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ORIGINAL REPORT

What Is the Best Treatment of Locally Advanced Nasopharyngeal Carcinoma? An Individual Patient Data Network Meta-Analysis

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ABSTRACT

Purpose

The role of adjuvant chemotherapy (AC) or induction chemotherapy (IC) in the treatment of locally advanced nasopharyngeal carcinoma is controversial. The individual patient data from the Meta-Analysis of Chemotherapy in Nasopharynx Carcinoma database were used to compare all available treatments.

Methods

All randomized trials of radiotherapy (RT) with or without chemotherapy in nonmetastatic nasopharyngeal carcinoma were considered. Overall, 20 trials and 5,144 patients were included. Treatments were grouped into seven categories: RT alone (RT), IC followed by RT (IC-RT), RT followed by AC (RT-AC), IC followed by RT followed by AC (IC-RT-AC), concomitant chemoradiotherapy (CRT), IC followed by CRT (IC-CRT), and CRT followed by AC (CRT-AC). P-score was used to rank the treatments. Fixed- and random-effects frequentist network meta-analysis models were applied.

Results

The three treatments with the highest probability of benefit on overall survival (OS) were CRT-AC, followed by CRT and IC-CRT, with respective hazard ratios (HRs [95% CIs]) compared with RT alone of 0.65 (0.56 to 0.75), 0.77 (0.64 to 0.92), and 0.81 (0.63 to 1.04). HRs (95% CIs) of CRT-AC compared with CRT for OS, progression-free survival (PFS), locoregional control, and distant control (DC) were, respectively, 0.85 (0.68 to 1.05), 0.81 (0.66 to 0.98), 0.70 (0.48 to 1.02), and 0.87 (0.61 to 1.25). IC-CRT ranked second for PFS and the best for DC. CRT never ranked first. HRs of CRT compared with IC-CRT for OS, PFS, locoregional control, and DC were, respectively, 0.95 (0.72 to 1.25), 1.13 (0.88 to 1.46), 1.05 (0.70 to 1.59), and 1.55 (0.94 to 2.56). Regimens with more chemotherapy were associated with increased risk of acute toxicity.

Conclusion

The addition of AC to CRT achieved the highest survival benefit and consistent improvement for all end points. The addition of IC to CRT achieved the highest effect on DC.

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INTRODUCTION

During the past decades, advances in the treatment of locally advanced nasopharyngeal carcinoma (NPC) have led to higher cure rates. The individual patient data (IPD) Meta-Analysis of Chemotherapy (MAC) in NPC (MAC-NPC) has clearly demonstrated that the addition of concomitant chemotherapy (CT) to radiotherapy (RT) improves overall survival (OS), progression-free survival (PFS), locoregional control, and distant control.[1] Controversy remains regarding the additional benefit of induction CT (IC) or adjuvant CT (AC) to concomitant chemoradiotherapy (CRT). Treatment guidelines, therefore, allow multiple treatment options.[2,3] In the MAC-NPC analysis, locoregional and distant failure rates at 5 years were both in the range of 20% in patients receiving CT.[1] Although the use of concomitant CT and intensity-modulated RT (IMRT) has reduced the occurrence of locoregional relapses,[4] distant recurrences remain a major concern. This underlines the potential role for additional systemic therapy.

The MAC-NPC meta-analysis mostly evaluated the addition of CT to RT compared with RT alone, but did not formally perform direct comparisons between the different timings of CT.

ASSOCIATED CONTENT

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Network meta-analysis (NMA) is a way to determine whether additional CT is beneficial in the management of NPC. NMA has been applied to head and neck squamous cell carcinomas[5] and was able to predict the results of randomized trials published afterward.[6] NMA was planned in the MAC-NPC protocol, and the presentation of its results is the purpose of this article.

