events to secure a conclusive outcome in this subgroup of patients. We closed the DAHANCA 7 protocol, but lengthened the inclusion period for glottic patients into the DAHANCA 6 protocol to Dec 31, 1999.

We estimated the actuarial values of the endpoints by Kaplan-Meier product-limit analysis, with BMDP 1L (version 7.0). The Mantel-Cox test was used for comparison, and a test for trend with equal weighting was done if more than two groups were compared. Two-tailed tests with a significance level of 5% were used. Data are presented as 5-year actuarial values with SE of the mean,

unless otherwise stated. We calculated odds ratios with 95% CI.

A multivariate Cox's proportional hazards analysis was used to assess prognostic factors and treatment for risk of locoregional failure and disease-specific death, with BMDP 2L (version 7.0). We included variables in the model by forward selection, and statistical analysis was by the Wald test.

We analysed outcomes by intention to treat. The time for final assessment of locoregional recurrence and disease-specific survival was 5 years after randomisation. The date for assessment was Aug 1, 2002, which gives a median observation time since randomisation of 92 months (range 32–128).

### Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the report for publication.

### Results

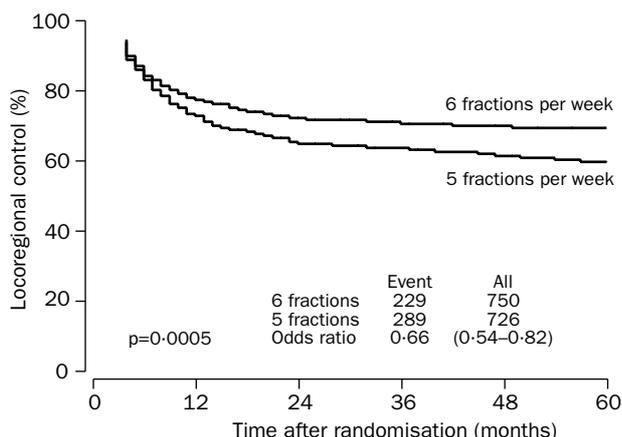
1485 patients were recruited, 791 in the DAHANCA 7 protocol and 694 in the DAHANCA 6 protocol. Nine were not eligible and, thus, 1476 assessable patients were included in the analysis (figure 1).

1229 patients were men and 247 women, with a median age at randomisation of 62 years (range 20–88). The distribution of patients' and tumour characteristics were similar in the two groups at baseline (table 1).

	Six fractions per week (n=750)	Five fractions per week (n=726)
<b>Protocol</b>		
DAHANCA 6	349 (47%)	341 (47%)
DAHANCA 7	401 (53%)	385 (53%)
<b>Characteristic</b>		
Median (range) age (years)	62 (21–88)	62 (20–85)
≤55	189 (25%)	205 (28%)
56–65	240 (32%)	224 (31%)
>65	321 (43%)	297 (41%)
Sex		
Male*	615 (82%)	614 (85%)
Female*	135 (18%)	112 (15%)
Primary site		
Glottic*	349 (47%)	341 (47%)
Supraglottic*	117 (16%)	101 (14%)
Pharynx*	213 (28%)	222 (31%)
Oral cavity*	71 (9%)	62 (8%)
Tumour node metastasis classification		
T1–2*	512 (68%)	494 (68%)
T3–4*	238 (32%)	232 (32%)
Nodal status		
Node negative	542 (72%)	504 (69%)
Node positive	208 (28%)	222 (31%)
Tumour stage		
I	218 (29%)	209 (29%)
II	194 (26%)	170 (23%)
III	148 (20%)	161 (22%)
IV	190 (25%)	186 (26%)
Differentiation		
Good	155 (21%)	180 (25%)
Moderate	290 (39%)	270 (37%)
Poor	192 (26%)	162 (22%)
Unknown	113 (15%)	114 (16%)
Haemoglobin concentration		
High*	475 (63%)	453 (62%)
Low*	275 (37%)	273 (38%)
Performance status		
WHO 0	490 (65%)	458 (63%)
WHO 1–2	260 (35%)	268 (37%)

\*Stratification group.

