Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis

Jean Bourhis, Jens Overgaard, Hélène Audry, Kian K Ang, Michele Saunders, Jacques Bernier, Jean-Claude Horiot, Aurélie Le Maître, Thomas F Pajak, Michael G Poulsen, Brian O'Sullivan, Werner Dobrowsky, Andrzej Hliniak, Krzysztof Skladowski, John H Hay, Luiz H J Pinto, Carlo Fallai, Karen K Fu, Richard Sylvester, Jean-Pierre Pignon, on behalf of the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group*

Lancet 2006; 368: 843–54

See **Comment** page 819

Published **Online** August 17, 2006
DOI:10.1016/S0140-6736(06)69121-6

Radiation Oncology Department (Prof J Bourhis MD) **and Biostatistics and Epidemiology Department** (H Audry MSc, A Lemaitre MSc, J-P Pignon MD), **Institut Gustave Roussy, Villejuif, France; Department of Experimental Clinical Oncology, Aarhus, Denmark** (Prof J Overgaard MD); **Radiation Oncology Department, MD Anderson Cancer Center, Houston, TX, USA** (Prof K K Ang MD); **Radiation Oncology, Mount Vernon Hospital, Northwood, UK** (Prof M Saunders MD); **Faculty of Medicine, University of Geneva, Switzerland** (J Bernier MD); **Centre F Leclerc, Dijon, France** (Prof J C Horiot MD); **RTOG Statistical Headquarters, Philadelphia, PA, USA** (T F Pajak PhD); **Southern Zone Radiation Oncology-Mater Centre, Brisbane, Queensland, Australia** (M G Poulsen MD); **Radiation Oncology Department, Princess Margaret Hospital, Toronto, Canada** (Prof B O'Sullivan MD); **Newcastle General Hospital, Newcastle, UK** (W Dobrowsky MD); **Center of Oncology Institute, Warsaw, Poland** (Prof A Hliniak MD); **Maria Curie Memorial Institute, Gliwice, Poland** (K Skladowski MD); **British Colombia Cancer Agency, Vancouver, BC, Canada** (J Hay MD); **Instituto Nacional de Cancer, Rio de Janeiro, Brazil** (L H Pinto MD); **Dipartimento di Radiotherapia, Istituto Nazionale Tumori, Milan, Italy** (C Fallai MD); **University of California, San Francisco, CA, USA** (K K Fu MD); **and EORTC Statistical Headquarters, Brussels, Belgium** (R Sylvester ScD)

*Dr Hliniak died in 2005

Correspondence to:
Dr J-P Pignon, Institut Gustave-Roussy; 39 rue Camille Desmoulins, 94805 Villejuif, France
jppignon@igr.fr

Summary

Background **Several trials have studied the role of unconventional fractionated radiotherapy in head and neck squamous cell carcinoma, but the effect of such treatment on survival is not clear. The aim of this meta-analysis was to assess whether this type of radiotherapy could improve survival.**

Methods **Randomised trials comparing conventional radiotherapy with hyperfractionated or accelerated radiotherapy, or both, in patients with non-metastatic HNSCC were identified and updated individual patient data were obtained. Overall survival was the main endpoint. Trials were grouped in three pre-specified categories: hyperfractionated, accelerated, and accelerated with total dose reduction.**

Findings **15 trials with 6515 patients were included. The median follow-up was 6 years. Tumours sites were mostly oropharynx and larynx; 5221 (74%) patients had stage III–IV disease (International Union Against Cancer, 1987). There was a significant survival benefit with altered fractionated radiotherapy, corresponding to an absolute benefit of 3·4% at 5 years (hazard ratio 0·92, 95% CI 0·86–0·97; p=0·003). The benefit was significantly higher with hyperfractionated radiotherapy (8% at 5 years) than with accelerated radiotherapy (2% with accelerated fractionation without total dose reduction and 1·7% with total dose reduction at 5 years, p=0·02). There was a benefit on locoregional control in favour of altered fractionation versus conventional radiotherapy (6·4% at 5 years; p<0·0001), which was particularly efficient in reducing local failure, whereas the benefit on nodal control was less pronounced. The benefit was significantly higher in the youngest patients (hazard ratio 0·78 [0·65–0·94] for under 50 year olds, 0·95 [0·83–1·09] for 51–60 year olds, 0·92 [0·81–1·06] for 61–70 year olds, and 1·08 [0·89–1·30] for over 70 year olds; test for trends p=0·007).**

Interpretation **Altered fractionated radiotherapy improves survival in patients with head and neck squamous cell carcinoma. Comparison of the different types of altered radiotherapy suggests that hyperfractionation has the greatest benefit.**

Introduction

Head and neck squamous cell carcinomas are frequent tumours, with more than 550 000 new cases of oral cavity, oropharynx, hypopharynx, and larynx cancer every year worldwide.[1] About 40% of patients have locally advanced disease at diagnosis. Surgery, radiation therapy, or both, have been used for decades to achieve locoregional control; the most commonly used schedule when radiotherapy is given alone is 2 Gy in a single fraction per day, 5 days a week, for 7 weeks. Despite these treatments, the prognosis of patients with head and neck squamous cell carcinomas with locally advanced disease remains poor, with 5-year survival rates of 30–35%.[2]

In the past decade, new radiotherapy regimens for the treatment of head and neck squamous cell carcinomas have been assessed. These regimens were designed to increase the dose-intensity by delivering a higher total dose in the same time,[3–6] the same total dose in 5–6 weeks instead of 7 weeks,[6–12] or a smaller total dose given in 3–4 weeks.[13–17] Reducing the total treatment time—ie, accelerating the treatment—should reduce the repopulation of tumour cells between sessions, resulting in improved locoregional control. In hyperfractionated regimens, two to three fractions are delivered each day, with a reduced dose per fraction equal to 1·1–1·2 Gy. The reduction of the dose per fraction might reduce the risk of late toxicity, despite an increased total dose. Acceleration and hyperfractionation can be combined, in particular for regimens in which overall treatment time is reduced.

In some randomised trials, altered fractionated radiotherapy has proved to be of benefit in locoregional control,[3–6,9,11,17] although no benefit in survival was generally detected. The use of altered fractionated radiotherapy is associated with some increase in toxicity, mostly due to mucositis,[6–9,17] and can add some practical constraints in radiotherapy departments[3–9,11–17]—eg, treatment two to three times a day or at a weekend—that need to be balanced by substantial benefit.

A meta-analysis of updated individual patient data is the most reliable way to assess whether altered fractionated radiotherapy could affect survival. This meta-analysis was undertaken by the MARCH (Meta-Analysis of Radiotherapy in Carcinomas of Head and neck) Collaborative Group. The main objective was to study the effect of altered fractionation in overall survival. A comparison between the effects of the three types of altered fractionated radiotherapy was also planned.

