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Original Research Article

Meta-analysis of chemotherapy in nasopharynx carcinoma (MAC-NPC): An update on 26 trials and 7080 patients

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ABSTRACT

Purpose: Chemotherapy, when added to radiotherapy, improves survival in locally advanced nasopharyngeal carcinoma (NPC). This article presents the second update of the Meta-Analysis of Chemotherapy in NPC.
Methods: Published or unpublished randomized trials assessing radiotherapy (±a second chemotherapy timing) with/without chemotherapy in non-metastatic NPC patients were identified. Updated data were sought for studies included in the previous rounds of the meta-analysis. The primary endpoint was overall survival. All trials were analyzed following the intent-to-treat principle using a fixed-effects model. Treatments were classified in five subsets according to chemotherapy timing. The statistical analysis plan was pre-specified.
Results: Eighteen new trials were identified. Individual patient data were available for seven. In total, the meta-analysis now included 26 trials and 7,080 patients. The addition of chemotherapy reduced the risk of death, with a hazard ratio (HR) of 0.79 (95% confidence interval (CI) [0.73; 0.85]), and an absolute survival increase at 5 and 10 years of 6.1% [+3.9; +8.3] and + 8.4% [+5.7; +11.1], respectively. The largest effect was observed for concomitant + adjuvant, induction (with concomitant in both arms) and concomitant chemotherapy, with respective HR [95%CI] of 0.68 [0.59; 0.79] (absolute survival increase at 5 years: 12.3% (7.0%;17.6%)), 0.73 [0.63; 0.86] (6.0% (2.5%;9.5%)) and 0.81 [0.70; 0.92] (5.2% (0.8%;9.6%)). The benefit of chemotherapy was also demonstrated by improvement in progression-free survival, cancer mortality, locoregional control and distant control. There was a significant interaction between patient age and chemotherapy effect.
Conclusion: This updated meta-analysis confirms the benefit of concomitant chemotherapy and concomitant + adjuvant chemotherapy, and suggests that addition of induction or adjuvant chemotherapy to concomitant chemotherapy improves tumor control and survival. The benefit of chemotherapy decreases with increasing patient age.

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Introduction

With >129 000 new cases globally in 2018, nasopharyngeal carcinoma (NPC) remains a major public health issue especially in endemic areas. In Asia, the age-standardized incidence rate is estimated to be 2.1 per 100 000 and up to 3.0 in China, compared to 0.44 in Europe or North America [1]. The majority of patients have non-keratinizing disease, which is related to Epstein Barr Virus (EBV) infection, and follows a different course compared to other head and neck cancers. Due to its anatomic location, in close vicinity to critical structures, its frequent lymphatic spread, risk for distant metastases and chemo-radiosensitivity, the mainstay of treatment of locoregionally advanced NPC has long been a combination of chemotherapy (CT) and radiotherapy (RT) [2]. However, the best sequence remains to be found and there is a controversy over the benefit of adding induction or adjuvant chemotherapy when concurrent chemoradiotherapy is given.

Since the publication of the previous meta-analysis of chemotherapy in nasopharyngeal cancer MAC-NPC) [3–4], multiple randomized trials have been conducted and novel induction regimens using taxane or gemcitabine have been studied [5–7]. In addition, quantitative plasma EBV DNA value at baseline and after chemoradiotherapy has a major prognostic role for recurrence and survival. Whether EBV DNA bears a predictive value for guiding personalized use of adjuvant chemotherapy remains to be demonstrated, as the first trial using EBV DNA after chemoradiotherapy to plan additional chemotherapy was reported negative [8].

The MAC-NPC collaborative group therefore decided in 2016 to update its analysis to focus on the role of induction chemotherapy as an adjunct to concomitant chemoradiotherapy.

Methods

This updated meta-analysis was performed according to a pre-specified protocol (available at https://46.18.130.247/sites/default/files/mac-npc3-protocol.pdf).

