Role of radiotherapy fractionation in head and neck cancers (MARCH)

an updated meta-analysis

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Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis

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Declaration of interests

AA, BL, J-PP, and PB report grants from Ligue National Contre le Cancer and Institut National du Cancer during the conduct of the study. All other authors declare no competing interests.

See Online for appendix

For the **meta-analysis protocol** see https://www.gustaveroussy.fr/sites/default/files/march2-protocol.pdf

For the **CHARTWEL trial** see https://clinicaltrials.gov/ct2/show/NCT00021125?term=NCT00021125&rank=1

For the **EORTC 22962 trial** see http://www.eortc.be/protoc/details.asp?protocol=22962

For the **protocol for these future analyses** see https://www.gustaveroussy.fr/sites/default/files/march2-hpv-protocol.pdf

For the **ongoing network meta-analysis** see https://www.gustaveroussy.fr/sites/default/files/machnc-network-protocol.pdf

Contributors

PB, JB, and J-PP, with the help of the steering committee members (appendix p 1), designed and supervised the study. PB, JB, and J-PP obtained funding. PB, JB, J-PP, and BL searched and selected the trials. The steering committee members contributed to the identification and selection of the trials. PB, BL, and J-PP collected and checked the data with the help of the investigators who validated the reanalysis of their trials; wrote the draft, with revisions from the other investigators; and did the statistical analyses. All authors contributed to the interpretation of the results during the investigator meeting. All investigators listed in the appendix (p 1) received the manuscript for revision

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Summary

Background—The Meta-Analysis of Radiotherapy in squamous cell Carcinomas of Head and neck (MARCH) showed that altered fractionation radiotherapy is associated with improved overall and progression-free survival compared with conventional radiotherapy, with hyperfractionated radiotherapy showing the greatest benefit. This update aims to confirm and explain the superiority of hyperfractionated radiotherapy over other altered fractionation radiotherapy regimens and to assess the benefit of altered fractionation within the context of concomitant chemotherapy with the inclusion of new trials.

Methods—For this updated meta-analysis, we searched bibliography databases, trials registries, and meeting proceedings for published or unpublished randomised trials done between Jan 1, 2009, and July 15, 2015, comparing primary or postoperative conventional fractionation radiotherapy versus altered fractionation radiotherapy (comparison 1) or conventional fractionation radiotherapy plus concomitant chemotherapy versus altered fractionation radiotherapy alone (comparison 2). Eligible trials had to start randomisation on or after Jan 1, 1970, and completed accrual before Dec 31, 2010; had to have been randomised in a way that precluded prior knowledge of treatment assignment; and had to include patients with non-metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx undergoing first-line curative treatment. Trials including a non-conventional radiotherapy control group, investigating hypofractionated radiotherapy, or including mostly nasopharyngeal carcinomas were excluded.

Trials were grouped in three types of altered fractionation: hyperfractionated, moderately accelerated, and very accelerated. Individual patient data were collected and combined with a fixed-effects model based on the intention-to-treat principle. The primary endpoint was overall survival.

Findings—Comparison 1 (conventional fractionation radiotherapy *vs* altered fractionation radiotherapy) included 33 trials and 11 423 patients. Altered fractionation radiotherapy was associated with a significant benefit on overall survival (hazard ratio [HR] 0·94, 95% CI 0·90–0·98; p=0·0033), with an absolute difference at 5 years of 3·1% (95% CI 1·3–4·9) and at 10 years of 1·2% (−0·8 to 3·2). We found a significant interaction (p=0·051) between type of fractionation and treatment effect, the overall survival benefit being restricted to the hyperfractionated group (HR 0·83, 0·74–0·92), with absolute differences at 5 years of 8·1% (3·4 to 12·8) and at 10 years of 3·9% (−0·6 to 8·4). Comparison 2 (conventional fractionation radiotherapy plus concomitant chemotherapy versus altered fractionation radiotherapy alone) included five trials and 986 patients. Overall survival was significantly worse with altered fractionation radiotherapy compared with concomitant chemoradiotherapy (HR 1·22, 1·05–1·42; p=0·0098), with absolute differences at 5 years of −5·8% (−11·9 to 0·3) and at 10 years of −5·1% (−13·0 to 2·8).

Interpretation—This update confirms, with more patients and a longer follow-up than the first version of MARCH, that hyperfractionated radiotherapy is, along with concomitant chemoradiotherapy, a standard of care for the treatment of locally advanced head and neck squamous cell cancers. The comparison between hyperfractionated radiotherapy and concomitant chemoradiotherapy remains to be specifically tested.

Introduction

Modifications of radiotherapy fractionation have long been studied in various disease sites, including head and neck cancer. Altered fractionation radiotherapy is believed to be effective through two mechanisms that together improve the therapeutic ratio: the delivery of small fractions twice per day reduces the frequency of late toxicity, allowing for higher total doses of radiation to be delivered than can be achieved with conventional dosing; and the shortening of the overall treatment time limits tumour repopulation. Both strategies could improve tumour control. Many randomised trials have assessed these radiotherapy schedules and provided conflicting results regarding tumour control and survival, mostly because of trial heterogeneity and small sample sizes. However, these trials have confirmed that fractionation modifications were usually associated with more frequent acute side-effects but similar or less frequent late toxicity than conventional fractionation radiotherapy.[1–4]

For squamous cell carcinoma of the head and neck, the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH)[1] showed that altered fractionation radiotherapy is associated with improved overall survival and progression-free survival when compared with conventional fractionation radiotherapy. Trials were grouped according to the type of altered fractionation used: hyperfractionation, which used a higher total dose than the reference group, using twice daily fractions but with the same overall treatment time; moderate acceleration, in which the total dose was unchanged (±5%) but delivered more quickly (generally about 1 week faster) than in the reference group; and very accelerated radiotherapy with dose reduction, in which radiotherapy duration was shortened by 50% or

more and total dose reduced by about 15% (range 11–23) compared with the reference groups. The meta-analysis[1] noted a significant interaction between treatment effect and altered fractionation regimens, the survival benefit being restricted to the hyperfractionation subgroup. The reasons for the superiority of hyperfractionation over other types of altered fractionation remained unclear, and hyperfractionation has not become a standard of care, mostly due to logistical issues, such as the difficulty to find two slots per day on machines or patient management between fractions, which favoured the delivery of con comitant chemoradiotherapy over hyperfractionation.

Because several new trials have been published since the original publication of MARCH, we provide an update, aiming to confirm and explain the superiority of hyperfractionation over the other altered fractionation regimens, to assess the benefit of altered fractionation within the context of concomitant chemotherapy or postoperative trials, and to provide a direct comparison of altered fractionation with conventional fractionation concomitant chemoradiotherapy.

Methods

Search strategy and selection criteria

This updated meta-analysis was done according to a prespecified protocol. The method is similar to our previous publications.[1,5–7]

We searched PubMed, Web of Science, the Cochrane Controlled Trials meta-register, ClinicalTrials.gov, and meeting proceedings for randomised trials published or presented between Jan 1, 2009, and July 15, 2015 (appendix p 2). To be eligible, published and unpublished trials had to compare primary or postoperative conventional fractionation radiotherapy with altered fractionation radiotherapy (with or without the same concomitant chemotherapy in both groups; comparison 1) or conventional fractionation radiotherapy plus con comitant chemoradiotherapy versus altered fractionation radio therapy without concomitant chemo therapy (comparison 2). Eligible trials had to have been randomised in a way that precluded prior knowledge of treatment assignment, started randomisation on or after Jan 1, 1970, completed accrual before Dec 31, 2010, and included patients with non-metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx undergoing first-line curative treatment. Eligible trials were grouped in three types of altered fractionation: hyperfractionated, moderately accelerated, and very accelerated. We excluded trials including a non-conventional radiotherapy control group or including mostly nasopharyngeal carcinomas. We also excluded trials investigating hypofractionated radiotherapy, defined as doses per fraction higher than 2·5 Gy, due to its use mostly in palliative cases.

Data extraction and checking

Individual patient data were requested for each eligible trial by the meta-analysis team and for all randomly assigned patients. Data collected included patient and tumour characteristics, dates of randomisation, failures and death, treatment group allocated, details

about treatments received, and acute and late toxicities. Follow-up information was updated whenever possible.

All data were checked with a standard procedure,[6,8] which follows the recommendations of the Cochrane working group on meta-analysis using individual patient data. Internal consistency was checked (chronology of dates, outlier values, etc) and data were compared with the trial protocol and published reports. Randomisation validity was assessed by checking patterns of treatment allocation and balance of baseline characteristics between treatment groups. Follow-up of patients was also compared between treatment groups.[8] Every question raised by the checking procedure was discussed with the trialists. Each trial was reanalysed and the analyses were sent to the trialists for validation.

