Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis

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Summary

Background A previous individual patient data meta-analysis by the Meta-Analysis of Chemotherapy in Nasopharynx Carcinoma (MAC-NPC) collaborative group to assess the addition of chemotherapy to radiotherapy showed that it improves overall survival in nasopharyngeal carcinoma. This benefit was restricted to patients receiving concomitant chemotherapy and radiotherapy. The aim of this study was to update the meta-analysis, include recent trials, and to analyse separately the benefit of concomitant plus adjuvant chemotherapy.

Methods We searched PubMed, Web of Science, Cochrane Controlled Trials meta-register, ClinicalTrials.gov, and meeting proceedings to identify published or unpublished randomised trials assessing radiotherapy with or without chemotherapy in patients with non-metastatic nasopharyngeal carcinoma and obtained updated data for previously analysed studies. The primary endpoint of interest was overall survival. All trial results were combined and analysed using a fixed-effects model. The statistical analysis plan was pre-specified in a protocol. All data were analysed on an intention-to-treat basis.

Findings We analysed data from 19 trials and 4806 patients. Median follow-up was 7·7 years (IQR 6·2–11·9). We found that the addition of chemotherapy to radiotherapy significantly improved overall survival (hazard ratio [HR] 0·79, 95% CI 0·73–0·86, p<0·0001; absolute benefit at 5 years 6·3%, 95% CI 3·5–9·1). The interaction between treatment effect (benefit of chemotherapy) on overall survival and the timing of chemotherapy was significant (p=0·01) in favour of concomitant plus adjuvant chemotherapy (HR 0·65, 0·56–0·76) and concomitant without adjuvant chemotherapy (0·80, 0·70–0·93) but not adjuvant chemotherapy alone (0·87, 0·68–1·12) or induction chemotherapy alone (0·96, 0·80–1·16). The benefit of the addition of chemotherapy was consistent for all endpoints analysed (all p<0·0001): progression-free survival (HR 0·75, 95% CI 0·69–0·81), locoregional control (0·73, 0·64–0·83), distant control (0·67, 0·59–0·75), and cancer mortality (0·76, 0·69–0·84).

Interpretation Our results confirm that the addition of concomitant chemotherapy to radiotherapy significantly improves survival in patients with locoregionally advanced nasopharyngeal carcinoma. To our knowledge, this is the first analysis that examines the effect of concomitant chemotherapy with and without adjuvant chemotherapy as distinct groups. Further studies on the specific benefits of adjuvant chemotherapy after concomitant chemoradiotherapy are needed.

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Introduction

Nasopharyngeal carcinoma is distinct from other head and neck carcinomas; it has a specific geographical distribution, is associated with the Epstein-Barr virus, has an aggressive natural locoregional history, and has a high risk of distant metastases.[1] Nevertheless, high proportions of patients are cured with standard therapy, even in cases of locoregionally advanced disease. Radiotherapy is the cornerstone of initial treatment due to the radiosensitive behaviour of nasopharyngeal carcinoma and its deep-seated location. The landmark Intergroup 0099 (INT-0099) trial[2] and the first Meta-Analysis of Chemotherapy in Nasopharynx Carcinoma (MAC-NPC)[3] showed that there was an overall survival benefit related to concomitant chemotherapy. However, this meta-analysis included only eight trials and 1753 patients, and combined results from trials of concomitant plus adjuvant chemotherapy and concomitant chemotherapy alone. Since those publications, additional trials have been done, including replications of the INT-0099 trial, allowing a study of the interaction between the timing of chemotherapy and the effect on various endpoints in more detail. The aim of this study was to update the meta-analysis, include recent trials, and to analyse separately the benefit of concomitant plus adjuvant chemotherapy.

Methods

Selection criteria and search strategy

This updated meta-analysis was done according to a pre-specified protocol. To be eligible, trials had to compare radiotherapy alone with radiotherapy plus chemotherapy,

