A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85

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Abstract

Purpose: A multicenter randomized and balanced double-blind trial with the objective of assessing the efficacy and tolerance of nimorazole given as a hypoxic radiosensitizer in conjunction with primary radiotherapy of invasive carcinoma of the supraglottic larynx and pharynx.

Patients and treatment: Between January 1986 and September 1990, 422 patients (414 eligible) with pharynx and supraglottic larynx carcinoma were double-blind randomized to receive the hypoxic cell radiosensitizer nimorazole, or placebo, in association with conventional primary radiotherapy (62–68 Gy, 2 Gy per fraction, five fractions per week). The median observation time was 112 months.

Results: Univariate analysis showed that the outcome (5-year actuarial loco-regional tumor control) was significantly related to T-classification (T1–T2 48% versus T3–T4 36%, \( P = 0.0008 \)), neck-nodes (N− 53% versus N+ 33%), pre-irradiation hemoglobin (Hb) concentration (high 46% versus low 37%, \( P = 0.02 \)) and sex (females 51% versus males 38%, \( P = 0.03 \)). Overall the nimorazole group showed a significantly better loco-regional control rate than the placebo group (49 versus 33%, \( P = 0.002 \)). A similar significant benefit of nimorazole was observed for the end-points of final loco-regional control (including surgical salvage) and cancer-related deaths (52 versus 41%, \( P = 0.002 \)). This trend was also found in the overall survival but to a lesser, non-significant extent (26 versus 16%, 10-year actuarial values, \( P = 0.32 \)). Cox multivariate regression analysis showed the most important prognostic parameters for loco-regional control to be positive neck nodes (relative risk 1.84 (1.38–2.45)), T3–T4 tumor (relative risk 1.65 (1.25–2.17)) and nimorazole (relative risk 0.69 (0.52–0.90)). The same parameters were also significantly related to the probability of dying from cancer. The compliance to radiotherapy was good and 98% of the patients received the planned dose. Late radiation-related morbidity was observed in 10% of the patients, irrespective of nimorazole treatment. Drug-related side-effects were minor and tolerable with transient nausea and vomiting being the most frequent complications.

Conclusion: Nimorazole significantly improves the effect of radiotherapeutic management of supraglottic and pharynx tumors and can be given without major side-effects. © 1998 Elsevier Science Ireland Ltd.

Keywords: Nimorazole; Radiotherapy; Head and neck carcinoma; Treatment-related morbidity; Hemoglobin; Randomized clinical trial

1. Introduction

Between 1979 and 1985, a randomized trial evaluating the hypoxic cell radiosensitizer, misonidazole, in the treatment of larynx and pharynx carcinoma (DAHANCA 2) was performed by the Danish Head and Neck Cancer Study Group [34]. Although no major overall significant benefit

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was found, there was a significant improvement of loco-
regional control in the strata of patients with pharynx
tumors. A similar tendency was observed in patients with
supraglottic larynx carcinoma, whereas patients with glottic
lesions did not show any benefit. Furthermore, the study
revealed that patients with a low hemoglobin value had a
significantly poorer prognosis if they belonged to the groups
which also showed a benefit of misonidazole. The hemoglo-
bin and misonidazole effects seemed to be independent and
probably additive. Unfortunately, misonidazole induced
significant peripheral neuropathy in 26% of the patients
and it was concluded that it is unsuitable for further clinical
use [34].

On this basis, it was decided to evaluate the less toxic
hypoxic radiosensitizer, nimorazole (1-(N-β-ethylmorpho-
line)-5-nitro-imidazole), in pharynx and supraglottic larynx
tumors. This drug had previously been evaluated in preclini-
cal and clinical phase I and II studies [38,39,47] and had
so far not demonstrated any significant toxicity except tran-
sient nausea and vomiting. Although the hypoxic radiosen-
sitizing ability is less than what theoretically can be
achieved with misonidazole, the drug shows a flat dose-
response curve implying that at clinically relevant doses,
the hypoxic radiosensitizing ability is fairly high (approxi-
mately 1.3) [38]. Furthermore, the drug can be given in
association with a conventional radiation therapy schedule
and was therefore found to be suitable for use in the new
study.

The observation from the DAHANCA 2 trial that a low
hemoglobin value was associated with a poor local control
was in agreement with numerous other studies [14,29,30]. A
few small clinical trials have indicated that blood transfu-
sions given to patients with low hemoglobin values may
increase the tumor control probability in patients with car-
cinoma of the uterine cervix or the head and neck
[5,14,29,44]. Therefore, this question was also addressed
in the current study.

The present report has been performed according to the
CONSORT guidelines for reporting clinical trials [2].

