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Meta analysis

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

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ABSTRACT

Background: Our previous individual patient data (IPD) meta-analysis showed that chemotherapy improved survival in patients curatively treated for non-metastatic head and neck squamous cell carcinoma (HNSCC), with a higher benefit with concomitant chemotherapy. However the heterogeneity of the results limited the conclusions and prompted us to confirm the results on a more complete database by adding the randomised trials conducted between 1994 and 2000.
Methods: The updated IPD meta-analysis included trials comparing loco-regional treatment to loco-regional treatment + chemotherapy in HNSCC patients and conducted between 1965 and 2000. The log-rank-test, stratified by trial, was used to compare treatments. The hazard ratios of death were calculated.
Results: Twenty-four new trials, most of them of concomitant chemotherapy, were included with a total of 87 trials and 16,485 patients. The hazard ratio of death was 0.88 ($p < 0.0001$) with an absolute benefit for chemotherapy of 4.5% at 5 years, and a significant interaction ($p < 0.0001$) between chemotherapy timing (adjuvant, induction or concomitant) and treatment. Both direct (6 trials) and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy as compared to induction chemotherapy. For the 50 concomitant trials, the hazard ratio was 0.81 ($p < 0.0001$) and the absolute benefit 6.5% at 5 years. There was a decreasing effect of chemotherapy with age ($p = 0.003$, test for trend).
Conclusion: The benefit of concomitant chemotherapy was confirmed and was greater than the benefit of induction chemotherapy.

Head and neck (oral cavity, oropharynx, hypopharynx, and larynx) squamous cell carcinomas (HNSCC) occur frequently with over 500,000 new cases diagnosed worldwide each year [1]. Our previous individual patient data meta-analysis of randomised trials showed that chemotherapy improved survival in non-metastatic HNSCC treated by surgery and/or radiotherapy (hazard ratio [HR] of 0.90, 95% confidence interval [CI] 0.85–0.94) with an overall 4% benefit at 5 years, from 32% to 36% [2]. Chemotherapy can be administrated before, at the same time or after loco-regional treatment corresponding to induction, concomitant or adjuvant chemotherapy. A greater benefit (8%) was observed in trials that gave chemotherapy concomitantly to radiotherapy. The meta-analysis pooled the data from trials performed between 1965 and 1993. Cisplatin started to be used in head and neck randomised trials in the early 80s. The observed heterogeneity of the results required cautious conclusions; indeed, five trials which represented about 7% of the data explained most of the heterogeneity and when they were excluded the higher benefit of concomitant chemotherapy disappeared [3]. Therefore the MACH-NC group decided to confirm the results by updating its database with the inclusion of the randomised trials performed between 1994 and 2000. Preliminary results were published in 2007 in a short report [4].

Materials and methods

The methods were pre-specified in a protocol (copy available on request).

Eligibility criteria

Trials were eligible if they had accrued previously untreated patients with HNSCC and compared loco-regional treatment with loco-regional treatment plus chemotherapy. Each trial had to be randomised in a way that those entering patients could not know in advance which treatment an individual would receive (avoiding the potential of allocation bias). Trials were eligible if accrual was

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completed before 31st December 2000, and if all randomised patients had undergone a potentially curative loco-regional treatment and had not been treated for another malignancy. Trials concerning tumours of the oral cavity, oropharynx, hypopharynx and larynx were included. Trials including only nasopharyngeal carcinomas were excluded.

Identification of trials

To avoid publication bias, both published and unpublished trials were included. Searches of Medline, Clinprot and Embase were supplemented with hand searches of meeting abstracts (ASCO, ESTRO, ASTRO, ESMO, ECCO) and references in review articles. Trial registers (PDQ, ClinProt, CCT mega-register) were consulted. Experts and all trialists who took part in the meta-analysis were also asked to identify trials.

Data

The data collected for each patient were: age, sex, tumour site, TNM or stage, performance status, treatment allocated, and date of randomisation. The date and site of the first recurrence, the date of second primary cancer and the cause of death were also collected. This last variable was only available for the recent trials. Updated information on survival status and date of last follow-up were collected.

All data were checked for internal consistency and were compared with the trial protocol and published reports. Range checks were performed and extreme values were verified with the trialists. Each trial was analysed individually, and the resulting survival analyses along with trial data were sent to the trialists for review.

Analysis

The main endpoint was overall survival. Event-free survival, cumulative loco-regional, and distant failure were secondary endpoints as were cancer and non-cancer mortality. Deaths attributed to causes other than head and neck cancer with no reported recurrence of head and neck cancer were described as "non-head and neck cancer deaths". All other deaths were described as "head and neck cancer deaths" including deaths from head and neck cancer, deaths from any cause after recurrence and deaths from unknown cause without reported recurrence.

All analyses were carried out on an intention-to-treat basis, i.e., all randomised patients were analysed in the allocated treatment group, irrespective of their actual treatment. Trials were divided into three groups according to the timing of chemotherapy: adjuvant, induction (also called neo-adjuvant) and concomitant as previously described [2].

Statistics

The median follow-up time was computed according to the reverse Kaplan Meier method by censoring deaths and using as events those censored in the Kaplan Meier method [5]. Survival analyses were stratified by trial, and the log-rank observed minus expected number of deaths ($O - E$) and its variance were used to calculate individual and overall pooled hazard ratios (HRs) using a fixed effect model [6]. To prevent late recurrences from biasing the analyses of cause-specific mortality, the log-rank analysis of non-head and neck cancer mortality covered only the period before recurrence (i.e., data are censored at the first recurrence) [7]. An unbiased – although potentially diluted – log-rank analysis of head and neck cancer mortality was obtained indirectly by subtracting the log-rank statistic for non-head and neck cancer mortality from the log-rank statistic for mortality from all causes (i.e., the two observed values are subtracted from each other, the two expected values are subtracted from each other, and the two variances are subtracted from each other). Then, this method takes into account the competing risk between the two types of mortality. Heterogeneity between trials and groups was investigated using Chi-square tests [8] and the I^2 index [9] that expresses the percentage variability of the results related to heterogeneity rather than to the sampling error. To study the interaction between treatment and a covariate, an analysis stratified by trial was performed for each covariate group, and the HRs for each covariate group (e.g. men and women), were compared by a test for interaction or trend as appropriate. Stratified survival curves were computed for control and experimental groups and were used to calculate absolute benefit at 2, and 5 years [10]. The absolute benefit depends on hazard ratio and survival rate. All p-values were two sided.