Table 1: Baseline characteristics



**Patients at risk**

Time (months)	0	12	24	36	48	60
6 fractions per week	750	520	440	363	296	193
5 fractions per week	726	492	400	334	283	182

Figure 2: **Primary locoregional tumour control as function of number of fractions per week**

750 patients were assigned six fractions per week, and 726 five fractions per week. This slight difference in numbers between treatment arms was due to having numerous stratification subgroups.

At the time of assessment, 518 patients had not achieved persistent locoregional control within the irradiated volume. 430 had died with uncontrolled cancer present or from the actual disease, and 828 patients had died overall.

The outcome analysis confirmed the major prognostic factors in head and neck cancer radiotherapy. Based on the previous DAHANCA 5 study, the stratification parameters were chosen to select equally balanced groups with distinct prognostic parameters. In univariate analysis (5-year actuarial locoregional tumour control), tumour site (glottic 76 vs supraglottic 56 vs pharynx 51 vs oral cavity 39%,  $p < 0.0001$ ), tumour size (T1-2 73 vs T3-4 40%,  $p < 0.0001$ ), and pretreatment haemoglobin (high 66

	Six fractions per week (n=750)	Five fractions per week (n=726)
<b>Site of failure</b>		
T failure	135 (18%)*	188 (26%)*
N failure	39 (5%)	30 (7%)
T+N failure	39 (5%)	48 (7%)
T+M failure	4 (1%)	5 (1%)
N+M failure	7 (1%)	8 (1%)
T+N+M failure	5 (1%)	12 (2%)
M failure	27 (4%)	14 (2%)

\* $p = 0.002$ .

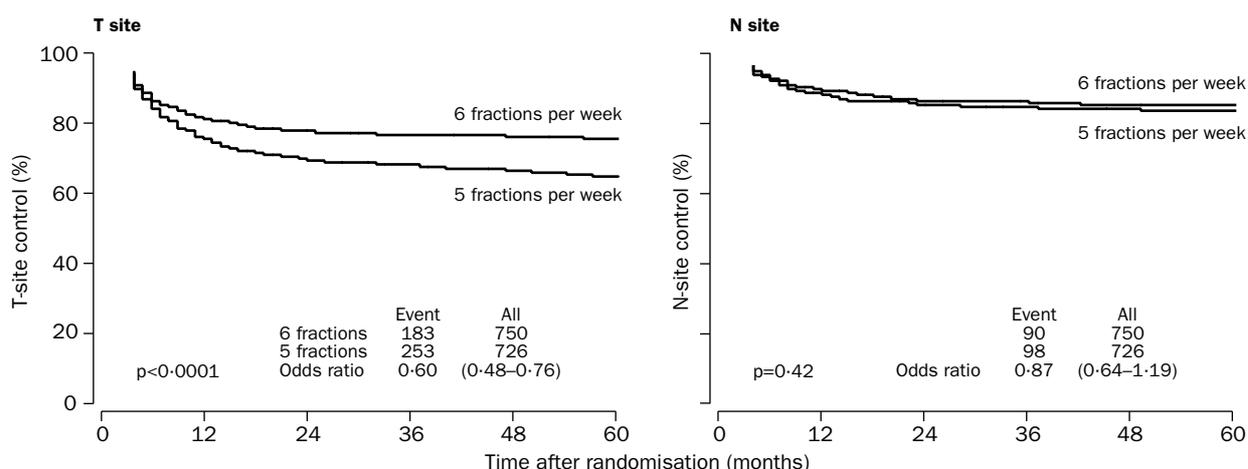
Table 2: **Patterns of failure**

vs low 58%,  $p = 0.006$ ) had good prognostic value. Sex, however, did not seem to affect outcome overall (female 63 vs male 63%,  $p = 0.83$ ), probably because of a male predominance among patients with glottic tumours.<sup>1</sup> The values for other prognostic factors not used for stratification were: nodal status (negative 70 vs positive 43%,  $p < 0.0001$ ) and WHO performance status (70 vs 49% for WHO 0 and WHO 1-2,  $p < 0.0001$ ).