2. Patients and methods

2.1. Protocol design and patient eligibility

The Danish Head and Neck Cancer Study Protocol 5-85
was activated in January 1986 as a multicenter randomized
and balanced double-blind trial with the objectives of asses-
sing (i) the efficacy of nimorazole given as a hypoxic radio-
sensitizer in conjunction with radiotherapy of invasive
carcinoma of the supraglottic larynx and pharynx, (ii) the
tolerance and toxicity of nimorazole and (iii) the influence
of hemoglobin concentration on tumor response to irradi-
ation.

The trial was a double-blind study in which the control
group received placebo instead of nimorazole. The study
design, stratification and randomization arms are shown in
Fig. 1.

The criteria for eligibility were invasive squamous cell
carcinoma of the supraglottic larynx (stages 2–4, UICC
1982) or pharynx (stages 1–4), no evidence of distant
metastases, normal liver and renal function and no neurolo-
gical disorders expected to interfere with the drug treatment.
The study was designed according to the Helsinki Declara-
tion II and was approved by the local ethical committees.

Prior to randomization the patients were stratified according
to sex, institution, tumor site (supraglottic versus pharynx),
tumor status (T1–T2 versus T3–T4) and hemoglobin con-
centration. The patients were then randomized to radiother-
apy with nimorazole or placebo. Patients with low
hemoglobin values were randomized to either receive or
not receive a blood transfusion prior to inclusion in the
nimorazole trial,

In patients where all eligibility criteria were fulfilled,
patient data was entered into a local computer which gen-
erated the correct strata and randomization number and at
the same time printed a confirmation letter which was sent
to the data center. Each institution was supplied with a batch
of consecutively numbered neutral looking sealed glasses.
Each glass contained a total of 150 capsules with 500 mg
nimorazole/placebo. The capsules were tasteless and were
swallowed whole, not giving any indication of the presence
of active drug. Each center was supplied with sealed envel-
opes indicating the randomization code. These envelopes
were kept outside the radiotherapy department (at the hos-
pital pharmacy) and could only be reached in the case of a
clinical situation where knowledge of the presence of active
drug was crucial for the further treatment of the patient. This
did not happen in the present study and all envelopes were
returned intact to the data center after completion of the
trial. The trial has been maintained blinded during follow-
up and the involved institutions are still unaware of which
drug treatment the individual patients received. The trial
profile and outcome are shown in Fig. 2.

2.2. Treatment

Radiotherapy was applied according to the DAHANCA
protocol. Tumor volume was estimated by clinical assess-
ment and biplaner computed tomography. Patients with
large tumors were treated with opposed parallel opposed
fields. For smaller tumors, one to two lateral fields were
used. The planning target volume was slightly increased
around the clinical target volume by a margin of 1 cm. A
single daily dose of 1.8–2.0 Gy was delivered except for
Fig. 1. Schematic representation of the trial design and randomization
procedure for the Danish Head and Neck Cancer Study Protocol 5-85.
guidelines and given with 4–6 MeV photons or Co-60 using parallel opposed fields. Electrons were used to treat the neck in order to reduce the spinal cord dose, which was less than 50 Gy in all patients. The treatment was applied according to standardized fields including primary tumor and involved lymph nodes. A minimal tumor dose of 62–68 Gy (2 Gy per fraction, five fractions per week) was prescribed. The dose depended on the size of the tumor, with the larger tumors receiving the largest doses. Thus, patients with primary tumors and/or lymph nodes with a largest diameter of 2 cm were given 62 Gy, tumors between 2 and 4 cm were treated with 64 Gy and tumors above 4 cm were treated with 66–68 Gy. These doses were the minimal recommendations and a larger dose was allowed (Fig. 3).

Table 1 gives the characteristics of radiotherapy treatment in the two randomization groups.

Nimorazole (or placebo) was obtained from Farmitalia, Milan. The dose and drug irradiation interval was based on prior pharmacokinetic toxicological evaluation [35,39,47]. The drug was administrated in the form of gelatine-coated capsules containing 500 mg active drug or placebo and was given orally 90 min prior to irradiation. The daily scheduled dose was approximately 1200 mg/m² body surface given in connection with the first 30 radiation treatment fractions. Patients with a surface of less than 1.6 m² received 1500 mg per day, those with a surface between 1.6 and 1.9 m² received 2000 mg per day and patients with a surface above 1.9 m² were given 2500 mg daily. The total dose was approximately 36 g/m² and was not allowed to exceed 40 g/m² or 75 g in total. Patients were instructed to take the capsules 90 min before radiation and the time was written on a schedule which was checked by the radiotherapy technician. Almost all radiation fractions were given with less than 15 min derivation from the planned 90 min.

Patients with low pre-irradiation hemoglobin (females <8 mmol/l; males <9 mmol/l) were randomized to receive or not to receive transfusion prior to final randomization to the hypoxic sensitizer. Transfusions were given with packed red blood cells to achieve a hemoglobin concentration in the ‘high’ value range. If during the treatment the hemoglobin level fell below the values indicated above, the transfusion was repeated. The hemoglobin level was measured every fortnight.