METHODS

MAC-NPC Database and End Point Definitions

The MAC-NPC is an IPD meta-analysis that comprises most randomized trials conducted up to December 31, 2010, evaluating the benefit of adding CT to local treatment in patients with nonmetastatic NPC. The inclusion criteria, trial search, trial flowchart, data collection, and checking have been detailed in a previous publication along with the results of the standard meta-analysis.[1] The primary end point was OS, defined as the time from randomization until death from any cause. The secondary end points were PFS and locoregional and distant control. PFS was defined as the time from randomization to first progression (locoregional or distant) or death. Locoregional and distant control were defined as the time from randomization to the occurrence of a locoregional or distant failure, respectively. If both a locoregional failure and a distant failure occurred at the same time, patients were considered as having a distant failure only. Patients without locoregional and distant failure were censored at the date of death or last follow-up for those alive. Only severe acute toxicity was studied. End points included in the network toxicity analysis were those with a sufficient number of patients, with a significant interaction with CT timing in the standard meta-analysis, and that were considered clinically relevant. Nausea-vomiting and hematologic toxicities other than neutropenia were not included. The toxicities retained for analysis were therefore acute neutropenia, mucositis, weight loss, and hearing loss.

Statistical Methods

The NMA was planned in the protocol of the MAC-NPC update. A detailed statistical analysis plan was written before NMA analysis. A two-step method was used, the first step being the computation of hazard ratios (HRs) on the basis of the IPD gathered by the MAC-NPC Collaborative Group, using the Peto estimator for OS and PFS,[7] and a competing risk model for locoregional and distant control.[8] The proportional hazards assumption was checked at each meta-analysis level for OS and PFS.[9] The second step was the actual NMA, using as input data for each trial the two treatments compared, the logarithm of the HRs, which is usually normally distributed,[5,10,11] and its variance. Therefore, all the analyses were stratified by trial. The first analysis was initially reported[12] using Bayesian modeling.[13] Because of easier computation and programming, especially for the handling of multiarm trials or inconsistency, the final analysis was performed using a frequentist approach and the R package netmeta,[14,15] but both methods gave similar results and provided the same ranking.

Heterogeneity was quantified using the I^2, which represents the proportion of total variation in study estimates that is due to heterogeneity.[16] To limit the number of tests for both heterogeneity and inconsistency, Rücker[14] has proposed a global test, called Q test. This test is a generalization of Cochran's test that is used to assess heterogeneity in conventional meta-analysis. The Q statistic is the sum of a statistic for heterogeneity and a statistic for inconsistency, which represents the variability of treatment effect between direct and indirect comparisons at the meta-analytic level. The protocol for the NMA stated that a fixed-effects model had to be used first and that in case of significant heterogeneity ($P < .1$), two solutions would be investigated: the use of random-effects models and the performance of sensitivity analyses after the exclusion of trials that were considered as outliers in the standard meta-analysis.[1] The netmeta package allows identifying in which closed loop the inconsistency is located.[15] The trials responsible for inconsistency could be determined by comparing direct and indirect estimates and trial forest plots within the inconsistent closed loop; the effect of trial removal on the network consistency and estimation could therefore be investigated.

Within the Bayesian framework, the treatments are ranked using the surface under the cumulative ranking curve.[17,18] Rücker and Schwarzer[19] have proposed a frequentist analog to surface under the cumulative ranking curve, which is named P-score, that works without resampling and measures the mean extent of certainty that a treatment is better than the competing treatments. P-score would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst.[19] Five-year absolute benefit was computed using the survival rate at 5 years for the RT-only arms in MAC-NPC[1] and the HR using the method by Stewart and Parmar.[20] One unplanned sensitivity analysis was performed using HR adjusted on patient sex, age, performance status, and stage. This work was performed in accordance with published guidelines.[21] P values $< .05$ were considered significant for the difference between treatments. All analyses were performed using the R software (version 3.0.2; R Foundation, Vienna, Austria).

RESULTS

Description of the Network and Patients

The network consists of 20 trials and 5,144 patients: 19 trials[22-39] (including one unpublished trial, VUMCA-95), which were included in the standard meta-analysis (4,806 patients, described in Blanchard et al[1]), and one trial (338 patients), which compared two timings of CT,[40] that was ineligible for the standard meta-analysis. Because of a factorial design in two trials, these 20 trials were split into 26 comparisons. There were seven different

