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Role of radiotherapy fractionation in head and neck cancers. An update of the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck on 34 trials and 11969 patients.

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Summary

Background: The Meta-Analysis of Radiotherapy in squamous cell carcinomas of Head and neck has demonstrated that altered fractionation radiotherapy (AFRT) was associated with improved overall survival (OS) and progression-free survival (PFS) compared to conventional fractionation (CFRT). This update aims at confirming and explaining the superiority of hyperfractionared RT over the other AFRT regimens and at evaluating the benefit of altered fractionation within the context of concomitant chemotherapy with the inclusion of new trials.

Methods: We searched bibliography databases, trials registries and meeting proceedings up to July 2015 to identify published or unpublished randomized trials comparing CFRT to AFRT (comparison 1) or CFRT with concomitant chemotherapy to AFRT alone (comparison 2). Trials had to start randomization on or after January 1st 1970 and completed accrual before December 31st 2010, and included patients with non-metastatic squamous cell carcinoma. Trials including a non-conventional RT control arm, investigating hypofractionated RT or including mostly nasopharyngeal carcinomas were excluded. Trials were grouped in three types of fractionation: hyperfractionated, moderately accelerated and very accelerated. Individual patient data were collected and combined using a fixed-effect model based on the intent-to-treat principle. Overall survival was the main endpoint.

Findings: Comparison 1 included 33 trials and 11423 patients. AFRT was associated with a significant benefit on OS (hazard ratio (HR)=0.94 [95% confidence interval: 0.90; 0.98], p=0.0033). There was a significant interaction (p=0.051) between type of fractionation and treatment effect, the OS benefit being restricted to the hyperfractionated group (HR=0.83 [0.74; 0.92]) with absolute differences at 5 and 10 years of +8.1% [+3.4; +12.8] and +3.9% [-0.6; +8.4]. PFS was improved by AFRT (HR=0.90 [0.86; 0.94], p<0.0001), without significant difference between type of fractionation, through an improvement in local (HR=0.79 [0.72; 0.85]) and regional (HR=0.89 [0.81; 0.98]) control. Comparison 2 included 5 trials and 986 patients. OS was significantly worse with AFRT compared to concomitant chemoradiotherapy (HR=1.22 [1.05; 1.42], p=0.0098) with absolute differences at 5 and 10 years of -5.8% [-11.9; +0.3] and -5.1% [-13.0; +2.8].

Interpretation: This update confirms, with more patients and a longer follow-up, that hyperfractionated RT 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 RT and concomitant chemoradiotherapy remains to be specifically tested.

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Introduction

The modifications of radiotherapy (RT) fractionation have long been studied in various disease sites, including head and neck cancer. They are believed to be effective through two mechanisms that together improve the therapeutic ratio: the delivery of small fractions twice a day leads to the reduction of late toxicity that allows for higher total doses to be delivered, and the shortening of the overall treatment time limits tumor repopulation. Both strategies could improve tumor control rates. Numerous randomized trials have evaluated these RT schedules and provided conflicting results regarding tumor control and survival, mostly due to trial heterogeneity and limited sample size. These trials have however confirmed that fractionation modifications were usually associated with increased acute side effects but similar or lower late toxicity rates than conventional fractionation RT.[1–4]

For squamous cell carcinoma of the head and neck, the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) has demonstrated that altered fractionation RT (AFRT) was associated with improved overall survival (OS) and progression-free survival (PFS) when compared to conventional fractionation RT.[1] Trials were grouped according to the type of altered fractionation used: hyperfractionation (HF), where a higher total dose in the same overall time than in the reference arm using twice daily fractions; moderate acceleration (Ac), where the total dose was unchanged (+/-5%) but delivered more quickly (generally approximately one week faster); and very accelerated RT with dose reduction (VAc), where RT duration was shortened by 50% or more, and total dose reduced. There was a significant interaction between treatment effect and altered fractionation regimens, the survival benefit being restricted to the HF subgroup.[1] The reasons for the superiority of HF over other types of altered fractionation remained unclear, and HF has not become a standard of care, mostly due to logistical issues that favored the delivery of concomitant chemoradiotherapy (CRT) over HF.

As several new trials have been published, an update of MARCH was performed, aiming at confirming and explaining the superiority of HF over the other altered fractionation regimens, evaluating the benefit of altered fractionation within the context of concomitant chemotherapy (CT) or post-operative trials and providing a direct comparison with conventional fractionation concomitant CRT.

Methods

This meta-analysis was performed according to a pre-specified protocol (available at https://www.gustaveroussy.fr/sites/default/files/march2-protocol.pdf). The method is similar to our previous publications.[1,5–7]

Selection criteria and search strategy

We searched PubMed, Web of Science, Cochrane Controlled Trials meta-register, ClinicalTrials.gov, and meeting proceedings up to July 2015 (Appendix page 2). To be eligible, published and unpublished trials had to compare primary or postoperative conventional fractionation RT to altered fractionation RT (+/- same concomitant CT in both arms) or conventional fractionation concomitant CRT to altered fractionation RT without concomitant CT. Trials had to be randomized in a way which precluded prior knowledge of treatment assignment, started randomization on or after January 1st 1970 and completed accrual before December 31st 2010, and included 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 RT control arm or including mostly nasopharyngeal carcinomas were excluded. Trials investigating hypofractionated RT, defined as doses per fraction above 2.5 Gy, were also excluded due to its use mostly in palliative cases.

Procedures

Individual patient data were requested for each eligible trial and for all randomized patients: patient and tumor characteristics, dates of randomization, failures and death, treatment arm allocated, details on 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 trial protocol and published reports. Randomization validity was evaluated by checking patterns of treatment allocation and balance of baseline characteristics between treatment arms. Follow-up of patients was also compared between treatment arms.[8] Every questions raised by the checking were discussed with the trialists. Each trial was reanalyzed and the analyses were sent to the trialists for validation.

Outcomes

The primary endpoint was OS, defined as the time from randomization until death from any cause. The secondary endpoints were PFS, local (LF), regional (RF) and loco-regional failures (LRF) rates, distant failure (DF) rates, cancer and non-cancer mortality, and non-hematological toxicities. PFS was defined as the time from randomization to first progression (loco-regional 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 LF, regional failure or concomitant regional and local failures without distant failure for RF, distant failure either alone or combined with local or regional failures for DF. Only the first event was collected, meaning that patients with another failure event were censored at that time. 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 considered as cancer mortality if they occurred within 5 years after randomization. Only trials with at least 80% of available data were considered eligible for non-hematological toxicity analysis. If at least 2000 patients were included in those trials, toxicity was analyzed. Moreover, for late toxicities, patients with a follow-up shorter than 6 months were excluded.

Statistical Analysis

All analyses were performed on an intention-to-treat basis. With 12000 patients (and at least 7000 deaths), it would be possible to detect with a power of 99.9 % an absolute improvement in survival from 30 % to 33 % at 5-years (two-sided log-rank test, α=5%). Median follow-up was estimated with the reverse Kaplan-Meier method.[9] Analyses were stratified by trial. Individual and overall pooled hazard ratios (HR) with 95% confidence intervals (CI) were calculated through a fixed-effect 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] χ^2 heterogeneity test and I^2 statistic were used to investigate the overall heterogeneity between trials.[12] In case of significant heterogeneity ($p<0.10$), trials whose 95% CI did not overlap with the 95% CI of the global HR were excluded. If heterogeneity was still significant, a random-effect model was used.[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.[1,13,14] In addition to the fixed-effect model, a competing risk model was used for local failure, regional failure and distant failure [15]. To estimate 5

and 10-years absolute differences, actuarial survival rates were computed on all patients and the hazard ratio at the corresponding time period was used to compute survival rates in each arm [1,13,14]. Restricted mean survival times, a new method to estimate absolute benefit, were also estimated.[16–18] Details on those methods and power computation are reported in appendix page 3.

Subset analyses were performed to study the interaction between treatment effect and trial level characteristics, using a test of heterogeneity among the different groups of trials. Residual heterogeneity within trial subgroups was computed by subtracting the χ^2 statistic of the heterogeneity test between groups from the χ^2 statistic of the overall heterogeneity test.[19] Predefined subsets were the altered fractionation regimen (HF, Ac or VAc), the use of concomitant CT and the performance of primary surgery. Interaction between treatment effect and patient subgroups (according to age, sex, performance status, primary site and overall stage) was estimated in a Cox model stratified by trial and containing treatment effect, covariate effect (for example age) and treatment-covariate interaction ("one-stage" model method).[20]

All p-values were two-sided. Analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC).

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 JPP had access to the raw data. The corresponding author had full access to all of the data and bears the final responsibility to submit for publication.