Results

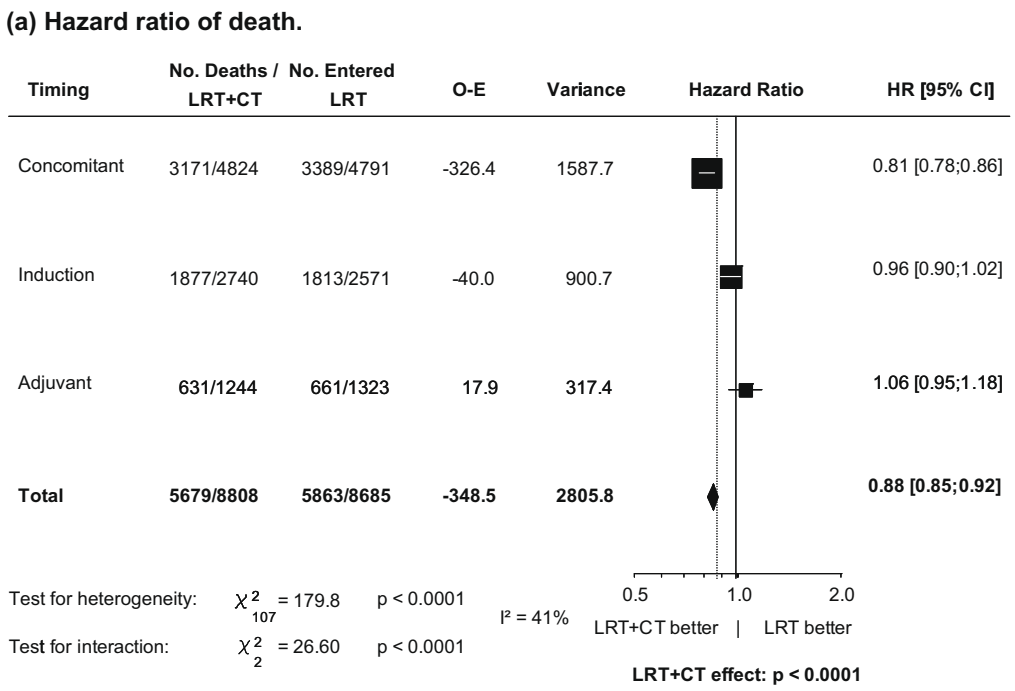
The meta-analysis included 87 randomised trials (16,485 patients) comparing loco-regional treatment versus the same loco-regional treatment + chemotherapy. The trials included in the previous MACH-NC meta-analysis have been described previously [2]. Twenty-four new trials (5744 patients) evaluated chemotherapy concomitant with radiotherapy. One trial [5 of the Web-appendix] evaluated both adjuvant and concomitant chemotherapy. Data from one trial [11] that included 86 patients were lost, and two trials [12] including 2172 patients were excluded after blind review because of potential bias in patients follow-up. Two trials (EORTC 22954 and 22962, 116 patients) were unpublished. We were able to collect data from 655 of the 791 randomised patients that had been excluded from the original published analyses. Updated follow-up was obtained for most of the trials and the overall median follow-up was 5.6 years. Because some trials had strata that corresponded to different loco-regional treatments or chemotherapies, and because some trials had 3-arms or a 2 by 2 design, some trial arms were utilised twice, such that the number of comparisons in the meta-analysis was 108 and the number of patients was 17,493. The description of the new trials included and their references can be found in Web-Table 1. The distribution of the treatment comparison according to timing of chemotherapy, type of loco-regional treatment, type of chemotherapy and period of accrual is given in Web-Table 2. The description of the overall population is given in Web-Table 3.

Effect of concomitant chemotherapy

The following analyses concern the 50 concomitant trials including 9615 patients (6560 deaths) with a median follow-up of 5.6 years.

Overall and event-free survival

The hazard ratio of death (Fig. 1a and Web-Fig. 1) was 0.81 (95% confidence interval: 0.78–0.86; $p < 0.0001$) in favour of chemotherapy with an absolute benefit of 6.5% at 5 years (Fig. 2a). The magnitude of the benefit was identical for the 1965–1993 trials and the 1994–2000 trials, without significant heterogeneity ($p = 0.27$) in the most recent trials. Excluding trials with less than 80 patients, or performed before 1980, or with a follow-up shorter than 5 years led to similar results (sensitivity analysis, Web-Table 4a). Analysis without arm duplication led to similar results (Web-Table 4a). In the recent trials, it was possible to separate cancer and non-cancer deaths. Cause of death was missing in less than 4% of the patients without recurrence. The benefit of chemotherapy was due to its effect on deaths related to head and neck cancer (HR 0.78 [0.73–0.84], $p < 0.0001$; Fig. 3) and with no effect on non-cancer deaths (0.96 [0.82–1.12], $p = 0.62$).