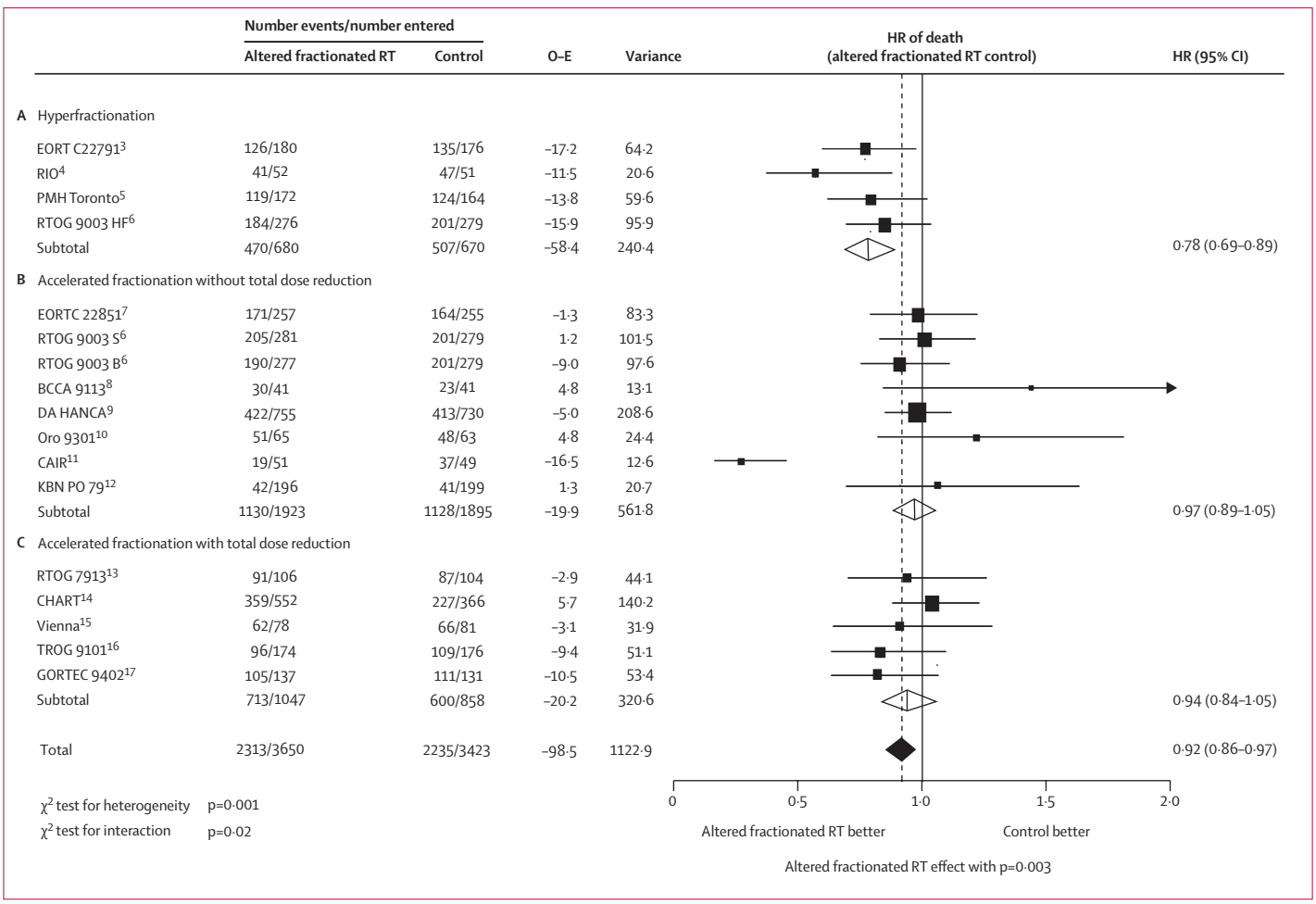


Figure 1: **Hazard ratio of death with altered fractionated radiotherapy versus conventional radiotherapy**
The centre of each square is the hazard ratio (HR) for individual trials and corresponding horizontal line is the 95% CI. The area of the square is proportional to the number of deaths in each trial. The broken line and centre of the black diamond is overall pooled HR and the horizontal tip of the diamond is the 95% CI. Open diamonds are the HR of different types of radiotherapy. BCCA=British Columbia Cancer Agency. CAIR=Continuous Accelerated Irradiation. CHART=Continuous Hyperfractionated Accelerated Radiation Therapy. DAHANCA=Danish Head and Neck Cancer Study Group. EORTC=European Organisation for Research and Treatment of Cancer. GORTEC=Groupe d'Oncologie Radiothérapie Tête et Cou. KBN=Komiet Badan Naukowych (Committee for Scientific Research). O–E=observed minus expected. PMH-Toronto=Princess Margaret Hospital, Toronto. RT=radiotherapy. RTOG=Radiation Therapy Oncology Group. TROG=Trans-Tansman Radiation Oncology Group.

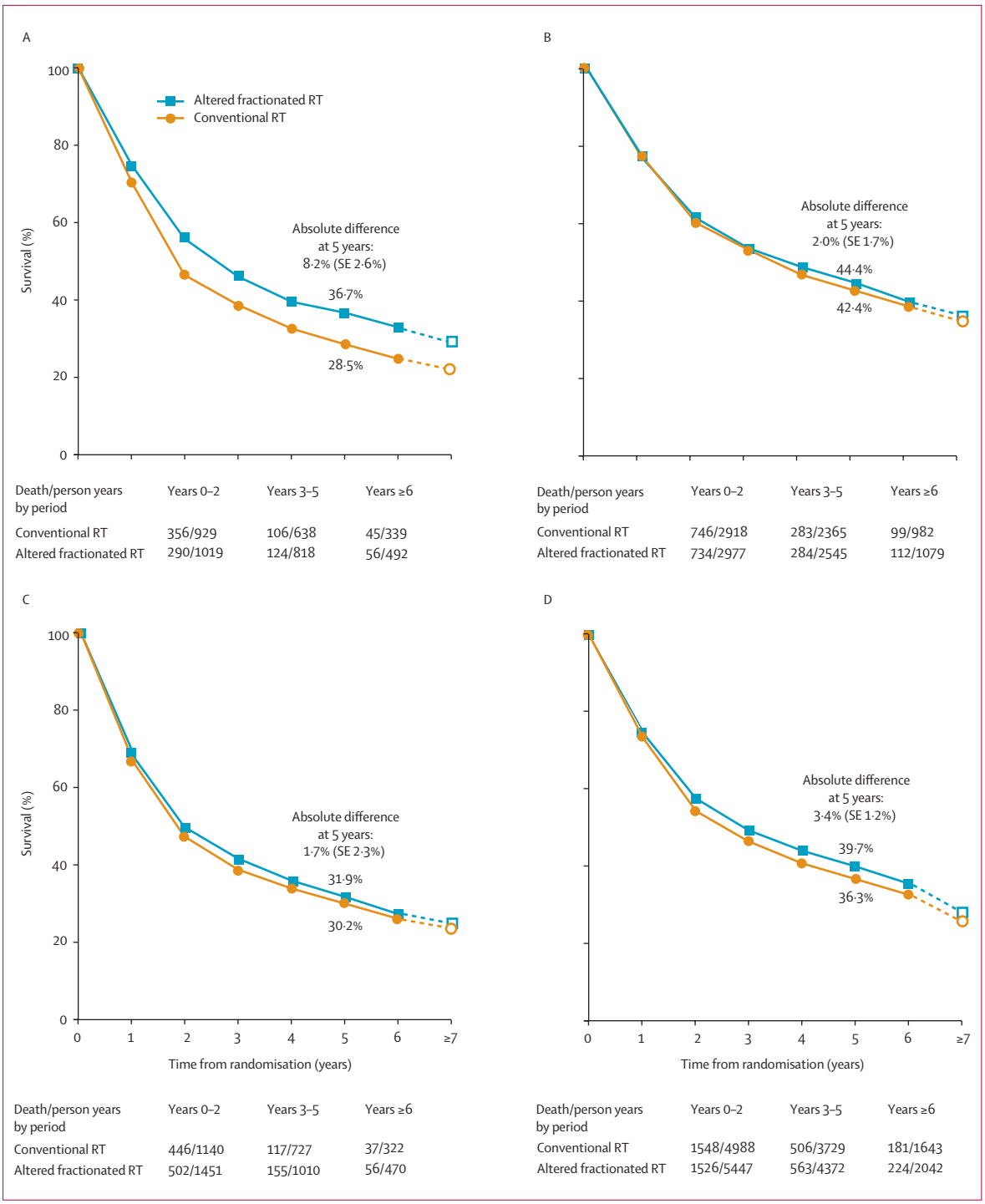
Methods

Selection of trials

The methods were specified in a protocol published in the Cochrane Library.[18] The collaborative group's steering committee prespecified three groups of trials with different modifications of fractionation that correspond to three distinct biological questions. The first group (hyperfractionation) examined the effect of a higher total dose in the same overall time than in the reference arm.[3–6] The second group (accelerated group) represented a pure test of the effect of accelerating radiotherapy, while keeping the total dose the same.[6–12] Finally, the third group (accelerated with reduced dose group) tested the effect of accelerating radiotherapy, but with reduced total dose.[13–17]

Trials that compared conventional radiotherapy with accelerated or hyperfractionated radiotherapy, or both, in previously untreated patients with non-metastatic head and neck squamous cell carcinomas were eligible. Trials that used doses per fraction higher than 2·5 Gy were not eligible. Radiotherapy had to be with curative intent. Conventional curative radiotherapy was defined as radiotherapy equivalent to 66–70 Gy, in 2 Gy fractions, for 5 days a week. Trials with post-operative radiotherapy were excluded because of their different total dose. Every trial had to be randomised in a way that ensured that investigators decided whether the patient was eligible without foreknowledge of the assigned treatment. Trials were eligible if recruitment began after 1969 and ended before 1999.

