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# Role of chemotherapy in patients with nasopharynx carcinoma treated with radiotherapy (MAC-NPC): an updated individual patient data network meta-analysis

Claire Petit, Anne Lee, Jun Ma, Benjamin Lacas, Wai Tong Ng, Anthony T C Chan, Ruey-Long Hong, Ming-Yuan Chen, Lei Chen, Wen-Fei Li, Pei-Yu Huang, Terence Tan, Roger K C Ngan, Guopei Zhu, Hai-Qiang Mai, Edwin P Hui, George Fountzilas, Li Zhang, Alexandra Carmel, Dora L W Kwong, James Moon, Jean Bourhis, Anne Auperin, Jean-Pierre Pignon, Pierre Blanchard, on behalf of the MAC-NPC Collaborative Group\*

## Summary

**Background** The meta-analysis of chemotherapy for nasopharynx carcinoma (MAC-NPC) collaborative group previously showed that the addition of adjuvant chemotherapy to concomitant chemoradiotherapy had the highest survival benefit of the studied treatment regimens in nasopharyngeal carcinoma. Due to the publication of new trials on induction chemotherapy, we updated the network meta-analysis.

**Methods** For this individual patient data network meta-analysis, trials of radiotherapy with or without chemotherapy in patients with non-metastatic nasopharyngeal carcinoma that completed accrual before Dec 31, 2016, were identified and updated individual patient data were obtained. Both general databases (eg, PubMed and Web of Science) and Chinese medical literature databases were searched. Overall survival was the primary endpoint. A frequentist network meta-analysis approach with a two-step random effect stratified by trial based on hazard ratio Peto estimator was used. Global Cochran Q statistic was used to assess homogeneity and consistency, and p score to rank treatments, with higher scores indicating higher benefit therapies. Treatments were grouped into the following categories: radiotherapy alone, induction chemotherapy followed by radiotherapy, induction chemotherapy without taxanes followed by chemoradiotherapy, induction chemotherapy with taxanes followed by chemoradiotherapy, chemoradiotherapy followed by adjuvant chemotherapy, and radiotherapy followed by adjuvant chemotherapy. This study is registered with PROSPERO, CRD42016042524.

**Findings** The network comprised 28 trials and included 8214 patients (6133 [74.7%] were men, 2073 [25.2%] were women, and eight [0.1%] had missing data) enrolled between Jan 1, 1988, and Dec 31, 2016. Median follow-up was 7.6 years (IQR 6.2–13.3). There was no evidence of heterogeneity ( $p=0.18$ ), and inconsistency was borderline ( $p=0.10$ ). The three treatments with the highest benefit for overall survival were induction chemotherapy with taxanes followed by chemoradiotherapy (hazard ratio 0.75; 95% CI 0.59–0.96; p score 92%), induction chemotherapy without taxanes followed by chemoradiotherapy (0.81; 0.69–0.95; p score 87%), and chemoradiotherapy followed by adjuvant chemotherapy (0.88; 0.75–1.04; p score 72%), compared with concomitant chemoradiotherapy (p score 46%).

**Interpretation** The inclusion of new trials modified the conclusion of the previous network meta-analysis. In this updated network meta-analysis, the addition of either induction chemotherapy or adjuvant chemotherapy to chemoradiotherapy improved overall survival over chemoradiotherapy alone in nasopharyngeal carcinoma.

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## Introduction

During the past two decades, the use of concomitant chemotherapy and intensity-modulated radiotherapy have reduced the occurrence of locoregional recurrences for locally advanced nasopharyngeal carcinoma, but distant relapses remain a major concern.<sup>1–6</sup> The overall survival rate is 70% at 5 years with chemoradiotherapy.<sup>7</sup> Our previous individual patient data network meta-analysis showed that the addition of adjuvant chemotherapy to chemoradiotherapy had the highest benefit on overall and progression-free survival and that the addition of induction chemotherapy to chemoradiotherapy had the highest effect on distant progression.<sup>8</sup>

Because additional randomised trials on induction chemotherapy have been reported,<sup>9–14</sup> including a trial that directly compared adjuvant chemotherapy after chemoradiotherapy with induction chemotherapy followed by chemoradiotherapy,<sup>4,15,16</sup> the meta-analysis of chemotherapy in nasopharynx carcinoma (MAC-NPC) collaborative group launched an update. The MAC-NPC first did a standard meta-analysis to determine absolute and relative benefit for the standard comparisons.<sup>7</sup> This meta-analysis confirmed the benefit of chemoradiotherapy and chemoradiotherapy plus adjuvant chemotherapy, and suggested that the addition of induction chemotherapy or adjuvant chemotherapy to chemoradiotherapy improved

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See Online for appendix

## Research in context

### Evidence before this study

Individual patient data meta-analyses and a previous network meta-analysis have shown that the addition of adjuvant chemotherapy to chemoradiotherapy had the highest survival benefit and that the addition of induction chemotherapy to chemoradiotherapy had the greatest effect on distant progression in the treatment of locally advanced non-metastatic nasopharyngeal carcinoma. Since publication of these meta-analyses, additional trials on induction chemotherapy have been done and a trial that directly compared the addition of adjuvant chemotherapy versus addition of induction chemotherapy with chemoradiotherapy has been published. We searched PubMed, Scopus, Web of Science, Cochrane Controlled Trials meta-register, ClinicalTrials.gov, and meeting proceedings, without language restriction, for published and unpublished studies that completed accrual before Dec 31, 2016 (detailed in a previous publication of the pairwise meta-analysis and in the appendix [p 37]).

### Added value of this study

Network meta-analyses allow the comparison of all treatment modalities with each other, using available direct and indirect

tumour control and survival,<sup>7</sup> although many comparisons were not estimated due to the absence of direct randomised trials. Moreover, two methods of induction chemotherapy could be individualised depending on the use or not of taxane in this updated meta-analysis. The network now has more trials, patients, treatment modalities, and longer follow-up.

Here we present the results of this individual patient data network meta-analysis of multiple treatment modalities for advanced nasopharyngeal carcinoma, and the relative and absolute differences among eight treatment modalities on efficacy and toxicity.

## Methods

### Search strategy and selection criteria

This individual patient data network meta-analysis included randomised controlled trials from the MAC-NPC database. The methods for how we compiled this database have been detailed in a previous publication, along with the results of the systematic review and pairwise meta-analysis.<sup>7</sup> Briefly, we included all randomised trials evaluating the benefit of adding chemotherapy to local treatment in patients with non-metastatic nasopharyngeal carcinoma that completed accrual before Dec 31, 2016. To be eligible, trials had to compare radiotherapy alone with radiotherapy plus chemotherapy, or to compare a treatment strategy—ie, radiotherapy plus concomitant chemotherapy alone, radiotherapy plus induction chemotherapy, or radiotherapy plus adjuvant chemotherapy—with the same treatment strategy plus another timing of chemotherapy (induction, concomitant, or adjuvant). The trials had to be

comparisons (through common comparators). The addition of induction chemotherapy or adjuvant chemotherapy to chemoradiotherapy improves disease control probability and overall survival over chemoradiotherapy alone. The relative efficacy of these two combinations does not allow us to identify the superiority of one over the other, except for distant progression, in which the results are in favour of induction chemotherapy over adjuvant chemotherapy.