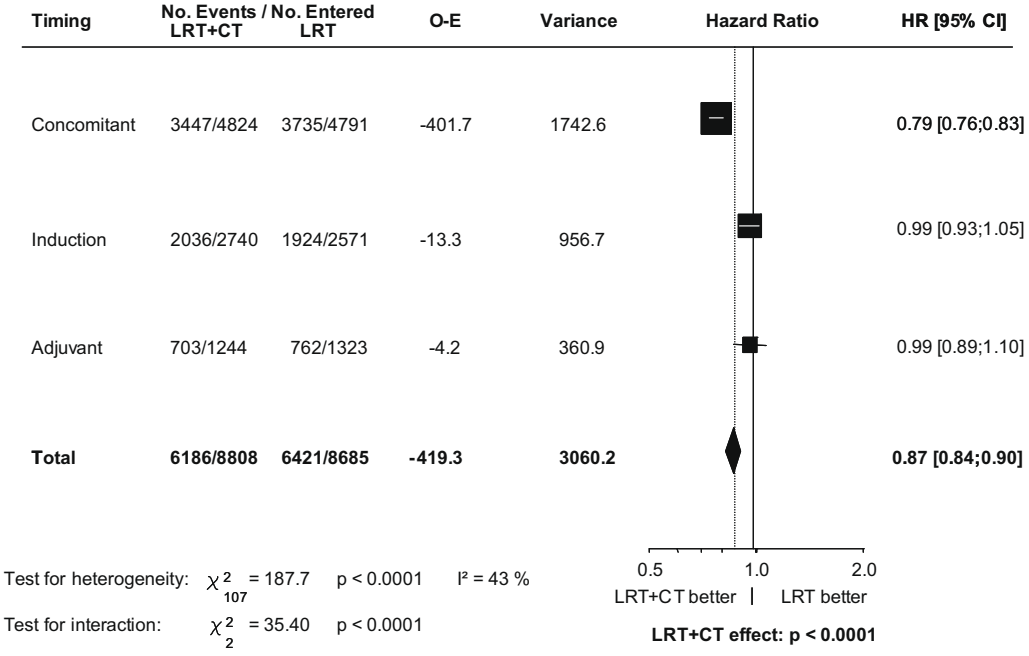
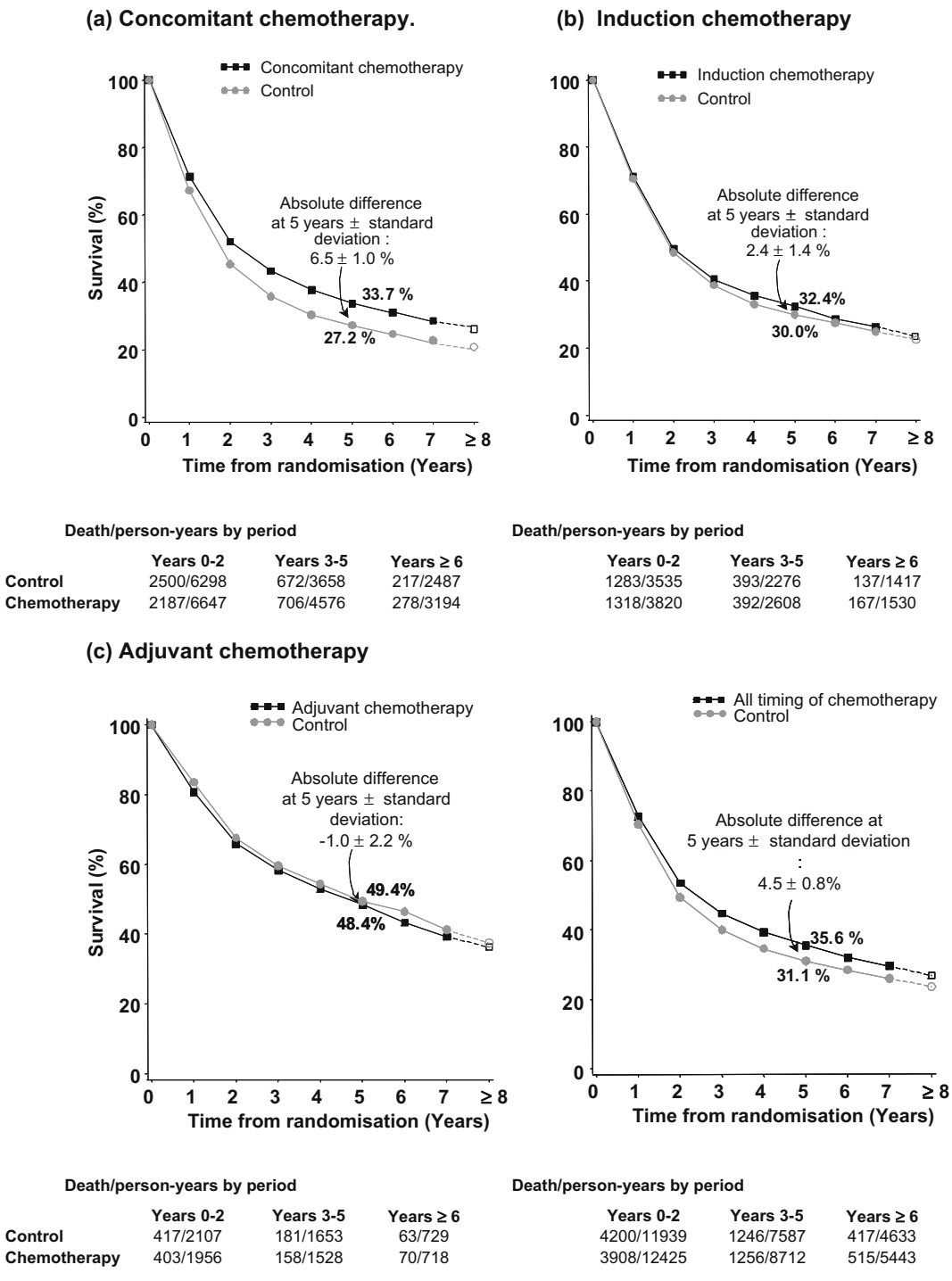


Fig. 1. Hazard ratio with loco-regional treatment plus chemotherapy versus loco-regional treatment alone by timing of chemotherapy. (a) Hazard ratio of death; (b) hazard ratio of recurrence or death. The broken line and centre of the black diamond correspond to overall pooled hazard ratio (HR) and the horizontal tip of the diamond is the 95% confidence interval (CI). The centre of black square corresponds to the HR of different types of chemotherapies. The area of the square is proportional to the number of deaths in each trial (or group of trials). CT, chemotherapy; LRT, loco-regional treatment; RT, radiotherapy; $O - E$, observed minus expected.

Similar results were observed for event-free survival, with a hazard ratio of 0.79 (0.76–0.83; $p < 0.0001$, Fig. 1b) and an absolute benefit of 6.2% at 5 years (from 23.1% to 29.3%).