Selection criteria and search strategy

To be eligible, trials had to compare RT alone versus RT plus CT, or to compare a treatment strategy, i.e. RT plus concomitant CT (CRT) or RT plus induction CT (IC) or RT plus adjuvant CT (AC) with the same treatment strategy plus CT (other timing). They had to be properly randomized and include untreated non-metastatic NPC patients. Trials were eligible if at least 60 patients had been included (30 patients per arm for trials with more than two arms) and if all patients had undergone potentially curative loco-regional treatment. Accrual had to be completed before December 31, 2016.

Both published and unpublished trials meeting the criteria were eligible. Trials search combined search in electronic publication databases, trial registries and meeting proceedings (details in web appendix 2).

Individual patient data collection

Individual patient data were requested for each eligible trial and for all randomized patients. Data requested included characteristics of patients and tumours, date of randomization and treatment arm allocated, dates of failures and death, details on treatments received, acute and late toxicities. Toxicity was scored locally according to the scale used at the time of the trial and hence only graded according to NCI CTCAE v4 as severe (grade $\geq$ 3 for all except xerostomia where it was grade $\geq$ 2) vs not. Follow-up information was updated whenever possible.

All data were checked according to a standard procedure and compared with the trial protocol and published reports. Missing values and discrepancies were discussed with the trialists. Randomization validity was evaluated by checking patterns of treatment allocation over time and balance of baseline characteristics between treatment arms. Follow-up of patients was also compared between treatment arms. [9] Each trial was reanalysed and the analyses were sent to the trialists for validation.

Endpoints

The primary endpoint was overall survival (OS), defined as the time from randomization until death from any cause. The secondary endpoints were progression-free survival (PFS), loco-regional failure (LRF), distant failure (DF), and cancer and non-cancer mortality. Progression-free survival was defined as the time from randomization to first progression (loco-regional or distant) or death from any cause. Non-cancer deaths were defined as deaths resulting from known causes other than nasopharynx cancer and without previous progression, and deaths from unknown cause occurring more than five years after randomization. Cancer deaths included deaths from nasopharynx cancer, deaths from any cause with previous progression and deaths from unknown cause within five years after randomization.

Statistical analysis

All analyses were performed on an intention-to-treat basis. Median follow-up was estimated with the reverse Kaplan-Meier method. [10] Analyses were stratified by trial. Individual and overall pooled hazard ratios (HR) with 95% confidence intervals (CI) were calculated through a fixed-effect model using the log-rank expected number of events and variance. [11] A similar model with chi-square instead of log-rank was used to estimate odds ratios (OR) for comparison of toxicity between arms. Rates of toxicity in the experimental arm were calculated using rate in the control arm and the OR. [12] Cumulative incidences of loco-regional failure and distant failure were analyzed with a competing risk method. [13] Only the first event was considered. If both a LRF and a DF occurred at the same time, the event was counted as DF only. For each endpoint, the studied type of failure was analyzed as the main event. The other type of failure and death without failure were analyzed as competing events. Subdistribution HR (sHR) for loco-regional failure and for distant failure were estimated in each trial using the Fine-Gray model and the global sHR were estimated with the Fine-Gray model stratified for trials. Chi-square heterogeneity tests and I^2 statistic were used to investigate the overall heterogeneity between trials. [14–15] In case of significant heterogeneity (defined by heterogeneity test p-value < 0.10), trials with 95% CI that did not cross the 95% CI of the pooled HR were excluded (i.e. outliers) as a sensitivity analysis. If heterogeneity remained significant, a random-effect model was used. With 7,000 patients, it would be possible to detect an absolute improvement in survival from 40 % to 45 % at 5-years with a power exceeding 95% (two-sided logrank test). Cancer mortality was obtained indirectly by subtracting the log-rank statistic for non-cancer mortality from the log-rank statistic for mortality from all causes. [14] Stratified survival curves were estimated for control and experimental groups using annual death rates and hazard ratios, and absolute benefit at five years with its 95% CI was calculated. [14]

Interaction between treatment effect on OS/PFS and patient subgroups (age, sex, performance status, and overall stage) was estimated directly in a single Cox model stratified on trial and containing treatment effect, covariate (for example age) effect and treatment-covariate interaction ("one-stage" model method), among the subset of trials using a "new" drug. [16] Bleomycin, epirubicin, floxuridine, hydroxyurea, oxaliplatin, mitomicyn, methotrexate, vincristine or tegafur/uracil were considered as old drugs. Only trials including all subgroups could be included in a given subgroup analysis.