The use of accelerated fractionation significantly improved the outcome for locoregional control (odds ratio 0.66 [95% CI 0.54-0.82]), and disease-specific survival (0.71 [0.56-0.88]), but overall survival did not improve (0.98 [0.80-1.21]). Locoregional tumour control improved significantly in the accelerated fractionation group compared with that in the conventional radiotherapy group (70 vs 60% 5-year actuarial rate,  $p = 0.0005$ ; figure 2).

When the locoregional endpoint was analysed for T-site and N-site failure individually, the whole benefit of acceleration was from improved T-site control (figure 3). Thus, patients with less nodal involvement (such as laryngeal carcinoma) especially had better control under the six fractions per week regimen. This better T-site control was also reflected in an improved preservation of the larynx and voice in 908 patients with laryngeal cancer (80 vs 68% for six and five fractions per week,  $p = 0.007$ ).

The benefit of accelerated fractionation was present in most of the subgroups (figure 4). The effect in laryngeal cancers was particularly good in moderately and well-differentiated tumours, whereas for poorly differentiated tumours there was no apparent benefit with the shortened treatment time.



**Patients at Risk**

Time (months)	0	12	24	36	48	60	0	12	24	36	48	60
6 fractions per week	750	520	440	363	296	193	750	520	440	363	296	193
5 fractions per week	726	492	400	334	283	182	726	492	400	334	283	182