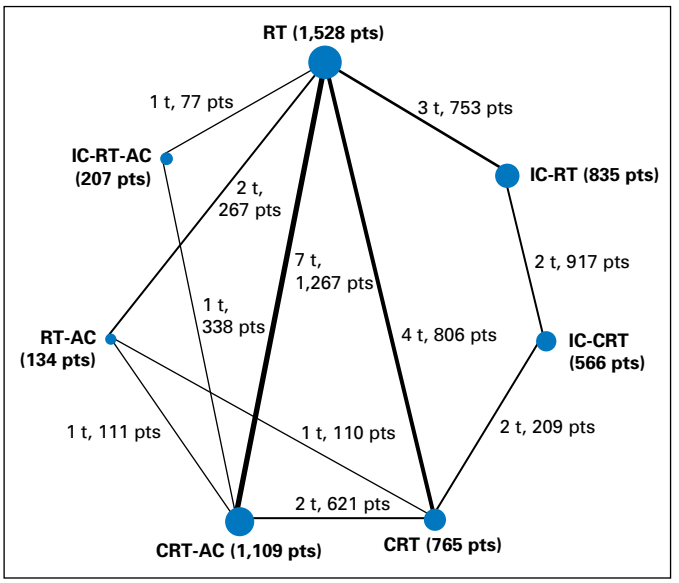

Fig 1. Graphical representation of the trial network for overall and progression-free survival. The size of the nodes is proportional to the number of patients (pts), which is given in parenthesis in each treatment category. The width of the lines is proportional to the number of comparisons. The number of trials (t) and pts in each comparison are displayed next to each line. The network included 26 comparisons from 20 trials. Six comparisons were counted for the QMH-95 trial (2 × 2 design) and two for the NPC-9902 trial (2 × 2 design; second randomization on radiotherapy [RT] modalities). Because of the duplication of QMH-95 trial arms, some pts are counted multiple times in this figure (in the RT, concomitant chemoradiotherapy [CRT], CRT-adjuvant chemotherapy [AC], and RT-AC groups). However, the statistical analysis takes into account the correlation structure in this design and does not give an excessive weight to duplicated patients. IC, induction chemotherapy.

treatments: RT alone, which was used as the reference category; IC followed by RT (IC-RT); RT followed by AC (RT-AC); IC followed by RT followed by AC (IC-RT-AC); CRT; IC followed by CRT (IC-CRT); and CRT followed by AC (CRT-AC). Only IC-CRT was not directly compared with RT. The network is represented in Figure 1. The network comprised five independent closed loops for consistency analysis and one 2 × 2 factorial design trial.[27]

Median follow-up (interquartile range) was 7.4 years (6.2 to 11.9). Patients (Data Supplement) were mostly male (3,826 patients; 74%), < 50 years of age (3,177 patients; 62%), and had good performance status (0 in 2,743 patients [65%] and 1 in 1,404 patients [33%]). Patients presented most frequently with locally advanced tumor (stage III in 2,519 patients [49%]; stage IVA-B in 2,133 [42%]; and nonkeratinizing histology [WHO grade I in 196 patients; 4%).

Overall Survival

The three treatments that had the highest effect on OS were CRT-AC, CRT, and IC-CRT, with respective P-scores (higher score meaning a higher probability of being the best treatment) of 96%, 70%, and 63%, respectively, and corresponding absolute benefit at 5 years of 12%, 8% and 6% compared with radiotherapy alone (Tables 1 and 2; Data Supplement). There was no significant heterogeneity (I^2 = 5.5%; P = .30) or inconsistency (P = .53), and the proportional hazards assumption was valid. The HRs (95% CIs) on the basis of the NMA for each pairwise comparison are presented in the lower left triangle of the league table and instructions for reading are given in the footnote of Table 2 (Data Supplement). Compared with RT alone, the HRs (95% CIs) for OS for CRT-AC, CRT, and IC-CRT, respectively, were 0.65 (0.56 to 0.75), 0.77 (0.64 to 0.92), and 0.81 (0.63 to 1.04). The HRs (95% CIs) of CRT-AC compared with CRT or IC-CRT showed no significant differences, with respective values of 0.85 (0.68 to 1.05) and 0.81 (0.61 to 1.07).