Results

Twenty-six new trials, published between 1995 and 2016, were identified. Data from four trials (n=185) were not collected: three[21–23] due to the inability to contact investigators and one due to early closure with very limited follow-up.[24] Five other trials were excluded after blind review by the steering committee, due to the absence of survival or randomization dates,[25,26] issues with the randomization 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]). Two post-operative trials previously identified[1] were also included[46,47] and a third was excluded due to unavailable data[48] (Appendix page 16). Thus, 19 new trials were included (Table 1). Updated data could be obtained for nine trials[2–4,49–54] included in the first MARCH round, increasing median follow-up from 6.1 (interquartile range (IQR): 4.4; 8.0) to 10.4 (5.7; 15.2) years for the 15 previous trials.[1]

Overall, 34 trials representing 11969 patients were included in the meta-analysis. The control arm of a four-arm trial[4] was triplicated, a 2x2 trial (EORTC 22962[45]) and 3 three-arm trials represented respectively three and two relevant comparisons for the meta-analysis.[36,37,55] The 33 trials included in the analysis of fractionation schedules (comparison 1) were divided into four predefined subgroups, depending on the type of radiotherapy: HF (8 comparisons, including the unpublished EORTC 22962),[4,33,44,45,49,50,56] Ac (19 comparisons),[2,4,30,32,34–39,41,42,46,54,55,57–59] VAc (7 comparisons, including the unpublished CHARTWEL)[3,47,51–53,60] and moderately hypofractionated (dose per fraction between 2-2.5 Gy, 2 comparisons)[31,40] (Appendix page 17). After discussion with the steering committee, the moderately hypofractionated trials were included in the Ac group. The analysis of altered fractionation RT versus conventional fractionation CRT (comparison 2) included 5 trials (four published[36,37,43,55] and EORTC 22962[45]). Patients' characteristics by trial are presented in appendix page 4.

Thirty-three trials and 11423 patients (36 comparisons, 11981 patients) were included in comparison 1. Median follow-up was 7.9 years (IQR: 5.3; 12.1); less than 5 years for 9 trials30, 35, 42, 44, 54, 56 (including the two unpublished; 1706 patients); and greater than 10 years for 6 trials[2,4,46,50,54,56] (3519 patients). Patients were mostly male and had a performance status of 0 or 1. Median age was 59 years (IQR: 52; 66). Tumors were mostly located in the oropharynx or larynx and were stage III-IV for 75.0% (8986/11981) of the patients. Among stage I-II tumors, 70.0% (2045/2922) were laryngeal carcinomas. Patients' characteristics are presented in appendix page 6.

The results of all endpoints are summarized in Table 2. There were 8014 deaths (Appendix page 8). OS was improved by altered fractionation RT (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]. Heterogeneity between trials was not

significant (p=0.14, I^2=20%). Interaction between the three altered fractionation regimens and the effect on OS was significant (p=0.051), the survival benefit being restricted to HF regimen (HR=0.83 [0.74; 0.92]) with 5 years difference of +8.1% [+3.4; +12.8] (Figures 1 and 2). The HRs for the Ac and VAc regimens were respectively 0.96 [0.91; 1.01] and 0.95 [0.86; 1.06].

Regarding PFS, 8758 patients have relapsed or died (Appendix page 9). PFS was improved by AFRT (HR=0.90 [0.86; 0.94], p<0.0001) with an absolute difference at 5 years of +3.7% [+2.0; +5.4] (Figures 3 and 4). Interaction between altered fractionation regimens and the effect on PFS was not significant (p=0.17). Heterogeneity between trials was significant (p=0.045, I^2=30%). The exclusion of the outlying CAIR trial[58] removed heterogeneity (p=0.55, I^2=0%), without modifying the overall HR and the interaction between altered fractionation regimens.

There were 5789 cancer related deaths, 2225 non-cancer related deaths, and 2189, 1729 and 1326 events respectively for local, regional and distant failures (Appendix page 9). AFRT was associated with significantly reduced cancer mortality, local and regional failures, with respective HRs of 0.91 [0.86; 0.96] (p=0.00022), 0.79 [0.72; 0.85] (p<0.0001) and 0.89 [0.81; 0.98] (p=0.016). No differences were observed in terms of non-cancer mortality or distant failure, with respective HRs of 1.02 [0.94; 1.11] (p=0.70) and 0.96 [0.86; 1.07] (p=0.43). Although no interaction was observed between altered fractionation regimens and the effect on local or regional control, HF was associated with a reduction of LF and RF; whereas Ac was only associated with a reduction of LF, and VAc had no effect on any of these endpoints (Table 2). Forest plots and survival curves are presented in appendix pages 19 to 27. Similar results were observed with competing risk methods for LF, RF and DF.

Planned subset analyses showed that there was no significant interaction between the effect on OS and the period of accrual, *i.e.* included in the first round of MARCH versus in the present update (p=0.94), postoperative versus definitive RT (p=0.45) and trials including only larynx carcinomas versus the others (p=0.70). For the subset analysis regarding chemotherapy, five trials included the same concurrent chemotherapy in both treatment arms. The altered fractionation radiotherapy was HF for one trial that was terminated early [45] and MAc for the four others [30,36,39,42]. None used adjuvant chemotherapy and only one used induction [42]. The effect of altered fractionation radiotherapy was not different between trials with and without chemotherapy in both arms (p=0.39). Similar results were observed for PFS, except for a borderline interaction between AFRT effect on PFS and the administration, or not, of chemotherapy in both arm (p=0.073), the benefit of altered fractionation being limited to trials without chemotherapy (Appendix page 10). After the exclusion of the 9 comparisons with unusual RT regimens (hypofractionated RT,[31,40] split course[4,30,55,57] or both hyperfractionated and moderately accelerated RT[44]) or confounded CT schedules (different

chemotherapy regimens between arms)[36,39], there was no significant interaction between type of fractionation and OS (p=0.11) (Appendix pages 28 and 29).

Planned subgroup analyses showed a significant interaction between treatment effect on PFS and age (p=0.052). There was a reduction of treatment effect when age increased for PFS (p=0.016) and OS when follow-up was censored at 5-year (p=0.026). There was no interaction between treatment effect on OS or PFS and patient performance status, sex, site of primary and tumor stage (Appendix pages 11 and 13). In the subset of HF trials, no interaction with the five studied covariates was observed (data not shown).

The effect of AFRT on regional control according to nodal status was studied as an unplanned analysis. In the 5592 node positive patients, there was a significant improvement in regional control with AFRT (HR=0.88 [0.79; 0.98], p=0.017) (Appendix page 30). The interaction between AFRT effect and radiotherapy fractionation regimens was borderline (p=0.060), in favor of the HF group with a HR of regional control of 0.67 [0.51; 0.89], compared to 0.96 [0.84; 1.09] and 0.81 [0.64; 1.03] for Ac and VAc respectively.

An unplanned analysis was performed to evaluate the evolution of the AFRT effect over time (Appendix pages 31 and 32). The HR for death was 0.92 [0.87; 0.96] in the first five years after randomization, and 1.04 [0.93; 1.15] beyond 5 years, with a significant interaction between time and AFRT effect (p=0.034). Results were similar for PFS. The increase in restricted mean survival time in favor of AFRT at 5 and 10 years horizons was 1.5 months [95% CI: 0.5; 2.5] and 3.3 months [1.3; 5.4] for OS and 2.7 months [1.5; 3.9] and 4.9 months [2.7; 7.1] for PFS. When only hyperfractionated trials were analyzed, these increases were 3.9 months [1.9; 5.9] and 7.1 months [2.9; 11.3] for OS and 4.6 months [2.4; 6.8] and 8.2 months [3.8; 12.5] for PFS.

The toxicity analysis (Table 3) showed an increased prevalence of acute mucositis and need for feeding tube during treatment for patients treated with AFRT (OR=2.02 [95% CI: 1.81; 2.26] and 1.75 [1.49; 2.05] respectively). Acute dermatitis was statistically increased only in the sensitivity analysis without trials responsible for the statistical heterogeneity (OR=1.20 [1.01; 1.42]). None of the late toxicities with sufficient available data (xerostomia, osteoradionecrosis, late mucosal toxicity, neck fibrosis) showed an increased prevalence with the use of AFRT.