Published and unpublished trials were included. Searches of MEDLINE and Embase were supplemented by searches of meeting abstracts and of references in review articles. The Physician Data Query clinical trial registry was also searched. Keywords used were: head and neck, or otolaryngologic, or mouth or oral cavity, lip, hypopharynx, oropharynx, larynx neoplasm; phase III



Death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	356/929	106/638	45/339
Altered fractionated RT	290/1019	124/818	56/492

Death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	746/2918	283/2365	99/982
Altered fractionated RT	734/2977	284/2545	112/1079

Death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	446/1140	117/727	37/322
Altered fractionated RT	502/1451	155/1010	56/470

Death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	1548/4988	506/3729	181/1643
Altered fractionated RT	1526/5447	563/4372	224/2042

Figure 2: **Survival curves by treatment arm for all trials and for the three groups of trials according to the type of altered fractionated radiotherapy**
(A) Hyperfractionation. (B) Accelerated fractionation without total dose reduction. (C) Accelerated fractionation with total dose reduction. (D) All three groups together. The slopes of the broken lines from year 6 to year ≥7 are based on the overall death rates in the seventh and subsequent years. RT=radiotherapy.

or randomised trial; radiation or radiotherapy or chemoradiotherapy. Experts and trialists who took part in the meta-analysis were also asked to identify trials.

Data extraction

Both the Institute Gustave-Roussy and the European Organisation for Research and Treatment of Cancer (EORTC) meta-analysis unit did data extraction. The

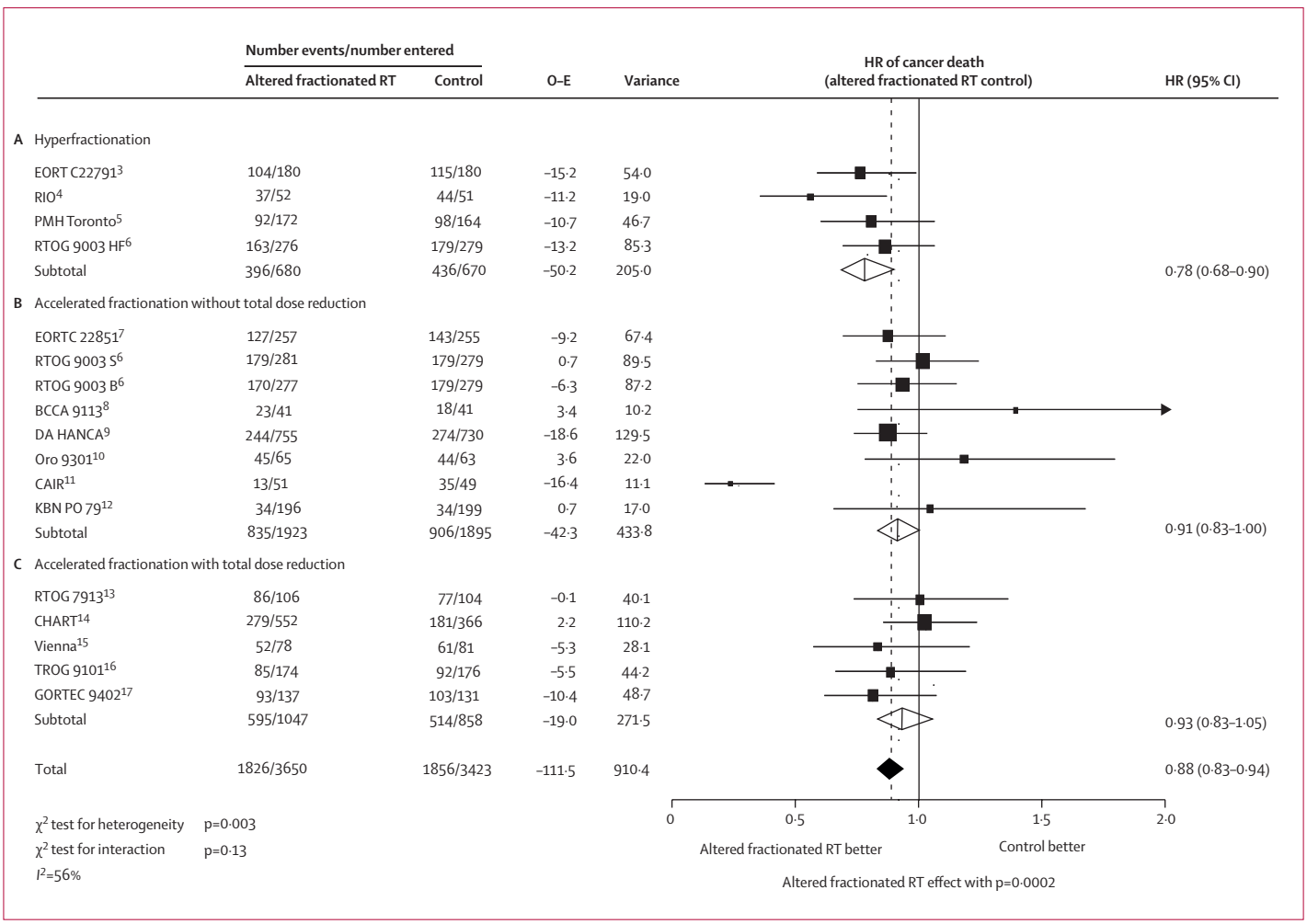


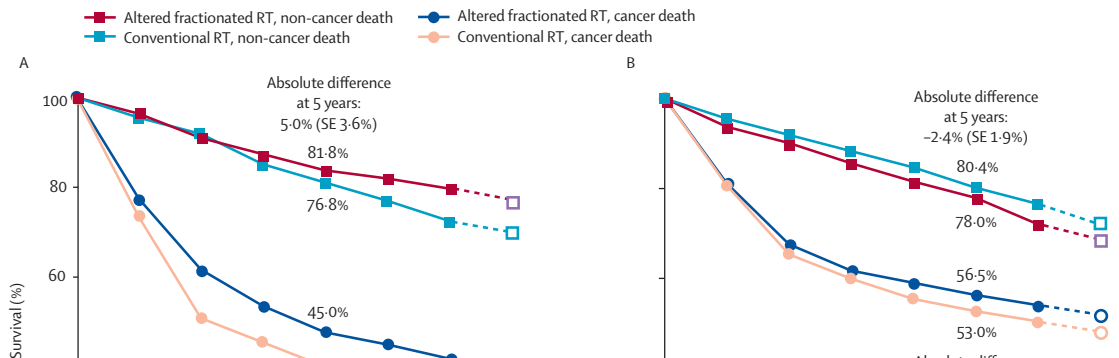
Figure 3: **Hazard ratio of head and neck cancer death with altered fractionated radiotherapy versus conventional radiotherapy**
The centre of each square is the hazard ratio (HR) for individual trials and corresponding horizontal line is the 95% CI. The area of the square is proportional to the number of events from each trial. The broken line and centre of the black diamond is overall pooled HR and the horizontal tip of the diamond is the 95% CI. Open diamonds are the HR of different types of radiotherapy. BCCA=British Columbia Cancer Agency. CAIR=Continuous Accelerated Irradiation. CHART=Continuous Hyperfractionated Accelerated Radiation Therapy. DAHANCA=Danish Head and Neck Cancer Study Group. EORTC=European Organisation for Research and Treatment of Cancer. GORTEC=Groupe d'Oncologie Radiothérapie Tête et Cou. KBN=Komiet Badan Naukowych (Committee for Scientific Research). O–E=observed minus expected. PMH-Toronto=Princess Margaret Hospital, Toronto. RT=radiotherapy. RTOG=Radiation Therapy Oncology Group. TROG=Trans-Tansman Radiation Oncology Group.

data requested for all patients were age, sex, tumour site, T and N classification, stage, histology, performance status, allocated treatment, and date of randomisation. The date and types of the first tumour failure, local, regional, or distant, and the date of second primary cancer were also recorded. Updated survival status and date of last follow-up were requested from the trialists. Data for patients excluded from the analysis after randomisation were obtained whenever possible. Data for morbidity and toxicity were not gathered because this information was not available in a common format. All data were checked for internal consistency and compared with the trial's protocol and published reports. Ranges and extremes were verified with trialists. Each trial was analysed individually and the survival analyses were sent to the trialists for validation.