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*Listed in the appendix

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See Online for appendix

For the **protocol** see http://bit.ly/1apnS9J

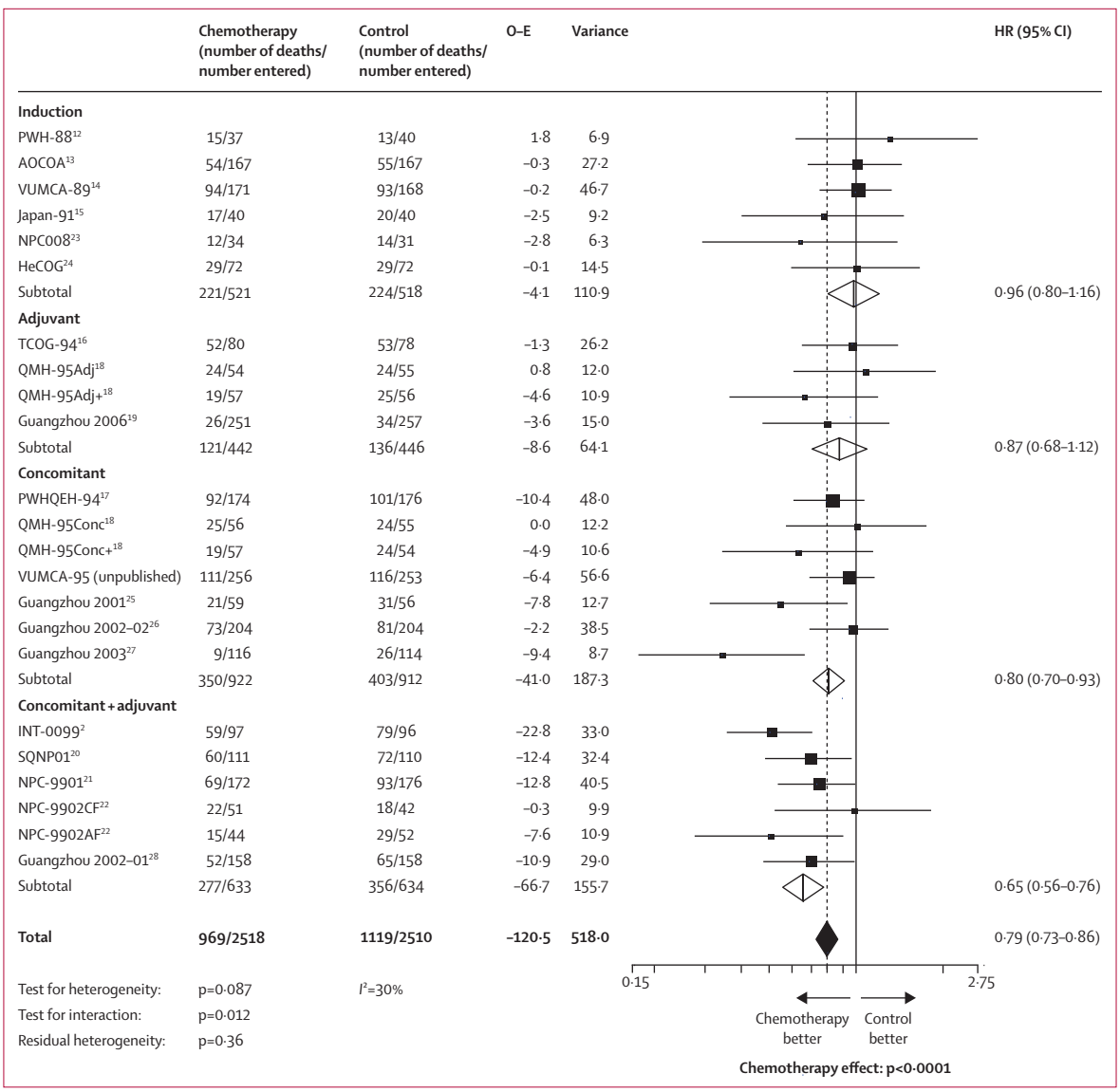


Figure 1: **Forest plots for overall survival with hazard ratios by timing of chemotherapy**
Within each timing category, trials are ordered according to accrual period from the oldest to the most recent. The centre of each square is the HR for individual trial comparison with the corresponding horizontal line showing the 95% CI. The size of the square is proportional to the number of deaths from the trial. The centre of the open diamonds is the HR for different timings of chemotherapy and the extremities are the 95% CIs. The broken line and centre of black diamonds represent the overall pooled HR with the extremities of the diamond showing the 95% CIs. PWH=Prince of Wales Hospital. AOCOA=Asian-Oceanian Clinical Oncology Association. VUMCA=International Nasopharynx Cancer Study Group (cavum). NPC=nasopharyngeal carcinoma. HeCOG=Hellenic Cooperative Oncology Group. TCOG=Taiwan Cooperative Oncology Group. QMH=Queen Mary Hospital (2 × 2 design, counted twice in the analysis). PWHQEH=Prince of Wales Hospital, Queen Elizabeth Hospital. INT-0099=SWOG (Southwest Oncology Group)-coordinated Intergroup trial, also known as SWOG 8892. SQNP=Singapore Naso-Pharynx. CF=conventional fractionation. AF=accelerated fractionation. O-E=observed–expected. HR=hazard ratio. Adj=radiotherapy versus radiotherapy plus adjuvant chemotherapy. Adj+=radiotherapy plus concomitant chemotherapy versus radiotherapy plus concomitant plus adjuvant chemotherapy. Conc=radiotherapy versus radiotherapy plus concomitant chemotherapy. Conc+=radiotherapy plus adjuvant chemotherapy versus radiotherapy plus adjuvant plus concomitant chemotherapy.

or to compare a treatment strategy with one chemotherapy timing (ie, radiotherapy plus concomitant chemotherapy, radiotherapy plus induction chemotherapy, or radiotherapy plus adjuvant chemotherapy) with the same treatment strategy plus chemotherapy at another timing. They had to be randomised and include patients with untreated non-metastatic nasopharyngeal carcinoma. Trials were eligible if at least 60 patients had been included (30 patients per group for trials with more than two groups) and if all patients had undergone potentially curative locoregional treatment. Accrual had to be completed before Dec 31, 2010.

Both published and unpublished trials meeting these criteria were eligible. We searched for trials in electronic