Secondary End Points

The results of PFS (Tables 1 and 2; Data Supplement) are in agreement with OS. No heterogeneity (I^2 = 0%; P = .25) or inconsistency (P = .96) was detected for this end point. The three best treatments were the same as for OS, with CRT-AC being the most effective, with a P-score of 94%; IC-CRT and CRT, with respective P-scores of 79% and 52%, ranked second and third. The HRs (95% CIs) of CRT-AC compared with CRT or IC-CRT were, respectively,

Table 1. Summary of Network Meta-Analysis Results for the Six Treatments Compared With RT Alone and the Four Efficacy End Points

Treatment Data	Overall Survival	Progression-Free Survival	Locoregional Control	Distant Control
20 trials,* 5,144 patients	26 comparisons,† 2,070 events	26 comparisons,† 2,489 events	26 comparisons,† 915 events	24 comparisons 1,129 events
P value heterogeneity/inconsistency	.39	.58	.68	0.07
P value heterogeneity (within design)	.30	.25	.50	0.07
P value inconsistency (between design)	.53	.96	.75	0.29
RT				
P-score, %	15	4	9	16
IC-RT				
HR (95% CI)	0.92 (0.75 to 1.12)	0.78 (0.66 to 0.93)	0.90 (0.70 to 1.15)	0.54 (0.37 to 0.79)
P-score, %	33	46	27	76
5y-AB, %	3	8	2	12
IC-CRT				
HR (95% CI)	0.81 (0.63 to 1.04)	0.68 (0.54 to 0.85)	0.80 (0.57 to 1.13)	0.44 (0.27 to 0.71)
P-score, %	63	79	47	95
5y-AB, %	6	13	4	15
CRT				
HR (95% CI)	0.77 (0.64 to 0.92)	0.77 (0.65 to 0.91)	0.85 (0.62 to 1.16)	0.68 (0.49 to 0.94)
P-score, %	70	52	37	48
5y-AB, %	8	10	3	8
CRT-AC				
HR (95% CI)	0.65 (0.56 to 0.75)	0.62 (0.54 to 0.71)	0.59 (0.46 to 0.76)	0.59 (0.46 to 0.77)
P-score, %	96	94	82	72
5y-AB, %	12	15	7	11
RT-AC				
HR (95% CI)	0.96 (0.71 to 1.29)	0.84 (0.63 to 1.11)	0.71 (0.44 to 1.17)	0.91 (0.54 to 1.54)
P-score, %	28	36	58	32
5y-AB, %	1	7	5	2
IC-RT-AC				
HR (95% CI)	0.87 (0.58 to 1.30)	0.83 (0.59 to 1.17)	0.50 (0.29 to 0.88)	1.13 (0.62 to 2.05)
P-score, %	45	39	90	10
5y-AB, %	4	6	9	−3

NOTE. HRs were estimated using the Peto estimator for overall survival and progression-free survival; subdistribution HRs based on competing risk analyses were used for locoregional control and distant control. Fixed-effects models were used for overall survival, progression-free survival, and locoregional control and a random-effects model for distant control. Individual trial (comparison) HRs are given in the Data Supplement.

Abbreviations: 5y-AB, absolute benefit at 5 years compared with RT alone; AC, adjuvant chemotherapy; CRT, concomitant chemoradiotherapy; HR, hazard ratio; IC, induction chemotherapy; RT, radiotherapy.

*Nineteen trials were previously described in the article by Blanchard et al,[1] and the last one was published by Xu et al.[40]

†One 2 × 2 factorial design trial[27] was analyzed as a multiarm trial and split into six comparisons for proper modeling in the netmeta package and as four independent trials for the distant control analysis because of computational constraint; the trial NPC-9902[25] was divided in two independent comparisons

Table 2. Summary Results for Concurrent CRT, With or Without IC or AC

Treatment Compared	Overall Survival	Progression-Free Survival	Locoregional Control	Distant Control
CRT-AC *v* CRT				
HR (95% CI)	0.85 (0.68 to 1.05)	0.81 (0.66 to 0.98)	0.70 (0.48 to 1.02)	0.87 (0.61 to 1.25)
5y-AB, %	3.3	5.3	3.3	2.3
CRT-AC *v* IC-CRT				
HR (95% CI)	0.81 (0.61 to 1.07)	0.92 (0.71 to 1.18)	0.74 (0.49 to 1.12)	1.35 (0.80 to 2.31)
5y-AB, %	5.8	2.7	4.7	−5.6
CRT *v* IC-CRT				
HR (95% CI)	0.95 (0.72 to 1.25)	1.13 (0.88 to 1.46)	1.05 (0.70 to 1.59)	1.55 (0.94 to 2.56)
5y-AB, %	1.5	−4.2	0.9	−8.7