Statistical analysis

Overall survival was the main endpoint, and was defined as the time from randomisation to the last follow-up or death, whatever the cause. The secondary endpoints were local or regional control rates, or both, distant control rates, and cause-specific mortality.

Median follow-up was computed by the reverse Kaplan-Meier method.[19] Survival analyses were stratified by trials, and the log-rank observed minus expected numbers of deaths (O–E) and their variances were used to calculate individual hazard ratios (HR) and overall HR with a fixed effect model. The weight of each trial in the pooled analysis was proportional to the variance of O–E, which is roughly equal to a quarter of the number of deaths.[20] To eliminate the potential bias of an incorrect determination of the cause of death after recurrence, the log-rank analysis of deaths from non-head and neck cancer



Non-cancer death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	28/659	31/484	12/261
Altered fractionated RT	35/787	25/652	14/400
Cancer death by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	328	75	33
Altered fractionated RT	255	99	42

Non-cancer death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	95/2279	83/1916	44/824
Altered fractionated RT	134/2479	104/2153	57/937
Cancer death by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	651	200	55
Altered fractionated RT	600	180	55

Non-cancer death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	36/779	36/596	14/296
Altered fractionated RT	49/1068	47/848	22/430
Cancer death by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	410	81	23
Altered fractionated RT	453	108	34

Non-cancer death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	159/3716	150/2995	70/1382
Altered fractionated RT	218/4333	176/3652	93/1765
Cancer death by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	1389	356	111
Altered fractionated RT	1308	387	131

Figure 4: **Non-cancer death and cancer death survival curves for all trials and for the three groups of trials according to the type of altered fractionated radiotherapy**

(A) Hyperfractionation. (B) Accelerated fractionation without total dose reduction. (C) Accelerated fractionation with total dose reduction. (D) All three groups together. The slopes of the broken lines from year 6 to year ≥7 are based on the overall death rates in the seventh and subsequent years. RT=radiotherapy.

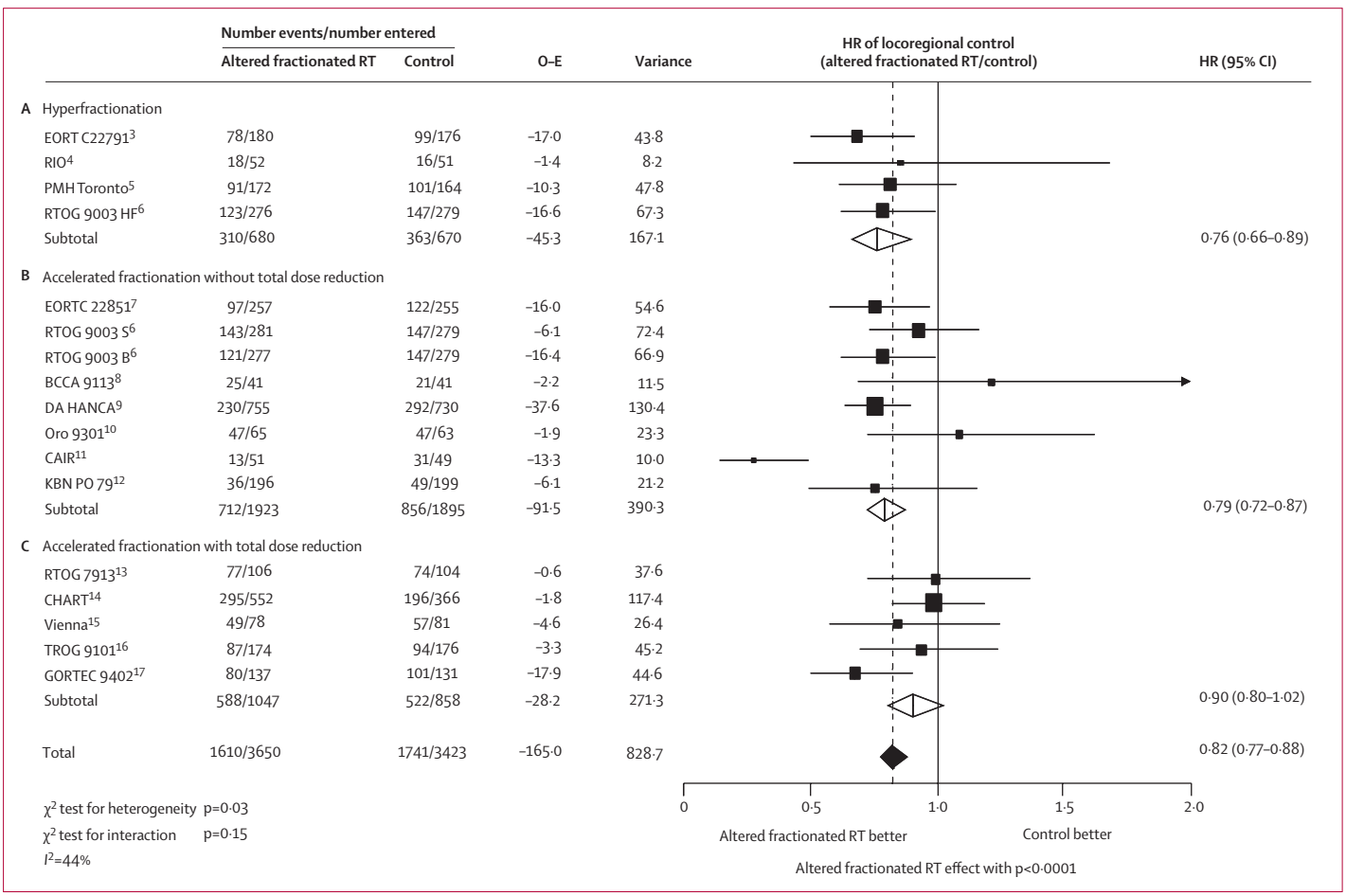


Figure 5: **Hazard ratio of locoregional control with altered fractionated radiotherapy versus conventional radiotherapy**
The centre of each square is the hazard ratio (HR) for individual trials and corresponding horizontal line is the 95% CI. The area of the square is proportional to the number of events from each trial. The broken line and centre of the black diamond is overall pooled HR and the horizontal tip of the diamond is the 95% CI. Open diamonds are the HR of different types of radiotherapy. BCCA=British Columbia Cancer Agency. CAIR=Continuous Accelerated Irradiation. CHART=Continuous Hyperfractionated Accelerated Radiation Therapy. DAHANCA=Danish Head and Neck Cancer Study Group. EORTC=European Organisation for Research and Treatment of Cancer. GORTEC=Groupe d'Oncologie Radiothérapie Tête et Cou. KBN=Komiet Badan Naukowych (Committee for Scientific Research). O–E=observed minus expected. PMH-Toronto=Princess Margaret Hospital, Toronto. RT=radiotherapy. RTOG=Radiation Therapy Oncology Group. TROG=Trans-Tasman Radiation Oncology Group.

covered only the period before recurrence (ie, data were censored at the first recurrence), as Peto and colleagues proposed.[21] An unbiased—although potentially diluted—log-rank analysis of head and neck cancer mortality was obtained indirectly by subtracting the log-rank statistic for non-head and neck cancer mortality from the log-rank statistic for mortality from all causes (ie, the two observed values are subtracted from each other, the two expected values are subtracted from each other, and the two variances are subtracted from each other). χ^2 tests were used to study heterogeneity between trials and between trial groups.[22] We used the I^2 statistic to estimate the proportion of variability of the results related to heterogeneity rather than to sampling error.[23] To study the interaction between treatment and covariates, an analysis stratified on trials was done for each covariate value, and the HR for the different values of the covariate were compared with a heterogeneity test. Stratified survival curves were computed for control and experimental groups with annual death rates and HR, and were then used to calculate absolute benefit at 2 years and 5 years.[24] All p values are two-sided.