### Implications of all the available evidence

The addition of induction or adjuvant chemotherapy to chemoradiotherapy improves survival outcomes compared with chemoradiotherapy alone, with a significant improvement of distant control in favour of the use of induction chemotherapy over adjuvant chemotherapy. Network meta-analyses have limitations due to the use of indirect information and these results would ideally be confirmed by randomised trials.

properly randomised and include patients with non-metastatic nasopharyngeal carcinoma who were recruited untreated and then had undergone potentially curative radiotherapy. Both published and unpublished trials meeting the criteria were eligible. Trials were identified by searching general electronic publication databases (eg, PubMed, Web of Science, and Cochrane), Chinese medical literature databases, trial registries, and meeting proceedings without language restrictions for the period 2009–15 (the previous period that was searched for the previous rounds of the meta-analysis) and updated in 2019 (details in Blanchard et al<sup>7</sup> and the appendix [p 37]). PB, BL, CP, WTN, AL, and J-PP contributed to the trial search. They discussed the eligibility of the identified trials. Inconsistency within the database and discrepancy with each identified publication were discussed among the members of the secretariat (PB, AL, CP, and J-PP) and the investigators of the trial were contacted to answer the queries. Criteria were the same for the systematic review and the meta-analysis. For studies published in Chinese, selection was first based on the abstract because an English version was available in most cases. If needed, key features of the paper were translated by WTN and AL and the authors of the paper contacted if further details were required. Once all relevant information had been collected, eligibility of the study for inclusion in the database was discussed with PB and J-PP.

The protocol for the MAC-NPC is available online. Two amendments were made in the protocol before analysis: the first (June 12, 2019) added 1 more year to the trial period inclusion; the second (Oct 24, 2019) expanded the statistical analysis plan for the network meta-analysis.

For the study protocol see <https://www.gustaveroussy.fr/sites/default/files/mac-npc3-protocol.pdf>

### Trial quality and risk of bias

All trials selected by the MAC-NPC group and for which individual patient data were successfully collected were checked according to a standardised protocol that follows the recommendations of the Cochrane Individual Participant Data Meta-analysis Methods Group and PRISMA IPD,<sup>17,18</sup> and compared with each trial protocol and published reports. Missing values and discrepancies were discussed with the trialists. Each trial was reanalysed, and the analyses were sent to the trialists for validation. The risk of bias was assessed by verifying that the randomisation process was homogeneous across time, that all patients randomly assigned to treatment were included, and that the median follow-up was identical between the groups. Independently of the method chosen in the original publication, we analysed patients according to the intention-to-treat principle. Due to the differences in type of intervention, no masking was done in any study. The information on trials allowing assessment of risk of bias (eg, randomisation method, treatment being studied, and comparison of the follow-up between groups) are described in the appendix (pp 7–11).<sup>5,6</sup> Four trials with bias detected during checking were excluded: three<sup>19–21</sup> during the initial analysis,<sup>5</sup> none during the first update,<sup>6</sup> and one<sup>22</sup> during the second update.<sup>7</sup>

### Outcomes

The primary endpoint was overall survival, defined as the time from randomisation until death due to any cause. The secondary endpoints were progression-free survival, locoregional and distant progression, and nasopharynx cancer death and non-nasopharynx cancer death. Progression-free survival was defined as the time from randomisation to first progression (locoregional or distant) or death, whichever occurred first. Locoregional and distant progression were defined as the time from randomisation to the occurrence of a locoregional or distant progression, respectively. If both a locoregional progression and a distant progression occurred at the same time, patients were considered as having a distant progression only. Patients without locoregional and distant progression were censored at the last follow-up visit or date of death. Nasopharynx cancer death included deaths from any cause in patients with a previous progression event and deaths from the treated nasopharyngeal cancer.<sup>23</sup> Deaths from an unknown cause without previous disease progression or recurrence were regarded as nasopharynx cancer deaths if they occurred within 5 years after randomisation and as non-nasopharynx cancer deaths if they occurred at exactly 5 years or longer after randomisation.

For the adverse event analysis, severe acute and late adverse events (ie, grade  $\geq 3$ ) were considered for analysis, with late defined as occurring between 1 and 5 years after randomisation. A trial was considered eligible if presence or not of the adverse events was reported in 60% of the

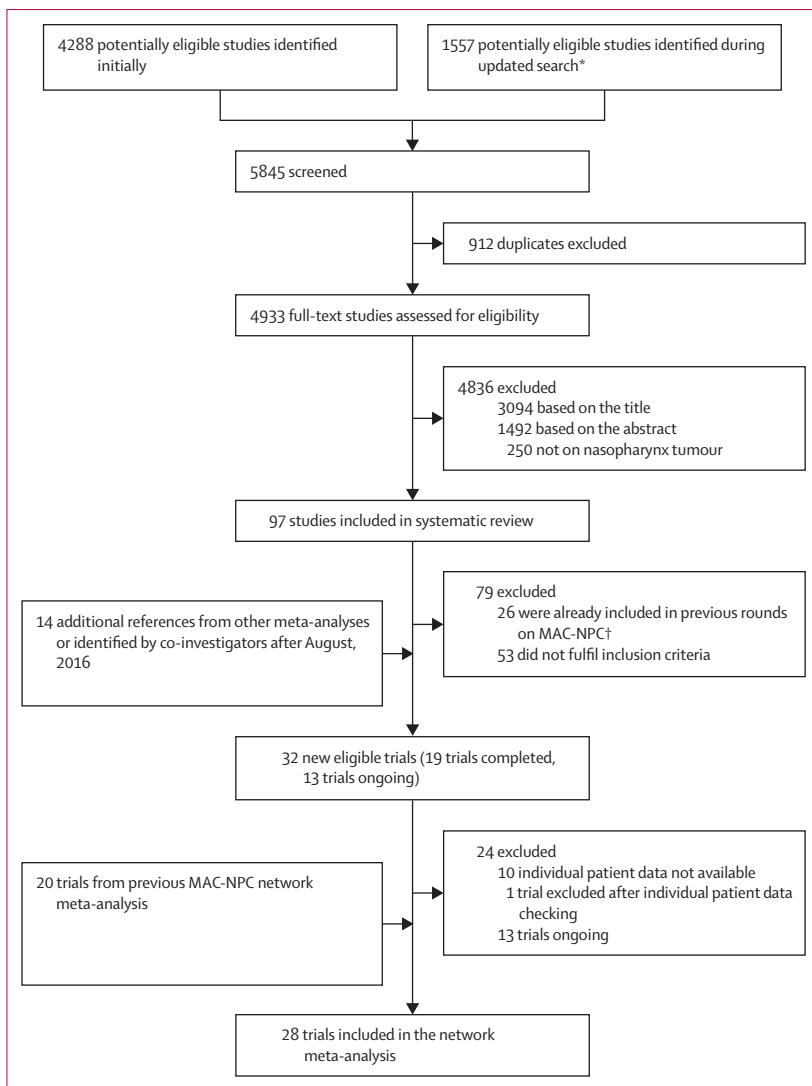
patients, and if there were at least five patients with an adverse event in each arm. For late adverse events, patients followed up for less than 1 year were excluded. Adverse events retained in the adverse event analysis were those with at least 2000 patients enrolled in the eligible trials and with at least five events in each treatment group. Compliance to chemotherapy was also a prespecified secondary outcome, and will be reported elsewhere.