Figure 3: **Effect of overall treatment time in T site and N site**

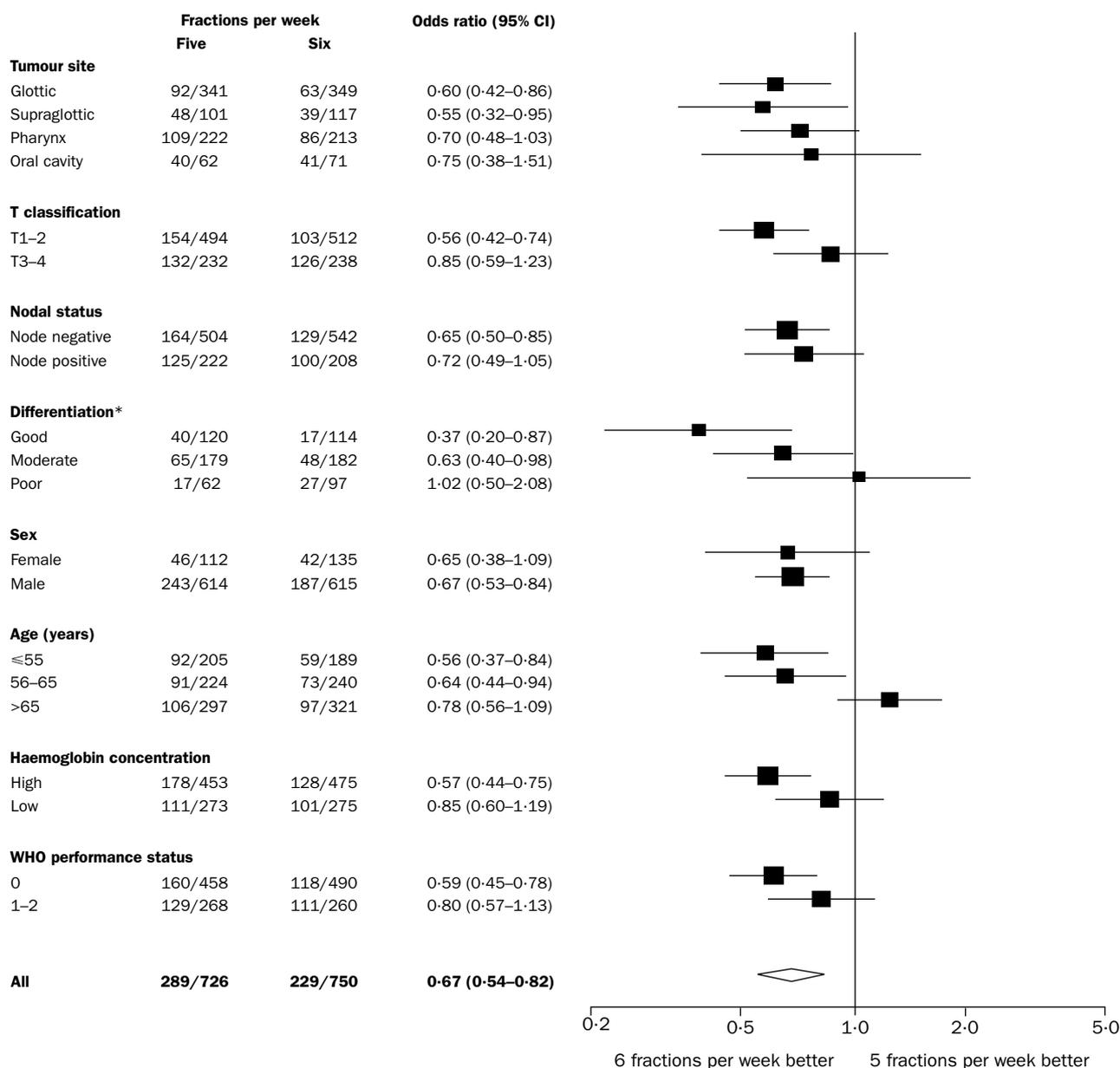


Figure 4: Relation between overall treatment time and locoregional tumour control by subgroup

\*754 laryngeal tumours with known differentiation.

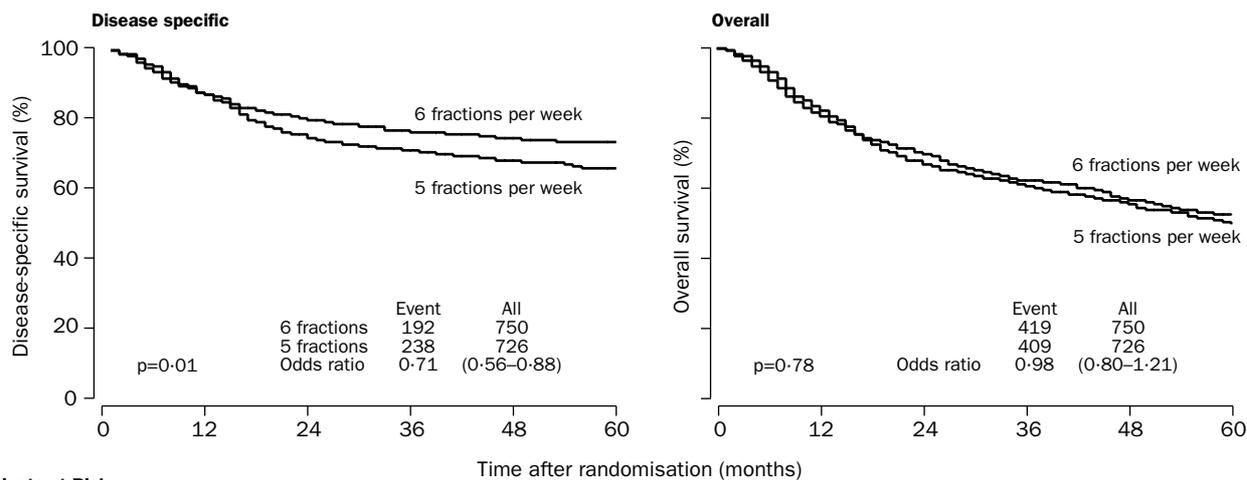
Salvage surgery was successful in 124 patients (61 in the six and 63 in five fractions per week regimen, respectively) who failed in the T or N site. No planned neck dissection was done after radiation, and neck surgery was done only if clinical evidence of recurrence was encountered. The most frequent salvage procedure was laryngectomy, which was successful in 51 and 55 patients in the six and five fractions per week regimens, respectively. The final 5-year locoregional control was, therefore, slightly better than after radiotherapy alone (75 vs 66% for six and five fractions per week,  $p=0.0006$ ).