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation until death from any cause. Secondary endpoints were progression-free survival; local, regional, and loco-regional failures; distant failure; cancer and non-cancer mortality; and non-haematological toxicities. Progression-free survival was defined as the time from randomisation to first progression (locoregional or distant) or death from any cause. Living patients without events were censored at their date of last follow-up. Events considered were local failure alone for local failures; regional failure or concomitant regional and local failures without distant failure for regional failures; and distant failure, either alone or combined with local or regional failures, for distant failures. Only the first event was recorded, then patients with an additional event other than the one studied were censored at the time of that event. Patients without failure events were censored at their time of last follow-up. Non-cancer mortality was defined as deaths without previous progression and resulting from known causes other than the treated head and neck cancer. Cancer mortality included deaths from any cause with previous progression and deaths from the treated head and neck cancer. Deaths from unknown cause without previous progression were regarded as cancer mortality if they occurred within 5 years after randomisation, and as non-cancer mortality otherwise. Only trials with at least 80% of available data were deemed eligible for nonhaematological toxicity analysis. If at least 2000 patients were included in those trials, toxicity was analysed. Moreover, for late toxicities, patients with a follow-up shorter than 6 months were excluded. Secondary endpoints also included HPV status and smoking status, which were available for only five trials and are currently being analysed, and compliance, which was collected but has not been analysed yet. Those endpoints will be reported separately.

Statistical analysis

All analyses were done on an intention-to-treat basis. With 12 000 patients (and at least 7000 deaths), an absolute improvement in survival from 30% to 33% at 5 years could be detected with a power of 99·9% (two-sided log-rank test, α=5%). We estimated median follow-up with the reverse Kaplan-Meier method.[9] Analyses were stratified by trial. We calculated individual and overall pooled hazard ratios (HRs) with 95% CIs through a fixed-effects model using the log-rank expected number of events and variance.[10] A similar model was used to estimate odds ratios (ORs) for the comparison of toxicity between groups, and

incidences of toxicity in the experimental group were calculated using the incidence in the control group and the OR.[10,11] The $\chi 2$ heterogeneity test and $I2$ statistic were used to investigate the overall heterogeneity between trials.[12] In case of significant heterogeneity ($p<0{\cdot}10$), trials that had a 95% CI that did not overlap with the 95% CI of the global HR were excluded. If heterogeneity was still significant, we used a random-effects model.[6] Methods used to estimate cancer and non-cancer mortality and to draw stratified curves were similar to the ones used in the previous meta-analysis (appendix p 3).[1,13,14] Methods used to study survival within and after 5 years were similar to those used to study cancer and non-cancer mortality (appendix p 3). In addition to the fixed-effects model, a competing risk model was used for local, regional, and distant failure.[15] To estimate 5-year and 10-year absolute differences in all outcomes, actuarial survival rates were computed on all patients and the HR at the corresponding time period was used to compute survival in each group.[1,13,14] We also estimated restricted mean survival times, a new method to estimate absolute benefit.[16–18] Details about those methods are reported in the appendix (p 3).

We did subset analyses to study the interaction between treatment effect and trial level characteristics, using a test of heterogeneity among the different groups of trials. We computed residual heterogeneity within trial subgroups by subtracting the $\chi 2$ statistic of the heterogeneity test between groups from the $\chi 2$ statistic of the overall heterogeneity test.[19] Predefined subsets were the altered fractionation regimen (hyperfractionation, moderately accelerated radiotherapy, or very accelerated radiotherapy), the use of concomitant chemotherapy, and the performance of primary surgery. We estimated interaction between treatment effect and patient subgroups (according to age, sex, performance status, primary site, and overall stage) in a Cox model stratified by trial and containing treatment effect, covariate effect (eg, age), and treatment–covariate interaction (one-stage model method).[20] An unplanned subgroup analysis on regional failure was performed in patient with node-positive disease.

All p values were two-sided. Analyses were done using SAS, version 9.3.

Role of the funding source

The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The submission of the paper for publication was decided by the MARCH collaborative group. PB, BL, and J-PP had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have seen and approved the final version and, after consultation with the collaborators, agreed to submit for publication.

Results

We identified 26 new trials published between 1995 and 2016 that were not included in the original MARCH analysis. We did not collect data from four trials (n=185): three[21–23] because we could not contact the investigators and one[24] because the study was closed early with very short follow-up. Five other trials were excluded after blind review by the steering committee because of the absence of survival or randomisation dates,[25,26] issues with the

randomisation process,[27,28] or very short and different follow-up between groups,[29] leaving 17 new trials: 15 published[30–44] and two unpublished (CHARTWEL, EORTC 22962[45]). We also included two postoperative trials[46,47] that had previously been identified[1] but not included and excluded a third trial[48] because of unavailable data (appendix p 16). As such, 19 new trials were included (table 1). Updated data could be obtained for nine trials[2–4,49–54] of the 15 included in the first MARCH meta-analysis, increasing median follow-up from 6·1 years (IQR 4·4–8·0) to 10·4 years (5·7–15·2).[1]

Overall, 34 trials representing 11 969 patients were included in the meta-analysis. The control group of a four-arm trial[4] was triplicated (ie, data for patients in the control group were copied twice to have three control arms to compare with each experimental arm), a 2 × 2 trial (EORTC 22962[45]) included three relevant comparisons for the meta-analysis, and three three-arm trials[36,37,55] included two relevant comparisons. The 33 trials included in the analysis of fractionation schedules (comparison 1) were divided into four predefined subgroups, depending on the type of radiotherapy: hyperfractionation (eight comparisons, including the unpublished EORTC 22962 trial),[4,33,44,45,49,50,56] moderately accelerated radiotherapy (19 comparisons),[2,4,30,32,34–39,41,42,46,54,55,57–59] very accelerated radiotherapy (seven comparisons, including the unpublished CHARTWEL trial),[3,47,51–53,60] and moderately hypofractionated (dose per fraction between 2–2·5 Gy [two comparisons];[31,40] appendix pp 17–18). After discussion with the steering committee, the moderately hypofractionated trials were included in the moderately accelerated radiotherapy group. The analysis of altered fractionation radiotherapy versus conventional fractionation chemoradiotherapy (comparison 2) included five trials (four published[36,37,43,55] and EORTC 22962[45]). Patients' characteristics by trial are presented in the appendix (pp 4–5).

33 trials and 11 423 patients (36 comparisons, 11 981 patients) were included in comparison 1 (the analysis of fractionation schedules). Median follow-up was 7·9 years (IQR 5·3–12·1); it was less than 5 years for nine trials[32,37,42,44,47,57,59] (including the two unpublished trials; 1706 patients) and longer than 10 years for six trials[2,4,46,50,54,56] (3519 patients). Patients were mostly male and had an Eastern Cooperative Oncology Group performance status of 0 or 1 (appendix pp 6–7). Median age was 59 years (IQR 52–66). Tumours were mostly located in the oropharynx or larynx (9020 [75%] of 11 981 patients) and were stage III–IV for 8986 (75%) of 11 981 patients. Among 2922 stage I–II tumours, 2045 (70%) were laryngeal carcinomas. Patients' characteristics are presented in the appendix (pp 6–7).

The results of all endpoints for comparison 1 are summarised in table 2. 8014 deaths occurred across all groups (appendix p 8). Altered fractionation radiotherapy was associated with a significant overall survival benefit compared with conventional radiotherapy (HR 0·94, 95% CI 0·90–0·98; p=0·0033), with an absolute difference at 5 years of 3·1% (95% CI 1·3–4·9) and at 10 years of 1·2% (–0·8 to 3·2; table 2, figures 1, 2A). Heterogeneity between trials was not significant (p=0·14, I^2=20%). Interaction between the three altered fractionation regimens and the effect on overall survival was significant (p=0·051), the survival benefit being restricted to the hyperfractionated regimen (HR 0·83, 95% CI 0·74–0·92), with absolute differences at 5 years of 8·1% (95% CI 3·4 to 12·8) and at 10 years of 3·9% (–0·6 to 8·4; table 2, figures 1, 2B). The moderately accelerated and very accelerated

radiotherapy regimens did not have a significant effect on overall survival compared with conventional radiotherapy (table 2, figure 1, 2C, 2D).

For the secondary endpoint of progression-free survival, 8758 of 11 981 patients in 33 trials had a disease progression or died (table 2, appendix p 9). Compared with conventional radiotherapy, altered fractionation radiotherapy had a significant benefit on progression-free survival (table 2; figures 3, 4). Interaction between altered fractionation regimens and the effect on progression-free survival was not significant (p=0·17). Heterogeneity between trials was significant (p=0·045, $I2$=30%). The exclusion of the outlying CAIR trial[58] removed heterogeneity (p=0·55, $I2$=0%), without modifying the overall HR and the interaction between altered fractionation regimens (table 2).

In the 11 981 patients included in comparison 1, there were 5789 cancer-related deaths, 2225 non-cancer-related deaths, 2189 local failure events, 1729 regional failure events, and 1326 distant failure events (table 2; appendix p 9). Altered fractionation radiotherapy was associated with significantly reduced cancer mortality, local failure, and regional failure (table 2). No significant differences were reported between conventional radiotherapy and altered fractionation radiotherapy in terms of non-cancer mortality or distant failure (table 2). Although no interaction was reported between altered fractionation regimens and the effect on local or regional control, hyperfractionation was associated with a reduction in local and regional failures (table 2). Moderately accelerated radiotherapy was only associated with a reduction in local failures (table 2), and very accelerated radiotherapy had no effect on any of these endpoints (table 2; appendix pp 19–27). Similar results were noted with competing risk methods for local, regional, and distant failures (data not shown).