Subset analyses

The benefit of chemotherapy on survival did not differ significantly (test for interaction, $p = 0.14$) between the group of trials with postoperative radiotherapy (HR 0.79 [0.68–0.91]), or curative radiotherapy with conventional (HR 0.83 [0.78–0.88]) or altered fractionation (HR 0.73 [0.65–0.82]; Web-Table 5). No significant difference ($p = 0.19$) was seen between mono-chemotherapy (HR 0.84) and poly-chemotherapy (HR 0.78). In the poly-chemotherapy group, the effect of chemotherapy was not significantly different ($p = 0.41$) between the different sub-groups: with cisplatin or carboplatin (platin) and 5-fluorouracil (5-FU), with either platin or 5-FU or with neither (Fig. 4). In the mono-chemotherapy group, the



Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	2500/6298	672/3658	217/2487
Chemotherapy	2187/6647	706/4576	278/3194

Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
	1283/3535	393/2276	137/1417
	1318/3820	392/2608	167/1530

Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	417/2107	181/1653	63/729
Chemotherapy	403/1956	158/1528	70/718

Death/person-years by period

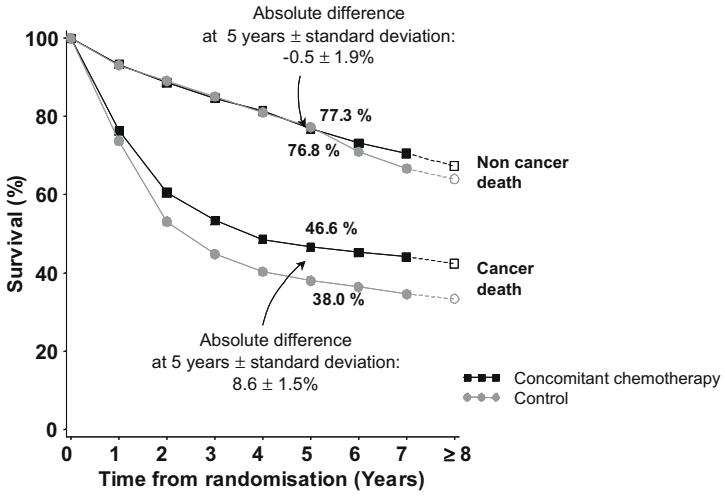
	Years 0-2	Years 3-5	Years ≥ 6
	4200/11939	1246/7587	417/4633
	3908/12425	1256/8712	515/5443

Fig. 2. Survival curves by treatment arm for all trials and for the three groups of trials according to the timing of chemotherapy. The slopes of the broken lines from year 7 to year 8 are based on the overall death rates in the seventh and subsequent years. (a) Concomitant chemotherapy; (b) induction chemotherapy; (c) adjuvant chemotherapy; (d) all three groups together. Absolute differences are given with their standard error.

effect of chemotherapy was significantly higher ($p = 0.006$) with platin than with other types of mono-chemotherapies (Fig. 4). Only five trials used carboplatin: two alone, and three with 5-FU (Web-Table 1 and Reference 2).

Sub-group analyses

Fig. 5 shows the effect of chemotherapy on survival according to patient characteristics. The only statistically significant result was a decreasing effect of chemotherapy on survival with increasing age (test for trend, $p = 0.003$; Fig. 5b). This effect could not be explained by an imbalance in the other covariates studied (data not shown). There was no significant variation of chemotherapy effect according to patient characteristics for event-free survival (data not shown). The cause of death was available only for the recent trials (1994–2000) and varied markedly according to age. As might be expected, the proportion of deaths not due to head and neck cancer increased progressively with age from 15% in patients less than 50–39% in patients 71 and over.



Non cancer death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	187/2985	86/1769	37/544
Chemotherapy	201/3301	106/2330	34/727

Cancer death by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	1268	290	32
Chemotherapy	1049	278	28

Fig. 3. Non-cancer death and cancer death survival curves in the recent trials comparing loco-regional treatment plus concomitant chemotherapy with loco-regional treatment alone.

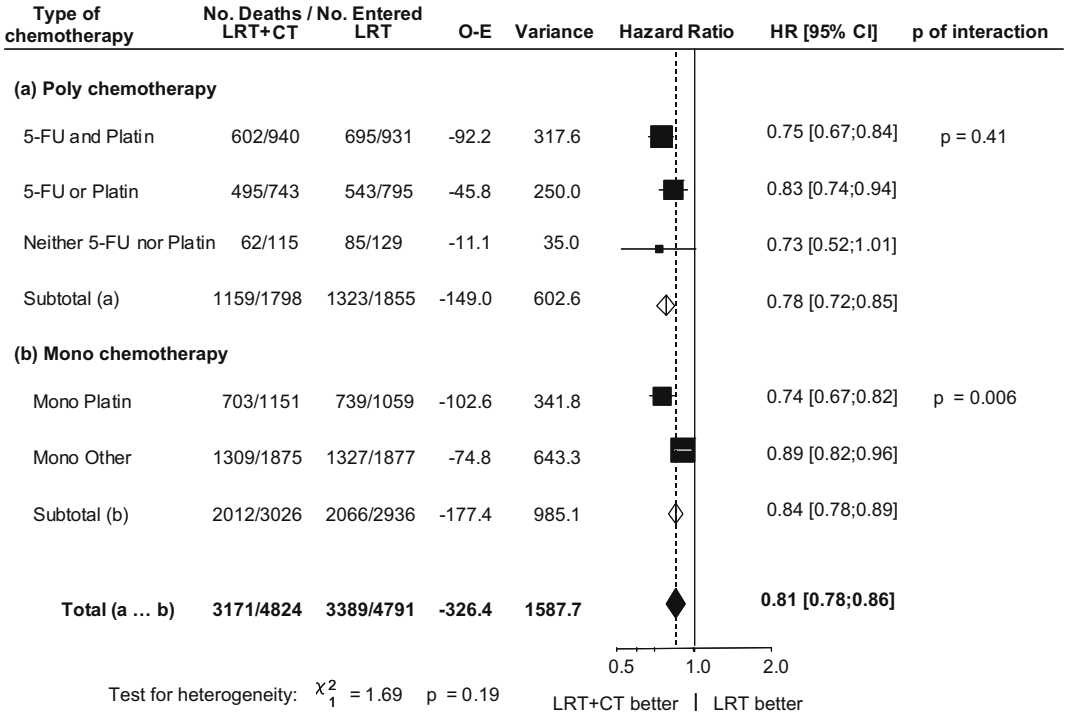


Fig. 4. Hazard ratio of death with loco-regional treatment plus concomitant chemotherapy versus loco-regional treatment alone by type of chemotherapy. CT, chemotherapy. The test of heterogeneity on the bottom corresponds to the comparison of the HRs for poly and mono-chemotherapy. The tests of interaction on the right correspond to the comparison of the HR of the type of chemotherapy within the poly-chemotherapy and mono-chemotherapy groups of trials.