2.3. Assessments

Patients were followed at the oncological centers for at least 5 years or until death, with the exception of one patient who emigrated 29 months after treatment. The patients were evaluated with clinical examination weekly during treatment, 2 months after treatment, thereafter with 3-month intervals for the first year and with 4-month intervals for the second year and then twice annually for up to 5 years after randomization. Further examination was only performed if the patients had symptoms or evidence of recurrent disease. In addition to the recording of recurrence and/or survival status an attempt was made to record treatment-
related morbidity. Only patients with recurrence or other problems were subjected to regular follow-up for more than 5 years.

In the case of a residual tumor, recurrence or progression of the disease salvage surgery or palliative treatment was performed, depending on the status of the individual patient, symptoms and previous treatment.

2.4. Evaluation and statistical methods

All diagnostic, therapeutic and follow-up data were validated and processed by the DAHANCA data center. To optimize the data quality, the events recorded were cross-checked with the hospital records to ensure correct registration of the site or sites of failure and course of death.

The trial was designed to include 400 evaluable patients and was closed after that number had completed treatment. This number was estimated to be recruited over a 3-year period. Assuming a true improvement of the loco-regional tumor control rate from 40 to 55%, the probability that such an event would be detected at a significant level of \( P < 0.05 \) was greater than 90%.

The primary end-point was loco-regional control after radiotherapy. The definition of this end-point was complete and persistent disappearance of the disease in the primary tumor (T-site) and regional lymph nodes (N-site) after radiotherapy. The evaluation was performed clinically and supplemented with endoscopy and/or biopsy in case of doubt. Failure was recorded in the event of a recurrent tumor, or if the primary tumor never completely disappeared. In the latter situation the tumor was then assumed to have failed at the time of randomization. Since some uncertainty may exist concerning the time to an early recurrence, this end-point was not graphically presented until 6 months after randomization (Fig. 4). The primary end-point does not include the effect of a successful procedure with salvage surgery.

Secondary end-points include overall loco-regional control (including salvage procedures), disease-specific survival, overall survival and treatment-related morbidity. The end-point used for disease-specific survival is death from or with the actual cancer. The end-point for survival is any death, irrespective of cause. All time estimates were done using the date of randomization as the initial value.

Radiation-related morbidity was evaluated as graded reactions of acute mucositis and edema and late fibrosis, edema or necrosis, using the scoring system previously described [36].

The actuarial values of the end-points were evaluated by the Kaplan–Meier product-limit analysis using the BMDP 1L program. The Mantel–Cox test was used for comparison and a test for trend with equal weighing was performed if more than two groups were compared. The \( P \)-values estimated are those for a two-tailed test and the significance level was chosen to be 5%. Data are presented as 5-year actuarial values ± standard error of the mean, unless otherwise mentioned. Odds ratios with 95% confidence limits were calculated as described by Stell [45].

A multivariate Cox proportional hazards analysis was used to evaluate prognostic parameters and treatment with respect to the risk of loco-regional failure and disease-specific death, using the BMDP 2L program (version 7.0). Parameters were included in the model using forward selection and statistical analysis was performed by the Wald test.

The treatment effect was evaluated using ‘the intention to treat’ principle and patients were included in their randomization group irrespective of whether or not they had completed the planned treatment. The time for evaluation of loco-regional recurrence and disease-specific survival was 5 years after randomization, since patients were only followed regularly for that period. However, the date for evaluation of overall survival was 31 August 1997, which gave a median observation time of 112 months for that end-point (range 84–140 months).

3. Results

From January 1986 to September 1990, 422 patients were included. The accrual rate was constant throughout the period. Of the 422 included patients, eight were not eligible for the protocol. One had distant metastasis at the time of diagnosis, five were supraglottic T1, N0 (stage 1), one had incorrect histology (carcinoid carcinoma) and one had received surgery (neck dissection) prior to radiotherapy. Thus, 414 patients were evaluable for analysis and will be described below (Fig. 2).