See Online for webappendix

Role of the funding source

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

Results

Of 26 potentially eligible randomised trials, nine were excluded: three were post-operative trials, one had biased randomisations, two used unconventional radiotherapy in the reference group, and three used hypofractionated radiotherapy in the experimental group (webappendix). Data from one eligible trial (212 patients) were lost.[25] 15 trials fulfilled all the inclusion criteria and data were

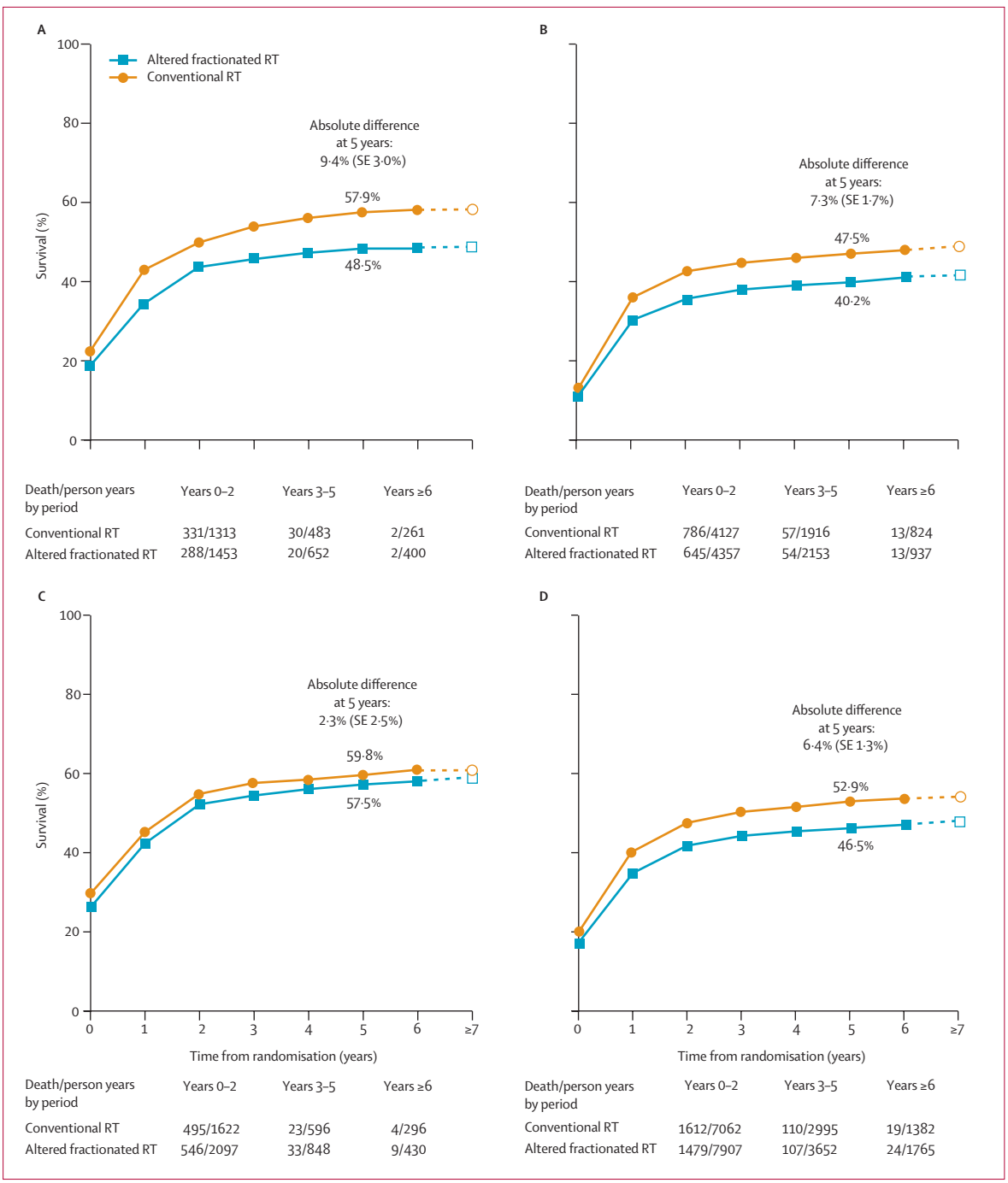


Figure 6: **Locoregional control curve by treatment arm according to the type of radiotherapy**
(A) Hyperfractionation. (B) Accelerated fractionation without total dose reduction. (C) Accelerated fractionation with total dose reduction. (D) All three groups together. The slopes of the broken lines from year 6 to year ≥7 are based on the overall death rates in the seventh and subsequent years. RT=radiotherapy.

available for 6515 patients.[3–17] The length of follow-up varied from 4 years to 10 years, with a median of 6 years. One trial, RTOG 9003,[6] was a four-arm trial, with a reference arm and three experimental arms. The reference arm of this trial was counted three times so that the three altered fraction modalities of the trial could be analysed separately. Overall, 17 comparisons were made for 7073 patients. We were able to gather data for 154 of the 163 randomised patients who had been excluded from the published analyses.

Trial and patient characteristics are presented in webtable 1, webtable 2, and webtable 3. There was a

See **Online** for webtables 1, 2, and 3

	Hyperfractionation	Accelerated fractionation without total dose reduction	Accelerated fractionation with total dose reduction	p*	Overall	p†
Locoregional control	0·76 (0·66–0·89)	0·79 (0·72–0·87)	0·90 (0·80–1·02)	0·15	0·82 (0·77–0·88)	<0·0001
Local control‡	0·75 (0·63–0·89)	0·74 (0·67–0·83)	0·83 (0·71–0·96)	0·50	0·77 (0·71–0·83)	<0·0001
Regional control‡	0·83 (0·66–1·03)	0·90 (0·77–1·04)	0·87 (0·72–1·06)	0·83	0·87 (0·79–0·97)	0·01
Metastatic control	1·09 (0·76–1·58)	0·93 (0·74–1·19)	0·95 (0·68–1·32)	0·77	0·97 (0·82–1·15)	0·75

*Comparison of the three hazard ratios for each type of radiotherapy. †Test of overall treatment effect. ‡Data from 14 trials; for three trials, only locoregional failure without specification if the failure was local, regional, or both, was available.

Table: **Hazard ratio (95% CI) of altered fractionated radiotherapy versus conventional radiotherapy on overall population and by type of radiotherapy for locoregional, local, regional, and metastatic control (n=7073)**