Analysis of the failure pattern showed that most treatment failures were due to insufficient locoregional tumour control. As a consequence, the disease-specific survival was strongly related to insufficient locoregional treatment, and, therefore, was also significantly better among patients receiving accelerated fractionation than among those receiving conventional fractionation (figure 5). However, we did not note this trend in the

overall survival because of a high rate of comorbidity and death from other causes in our patients (figure 5).

In the final Cox's proportional hazards analysis with risk of locoregional failure as the endpoint, low tumour classification (T1–2, relative risk 0.46 [95% CI 0.38–0.56]), negative neck nodes (0.58 [0.47–0.73]), good performance status (WHO 0, 0.69 [0.58–0.82]), and treatment with six fractions per week (0.77 [0.65–0.92]) were independent factors of good prognosis. With deaths from cancer as the endpoint the results were similar for T1–2 tumours (0.48 [0.39–0.59]), negative nodes (0.50 [0.39–0.62]), good performance status (0.62 [0.51–0.75]), and six fractions per week (0.80 [0.66–0.97]). No other parameters were independently associated with prognosis.

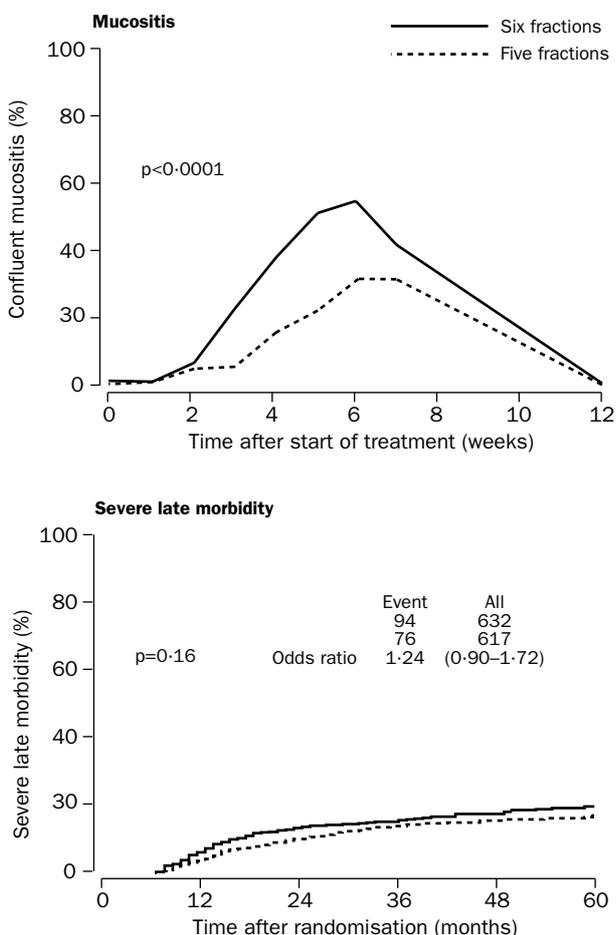
The two radiotherapy schedules were well tolerated. Adherence to radiotherapy was the same in the two treatment groups, with 98% of patients receiving the scheduled radiation dose. The overall treatment time,



**Patients at Risk**

	0	12	24	36	48	60	0	12	24	36	48	60
6 fractions per week	750	610	528	450	375	317	750	610	528	450	375	317
5 fractions per week	726	603	490	422	296	296	726	603	490	422	355	296