There were 110 females and 304 males with a median age at randomization of 60 years (range 21–84 years). Distribution as a function of the stratification group followed the expected pattern (Table 2) and with the exception of more N3 patients in the placebo arm, no significant differences were found between the nimorazole and placebo groups.
Table 2
Characteristics of 414 evaluable patients and tumors as a function of the randomization group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Radiotherapy alone</th>
<th>Radiotherapy + nimorazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>195</td>
<td>219</td>
</tr>
<tr>
<td>Age (years) Median</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Range</td>
<td>24–84</td>
<td>21–84</td>
</tr>
<tr>
<td>Sex female</td>
<td>49</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>146</td>
<td>157</td>
</tr>
<tr>
<td>Tumor site</td>
<td></td>
<td></td>
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<tr>
<td>Supraglottic</td>
<td>57</td>
<td>68</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>91</td>
<td>96</td>
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<td>Hypopharynx</td>
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<td>28</td>
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<tr>
<td>Rhinopharynx</td>
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<td>27</td>
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<tr>
<td>T-classification</td>
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</tr>
<tr>
<td>T1</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>T2</td>
<td>62</td>
<td>69</td>
</tr>
<tr>
<td>T3</td>
<td>62</td>
<td>72</td>
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<td>T4</td>
<td>41</td>
<td>42</td>
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<tr>
<td>N-classification</td>
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<tr>
<td>N0</td>
<td>79</td>
<td>108</td>
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<tr>
<td>N1</td>
<td>52</td>
<td>53</td>
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<td>56</td>
<td>39</td>
</tr>
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<td>Staging (UICC 1978)</td>
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</tr>
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<td>16</td>
</tr>
<tr>
<td>Stage 2</td>
<td>34</td>
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<td>Stage 3</td>
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<td>85</td>
</tr>
<tr>
<td>Stage 4</td>
<td>89</td>
<td>82</td>
</tr>
<tr>
<td>Histopathological differ.</td>
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<td></td>
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<tr>
<td>Well</td>
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<td>24</td>
</tr>
<tr>
<td>Medium</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>Poor/undifferentiated</td>
<td>67</td>
<td>84</td>
</tr>
<tr>
<td>Not determined</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
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<tr>
<td>High</td>
<td>116</td>
<td>127</td>
</tr>
<tr>
<td>Low*</td>
<td>79</td>
<td>92</td>
</tr>
<tr>
<td>Transfused</td>
<td>34</td>
<td>48</td>
</tr>
<tr>
<td>Not transfused</td>
<td>45</td>
<td>44</td>
</tr>
</tbody>
</table>

*Females <8, males <9 mmol/l.

However, there were more patients randomized to the nimorazole arm due to an imbalance in randomization which by chance was caused by the large number of stratification groups. A total of 219 patients were randomized to receive irradiation plus nimorazole and a total of 195 patients were randomized to receive irradiation plus placebo.

At the time of evaluation, 229 patients had failed to achieve persistent loco-regional control within the irradiated volume. A total of 213 patients had died with or of the actual disease and overall 307 patients had died. All patients alive at the time of analysis were free from disease.

The use of nimorazole significantly improved the outcome (Table 3), with univariate odds ratios of 1.97 (95% CI 1.33–2.93) for loco-regional control and 1.92 (95% CI 1.30–2.84) for disease-specific survival and with a non-significant trend towards improvement in the overall survival with an odds ratio of 1.32 (95% CI 0.84–2.05). In contrast, the risk of development of radiation-related severe late morbidity was not influenced by nimorazole.

The primary loco-regional tumor control after radiotherapy is analyzed in Table 4 and Fig. 4. A statistically significant improvement in loco-regional tumor control was found in nimorazole-treated patients compared to patients receiving radiotherapy and placebo (5-year actuarial rate of 49 versus 33%, P < 0.002). This difference was observed in both the primary tumor and neck node response. Thus, the difference in 5-year actuarial values for T-site control was 57 versus 40% (P < 0.004) for the nimorazole- and placebo-treated groups, respectively. For neck node control the corresponding values were 71 versus 59% (P < 0.04), respectively.

The outcome also confirms the major prognostic factors in head and neck cancer (Table 4). Based on the previous DAHANCA 2 study, the stratification parameters in the DAHANCA 5 protocol were chosen to select equally balanced groups with distinct prognostic parameters. Univariate analysis (5-year actuarial loco-regional tumor control) showed a prognostic influence of T-classification (T1–T2 48% versus T3–T4 36%, P = 0.0008), pre-treatment hemoglobin (high 46% versus low 37%, P = 0.02) and sex (females 51% versus males 38%, P = 0.03). On the other hand, patients with supraglottic larynx cancers did not seem to differ from patients with pharynx tumors (Table 4), but it should be remembered that stage 1 supraglottic patients were not included in the trial.

The beneficial effect of nimorazole was present in most of the subgroups analyzed (Table 5), suggesting that the effect of the hypoxic sensitizer was not limited to certain subpopulations or tumor types.

Salvage surgery was successfully performed in 29 patients with failure in the T- or N-site. The final loco-regional control was therefore slightly better than after radiotherapy (Table 3), but since salvage procedures were at least as successful in the nimorazole-treated patients, the final loco-regional tumor control (including salvage) was also significantly better in the nimorazole group. In a similar way nimorazole treatment also resulted in a significantly higher cure rate with organ (i.e. larynx) preservation (Table 3).

Analysis of the failure pattern after treatment showed that the large majority of treatment failure was due to insufficient loco-regional tumor control. As a consequence the disease-specific survival was strongly related to insufficient loco-regional treatment and therefore also significantly better in patients given nimorazole (Fig. 5). This trend was also found in the overall survival but to a lesser, non-significant extent with 10-year actuarial survival rates of 26 and 16% (P = 0.32) for patients given nimorazole and placebo, respectively. This smaller difference in overall survival was probably due to a high incidence of death from other causes in this kind of patient.