Subset analyses were performed to study the interaction between treatment effect on OS/PFS and trial level characteristics, using a test of heterogeneity between the different groups of trials (called interaction). 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. [17] Predefined subsets were timing of randomized CT (adjuvant [after RT/CRT] (AC), induction [before RT] (IC), concomitant [during RT] (CRT), concomitant plus adjuvant (CRT-AC), induction [before concomitant chemoradiotherapy] (IC-(CRT))), CT drug ("old" vs "new" drug, with "new" drugs being the ones that are still used routinely nowadays), trial size, randomization method and radiotherapy technique.

Sensitivity analyses were performed after the exclusion of trials including<100 patients, trials including two different CT timings with only one being randomized, trials with a median follow-up shorter than five years, outliers, and patients with WHO type 1 cancer.

All p-values were two-sided. Analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC), except for loco-regional failure and distant failure, which were analysed with the packages "cmprsk" and "crrSC" of the R software (version 3.6.3).

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, BL, 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

Description of the trials and patients

Eighteen new trials (3,746 patients) were identified. Individual patient data were not available for 10 trials (1,385 patients) because of data loss (n = 4), a change in activities (n = 2), the impossibility to obtain a final answer from the trial's team (n = 3) or the impossibility to contact the trial's authors (n = 1). Another trial was excluded post-checking (94 patients) because follow-up was inferior to two years and no deaths were recorded. [18] Therefore, seven new trials (2,274 patients) were included. All of them had CRT as control arm, six studied the addition of IC before CRT and one the addition of AC after CRT. The data of 29 patients (0.4%) excluded after randomization in their respective trials were retrieved for this analysis. The data of 13 patients (0.2%) included in two trials [19–20] could not be retrieved.

Overall, the meta-analysis included 26 trials (7,080 patients, see web table 1 for the description of each trial, including patient population, chemotherapy regimen and timing, radiotherapy dose range and technique, sample size and follow-up). Among the two trials with 2x2 factorial plan, one [21] was counted as four comparisons and the other [22] as two comparisons, leading to 30 comparisons (7,302 patients). Fifteen trials (3,170 patients) compared CT vs. nil. In the 11 remaining trials (4,132 patients), all patients received one timing of CT and were randomized to an additional timing. The breakdown per CT subset is as follows:

- IC: 4 comparisons (830 pts),
- IC-(CRT): 8 comparisons (2,379 pts) – corresponds to trials in which all patients received CRT and only IC was randomized
- CRT: 7 comparisons (1,834 pts including 2 comparisons in which all patients received IC, VUMCA-95 (unpublished) and Guangzhou 2002–02 [23]),
- AC: 5 comparisons (992 pts including three comparisons with CRT in both arms (QMH-95 [21,24], Guangzhou 2006 [25], NPC 0502 [8]),
- CRT-AC: 6 comparisons (1,267 pts).

The median follow-up for all trials was 7.4 years (interquartile range: 5.5; 12.5), with 13 trials over 10 years of follow-up [21–23,26–36]. Follow-up varied widely according to the subset of trials, from 6.1 and 6.3 years for IC and IC-(CRT) trials, 6.8 years for AC trials, to 12.1 years for CRT trials and 15.1 for CRT-AC trials.

Patient characteristics, by trial subset and the breakdown by disease stage, can be found in web tables 2, 3 and 4. Briefly, 74.4% of patients were male, with a median age of 45 years, and most had a non-keratinizing histology (97%). Stage III accounted for 44.9% and stage IV for 46.5%.