Figure 5: Effect of overall treatment time on disease-specific survival and overall survival



**Patients at risk**

	0	12	24	36	48	60
6 fractions per week	632	485	398	347	292	184
5 fractions per week	617	475	382	332	280	177

Figure 6: Early and late radiation-related morbidity

Acute confluent mucositis in 1420 patients and actuarial probability of developing severe late reactions in 1249 patients.

which was the explored topic in the trial, was kept as planned, with a median treatment time of 39 days in the six fractions per week schedule and 46 days in the five fractions per week schedule. Most patients in the accelerated fractionation group received the extra fractions on weekdays, since only one institution treated patients at weekends as routine.

The rate of acute radiation-related morbidity was significantly higher in the accelerated fractionation group with a 53% frequency of confluent mucositis compared with 33% in the conventional treatment group ( $p < 0.0001$ ). Moreover, the mucositis persisted longer in the accelerated fractionation patients, but all healed within 3 months of the start of treatment (figure 6).

Late radiation-induced morbidity was recorded in 1249 patients with at least 6 months of follow-up. Figure 6 shows that, after 5 years of observation, the probability of developing a severe late reaction was less than 20%. Furthermore, the probability of developing any severe late radiation-related complication, mainly in the form of late cutaneous fibrosis, mucosal atrophy, or necrosis, did not differ significantly between the fractionation groups.

Adherence to nimorazole has been previously reported, with around 75% of patients receiving at least 25 treatments. The remaining patients mainly had their treatment discontinued because of nausea. No late nimorazole-related toxic effects were noted.

**Discussion**

Accelerated radiotherapy applied to squamous-cell carcinoma of the head and neck yields better locoregional control than does a conventional schedule with identical dose and fractionation. This finding is in agreement with several similar but smaller randomised studies.<sup>10-14</sup>

In trials in which shorter treatment times were applied, but the total dose was also reduced,<sup>15-18</sup> a better or equivalent tumour response in the accelerated fractionation group was found. Accelerated regimens, however, increase the treatment-associated acute morbidity, and if this effect becomes too severe it could also raise the frequency of late radiation effects.<sup>19</sup> We saw no such effect since the increase in acute mucositis after six fractionations per week was transient and the rate of late effects did not differ from that for conventional treatment. Similar findings have been

noted in comparable studies,<sup>10,12</sup> whereas in trials in which the acceleration was more prominent, late morbidity became unacceptable if the total dose was not reduced.<sup>13,19</sup> Thus, the window of opportunity for the benefit of acceleration is narrow, and with the applied radiation technique a 1-week reduction seems to be the optimum balance between improved tumour control and avoidance of excess late morbidity.

In our previous studies, the use of hypoxic radiosensitisers significantly improved the outcome in patients with supraglottic and pharyngeal cancers. We therefore used nimorazole in the current study. The findings for patients in the five fractions per week group compared with in the comparable group in DAHANCA 5 were almost identical (data not shown). Therefore, the benefit of acceleration is additional to the effect achieved by the use of hypoxic modification. We suggest that one way to achieve optimum radiotherapy in head and neck carcinoma could be through use of hypoxic modification and an altered fractionated regimen. Such a combined strategy is currently being assessed in a Dutch trial.<sup>20</sup>

The improvement in overall outcome with accelerated fractionation does not necessarily indicate that all patients will benefit equally from such treatment. The effect of acceleration we saw on locoregional control was entirely related to a better response in the T site, but did not alter radiation effect on metastatic lymph node disease. Outcomes in patients in the two treatment groups with large nodal burden (N2–3) did not differ, irrespective of T site, whereas in those with no or a small nodal tumour burden, locoregional control was substantially improved with six fractions per week. The corollary of this finding is a better effect of acceleration in laryngeal tumours, since these tumours have less nodal involvement than those in the pharynx and oral cavity. To what extent a more aggressive surgical approach with elective neck dissections in N2–3 patients would change that conclusion is unclear.