Five trials and 986 patients were included[36,37,43,45,55] in comparison 2 (Table 1). Median follow-up was 5.4 years (IQR: 4.7; 8.2), was less than 5 years for 2 trials[37,45] (161 patients) and greater than 10 years for one trial[43] (136 patients). One trial, which compared CRT to VAc, accounted for 57% (560/986) of patients and 59% (403/684) of deaths.[36] Stage III and IV tumors were found in 21.9% (216/986) and

76.6% (755/986) of patients, respectively. The majority of tumors were located in the oropharynx (Appendix page 14). AFRT was associated with a significant decrease in OS compared to concomitant CRT (HR=1.22 [1.05; 1.42], p=0.0098) with an absolute difference at 5 years of -5.8% [-11.9; +0.3]. There was no significant heterogeneity between trials (p=0.87, I^2=0%) (Figures 5 and Appendix page 33). PFS was lower with AFRT (HR=1.26 [1.09; 1.45], p=0.0020) (Appendix pages 34 and 35). A decrease in locoregional control was observed with AFRT (HR=1.42 [1.16; 1.73], p=0.00054), with an absolute decrease at 5 years of - 9.9% [+2.7; +17.1]) but not for distant control (HR=0.99 [0.72; 1.37], p=0.95), Appendix pages 36 to 39). No specific analysis was performed for local or regional control due to a low number of patients in this comparison.

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 meta-analysis[1], that AFRT was associated with a small but significant improvement in OS when compared with standard fractionation RT. However, this improvement in OS was modest in the overall population, +3.1% at 5 years, and was only significant in the HF group. Indeed there was a significant interaction between the effect on OS and altered fractionation regimens, and the absolute difference at 5 years was +8.1% for the HF group. The survival benefit decreased when age increased, but is otherwise consistent in all patient subgroups. There was a clear benefit on local control, a more limited benefit on regional (nodal) control and no benefit on distant metastases. AFRT was associated with increased acute mucositis and need for feeding tube placement but there was no significant difference in late toxicity. The new meta-analysis of trials investigating the direct comparison between AFRT and concomitant CRT demonstrated the superiority of concomitant CRT regarding OS, PFS 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 re-analyzed and validated by the trialists. Unpublished trials were also included in order to avoid publication bias. Indeed, it is well known that positive trials are more frequently published than negative trials, especially in English medical literature [61,62]. There was 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 OS and PFS between the first round of the meta-analysis[1] and the new trials included here, as demonstrated by the absence of interaction between meta-analysis round and treatment effect (OS: p=0.94; PFS: p=0.64), is an indicator of the robustness of the findings. At the time of this update, seven trials representing 3655 patients had a follow-up longer than 10 years,[2,4,43,46,50,54,56] which allowed for long term analyses to be conducted. The large number of patients allowed secondary endpoints to be evaluated and subgroup and subset analyses to be done with adequate power.

This second round of the meta-analysis provided a hypothetical explanation for the superiority of HF over the other altered fractionation regimens. HF was associated with a benefit both in local and regional control whereas accelerated regimens only provided an improvement in local control. When restricting the analysis to node positive patients, the interaction between altered fractionation regimens and regional control almost reached statistical significance (p=0.060) whereas it was not significant in the overall population (p=0.35). The explanation for this difference on nodal control favoring HF is unclear, but might be related to the increase in absolute dose provided by HF. Pure

acceleration should therefore be considered only for patients with a low nodal burden. Last, the collection of toxicity data allowed the analysis of the pattern of adverse events associated with AFRT.

There are several limitations to this work. First, almost all of the trials used outdated radiotherapy (two or three dimensional), which is a concern since intensity modulated radiotherapy (IMRT) is the current standard of care for head and neck cancers. However the dose-intensity/efficacy relationship demonstrated here certainly remains valid even in the IMRT era given the fact that dose to gross tumor has not changed and is around 2 Gy per fraction. HF or acceleration can be performed with IMRT in the same way as they were done with 2D-RT and there is no reason to expect a different efficacy profile. They also outdate the *Human Papilloma Virus* (HPV) era and the collection of smoking status, which were available in very few trials of the meta-analysis. Since HPV-positivity is a major prognostic factor in oropharyngeal carcinoma [39], extensive analyses will be performed in trials that provided HPV/smoking data in the search for prognostic and predictive markers of fractionation modification efficacy (protocol: https://www.gustaveroussy.fr/sites/default/files/march2-hpv-protocol.pdf). The trials' accrual period ranged from 1979 to 2010 and this long time span might add heterogeneity in the meta-analysis, although no interaction between meta-analysis round and OS or PFS could be demonstrated. The second 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 this data were available, and was not feasible for comparison 2 due to insufficient data. Third, only 5 trials compared AFRT to standard RT with chemotherapy in both arms and 3 have a lower dose of chemotherapy in the arm with AFRT than in the standard RT arm.[30,36,39] Last, the important number of endpoints analyzed 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 pre-specified. Subset (by trial characteristics) or subgroup (by patient characteristics) analyses are considered of lower level of evidence and 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 AFRT and concomitant CRT showed the superiority of the addition of concomitant chemotherapy over pure fractionation modification. This is providing an additional contribution to the bulk of randomized data having shown the superiority of CRT over RT alone.[5] This is also in agreement with the results of a network meta-analysis performed previously where AFRT always ranked lower than concomitant CRT.[63] Concomitant CRT should remain the standard of care for locally advanced node positive tumors. However, one should keep in mind that the altered fractionation regimens used in this direct comparison were HF for one trial [45], Ac for three trials

[37,43,55] and VAc for one trial (majority of the data).[36] Since HF appeared superior to the other altered fractionation regimens, the comparison between concomitant CRT and HF is relevant. It cannot be done with this meta-analysis due to the low number of patients in this comparison. It remains to be performed and there is currently no suggestion that one would perform better than the other since the difference in OS at 5 years in favor of HF in this meta-analysis was 8.1% and very close to the one due to the addition of chemotherapy concomitant to RT which was 6.5% in the last update of the MACH-NC meta-analysis.[5] A network meta-analysis is ongoing and will try to answer that question (protocol: https://www.gustaveroussy.fr/sites/default/files/machnc-network-protocol.pdf).

Ongoing research efforts using the MARCH database include also extensive analysis of trials that provided information on the pathology findings for patients who have undergone primary surgery followed by postoperative RT. The findings might provide new insights into RT dose relationship in the postoperative setting which remains a controversial area.

Other areas of improvement should include cost-effectiveness analyses comparing concomitant CRT and HF radiotherapy without concomitant chemotherapy, health services research to address patients' and physicians' difficulties in the implementation of HF radiotherapy, and better documentation of long term toxicity and patient reported outcomes.

In conclusion, this updated individual patient data confirms the efficacy of AFRT over conventional fractionation RT and the superiority of hyperfractionated RT over the other AFRT schedules. The effect of acceleration is limited to local control, whereas HF appears to improve both local and regional control, and might thus be preferred for patients with node positive tumors. The direct comparison between AFRT and concomitant CRT suggests the superiority of concomitant CRT. Future research remains warranted to compare efficacy of hyperfractionated RT and concomitant CRT and to look for predictive markers of treatment efficacy.

Research in context

Evidence before the study

The Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) based on 15 trials and 6515 patients has demonstrated that altered fractionation radiotherapy was associated with improved overall survival and progression-free survival when compared to conventional fractionation radiotherapy. For this update, we searched published and unpublished trials in PubMed, Web of Science, Cochrane Controlled Trials meta-register, ClinicalTrials.gov, and meeting proceedings, up to July 2015, without language restriction, for "randomized trials" of "radiotherapy fractionation" in "head and neck cancer". Randomized trials comparing conventional fractionation radiotherapy to altered fractionation radiotherapy, or conventional fractionation radiotherapy with concomitant chemotherapy to altered fractionation radiotherapy alone were eligible. Trials had to start randomization on or after January 1st 1970 and completed accrual before December 31st 2010, and included patients with non-metastatic squamous cell carcinoma. Trials including a non-conventional RT control arm, investigating hypofractionated RT or including mostly nasopharyngeal carcinomas were excluded. Individual patient data were requested for each eligible trial. Risk of bias was checked with a standard procedure; each trial was reanalyzed and compared with trial protocol and published reports. Trials with quality issues were discussed with their investigators. 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 randomized trials provide the highest level of evidence. This update of the MARCH meta-analysis has almost doubled the number of patients and trials included, reaching 34 trials and 11969 patients. The median follow-up was increased, being now 7.9 years overall (IQR: 5.3; 12.1) and 10.4 years (5.7; 15.2) for the trials previously included in the MARCH meta-analysis. Data on acute and late toxicity were collected. Finally, a separate meta-analysis was conducted that compared altered fractionation radiotherapy and concomitant chemoradiotherapy. Altered fractionation radiotherapy was associated with a significant benefit on overall survival. However the overall survival benefit being 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 significant difference between type of fractionation, through an improvement in local and regional control. Acute mucositis and the need for feeding tube during treatment were increased in the altered fractionation arm but late toxicities were similar between the arms. The second comparison demonstrated that altered fractionation radiotherapy had significantly lower overall survival compared to concomitant chemoradiotherapy,

although trials altered fractionation regimens in this comparison were almost only accelerated radiotherapy, which has not been shown to increase survival.