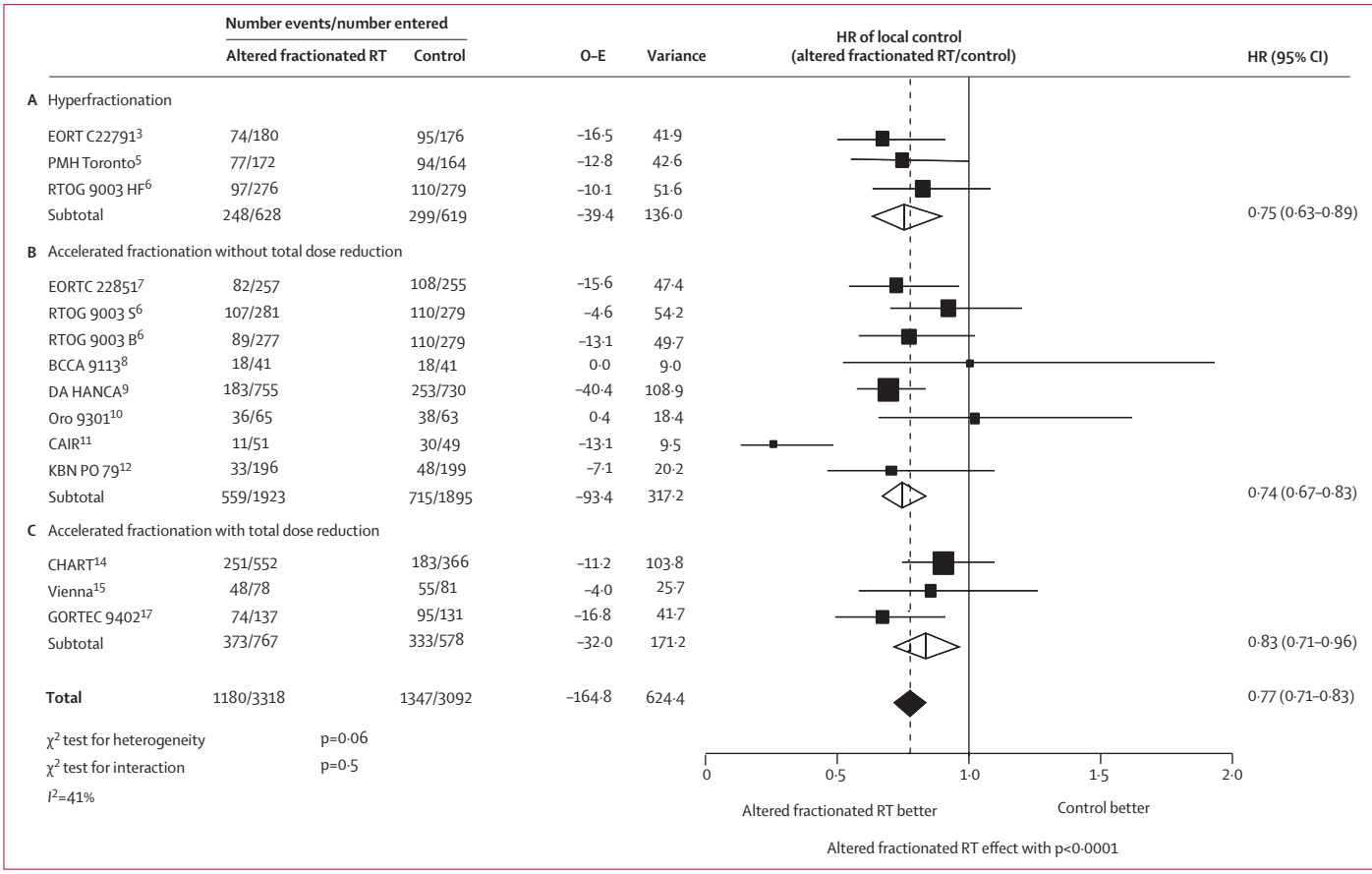


Figure 7: **Hazard ratio of local control with altered fractionated radiotherapy versus conventional radiotherapy**

The centre of each square is the hazard ratio (HR) for individual trials and corresponding horizontal line is the 95% CI. The area of the square is proportional to the number of events from each trial. The broken line and centre of the black diamond is overall pooled HR and the horizontal tip of the diamond is the 95% CI. Open diamonds are the HR of different types of radiotherapy. BCCA=British Columbia Cancer Agency. CAIR=Continuous Accelerated Irradiation. CHART=Continuous Hyperfractionated Accelerated Radiation Therapy. DAHANCA=Danish Head and Neck Cancer Study Group. EORTC=European Organisation for Research and Treatment of Cancer. GORTEC=Groupe d'Oncologie Radiothérapie Tête et Cou. KBN=Komiet Badan Naukowych (Committee for Scientific Research). O–E=observed minus expected. PMH-Toronto=Princess Margaret Hospital, Toronto. RT=radiotherapy. RTOG=Radiation Therapy Oncology Group. TROG=Trans-Tasman Radiation Oncology Group.

good balance between the trial arms for site, stage, sex, histology, age, and performance status. The main tumour sites were oropharynx (3079 patients, 44%) and larynx (2377, 34%); 1812 (26%) patients had stage I and II and 5221 (74%) had stage III–IV tumours (International Union Against Cancer, 1987).

There was a significant benefit for overall survival with altered fractionated radiotherapy compared with conventional radiotherapy (figure 1 and figure 2). This benefit corresponded to an 8% (95% CI 3–14) reduction in the risk of dying and an absolute benefit of 3·3% (0·9–5·7) and 3·4% (1·0–5·8) at 2 and 5 years, respectively. Heterogeneity was significant between trials (p=0·001; I^2=58%). Altered fractionated radiotherapy had no effect on death not related to cancer (HR 1·06, 95% CI 0·93–1·22), and the overall benefit was due to

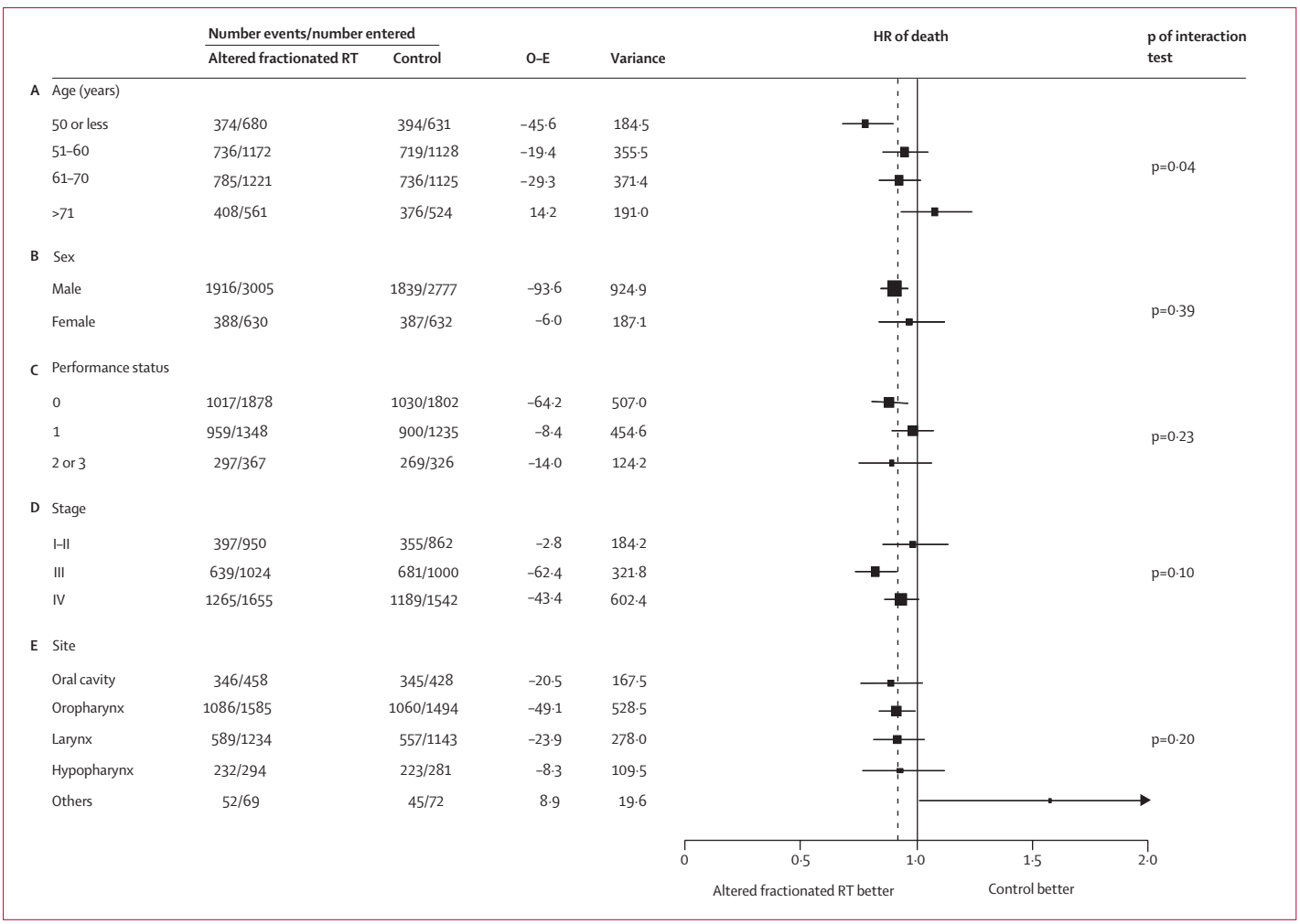


Figure 8: **Hazard ratio of death with altered fractionated radiotherapy versus conventional radiotherapy by age, sex, performance status, stage, and site of tumour**
Test for trend was significant for age (p=0·007). The centre of each square is the hazard ratio (HR) for variable categories and corresponding horizontal line is the 95% CI. The area of the square is proportional to the number of deaths in each trial. The broken line is the overall pooled HR. O–E=observed minus expected. RT=radiotherapy.