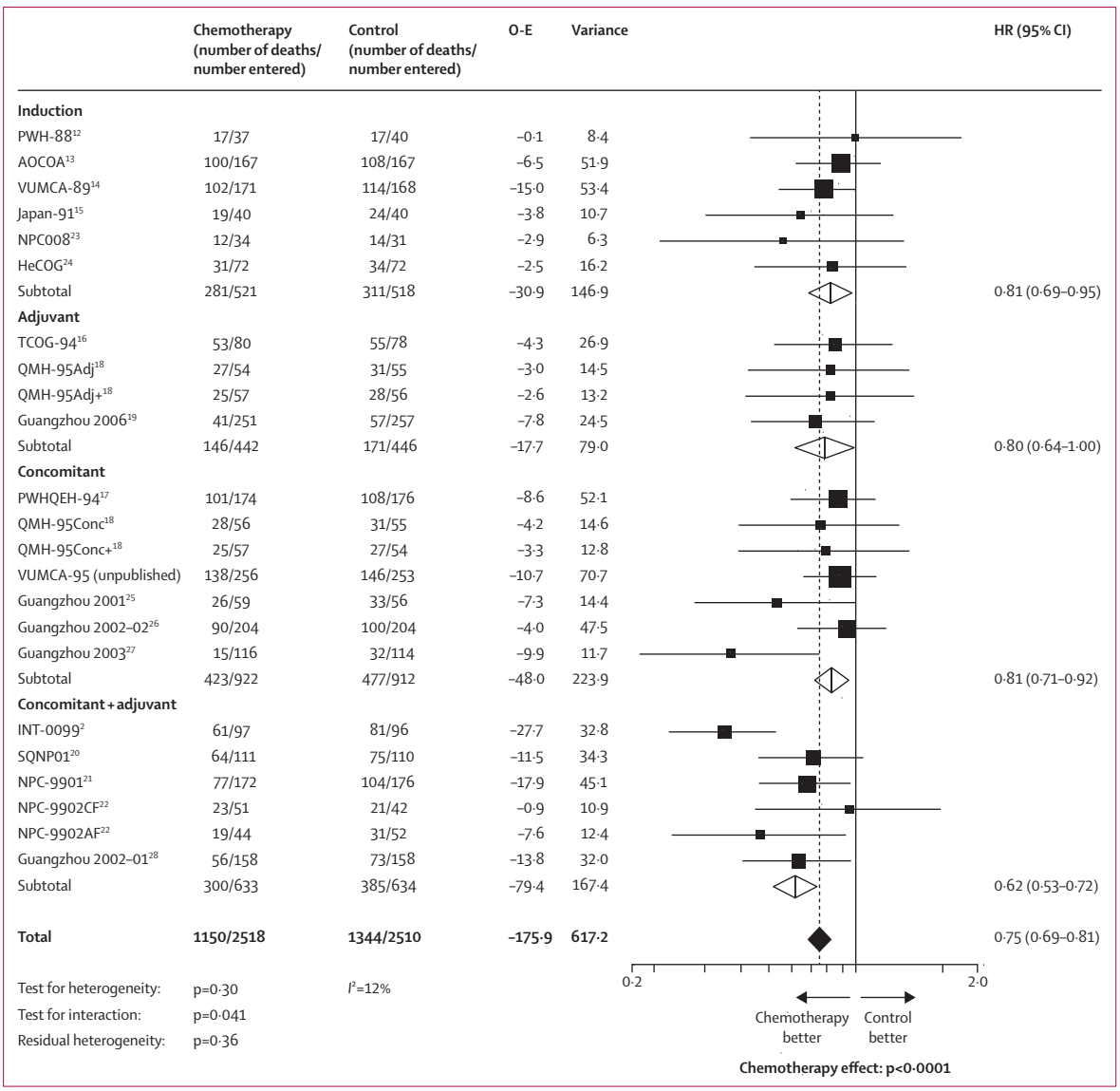


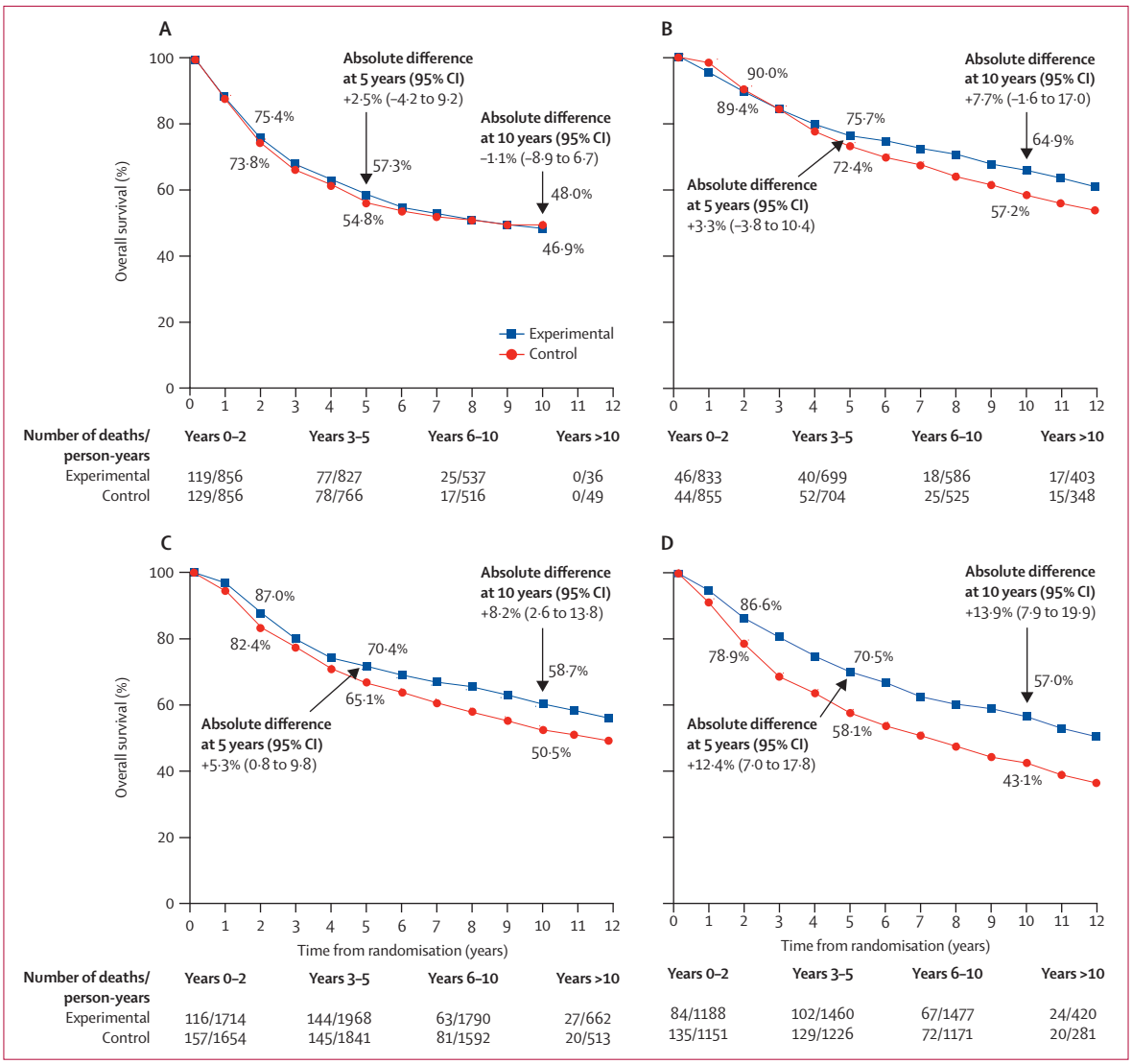
Figure 2: **Forest plots for progression-free survival with hazard ratios by timing of chemotherapy**
Within each timing category, trials are ordered according to accrual period from the oldest to the most recent. The centre of each square is the HR for individual trial comparison with the corresponding horizontal line showing the 95% CI. The size of the square is proportional to the number of relapses or deaths from the trial. The centre of the open diamonds is the HR for different timings of chemotherapy and the extremities are the 95% CIs. The broken line and centre of black diamonds represent the overall pooled HR with the extremities of the diamond showing the 95% CIs. PWH=Prince of Wales Hospital. AOCOA=Asian-Oceanian Clinical Oncology Association. VUMCA=International Nasopharynx Cancer Study Group (cavum). NPC=nasopharyngeal carcinoma. HeCOG=Hellenic Cooperative Oncology Group. TCOG=Taiwan Cooperative Oncology Group. QMH=Queen Mary Hospital (2×2 design, counted twice in the analysis). PWHQEH=Prince of Wales Hospital, Queen Elizabeth Hospital. INT-0099=SWOG (Southwest Oncology Group)-coordinated Intergroup trial, also known as SWOG 8892. SQNP=Singapore Naso-Pharynx. CF=conventional fractionation. AF=accelerated fractionation. O-E=observed–expected. HR=hazard ratio. Adj=radiotherapy versus radiotherapy plus adjuvant chemotherapy. Adj+=radiotherapy plus concomitant chemotherapy versus radiotherapy plus concomitant plus adjuvant chemotherapy. Conc=radiotherapy versus radiotherapy plus concomitant chemotherapy. Conc+=radiotherapy plus adjuvant chemotherapy versus radiotherapy plus adjuvant plus concomitant chemotherapy.

publication databases, trial registries, and meeting proceedings (details in appendix).

Individual patient data collection

We contacted the study investigators and requested individual patient data for patient and tumour characteristics, date of randomisation and treatment group allocation, dates of failures and death, treatment details, and acute and late toxicities for each trial. Information was updated for previously analysed trials whenever possible.

We checked the data according to a standard procedure, and compared with the trial protocol and published reports. Missing values and discrepancies were discussed with the trialists. Randomisation validity was assessed by



Number of deaths/ person-years	Years 0–2	Years 3–5	Years 6–10	Years >10
Experimental	119/856	77/827	25/537	0/36
Control	129/856	78/766	17/516	0/49

Number of deaths/ person-years	Years 0–2	Years 3–5	Years 6–10	Years >10
Experimental	46/833	40/699	18/586	17/403
Control	44/855	52/704	25/525	15/348

Number of deaths/ person-years	Years 0–2	Years 3–5	Years 6–10	Years >10
Experimental	116/1714	144/1968	63/1790	27/662
Control	157/1654	145/1841	81/1592	20/513

Number of deaths/ person-years	Years 0–2	Years 3–5	Years 6–10	Years >10
Experimental	84/1188	102/1460	67/1477	24/420
Control	135/1151	129/1226	72/1171	20/281

Figure 3: **Survival curves for overall survival in trials investigating (A) induction, (B) adjuvant, (C) concomitant, and (D) concomitant plus adjuvant chemotherapy**

checking the patterns of treatment allocation and the balance of baseline characteristics between treatment groups. Follow-up of patients was also compared between treatment groups.[4] Each trial was reanalysed and the analyses were sent to the trialists for validation. The quality of the additional trials was assessed and no major bias was identified (appendix).