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 appears to improve both local and regional control, and might thus be preferred for patients with node positive tumors. Hyperfractionated radiotherapy should therefore be considered a standard of care along with concomitant chemoradiotherapy for the treatment of locally advanced head and neck cancers. Head to head comparison between hyperfractionated radiotherapy and concomitant chemoradiotherapy are lacking.

Contributors

PB, JB, and JPP with the help of the steering committee members designed and supervised the study.
PB, JB and JPP obtained funding.
PB, JB, JPP and BL searched and selected the trials. Steering committee members contributed to the identification and selection of the trials.
PB, BL and JPP collected and checked data with the help of the investigators who validated the re-analysis of their trials.
BL, PB and JPP did the statistical analyses.
PB, BL and JPP wrote the draft, with revisions from the other investigators.
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 and, after consultation with the collaborators, had final responsibility for the decision to submit for publication.

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Declaration of interests

AA, BL, JPP and PB report grants from Ligue National Contre le Cancer and grants from Institut National du Cancer during the conduct of the study.

The other authors declared no conflicts of interest.

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Table 1: Description of the nineteen new trials

Trials[ref]	Inclusion period	Sites	Stage[§§]	Radiotherapy dose / duration	No. weekly / daily fractions	Dose per fraction (Gray)	No. fractions	Chemotherapy drug/dose (mg/m²)	No. patients analyzed / randomized	Median follow-up in years (IQR)
EORTC 22843[30]	1984-1987	OC, OP, HP, L, O	III/IV	70 Gy /7 wks	5/wk; 1/day	2	35	C: 6 mg/m²/day during 35 days	53 / 53	5.0 (4.0 ; 5.2)
				72 Gy /7 wks **sc**	wk 1,4,7; 3/day	1.6	45	C: 10 mg/m²/day d1-5 on wk 1,4,7		
Cairo 1990[47]	1990-1997	OC, OP, HP, L	II-IV	60 Gy / 6.0 wks **po**	5/wk; 1/day	2	30		70 / 70	3.8 (1.6 ; 4.7)
				46.2 Gy / 2 wks **po**	6/wk; 3/day	1.4	33			
CRT 90-002[46]	1991-1996	OC, OP, HP, L	II-IV	63 Gy / 7 wks **po**	5/wk; 1/day	1.8	35		151 / 151	13.8 (8.0 ; 16.9)
				63 Gy / 5 wks **po**	5/wk; 1/day for 3 wks + 10/wk; 2/day for 2 wks	1.8 +1.8	15 +20			
INRC-HN9[43§]	1992-1998	OC, OP, HP, L	II-IV	60 Gy / 6 wks **sc**	5/wk; 1/day	2	30	C: 20 mg/m²/day on wk 1,4,7,10	136 / 136	18.5 (16.6 ; 20.8)
				75 Gy / 6 wks	5/wk; 1/day + 5/wk; 1/day on wks 5-6	2 +1.5	30 +10			
Osaka 1993[31]	1993-2001	L	I	60-66 Gy / 6-6.6 wks	5/wk; 1/day	2	30-33		189 / 189	5.9 (4.6 ; 7.9)
				56.25-63 Gy / 5-5.6 wks	5/wk; 1/day	2.25	25-28			
INRC-HN-10[32]	1994-2001	OC, OP, HP, L	I-IV	60 Gy / 6 wks **po**	5/wk; 1/day	2	30		226 / 226	4.5[†] (3.4 ; 6.2)
				64 Gy / 5 wks **po**	5/wk; 1/day (bid during wks 1 and 5)	2 +1.4/1.6	25 10			
EORTC22962[45*§u]	1996-1999	OC, OP, HP, L	II-IV	70 Gy / 7 wks	5/wk; 1/day	2	35		57 / 57	4.4 (2.1 ; 4.9)
				80.5 Gy / 7 wks	10/wk; 2/day	1.15	70			
				70 Gy / 7 wks	5/wk; 1/day	2	35	C: 100 mg/m², wk 1,4,7		
				80.5 Gy / 7 wks	10/wk; 2/day	1.15	70	C: 100 mg/m², wk 1,4,7		
RTOG 9512[33]	1996-2003	L	II-IV	70 Gy / 7 wks	5/wk; 1/day	2	35		249 / 250[**]	8.5 (7.0 ; 10.7)
				79.2 Gy / 6.5 wks	10/wk; 2/day	1.2	66			
ARTSCAN[34]	1998-2006	OC, OP, HP, L	I-IV	68 Gy / 6.5-7 wks	5/wk; 1/day	2	34		750 / 750	9.1 (7.3 ; 11.4)
				68 Gy / 4.5 wks	5/wk; 1/day for 4.5 wks + 5/wk; 1/day on wks 1-4	2 + 1.1	23 + 20			
IAEA-CRP-ACC[35]	1999-2004	OC, OP, HP, L	I-IV	66-70 Gy / 6.5-7 wks	5/wk; 1/day	2	33-35		906 / 908[**]	5.9 (3.7 ; 8.2)
				66-70 Gy / 5.5-6 wks	6/wk; 1/day	2	33-35			

Trials[ref]	Inclusion period	Sites	Stage[§§]	Radiotherapy dose / duration	No. weekly / daily fractions	Dose per fraction (Gray)	No. fractions	Chemotherapy drug/dose (mg/m²)	No. patients analyzed / randomized	Median follow-up in years (IQR)
DAHANCA 9[44]	2000-2006	OP, HP, L	I-IV	66 Gy / 5.5 wks	6/wk; 1/day	2	33		77 / 77	4.2 (2.1 ; 5.2)
				76 Gy / 5.5 wks	10/wk; 2/day	1.35	56			
GORTEC 9902[§36]	2000-2007	OC, OP, HP, L, O	III/IV	70 Gy / 7 wks	5/wk; 1/day	2	35	5FU : 600 mg/m²/day Cb: 70 mg/m²/day d1-4 on wk 1,4,7	840 / 840	5.2 (4.9 ; 6.2)
				70 Gy / 6 wks	5/wk; 1/day for 4 wks + 5/wk; 2/day for 2 wks	2 + 1.5	20 + 20	5FU: 600 mg/m²/day Cb: 70 mg/m²/day d1-5 on wk 1,4		
				64.8 Gy / 3.5 wks	5/wk; 2/day	1.8	36			
TMH 1114[§37]	2000-2008	OP, HP, L	II-IV	66-70 Gy / 6-7 wks	5/wk; 1/day	2	33-35		199 / NA	4.5 (2.0 ; 7.8)
				66-70 Gy / 6-7 wks	5/wk; 1/day	2	33-35	C: 30 mg/m²/wk, wks 1-7		
				66-70 Gy / 5.5-6wks	6/wk; 1/day	2	35			
CHARTWEL[u]	2001-2005	OC, OP, HP, L,O	I-IV	60-64 Gy / 6-6.5 wks **po**	1/day	2	30-32		114 / NA	4.8 (3.9 ; 5.4)
				51-54 Gy / 2.4 wks **po**	5/wk; 3/day for 2.4 wks	1.5	30			
pCAIR[38]	2001-2004	OC, OP, L	I-IV	63 Gy / 7 wks **po**	5/wk; 1/day	1.8	35		279 / 279	7.2† (6.3 ; 8.0)
				63 Gy / 5 wks **po**	7/wk; 1/day	1.8	35			
RTOG 0129[39]	2002-2005	OC, OP, HP, L	II-IV	70 Gy / 7 wks	5/wk; 1/day	2	35	C: 100 mg/m², wk 1,4,7	738 / 743[**]	7.9 (7.0 ; 8.8)
				72 Gy / 6 wks	5/wk; 1/day for 6 wks + 1/day for the last 12 days	1.8 + 1.5	30 + 12	C: 100 mg/m²,wk1,4		
KROG 0201[40]	2002-2010	L	I/II	66-70 Gy / 6.5-7 wks	5/wk; 1/day	2	33-35		156 / 156	5.3 (3.4 ; 6.7)
				63-67.5 Gy / 5.5-6 wks	5/wk; 1/day	2.25	28-30			
POPART[41]	2003-2008	OC, OP, HP, L	I-IV	66Gy / 7 wks **po**	5/wk; 1/day	2	33		148 / 148	6.3 (5.3 ; 8.0)
				66Gy / 5 wks **po**	5/wk; 1/day for 2 wks + 5/wk; 2/day for 3 wks	2 + 1.8 and 1.3	10 + 30			
CONDOR[42]	2009-2012	OC, OP, HP, L	III/IV	70Gy / 7 wks	5/wk; 1/day	2	35	C: 40 mg/m², wks 1-6	56 / 56[‡]	2.8 (1.8 ; 3.3)
				70 Gy / 6 wks	6/wk for 6 wks	2	35	C: 40 mg/m², wks 1-6		

ARTSCAN: Accelerated RadioTherapy of Squamous cell CArcinomas in the head and Neck, CAIR: Continuous Accelerated Irradiation,. CHARTWEL: Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) Week-end-Less, CRT: Clinical Randomized Trial, CONDOR: Dutch Head and Neck Society 08-01, DAHANCA: Danish Head and Neck Cancer Group, EORTC: European Organisation for Research and Treatment of Cancer, GORTEC: Groupe d'Oncologie Radiothérapie Tête et Cou, IAEA-CRP-ACC: International Atomic Energy Agency Coordinated Research Projects ACCelerated, INRC-HN: Instituto Nazionale per la Ricerca sul Cancro-Head and Neck, KROG: Korean Radiation Oncology Group, POPART: Post-Operative Accelerated RadioTherapy, pCAIR: post-operative Continuous Accelerated Irradiation (CAIR), RTOG: Radiation Therapy Oncology Group, TMH: Tata Memorial Hospital.