Effect of induction chemotherapy

The following analyses concern 31 induction chemotherapy trials including 5311 patients (3690 deaths) with a median follow-up of 6.1 years. The HR of death (Fig. 1a and Web-Fig. 2) was 0.96 ([0.90–1.02] $p = 0.18$) in favour of induction chemotherapy with an absolute benefit of 2.4% at 5 years (Fig. 2b). There was no significant ($p = 0.23$) variation of the effect according to the type of chemotherapy: 0.90 (0.82–0.99) for 5-FU-platin, 1.01 (0.91–1.12) for

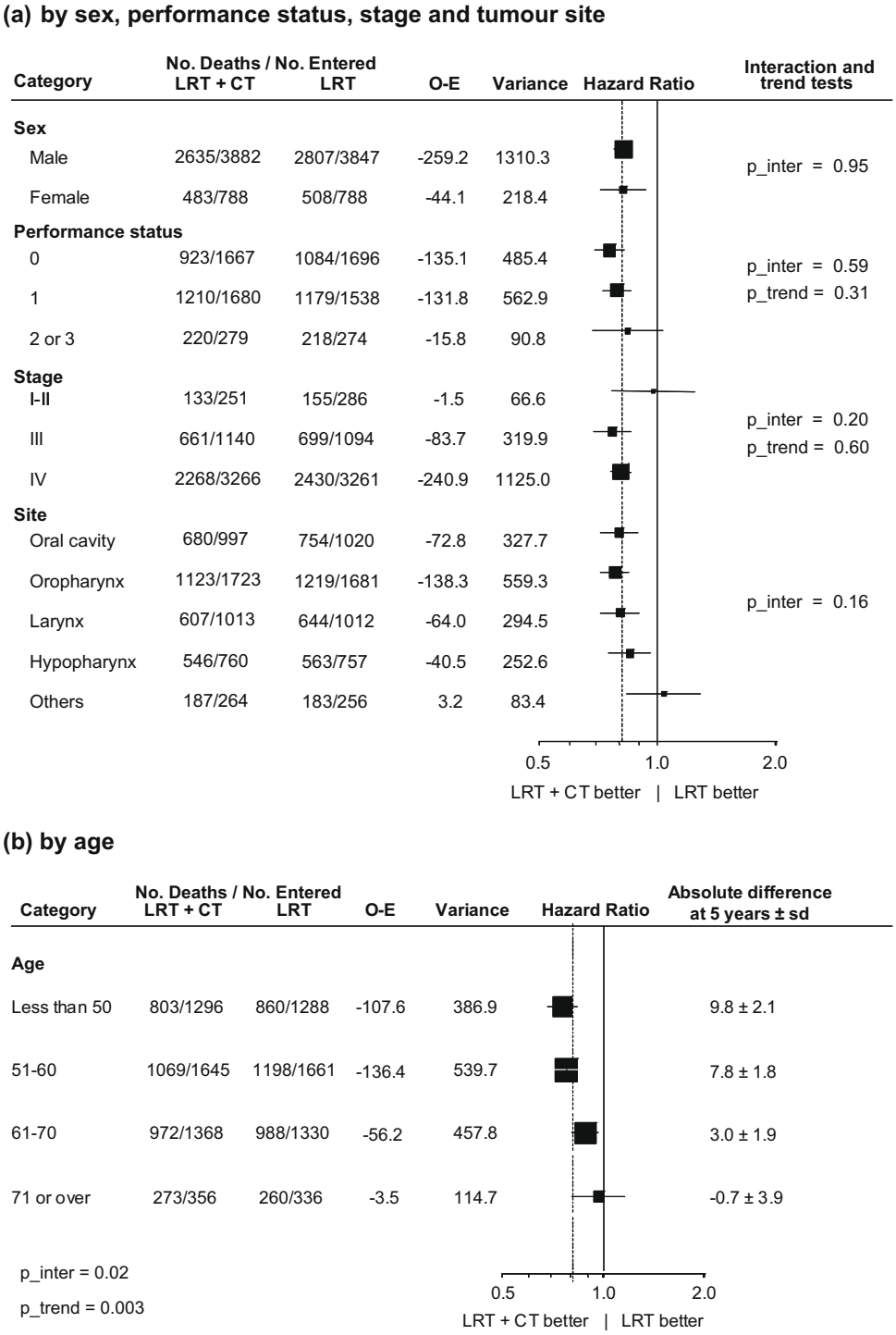


Fig. 5. Hazard ratio of death with loco-regional treatment plus concomitant chemotherapy versus loco-regional treatment alone by patient characteristics. (a) By sex, performance status, stage and tumour site; (b) by age. *p*_heter: *p*-value of the test of heterogeneity, *p*_trend: *p*-value of the test for trend.

other poly-chemotherapy, 0.99 (0.84–1.18) for mono-chemotherapy (no trial with platin). Sensitivity analyses are reported in Web-Table 4b. Similar results were observed for event-free survival, with a hazard ratio of 0.99 (0.93–1.05; $p = 0.67$) and an absolute benefit of 1.3% at 5 years (from 26.3% to 27.6%). The hazard ratios of death were not significantly different ($p = 0.68$) between trials using radiotherapy alone, surgery plus postoperative radiotherapy or other loco-regional treatment (Web-Table 5). There was no clear evidence of a differential effect of induction chemotherapy on survival according to age, sex, performance, stage or tumour site.