### Statistical analysis

For our analysis, we used a two-step method. The first step was to calculate hazard ratios (HRs) for each trial on the basis of individual patient data using the Peto estimator for overall survival and progression-free survival,<sup>24</sup> and a competing risk model for estimating the subdistribution HR of locoregional and distant progression (as only the first event of failure was available).<sup>25</sup> The proportional hazards assumption was checked at the level of each meta-analysis for overall survival and progression-free survival.<sup>26</sup> The second step was the frequentist network meta-analysis using the logarithm of the HR, and its variance, as input data for each trial comparing the two treatments allocated. Restricted mean survival time difference, which provides the number of months gained (95% CIs), was also applied because of its robustness to non-proportionality of hazards and its applicability to meta-analysis and network meta-analysis.<sup>27,28</sup> We applied it for overall survival and progression-free survival with a restriction at a special time  $t^*$  that we selected to be  $t^*=5$  years, time determined clinically, so no extrapolation was needed (all trials had at least one event after 5 years). We present HRs using chemoradiotherapy as reference because this treatment modality is considered as the reference in nasopharyngeal cancer.

To limit the number of tests for both heterogeneity and inconsistency, we used Rücker and colleagues' proposed global test, called the Q test.<sup>29</sup> This test is a generalisation of Cochran's test used to assess heterogeneity in pairwise meta-analyses. The Q statistic is the sum of a statistic for heterogeneity (within designs) and a statistic for inconsistency (between designs). Inconsistency can be defined as the variability of treatment effect between direct and indirect comparisons at the meta-analytical level. We used a random effects model to aggregate trials in case of heterogeneity ( $p$  value  $< 0.1$ ), and a fixed-effect model otherwise.

We ranked the treatments using the p score, which measures the mean extent of certainty that a treatment is better than the competing treatments.<sup>30</sup> The p score for all endpoints would be equal to 1 when a treatment is certain to be the best and equal to 0 when a treatment is certain to be the worst. We calculated the 5-year absolute benefit using the survival rate at 5 years for the chemoradiotherapy group as the reference, and we calculated the HR (95% CI) using the method of Stewart and Parmar<sup>31</sup> for overall survival.



**Figure 1: Study selection**

MAC-NPC=meta-analysis of chemotherapy in nasopharynx carcinoma. \*An updated search took place in August, 2016. †Because we aimed to collate only newly identified studies, we initially excluded studies that had been included in previous round of MAC-NPC, and then once we had identified all new eligible trials, we included these previously identified trials for our meta-analysis.

We did prespecified sensitivity analyses for overall survival after the exclusion of: outliers in the standard meta-analysis (two outliers were identified [INT-0099<sup>32</sup> and Guangzhou 2003<sup>33</sup>] using a pragmatic approach, on the forest plot, by looking for trials for which the confidence interval of the HR did not overlap the confidence interval of the overall HR), trials that used drugs that are not in common use anymore (ie, vincristine, bleomycin, floxuridine, methotrexate, and epirubicin), trials that used a newer generation of platinum agent (eg, oxaliplatin), trials comparing two isolated treatment modalities (induction chemotherapy followed by radiotherapy and radiotherapy followed by adjuvant chemotherapy), trials with quality issues (eg, fewer than 100 patients, follow-up of less than 5 years, and using sealed envelopes for

randomisation; appendix pp 38–39). Additional post-hoc sensitivity analyses, suggested by the MAC-NPC investigators were: (1) combining induction chemotherapy with taxanes followed by chemoradiotherapy and induction chemotherapy without taxanes followed by chemoradiotherapy, to study the overall effect of induction chemotherapy followed by chemoradiotherapy; (2) exclusion of the NPC 0502 trial,<sup>34</sup> because of heterogeneity in locoregional treatments; and (3) exclusion of QMH-95,<sup>35,36</sup> because of the multigroup nature of this trial requiring duplication of the control groups. For progression-free survival, locoregional progression, distant progression, and nasopharynx cancer death, we did prespecified sensitivity analyses after exclusion of outliers (progression-free survival and cancer death only), drug combinations including those not in common use anymore or that included a newer generation of platinum agent, trials comparing two isolated methods (induction chemotherapy followed by radiotherapy and radiotherapy followed by adjuvant chemotherapy), follow-up of less than 5 years, sealed envelope used for randomisation, and the effects of combining induction chemotherapy with taxanes followed by chemoradiotherapy and induction chemotherapy without taxanes followed by chemoradiotherapy.

To take into account the effect of age, we did a prespecified exploratory analysis of overall survival and progression-free survival with a one-step network meta-analysis using a Cox-model,<sup>37</sup> with two types of modelling: the first was a fixed-effect model with stratification on trial and adjustment on age, and the second was a random-effect model on trial and adjustment on age. The variable age was centred on the mean age of patients included in the network meta-analysis and modelled continuously (in years). For each model, the effect of age was estimated on the baseline risk and the effect of each treatment with radiotherapy as the reference treatment.

For the adverse event analysis, we calculated odds ratios and 95% CIs using the Peto estimator. We calculated p values for heterogeneity and inconsistency as described earlier. We used random-effect models in case of heterogeneity ( $p < 0.1$ ), and fixed-effects models otherwise.

This work was done in accordance with network meta-analysis guidelines.<sup>38</sup> p values of less than 0.05 were considered significant for the difference between treatments. All analyses were done using R (version 3.6.1) with the R package netmeta<sup>39</sup> and survRM2.<sup>40</sup> This study is registered with PROSPERO, CRD42016042524.

#### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

#### Results

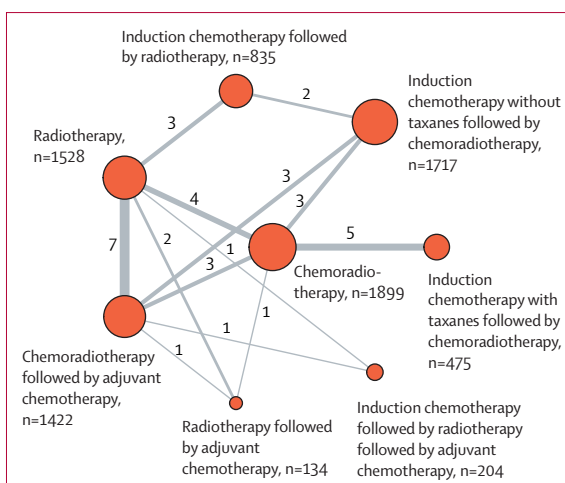
The network consists of 28 trials and 8214 patients (6133 [74.7%] men, 2073 [25.2%] women, and eight [0.1%]



had missing data) enrolled between Jan 1, 1988, and Dec 31, 2016 (figures 1, 2).<sup>9–16,32–36,41–58</sup> Because of a factorial design in three trials,<sup>15,35,41</sup> these 28 trials were split into 36 trial comparisons. There were eight different treatment modalities identified: radiotherapy alone; induction chemotherapy followed by radiotherapy; radiotherapy followed by adjuvant chemotherapy; induction chemotherapy followed by radiotherapy followed by adjuvant chemotherapy; concomitant chemoradiotherapy; induction chemotherapy with or without taxanes followed by chemoradiotherapy; and chemoradiotherapy followed by adjuvant chemotherapy. Induction chemotherapy with or without taxanes followed by chemoradiotherapy were not directly compared with radiotherapy. We chose to split induction chemotherapy into the categories of with and without use of taxanes because taxane-based regimens were considered standard of care for induction chemotherapy until 2019. Median follow-up was 7.6 years (IQR 6.2–13.3). A list of trials included in each treatment comparison, the main characteristics of each trial, and the repartition of events given the treatment modality and efficacy endpoint are summarised in the appendix (pp 6–12).