Overall survival

There were 2,879 (39.4%) deaths in 7,302 patients, which represents a 37% increase compared to the previous round of the meta-analysis. Causes of deaths are reported in web table 5. The addition of chemotherapy reduced the risk of death, with a HR [95%CI] of 0.79 [0.73; 0.85] ($p < 0.0001$), and an absolute survival increase at 5 and 10 years of 6.1% [+3.9; +8.3] and + 8.4% [+5.7; +11.1] (Figs. 1 and 2). The heterogeneity ($p = 0.08$; $I^2 = 28\%$) was reduced after exclusion of two outliers [26,34] without a change in the results. There was a significant interaction ($p = 0.03$) between chemotherapy timing and efficacy on overall survival. The largest effects were observed for CRT-AC, IC-(CRT) and CRT, with respective HR of 0.68 [0.59; 0.79], 0.73 [0.63; 0.86] and 0.81 [0.70; 0.92].

Secondary endpoints

The addition of chemotherapy to radiotherapy improved PFS (Figs. 1 and 3), cancer mortality, locoregional control and distant control, with respective HR/sHR of 0.75 [0.70; 0.80], 0.74 [0.68; 0.81], 0.79 [0.70; 0.89] and 0.70 [0.62; 0.78] (see forest plots and survival curves in web Figs. 1-3, and patterns of events for PFS or cancer mortality in web tables 6 and 7). The use of chemotherapy did not significantly increase the rate of non-cancer death, with a HR of 1.16 [0.96; 1.40] (Fig. 4). Full results, on the entire population and by treatment timing, including absolute benefits at 5 and 10 years, are summarized in Table 1.

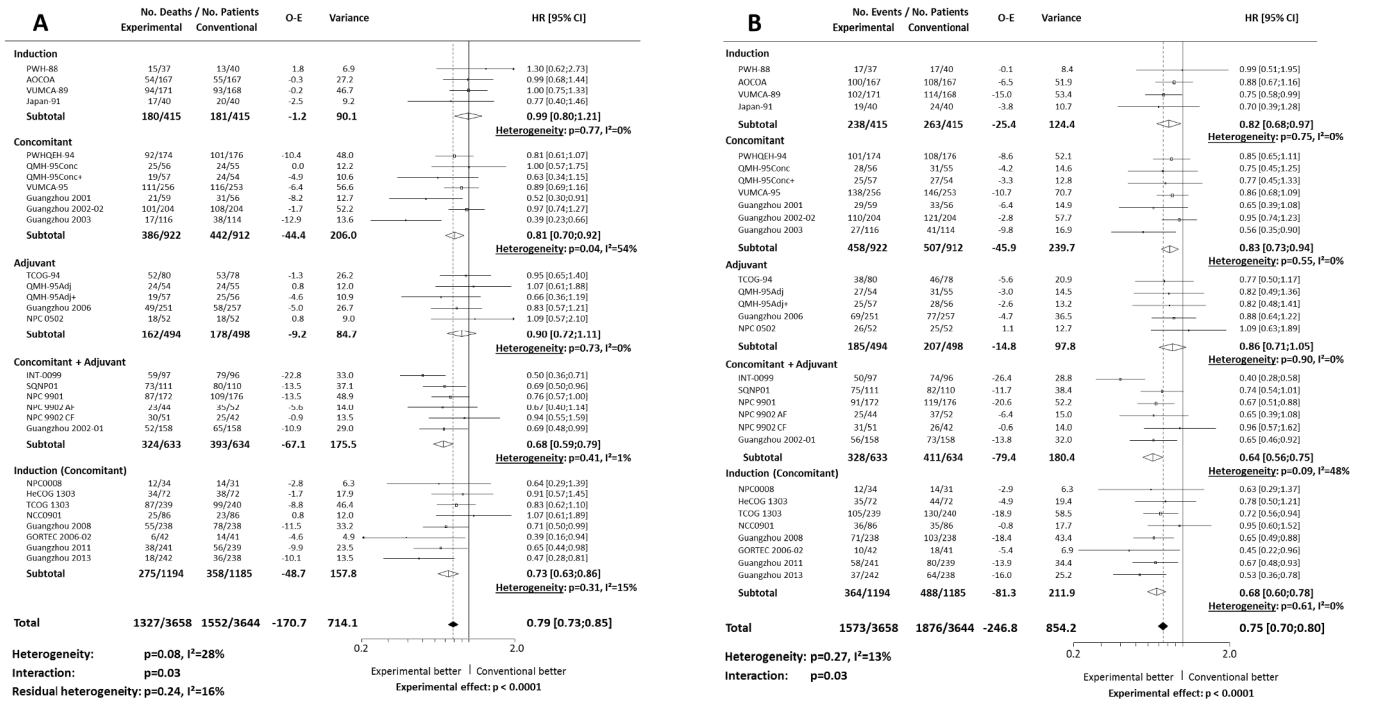
Subgroup, subset and sensitivity analyses