C: Cisplatin, Cb: Carboplatin, d: day, Gy: Gray, HP: Hypopharynx, IQR: InterQuartile Range; L: Larynx, NA: Not Available, O: Other, OC: Oral Cavity, OP: Oropharynx, po**:** post-operative, sc: split course, wk/wks: week/weeks, 5FU: 5-Fluorouracil

[ref] references used are those used in the paper

[*] 2x2 design

[**] 8 withdrew their consent in the two RTOG trials and in the IAEA trial and their data were not provided.

[†] Follow-up significantly different between the two treatment groups; for INRC-HR 10, the medians of follow-up were respectively 4.2 (IQR: 3.5; 5.8) and 4.8 (3.4; 6.9) years in the control and experimental arm; for pCAIR, the medians of follow-up were respectively 6.8 (6.2; 7.8) and 7.6 (6.5; 8.5) years in the control and experimental arm.

[‡] 18 patients included in 2011 and 2012

[§] Included in comparison 1 and/or 2 (altered fractionated radiotherapy versus concomitant chemoradiotherapy); INRC-HN9 used alternated RT-CT with 3 series of RT (20 Gy/2wk) at weeks 2–3, 5–6, and 8–9.

[§§] Stage computed using TNM and UICC classification 7th edition; may be different from trial's publication

[u] Unpublished

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							
No. events / No. patients	1313 / 1733	1413 / 1733	969 / 1733	344 / 1733	402 / 1729	289 / 1729	181 / 1729
Hazard ratio of treatment effect	0.83 [0.74; 0.92] p=0.00063	0.82 [0.74; 0.91] p=0.00019	0.81 [0.72; 0.92] p=0.0014	0.87 [0.70; 1.07] p=0.19	0.80 [0.66; 0.98] p=0.029	0.76 [0.61; 0.96] p=0.022	0.96 [0.72; 1.29] p=0.80
Absolute difference at 5 years (%)	+8.1 [+3.4; +12.8]	+6.8 [+2.4; +11.2]	-7.7 [-12.7; -2.7]	-4.3 [-9.0; +0.4]	-6.2 [-11.4; -1.0]	-4.1 [-9.0; +0.87]	+0.4 [-4.4; +5.2]
Absolute difference at 10 years (%)	+3.9 [-0.6; +8.4]	+4.0 [0.0; +8.0]	NA	NA	NA	NA	NA
Moderately accelerated							
No. events / No. patients	5239 / 8159	5699 / 8159	3603 / 8159	1636 / 8159	1470 / 7555	1107 / 7366	829 / 7923
Hazard ratio of treatment effect	0.96 [0.91; 1.01] p=0.14	0.91 [0.87; 0.96] p=0.00077	0.92 [0.86; 0.98] p=0.014	1.05 [0.95; 1.16] p=0.32	0.76 [0.69; 0.84] p<0.0001	0.92 [0.82; 1.04] p=0.19	0.96 [0.84; 1.10] p=0.55
Absolute difference at 5 years (%)	+2.2 [0.0; +4.4]	+3.3 [+1.1; +5.5]	-2.9 [-5.2; -0.6]	+0.4 [-1.8; +2.6]	-6.0 [-8.3; -3.7]	-0.8 [-2.8; +1.2]	-0.7 [-2.7; +1.3]
Absolute difference at 10 years (%)	+0.6 [-1.9; +3.1]	+2.2 [-0.1; +4.5]	NA	NA	NA	NA	NA
Very accelerated							
No. events / No. patients	1462 / 2089	1646 / 2089	1217 / 2089	245 / 2089	317 / 1429	331 / 1429	316 / 2058
Hazard ratio of treatment effect	0.95 [0.86; 1.06] p=0.37	0.91 [0.83; 1.01] p=0.069	0.94 [0.84; 1.06] p=0.31	1.01 [0.78; 1.31] p=0.92	0.88 [0.70; 1.10] p=0.26	0.89 [0.72; 1.11] p=0.31	0.95 [0.76; 1.19] p=0.64
Absolute difference at 5 years (%)	+1.8 [-2.5; +6.1]	+1.6 [-2.1; +5.3]	-2.0 [-6.5; +2.5]-	+0.5 [-5.4; +4.4]	-2.3 [-8.7; +4.1]	NA	-1.5 [-7.2; +4.2]
Absolute difference at 10 years (%)	+0.4 [-4.4; +5.2]	-0.3 [-4.3; +3.7]	NA	NA	NA	NA	NA
All types of fractionation							
No. events / No. patients	8014 / 11981	8758 / 11981	5789 / 11981	2225 / 11981	2189 / 10713	1727 / 10524	1326 / 11710
Hazard ratio of treatment effect	0.94 [0.90; 0.98] p=0.0033	0.90 [0.86; 0.94] p<0.0001	0.91 [0.86;0.96] p=0.00022	1.02 [0.94; 1.11] p=0.70	0.79 [0.72; 0.85] p<0.0001	0.89 [0.81; 0.98] p=0.016	0.96 [0.86; 1.07] p=0.43
Absolute difference at 5 years (%)	+3.1 [+1.3; +4.9]	+3.7 [+2.0; +5.4]	-3.5 [-5.4; -1.6]	-0.4 [-2.4; +1.4]	-5.7 [-7.7; -3.7]	-1.4 [-3.2; +0.4]	-0.8 [-2.6; +1.0]
Absolute difference at 10 years (%)	+1.2 [-0.8; +3.2]	+2.3 [+0.5; +4.1]	NA	NA	NA	NA	NA
Interaction between type of fractionation	p=0.051	p=0.17	p=0.17	p=0.28	p=0.51	p=0.35	p>0.99
Heterogeneity between trials	p=0.14, I^2=20%[*]	p=0.045, I^2=30%[*]	p=0.035, I^2=32%[*]	p=0.67, I^2=0%	p=0.0032, I^2=45%[†]	p=0.23, I^2=15%[‡]	p=0.95, I^2=0%

Results are presented with [95% confidence interval], Hazard ratios are: altered fractionated RT versus conventional RT. NA: Not Available because not enough data at 10 years

Absolute variations are between survival rates for the overall and progression-free survival, between failure rates for local failure, regional failure and distant failure, and between mortality rates for cancer and non-cancer deaths.

[+] RTOG 7913 (210 patients), Cairo 1990 (n=70), TROG-9101 (350 patients) and GORTEC 9902 (n=559) did not distinguish between local and regional failure for all their patients.

[£] No regional failure but only local and distant failures for the Osaka 1993 trial (n=189).

[*] 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], Osaka 1993[31])

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

Table 3: Acute and late severe toxicity between conventional and altered fractionation radiotherapy