Planned subset analyses showed no significant interaction between the effect on overall survival and the period of accrual (ie, included in the first round of MARCH *vs* in the present update [p=0·94]; postoperative *vs* definitive radiotherapy [p=0·45]; and trials including only larynx carcinomas *vs* the others [p=0·70]; appendix p 10). For the subset analysis regarding chemotherapy, five trials included the same concurrent chemotherapy in both treatment groups. The altered fractionation radiotherapy was hyperfractionation for one trial that was terminated early (EORTC 22962)[45] and moderately accelerated radiotherapy for the four others.[30,36,39,42] None used adjuvant chemotherapy and only one used induction.[42] The effect of altered fractionation radiotherapy did not differ between trials with and without chemotherapy in both groups (p=0·39; appendix p 10). Similar results were found for progression-free survival (appendix p 10). After the exclusion of the nine comparisons with unusual radiotherapy regimens (hypofractionated radiotherapy,[31,40] split course,[4,30,55,57] or both hyperfractionated and moderately accelerated radiotherapy)[44] or confounded chemotherapy schedules (ie, different chemotherapy regimens between groups),[36,39] no significant interaction was found between type of fractionation and overall survival (p=0·11; appendix pp 28–29).

Planned subgroup analyses showed no significant interaction between treatment effect on progression-free survival and age (p=0·052). We found a reduction in treatment effect when age increased for progression-free survival (p=0·016) and when follow-up was censored at year 5 for those alive 5 years after randomisation for overall survival (p=0·026). We found

no interaction between treatment effect on overall survival or progression-free survival and patient performance status, sex, site of primary tumour, and tumour stage (appendix pp 11–13). In the subset of hyperfractionation trials, we found no interaction with the five studied covariates (data not shown).

The effect of altered fractionation radiotherapy on regional control according to nodal status was studied as an unplanned post-hoc analysis. In the 5592 node-positive patients, we found a significant improvement in regional control with altered fractionation radiotherapy compared with conventional fractionation radiotherapy (HR 0·88, 95% CI 0·79–0·98; p=0·017; appendix p 30). This effect was not significantly different (p=0·060) according to the type of altered radiotherapy, but it was significant for hyperfractionated radiotherapy.

An unplanned analysis including all 33 trials and all patients (n=11981) was done to assess the evolution of the effect of altered fractionation radiotherapy over time (appendix pp 31–32). The HR for death was 0·92 (95% CI 0·87–0·96) in the first 5 years after randomisation, and 1·04 (0·93–1·15) beyond 5 years, with a significant interaction between time and effect of altered fractionation radiotherapy (p=0·034; appendix p 31). Results were similar for progression-free survival, but the interaction between time and effect of altered fractionation radiotherapy was not significant (p=0·071; appendix p 32). The increase in restricted mean survival time in favour of altered fractionation radio therapy compared with conventional fractionation radiotherapy at 5-year versus 10-year horizons was 1·5 months (95% CI 0·5–2·5) versus 3·3 months (1·3–5·4) for overall survival, and 2·7 months (1·5–3·9) versus 4·9 months (2·7–7·1) for progression-free survival. When only hyperfractionated trials were analysed, these increases were 3·9 months (95% CI 1·9–5·9) versus 7·1 months (2·9–11·3) for overall survival, and 4·6 months (2·4–6·8) versus 8·2 months (3·8–12·5) for progression-free survival.

The toxicity analysis showed a significantly increased prevalence of acute mucositis (OR 2·02, 95% CI 1·81–2·26) and need for a feeding tube during treatment (1·75, 1·49–2·05) for patients treated with altered fractionation radiotherapy compared with those given conventional radiotherapy (table 3). Acute dermatitis was significantly increased in patients treated with altered fractionation radiotherapy only in the sensitivity analysis without trials responsible for the statistical heterogeneity (table 3). None of the late toxicities with sufficient available data showed an increased prevalence with the use of altered fractionation radiotherapy (table 3).

Five trials and 986 patients[36,37,43,45,55] were included in comparison 2 (conventional fractionation radiotherapy plus concomitant chemotherapy *vs* altered fractionation radiotherapy alone; table 1). Median follow-up was 5·4 years (IQR 4·7–8·2), was less than 5 years for two trials[37,45] (n=161), and longer than 10 years for one trial[43] (n=136). One trial,[36] which compared chemoradiotherapy with very accelerated radiotherapy, accounted for 560 (57%) of 986 patients and 403 (59%) of 684 deaths in this comparison. Stage III tumours were found in 216 (22%) of 986 patients' and stage IV tumours were found in 755 (77%) of 986 patients. Most tumours were located in the oropharynx (appendix pp 14–15). Altered fractionation radiotherapy was associated with a significant decrease in overall survival compared with concomitant chemo radiotherapy (HR 1·22, 95% CI 1·05–1·42;

p=0·0098; figure 5), with absolute differences at 5 years of –5·8% (95% CI –11·9 to 0·3) and at 10 years of –5·1% (–13·0 to 2·8; appendix p 33). We found no significant heterogeneity between trials (figure 5). Progression-free survival was shorter with altered fractionation radiotherapy than with concomitant chemoradiotherapy (appendix pp 34–35). A decrease in locoregional control was seen with altered fractionation radiotherapy versus concomitant chemoradiotherapy but no difference was seen for distant control (appendix pp 36–39). No specific analysis was done for local or regional control because of the low number of patients in this comparison. Toxicities were not analysed for this comparison because of insufficient data.

Discussion

This updated individual patient data meta-analysis confirmed, with nearly twice as many patients and a longer follow-up than in the first round of the MARCH meta-analysis,[1] that altered fractionation radiotherapy was associated with a small but significant improvement in overall survival when compared with standard fractionation radiotherapy. However, this improvement in overall survival was slight in the overall population (3·1% at 5 years) and was only significant in the hyperfractionated radiotherapy group. There was a significant interaction between the effect on overall survival and altered fractionation regimens, and the absolute difference at 5 years was 8·1% for the hyperfractionation group. The survival benefit decreased when age increased when follow-up was censored at 5 years, but was otherwise consistent in all patient subgroups. There was a clear benefit on local control, a smaller benefit on regional (nodal) control and cancer mortality, and no benefit on distant metastases and non-cancer-related mortality. Altered fractionation radiotherapy was associated with increased acute mucositis and need for feeding tube placement but we found no significant difference in late toxicity between conventional and altered fractionated radiotherapy. The new meta-analysis of trials investigating the direct comparison between altered fractionation radiotherapy and concomitant chemo radiotherapy showed the superiority of concomitant chemoradiotherapy regarding overall survival, progression-free survival, and locoregional control.

The strengths of this meta-analysis are its size and the use of individual patient data, which allowed detailed checking of each trial that was subsequently reanalysed and validated by the trialists. Unpublished trials were also included to avoid publication bias because positive trials are known to be published more frequently than negative trials, especially in the English language medical literature.[61,62] We found no significant overlap between our definitions of fractionation, meaning that a trial could be included in only one type of fractionation group. The steering committee was consulted if a discussion about the fractionation category was necessary. The intention-to-treat principle was respected for all analyses. The reproducibility of the findings regarding overall survival and progression-free survival between the first round of the meta-analysis[1] and the new trials included in this update—as shown by the absence of interaction between meta-analysis round and treatment effect—is an indicator of the robustness of the findings. At the time of this update, seven trials representing 3655 patients had a follow-up of longer than 10 years,[2,4,43,46,50,54,56] which enabled long-term analyses to be done. The large number of patients allowed secondary endpoints to be assessed and subgroup and subset analyses to be done with

adequate power. Finally, the collection of toxicity data allowed the analysis of the pattern of adverse events associated with altered fractionation radiotherapy.

This second round of the meta-analysis provided a hypothetical explanation for the superiority of hyperfractionation over the other altered fractionation regimens. Hyperfractionation was associated with a benefit both in local and regional control whereas accelerated regimens only provided an improvement in local control. When the analysis was restricted to node-positive patients, the interaction between altered fractionated regimens and regional control was not significant, but the effect of altered fractionated radiotherapy was significant only for hyperfractionated radiotherapy. The explanation for this difference on nodal control favouring hyperfractionation is unclear, but might be related to the increase in absolute dose provided by hyperfractionation. Pure acceleration (the delivery of 66–70 Gy in 5·5–6 weeks) should therefore be considered only for patients with a low nodal burden.

This meta-analysis has several limitations. First, almost all of the trials included used outdated radiotherapy techniques (two-dimensional or three-dimensional radiotherapy), which is a concern because intensity-modulated radiotherapy is the present standard of care for head and neck cancers. However, the dose-intensity– efficacy association shown in this meta-analysis certainly remains valid, even in the intensity-modulated radiotherapy era because dose to gross tumour has not changed and is around 2 Gy per fraction. Hyper fractionation or acceleration can be done with intensity-modulated radiotherapy in the same way as they were done with two-dimensional radiotherapy and no reason exists to expect a different efficacy profile. The included trials also come before the human papillomavirus (HPV) era and often did not record smoking status, with data for these variables available in very few trials in the meta-analysis. Because positivity for HPV is a major prognostic factor in oropharyngeal carcinoma,[39] extensive analyses will be done in trials that provided data about HPV and smoking status in the search for prognostic and predictive markers of fractionation modification efficacy.