On the 8214 patients, 3073 (37.4%) died during study follow up. The three treatments that had the highest effect on overall survival were induction chemotherapy with taxanes followed by chemoradiotherapy (p score 92%), induction chemotherapy without taxanes followed by chemoradiotherapy (87%), and chemoradiotherapy followed by adjuvant chemotherapy (72%; table 1). There was no evidence of significant heterogeneity ( $p=0.18$ ); although inconsistency was borderline ( $p=0.10$ ). Compared with chemoradiotherapy, overall survival for induction chemotherapy with taxanes followed by chemoradiotherapy (HR 0.75; 95% CI 0.59 to 0.96) and induction chemotherapy without taxanes followed by chemoradiotherapy (0.81; 0.69 to 0.95) was significantly different, but was not significantly different for chemoradiotherapy followed by adjuvant chemotherapy (0.88; 0.75 to 1.04; table 1; appendix p 13). There were no significant differences between these three treatments: induction chemotherapy with taxanes followed by chemoradiotherapy compared with induction chemotherapy without taxanes followed by chemoradiotherapy (HR 0.93; 95% CI 0.70 to 1.25), and chemoradiotherapy followed by adjuvant chemotherapy (0.85; 0.64 to 1.15); and induction chemotherapy without taxanes followed by chemoradiotherapy compared with chemoradiotherapy followed by adjuvant chemotherapy (0.92; 0.77 to 1.09; appendix p 13). Results (including p scores) obtained with the restricted mean survival time difference instead of HR as input data showed similar results with a similar ranking for the top three treatments (appendix p 15).

The results of progression-free survival are similar to those for overall survival, with the same three top-ranking treatments (table 1; appendix p 14).



**Figure 2: The trial network for overall survival and progression-free survival**  
The size of the nodes is proportional to the number of patients, which is given for each treatment category. The width of the lines is proportional to the number of comparisons, which is displayed next to each line. The network included 36 comparisons from 28 trials. Six comparisons were counted for the QMH-95 trial<sup>35,36</sup> ( $2 \times 2$  design), two for the NPC-9902 trial<sup>41</sup> ( $2 \times 2$  design; second randomisation on radiotherapy methods), and three (chemotherapy comparisons) for the nasopharyngeal carcinoma 0501 trial<sup>4,15</sup> ( $2 \times 2$  design; three methods of chemotherapy with pooling of the two induction methods in the meta-analysis and two types of radiotherapy [accelerated fractionation randomised and conventional fractionation randomised]). For radiotherapy, there is a third group of patients not randomly assigned between the two radiotherapy methods and receiving conventional radiotherapy, but instead randomly assigned between the three chemotherapy methods [conventional fractionation not randomised]).

A graphical assessment of direct comparison with results of pairwise meta-analysis and network meta-analysis for overall survival and progression-free survival is shown in figure 3.

For progression-free survival, the proportional hazards assumption was not valid in four comparisons: radiotherapy versus chemoradiotherapy followed by adjuvant chemotherapy, radiotherapy versus chemoradiotherapy, induction chemotherapy with taxanes followed by chemoradiotherapy versus chemoradiotherapy, and induction chemotherapy without taxanes followed by chemoradiotherapy versus chemoradiotherapy followed by adjuvant chemotherapy. The trials with invalid proportional hazards assumption were the INT-0099 trial,<sup>32</sup> Guangzhou 2001 trial,<sup>49</sup> NCC0901 trial,<sup>9</sup> NPC 008 trial,<sup>56</sup> and the NPC 0501 CFr trial.<sup>4,15</sup> However, analyses based on the restricted mean survival time difference, which are insensitive to non-proportionality, showed similar results and the same three treatments had the largest effect as in the main analysis (appendix p 16).

Results for locoregional and distant progression with chemoradiotherapy as reference treatment are shown in table 1, and the league tables are shown in the appendix (pp 17–18).

In terms of most beneficial treatments, the results for nasopharynx cancer death are similar to those for overall survival, progression-free survival, and distant progression

	Overall survival (primary endpoint)	Progression-free survival	Locoregional progression	Distant progression	Nasopharynx cancer death	Non-nasopharynx cancer death
Treatment data	28 trials; 36 comparisons; 8214 patients; 3073 events	28 trials; 36 comparisons; 8214 patients; 3694 events	24 trials; 32 comparisons; 7239 patients; 1170 events	24 trials; 32 comparisons; 7239 patients; 1481 events	25 trials; 33 comparisons; 7498 patients; 2217 events	25 trials; 33 comparisons; 7498 patients; 457 events
Concomitant chemoradiotherapy	1 (ref); 46%	1 (ref); 33%	1 (ref); 28%	1 (ref); 39%	1 (ref); 47%	1 (ref); 38%
Induction chemotherapy with taxanes followed by chemoradiotherapy	0.75 (0.59–0.96); 92%	0.72 (0.58–0.89); 89%	0.82 (0.55–1.24); 58%	0.66 (0.47–0.93); 87%	0.70 (0.53–0.91); 94%	1.11 (0.53–2.34); 33%
Induction chemotherapy without taxanes followed by chemoradiotherapy	0.81 (0.69–0.95); 87%	0.72 (0.63–0.83); 92%	0.79 (0.62–1.00); 67%	0.65 (0.53–0.80); 91%	0.77 (0.64–0.92); 87%	0.80 (0.44–1.47); 62%
Chemoradiotherapy followed by adjuvant chemotherapy	0.88 (0.75–1.04); 72%	0.84 (0.72–0.98); 68%	0.80 (0.61–1.06); 63%	0.85 (0.68–1.06); 60%	0.87 (0.72–1.05); 71%	0.90 (0.53–1.51); 49%
Induction chemotherapy followed by radiotherapy	1.01 (0.83–1.22); 45.7%	0.89 (0.75–1.06); 55%	0.96 (0.73–1.27); 24%	0.78 (0.57–1.07); 70%	1.04 (0.82–1.31); 41%	1.14 (0.49–2.63); 30%
Induction chemotherapy followed by radiotherapy followed by adjuvant chemotherapy	1.15 (0.76–1.75); 28%	1.10 (0.77–1.57); 24%	0.62 (0.35–1.10); 80%	1.54 (0.92–2.56); 7%	1.15 (0.74–1.78); 30%	0.94 (0.16–5.67); 48%
Radiotherapy followed by adjuvant chemotherapy	1.22 (0.88–1.68); 18%	1.01 (0.73–1.39); 36%	0.75 (0.43–1.32); 75%	1.09 (0.67–1.76); 33%	1.22 (0.84–1.77); 22%	0.75 (0.34–1.64); 66%
Radiotherapy	1.26 (1.08–1.47); 11%	1.25 (1.09–1.44); 4%	1.13 (0.88–1.44); 5%	1.29 (1.03–1.61); 14%	1.34 (1.11–1.60); 8%	0.72 (0.43–1.22); 75%
p value for heterogeneity and inconsistency	0.08	0.35	0.93	0.35	0.48	0.02
p value for heterogeneity	0.18	0.27	0.82	0.50	0.51	0.08
p value for inconsistency	0.10	0.56	0.87	0.22	0.39	0.03

Data are hazard ratio (95% CI) and p score, unless otherwise stated. Subdistribution hazard ratios are provided for locoregional progression and distant progression. Treatments are ranked according to the p score for the overall survival analysis. Fixed-effects models were used for overall survival, progression-free survival, locoregional progression, distant progression, and cancer death. Random-effects models were used for non-cancer death, and for this endpoint, QMH-95<sup>29,30</sup> could not be considered as a multigroup trial. The corresponding league tables are in the appendix (pp 13–14, 17–20).