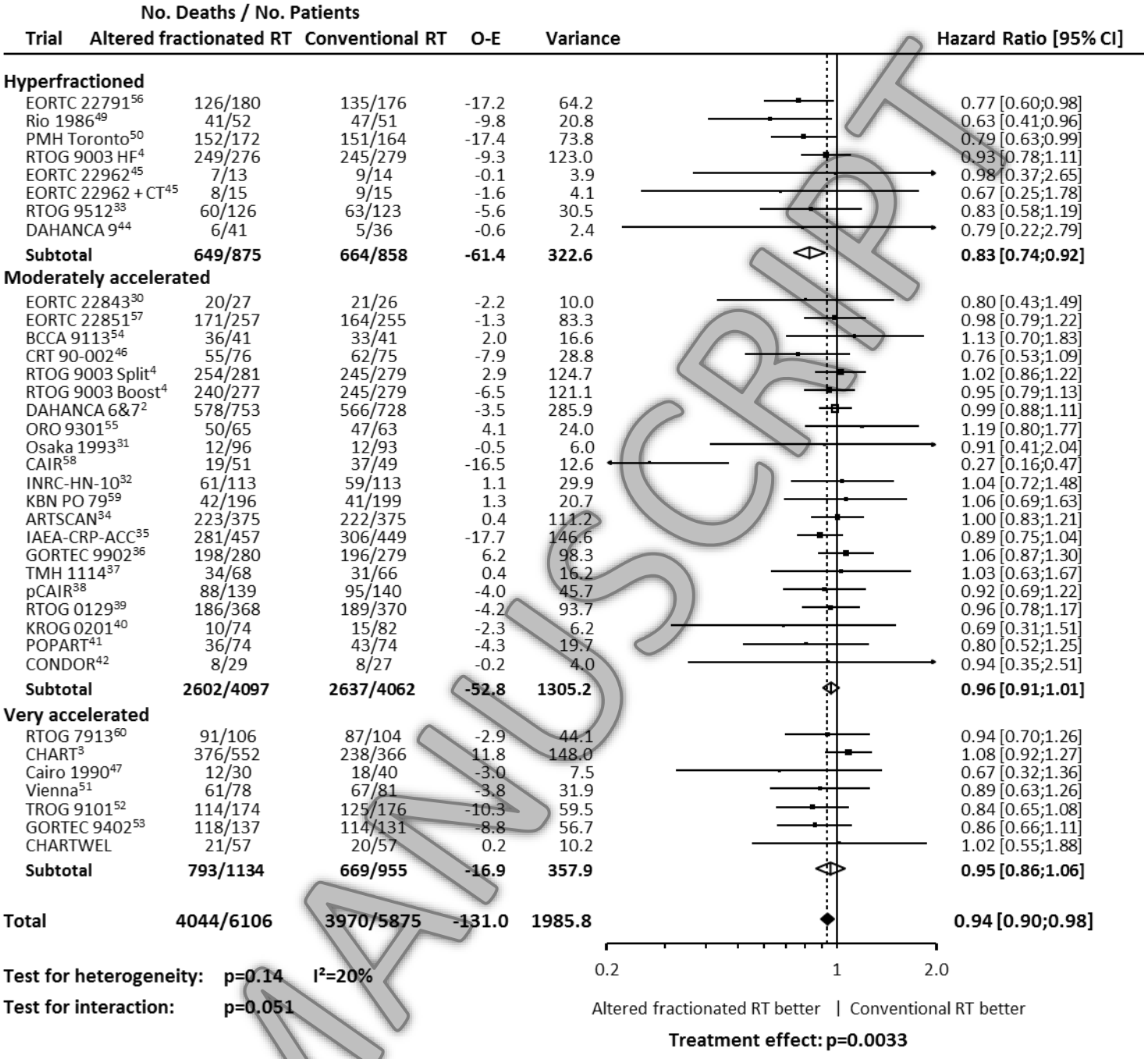
Severe toxicities are Grade 3-4 toxicities except for xerostomia where grade 2-3 were considered. "No heterogeneity" refers to a sensitivity analysis where trials responsible for statistical heterogeneity were excluded. The absence of change in the p-value for efficacy shows that the statistical significance is independent from the trial heterogeneity.

Toxicity		No. comparisons	No. patients	Toxicity rate in altered fractionated RT (%)*	Toxicity rate in conventional RT (%)	Odds Ratio [95% CI]	p-value safety	I^2	p-value heterogeneity
Acute toxicities									
Mucositis	All trials	20	8541	38.9	27.3	2.02 [1.81 ; 2.26]	< 0.0001	78%	< 0.0001
	No heterogeneity	16	7051	35.2	24.2	2.10 [1.84 ; 2.41]	< 0.0001	0%	0.66
Dermatitis	All trials	15	4997	17.7	16.5	1.09 [0.93 ; 1.29]	0.29	36%	0.083
	No heterogeneity	13	4314	20.1	17.6	1.20 [1.01 ; 1.42]	0.041	0%	0.83
Weight loss	All trials	5	2053	3.6	4.2	0.87 [0.56 ; 1.36]	0.54	7%	0.37
Need for feeding tube	All trials	6	2859	52.1	39.7	1.75 [1.49 ; 2.05]	< 0.0001	89%	< 0.0001
	No heterogeneity	4	1871	35.6	27.1	1.63 [1.34 ; 1.99]	< 0.0001	3%	0.38
Late toxicities									
Xerostomia	All trials	12	4726	51.3	51.1	1.01 [0.88 ; 1.14]	0.94	20%	0.25
	No heterogeneity	11	4414	54.6	54.1	1.02 [0.90 ; 1.17]	0.73	0%	0.50
Bone toxicity	All trials	11	3219	4.4	4.0	1.12 [0.80 ; 1.57]	0.52	0%	0.77
Mucosal toxicity	All trials	8	2298	14.5	13.4	1.10 [0.87 ; 1.40]	0.41	49%	0.058
	No heterogeneity	7	1921	14.4	14.9	0.96 [0.74 ; 1.24]	0.74	0%	0.64
Neck fibrosis	All trials	15	5557	7.6	6.9	1.13 [0.92 ; 1.39]	0.23	70%	< 0.0001
	No heterogeneity	12	4250	7.0	6.5	1.09 [0.85 ; 1.38]	0.50	0%	0.45

CI, confidence interval; RT, radiotherapy

Figure 1: Forest plot of overall survival for trials comparing altered fractionation and conventional fractionation radiotherapy

See Table 1 for trials abbreviations



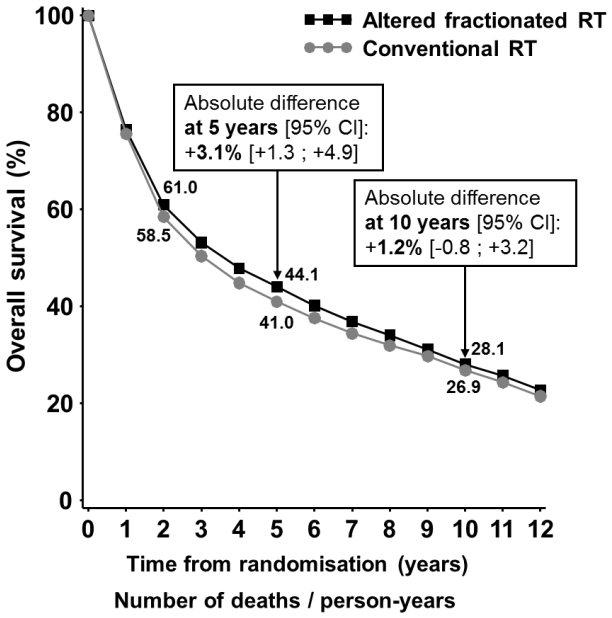
The centre of each square is the hazard ratio (HR) for individual trials and corresponding horizontal line is the 95% confidence interval (CI). The area of the square is proportional to the number of deaths in each trial. The broken line and centre of the black diamond is overall pooled HR and the horizontal tip of the diamond is the 95% CI. Open diamonds are the HR of different types of radiotherapy. The exclusion of the outlying CAIR trial(58) reduced the heterogeneity further (p=0.89, I2=0%), increased the statistical interaction between altered fractionation regimens and survival (p=0.033) while not affecting the overall effect of altered fractionation radiotherapy on survival.

CI: Confidence Interval, O–E: Observed minus Expected, RT: Radiotherapy,

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

A: All radiotherapy types, B: Hyperfractionated, C: Moderately accelerated, D: Very accelerated

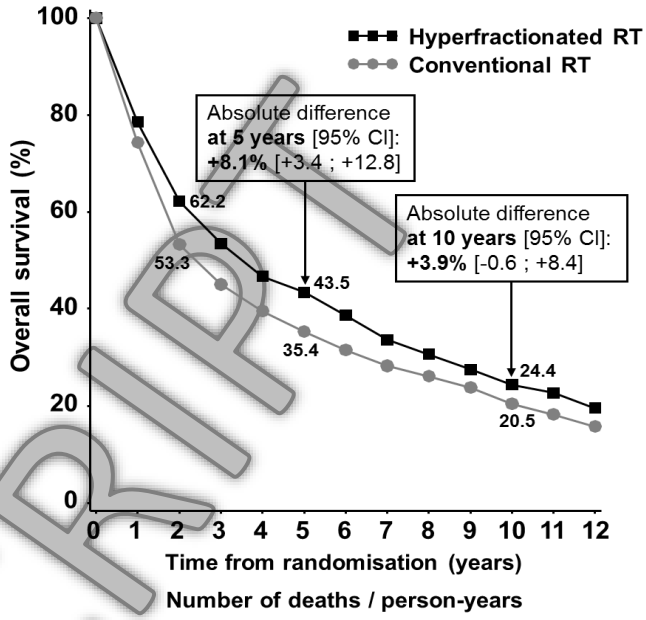
A



Number of deaths / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
Altered fractionated RT	2340 / 9351	936 / 8374	548 / 6153	220 / 1931
Conventional RT	2401 / 8866	918 / 7531	452 / 5431	199 / 1723