NOTE. HRs were estimated using the Peto estimator for OS and PFS; subdistribution HRs based on competing risk analyses were used for locoregional control and distant control. Fixed-effects models were used for OS, PFS, and locoregional control and a random-effects model for distant control. Individual trial (comparison) HRs are given in the Data Supplement.

Abbreviations: 5y-AB, absolute benefit at 5 years compared with radiotherapy alone; AC, adjuvant chemotherapy; CRT, concomitant chemoradiotherapy; HR, hazard ratio; IC, induction chemotherapy.

*Nineteen trials were previously described in the article by Blanchard et al,[1] and the last one was published by Xu et al.[40]

†One 2 × 2 factorial design trial[27] was analyzed as a multiarm trial and split into six comparisons for proper modeling in the netmeta package and as four independent trials for the distant control analysis because of computational constraint; the trial NPC-9902[25] was divided into two independent comparisons.

0.81 (0.66 to 0.98) and 0.92 (0.71 to 1.18). A graphical assessment of local heterogeneity and inconsistency for OS and PFS is presented in Figure 2. For PFS, the proportional hazards assumption was not valid for the comparison of RT to CRT-AC because of the absence of proportional hazards in the INT-0099 trial. Results of a planned sensitivity performed after the exclusion of this trial showed the robustness of the results and the validity of the proportional hazards assumption (Data Supplement).

The three best treatments for locoregional control were IC-RT-AC, CRT-AC, and RT-AC, with respective P-scores of 90%, 82%, and 58% (Tables 1 and 2; Data Supplement). There was no heterogeneity ($I^2 = 0\%$, $P = .50$) or inconsistency ($P = 0.75$) for this end point. The comparison between CRT-AC and CRT showed a nonsignificant difference in favor of CRT-AC, with an HR (95% CI) of 0.70 (0.48 to 1.02). Regarding distant control (Tables 1 and 2; Data Supplement), the results are presented using a random effects NMA because of the presence of heterogeneity ($P = .07$). No inconsistency was noticed ($P = .29$). The three best treatments for distant control were IC-CRT, IC-RT, and CRT-AC, with respective P-scores of 95%, 76%, and 72%. The comparison between CRT-AC and CRT showed the absence of significant difference, with an HR (95% CI) of 0.87 (0.61 to 1.25). CRT was nonsignificantly inferior to IC-CRT, with an HR (95% CI) of 1.55 (0.94 to 2.56).

Sensitivity Analyses

Two sensitivity analyses for OS were planned after the exclusion of the two outliers in the standard meta-analysis (INT-0099,[26] Guangzhou 2003[29]) and after excluding the trials that did not include cisplatin as part of the randomized CT. In these two analyses, CRT-AC remained ranked first and IC-CRT was ranked second, although closely followed by CRT (Data Supplement). The unplanned sensitivity analysis on the basis of HR adjusted on covariates instead of unadjusted HR for OS and PFS did not significantly modify the network estimates, the two first treatments being the same in both cases (Data Supplement).

Results for distant control were not entirely robust to sensitivity analyses. The exclusion of the two trials responsible for heterogeneity in the standard meta-analysis for distant control (Int-0099[26] and QMH-95[27]) reduced heterogeneity ($P = .24$) and improved consistency ($P = .41$) but changed notably the estimates and ranking. IC-CRT remained ranked first (P-score, 88%; Data Supplement), but the three next best treatments were RT-AC, IC-RT, and CRT-AC. When only trials using cisplatin were included (Data Supplement), IC-CRT and CRT-AC were respectively ranked first and second, with P-scores of 99% and 74%. From a statistical standpoint, the analyses of locoregional control and distant control using the Peto estimator led to results similar to the analysis using competing risk (Data Supplement).