The trials' accrual period ranged from 1979 to 2010 and this long time span might add heterogeneity to the meta-analysis, although no interaction between meta-analysis round and overall survival or progression-free survival was recorded. A further limitation concerns the quality of data collected for the toxicity analysis. Although this analysis was planned, it was based on a limited subset of trials for which these data were available, and was not feasible for comparison 2 because of insufficient data. Third, only five trials compared altered fractionation radiotherapy with standard radiotherapy plus chemotherapy in both groups, and three trials have a lower dose of chemotherapy in the group with altered fractionation radiotherapy than in the standard radiotherapy group.[30,36,39] Last, the important number of endpoints analysed raises the question of multiplicity of testing and the inflation of type I error. Overall survival was the primary endpoint of the meta-analysis. Regarding secondary endpoints, most analyses presented in this Article were prespecified. Subset (by trial characteristics) or subgroup (by patient characteristics) analyses are regarded as a lower level of evidence than the analyses on overall population. They are mostly explanatory or hypothesis generating. The readers should pay careful attention to the consistency between the results obtained across the different endpoints, which reinforces the confidence in the analysis.

The direct comparison between altered fractionation radiotherapy and concomitant chemoradiotherapy showed the superiority of the addition of concomitant chemotherapy over pure fractionation modification. This comparison provides an additional contribution to the bulk of randomised data, having shown the superiority of chemoradiotherapy over radiotherapy alone.[5] This finding is also in agreement with the preliminary results of an ongoing network meta-analysis[63] in which altered fractionation radiotherapy ranked lower than platinum-based concomitant chemoradiotherapy for overall and progression-free survival. Concomitant chemo radiotherapy should remain the standard of care for locally advanced node-positive tumours. Notably, however, the altered fractionation regimens used in this direct comparison were hyperfractionation for one trial,[45] moderately accelerated radiotherapy for three trials,[37,43,55] and very accelerated radiotherapy for one trial (which accounts for most of the data).[36] Because hyperfractionation seemed superior to the other altered fractionation regimens in comparison 1, the comparison between concomitant chemoradiotherapy and hyperfractionation is relevant. This comparison cannot be made in this meta-analysis because of the low number of patients available for comparison 2. The comparison between concomitant chemoradiotherapy and hyperfractionation remains to be done and there is currently no suggestion that one treatment would perform better than the other because the difference in overall survival at 5 years in favour of hyperfractionation in this meta-analysis was 8·1% and very close to the overall survival results reported in the last update of the MACH-NC meta-analysis[5] for concomitant chemotherapy plus radiotherapy (6·5%). The ongoing network meta-analysis will try to answer that question.

Ongoing research efforts using the MARCH database also include extensive analysis of trials that provided information about the pathology findings for patients who have undergone primary surgery followed by postoperative radiotherapy. The findings might provide new insights into the radiotherapy dose fractionation issue in the postoperative setting, which remains a controversial area. Other areas of improvement should include cost-effectiveness analyses comparing concomitant chemoradiotherapy and hyperfractionation radiotherapy without concomitant chemotherapy, health services research to address patients' and physicians' difficulties in the implementation of hyperfractionation radiotherapy, and improved documentation of long-term toxicity and patient reported outcomes.

In conclusion, this updated individual patient data meta-analysis confirms the efficacy of altered fractionation radiotherapy over conventional fractionation radiotherapy and the superiority of hyperfractionated radiotherapy over the other altered fractionation radiotherapy schedules. The effect of a moderate acceleration is limited to local control, whereas hyperfractionation seems to improve both local and regional control, and might therefore be preferred for patients with node-positive tumours. The direct comparison between altered fractionation radiotherapy and concomitant chemoradiotherapy suggests the superiority of concomitant chemoradiotherapy. Further research is still needed to compare efficacy of hyperfractionated radiotherapy and con comitant chemoradiotherapy, and to look for predictive markers of treatment efficacy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in context

Evidence before this study

The Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) based on 15 trials and 6515 patients showed that altered fractionation radiotherapy is associated with improved overall survival and progression-free survival when compared with conventional fractionation radiotherapy. For this update, we searched PubMed, Web of Science, Cochrane Controlled Trials meta-register, ClinicalTrials.gov, and meeting proceedings, without language restriction, for published and unpublished “randomized trials” of “radiotherapy fractionation” in “head and neck cancer” published or presented between Jan 1, 2009, and July 15, 2015. Randomised trials comparing conventional fractionation radiotherapy with altered fractionation radiotherapy (with or without the same concomitant chemotherapy in both groups), or conventional fractionation radiotherapy plus concomitant chemotherapy versus altered fractionation radiotherapy alone, in patients with non-metastatic squamous cell carcinoma were eligible as long as they had started randomisation on or after Jan 1, 1970, and completed accrual before Dec 31, 2010. For the trials previously included in the first round of MARCH, a follow-up update was requested.

Added value of this study

Individual patient data meta-analyses of randomised trials provide the highest level of evidence. This update of the MARCH meta-analysis almost doubled the number of patients and trials included, reaching 34 trials and 11 969 patients. The median follow-up was increased, and is now 7·9 years overall (IQR 5·3–12·1) and 10·4 years (5·7–15·2) for the 15 trials previously included in the MARCH meta-analysis. Data on acute and late toxicity were collected. Finally, a separate meta-analysis was done that compared altered fractionation radiotherapy and concomitant chemoradiotherapy. Altered fractionation radiotherapy was associated with a significant overall survival benefit compared with conventional fractionation. However, the overall survival benefit was restricted to the hyperfractionated group due to a significant interaction between type of fractionation and treatment effect. Progression-free survival was improved by altered fractionation radiotherapy, without a significant difference between type of fractionation, through an improvement in local and regional control. Acute mucositis and the need for a feeding tube during treatment were increased in the altered fractionation group but late toxicities were similar between the groups. Altered fractionation radiotherapy had significantly lower overall survival compared with conventional radiotherapy plus concomitant chemotherapy although the altered fractionation regimens of trials in this comparison were mainly accelerated radiotherapy, which has not been shown to increase survival compared with conventional fractionation.

Implications of all the available evidence

This updated meta-analysis confirms the efficacy of altered fractionation radiotherapy over conventional fractionation radiotherapy and the superiority of hyperfractionated radiotherapy over the other altered fractionation radiotherapy schedules. The effect of accelerated radiotherapy is limited to local control, whereas hyperfractionated

radiotherapy seems to improve both local and regional control, and might therefore be preferred for patients with node-positive tumours. Hyperfractionated radiotherapy should therefore be regarded as a standard of care along with concomitant chemoradiotherapy for the treatment of locally advanced head and neck cancers. Head-to-head comparisons between hyperfractionated radiotherapy and concomitant chemoradiotherapy are scarce

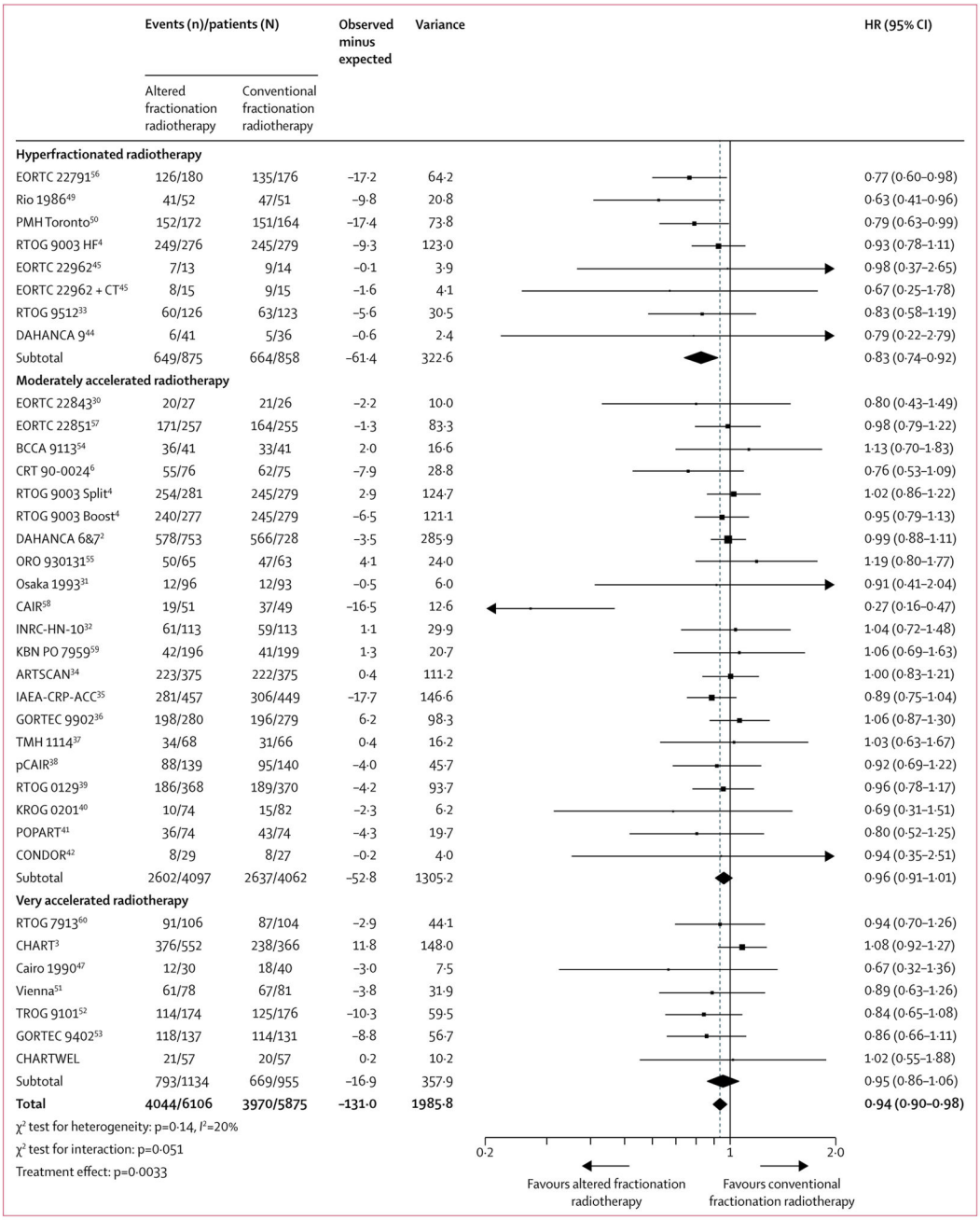

Figure 1. Overall survival for trials comparing altered fractionation and conventional fractionation radiotherapy

