Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): a randomised, multicentre trial

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Summary

Background Several large randomised studies from western Europe and the USA have shown that accelerated fractionation of radiotherapy might be beneficial in the treatment of squamous-cell carcinoma of the head and neck (HNSCC). The aim of this study—the International Atomic Energy Agency (IAEA) ACC trial—was to determine whether accelerated fractionation could be applied in developing countries, where there are fewer therapeutic resources and where tumour burdens can be heavier.

Methods Between Jan 6, 1999, to March 31, 2004, nine centres from Asia, Europe, the Middle East, Africa, and South America recruited patients with HNSCC of the larynx, pharynx, and oral cavity who were eligible for curative radiotherapy. Patients were randomly assigned in this open-label trial to receive an accelerated regimen of six fractions of radiotherapy per week (n=458) or to receive a conventional radiotherapy regimen of five fractions per week (n=450), receiving a total dose of 66–70 Gy in 33–35 fractions. Patients were stratified by tumour localisation, T classification, histopathological grade, and institution. Randomisation was done by a central computer-generated balanced randomisation algorithm. The primary endpoint was locoregional control, analysed for all eligible patients, irrespective of whether or not they had completed the course of radiotherapy. This trial is registered with ClinicalTrials.gov, number NCT00120211.

Findings Six patients in the accelerated group and two in the conventional group were excluded from analyses because of withdrawal of consent or missing data. The planned total radiotherapy dose was received by 418 (92%) of the 452 eligible patients in the accelerated radiotherapy group and 413 (92%) of the 448 patients in the conventional radiotherapy group. Median treatment time was 40 days in the accelerated group and 47 days in the conventional group. The 5-year actuarial rate of locoregional control was 42% in the accelerated group versus 30% in the conventional group (hazard ratio [HR] 0·63, 95% CI 0·49–0·83; p=0·004). Acute morbidity in the form of confluent mucositis was noted in 45 patients in the accelerated group and 22 patients in the conventional group (2·15, 1·27–3·35); severe skin reactions were noted in 87 patients in the accelerated group and 50 patients in the conventional group (1·91, 1·31–2·79). There were no significant differences in late radiation side-effects.

Interpretation An accelerated schedule of radiotherapy for HNSCC was more effective than conventional fractionation, and since it does not require additional resources, might be a suitable new worldwide standard baseline treatment for radiotherapy of HNSCC.

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Introduction

The incidence of squamous-cell carcinoma of the head and neck (HNSCC) is increasing, and it is now the fourth most common malignant disease in the world, with more than 70% of cases occurring in the developing world.[1] HNSCC is a locoregional disease confined to the primary tumour and the regional lymph nodes; distant metastases are rarely seen at the time of diagnosis. Radiotherapy and surgery are thus the treatments of choice, with radiotherapy being the favoured treatment if organ conservation is required.[2]

One of the most important biological factors related to the outcome of radiotherapy in squamous-cell carcinoma is the proliferation of tumour stem cells during treatment.[3] A prolonged overall treatment time might reduce the chance of tumour control,[4–6] and a substantial number of clinical reports show a reduction in overall treatment time might improve tumour control.[7–9] A shorter treatment time can be obtained by applying a higher dose per fraction, but this will result in a disproportionate increase in the incidence of late complications.[10,11] Accelerated fractionation is therefore only possible if the weekly number of fractions is increased without increasing the dose per fraction.

The Danish Head and Neck Cancer Group (DAHANCA) 6&7 trial compared the same total dose of radiotherapy given to patients with HNSCC either conventionally (five fractions per week) or accelerated (six fractions per

week).[7] The accelerated schedule enabled a treatment of 66 Gy in 33 fractions to be given in 8 days less than the conventional schedule, with an overall treatment benefit of around 15% more than the conventional schedule and an acceptable number of complications.[7] Thus, decreasing treatment time can result in better tumour control, provided the total dose is not reduced, without requiring additional resources. However, such a regimen might also result in increased acute radiation morbidity, and cannot be accepted as routine without evidence from broad-based controlled clinical trials done in the health-care environments where it will be used.