In a Cox multivariate regression analysis, positive neck
nodes, advanced T-classification and absence of nimorazole treatment turned out to be the independent significant prognostic parameters using time to loco-regional failure as the end-point. The same parameters, with the addition of male sex, were also significant independent prognostic indicators with regard to the probability of dying from cancer (Table 6).

3.1. Hemoglobin and transfusion

A total of 171 patients had low hemoglobin values, as defined above. Among these, 82 were randomized to receive transfusion with packed red blood cells prior to the start of radiotherapy. Six patients did not receive transfusion, either because the hemoglobin value in a subsequent measurement was above the required value or due to in compliance with the protocol. The remaining patients received between 1 and 6 units of blood, but only 29 reached and maintained a hemoglobin level above the target value.

The expected prognostic effect of high and low hemoglobin values was demonstrated in univariate analyses (Table 4). This significant difference (46 versus 37%) was observed despite the fact that almost half of the low hemoglobin patients had received a blood transfusion. However, transfusion of patients with low hemoglobin concentrations did not significantly improve the outcome (Table 4). The number of patients submitted to this subrandomization was, however, too small to reach definitive conclusions and at the time of closure of the present protocol, it was therefore decided to continue to address this problem in the subsequent DAHANCA 7 study. Thus, further analysis of the influence of transfusion on the outcome of radiotherapy in head and neck cancer in patients treated with or without additional hypoxic radiosensitization with nimorazole awaits an overall analysis of the two studies.

The relationship between tumor response, nimorazole and hemoglobin concentration is seen in Table 5. This table shows that both a high hemoglobin concentration and the presence of nimorazole were good prognostic parameters and that nimorazole apparently sensitizes patients with both high and low hemoglobin values.

3.2. Radiation-related compliance and morbidity

Both radiotherapy and drug treatment were relatively well tolerated. Compliance with radiotherapy was the same in both treatment groups and only 10 patients did not complete the scheduled radiation treatment (five in each randomization group), due to deterioration in the general condition or death during treatment. Thus 98% of the patients completed the planned radiotherapy (Fig. 3).

The acute radiation-related morbidity was the same in the two randomization groups, with an incidence of moderate to severe mucositis of 60 and 62% in patients treated with nimorazole and placebo, respectively. For the same groups the incidences of severe acute edema were 10 and 9%, respectively.

Late radiation-related morbidity could be recorded in 289 patients.

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Table 3

<table>
<thead>
<tr>
<th>Overall status of primary and secondary end-points</th>
<th>No. of patients</th>
<th>Total no. of patients</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loco-regional control (primary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nimorazole</td>
<td>115</td>
<td>219</td>
<td>1.97 (1.33–2.93)</td>
</tr>
<tr>
<td>Placebo</td>
<td>70</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>185</td>
<td>414</td>
<td></td>
</tr>
<tr>
<td>Loco-regional control (salvage)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nimorazole</td>
<td>131</td>
<td>219</td>
<td>2.05 (1.35–2.95)</td>
</tr>
<tr>
<td>Placebo</td>
<td>82</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>213</td>
<td>414</td>
<td></td>
</tr>
<tr>
<td>Organ preservation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nimorazole</td>
<td>119</td>
<td>219</td>
<td>1.99 (1.34–2.95)</td>
</tr>
<tr>
<td>Placebo</td>
<td>73</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>192</td>
<td>414</td>
<td></td>
</tr>
<tr>
<td>Disease-specific survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nimorazole</td>
<td>123</td>
<td>219</td>
<td>1.92 (1.30–2.84)</td>
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<tr>
<td>Placebo</td>
<td>78</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>201</td>
<td>414</td>
<td></td>
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<tr>
<td>Overall survival</td>
<td></td>
<td></td>
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<tr>
<td>Nimorazole</td>
<td>62</td>
<td>219</td>
<td>1.32 (0.84–2.05)</td>
</tr>
<tr>
<td>Placebo</td>
<td>45</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>107</td>
<td>414</td>
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<tr>
<td>Severe late radiation morbidity</td>
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</tr>
<tr>
<td>Nimorazole</td>
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<td>150</td>
<td>0.71 (0.24–2.04)</td>
</tr>
<tr>
<td>Placebo</td>
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</tr>
<tr>
<td>All</td>
<td>15</td>
<td>289</td>
<td></td>
</tr>
</tbody>
</table>

*An odds ratio above unity indicates a benefit in the nimorazole-treated group.*
patients achieved the planned drug treatment (nimorazole toxicity in the nimorazole group. As a whole, 60% of the placebo, especially due to the increased gastrointestinal dependence on whether the patient received nimorazole or shown in Table 7. Compliance with drug treatment was 3.3. Drug tolerance and toxicity related side-effects. that nimorazole did not significantly influence the radiation-9% for patients given placebo (<0.001). This implies that nimorazole has demonstrated a lack of important toxicity. No relationship between sex or the given drug dose has been found. In addition 12% of the placebo patients indicated side-effects. Thus, the toxicity has so far been acceptable and has been expressed as acute and reversible changes which have caused no major discomfort to patients.