The area of each plotted square is proportional to the number of deaths in each trial. The vertical dashed line represents the overall pooled HR. The exclusion of the outlying CAIR trial[58] reduced the heterogeneity further (p=0·89, I^2=0%), increasing the statistical interaction between altered fractionation regimens and survival (p=0·033) without affecting the overall effect of altered fractionation radiotherapy on survival. HR=hazard ratio.

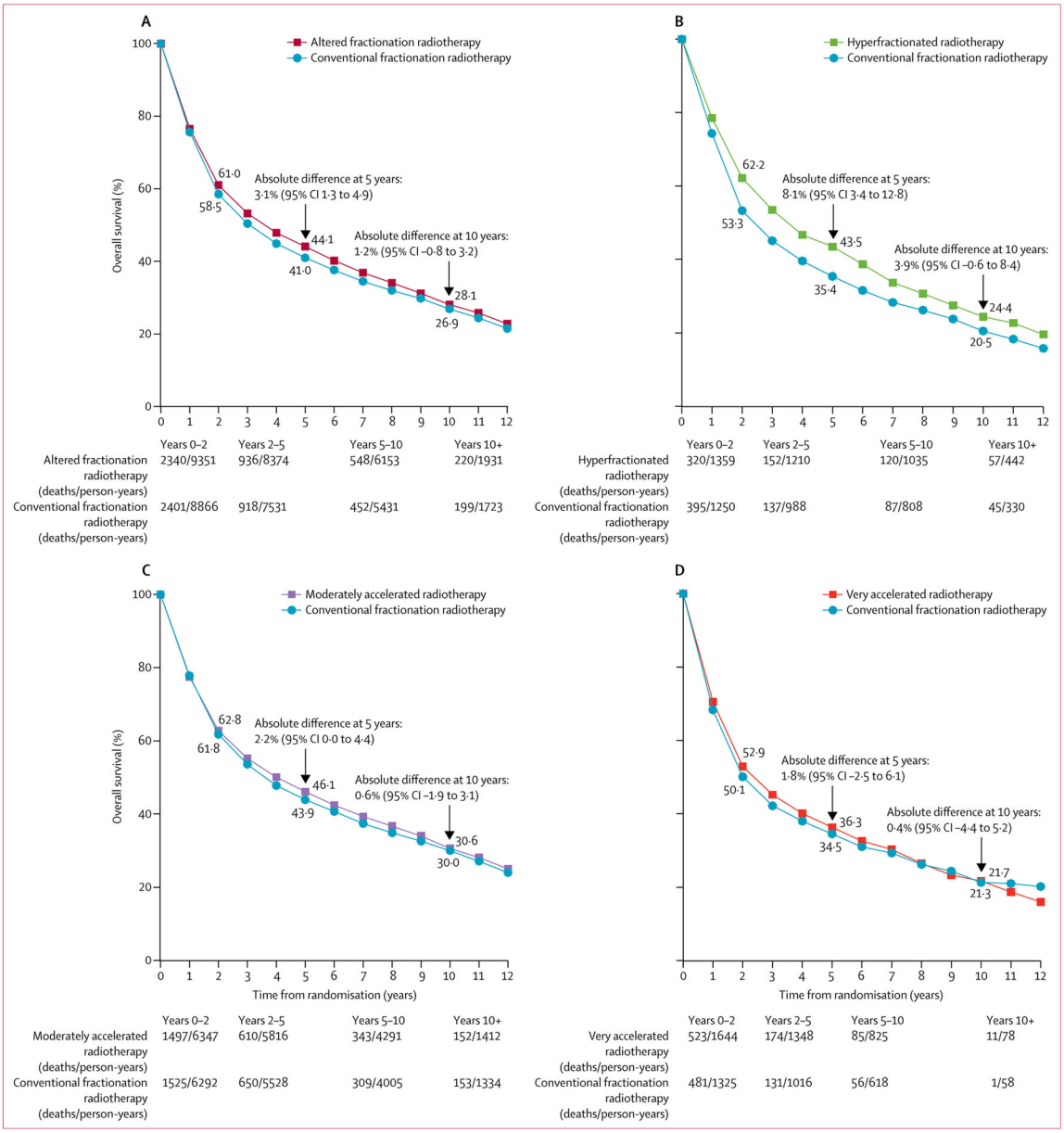

Figure 2. Overall survival curves for trials comparing altered fractionation and conventional fractionation radiotherapy

(A) All types of altered fractionation radiotherapy. (B) Hyperfractionated radiotherapy. (C) Moderately accelerated radiotherapy. (D) Very accelerated radiotherapy.

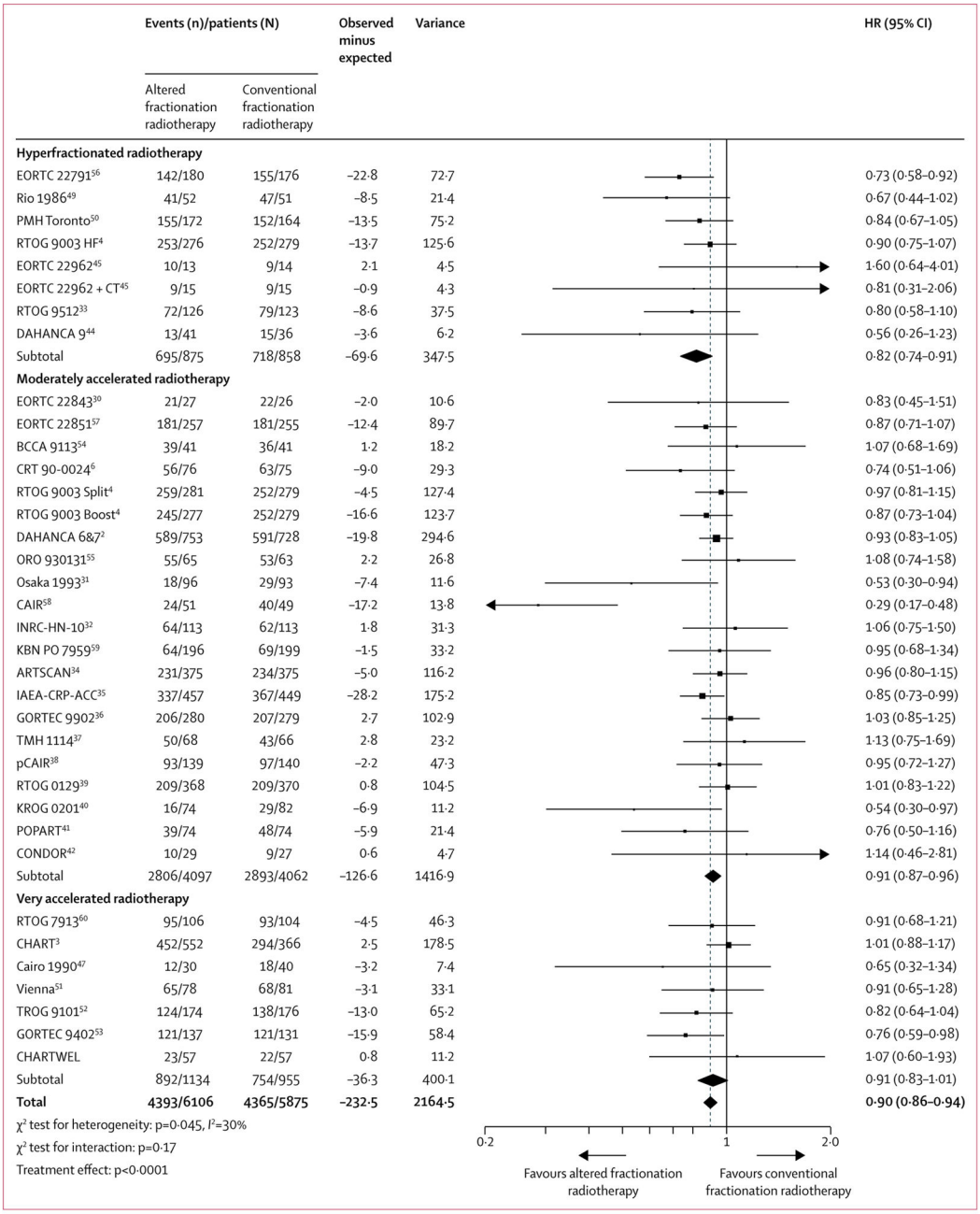

Figure 3. Progression-free survival for trials comparing altered fractionation and conventional fractionation radiotherapy

The area of each plotted square is proportional to the number of progression events or deaths in each trial. The vertical dashed line represents the overall pooled HR. HR=hazard ratio.