Comparison of concomitant and induction chemotherapy

Direct comparison

This analysis concerns the 6 randomised trials which have used the same drugs in both arms, and compared the timing of their use relatively to radiotherapy. These trials have included a total of 861

patients (717 deaths) with a median follow-up of 10.9 years. The trials and the patients of this analysis have been described previously [2]. Data for event-free survival and loco-regional failure were available for 5 trials. Data on distant failure were missing for most of the trials. The three endpoints studied (Fig. 6) showed results in favour of the concomitant group: hazard ratio of 0.90 for overall survival ($p = 0.15$) with an absolute benefit of 3.5% at 5 years (from 24.3 to 27.8; Fig. 6b); hazard ratio of 0.81 for event-free survival ($p = 0.01$); hazard ratio of 0.77 for loco-regional failure ($p = 0.005$). The corresponding hazard ratio plots are given in Web-Fig. 4a, b and c.

Indirect comparison

This analysis is based on the comparison of the chemotherapy effect observed in the 50 concomitant chemotherapy trials and in 31 induction chemotherapy trials mentioned above.

Overall survival

The observed benefit of chemotherapy was significantly greater in the concomitant group (HR 0.81 [0.78–0.86]) than in the induction group (HR 0.96 [0.90–1.02]; test for interaction $p < 0.0001$). A significant difference was also observed in favour of concomitant chemotherapy when the analysis included only trials with 5-FU-platin ($p = 0.01$).

Cumulative loco-regional and distant failure

Data on loco-regional failure were available for 50 concomitant and 30 induction trials, respectively, whereas the data for distant metastasis were available for 44 concomitant and 26 induction trials, respectively. Regarding loco-regional failure, the benefit of concomitant chemotherapy was significant (HR 0.74 [0.70–0.79] $p < 0.0001$; p for heterogeneity 0.006; $I^2 = 34\%$), but there was no such effect of induction chemotherapy (HR 1.03 [0.95–1.13]; $p = 0.43$; p for heterogeneity $p < 0.0001$; $I^2 = 63\%$; Fig. 7a). The two hazard ratios were significantly different ($p < 0.0001$) in favour of the concomitant group. The difference between concomitant and induction chemotherapies was even more pronounced when the combination of 5-FU-platin was considered (HR 0.66 versus 1.02, $p < 0.0001$, Fig. 7b). Regarding distant failure, the benefit of concomitant chemotherapy appeared significant with a hazard ratio of 0.88 [0.77–1.00] $p = 0.04$; p for heterogeneity 0.39; $I^2 = 4\%$; Fig. 7a) whereas the benefit of induction chemotherapy was also

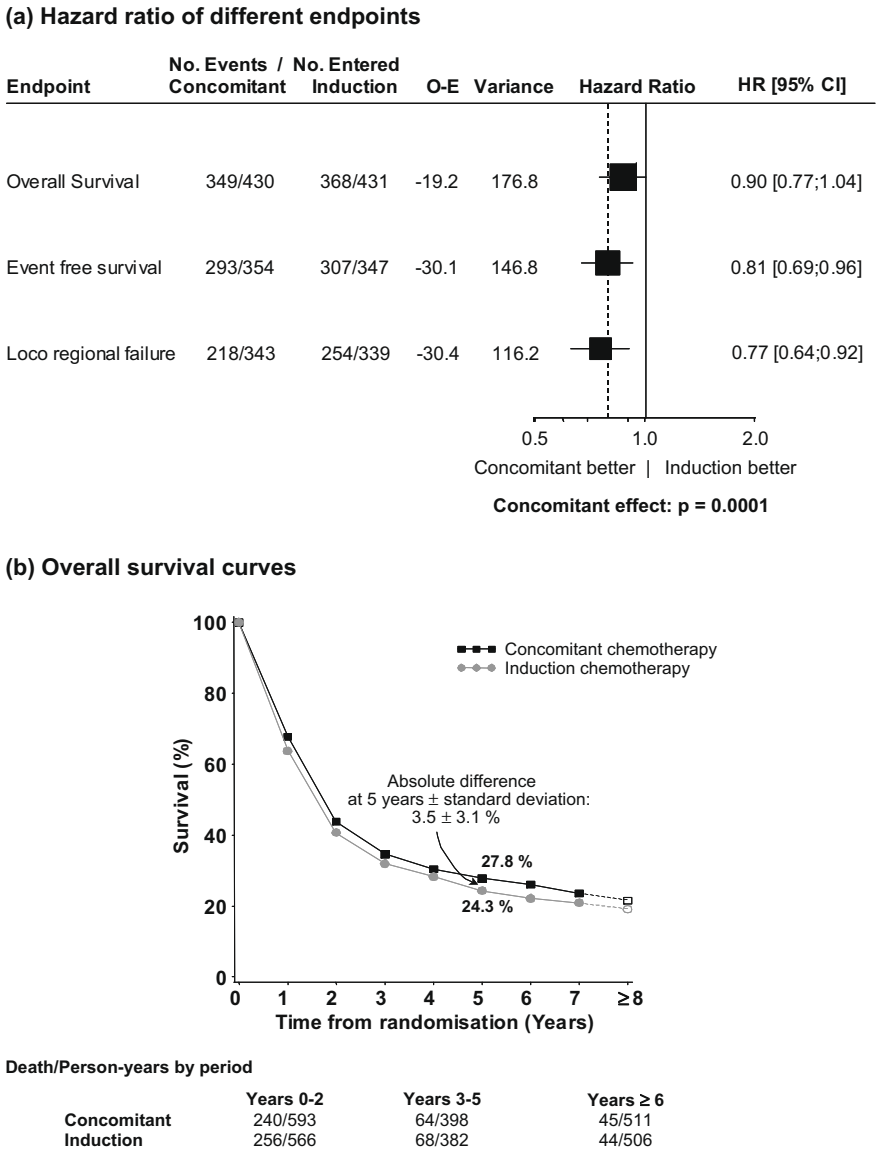
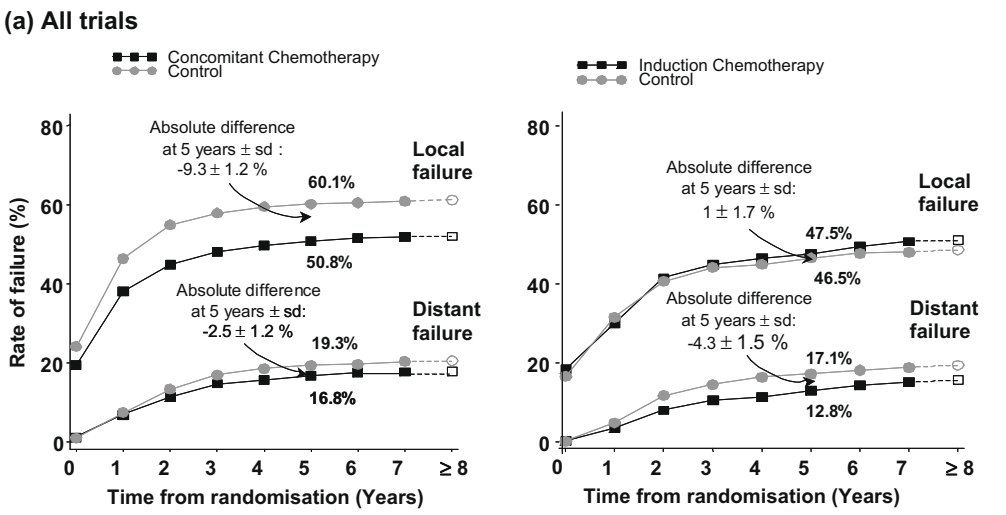
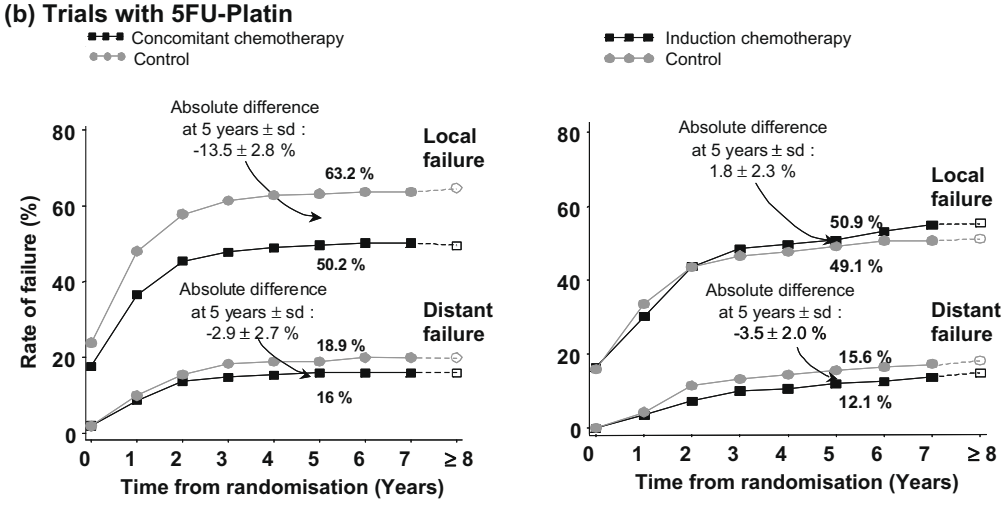