**Table 1: Summary of network meta-analysis results for the eight treatments compared with concomitant chemoradiotherapy alone and the six efficacy endpoints**

(table 1; appendix p 19). There was no evidence of heterogeneity ( $p=0.51$ ) or inconsistency ( $p=0.39$ ) for this endpoint. For non-nasopharynx cancer death, there was heterogeneity ( $p=0.08$ ) and inconsistency ( $p=0.03$ ; table 1). No treatment modality was significantly different from chemoradiotherapy or radiotherapy with respect to non-nasopharynx cancer death (appendix p 20).

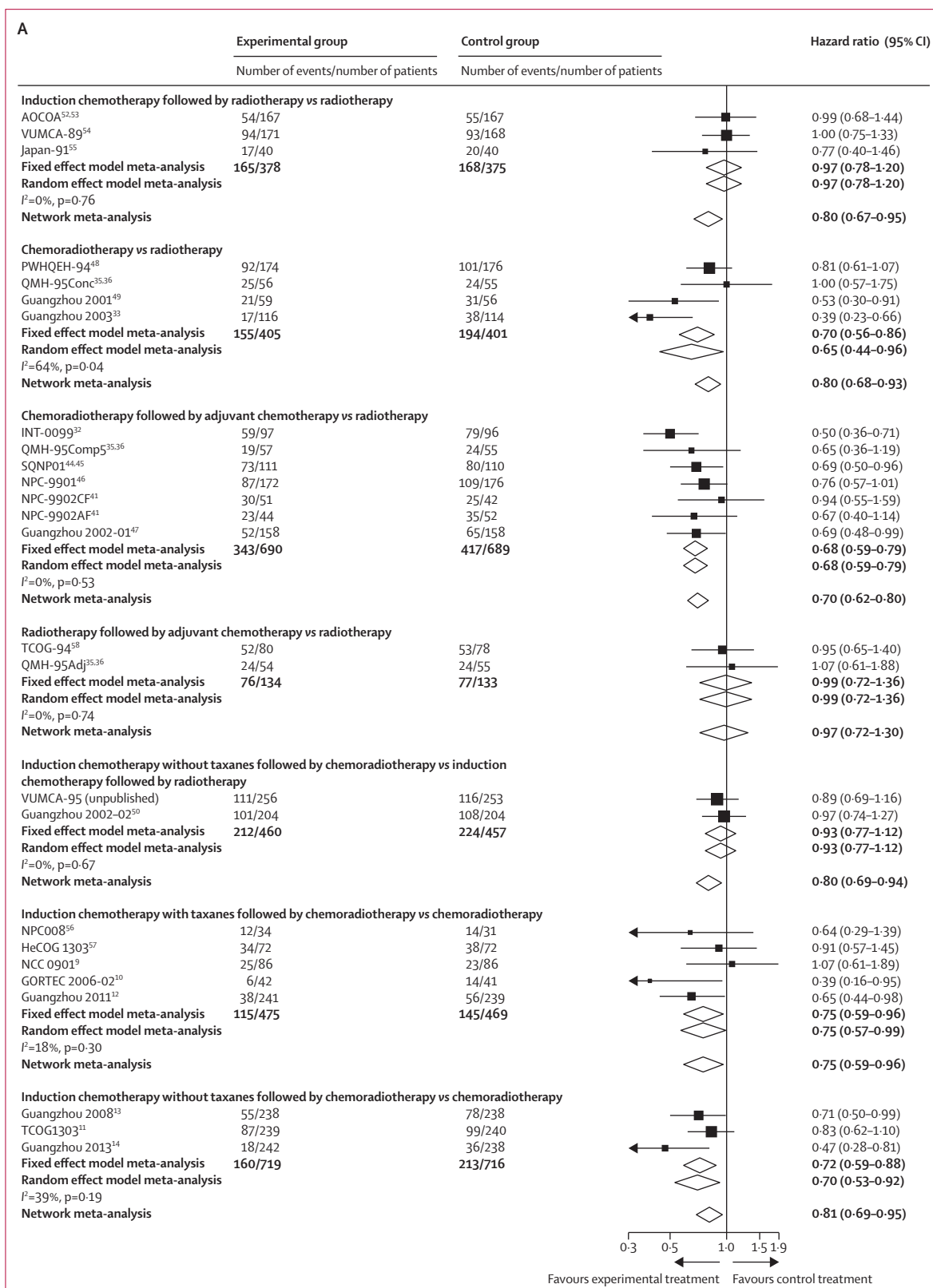
Results of our prespecified and post-hoc sensitivity analyses for overall survival and other endpoints are shown in the appendix (pp 21–25) and did not alter the conclusion of the main analysis. In the sensitivity analyses without trials with drugs not used anymore, with oxaliplatin, or comparing two isolated modalities, results were mostly similar to the main analyses, except that induction chemotherapy without taxanes followed by chemoradiotherapy ranked better than induction chemotherapy with taxanes followed by chemoradiotherapy for overall survival, progression-free survival, and distant progression, and the HR of induction chemotherapy without taxanes followed by chemoradiotherapy versus chemoradiotherapy followed by adjuvant chemotherapy was significant in favor of induction for these three endpoints (appendix pp 21–24).

Adverse event analyses were based on slightly different networks depending on data available (appendix pp 3–5). Adverse events eligible and included in the analysis were: acute adverse events of neutropenia, thrombopenia, anaemia, febrile neutropenia, weight loss, mucositis,

hearing loss, neurological toxicity, and nausea or vomiting; and late adverse events of cutaneous toxicity, xerostomia, bone necrosis, brainstem toxicity, cranial nerve toxicity, definite hearing loss, symptomatic temporal lobe necrosis, trismus, definite visual toxicity, and massive bleeding. Adverse events that were eligible but that were not included based on prespecified criteria in our analysis were: acute kidney failure, acute cutaneous toxicity, acneiform rash, infusion-related reaction, need for feeding tube, persistence of feeding tube after 1 year of treatment, endocrine dysfunction, cranial nerve palsy, and stroke.