Toxicity

Toxicity analyses were based on slightly different networks (Data Supplement), and their results are presented in Table 3. CRT-AC and RT-AC were the most toxic regimens, as measured by their P-scores, for mucositis/hearing loss and neutropenia/weight loss, respectively, which underlines the potential toxicity of AC, either alone or administered with CRT.

DISCUSSION

The major findings of this IPD NMA of CT in NPC can be summarized as follows. First, schedules containing concomitant CT most often ranked better than schedules without concomitant CT. Second, when focusing on schedules containing concomitant CT, the ones with the addition of AC always ranked better than concomitant CT alone, although the differences in head-to-head comparison were only significant for PFS and locoregional control, whereas IC added to CRT ranked better than CRT for PFS, locoregional control, and distant control. These results were overall consistent between end points and robust to sensitivity analyses. Finally, although toxicity data were available for only a minority of acute toxicities and a subset of trials, the schedules containing more than one timing of CT generally resulted in more toxicity than the use of only one timing.

Four NMAs on the role of CT in NPC on the basis of published data have been reported[41-44] in the past year, one as a full network of all treatments[43] and the other three as small

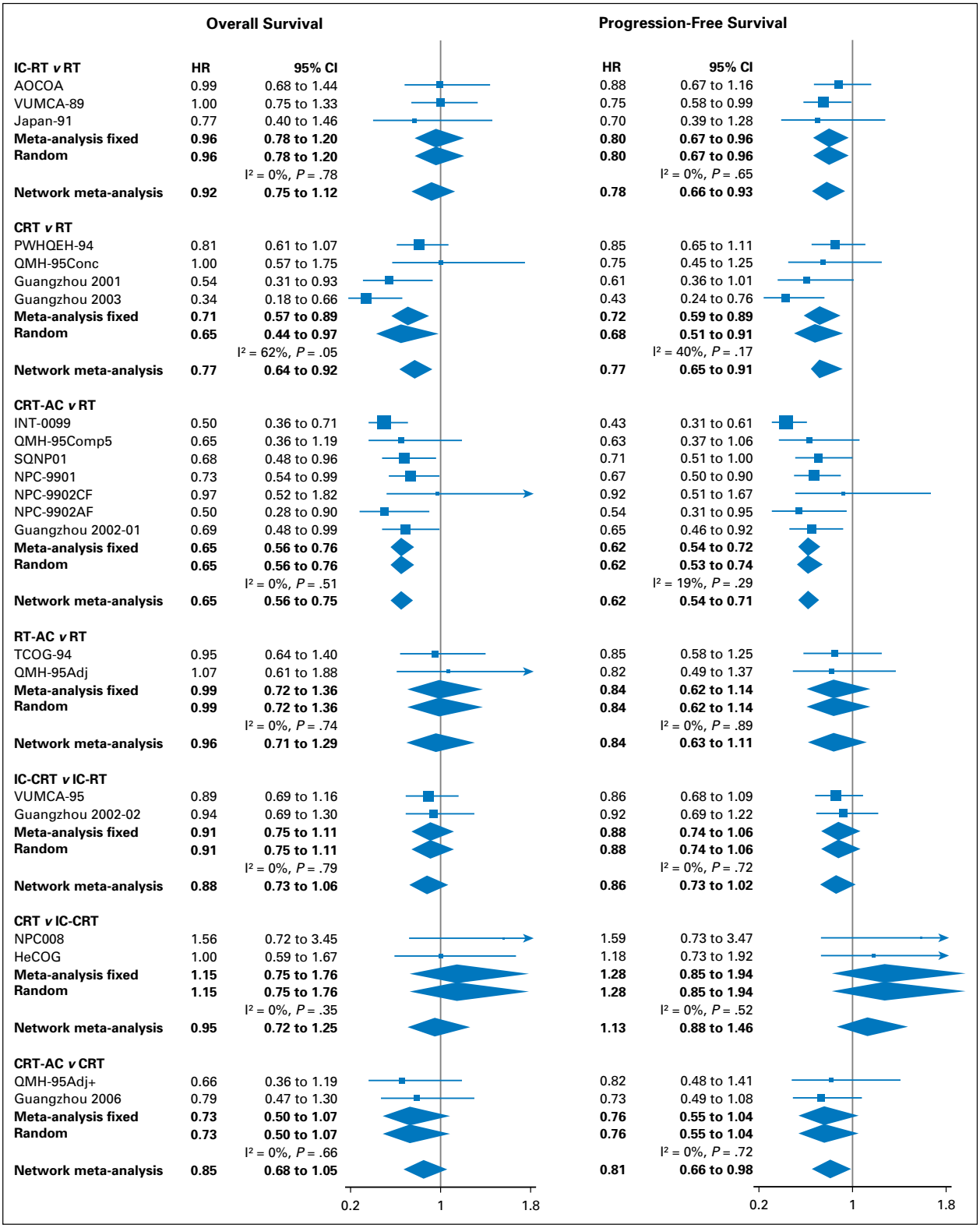

Fig 2. Forest plot for overall survival (on the left) and progression-free survival (on the right), showing results from direct comparisons and network meta-analysis. HR < 1 is in favor of the first treatment mentioned in the title (ie, IC-RT for the comparison IC-RT *v* RT). Only comparisons involving two trials or more are presented here. For comparisons with only one trial, the hazard ratios used are reported in the Data Supplement. AC, adjuvant chemotherapy; CRT, concomitant chemoradiotherapy; HR, hazard ratio; IC, induction chemotherapy; RT, radiotherapy;