The purpose of this study—the International Atomic Energy Agency (IAEA) ACC trial—was to determine the feasibility and effectiveness of accelerated fractionation of radiotherapy for patients with HNSCC in resource-limited settings. The protocol was designed to exclude as few patients as possible to get a true impression of the suitability of such therapy in an unselected patient population.

Methods

Patients

For the **full protocol of this study** see http://www.dahanca.dk/get_media_file.php?mediaid=248

Patients were enrolled at nine centres from Asia (New Delhi, Mumbai, Peshawar, Islamabad), Europe (Tallinn), the Middle East (Riyadh, Beirut), Africa (Cape Town), and South America (Santiago). Patients underwent a full clinical examination before treatment, together with recording of histopathology and differentiation of the primary tumour;[12,13] Tumour, Node, Metastasis (TNM) classification;[14] assessment of the localisation and the size of the primary tumour and regional lymph-node metastases by either clinical examination, endoscopy, radiography, CT scan, or ultrasound; assessment of performance status according to WHO criteria; and chest radiograph. Human papillomavirus (HPV) status was not assessed in this trial.

Criteria for eligibility were age over 18 years, performance status of 0–2, stage 1–4 invasive squamous-cell carcinoma of the larynx, pharynx, and oral cavity (except nasopharynx and stage 1 glottic carcinoma), and no evidence of distant metastases. Eligible patients were candidates for primary curative radiotherapy alone (without previous or planned surgical excision of the primary tumour or lymph nodes), and, with the exception of the disease in question, could not be in a state or condition which could be expected to affect compliance to, or outcome of, the radiation treatment or complicate the assessment of the treatment. All patients were requested to undergo orodental assessment with revision of potential infectious foci, and dental care including prophylaxis for caries was recommended during and after radiotherapy.

The trial was done in accordance with the Declaration of Helsinki and approved by all relevant local and national ethical committees. Informed consent was obtained from all participants.

Randomisation and masking

Before randomisation, patients were stratified according to tumour site (larynx, pharynx or oral cavity), tumour classification (T1–2 *vs* T3–4), histopathological differentiation (poor, moderate or well, unknown), and institution. Randomisation was done by a fax to the IAEA-ACC data centre, where the eligibility criteria were checked and patients allocated to treatment. The trial was open label, and patients were allocated to treatment by a computer-generated balanced randomisation algorithm.

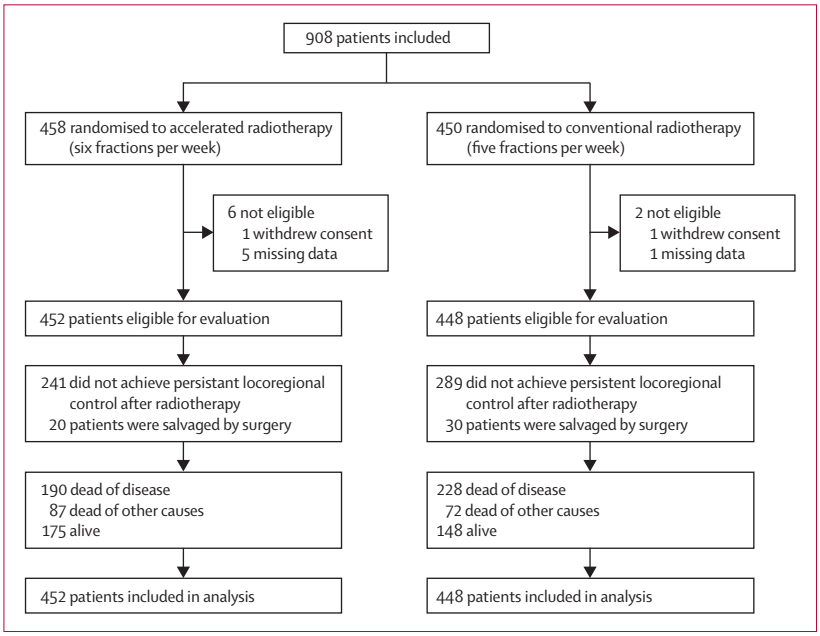

Figure 1: **Trial profile**

Procedures

Patients were randomly assigned to five or six fractions per week of 2 Gy. Patients assigned to five fractions per week were given one fraction per day on five consecutive days from Monday to Friday. Patients assigned to receive six fractions per week were similarly given one fraction per day; the sixth fraction was given on another day, or as an extra fraction on one of the first five days, but always allowing at least a 6-h interval between fractions. If any unintended interruption of the treatment occurred, this missing treatment was given as soon as possible, preferably within a week, but not allowing more than 14 Gy to be given during any 7-day period.