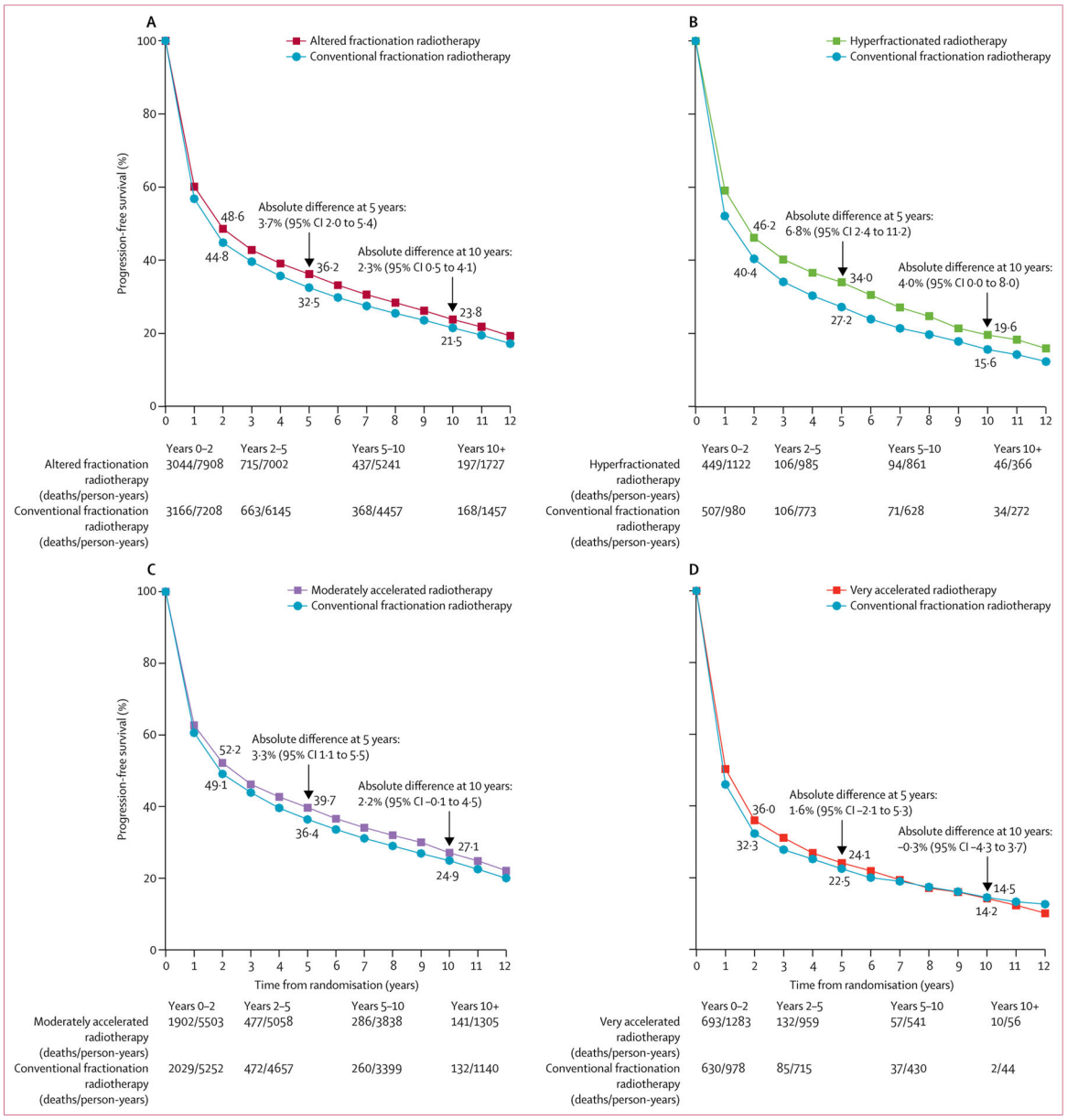

Figure 4. Progression-free survival curves for trials comparing altered fractionation and conventional fractionation radiotherapy

(A) All types of altered fractionation radiotherapy. (B) Hyperfractionated radiotherapy. (C) Moderately accelerated radiotherapy. (D) Very accelerated radiotherapy.

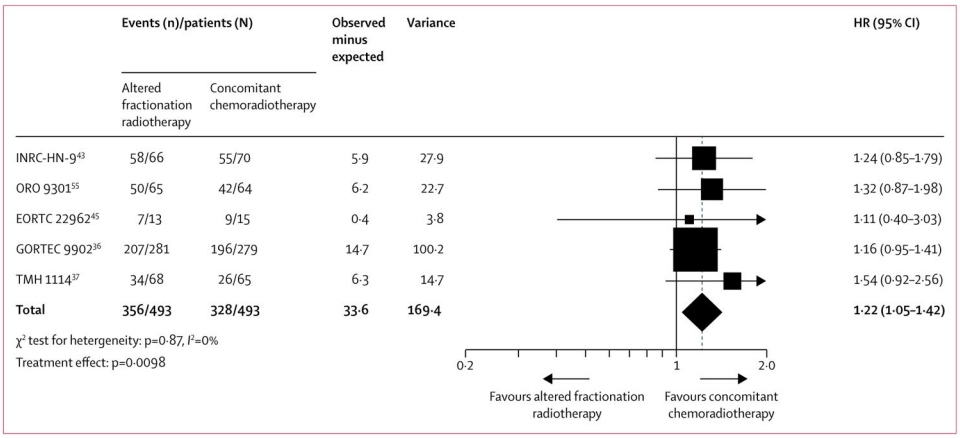

Figure 5. Overall survival for trials comparing altered fractionation radiotherapy and concomitant chemoradiotherapy (using conventional fractionation)

The area of each plotted square is proportional to the number of deaths in each trial. The vertical dashed line represents the overall pooled HR. HR=hazard ratio.

Table 1

Description of the 19 new trials

	Inclusion period	Sites	Stage*	Radiotherapy dosing details	Chemotherapy drug and dose	Patients (n)	Median follow-up (years; IQR)
EORTC 22843[30]	1984–87	Oral cavity, oropharynx, hypopharynx, larynx, other	III/IV	70 Gy in 2 Gy per fraction once daily (five times per week) for 7 weeks (total 35 fractions) *vs* 72 Gy in 1·6 Gy per fraction three times per day for 7 weeks on weeks 1, 4, and 7 (split course; total 45 fractions)	Cisplatin 6 mg/m^2 per day for 35 days *vs* cisplatin 10 mg/m^2 per day on days 1–5 of weeks 1, 4, and 7	53	5·0 (4·0–5·2)
Cairo 1990[47]	1990–97	Oral cavity, oropharynx, hypopharynx, larynx	II–IV	60 Gy in 2 Gy per fraction once daily (five times per week) for 6 weeks postoperatively (total 30 fractions) *vs* 46·2 Gy in 1·4 Gy per fraction three times daily (six times per week) for 2 weeks postoperatively (total 33 fractions)	None	70	3·8 (1·6–4·7)
CRT 90-002[46]	1991–96	Oral cavity, oropharynx, hypopharynx, larynx	II–IV	63 Gy in 1·8 Gy per fraction once daily (five times per week) for 7 weeks postoperatively (total 35 fractions) *vs* 63 Gy in 1·8 Gy per fraction once daily (five times per week) for 3 weeks for 15 fractions plus additional 1·8 Gy per fraction twice daily (ten times per week) for 2 weeks (20 additional fractions), for a total of 5 weeks postoperatively	None	151	13·8 (8·0–16·9)
INRC-HN9[43] †	1992–98	Oral cavity, oropharynx, hypopharynx, larynx	II–IV	60 Gy in 2 Gy per fraction once daily (five fractions per week) for 6 weeks (split course; total 30 fractions) *vs* 75 Gy in 2 Gy per fraction once daily (five times per week) for the first 4 weeks (total 30 fractions) plus additional 1·5 Gy per fraction once daily (five times per week) on weeks 5–6 (total ten fractions)	Cisplatin 20 mg/m^2 per day on weeks 1, 4, 7, and 10	136	18·5 (16·6–20·8)
Osaka 1993[31]	1993–2001	Larynx	I	60–66 Gy in 2 Gy per fraction once daily (five times per week) for 6–6·6 weeks (total 30–33 fractions) *vs* 56·25–63 Gy in 2·25 Gy per fraction once daily (five times per week) for 5–5·6 weeks (total 25–28 fractions)	None	189	5·9 (4·6–7·9)
INRC-HN-10[32]	1994–2001	Oral cavity, oropharynx, hypopharynx, larynx	I–IV	60 Gy in 2 Gy per fraction once daily (five times per week) for 6 weeks postoperatively (total 30 fractions) *vs* 64 Gy in 2 Gy per fraction once daily for 25 fractions plus additional 1·4 or 1·6 Gy per fraction twice daily in weeks 1 and 5 for ten fractions for 5 weeks postoperatively	None	226	4·5‡ (3·4–6·2)
EORTC 22962[45] §¶‖	1996–99	Oral cavity, oropharynx, hypopharynx, larynx	II–IV	2 x 2 design: 70 Gy in 2 Gy per fraction once daily (five times per week) for 7 weeks (total 35 fractions) *vs* 80·5 Gy in 1·15 Gy per	2 x 2 design: cisplatin 100 mg/m^2 on weeks	57	4·4 (2·1–4·9)