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation until death from any cause. The secondary endpoints were progression-free survival, locoregional and distant failure, and cancer and non-cancer mortality. Progression-free survival was defined as the time from randomisation to first progression (locoregional or distant) or death from any cause. Patients with a distant failure as a first event were censored for locoregional failure and vice versa. If both a locoregional failure and a distant failure occurred at the same time, patients were considered as having an event for distant failure only. Living patients without an event corresponding to any endpoint were censored at the date of their last follow-up. Non-cancer deaths were defined as deaths from known causes other than nasopharyngeal carcinoma for patients without progression. Cancer deaths included deaths from any cause with previous progression and deaths from nasopharyngeal carcinoma or unknown cause.

Statistical analysis

We analysed all the data on an intention-to-treat basis. We estimated median follow-up with the reverse Kaplan-Meier method.[5] Analyses were stratified by trial. Individual and overall pooled hazard ratios (HRs) with 95% CIs were

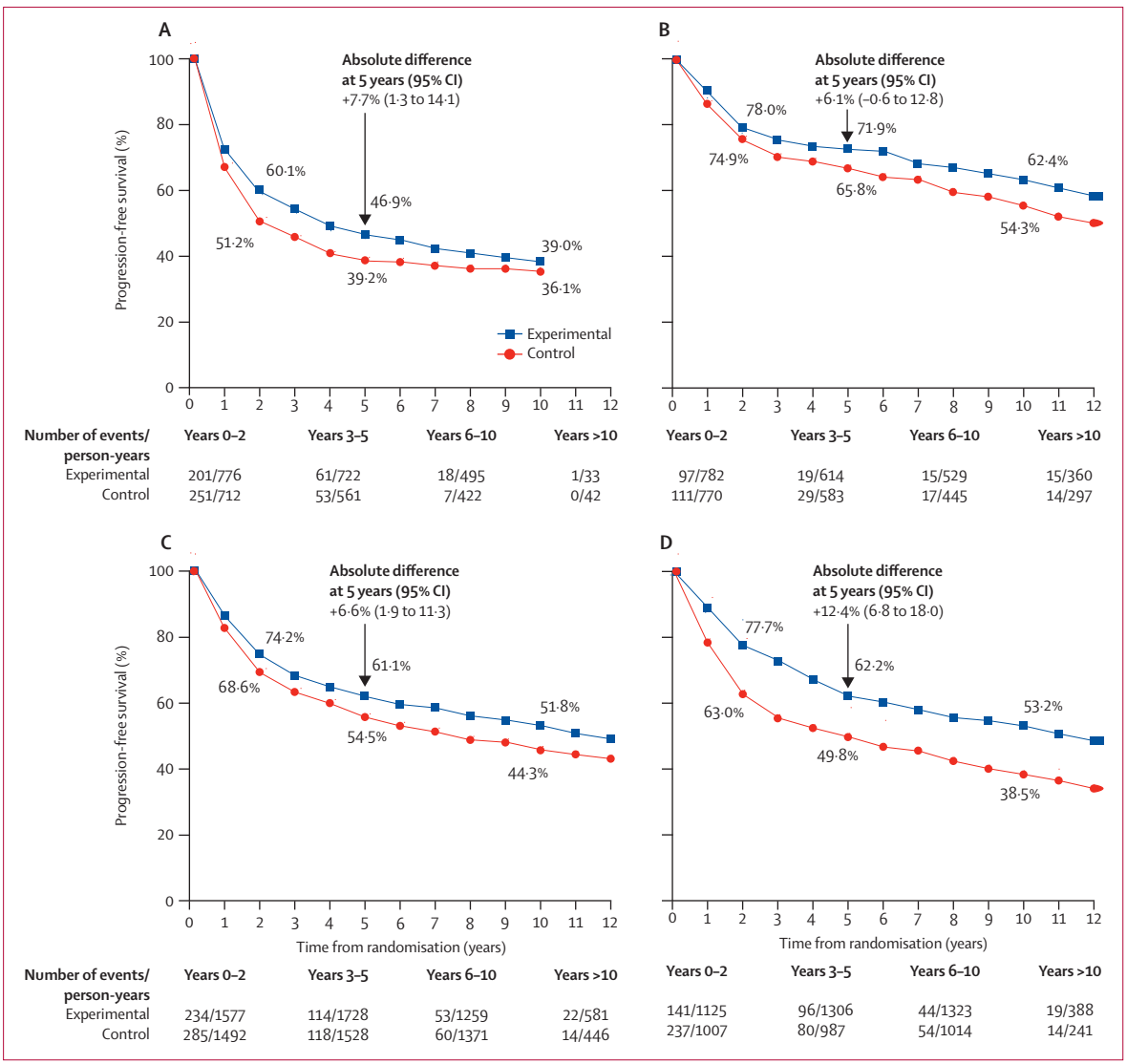


Figure 4: **Survival curves for progression-free survival in trials investigating (A) induction, (B) adjuvant, (C) concomitant, and (D) concomitant plus adjuvant chemotherapy**

calculated with a fixed-effect model using the log-rank expected number of events and variance.[6] 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.[7] χ^2 heterogeneity tests and the I^2 statistic were used to investigate the overall heterogeneity between trials.[8,9] The use of a random-effects model was planned in the case of important and unexplained heterogeneity. With 4500 patients it would be possible to detect, with a power exceeding 90%, an absolute improvement in survival from 40% to 45% at 5 years (two-sided log-rank test with an alpha of 5%). Cancer mortality was calculated indirectly by subtracting the log-rank statistic for non-cancer mortality from the log-rank statistic for mortality from all causes.[8] Stratified survival curves were estimated for control and experimental groups using annual death rates and HRs, and absolute benefit at 5 years with 95% CI was calculated.[8]

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. 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.[10] Predefined subsets were the timing of randomised chemotherapy (adjuvant [after radiotherapy] *vs* induction [before radiotherapy] *vs* concomitant [during radiotherapy] *vs* concomitant plus adjuvant), chemotherapy drug, trial size, and method of randomisation. The interaction between treatment effect and patient subgroups (according to age, sex, performance