the effect on death related to cancer (figure 3 and figure 4). The magnitude of the survival benefit was significantly higher in the hyperfractionation group than in the two other groups (test for interaction, p=0·02; figure 1 and figure 2). This comparison should be interpreted with caution because the populations included in the three groups were dissimilar (webtable 4)—eg, more patients with early stage or larynx tumour were included in the group with accelerated fractionation and the same total dose.

Data about local and regional failures were available for only 14 of 17 trials (6410 patients; webtable 5). Local recurrence was the main cause of first failure (2527 patients [39%], isolated in 1544 patients [24%], and associated with only a regional neck lymph node failure in 909 [14%]), whereas regional failure was reported in 1407 (22%) patients (isolated in 419 [7%]). Finally, distant metastases were reported in 533 (8%) patients (isolated in 360 [5%]).

There was a significant benefit on locoregional control for altered fractionation compared with conventional radiotherapy (p<0·0001; figure 5 and figure 6). This benefit was seen in all three groups, but was slightly more pronounced in the two groups that did not decrease the total dose, compared with the reference arm (figure 5, figure 6, and table).

See Online for webtables 4 and 5

Altered fractionated radiotherapy was especially effective in the reduction of local failure in all three groups (figure 7), with a 23% reduction in the risk and an absolute benefit of 8·5% (5·7–11·3) at 5 years. The benefit of this treatment on regional control was also significant, with a 13% reduction in the risk and an absolute benefit of 1·9% (–0·7 to 4·5) at 5 years, although much less pronounced than for local control (table). No effect of altered fractionated radiotherapy could be detected on distant metastases. The fact that the hyperfractionation group and the group with accelerated fractionation without total dose reduction shared the same benefit for local control

(figure 7), but a different effect on survival (figure 1 and figure 2), could be attributable to an excess of non-cancer related deaths in the group with accelerated fractionation without total dose reduction (figure 4). At 5 years, for example, 2·4% more patients in the group with accelerated fractionation without total dose reduction had non-cancer related deaths.

We did several sensitivity analyses on overall survival, cancer mortality, and locoregional control endpoints. These analyses excluded stage I and II tumours, the CAIR trial[11] (a trial with outlier results), the ORO 9301[10] and RTOG 9003S[6] (trials that did not fit perfectly in the group with accelerated fractionation without total dose reduction), and counted only once the control group of the RTOG 9003 trial (data not shown). These analyses led to very similar overall results and often to a decrease of the heterogeneity and its disappearance for all analyses excluding the CAIR trial.

There was no significant interaction between sex, performance status, tumour stage, nodal stage, overall stage, tumour site, and the treatment effect on overall survival, but an interaction with age was recorded (figure 8). Indeed, a test for trend revealed a significant interaction between age and treatment effect for overall survival (p=0·007), and death related to cancer (p=0·008), local control (p=0·002), and locoregional control (p=0·002). A significant interaction was also noted between performance status and treatment effect, but only for tumour control (test for trends, p<0·0001 for locoregional control, p=0·0001 for local control, p=0·004 for regional control). The effect of altered fractionated radiotherapy on tumour control was higher in patients with good performance status. The effect of altered fractionated radiotherapy on tumour control did not differ significantly according to tumour stage and tumour site. Treatment effect on locoregional failure was better for N0 and N1 than for N2 or N3 nodal stage (test for trends p=0·02).

Discussion

This meta-analysis of individual patient data showed that different types of altered fractionated radiotherapy could improve the effectiveness of radiotherapy in head and neck squamous cell carcinomas, compared with conventional radiotherapy, with a small but significant benefit in survival and a more pronounced benefit in locoregional and local control. Our findings provide strong evidence that altered fractionated radiotherapy can improve survival in this disease. The survival benefit was mainly seen in the group with increased total dose (ie, hyperfractionated radiotherapy), and corresponded to an absolute benefit of 8% at 5 years in this group. This benefit is of the same size as the effect due to the use of chemotherapy concomitantly with radiotherapy in this type of cancer (ie, 8% at 5 years with the method used in a meta-analysis of chemotherapy[2,26] and 6·5% with the same method used here).

Prespecified analyses of the different types of altered radiotherapy suggested that the hyperfractionation group showed the greatest benefit (p=0·02). However, this difference was noted only for survival, whereas for locoregional control, a non-significant trend only was recorded in favour of hyperfractionation and of accelerated fractionation without total dose reduction. These findings suggest that substantial acceleration could only partly compensate for decreasing the total dose (figure 5, figure 6, and figure 7). Increasing the total dose in hyperfractionated radiotherapy could be an attractive option, since this is the only group in which a benefit was seen both on survival and local control. However, the benefit on locoregional control was much the same in the group of trials with moderate acceleration and in which the total dose was kept the same as in the reference arm.

We need to define which characteristics of the patients and tumours could be used to select the optimum altered fractionated radiotherapy for individual patients. The modest 3·4% survival benefit of altered fractionated radiotherapy at 5 years could be offset by an increased risk in late toxicities. Of the four trials reporting significant differences in late toxicity, two[7,8] showed an increased risk with accelerated fractionation without total dose reduction and two[14,16] showed a decreased risk with accelerated fractionation with total dose reduction.

The effect of altered fractionation was significantly more pronounced on the primary tumour than on nodal disease. The interpretation of this observation is not easy, since we studied only the first site of failure and simultaneous failures in the primary and nodes were frequent. Altered fractionated radiotherapy could be appropriate for patients with N0 and N1 disease, whereas combinations of chemotherapy and radiotherapy could be more appropriate for patients with more advanced nodal disease.

Altered fractionation had no effect on distant metastases (table). However, this result should be viewed with caution as the low observed rate of distant metastases could be related to poor recording, thus resulting in low power for this analysis. In the patients randomly assigned to the conventional radiotherapy group, the overall survival of the larynx subgroup was significantly better than that for the other sites (data not shown). However, the effect of altered fractionated radiotherapy was not different for the larynx compared with the other sites. A stratification of data on the larynx site did not change the results (data not shown). The strong suggestion of a decreasing effect of altered fractionated radiotherapy with increasing age and with poor performance status might be partly explained by an excess of non-cancer related deaths in patients aged 71 years and over[27] but also by lower compliance and tolerance in these patients and in patients with poor general health status.[28] However, tolerance was difficult to assess from our database, since recording and scoring acute and late radiation effects could vary between trials.

The decreasing effect of more intense treatment in older patients has also been reported in patients with head and neck squamous cell carcinomas treated with concomitant chemotherapy and radiotherapy.[2,29]

In conclusion, we have shown that altered fractionated radiotherapy was better than conventional radiotherapy for tumour control and survival. The effect was greater for the primary tumour than for nodal disease. The effect was also more pronounced in younger patients and in those with good performance status. Hyperfractionation seemed to yield a more consistent advantage for survival than accelerated radiotherapy. However, there was more diversity in accelerated fractionation regimens than in hyperfractionated regimens, and some of these regimens might be associated with higher non-cancer related death, offsetting its benefit in improving tumour control. Current trials will show whether the benefit of hyperfractionated radiotherapy versus standard radiotherapy persists when combined with concomitant chemotherapy. Strategies with intensity-modulated radiotherapy or chemotherapy or targeted therapy will have to be assessed.