Fig. 6. Direct comparison of loco-regional treatment plus concomitant chemotherapy with loco-regional treatment plus induction chemotherapy. (a) Hazard ratio of different endpoints; (b) overall survival curves.



Local failure and distant failure /person-years by period

	Years 0-2	Years 3-5	Years ≥ 6	Years 0-2	Years 3-5	Years ≥ 6
Local failure						
Control	2509/8969	127/2812	18/2016	942/5335	70/1897	16/1202
Chemotherapy	2045/9789	162/3881	21/2822	1049/5737	85/2165	27/1245
Distant failure						
Control	382/9817	82/3026	9/2195	183/5717	45/2025	11/1328
Chemotherapy	370/10438	96/4010	10/2896	143/6207	46/2329	16/1391



Local failure and distant failure /person-years by period

	Years 0-2	Years 3-5	Years ≥ 6	Years 0-2	Years 3-5	Years ≥ 6
Local failure						
Control	493/1648	22/406	2/165	497/2627	38/1073	10/684
Chemotherapy	373/1837	20/603	1/240	519/2749	58/1142	22/751
Distant failure						
Control	82/1756	8/416	1/166	90/2788	18/1116	8/711
Chemotherapy	83/1915	6/616	0/241	62/2929	23/1204	9/773

Fig. 7. Loco-regional and distant failure cumulative rates in trials comparing loco-regional treatment plus concomitant with loco-regional treatment alone and induction chemotherapy with loco-regional treatment alone. (a) All type of chemotherapy; (b) 5-FU-platin. sd, standard deviation.

significant and more pronounced (HR 0.73 [0.61–0.88], $p = 0.001$; p for heterogeneity 0.19; $I^2 = 19\%$). The comparison of the two hazard ratios was not significant ($p = 0.12$ for all trials, $p = 0.56$ for 5-FU-platin trials, Fig. 7b).

Overall effect of adding chemotherapy to loco-regional treatment

As shown in Figs. 1 and 2, a significant benefit of chemotherapy ($p < 0.0001$) was observed for overall survival (HR 0.88, 0.85–0.92), with an absolute improvement of 4.5% in 5 years survival. There was a heterogeneity of chemotherapy effect between trials ($p < 0.0001$; $I^2 = 41\%$) which was observed only in the concomitant group ($p = 0.0001$, $I^2 = 45\%$). A larger effect of chemotherapy was observed in the concomitant trials than in the other two groups (test for interaction $p < 0.0001$; Figs. 1 and 2). There was no good evidence of an effect of chemotherapy for induction or adjuvant (HR 1.06 [0.95–1.18] $p = 0.32$; $I^2 = 10\%$) chemotherapy. The detailed HR plots for each type of

chemotherapy are shown in Web-Figs. 1–3. There was no variation of the chemotherapy effect on overall survival according to loco-regional treatment among each chemotherapy timing trial group (Web-Table 5).

Similar results were observed for event-free survival (Fig. 1b), both for the whole population and for the three groups. For the whole population the hazard ratio was 0.87 (0.84–0.90; $p < 0.0001$) with an absolute benefit of 4.1% at 5 years (from 26.8 to 30.9%).