Patients were treated with external radiotherapy given with a linear accelerator or Co-60. Dosimetry was verified through the IAEA secondary standards dosimetry laboratory network or equivalent quality control service. The treatment principles and dose specifications were as previously used in IAEA protocols[15] and in agreement with the guidelines given in the ICRU-50 report.[16] A centrally absorbed target dose of 2 Gy was given per fraction. The clinical target volume dose (large fields)

was at least 44 Gy, whereas the spinal cord was not allowed to receive a total dose larger than 50 Gy. The gross tumour volume (the boost field) was treated with a dose of 66–70 Gy in 33–35 fractions.

No planned neck dissection was done before or after radiation. In cases of residual tumour, recurrence, or progression of the disease, salvage surgery was done or palliative treatment given, depending on the status of the individual patient, symptoms, and previous treatment.

The primary endpoint was locoregional control after radiotherapy, defined as complete and persistent disappearance of the disease in the primary tumour and regional lymph nodes after radiotherapy, not including salvage procedures. Failure was recorded in the event of recurrence, or if the primary tumour never completely disappeared, in which case the tumour was then assumed to have failed at the time of randomisation. Secondary endpoints included local control at the primary tumour site and regional control at the lymph nodes with and without salvage procedures, disease-specific survival, overall survival, and early and late treatment-related morbidity. All time estimates were calculated using the date of randomisation as the initial value. We planned to follow-up patients for at least 5 years or until death.

An off-line sample audit of the validity of the reported data was done in which 10% of each centre's patients were randomly selected by the trial secretariat. The centres were asked to submit documentation for the following reported entries: tumour localisation, TNM-classifications, date of first and last fraction, total dose, number of fractions per week, tumour status at last visit, vital status (alive or dead, date and cause of death). From the submitted documentation, protocol adherence and data reporting quality was scored by the study coordinators as compliant, minor violation (no clinical importance), or major violation (potential clinical importance).

Statistical analysis

The trial was designed to include 1000 evaluable patients recruited over a 3-year period. Assuming a true improvement of the locoregional tumour control from 45% to 60%, the probability that such an event would be detected at a significant level of p less than 0·05 was greater than 90%.

The actuarial values of the endpoints were assessed by the Kaplan-Meier product-limit method using the BMDP 1L program (version 7.0). The Mantel-Cox test was used for comparison, and a test for trend with equal weighing was done when more than two groups were compared. The p values estimated were for a two-tailed test, and the significance level was set at 5%. Data are presented as 5-year actuarial values. Hazard ratios (HR) are presented with 95% CI. Forest plots and odds ratios (OR) were calculated with the Comprehensive Meta Analysis program (version 2.0).

A multivariate Cox proportional hazards analysis was done with the BMDP 2L program to assess the effect of prognostic parameters and treatment on locoregional failure and disease-specific death. Parameters were included in the model using forward selection, and statistical analysis was done with the Wald test.

Outcomes were assessed with patients included in their randomisation group irrespective of whether or not they had completed the planned treatment. The primary endpoint was evaluable in all eligible patients, whereas data on some secondary morbidity endpoints were missing, and the patients were excluded from the relevant analysis.