	Concomitant chemotherapy (seven comparisons and 1834 patients)	Concomitant plus adjuvant chemotherapy (six comparisons and 1267 patients)
Type of chemotherapy		
Cisplatin	Two comparisons (580 patients)	All comparisons
Carboplatin or oxaliplatin	Two comparisons (523 patients)	None
Non-platin	Three comparisons (731 patients)	None
Other timing of chemotherapy		
None	Four comparisons (806 patients)	All comparisons
Induction chemotherapy	Two comparisons (917 patients)	None
Adjuvant chemotherapy	One comparison (111 patients)	None
Sensitivity analysis excluding trials with another timing of chemotherapy in both groups*	OS 0·71 (0·57–0·89)†; PFS 0·72 (0·59–0·89)‡	NA
Histology (WHO classification)		
1	127 (7%)	49 (4%)
2–3	1701 (93%)	1218 (96%)
Missing	6 (<1%)	0 (0%)
Sensitivity analysis excluding patients with WHO type 1 histology*	OS 0·81 (0·70–0·94)†; PFS 0·81 (0·70–0·93)‡	OS 0·67 (0·57–0·79)§; PFS 0·65 (0·55–0·76)¶
Overall stage		
Stage II	359 (20%)	6 (<1%)
Stage III	784 (43%)	671 (53%)
Stage IV	691 (38%)	590 (47%)
Sensitivity analysis (unplanned) without patients with stage II disease*	OS 0·80 (0·69–0·93)†; PFS 0·82 (0·71–0·94)‡	OS 0·65 (0·56–0·77)§; PFS 0·62 (0·54–0·73)¶
Length of follow-up		
Median (range)	7·9 years (5·8–14·1)	10·2 years (6·2–16·8)
Overall survival in control group		
At 2 years	82·5%	78·9%
At 5 years	64·5%	58·1%
At 10 years	49·5%	43·1%

Data are n (%) unless otherwise stated. NA=not applicable. OS=overall survival. PFS=progression-free survival. *Hazard ratio (95% CI). †Compared with 0·80 (0·70–0·93) in the overall analysis. ‡Compared with 0·81 (0·71–0·92) in the overall analysis. §Compared with 0·65 (0·56–0·76) in the overall analysis. ¶Compared with 0·62 (0·53–0·72) in the overall analysis.

Table 1: **Main differences between trials investigating concomitant chemotherapy and those investigating concomitant plus adjuvant chemotherapy**

status, and overall stage) was estimated directly in a single Cox model stratified by trial and containing treatment effect, covariate (eg, age) effect, and treatment–covariate interaction (one-stage model method).[11] Sensitivity analyses were done after the exclusion of trials including less than 100 patients, trials including two different chemotherapy timings where only one was randomised, trials with a median follow-up shorter than 5 years, outliers, and patients with WHO type 1 cancer.

All p values were two-sided. We used SAS software, 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 MAC-NPC Collaborative Group. PB, SM, JL, and JPP had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Eight trials (1753 patients)[2,12–18] were included in our previous meta-analysis. This study includes 4806 patients from 19 trials (appendix), including one unpublished trial (VUMCA-95: International Nasopharynx Cancer Study Group, NCT00180973). Median follow-up was 7·7 years (IQR 6·2–11·9). Only two trials[12,19] (585 patients) had a median follow-up shorter than 5 years, and seven trials[2,16–18,20–22] (1681 patients) had a median follow-up longer than 10 years. Updated follow-up or additional data on toxicity were obtained for all but three trials included in the previous meta-analysis.[12,13,15] One 2×2 design trial (222 patients)[18] was counted twice (four comparisons, appendix) and another[22] was split into two comparisons, leading to a total of 23 comparisons and 5028 patients. Six comparisons (1039 patients)[12–15,23,24] investigated induction therapy, including one (77 patients)[12] with the addition of adjuvant chemotherapy in the treatment group and two (209 patients)[23,24] with the addition of concomitant chemotherapy in both groups. Four comparisons (888 patients,

one trial with two comparisons)[16,18,19] investigated adjuvant chemotherapy, including two (621 patients)[18,19] with addition of concomitant chemotherapy in both groups. Seven comparisons (1834 patients, one trial with two comparisons; including the VUMCA-95 trial),[17,18,25–27] investigated concomitant chemotherapy, including one (111 patients)[18] with addition of adjuvant chemotherapy in both groups and two (917 patients; including the VUMCA-95 trial)[26] with addition of induction chemotherapy in both groups. Six comparisons (1267 patients, one trial with two comparisons)[2,20–22,28] investigated concomitant plus adjuvant chemotherapy.

Most patients were male (3734 [74%] of 5020) and younger than 50 years of age (3149 [63%] of 5020), with a performance status of 0 to 1 (4031 [98%] of 4113). 4493 (89%) of 5028 had a stage III or IV cancer and 4759 (96%) of 4957 had a WHO histological type 2 or 3 cancer (appendix).

Overall survival and progression-free survival analyses were based on 2088 (42%) deaths and 2494 (50%) events, respectively, out of 5028 patients. The causes of death and the types of progression events are provided in the appendix. The addition of chemotherapy to radiotherapy improved overall survival (HR 0·79, 95% CI 0·73–0·86; p<0·0001) and progression-free survival (HR 0·75, 95% CI 0·69–0·81; p<0·0001; figures 1 and 2). There was an absolute benefit in overall survival at 5 years of 6·3% (95% CI 3·5–9·1). Low heterogeneity was observed among trials for overall survival (p=0·087, I^2=30%). Heterogeneity was mainly attributable to the timing of chemotherapy ($p_{interaction}$=0·012) and no heterogeneity remained after taking this into account (p=0·36). The interaction between chemotherapy timing and chemotherapy effect was also significant for progression-free survival ($p_{interaction}$=0·041). Subset analyses showed that trials investigating concomitant chemotherapy or concomitant plus adjuvant chemotherapy were the only subsets to show a significant improvement in both overall survival and progression-free survival. Survival curves assessing the effect of chemotherapy timing on overall survival and progression-free survival are shown in figures 3 and 4. An unplanned sensitivity analysis showed that the benefit of the addition of chemotherapy on overall survival was not different between the trials included in the first meta-analysis[2,12–18] (HR 0·83, 95% CI 0·73–0·95) and the new trials included in this update[19–27,29] (including the VUMCA-95 trial) (HR 0·76, 95% CI 0·67–0·85; $p_{interaction}$=0·28).