3.4. Plasma nimorazole

Routine pharmacokinetic analysis was performed in 166 patients during the initial treatment with nimorazole. Multiple plasma samples were drawn during the first 6–8 h in order to get information about the pharmacokinetic properties of the drug. In order not to reveal the treatment code blood samples were drawn from both nimorazole- and placebo-treated patients. The plasma concentrations were measured on HPLC as previously described [38,39]. The peak plasma concentration ranged from 14 to 84 mg/l with a median value of 32 mg/l. In most patients (67%) the peak plasma concentration is achieved within 90 min after intake of the capsules but a considerable variation in absorption times has been found. A significant decrease in peak plasma concentration with increasing peak time was observed [35]. A total of 86% of the patients obtained peak plasma values at or above 25 mg/l which was considered satisfactory. Therefore, with the exception of 26 patients, where peak absorption times occurred later than 2.5 h after intake, all pharmacokinetic observations were as expected.

4. Discussion

The current study shows an improvement in tumor control when compared to the similar patient group in the DAHANCA 2 trial [17,34]. Although this may not solely be due to the use of nimorazole, but also be a consequence
of changing the radiotherapy schedule from split-course to continuous irradiation [17,36], it does demonstrate the usefulness of pursuing a constant policy within the nationwide DAHANCA study group.

The beneficial tumor response in favor of nimorazole appears promising. The results are further encouraged by the observation that an apparent independent and additive relationship exists between the use of the hypoxic radiosensitizer and the hemoglobin concentration (Table 5). This is probably due to a combination of a hemoglobin concentration-dependent oxygen delivery to the tumor together with the hypoxic sensitization. This is in agreement with the DAHANCA 2 trial and a striking similarity between the two studies has appeared [34,41]. It is remarkable that the Danish head and neck cancer studies so far have been the only large randomized clinical trials which have shown an apparent benefit of the use of hypoxic radiosensitizers [8,30,32]. There is substantial evidence from hyperbaric oxygen trials, measurements of oxygen concentrations in tumors and the relationship between hemoglobin concentration and tumor control which indicates that hypoxia may be a critical factor when treating carcinomas of the head and neck by radiotherapy [28,30,37]. However, the experience has also pointed towards a substantial het-

Table 5
Loco-regional control (5-year actuarial value) as a function of nimorazole and stratification group or other factors of significance for the radiation response

<table>
<thead>
<tr>
<th>Stratification group</th>
<th>Placebo</th>
<th>Nimorazole</th>
<th>Stratified P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Control (%)</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
<td>45 ± 7</td>
<td>62</td>
</tr>
<tr>
<td>Male</td>
<td>147</td>
<td>30 ± 4</td>
<td>157</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraglottic</td>
<td>57</td>
<td>35 ± 6</td>
<td>68</td>
</tr>
<tr>
<td>Pharynx</td>
<td>138</td>
<td>33 ± 4</td>
<td>151</td>
</tr>
<tr>
<td>T-classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1–T2</td>
<td>92</td>
<td>42 ± 5</td>
<td>105</td>
</tr>
<tr>
<td>T3–T4</td>
<td>103</td>
<td>27 ± 5</td>
<td>114</td>
</tr>
<tr>
<td>N-status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>79</td>
<td>43 ± 6</td>
<td>108</td>
</tr>
<tr>
<td>N +</td>
<td>116</td>
<td>27 ± 5</td>
<td>111</td>
</tr>
<tr>
<td>Staging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>5</td>
<td>40 ± 21</td>
<td>16</td>
</tr>
<tr>
<td>Stage 2</td>
<td>34</td>
<td>51 ± 9</td>
<td>36</td>
</tr>
<tr>
<td>Stage 3</td>
<td>67</td>
<td>47 ± 7</td>
<td>85</td>
</tr>
<tr>
<td>Stage 4</td>
<td>89</td>
<td>18 ± 4</td>
<td>82</td>
</tr>
<tr>
<td>Differentiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>20</td>
<td>20 ± 9</td>
<td>24</td>
</tr>
<tr>
<td>Moderate</td>
<td>55</td>
<td>31 ± 6</td>
<td>60</td>
</tr>
<tr>
<td>Poor/undifferentiated</td>
<td>67</td>
<td>35 ± 6</td>
<td>84</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>116</td>
<td>37 ± 5</td>
<td>127</td>
</tr>
<tr>
<td>Low</td>
<td>79</td>
<td>29 ± 6</td>
<td>92</td>
</tr>
<tr>
<td>Transfused</td>
<td>34</td>
<td>29 ± 9</td>
<td>48</td>
</tr>
<tr>
<td>Not transfused</td>
<td>45</td>
<td>30 ± 8</td>
<td>44</td>
</tr>
</tbody>
</table>

* Females <8, males <9 mmol/d.