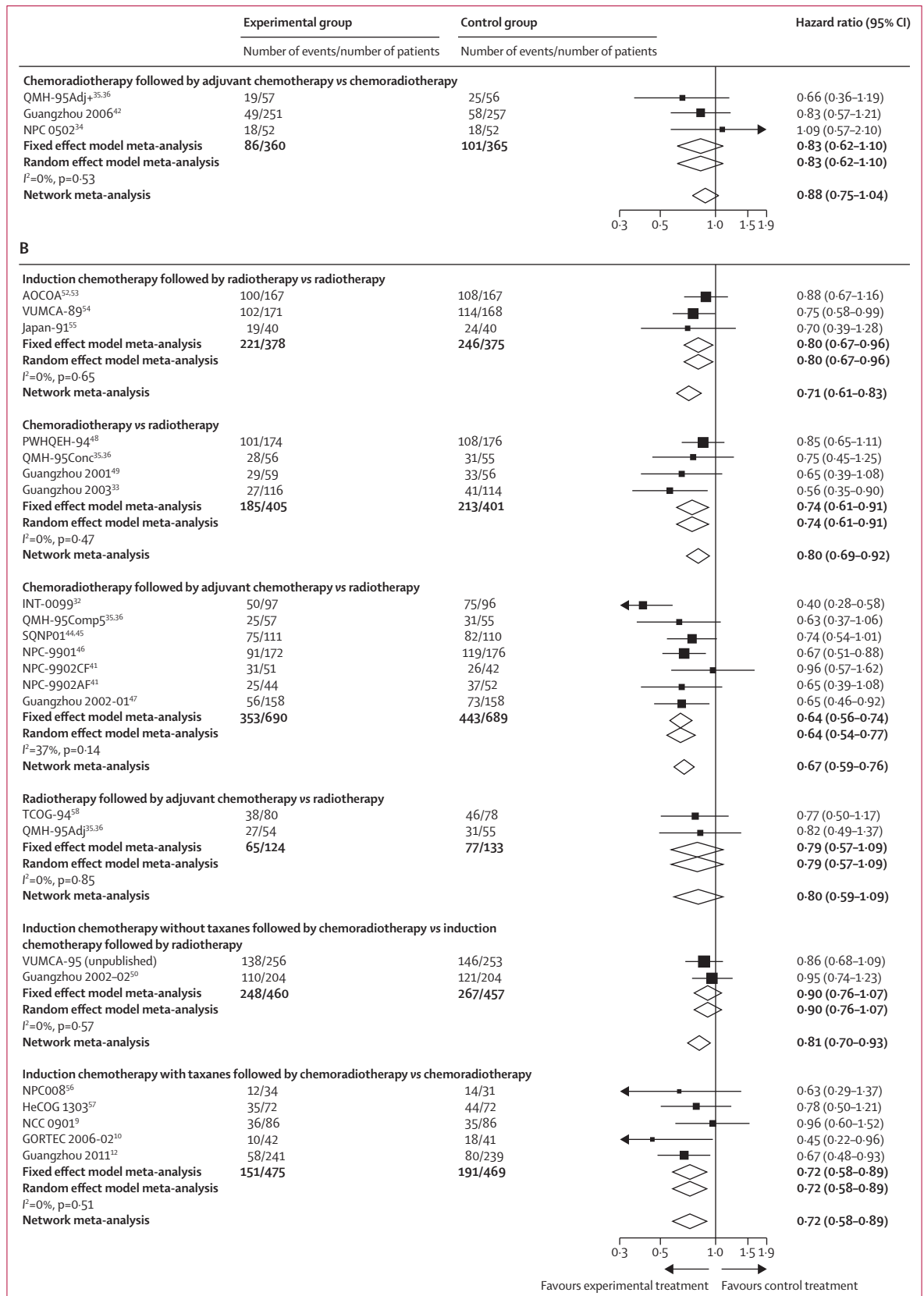
The results of the most clinically relevant adverse events are presented in table 2 and all results for acute and late adverse events are in the appendix (pp 26–27).

In prespecified exploratory analysis, as expected, there was a prognostic effect of age on overall survival per year (appendix p 28). We found no significant age or treatment interaction except for the induction chemotherapy followed by radiotherapy followed by adjuvant chemotherapy treatment modality, with a decreasing effect of treatment with increasing patient age. Additionally, the ranking of treatments was similar using age-adjusted Cox analysis and with the two-step frequentist method (appendix p 28). For progression-free survival, there was a prognostic effect of age per year (appendix p 29). For this endpoint, there was a significant interaction for the induction chemotherapy followed by radiotherapy followed by



(Figure 3 continues on next page)





(Figure 3 continues on next page)

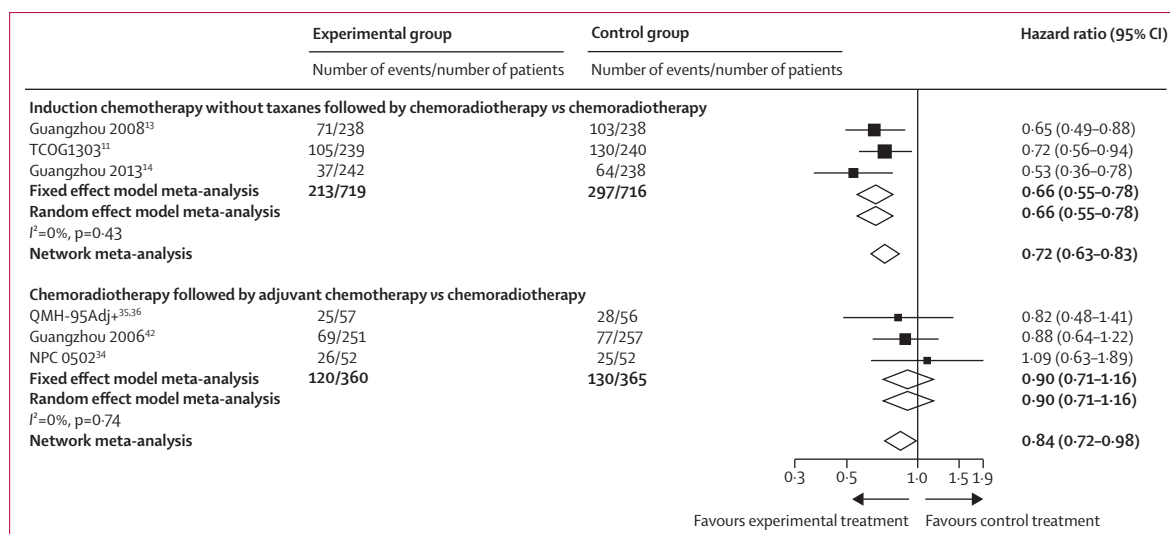


Figure 3: Forest plots for overall survival (A) and progression-free survival (B)

Results from direct comparisons and network meta-analysis. Concerning heterogeneity,  $I^2$  value, and p value for Cochran test is given for each pairwise meta-analysis.<sup>64,65</sup> A hazard ratio of less than 1 is in favour of the first treatment listed for each comparison. Only comparisons involving two trials or more are presented here. Further details about studies are in the appendix (pp 7-11).