Table 1 summarises the main differences between trials investigating concomitant chemotherapy and concomitant plus adjuvant chemotherapy. All comparisons investigating concomitant plus adjuvant chemotherapy used cisplatin-based chemotherapy, but among those investigating concomitant chemotherapy, two used cisplatin,[17,27] two carboplatin[26] or oxaliplatin,[25] and three non-platinum-based chemotherapy (including the VUMCA-95 trial).[18] Overall survival in the control group was higher in the concomitant chemotherapy group than in the concomitant plus adjuvant chemotherapy group, and there was a higher proportion of patients with stage II disease in the concomitant chemotherapy group. Exclusion of stage II patients in an unplanned sensitivity analysis led to results similar to the main analysis (table 1). Three comparisons investigating concomitant chemotherapy added induction (including the VUMCA-95 trial)[26] or adjuvant[18] chemotherapy in both groups (control groups were induction chemotherapy and radiotherapy, and radiotherapy plus adjuvant chemotherapy, respectively). A planned sensitivity analysis excluding these comparisons increased

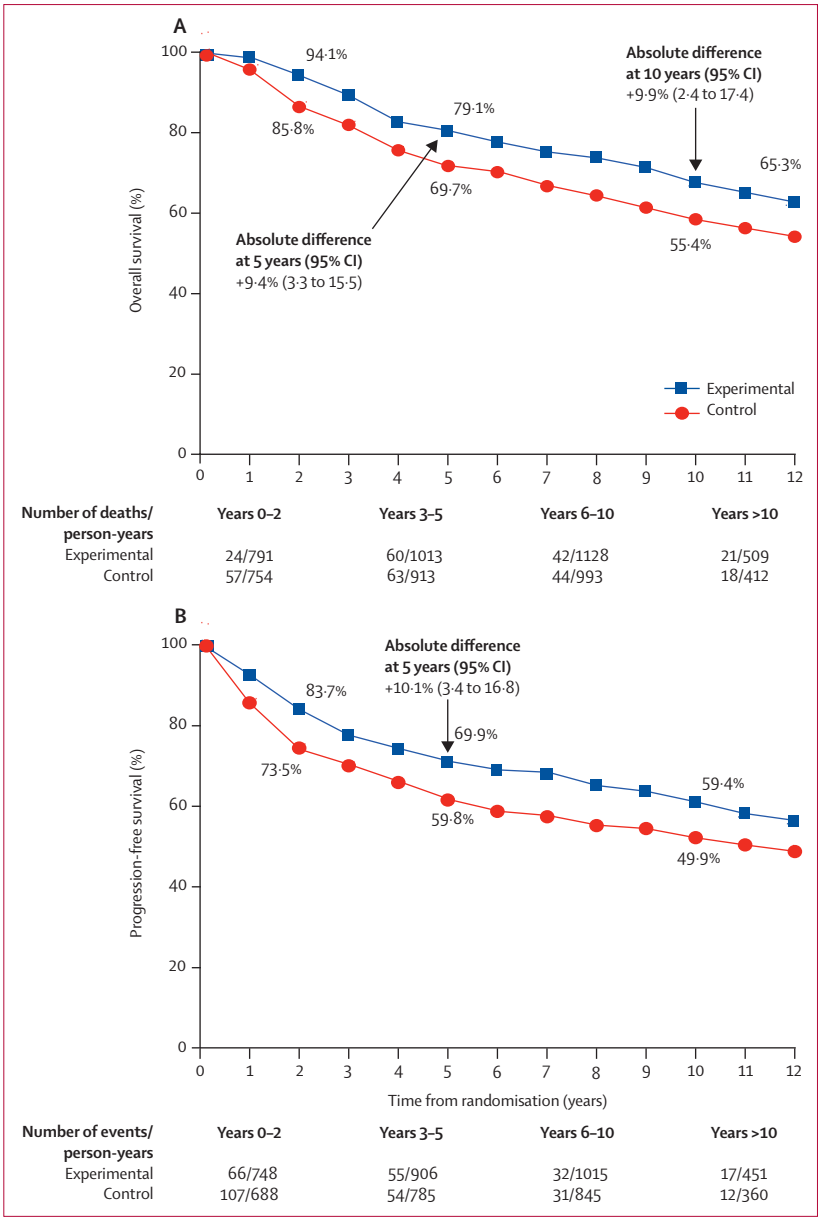
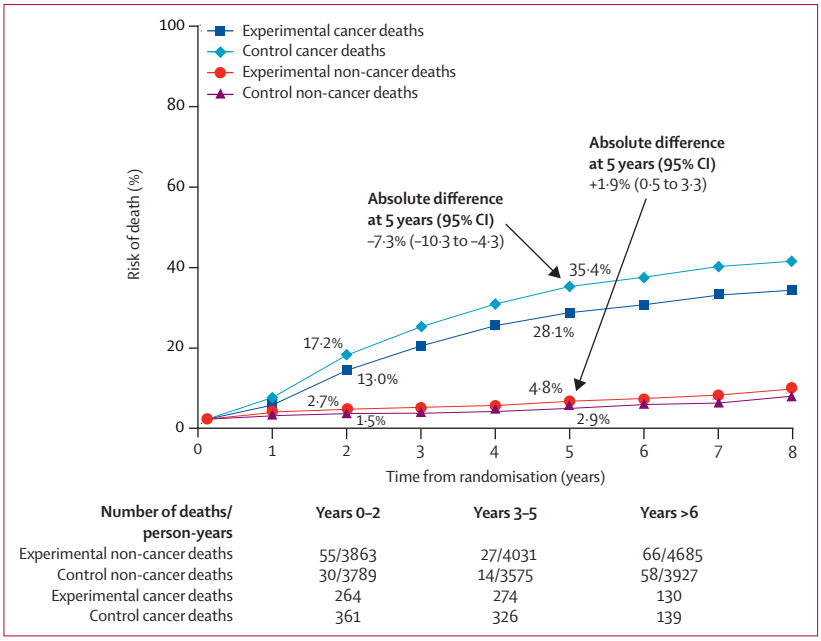


Figure 5: **Survival curves for (A) overall survival and (B) progression-free survival in trials investigating concomitant chemotherapy without addition of induction or adjuvant chemotherapy in both groups**



Number of deaths/ person-years	Years 0–2	Years 3–5	Years >6
Experimental non-cancer deaths	55/3863	27/4031	66/4685
Control non-cancer deaths	30/3789	14/3575	58/3927
Experimental cancer deaths	264	274	130
Control cancer deaths	361	326	139

Figure 6: **Survival curves for cancer and non-cancer deaths**

overall survival and progression-free survival for concomitant chemotherapy (overall survival: HR 0·71, 95% CI 0·57–0·89; progression-free survival: 0·72, 0·59–0·89; figure 5, appendix), of the same magnitude as the concomitant plus adjuvant group. Risk reduction was higher with concomitant plus adjuvant chemotherapy, but the difference with concomitant chemotherapy only was not statistically significant (overlap of the CIs; appendix).