Table 6
Cox proportional hazards analysis using loco-regional failure and death from cancer as end-points

<table>
<thead>
<tr>
<th>Variable</th>
<th>Loco-regional failure</th>
<th>Dead from cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-value</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>T1–T2 versus T3–T4</td>
<td>0.0002</td>
<td>1.65 (1.25–2.17)</td>
</tr>
<tr>
<td>N0 versus N+</td>
<td>&lt;0.0001</td>
<td>1.84 (1.38–2.45)</td>
</tr>
<tr>
<td>Placebo versus nimorazole</td>
<td>0.005</td>
<td>0.69 (0.52–0.90)</td>
</tr>
<tr>
<td>Males versus females</td>
<td>0.06</td>
<td>NE</td>
</tr>
<tr>
<td>High versus low hemoglobin</td>
<td>0.13</td>
<td>NE</td>
</tr>
<tr>
<td>Supraglottic versus pharynx</td>
<td>0.88</td>
<td>NE</td>
</tr>
</tbody>
</table>

RR, relative risk. NE, not estimated.
* Indicates the risk of failure or death for the last mentioned variable relative to the first, e.g. risk of failure for T3–T4 tumors relative to T1–T2 tumors.
strated a significant improvement in (disease-specific) ment in loco-regional control, the overview also demon-
study from the analysis. As a consequence of the improve-
itits conclusion, which is maintained after elimination of the 
uted to this meta-analysis, but do not significantly influence 
side-effects alone. In addition, there is a substantial placebo 
effect and the large capsules may be related to the double-
blind design of the trial because the patients were very care-
ful instructed about potential side-effects and the capsules 
patients were unable to comply with the drug, mainly due to 
problems with swallowing the capsules. Both the placebo 
effect and the large capsules may be related to the double-
blind design of the trial because the patients were very care-
fully instructed about potential side-effects and the capsules 
had to be made larger in order to make the drug tasteless and 
blinded. Since the completion of the DAHANCA 3 proto-
col, nimorazole has been part of the standard treatment of 
most head and neck cancer patients and their compliance 
has substantially improved partly due to the use of coated

Fig. 5. Actuarial estimated disease-specific survival rate in patients rando-
mized to receive nimorazole or placebo in conjunction with conventional 
radiotherapy for carcinoma of the pharynx and supraglottic larynx.

The compliance to nimorazole in the present trial was less 
than anticipated, but cannot be explained by drug-related 
side-effects alone. In addition, there is a substantial placebo 
effect (Table 7) and it was also observed that 16% of the 
patients were unable to comply with the drug, mainly due to 
problems with swallowing the capsules. Both the placebo 
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Survival [37]. Thus, substantial evidence exists indicating 
that hypoxic modification is likely to improve the outcome 
of radiotherapy in head and neck cancer. Provided such 
modification can be performed without major morbidity or 
other difficulties, it will therefore be considered a part of 
standard therapy as we consider the evidence for its ben-
eficial efficacy to be sufficient.

In contrast to the current results, two more recent large 
randomized trials evaluating the hypoxic sensitizer etanida-
zole in head and neck cancer have not demonstrated a sig-
nificant difference [11,25] and obviously the outcome from 
various clinical trials are not demonstrating a uniform ben-
efit of hypoxic modification. The reason for this discrepancy 
should probably be seen in both the heterogeneity of the 
included tumors and in the efficacy of the hypoxic modifi-
cation.

The use of nitroimidazoles has major limitations since the 
most potent drugs are associated with substantial toxicity 
and therefore can only be given in small and infrequent 
doses. As previously discussed [32], there is a discrepancy 
between the preclinical evaluation of new sensitizers and 
the clinical applicability. In preclinical animal studies the 
2-nitroimidazoles have been shown to be the most potent 
drugs [38]. However, when applied in clinical practice these 
drugs can only be given in low doses, which in association 
with a smaller tumor/plasma ratio results in a significant 
reduction of the drug in the tumor when given in a fraction-
ated treatment. The 5-nitroimidazoles are less active at 
high concentrations, but in clinically usable doses they 
seem to yield at least the same extent of hypoxic radiosens-
itization as more potent drugs. Furthermore, they can be 
delivered in substantially higher tumor concentrations [32]. 
The difference between the etanidazole trials and the current 
study therefore could simply be a consequence of the extent 
of hypoxic radiosensitization. As previously demonstrated, 
the amount of drug available in a tumor per fraction in a 30-
fraction regime with nimorazole is almost twice that of 
etanidazole [32].

No important or chronic toxicity has been noted with the 
use of nimorazole and the drug response and the side-effect 
profile are in agreement with the previous phase I and II 
studies [35,39,47].