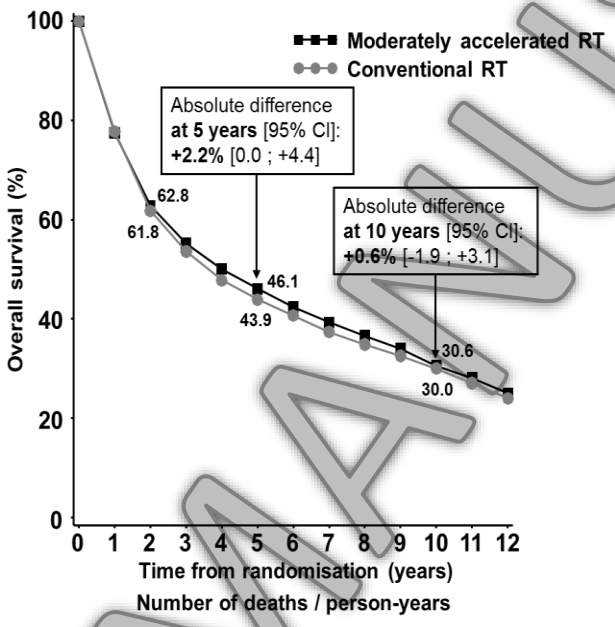
B



Number of deaths / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
Hyperfractionated RT	320 / 1359	152 / 1210	120 / 1035	57 / 442
Conventional RT	395 / 1250	137 / 988	87 / 808	45 / 330

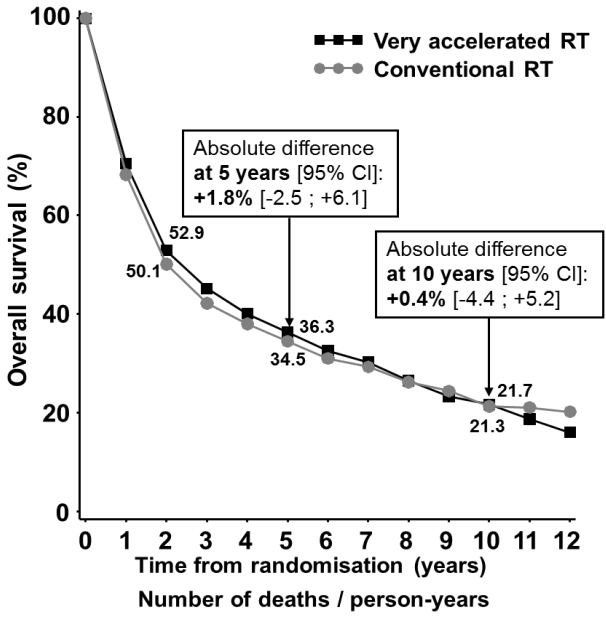
C



Number of deaths / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
Moderately acceleratedRT	1497 / 6347	610 / 5816	343 / 4291	152 / 1412
Conventional RT	1525 / 6292	650 / 5528	309 / 4005	153 / 1334

D

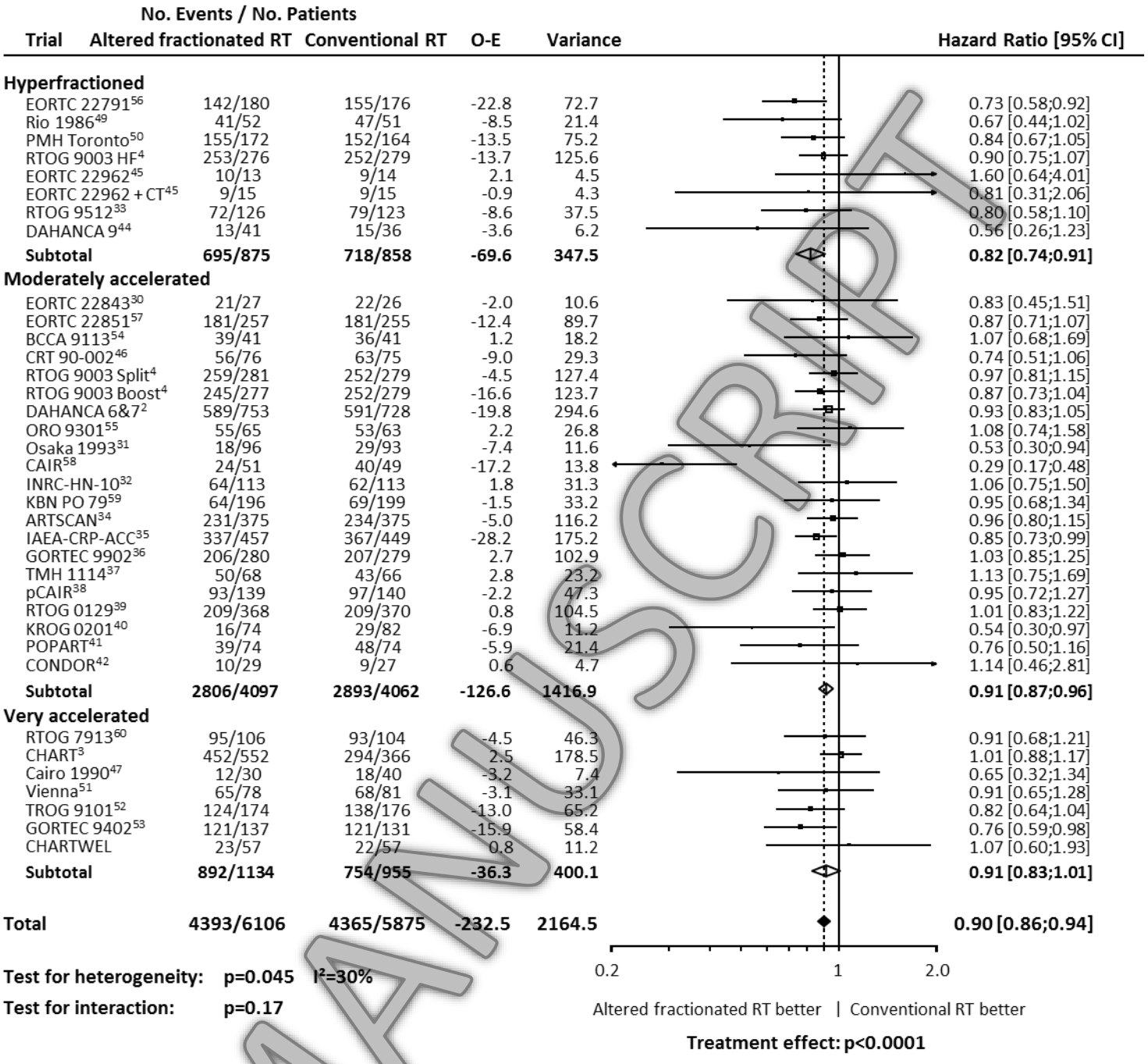


Number of deaths / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
Very accelerated RT	523 / 1644	174 / 1348	85 / 825	11 / 78
Conventional RT	481 / 1325	131 / 1016	56 / 618	1 / 58

CI: Confidence Interval, RT: Radiotherapy

Figure 3: Forest plot of progression-free survival for trials comparing altered fractionation and conventional fractionation radiotherapy
See Table 1 for trials abbreviations

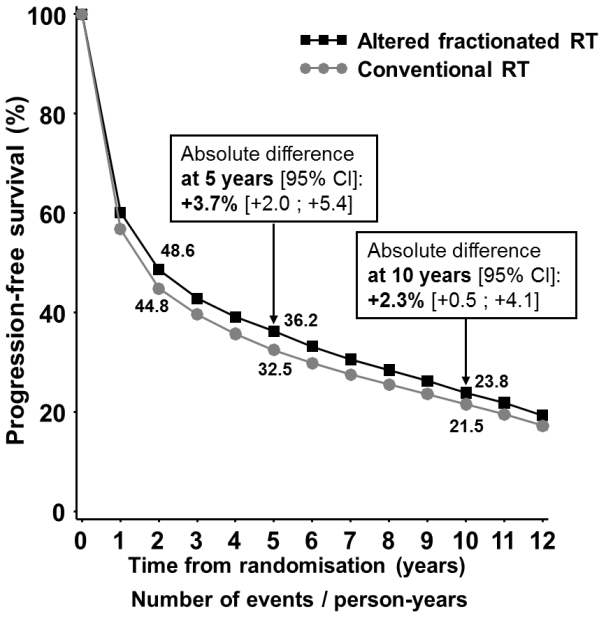


CI: Confidence Interval, O–E: Observed minus Expected, RT: Radiotherapy

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

A: All radiotherapy types, B: Hyperfractionated, C: Moderately accelerated, D: Very accelerated