Out of 5028 patients, 910 (18%) had locoregional failure and 1115 (22%) had distant failure. Chemotherapy reduced the risk of locoregional failure (HR 0·73, 95% CI 0·64–0·83; p<0·0001) and distant failure (HR 0·67, 95% CI 0·59–0·75; p<0·0001; appendix). Heterogeneity among trials was observed for distant failure rate (p=0·024, I^2=41%), but not for locoregional failure rate (p=0·48, I^2=0%). After excluding two outliers (306 patients),[2,18] the heterogeneity was no longer significant (p=0·12, I^2=28%). No evidence of interaction between chemotherapy timing and chemotherapy effect was observed for distant failure rate ($p_{interaction}$=0·18) or locoregional failure rate ($p_{interaction}$=0·054). Survival curves are presented in the appendix. Cancer and non-cancer mortality analyses were based on only 4312 patients because the cause of death was missing for three trials.[2,25,26] 1494 (35%) cancer deaths and 250 (6%) non-cancer deaths occurred (appendix). The use of chemotherapy was associated with a decrease in cancer-related deaths (HR 0·76, 95% CI 0·69–0·84; p<0·0001) (figure 6). Chemotherapy was not associated with an increase in non-cancer mortality (HR 1·27, 95% CI 0·99–1·64; p=0·056), and this did not change after excluding one trial[14] (339 patients) that had a high level of chemotherapy-related toxicity (HR without this trial 1·14, 95% CI 0·88–1·48; p=0·33). This sensitivity analysis was done to assess the robustness of the results because this trial was the only one to show a significant excess of non-cancer death and used an outdated induction chemotherapy regimen (bleomycin, epirubicin, cisplatin). Table 2 summarises the results for all endpoints.

No interaction was observed between treatment effect on overall survival and choice of chemotherapy drug ($p_{interaction}$=0·36), trial size ($p_{interaction}$=0·15), method of randomisation ($p_{interaction}$=0·38), patient age ($p_{interaction}$=0·66), patient sex ($p_{interaction}$=0·84), performance status ($p_{interaction}$=0·28), or tumour stage ($p_{interaction}$=0·41) (appendix). Because of the variation in the risk of death in the control group according to age and tumour stage, the 5-year absolute benefit of chemotherapy on overall survival was larger for older patients and patients with advanced stages. For progression-free survival, the p value for the trend between treatment effect and increasing patient age was 0·10, with a HR for patients younger than 50 years of 0·72 (95% CI 0·65–0·80), of 0·81 (0·70–0·95) for patients aged between 50 and 59 years, and 0·84 (0·70–1·01) for patients aged 60 years or older.

Sensitivity analyses (appendix) that excluded trials with fewer than 100 patients, a median follow-up shorter than 5 years, patients with WHO type 1 cancer, and patients with stage I–II disease (unplanned analysis) led to similar results from the main analysis. The difference of treatment effect on overall survival between trials of pure concomitant chemotherapy or concomitant plus adjuvant chemotherapy and the subsets of trials investigating induction chemotherapy and adjuvant chemotherapy was enhanced (appendix). An interaction between chemotherapy effect and chemotherapy timing for overall survival and progression-free survival was not significant after exclusion of two trials[2,27] (423 patients) that were outliers for overall survival ($p_{interaction}$=0·10) and one trial[2] (193 patients) that was a progression-free survival outlier ($p_{interaction}$=0·39).

Table 3 describes the acute and late severe toxicities that were observed in these studies. Acute toxicities were consistent with those expected for the cisplatin-based chemotherapy regimens. Results for the interaction of toxicity with the timing of chemotherapy are summarised in the appendix. Concomitant plus adjuvant chemotherapy was associated with the highest frequency of acute toxicities. Among the late toxicities, which were mainly related to radiotherapy, only cranial nerve palsy and hearing deficit were increased by chemotherapy.

Discussion

This updated individual patient data meta-analysis of the role of chemotherapy in nasopharyngeal carcinoma confirms the benefits associated with the use of chemotherapy in addition to radiotherapy, including significant and clinically relevant improvements in overall survival and progression-free survival, and

	Overall survival	Progression-free survival	Locoregional control	Distant control	Cancer death*	Non-cancer death*
Induction	0·96 (0·80–1·16)	0·81 (0·69–0·95)	0·84 (0·66–1·07)	0·62 (0·48–0·79)	0·89 (0·73–1·09)	1·85† (1·05–3·29)
Adjuvant	0·87 (0·68–1·12)	0·80 (0·64–1·00)	0·61 (0·41–0·92)	0·80 (0·59–1·09)	0·84 (0·64–1·10)	1·08 (0·59–1·95)
Concomitant	0·80 (0·70–0·93)	0·81 (0·71–0·92)	0·82 (0·67–1·01)	0·74 (0·61–0·90)	0·74 (0·62–0·89)	1·20 (0·77–1·87)
Concomitant plus adjuvant	0·65 (0·56–0·76)	0·62 (0·53–0·72)	0·54 (0·41–0·71)	0·56 (0·45–0·70)	0·63 (0·52–0·77)	1·19 (0·77–1·85)
Overall	0·79 (0·73–0·86)	0·75 (0·69–0·81)	0·73 (0·64–0·83)	0·67 (0·59–0·75)	0·76 (0·69–0·84)	1·27 (0·99–1·64)
Overall test	p<0·0001	p<0·0001	p<0·0001	p<0·0001	p<0·0001	p=0·056
Interaction test (timing × treatment effect)	p=0·012	p=0·041	p=0·054	p=0·18	p=0·084	p=0·55
Residual heterogeneity test	p=0·36	p=0·62	p=0·78	p=0·031	p=0·54	p=0·25

Data are HR (95% CI) or p value. *Analyses based on 20 comparisons (4312 patients) because the cause of death was missing for three trials.[2,25,26] †No difference (HR 0·91, 95% CI 0·39–2·15) was seen in a sensitivity analysis, excluding one trial (339 patients)[14] that was a clear outlier.

Table 2: **Summary of the results overall, and by chemotherapy timing, for all endpoints**