	Inclusion period	Sites	Stage*	Radiotherapy dosing details	Chemotherapy drug and dose	Patients (n)	Median follow-up (years; IQR)
				fraction twice daily (ten times per week) for 7 weeks (total 70 fractions)	1, 4, and 7 *vs* none		
RTOG 9512[33]	1996–2003	Larynx	II–IV	70 Gy in 2 Gy per fraction once daily (five times per week) for 7 weeks (total 35 fractions) *vs* 79·2 Gy in 1·2 Gy per fraction twice daily (ten times per week) for 6·5 weeks (total 66 fractions)	None	249 analysed (250 randomised**)	8·5 (7·0–10·7)
ARTSCAN[34]	1998–2006	Oral cavity, oropharynx, hypopharynx, larynx	I–IV	68 Gy in 2 Gy per fraction once daily (five times per week) for 6·5–7 weeks (total 34 fractions) *vs* 68 Gy in 2 Gy per fraction once daily (five times per week) for 4·5 weeks (total 23 fractions) plus additional 1·1 Gy per fraction once daily (five times per week) on weeks 1–4 (total 20 additional fractions)	None	750	9·1 (7·3–11·4)
IAEA-CRP-ACC[35]	1999–2004	Oral cavity, oropharynx, hypopharynx, larynx	I–IV	66–70 Gy in 2 Gy per fraction once daily (five times per week) for 6·5–7 weeks (total 33–35 fractions) *vs* 66–70 Gy in 2 Gy per fraction once daily (six times per week) for 5·5–6 weeks (total 33–35 fractions)	None	906 analysed (908 randomised**)	5·9 (3·7–8·2)
DAHANCA 9[44]	2000–06	Oropharynx, hypopharynx, larynx	I–IV	66 Gy in 2 Gy per fraction once daily (six times per week) for 5·5 weeks (total 33 fractions) *vs* 76 Gy in 1·35 Gy per fraction twice daily (ten times per week) for 5·5 weeks (total 56 fractions)	None	77	4·2 (2·1–5·2)
GORTEC 9902[36]//	2000–07	Oral cavity, oropharynx, hypopharynx, larynx, other	III/IV	70 Gy in 2 Gy per fraction once daily (five times per week) for 7 weeks (total 35 fractions) *vs* 70 Gy in 2 Gy per fraction once daily for 4 weeks (five times per week) plus additional 1·5 Gy per fraction twice daily for 2 weeks (five times per week) for a total of 6 weeks (total 20 fractions + 20 additional fractions) *vs* 64·8 Gy in 1·8 Gy per fraction twice daily (ten times per week) for 3·5 weeks (total 36 fractions)	Fluorouracil 600 mg/m^2 per day and carboplatin 70 mg/m^2 per day on days 1–4 on weeks 1, 4, and 7 for the first two arms and no chemotherapy for the third arm	840	5·2 (4·9–6·2)
TMH 1114[37]//	2000–08	Oropharynx, hypopharynx, larynx	II–IV	66–70 Gy in 2 Gy per fraction once daily (five times per week) for 6–7 weeks (total 33–35 fractions) *vs* 66–70 Gy in 2 Gy per fraction once daily (five times per week) for 6–7 weeks (total 33–35 fractions) combined with cisplatin chemotherapy *vs* 66–70 Gy in 2 Gy per fraction once daily (six times per week) for 5·5–6 weeks (total 35 fractions)	In the group with added chemotherapy: cisplatin 30 mg/m^2 on weeks 1–7	199 analysed (number randomised NA)	4·5 (2·0–7·8)
CHARTWEL¶	2001–05	Oral cavity, oropharynx, hypopharynx, larynx, other	I–IV	60–64 Gy in 2 Gy per fraction once daily for 6–6·5 weeks postoperatively (total 30–32 fractions) *vs* 51–54 Gy in 1·5 Gy per fraction three times daily (five times per week) for 2·4 weeks postoperatively (total 30 fractions)	None	114 analysed (number randomised NA)	4·8 (3·9–5·4)

	Inclusion period	Sites	Stage*	Radiotherapy dosing details	Chemotherapy drug and dose	Patients (n)	Median follow-up (years; IQR)
pCAIR[38]	2001–04	Oral cavity, oropharynx, larynx	I–IV	63 Gy in 1·8 Gy per fraction once daily (five times per week) for 7 weeks postoperatively (total 35 fractions) *vs* 63 Gy in 1·8 Gy per fraction once daily (seven times per week) for 5 weeks postoperatively (total 35 fractions)	None	279	7·2‡ (6·3–8·0)
RTOG 0129[39]	2002–05	Oral cavity, oropharynx, hypopharynx, larynx	II–IV	70 Gy in 2 Gy per fraction once daily (five times per week) for 7 weeks (total 35 fractions) *vs* 72 Gy in 1·8 Gy per fraction once daily (five times per week) for 6 weeks (total 30 fractions) plus an additional 1·5 Gy fraction once daily for the last 12 days (an additional 12 fractions)	Cisplatin 100 mg/m^2 on days 1, 22, and 43 *vs* cisplatin 100 mg/m^2 on days 1 and 22	738 analysed (743 randomised**)	7·9 (7·0–8·8)
KROG 0201[40]	2002–10	Larynx	I/II	66–70 Gy in in 2 Gy per fraction once daily (five times per week) for 6·5–7 weeks (total 33–35 fractions) *vs* 63–67·5 Gy in 2·25 Gy per fraction once daily (five times per week) for 5·5–6 weeks (total 28–30 fractions)	None	156	5·3 (3·4–6·7)
POPART[41]	2003–08	Oral cavity, oropharynx, hypopharynx, larynx	I–IV	66 Gy in 2 Gy per fraction once daily (five times per week) for 7 weeks postoperatively (total 33 fractions) *vs* 66 Gy in 2 Gy per fraction of 1·8 Gy once daily and 1·3 Gy once daily (five times per week) for 2 weeks (total ten fractions) followed by additional fractions of 1·8 Gy or 1·3 Gy twice daily (five times per week) for 3 weeks (total 30 additional fractions), for a total of 5 weeks postoperatively	None	148	6·3 (5·3–8·0)
CONDOR[42]	2009–12	Oral cavity, oropharynx, hypopharynx, larynx	III/IV	70 Gy in 2 Gy per fraction once daily (five times per week) for 7 weeks (total 35 fractions) *vs* 70 Gy in 2 Gy per fraction once daily (six times per week) for 6 weeks (total 35 fractions)	Cisplatin 40 mg/m^2 on weeks 1–6 in both groups	56††	2·8 (1·8–3·3)

EORTC=European Organisation for Research and Treatment of Cancer. CRT=Clinical Randomized Trial. INRC-HN=Instituto Nazionale per la Ricerca sul Cancro-Head and Neck. RTOG=Radiation Therapy Oncology Group. ARTSCAN=Accelerated RadioTherapy of Squamous cell CArcinomas in the head and Neck. IAEA-CRP-ACC=International Atomic Energy Agency Coordinated Research Projects ACCelerated. DAHANCA=Danish Head and Neck Cancer Group. GORTEC=Groupe d'Oncologie Radiotherapie Tete et Cou. TMH=Tata Memorial Hospital. NA=not available. CHARTWEL=Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) Week-end-Less. pCAIR=post-operative Continuous Accelerated Irradiation (CAIR). KROG=Korean Radiation Oncology Group. POPART=Post-Operative Accelerated RadioTherapy. CONDOR=Dutch Head and Neck Society 08-01.

*Stage computed using TNM and Union for International Cancer Control classification, 7th edition; might be different from the trial's publication.

†INRC-HN9 used alternated radiotherapy and chemotherapy with three series of radiotherapy (20 Gy over 2 weeks) at weeks 2–3, 5–6, and 8–9.

‡Follow-up was significantly different between the two treatment groups; for INRC-HR-10, the median follow-up was 4·2 years (IQR 3·5–5·8) in the control group and 4·8 years (3·4–6·9) in the experimental group; for pCAIR, the median follow-up was 6·8 years (6·2–7·8) in the control group and 7·6 years (6·5–8·5) in the experimental group.

§2 × 2 design.

¶ Unpublished.

‖ Three-arm trials (GORTC 9902, TMH 1114) with two arms eligible for each comparison; four-arm trial (EORTC 22962) with four arms eligible for comparison 1 and two arms for comparison 2

** A total of eight patients withdrew their consent in the two RTOG trials and in the IAEA trial; data from these patients were not provided.