	Five fractions per week (N=448)	Six fractions per week (N=452)
Recruiting centre		
New Delhi	126 (28%)	128 (28%)
Peshawar	104 (23%)	105 (23%)
Islamabad	70 (16%)	69 (15%)
Mumbai	64 (14%)	63 (14%)
Tallinn	53 (12%)	53 (12%)
Santiago	14 (3%)	12 (3%)
Riyadh	9 (2%)	10 (2%)
Cape Town	6 (1%)	10 (2%)
Beirut	2 (1%)	2 (1%)
Age (years)		
≤55	187 (42%)	217 (48%)
56–65	159 (35%)	147 (33%)
>65	102 (23%)	88 (19%)
Sex		
Male	370 (82%)	353 (78%)
Female	78 (18%)	99 (22%)
Performance status		
WHO 0	328 (65%)	347 (63%)
WHO 1–2	120 (35%)	105 (37%)
Primary site		
Larynx	108 (24%)	105 (23%)
Pharynx	235 (52%)	240 (53%)
Oral cavity	105 (24%)	107 (24%)
TNM classification		
T1–2	193 (43%)	189 (42%)
T3–4	255 (57%)	263 (58%)
N negative	260 (58%)	255 (56%)
N positive	188 (42%)	197 (44%)
Stage 1	18 (4%)	10 (2%)
Stage 2	116 (26%)	110 (24%)
Stage 3	167 (37%)	170 (38%)
Stage 4	147 (33%)	162 (36%)
Differentiation		
Well	144 (32%)	157 (35%)
Moderate	180 (40%)	172 (38%)
Poor	44 (10%)	41 (9%)
Unknown	80 (18%)	82 (18%)

Data are n (%). WHO=World Health Organization. TNM=Tumour, Node, Metastasis.

Table 1: **Baseline patient and tumour characteristics by treatment group**

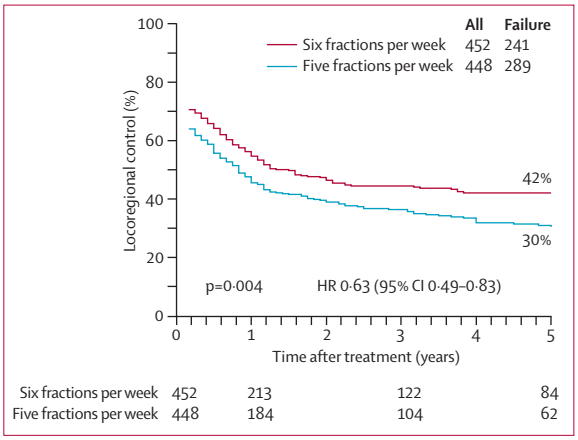

Figure 2: **Locoregional tumour control**

This trial is registered with ClinicalTrials.gov, number NCT00120211.

Role of the funding source

The study sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Due to slow intake and lack of funding it was decided to close the study after 5 years. During this time (Jan 6, 1999, to March 31, 2004), 908 patients were recruited and randomly assigned to treatment. Of these, eight were not eligible for the study and were excluded from analyses (figure 1). The baseline characteristics of the 900 evaluable patients are shown in table 1. There were 723 men and 177 women, with a median age at randomisation of 58 years (range 22–85 years); there were no significant differences in terms of tumour characteristics between the groups. The use of betel chewing was equally common in the two treatment groups (about 9% of all patients).

Compliance with radiotherapy was the same in both treatment groups, with 413 (92%) patients assigned to receive five fractions and 418 (92%) of those assigned to receive six fractions completing planned radiotherapy. Median overall treatment time was 40 days for the accelerated schedule and 47 days for the conventional schedule.

At the time of final assessment (Aug 1, 2009), after a median follow-up since randomisation of 99 months (range 65–128 months), 500 patients had failed to achieve persistent locoregional control after primary irradiation; 50 of the recurrences were salvaged by additional surgery (figure 1). 418 patients died from HNSCC, with 577 deaths overall.

The proportion of patients with locoregional tumour control after radiotherapy is shown in figure 2. At 5 years, the actuarial rate of locoregional control was significantly greater for patients in the accelerated schedule group than for those in the conventional schedule group (42% *vs* 30% at 5 years; HR 0·63, 95% CI 0·49–0·83; p=0·004). When locoregional control was assessed by site of the primary tumour and regional lymph nodes, the benefit of acceleration was confirmed for primary tumour site, but there was no significant difference in terms of control at the regional lymph nodes between the two schedules (figure 3). When analysed by subgroup (figure 4), accelerated fractionation was of greatest benefit in patients with tumours of the larynx and of less benefit for more advanced tumours (all sites) with a large nodal burden. Histopathological differentiation status did not seem to have any effect on the benefit from accelerated fractionation.