	Availability		Incidence of toxicity		OR (95% CI)	Efficacy p value	Heterogeneity		p value for interaction with chemotherapy timing‡
	Number of trials* (comparisons)	Number of patients	Chemo-therapy†	Control			I^2	p value	
Acute toxicity									
Anaemia	15 (19)	4059	4·3%	1·5%	2·95 (2·11–4·12)	<0·0001	48%	0·011	0·011
Neutropenia	15 (19)	4028	25·7%	4·9%	6·71 (5·53–8·14)	<0·0001	84%	<0·0001	0·0032
Mucositis	14 (18)	3870	40·6%	31·2%	1·51 (1·31–1·73)	<0·0001	40%	0·042	0·00053
Cutaneous	13 (17)	3838	12·7%	11·0%	1·18 (0·97–1·44)	0·10	54%	0·0039	0·040
Nausea and vomiting	13 (17)	3585	12·2%	5·3%	2·49 (1·97–3·13)	<0·0001	60%	0·00076	<0·0001
Thrombocytopenia	14 (18)	3737	3·0%	1·5%	2·06 (1·39–3·06)	0·00034	0%	0·92	0·15
Kidney failure	12 (16)	3542	0·2%	0·1%	1·94 (0·91–4·14)	0·086	0%	1·00	0·39
Neurotoxicity	11 (14)	2998	0·2%	0·1%	1·65 (0·73–3·75)	0·23	0%	1·00	0·69
Hearing loss	11 (15)	3037	2·9%	1·3%	2·28 (1·46–3·55)	0·00029	37%	0·076	0·00019
Weight loss	9 (12)	2350	14·4%	8·2%	1·88 (1·44–2·45)	<0·0001	55%	0·011	0·00048
Febrile neutropenia	8 (11)	1995	3·0%	2·3%	1·30 (0·79–2·16)	0·31	40%	0·082	0·059
Late toxicity									
Bone necrosis	10 (14)	2404§	0·5%	0·4%	1·17 (0·51–2·66)	0·71	0%	1·00	0·87
Visual deficit	9 (13)	2324§	1·7%	1·3%	1·28 (0·69–2·38)	0·44	0%	0·99	0·60
Brainstem or spinal cord damage	9 (13)	2298§	0·7%	0·5%	1·25 (0·57–2·74)	0·58	0%	0·94	0·49
Symptomatic temporal lobe necrosis (yes or no)	9 (13)	2266§	1·9%	2·1%	0·91 (0·52–1·60)	0·75	0%	0·96	1·00
Xerostomia	9 (12)	2030§	5·1%	3·6%	1·45 (0·95–2·21)	0·087	0%	0·97	0·50
Cranial nerve palsy	9 (13)	2013§	11·4%	8·7%	1·35 (1·00–1·82)	0·052	19%	0·25	0·21
Hearing deficit	9 (13)	2009§	20·9%	15·1%	1·49 (1·18–1·87)	0·00068	20%	0·24	0·58
Cutaneous fibrosis	7 (7)	1643§	2·6%	2·1%	1·25 (0·67–2·32)	0·48	0%	0·86	0·68
Trismus	7 (10)	1686§	1·5%	1·2%	1·26 (0·62–2·60)	0·52	0%	1·00	0·85

OR=odds ratio. *Only trials having more than 60% of patients with available data were used for the analyses. †Computed rates (see Methods). ‡p values are summarised from appendix. §Only patients with a follow-up longer than 6 months were included in the analyses.

Table 3: **Toxicity data**

reductions in locoregional failure, distant failure, and nasopharyngeal carcinoma-related mortality. The findings further support the use of concomitant chemotherapy; there is a significant association between chemotherapy timing and overall and progression-free survival in favour of concomitant administration. Compared with our previous meta-analysis,[3] this study has analysed more trials and patients and has added new data (toxicities). Given the characteristics of the additional trials, it was possible to create a specific group of trials for the analysis of concomitant plus adjuvant chemotherapy administration separate from the concomitant only regimen. The results of the INT-0099 trial was validated in four independent trials (five comparisons in the meta-analysis), although with a smaller magnitude than in INT-0099. However, this analysis does not completely answer the question whether there is a benefit of the adjuvant phase in the concomitant setting.

The strengths of this meta-analysis are its size and its use of individual patient data, which allowed detailed checking and re-analysis of each trial that was subsequently validated by the trial investigator. At the time of this update, seven trials had a follow-up longer than 10 years. The large number of patients allowed for subgroup and subset analyses to be done with adequate power while respecting the intention-to-treat principle. Sensitivity analyses show that the results are robust (appendix). The major limitations of this study are the heterogeneity of trial designs and chemotherapy regimens, and the use of outdated radiotherapy (two dimensional) in more than three-quarters of the patients with data available. The analysis of long-term toxicities was restricted due to the quality of the data and the low number of events. Data on dose intensity and cumulative dose of cisplatin were not collected so an analysis of the effect of chemotherapy dose on outcome could not be done.

The benefit of the concomitant plus adjuvant chemotherapy schedule for all tumour-related outcomes is the greatest compared with other treatment modalities, suggesting that this regimen has the greatest efficacy. However, differences between trials assessing concomitant chemotherapy and those assessing concomitant plus adjuvant chemotherapy (table 1) prevent an unbiased comparison between these two treatment schedules. When trials assessing only concomitant chemotherapy are analysed, the HR for overall survival is 0·71 (95% CI 0·57–0·89) and the difference between these schedules (concomitant chemotherapy *vs* concomitant plus adjuvant chemotherapy), which was already not significant, decreases further. This finding suggests that these two schedules are very close in terms of benefit.

Compliance with chemotherapy or radiotherapy can potentially affect treatment outcome. A correlation was shown between the number of adjuvant cycles of chemotherapy and the occurrence of distant relapse in an exploratory analysis of a randomised trial.[30] In a disease where more than half of the progression events are distant failures, reducing the occurrence of metastatic relapse is a major goal. But given the limited compliance to adjuvant chemotherapy after concomitant chemoradiotherapy (between half and three-quarters of the patients in this meta-analysis received the three planned chemotherapy cycles), and the uncertain benefit and real risks of adjuvant treatment, selecting patients at risk for distant relapse could be an option to individualise therapy in the adjuvant phase. The concentration of circulating Epstein-Barr virus DNA is an attractive biomarker. Persistence of detectable circulating Epstein-Barr virus DNA after local therapy is associated with a high risk of tumour recurrence.[1] Large-scale trials are exploring this biomarker-driven strategy to personalise the decision for adjuvant chemotherapy (NCT00370890 and NCT02135042). Another option is to give chemotherapy before local treatment, because induction chemotherapy is generally better tolerated than adjuvant chemotherapy and allows the potential reduction of locoregional and distant failures. This strategy has been compared with concomitant and adjuvant chemotherapy in the Hong Kong nasopharyngeal carcinoma study group (HKNPCSG 0501) trial with similar results[31] to the administration of concomitant plus adjuvant chemotherapy, and is now considered a potential option in the 2014 National Comprehensive Cancer Network guidelines.[32] The use of modern induction chemotherapy regimens comprising a taxane or gemcitabine in head and neck squamous cell carcinoma is also being assessed in clinical trials and might change treatment options in the future.[33]

In conclusion, this individual patient data meta-analysis confirms the benefits associated with the addition of chemotherapy to radiotherapy in nasopharyngeal carcinoma; the greatest benefit was found in the groups with concomitant administration. The benefits of the addition of induction or adjuvant chemotherapy in the context of concomitant chemo-radiation still need further assessment.

Contributors

PB, JB, AL, WTN, and JPP designed and supervised the study. JPP, PB, AL, and WTN obtained funding. JPP, PB, WTN, and T-XL searched and selected the trials. SM, JL, PB, and JPP participated in data collection and checking. SM, JL, and JPP did the statistical analyses. PB, JB, AL, SM, JL, WTN, and JPP wrote the draft, with revisions from the other investigators. All 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 members (appendix) revised the protocol, and contributed to the identification and selection of the trials. Most steering committee members took part in an investigator meeting where preliminary results were presented and discussed; they revised the manuscript. Trialists (appendix) contributed to the study by providing data, replying to the secretariat queries, and validating the re-analysis of their trial. Most trialists took part in an investigator meeting; they revised the manuscript.

Declaration of interests

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