In an exploratory analysis, mortality at 90 days was used as a proxy of early deaths related to treatment. The hazard ratio was 1.14 (0.98–1.31; $p = 0.08$; test for heterogeneity $p = 0.30$; $I^2 = 6\%$). The excess of early death due to the chemotherapy was significantly higher in the adjuvant setting (test for interaction $p = 0.02$): HR of 2.1 (1.31–3.36) for the adjuvant group versus 1.09 and 1.03 for the concomitant and induction groups, respectively (Web-Fig. 5).

Discussion

This updated individual patient data meta-analysis provides a reliable evaluation of the effect of chemotherapy in locally advanced head and neck cancer. Compared to the previous study, a large number of patients and randomised trials have been added and the follow-up has been markedly increased, including for the older trials. Consequently, the statistical power has been increased and we were able to undertake more complete analyses with new endpoints (effect of different types of chemotherapies, effect on distant versus local failure, etc.). Overall the current results appear stronger, compared to the previous MACH-NC meta-analysis and should be useful to determine standard treatment in this disease, as well as generating new hypotheses to be tested in future randomised trials.

Adding new data did not change the magnitude of the observed survival benefit resulting from the addition of chemotherapy, which was confirmed to be around 4%. This benefit was larger for concomitant chemotherapy, whereas there was no clear evidence of a benefit for induction and adjuvant chemotherapies. Adding the data from 24 new trials did not modify the magnitude of the relative benefit of concomitant chemotherapy from that reported previously (HR = 0.82 versus 0.81).

Importantly, there was a minimal heterogeneity between the 24 new trials ($I^2 = 34\%$), suggesting a strong consistency in the results of these randomised trials, and reinforcing the strength of the evidence of the observed benefit. In addition, the analysis of the concomitant group of trials allowed new and important conclusions to be drawn. Firstly, the fact that there was no excess of non-cancer deaths, strongly suggests that this treatment was effective in reducing cancer-related mortality without deleterious effect on death from other causes. We did not have data on compliance and toxicity.

Regarding the type of drugs to be combined concomitantly with radiotherapy, cisplatin alone, cisplatin or carboplatin associated with 5-FU or other poly-chemotherapy including either platin or 5-FU gave a benefit of the same order of magnitude. In contrast mono-chemotherapy with a drug other than cisplatin led to inferior results and should not be recommended in routine practice (Fig. 4). Single agent cisplatin appears to be one of the standard treatments in combination with radiotherapy. Most of the randomised trials have used a dose of cisplatin of 100 mg/m^2, three times throughout the course of radiotherapy (cumulative dose of 300 mg/m^2). Interestingly, the only negative "cisplatin alone" trial in this meta-analysis used a cumulative dose of 140 mg/m^2 (20 mg/m^2 × 7) [13] suggesting that the total dose of cisplatin could be important.

Another key message is that the benefit of concomitant chemotherapy appears to be similar irrespective of whether the radiotherapy was given conventionally or using altered fractionation. Finally, this meta-analysis confirmed that the magnitude of the benefit of concomitant chemotherapy is less in older patients, a feature that has also been observed with altered fractionation compared to conventional radiotherapy in head and neck cancer [14] and also when combining cetuximab plus radiotherapy [15]. One of the explanations is that older patients more frequently die from other causes than their head and neck cancer, which makes more difficult to observe the benefit in these patients (dilution effect). The absence of significant interaction with age on event-free survival is in favour of an effect on cancer death independent of age. Another explanation could be an increase in non-cancer deaths by the chemotherapy in old patients. The number of non-cancer deaths in the 71+ group was too small ($n = 93$) to study the impact of chemotherapy on non-cancer deaths.

This meta-analysis also allowed a new comparison of the benefit associated with concomitant versus induction chemotherapy. It is interesting to note that both the indirect and the direct comparisons were consistent on survival, event-free survival and loco-regional failure, showing a clear advantage in favour of concomitant chemotherapy. Indirect comparison should be interpreted with caution as the loco-regional treatment alone arm may not be comparable in the concomitant and induction trials. The 5 year survival rates in the control arm were, respectively, 27% and 30% in concomitant and induction trials.

However, one of the most striking observations was that concomitant chemotherapy had a pronounced effect on loco-regional failure, which was not observed for induction chemotherapy. On the other hand, induction chemotherapy provided a relatively more pronounced effect on distant metastases, compared to concomitant chemotherapy, suggesting the need to use a relatively high dose of chemotherapy to influence the occurrence of distant metastases. This also suggests that concomitant and induction chemotherapies may be complementary for this type of cancer and justifies the ongoing current randomised trials evaluating the benefit of adding induction chemotherapy before concomitant radio-chemotherapy. It is also important in these ongoing trials to evaluate whether induction chemotherapy adversely affects the compliance to the concomitant radio-chemotherapy part of the treatment, which appears to be the most important component of this sequential strategy. Since taxane-based induction chemotherapy also proved, in three recent randomised trials [16–18], to be superior to the reference 5-FU-platin-based induction chemotherapy, it is not possible to rule out that the benefit due to induction chemotherapy could be more pronounced that it appears to be in this meta-analysis. However, this needs to be tested in ongoing randomised trials which add induction chemotherapy to concomitant radio-chemotherapy. Finally, in locally advanced patients who received chemotherapy, the role of cetuximab, which improves the effect of radiotherapy [19], remains to be determined.

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Investigator contribution (see list of investigator at the end of the paper)

Secretariat: J.P.P., J.B., B.L., J.L.L., J.P.A. conceived, designed and supervised the study;

J.P.P., J.B. obtained funding;

C.A., N.S., A.L.M., E.M., J.P.P. participated in data collection and checking;

C.A., A.L.M., E.M., J.P.P. did statistical analyses;

J.P.P., J.B., A.L.M., E.M. wrote the draft, with revision from the other investigator.

The authors had full access to all the data and analyses and, after consultation with the collaborators, had final responsibility for the decision to submit for publication.

Steering committee: Its members revised the protocol, contributed to the selection of the trials, and revised the manuscript.

Other investigators were trialists and contributed to the study by providing data, replying to the secretariat queries and validating the re-analysis of their trial. Most of them participated in investigator meetings on preliminary results and had the opportunity to review the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2009.04.014.

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