Salvage surgery was successfully done in 50 patients with failure at the primary tumour site or regional lymph nodes. The final locoregional control after salvage was therefore slightly better than after

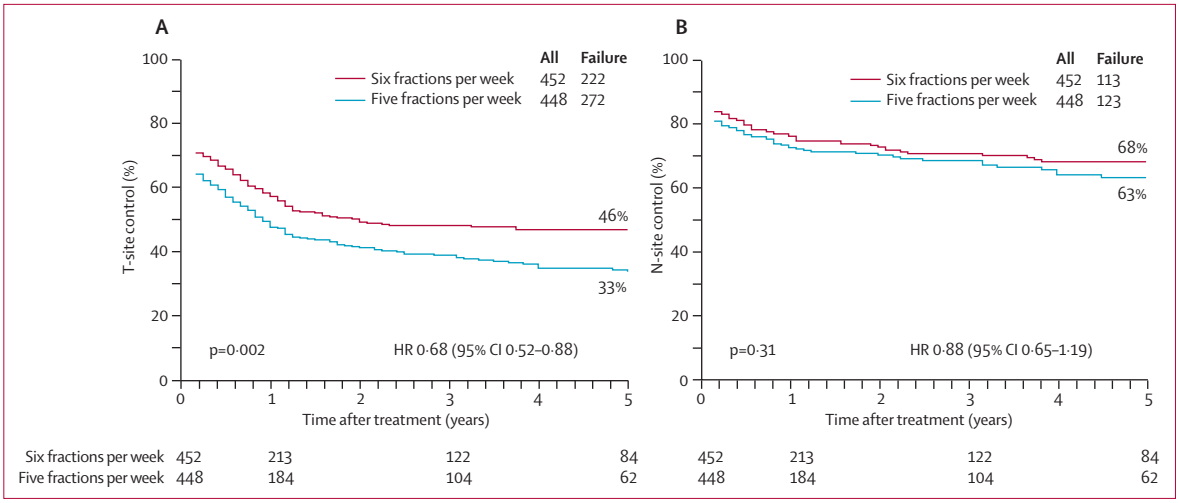

Figure 3: **Locoregional tumour control at the primary tumour site (A) and in the regional lymph nodes (B)**

radiotherapy alone, with 5-year locoregional control in 46% of patients in the accelerated group versus 35% for patients in the conventional group (HR 0·70, 95% CI 0·54–0·91; p=0·01).

At 5 years, the actuarial rate of disease-free survival was 50% for those patients in the accelerated group versus 40% for those in the conventional group (HR 0·70, 95% CI 0·54–0·91; p=0·03; figure 5); overall survival was 35% for those in the accelerated group versus 28% for those in the conventional group (0·78, 0·59–1·03; p=0·07; figure 5).

Univariate analysis of 5-year actuarial locoregional tumour control showed that tumour site (larynx 46% vs pharynx 37% *vs* oral cavity 25%; p<0·0001) and tumour size (T1–T2 46% *vs* T3–T4 29%; p<0·0001) were of prognostic significance. However, histopathological differentiation (well or moderate 36% *vs* poor 37%; p=0·51) did not seem to affect locoregional control, nor were there any important variations among patients from the different participating institutions (data not shown). Other factors that were not part of the stratification parameters included nodal status (node negative 42% *vs* node positive 28%; p<0·0001); sex (female 36% *vs* male 37%; p=0·51); and performance status (WHO 0 37% *vs* WHO 1–2 32%; p=0·20).

In a Cox multivariate regression analysis stratified by tumour site with time to locoregional failure as the endpoint, negative neck nodes (HR 0·69, 95% CI 0·58–0·83), low T classification (T1–2; 0·65, 0·54–0·78), and six fractions per week (0·79, 0·67–0·93) were significant independent predictors of a good prognosis. The same parameters were also significant independent prognostic indicators of the probability of dying from cancer (negative neck nodes [0·57, 0·47–0·70]; low T classification [0·53, 0·36–0·79]; and six fractions per week [0·79, 0·66–0·96]).