Table 3. Summary Table of the Network Meta-Analysis for Acute Toxicity

Treatment Data	Neutropenia (16 trials, 4,165 patients, 547 events)	Mucositis (15 trials, 3,989 patients, 1,439 events)	Hearing Loss (12 trials, 3,156 patients, 71 events)	Weight Loss (nine trials, 2,140 patients, 230 events)
P value heterogeneity/inconsistency	< .001	.48	1.00	.41
P value heterogeneity (within design)	< .001	.81	.97	.36
P value inconsistency (between design)	.66	.17	1.00	.41
RT				
P-score, %	100	70	60	93
IC-RT				
OR (95% CI)	2.75 (0.41 to 18.37)	0.79 (0.51 to 1.23)	0.26 (0.09 to 0.77)	1.37 (0.79 to 2.39)
P-score, %	74	91	96	72
IC-CRT				
OR (95% CI)	14.57 (2.86 to 74.15)	1.40 (0.89 to 2.21)	0.81 (0.13 to 5.00)	1.94 (1.01 to 3.73)
P-score, %	16	37	64	45
CRT				
OR (95% CI)	2.41 (0.84 to 6.90)	1.77 (1.34 to 2.33)	1.13 (0.34 to 3.80)	1.40 (0.68 to 2.91)
P-score, %	76	16	55	70
CRT-AC				
OR (95% CI)	10.49 (5.14 to 21.41)	1.94 (1.56 to 2.41)	4.69 (2.54 to 8.66)	5.10 (2.52 to 10.34)
P-score, %	42	6	10	12
RT-AC				
OR (95% CI)	18.00 (5.41 to 59.77)	1.07 (0.68 to 1.71)	1.81 (0.57 to 5.78)	5.54 (3.00 to 10.22)
P-score, %	9	62	38	8
IC-RT-AC				
OR (95% CI)	11.71 (1.51 to 90.67)	1.00 (0.62 to 1.61)	4.63 (0.09 to 244.79)	—
P-score, %	34	70	27	—

NOTE. Results are presented as ORs, 95% CIs, and P-scores for all treatments compared with RT alone. A lower OR and a higher P-score indicate a lower risk of toxicity. ORs were calculated using fixed-effects models for mucositis, hearing loss, and weight loss, and a random-effects model for neutropenia (because of heterogeneity). Individual trial (comparison) ORs are given in the Data Supplement. The Data Supplement shows the network for each end point and the complete list of trials included.
Abbreviations: AC, adjuvant chemotherapy; CRT, concomitant chemoradiotherapy; IC, induction chemotherapy; OR, odds ratio; RT, radiotherapy.