Contributors

J Bourhis, J-P Pignon, L Duchateau, R Sylvester, and M Bolla, with the help of the member of the steering committee, contributed to the conception of the study. J-P Pignon, N Syz, H Audry, L Duchateau, and R Sylvester collected and checked the data with the help of the investigators who validated the re-analysis of their trials. J-P Pignon, H Audry, and A Le Maître did the statistical analysis. The manuscript was drafted by J Bourhis, J Overgard, K Ang, A Le Maître, and J-P Pignon and submitted for comments to the members of the secretariat and the steering committee. The investigators contributed to the interpretation of the results during the investigator meeting and revision of the manuscript. All authors have seen and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

MARCH collaborative group

Secretariat—H Audry, J Bourhis, M Bolla, L Duchateau, C Hill, A Le Maître, J-P Pignon, R Sylvester, N Syz.
Steering Committee—K K Ang, J Bernier, S Dische, F Eschwege, K K Fu, J-C Horiot, J Overgaard, M K B Parmar.
Investigators—K K Ang, H K Awwad, B Baerg, E Benhamou, J Bernier, J Bourhis, L Collette, B J Cummings, S Dische, W Dobrowsky, J W Denham, C Fallai, K K Fu, C Grau, H Sand Hansen, J H Hay, A Hliniak, J-C Horiot, S M Jacskon, E Kraszewska, M Lotayef, B Maciejewski, P Olmi, B O'Sullivan, J Overgaard, T F Pajak, M K B Parmar, M Pintilie, L H J Pinto, M G Poulsen, M Saunders, K Skladowski, N Tandon, V Torri, J Widder.

Acknowledgments

We thank the trialists who agreed to share and update their data and the following institutions for funding the investigators meeting or the meta-analysis project: Association pour la Recherche sur le Cancer (ARC number 5137), Institut Gustave-Roussy, Programme Hospitalier de Recherche Clinique (number IDF 98083), Ligue Nationale Contre le Cancer, Sanofi-Aventis (unrestricted grants), and US National Cancer Institute (grant 2U10CA11488-36). We thank Denise Avenell for secretarial assistance and Francine Courtial for electronic literature searches.

References

1 Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC Cancer Base number 5, version 2.0. Lyon, France: IARC Press, 2004.
2 Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. *Lancet* 2000; **355:** 949–55.
3 Horiot JC, LeFur R, N'Guyen T, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. *Radiother Oncol* 1992; **25:** 231–41.
4 Pinto LH, Canary PC, Araujo CM, Bacelar SC, Souhami L. Prospective randomized trial comparing hyperfractionated versus conventional radiotherapy in stage III and IV oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 1991; **21:** 557–62.
5 Cummings B, O'Sullivan B, Keane T, et al. 5-year results of 4 week/twice daily radiation schedule—the Toronto trial. *Radiother Oncol* 2000; **56** (suppl 1)**:** S8.
6 Fu KK, Pajak TF, Trotti A, et al. A radiation therapy oncology group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000; **48:** 7–16.
7 Horiot JC, Bontemps P, Van Den Bogaert W, et al. Accelerated fractionation compared to conventional fractionation improves locoregional control in the radiotherapy of advanced head and neck cancer: results of the EORTC 22851 randomized trial. *Radiother Oncol* 1997; **44:** 39–46.
8 Jackson SM, Weir LM, Hay JH, Tsang VH, Durham JS. A randomized trial of accelerated versus conventional radiotherapy in head and neck cancer. *Radiother Oncol* 1997; **43:** 39–46.
9 Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial. *Lancet* 2003; **362:** 933–40.
10 Olmi P, Crispino S, Fallai C, et al. Locoregionally advanced carcinoma of the oropharynx: conventional radiotherapy versus accelerated hyperfractionated radiotherapy versus concomitant radiotherapy and chemotherapy—a multicenter randomized trial. *Int J Radiat Oncol Biol Phys* 2003; **55:** 78–92.
11 Skladowski K, Maciejewski B, Golen M, Pilecki, B, Przeorek W, Tarnawski R. Randomized clinical trial on 7-days-continuous accelerated irradiation (CAIR) of head and neck cancer–report on 3-year tumor control and normal tissue toxicity. *Radiother Oncol* 2000; **55:** 101–10.
12 Hliniak A, Gwiazdowska B, Szutkowski Z, et al. A multicenter randomized/controlled trial of a conventional versus modestly accelerated radiotherapy in the laryngeal cancer: influence of a 1 week shortening overall time. *Radiother Oncol* 2002; **62:** 1–10.
13 Marcial VA, Pajak TF, Chang C, Tupchong L, Stetz J. Hyperfractionated photon radiation therapy in the treatment of advanced squamous cell carcinoma of the oral cavity, pharynx, larynx, and sinuses, using radiation therapy as the only planned modality: (preliminary report) by the Radiation Therapy Oncology Group (RTOG). *Int J Radiat Oncol Biol Phys* 1987; **13:** 41–47.
14 Dische S, Saunders M, Barrett A, Harvey A, Gibson D, Parmar M. A randomized multicentre trial of CHART vs conventional radiotherapy in head and neck cancer. *Radiother Oncol* 1997; **44:** 123–36.
15 Dobrowsky W, Naudé J. Continuous hyperfractionated accelerated radiotherapy with/without mitomycin C in head and neck cancer. *Radiother Oncol* 2000; **57:** 119–24.
16 Poulsen MG, Denham JW, Peters LJ, et al. A randomised trial of accelerated and conventional radiotherapy for stage III and IV squamous carcinoma of the head and neck: a Trans-Tasman Radiation Oncology Group Study. *Radiother Oncol* 2001; **60:** 113–22.
17 Bourhis J, Lapeyre M, Tortochaux J, et al. Phase III randomized trial of very accelerated radiation therapy compared with conventional radiation therapy in squamous cell head and neck cancer: a GORTEC trial. *J Clin Oncol* 2006; **24:** 2873–78.
18 Pignon JP, Sylvester R, Bourhis J. Hyperfractionated and/or accelerated radiotherapy for head and neck cancer (protocol). In: The Cochrane Library, issue 2. Oxford: Update Software, 2000.
19 Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17:** 343–46.
20 Yusuf S, Peto R, Lewis J, Collins R, Sleight T. Beta blockade during and after myocardial infarction: an overview of randomised clinical trials. *Prog Cardiovasc Dis* 1985; **27:** 335–71.
21 Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of randomized trials. *N Engl J Med* 1995; **333:** 1444–55.

22 Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. *BMJ* 1995; **311:** 899–909.

23 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21:** 1539–58.

24 Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31000 recurrences and 24000 death among 75000 women. *Lancet* 1992; **339:** 1–15.

25 Datta NR, Dutta Choudhry A, Gupta S, Bose AK. Twice a day versus once a day radiation therapy in head and neck cancer. *Int J Radiat Oncol Biol Phys* 1989; **17** (suppl 1)**:** 132–33.

26 Stewart LA, Parmar MK. Meta-analysis of the literature or meta-analysis of individual patient data: is there a difference? *Lancet* 1993; **341:** 418–22.

27 Bourhis J, Le Maître A, Pignon J, et al. Impact of age on treatment effect in locally advanced head and neck cancer (HNC): two individual patient data meta-analyses. *Proc Am Soc Clin Oncol* 2006; **24:** 280s.

28 Khalil AA, Bentzen SM, Bernier J, et al. Compliance to the prescribed dose and overall treatment time in five randomized clinical trials of altered fractionation in radiotherapy for head-and-neck carcinomas. *Int J Radiat Oncol Biol Phys* 2003; **55:** 568–75.

29 Bourhis J Armand C, Pignon JP, on behalf of the MACH-NC Collaborative Group. Update of MACH-NC (Meta-Analysis of Chemotherapy in Head & Neck Cancer) database focused on concomitant chemo-radiotherapy. *Proc Am Soc Clin Oncol* 2004; **22:** 488.