The lack of overall survival benefit, despite differences in disease-specific death has been noted in similar studies.<sup>18,21</sup> The reason for this finding is unclear, but may be related to the general poor health that characterises this group of patients, many of whom smoke and might drink excessive alcohol.

The histopathological differentiation of the tumour might affect the response to changes in overall treatment time. Thus, prolongation of the overall treatment time through split-course radiotherapy especially decreased the outcome among patients who had moderately and well-differentiated tumours, whereas poorly differentiated tumours were much less sensitive to variations in overall treatment time.<sup>22</sup> The reduction of the treatment time was, therefore, more beneficial in the moderately to well-differentiated tumours that overall seem to be most sensitive to changes in treatment time. Similar dependency of differentiation and treatment time was noted in the CHART study.<sup>15</sup> On the basis of this finding we formed the hypothesis that the mechanism of repopulation in squamous-cell carcinomas of the head and neck is similar to the response in the normal mucosa from where the tumour has originated. We propose also that the T-site tumour simply responds to a trauma (eg, irradiation) in a way similar to that seen in the epithelium. To secure such a response, the tumour needs to have a functional mechanism capable of regeneration, which is most likely to happen in well-differentiated tumours. Furthermore, the reaction might be controlled by signalling from the surrounding normal mucosa, and the response is, therefore, seen only in the T position and not the nodal metastases.<sup>23</sup>

Although this hypothesis needs to be elaborated, it is supported by the observation that epidermal-growth-factor-receptor expression is also linked to repopulation. Thus, tumours with high epidermal-growth-factor-receptor expression that are also moderately to well differentiated show a prominent relation between outcome to radiotherapy and overall treatment time (long term or accelerated). This relation is much less frequent in tumours that are poorly differentiated, have low epidermal-growth-factor-receptor expression, or both.<sup>24,25</sup> Further studies are needed to explore the mechanisms behind repopulation, which will hopefully consequently identify predictive factors to help to improve treatment strategies and define targets for therapeutic intervention.<sup>26,27</sup>

Despite the heterogeneity in response, moderately accelerated radiotherapy in head and neck cancer with a 1-week reduction in overall treatment time, but with no change to total dose and number of fractions, is better than a conventional treatment schedule. We recommend that modified fractionation schedules should constitute a new baseline for further exploration of radiotherapy in head and neck cancer. The six fractions per week regimen, together with nimorazole, has become the new standard treatment in the Danish national treatment guidelines of head and neck cancer.

Additional improvement is likely to come from increasing the total dose by applying hyperfractionated schedule, in which an increased total dose is given with more and smaller fraction sizes.<sup>10,28</sup> In several studies such treatment has proven beneficial in primary tumour and nodal sites. Alternatively, radiotherapy can be combined with chemotherapy.<sup>9</sup> However, these two such strategies increase morbidity, which limits the aggressiveness of the treatment schedules. Altered fractionation and chemoradiotherapy have shown better results than conventional treatment schedules, and meta-analyses suggest a similar clinical benefit in local control and survival from these strategies.<sup>21,29</sup> How we can use this knowledge in an optimum way should be explored, taking advantage of the improvement in radiotherapy technology to reduce morbidity.

Some of the tumours we studied might be treated initially by surgery in other countries. There is a lack of controlled trials comparing these therapeutic strategies, but based on available evidence, neither seems to be better than the other for tumour response.<sup>30</sup> However, the use of primary radiotherapy is more organ conserving than surgery, and leaves more patients with voice intact.

#### Contributors

All researchers contributed to the study design, implementation of the study, and collection of the data. J Overgaard and C Grau analysed the data. J Overgaard drafted the report. All researchers took part in the critical revision of the paper and approved the final version.

#### Conflict of interest statement

None declared.

#### Acknowledgment

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