subnetworks, centered around the comparison between CRT and CRT-AC,[41] CRT, and IC-CRT[42] or CRT, CRT-AC, and IC-CRT.[44] All four reports concluded that CRT was as efficacious as more intensified treatments, such as CRT-AC or IC-CRT, and should be the preferred treatment in locally advanced NPC. The differences between their findings and ours can be explained by the selection of trials, the performance of analyses on secondary/limited networks,[41,42,44] the use of published data of unchecked quality, the absence of data updates or use of intent-to-treat analysis, and the potential inaccuracy of some data used. Indeed, when the HRs are not reported in the publications, their estimates on the basis of other parameters, such as survival curves, are known to be imprecise.[45] These differences might be diluted and less easy to point out in NMA compared with standard meta-analysis, because the amount of data analyzed and statistical tests produced can be overwhelming for readers. We believe that the high quality of data with updated follow-up, the use of IPD, multiple standardized secondary end points such as PFS and locoregional/distant control, and the rigorous methodology are major strengths of our work. Our work highlights once more that IPD meta-analyses are the gold standard method and probably even more so in the context of NMA. The publication of multiple articles on the same meta-analysis is also typical of the type of research waste[46] that is seen more and more often. It does not add much value but produces confusion in the scientific debate. The use of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension to network meta-analyses[21] and the prospective registration of meta-analyses in a centralized database[47] might help select the meta-analyses that are trustworthy in the future.

The present work has limitations. First, patients with stage II disease or WHO grade I histology were included, but they represent a minority of patients with NPC in both clinical practice and trials (Data Supplement). The results of the entire network might not apply to these patients, and their inclusion might also bias its results. However, because there was no interaction between tumor stage and treatment effect in the standard meta-analysis,[1] it is unlikely that the exclusion of such patients would lead to anything but a lower power of the NMA and increased confusion due to postrandomization exclusion. Besides, no differences were seen when using adjusted HRs as input data for the NMA. Second, although treatment ranking is an attractive output of NMAs, readers should be aware that the computation of ranking probabilities mostly relies on the point estimates (the hazard and odds ratios here).[19] Ranking is also influenced by the network geometry.[48] To evaluate the certainty that a treatment is superior to another, attention should be paid to the HR estimates along with their CIs, as well as the consistency of the HR estimates across different end points and not entirely rely on the treatment ranking. Moreover, the ranking uncertainty could not be computed. Third, incomplete and probably heterogeneous data were available on acute toxicity, along with few reliable data on late toxicity, and given the old RT techniques used, even if these data had been recorded correctly, they would have been difficult to interpret in light of the major technical changes in radiotherapy techniques. Fourth, because results on distant control are not entirely robust to sensitivity analyses, they should be considered with caution. Fifth, although we have performed a thorough search on the basis of publications and clinical trial databases, a publication bias cannot

be completely ruled out. Finally, although network meta-analyses are now accepted by multiple public health agencies as a way to perform systematic evidence synthesis and guidelines have been published,[21,49] readers should keep in mind the limitations associated with the use of indirect comparisons.

Our interpretation is that giving more CT to patients with locally advanced NPC, as induction or adjuvant, provided they receive concomitant CT, achieves a reduction in recurrence rates. This statement is supported by the fact that HR and ranking almost always favor CRT-AC or IC-CRT. The choice of the most suited regimen for a given patient must include a consideration of the risk–benefit ratio. The data on IC before CRT remain conflicting. Indeed, a recent randomized trial evaluating induction gemcitabine, carboplatin, and paclitaxel followed by CRT versus upfront CRT was negative,[50] whereas a small randomized trial evaluating induction docetaxel, cisplatin, and fluorouracil before CRT, presented in 2015, was positive for OS.[51] Additional trials on IC should be reported in the near future and might help clarify this issue (NCT01245959, NCT01536223, NCT01872962, and NCT02512315). Ongoing research is warranted in the fields of systemic treatment and predictive biomarkers to allow the selection of patients for whom the addition of AC or IC to CRT would be needed, such as is being investigated by NRG Oncology using Epstein-Barr virus quantitative circulating DNA levels (NCT02135042).

Until then, clinical judgment, evaluation of the risk of local and distant relapse, and discussion with the patient about the potential risks and benefits of the different treatment regimens should guide clinical practice. The data presented here should be of major help because they represent the most up to date and least biased analysis of the medical literature. Additional data will help us personalize treatments to each patient's needs.

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Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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