Acute radiation-related morbidity was significantly more common in the accelerated group than in the conventional group (table 2). Additionally, mucositis tended to persist longer in the patients who underwent accelerated treatment than in those who received conventional treatment (data not shown), although it resolved within 3 months of the start of treatment. The more frequent mucosal reactions in the accelerated treatment group resulted in a significantly increased use of tube feeding during treatment compared with the conventional treatment group. Acute severe skin reactions were also more common in the accelerated treatment group than in the conventional treatment group, but did not affect compliance. Late radiation-related morbidity was assessed in 725 patients; no significant difference was noted between the fractionation schedules (table 2), indicating that the moderate reduction in overall treatment time of 1 week did not have any effect on late radiation-related effects.

A total of 1288 entries from 92 patients were audited for quality purposes. The audit showed agreement with the reported data in 99% of cases, with no difference between the two randomisation groups. Two major deviations, both in the accelerated group were noted. In one case a patient was treated with five fractions per week instead of six: the patient was still included in the accelerated schedule group for the analyses in accordance with the intention-to-treat design. For the other case a local recurrence was not reported; this was corrected and included the analyses.

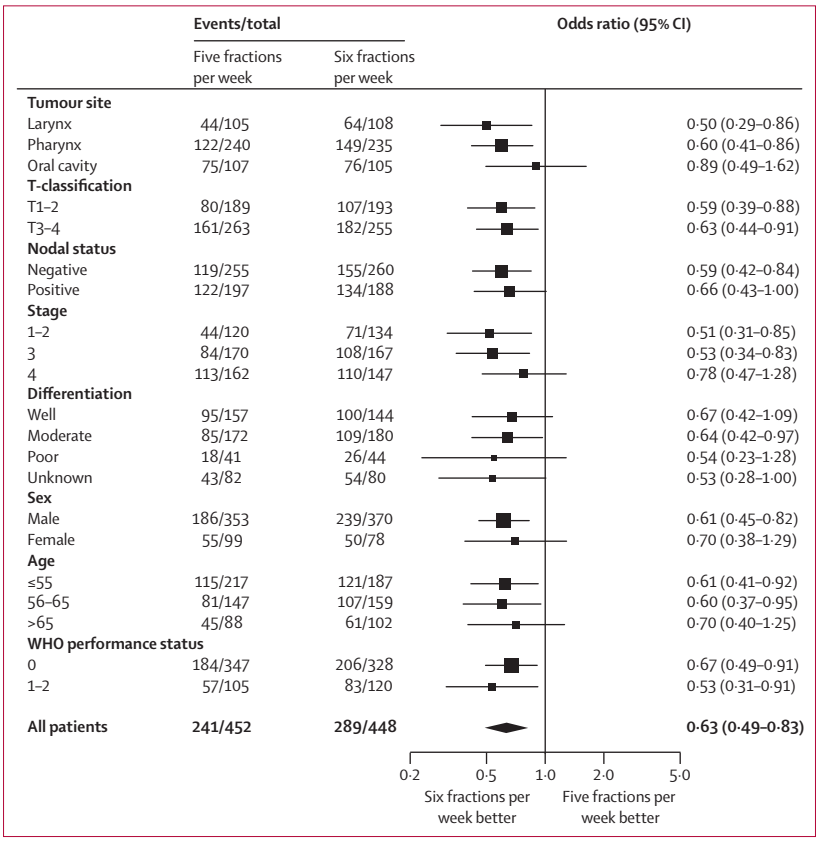

Figure 4: **Locoregional control by pre-treatment characteristics**

Discussion

Our study shows that accelerated fractionation of radiotherapy given to patients with HNSCC in resource-limited countries results in significantly better locoregional control at 5 years than does a conventional schedule. This conclusion is in agreement with several randomised studies and a large meta-analysis.[7–9] Our study also confirms the results from the DAHANCA 6&7 trial[7] and underlines the general benefit of accelerated fractionation in HNSCC.