	Neutropenia (acute)	Mucositis (acute)	Hearing loss (acute)	Weight loss (acute)	Xerostomia (late)
Treatment data	22 trials; 30 comparisons; 6697 patients; 1327 events	21 trials; 29 comparisons; 6494 patients; 2365 events	17 trials; 25 comparisons; 5554 patients; 356 events	13 trials; 20 comparisons; 4058 patients; 300 events	19 trials; 26 comparisons; 5212 patients; 229 events
Radiotherapy	1 (ref); 100%	1 (ref); 79%	1 (ref); 66%	1 (ref); 86%	1 (ref); 78%
Induction chemotherapy with taxanes followed by chemoradiotherapy	16.58 (6.09-45.13); 28%	1.84 (1.27-2.67); 24%	0.73 (0.14-3.85); 77%	1.16 (0.45-3.01); 72%	1.71 (0.67-4.35); 44%
Induction chemotherapy without taxanes followed by chemoradiotherapy	19.69 (9.16-42.31); 19%	1.69 (1.29-2.21); 36%	16.12 (9.32-27.90); 2%	1.91 (1.10-3.32); 38%	2.02 (0.84-4.82); 30%
Chemoradiotherapy followed by adjuvant chemotherapy	10.62 (6.33-17.83); 48%	1.99 (1.61-2.44); 12%	6.98 (4.41-11.03); 34%	6.39 (3.79-10.79); 8%	1.70 (0.92-3.13); 43%
Concomitant chemoradiotherapy	2.55 (1.26-5.17); 81%	1.96 (1.51-2.53); 14%	0.58 (0.24-1.43); 85%	1.13 (0.60-2.16); 76%	1.74 (0.92-3.31); 41%
Induction chemotherapy followed by radiotherapy	3.58 (1.25-10.22); 74%	1.04 (0.75-1.44); 75%	0.55 (0.21-1.45); 86%	1.36 (0.82-2.27); 62%	1.31 (0.43-4.05); 61%
Induction chemotherapy followed by radiotherapy followed by adjuvant chemotherapy	11.87 (2.37-59.32); 39%	1.02 (0.63-1.64); 77%	7.80 (3.41-17.85); 28%	NA	8.77 (1.11-69.54); 5%
Radiotherapy followed by adjuvant chemotherapy	25.12 (10.66-59.17); 11%	0.95 (0.57-1.56); 82%	9.11 (3.72-22.30); 22%	6.19 (3.59-10.68); 9%	0.38 (0.11-1.26); 98%
p value for heterogeneity and inconsistency	<0.0001	0.15	0.0006	0.57	0.97
p value for heterogeneity	<0.0001	0.43	0.28	0.27	0.94
p value for inconsistency	0.0034	0.06	<0.0001	0.92	0.82

Data are odds ratio (95% CI) and p score, unless otherwise stated. Fixed-effect models were used for mucositis, hearing loss, weight loss, and xerostomia endpoints. Random-effects models were used for neutropenia endpoint. The corresponding network graphs are in the appendix (pp 3-5). QMH-95<sup>35,36</sup> could not be considered as a multigroup trial for neutropenia, hearing loss, weight loss, and xerostomia endpoints. The lowest p scores correspond to the treatment with the highest toxicity. NA=not available (not collected or not enough data to perform the analysis).

Table 2: Summary of network meta-analysis results for the eight treatments compared with radiotherapy alone and a selection of toxicity endpoints

adjuvant chemotherapy and the chemoradiotherapy followed by adjuvant chemotherapy, with a decreasing effect of treatment with increasing patient age, but not for any other the other treatment methods (appendix p 29).

### Discussion

This updated individual patient data network meta-analysis of chemotherapy in nasopharyngeal carcinoma provides important new information compared with the

previous round. First, supporting previous findings, treatment modalities containing concomitant chemoradiotherapy most often ranked better in terms of overall survival outcomes than methods without concomitant chemoradiotherapy. Second, when focusing on schedules containing concomitant chemotherapy, the ones with the addition of induction chemotherapy consistently ranked better than those including adjuvant chemotherapy or concomitant chemotherapy alone. Nevertheless, the differences in head-to-head comparison were not significant between induction chemotherapy and adjuvant chemotherapy. For distant progression, induction chemotherapy seemed to have the greatest benefit, whereas for locoregional progression, adjuvant chemotherapy seemed to have the greatest survival benefit. Overall, these results were consistent between endpoints and robust to sensitivity analyses. Finally, adverse event data were available for several acute and late events. The schedules containing more than one timing of chemotherapy generally resulted in more toxicity than the use of only one timing.

Since the previous network meta-analysis, several trials were done to address the effect of induction chemotherapy.<sup>9–15</sup> Hence we have been able to define two methods of induction chemotherapy in this network meta-analysis on the basis of the use of taxanes or not (ie, induction chemotherapy with or without taxanes followed by chemoradiotherapy). Induction chemotherapy (with or without taxanes) has the highest p score for overall survival, progression-free survival, distant progression, and nasopharynx cancer death, and its effect was higher than that of chemoradiotherapy. Chemoradiotherapy followed by adjuvant chemotherapy was always ranked below induction chemotherapy followed by chemoradiotherapy, except for the endpoint of locoregional progression and non-nasopharynx cancer death, and its effect was significantly better than chemoradiotherapy only for progression-free survival. By combining the two modalities of induction chemotherapy, based on the similar results of induction chemotherapy with or without taxanes followed by chemoradiotherapy in respective trials, additional sensitivity analyses showed that induction chemotherapy followed by chemoradiotherapy ranked first for all endpoints except locoregional progression. Additionally, induction chemotherapy without taxanes followed by chemoradiotherapy was significantly better than chemoradiotherapy followed by adjuvant chemotherapy for distant progression. As the results of the network meta-analysis are more heavily influenced by direct than by indirect comparisons, the results of the NPC0501 trial<sup>15</sup> have a significant effect on the results of the network meta-analysis, especially regarding the comparison of induction chemotherapy and adjuvant chemotherapy added to chemoradiotherapy. This trial directly compared two different regimens of induction chemotherapy followed by chemoradiotherapy with chemoradiotherapy followed by adjuvant chemo-

therapy, with the radiotherapy further randomised to standard or accelerated fractionation. Due to the special design of this trial, the only one directly comparing induction chemotherapy followed by chemoradiotherapy to chemoradiotherapy followed by adjuvant chemotherapy, caution is required when interpreting the results and additional trials comparing induction chemotherapy followed by chemoradiotherapy with chemoradiotherapy followed by adjuvant chemotherapy are needed to identify which of these two sequences is the best. Two trials are currently underway; the first compares induction taxane-based chemotherapy (paclitaxel plus cisplatin plus fluorouracil) followed by chemoradiotherapy versus chemoradiotherapy followed by adjuvant chemotherapy (cisplatin plus fluorouracil; NCT03306121). The second trial compares induction versus adjuvant chemotherapy using paclitaxel and cisplatin, with chemoradiotherapy using cisplatin in both groups (NCT01797900). The optimal regimen of induction chemotherapy could not be identified by this network meta-analysis because there were no differences in overall survival or progression-free survival between regimens with or without taxanes. The specific question of the comparison between taxane-based induction chemotherapy and gemcitabine–cisplatin that the initial results, which were used in this network meta-analysis and were confirmed with longer follow-up, is not addressed in this study,<sup>59</sup> and ideally, these two regimens should be compared in a randomised trial to answer the question. Until such trials are done, the choice between one regimen or the other should be guided by clinical judgement.