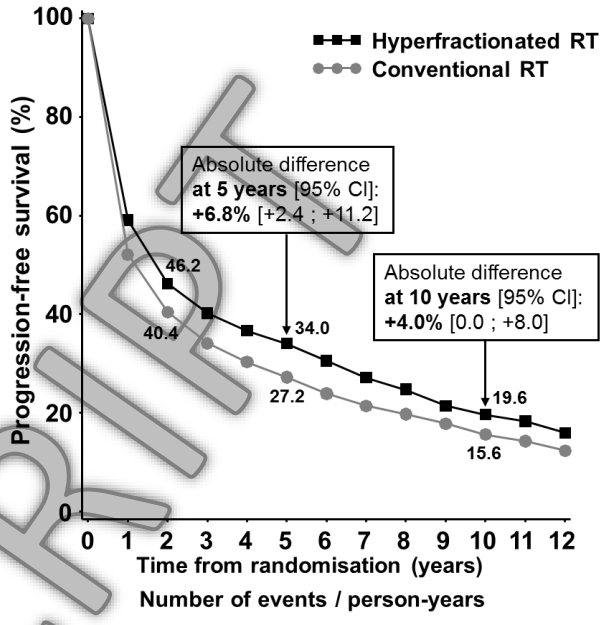
A



Number of events / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
Altered fractionated RT	3044 / 7908	715 / 7002	437 / 5241	197 / 1727
Conventional RT	3166 / 7208	663 / 6145	368 / 4457	168 / 1457

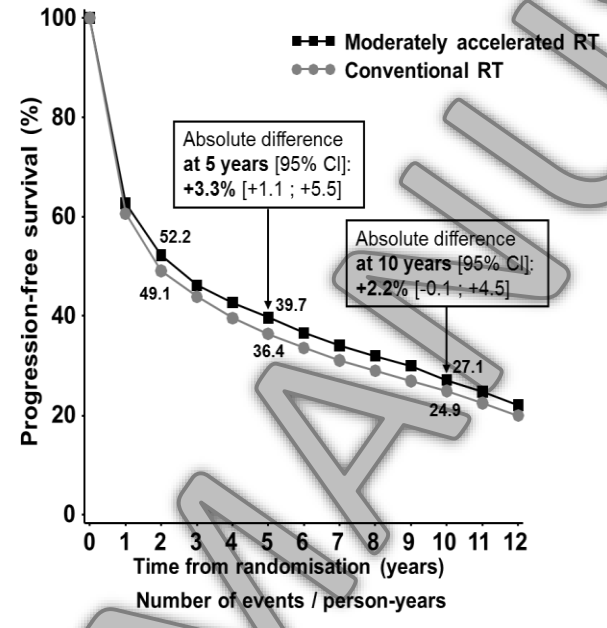
B



Number of events / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
Hyperfractionated RT	449 / 1122	106 / 985	94 / 861	46 / 366
Conventional RT	507 / 980	106 / 773	71 / 628	34 / 272

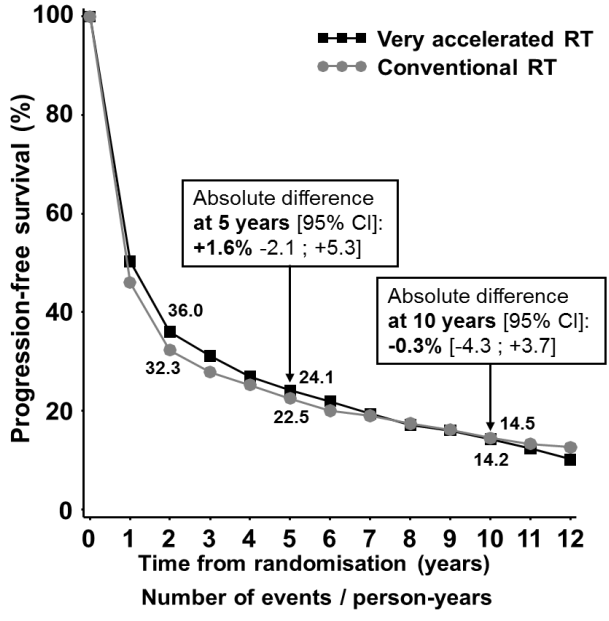
C



Number of events / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
Moderately accelerated RT	1902 / 5503	477 / 5058	286 / 3838	141 / 1305
Conventional RT	2029 / 5252	472 / 4657	260 / 3399	132 / 1140

D

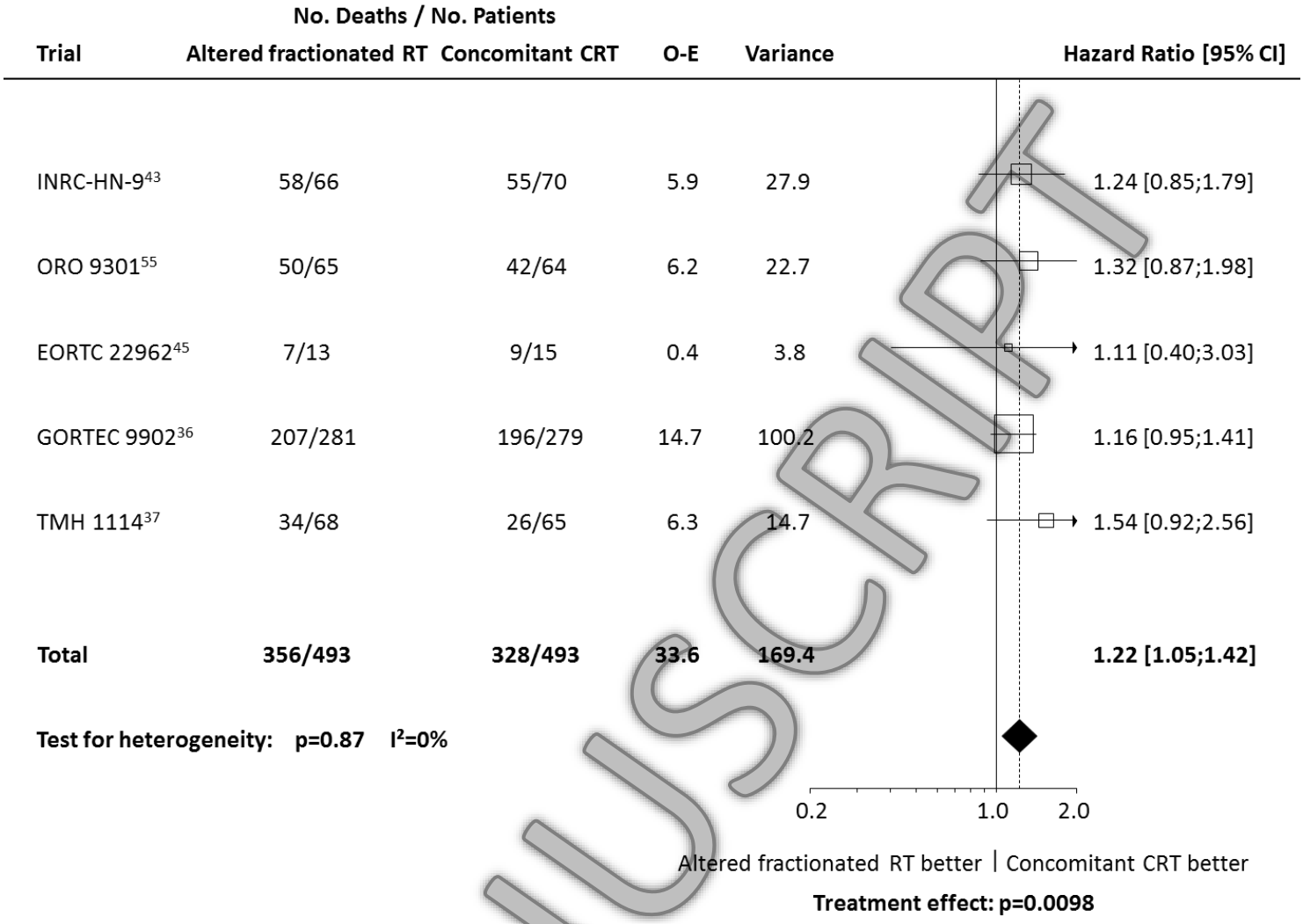


Number of events / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
Very accelerated RT	693 / 1283	132 / 959	57 / 541	10 / 56
Conventional RT	630 / 978	85 / 715	37 / 430	2 / 44

CI: Confidence Interval, RT: Radiotherapy

Figure 5: Forest plots of overall survival for trials comparing altered fractionation radiotherapy and concomitant chemoradiotherapy (using conventional fractionation)
See Table 1 for trials abbreviations



CI: Confidence Interval, CRT: Chemoradiotherapy, O–E: Observed minus Expected, RT: Radiotherapy