Analysis of the failure pattern after treatment showed that almost all treatment failures were due to insufficient locoregional tumour control (data not shown). As a consequence, disease-specific survival was strongly related to insufficient locoregional control, and was therefore significantly better in patients receiving six factions per week than for those who received five fractions per week. However, there was no significant

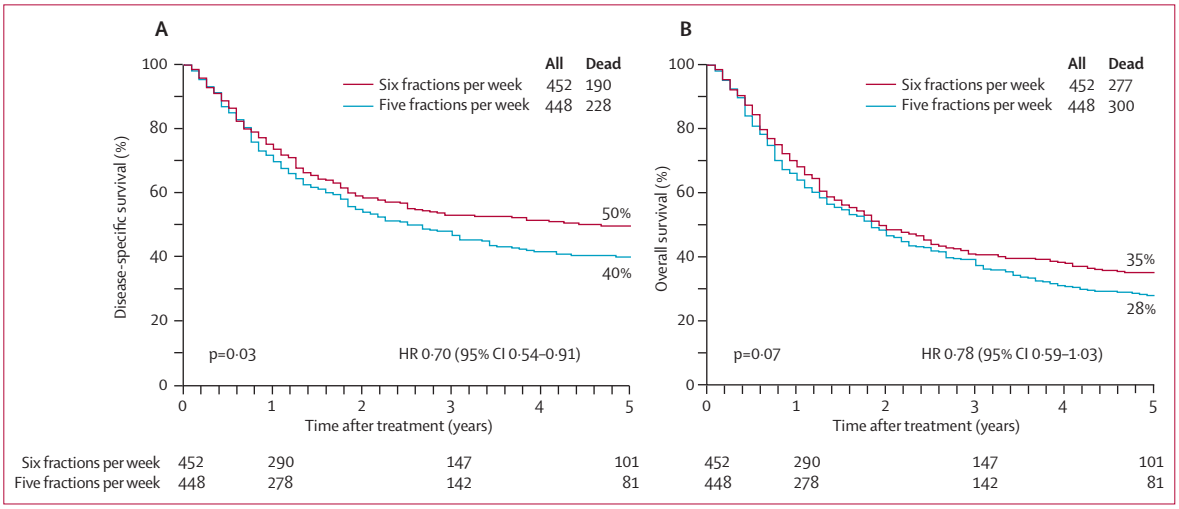

Figure 5: **Disease-specific survival (A) and overall survival (B)**

	Five fractions per week	Six fractions per week	Hazard ratio (95% CI)
Acute morbidity			
Severe skin reaction	50/439 (11%)	87/441 (20%)	1·91 (1·31–2·79)
Confluent mucositis	22/439 (5%)	45/441 (10%)	2·15 (1·27–3·35)
Tube feeding	198/439 (45%)	231/441 (52%)	1·34 (1·03–1·75)
Late morbidity			
Moderate fibrosis	107/366 (29%)	126/359 (35%)	1·31 (0·96–1·79)
Severe fibrosis	7/366 (2%)	4/359 (1%)	0·58 (0·17–1·99)
Moderate or severe laryngeal oedema	62/359 (17%)	53/356 (15%)	0·84 (0·56–1·25)
Moderate or severe xerostomia	175/365 (48%)	167/359 (44%)	0·94 (0·71–1·26)

Data are number of events/number of patients with data recorded (%), unless otherwise stated.

Table 2: **Acute and late radiation-related morbidity by fractionation schedule**

difference in overall survival at 5 years, probably due to comorbidity and death from other causes. Of note, the 5-year overall survival reported for the conventional group here is similar to that seen in an analysis of a large cohort of patients with HNSCC in India, which showed that conventional curative radiotherapy results in 5-year overall survival of around 30% in an unselected population from a developing country.[17]

Accelerated regimens have been shown to increase treatment-associated acute morbidity, which in severe cases might lead to an increase in late radiation effects. This was not seen in our study: the increase in confluent mucositis was transient, and no difference in late effects between the groups was noted. Similar observations have been made in other studies,[7,8] whereas trials in which the acceleration has been more aggressive have resulted in unacceptable late morbidity if the total dose was not reduced.[18,19] The six fractions per week schedule, resulting in a 1-week reduction in treatment time relative to conventional treatment, seems to give a good balance between improved tumour control and avoidance of excess late morbidity.