†† 18 patients included in 2011 and 2012.

Table 2

Summary of main results for trials comparing altered fractionation and conventional fractionation radiotherapy

	Overall survival	Progression-free survival	Cancer mortality	Non-cancer mortality	Local failure*	Regional failure*	Distant failure
Hyperfractionated radiotherapy							
Number of events/ number of patients	1313/1733	1413/1733	969/1733	344/1733	402/1729	289/1729	181/1729
Hazard ratio of treatment effect (95% CI); p value	0·83 (0·74 to 0·92); 0·00063	0·82 (0·74 to 0·91); 0·00019	0·81 (0·72 to 0·92); 0·0014	0·87 (0·70 to 1·07); 0·19	0·80 (0·66 to 0·98); 0·029	0·76 (0·61 to 0·96); 0·022	0·96 (0·72 to 1·29); 0·80
Absolute difference at 5 years (95% CI)	8·1% (3·4 to 12·8)	6·8% (2·4 to 11·2)	–7·7% (–12·7 to –2·7)	–4·3% (–9·0 to 0·4)	–6·2% (–11·4 to –1·0)	–4·1% (–9·0 to 0·87)	0·4% (–4·4 to 5·2)
Absolute difference at 10 years (95% CI)	3·9% (–0·6 to 8·4)	4·0% (0·0 to 8·0)	NA	NA	NA	NA	NA
Moderately accelerated radiotherapy							
Number of events/ number of patients	5239/8159	5699/8159	3603/8159	1636/8159	1470/7555	1107/7366	829/7923
Hazard ratio of treatment effect (95% CI); p value	0·96 (0·91 to 1·01); 0·14	0·91 (0·87 to 0·96); 0·00077	0·92 (0·86 to 0·98); 0·014	1·05 (0·95 to 1·16); 0·32	0·76 (0·69 to 0·84); <0·0001	0·92 (0·82 to 1·04); 0·19	0·96 (0·84 to 1·10); 0·55
Absolute difference at 5 years (95% CI)	2·2% (0·0 to 4·4)	3·3% (1·1 to 5·5)	–2·9% (–5·2 to –0·6)	0·4% (–1·8 to 2·6)	–6·0% (–8·3 to –3·7)	–0·8% (–2·8 to 1·2)	–0·7% (–2·7 to 1·3)
Absolute difference at 10 years (95% CI)	0·6% (–1·9 to 3·1)	2·2% (–0·1 to 4·5)	NA	NA	NA	NA	NA
Very accelerated radiotherapy							
Number of events/ number of patients	1462/2089	1646/2089	1217/2089	245/2089	317/1429	331/1429	316/2058
Hazard ratio of treatment effect (95% CI); p value	0·95 (0·86 to 1·06); 0·37	0·91 (0·83 to 1·01); 0·069	0·94 (0·84 to 1·06); 0·31	1·01 (0·78 to 1·31); 0·92	0·88 (0·70 to 1·10); 0·26	0·89 (0·72 to 1·11); 0·31	0·95 (0·76 to 1·19); 0·64
Absolute difference at 5 years (95% CI)	1·8% (–2·5 to 6·1)	1·6% (–2·1 to 5·3)	–2·0% (–6·5 to 2·5)	0·5% (–5·4 to 4·4)	–2·3% (–8·7 to 4·1)	NA	–1·5% (–7·2 to 4·2)
Absolute difference at 10 years (95% CI)	0·4% (–4·4 to 5·2)	–0·3% (–4·3 to 3·7)	NA	NA	NA	NA	NA
All types of fractionation							

	Overall survival	Progression-free survival	Cancer mortality	Non-cancer mortality	Local failure*	Regional failure*	Distant failure
Number of events/ number of patients	8014/11 981	8758/11 981	5789/11 981	2225/11981	2189/10 713	1727/10 524‡	1326/11 710§
Hazard ratio of treatment effect (95% CI); p value	0·94 (0·90 to 0·98); 0·0033	0·90 (0·86 to 0·94); <0·0001	0·91 (0·86 to 0·96); 0·00022	1·02 (0·94 to 1·11); 0·70	0·79 (0·72 to 0·85); <0·0001	0·89 (0·81 to 0·98); 0·016	0·96 (0·86 to 1·07); 0·43
Absolute difference at 5 years (95% CI)	3·1% (1·3 to 4·9)	3·7% (2·0 to 5·4)	–3·5% (–5·4 to –1·6)	–0·4% (–2·4 to 1·4)	–5·7% (–7·7 to –3·7)	–1·4% (–3·2 to 0·4)	–0·8% (–2·6 to 1·0)
Absolute difference at 10 years (95% CI)	1·2% (–0·8 to 3·2)	2·3% (0·5 to 4·1)	NA	NA	NA	NA	NA
Interaction between type of fractionation (p value)	0·051	0·17	0·17	0·28	0·51	0·35	>0·99
Heterogeneity across trials							
p value	0·14	0·045	0·035	0·67	0·0032	0·23	0·95
I^2	20%¶	30%¶	32%¶	0%	45%//	15%**	0%

Hazard ratios are altered fractionated radiotherapy versus conventional radiotherapy. Absolute differences are between the survival rates for overall and progression-free survival; between failure rates for local, regional, and distant failure; and between the mortality rates for cancer-related mortality and non-cancer-related mortality. NA=not available (not enough data at 10 years).

*RTOG 7913 (n=210), Cairo 1990 (n=70), TROG-9101 (n=350), and GORTEC 9902 (n=559) did not distinguish between local and regional failure for all their patients and 79 additional patients were excluded due to missing type of failure.

†No regional failure; only local and distant failures occurred during the Osaka 1993 trial (n=189).

‡Two patients who had regional failures were excluded due to missing survival time.

§82 additional patients were excluded due to missing type of failure.

¶No heterogeneity (I^2=0%) after the exclusion of one trial (CAIR[58]).

//No heterogeneity (I^2=2%) after the exclusion of four trials (CAIR,[58] Rio,[49] TMH 1114,[37] and Osaka 1993[31]).

**No heterogeneity (I^2=1%) after the exclusion of one trial (Rio[49]).

Table 3

Acute and late severe toxicities between conventional and altered fractionation radiotherapy

	Comparisons (n)	Patients (n)	Proportion of patients with toxicity receiving altered fractionation radiotherapy*	Proportion of patients with toxicity receiving conventional radiotherapy, n/N (%)	Odds ratio (95% CI)	p value for safety	I^2	p value for heterogeneity
Acute toxicities								
Mucositis (all trials)	20	8541	38·9%	1155/4233 (27·3%)	2·02 (1·81–2·26)	<0·0001	78%	<0·0001
Mucositis (no heterogeneity)	16	7051	35·2%	845/3499 (24·1%)	2·10 (1·84–2·41)	<0·0001	0%	0·66
Dermatitis (all trials)	15	4997	17·7%	410/2483 (16·5%)	1·09 (0·93–1·29)	0·29	36%	0·083
Dermatitis (no heterogeneity)	13	4314	20·1%	376/2143 (17·5%)	1·20 (1·01–1·42)	0·041	0%	0·83
Weight loss (all trials)	5	2053	3·6%	43/1023 (4·2%)	0·87 (0·56–1·36)	0·54	7%	0·37
Need for feeding tube (all trials)	6	2859	52·1%	563/1420 (39·6%)	1·75 (1·49–2·05)	<0·0001	89%	<0·0001
Need for feeding tube (no heterogeneity)	4	1871	35·6%	252/929 (27·1%)	1·63 (1·34–1·99)	<0·0001	3%	0·38
Late toxicities								
Xerostomia (all trials)	12	4726	51·3%	1193/2337 (51·0%)	1·01 (0·88–1·14)	0·94	20%	0·25
Xerostomia (no heterogeneity)	11	4414	54·6%	1181/2182 (54·1%)	1·02 (0·90–1·17)	0·73	0%	0·50
Bone toxicity (all trials)	11	3219	4·4%	64/1585 (4·0%)	1·12 (0·80–1·57)	0·52	0%	0·77
Mucosal toxicity (all trials)	8	2298	14·5%	149/1114 (13·4%)	1·10 (0·87–1·40)	0·41	49%	0·058
Mucosal toxicity (no heterogeneity)	7	1921	14·4%	140/937 (14·9%)	0·96 (0·74–1·24)	0·74	0%	0·64
Neck fibrosis (all trials)	15	5557	7·6%	188/2744 (6·9%)	1·13 (0·92–1·39)	0·23	70%	<0·0001
Neck fibrosis (no heterogeneity)	12	4250	7·0%	138/2109 (6·5%)	1·09 (0·85–1·38)	0·50	0%	0·45

Data include grade 3–4 toxicities (severe toxicities) and grade 2–3 xerostomia. Acute toxicities are toxicities that occurred in the first 6 months after randomisation; they are due to the treatment. Late toxicities are toxicities that occurred later than 6 months after randomisation; they are long-term toxicities. No heterogeneity refers to a sensitivity analysis in which trials causing statistical heterogeneity were excluded. The absence of change in the p value for efficacy shows that the statistical significance is independent from the trial heterogeneity.

*Calculated with the Stewart method[11] and compared with the reference group using odds ratios stratified by trial.[10]