Our work has several strengths. The first is the methods, including the use of individual patient data, which were verified and reanalysed by our team to identify and exclude trials at risk of bias; the use of competitive risks for locoregional and distant progression; the use of a validated frequentist method;<sup>29</sup> the compliance with the assumptions of the network meta-analysis; and the robustness of the main results to sensitivity analyses. Hence, we have followed CiNeMA guidelines adapted for the use of individual patient data.<sup>60</sup> The second is that this study is of great clinical interest, with a rich network of eight treatment modalities, large number of trials, and a sufficient length of follow-up. Additionally, the ranking results obtained for overall survival and progression-free survival were very consistent, which was expected since progression-free survival has been shown to be a surrogate of overall survival in the MAC-NPC database using patient-level and trial-level correlation approach.<sup>61</sup> The results were further validated with the use of the restricted mean survival time difference with a 5-year time horizon, which allowed the consideration of potential non-compliance to the proportionality assumption. And third, we did an exploratory Cox analysis to consider the interaction between age and treatment effect highlighted in the pairwise meta-analysis.<sup>7</sup>

The exploratory analysis on the effect of age identified a significant deleterious prognostic effect of increasing age in the network meta-analysis, which is expected because older patients are more likely to die of causes other than nasopharyngeal cancer than younger patients. There was no interaction between age and treatment effect for overall survival except for induction chemotherapy followed by radiotherapy followed by adjuvant chemotherapy (which only benefited younger patients), but the reason for this specificity is unclear. For progression-free survival, there was a significant interaction for induction chemotherapy followed by radiotherapy followed by adjuvant chemotherapy and chemoradiotherapy followed by adjuvant chemotherapy, with a decrease in efficaciousness with age. The method we used for this exploratory analysis was different from that used for the analysis of treatment efficacy because the two-step frequentist method does not yet allow for covariates. The Cox model has the advantage of being a simple method, accounting for age from individual data in a single-step analysis. It also allows adjustment on several covariates. However, no simple solution for the assessment of heterogeneity and coherence in the network is available, and no score has been developed to rank treatment methods such as the p score in frequentist or the surface under the cumulative ranking curve in Bayesian frameworks. Moreover, if the hypothesis of proportionality of hazard is not verified, the use of the Cox model is no longer valid. In this case, the use of the restricted mean survival time difference is preferred, but cannot be easily adjusted for covariates. If this age-adjusted analysis is true, then this treatment would be beneficial to younger patients, and a comparison with standards of care in a younger population could be investigated in a prospective trial. Standard of care in younger population could, to some extent, correspond to the management of nasopharyngeal carcinoma in the paediatric population, in which patients typically receive induction chemotherapy and then response adapted radiotherapy alone. Nevertheless, these patients do not receive adjuvant chemotherapy.

Our study had several limitations. First, trials included were conducted over an extended period, with the oldest trial enrolling patients from 1988, such that some trials included used older chemotherapy regimens and suboptimal two-dimensional or three-dimensional radiotherapy techniques. Additionally, no data were available regarding the use of second-line treatment. To deal with older chemotherapy regimens, we did a sensitivity analysis in which we excluded chemotherapy regimens that are no longer in common use and treatment modalities without concomitant chemotherapy. Results of the sensitivity analyses without older chemotherapy regimens mostly confirmed the main analyses. Regarding locoregional progression, adjuvant chemotherapy had a better ranking than induction chemotherapy in most of the cases with induction chemotherapy followed by radiotherapy followed by adjuvant chemotherapy ranking

first, but no treatment modality was significantly different from chemoradiotherapy, hence why the ranking needs to be considered with caution. Second, we had no information about plasma Epstein-Barr virus DNA level before treatment or response after induction chemotherapy, and these could be used for more personalised treatment selection for locoregionally advanced nasopharyngeal carcinoma.<sup>34,62,63</sup> Third, the quality of toxicity data was limited by missing or incomplete data collection because they are under-evaluated, especially for late toxicity, so our finding should be interpreted with caution.

In summary, the update of this network meta-analysis and the integration of the most recent trials suggest the superiority of the combinations of induction chemotherapy with chemoradiotherapy and the combination of chemoradiotherapy with adjuvant chemotherapy over other regimens, including chemoradiotherapy alone. The relative efficacy of these two combinations is not significantly different, except for distant progression, in which the results favour induction chemotherapy. Ideally, these two treatment methods should be further compared in randomised trials.

#### Contributors

CP, PB, AL, AA, and J-PP, with the help of the steering committee members, designed and supervised the study. PB and J-PP obtained funding. CP, PB, WTN, and J-PP searched for and selected the trials. Steering committee members contributed to the identification and selection of the trials. CP, WTN, PB, BL, and J-PP did the statistical analyses and wrote the first draft, with revisions from the other authors. All authors contributed to the interpretation of the results during the investigator meeting and the revision of the manuscript. All investigators listed in the appendix (p 36) received the manuscript for revision. PB and CP had full access to all the data in the study and had final responsibility for the decision to submit for publication. CP, AC, J-PP, and PB accessed and verified the data. CP, BL, J-PP and PB had access to all the data (including individual patient data) reported in the study. All other coauthors had access to the statistical report of the meta-analysis.

#### Declaration of interests

AA reports payment to her institution by MSD France for the participation on a data safety monitoring board or advisory board. P-YH reports grants from JunShi Pharm, outside the submitted work. CP reports a fellow grant from Fondation de France, outside the submitted work. LZ reports research grants from Hengrui Pharm, Beigen Pharm, and Eli Lilly. JMo reports a grant from the US National Cancer Institute to SWOG Statistics and Data Management Center. RKC reports consulting fees from Pfizer, Novartis, Sanofi, AstraZeneca, Eli Lilly, MSD, Zai Lab, Roche, Eisai, and Merck; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Novartis, AstraZeneca, Sanofi, Pfizer, Zai Lab, Eisai, Eli Lilly, and MSD; support for attending meetings or travel from Pfizer, Astellas, Novartis, MSD, Roche, Eisai, Merck, Sanofi, Bristol Myers Squibb (BMS), and ZaiLab; payment to his institution from Nuance for participation on a data safety monitoring board or advisory board. GF reports payment from Novartis for an advisory role, and stock or stock options from Genprex, Daiichi Sankyo, Ariad, RFL Holdings, and Formycon. ATCC reports grants to his institution from Merck Serono, MSD, Novartis, Pfizer, and Eli Lilly; consulting fees from MSD, Merck Serono, and Cullinan Management; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Beigene, Springer, Merck, and Pfizer; support for attending meetings or travel from BMS, MSD, Pfizer, Roche, Novartis, and AstraZeneca; participation on a data safety monitoring board or advisory board from MSD and Tessa Therapeutics; and other non-financial interests from Immunomic Therapeutics, Angene Biotechnology, and Owlstone Medical. JB reports consulting

fees from Merck, MSD, Roche, BMS, and Nanobiotix. All other authors declare no competing interests.

#### Data sharing

Individual patient data are not available for sharing but the data used at the second step level (hazard ratio) of the meta-analysis are provided in the appendix (pp 30–35, 40). Individual patient data for each study can only be requested by directly contacting the corresponding author for the study of interest.

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