The fact that acceleration resulted in a better outcome might not necessarily indicate that all patients are likely to benefit from such treatment. The effect of acceleration on locoregional control was mainly related to a better response at the primary tumour site; there was no difference in the effect on the lymph nodes between treatment groups. This implies that patients with a large nodal burden are less likely to benefit from acceleration. Our study found no significant difference between the two treatment groups in patients with N2 and N3 nodes irrespective of the site of the primary tumour (HR 0·66, 95% CI 0·35–1·27), whereas patients with no or small nodal burden (N0–1) had significantly improved locoregional control when treated with six fractions per week (HR 0·60, 0·44–0·80; data not shown). To what extent a more aggressive surgical approach with elective neck dissections in N2 and N3 patients would improve the situation is unclear.

Based on previous experience,[7,20,21] we stratified patients according to histopathological differentiation, but we were unable to confirm previous findings of an association between well and moderate differentiation and the benefit of accelerated fractionation. This might be due to the fact that only a few patients had poorly differentiated tumours.

There is accumulating evidence that the aetiology of HNSCC is associated with HPV infection, especially in oropharyngeal tumours. Such tumours seem to respond more favourably to radiotherapy,[22] although it remains to be clarified whether they have the same radiobiological sensitivity as other tumours when it comes to the effect of altered fractionation, hypoxia, and the interaction of radiation with chemotherapy and targeted drugs. Although HPV-positive tumours might derive less benefit from hypoxic modification,[23] there are strong indications that the response to accelerated fractionation is unrelated to the aetiology.[24] This is also supported by the fact that although the frequency of HPV-related tumours is probably less in the developing part of the world than in

the more developed areas,[25] the results of our study are almost identical to those of studies done in western Europe and North America.[7,8]

Additional improvement is likely to come from increasing the total dose by applying hyperfractionated schedules, where an increased total dose, given with more and smaller fraction sizes, is possible at the same level of late morbidity. Several studies and a subsequent meta-analysis have strongly indicated that such treatment is both feasible and beneficial, and contrary to the present schedule it might improve outcome in both the primary tumour and nodal sites.[8,9,26] Unfortunately, such a schedule demands more resources, which makes it less attractive in developing countries. Alternatively, the radiotherapy could be combined with concurrent chemotherapy.[27,28] Both strategies increase morbidity and reduce compliance, which limits the effectiveness of the treatment schedules.[26,29,30] Less morbidity might be associated with the combined use of radiotherapy and epidermal growth factor receptor inhibitors,[31] but such an expensive treatment approach needs more validation before it can be considered in developing countries. Both altered fractionation and chemo-radiotherapy have been shown to be better than conventional treatment schedules, and meta-analyses indicate that they confer about the same level of benefit in terms of locoregional control and survival.[9,27,28] How to best apply this knowledge in a resource-limited environment should be elucidated by future trials, which should also take advantage of the improvement in radiotherapy technology and, by reducing the involved volume, try to minimise morbidity.

HNSCC are known to show hypoxic radioresistance.[32] However, this can be circumvented by the use of hypoxic modifiers such as nimorazole.[33] Although not all tumours need such hypoxic modification,[23,34] it is likely to improve the overall outcome of radiotherapy for HNSCC, particularly in HPV-negative tumours.[22] Hypoxic modification is therefore attractive in developing countries, since it is inexpensive and does not cause significant morbidity. Additionally, the effect of hypoxic modification does not seem to be related to overall treatment time,[32] and it might be useful to combine hypoxic modification with accelerated fractionation. The importance of such a strategy will be explored in a forthcoming randomised trial by the International Atomic Energy Agency.

In conclusion, reducing the overall treatment time by increasing the number of weekly fractions from five to six while maintaining the same overall radiation dose resulted in a significant increase in tumour control and disease-free survival in patients with HNSCC in resource-limited countries. The accelerated regimen was associated with an increased—but tolerable—acute morbidity relative to the conventional radiotherapy schedule, with no evidence of increased late radiation complications. The accelerated schedule is therefore more effective than conventional fractionation, and since it does not require additional resources it might be a suitable new international standard of treatment.

Contributors

JO and CG were responsible for the concept and design of the study. CG, JO, BKM, NB, RA, JPA, MK, and HT drafted the protocol. BKM, NB, RA JPA, MK, and SB provided study materials and patients. CG and JO collected the data. CG organised the trial infrastructure and quality assurance program. JO and CG analysed and interpreted the data and wrote the manuscript. All authors approved the final manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

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