The compliance to nimorazole in the present trial was less 
than anticipated, but cannot be explained by drug-related 
side-effects alone. In addition, there is a substantial placebo 
effect (Table 7) and it was also observed that 16% of the 
patients were unable to comply with the drug, mainly due to 
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blinded. Since the completion of the DAHANCA 3 proto-
col, nimorazole has been part of the standard treatment of 
most head and neck cancer patients and their compliance 
has substantially improved partly due to the use of coated
The relationship between hemoglobin and tumor response is intriguing, although not uniformly observed in all trials [13]. It is obvious that hemoglobin by itself may not reflect the true oxygen status of the tumor, partly due to variations in tumor blood flow and partly because the oxygen unloading capacity of the blood may widely differ [4,20,29]. The latter may especially be a consequence of smoking habits [14,37]. Since almost all patients with head and neck carcinomas are smokers (also during radiotherapy), variations in oxygen availability may be as substantial in patients with the same hemoglobin value. An analysis of this problem is in progress. However, it should not be forgotten that a low hemoglobin value by itself may just indicate a poorer general condition of the patient, which in turn may lead to a worse prognosis.

The protocol also addresses the issue of the transfusion of low hemoglobin patients to a high hemoglobin level. Whether this will be a successful procedure remains to be analyzed. This will require a more detailed study of the hemoglobin level in transfused patients and this was not performed in the current analysis.

As previously observed [40], this trial also demonstrated that women had a better prognosis. This may be partly explained by a different distribution in stage and tumor site, but an additional independent sex-related prognostic parameter seems to exist.

The potential presence of hypoxia in head and neck tumors may not be the only cause of radioresistance. Proliferation of tumor cells during treatment and intrinsic resistance are also known to be responsible for failure to respond to radiotherapy and reducing the overall treatment time may improve the outcome [1,9,21,31,42]. The difference between the outcome in the DAHANCA 2 and 5 trials should therefore be seen in the light of a poorer tumor control after split-course therapy with an overall treatment time of 9.5 weeks. This effect may especially be found in the well-differentiated tumors [17], whereas the effect of nimorazole appeared to be present irrespective of the histopathological grade (Table 4). Therefore, future strategies towards improving the effect of radiotherapy in head and neck cancer must not only attempt to minimize the influence of hypoxia, but also aim to reduce the overall treatment time. The latter is preferable without reducing the total

---

### Table 7

<table>
<thead>
<tr>
<th>Toxicity/compliance</th>
<th>Nimorazole (n = 219) (%)</th>
<th>Placebo (n = 195) (%)</th>
<th>All (n = 414) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed as scheduled without any side-effects</td>
<td>107 (49)</td>
<td>140 (72)</td>
<td>247 (60)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>77 (35)</td>
<td>24 (12)</td>
<td>101 (24)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>46 (26)</td>
<td>16 (7)</td>
<td>62</td>
</tr>
<tr>
<td>Other</td>
<td>12 (8)</td>
<td>3 (1)</td>
<td>15</td>
</tr>
<tr>
<td>Other non-compliance (not drug-related)</td>
<td>14 (8)</td>
<td>4 (2)</td>
<td>18</td>
</tr>
</tbody>
</table>

Numbers in bold typeface indicate patients in whom the treatment was not completed (i.e., <25 drug treatments); nimorazole 83 patients (38%); placebo 40 patients (21%).
Table 8

‘Bottom-line’ calculation of the effect of nimorazole

<table>
<thead>
<tr>
<th>Loco-regional control</th>
<th>Disease-specific survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk 0.74</td>
<td>0.73</td>
<td>0.93</td>
</tr>
<tr>
<td>Relative risk reduction (%) 26</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>Absolute risk reduction (%) 17</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>No. of patients needed* 6</td>
<td>6</td>
<td>19</td>
</tr>
</tbody>
</table>

*Number of patients (on average) needed to treat to achieve the benefit of nimorazole in one patient.

dose to avoid failures due to intrinsic radioresistance. Such a treatment strategy is the basis of the DAHANCA 7 protocol in which patients receiving nimorazole are randomized between radiotherapy given with five or six fractions of 2 Gy per week to the same total dose [42].

The outcome of a randomized trial may be difficult to interpret since the data can be presented in various ways. It may therefore be useful to indicate the outcome in the form of a ‘bottom-line’ using various effect parameters to illustrate the magnitude of the results [15]. Table 8 shows the calculation of such a ‘bottom-line’ effect of the use of nimorazole in terms of the likely benefit for the individual patients, taking into consideration that the treatment intervention is economically affordable, has no major side-effects and is easy to administer. Since the intervention is rather simple and can be performed without major problems, it is our conclusion that it has such a magnitude and benefit that it should be part of routine radiotherapy of the relevant tumors until other alternatives have been proven to be more effective.

Acknowledgements

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