There was a significant interaction between patient age and chemotherapy effect on survival, with the larger benefit observed in younger patients (Table 2). As an example, the absolute OS difference at 5 years decreased from 8.5% to 7.1%, 6.1% and 3.9% in patients younger than 40, aged between 40 and 49, aged between 50 and 59 and older than 60 respectively. When looking at specific mortality, there was a significant trend ($p = 0.03$) towards a decreased efficacy of chemotherapy in terms of cancer death with increasing age while there was no effect on non-cancer death, suggesting that increased treatment related death is not the major mechanism involved in the decreasing effect of treatment with increasing age (web table 8). There was no significant interaction for OS or PFS with the other patient level characteristics tested: gender, performance status, T Stage, N Stage, overall stage or imaging modality used. Due to missing data or small sample, analyses were not performed according to histology subtype or EBV DNA status.

Among subset of trials, there was a significant interaction between OS and PFS and the type of chemotherapy drug used. "New" drugs (i.e. those that remain used nowadays, representing 19 comparisons and 4,530 patients) yielded better outcomes than old drugs, with respective HR for death of 0.72 [0.65; 0.79] and 0.89 [0.79;0.99] (interaction $p = 0.0005$). No interaction was seen between chemotherapy effect on OS or PFS and any of the other tested subset characteristics: trial size, randomization method and radiotherapy technique (Web tables 9 and 10). Sensitivity analyses showed similar results (Web table 11).

Toxicity

Among acute toxicity, neutropenia, thrombocytopenia, anemia, weight loss, dermatitis, mucositis, hearing loss and nausea/vomiting



Abbreviations: CI: Confidence Interval, E: Expected, HR: Hazard Ratio, O: Observed

Fig. 1. Forest plots for (A) overall survival and (B) progression-free survival with hazard ratios by timing of chemotherapy.

were increased with the use of chemotherapy (Table 3). For all of the above mentioned except dermatitis, there was also a significant interaction with chemotherapy timing (Web Table 12). In general, the addition of a second timing of chemotherapy, in the concomitant + adjuvant or induction (with concomitant) subsets, was responsible for more acute hematological toxicity. Mucositis was especially increased in arms with concomitant chemotherapy. Late toxicities were unfortunately poorly recorded, as seen in the overall small rate of toxicities observed compared with what would be expected in such a population. Only hearing deficit was increased with the use of chemotherapy (Odds Ratio (OR): 1.30 [1.08; 1.55]), and no interaction could be found between chemotherapy timing and late toxicity.

Discussion

Compared to the previous round of the meta-analysis, this update reconfirms that chemotherapy improves outcomes in patients with locally advanced nasopharyngeal cancer, especially when it is delivered as concomitant, concomitant + adjuvant, or induction in addition to concomitant. The benefit is maintained and even increased in the long term, with absolute survival benefits at 10 years that surpass those at five years. However, the benefit decreased in patients aged 60 or older. Acute toxicity was increased with the addition of chemotherapy, especially when two timings were used. This work supports NCCN and CSCO/ASCO guidelines which recommend IC + CRT or CRT + AC for locally advanced NPC [37–38].

The benefit risk ratio is key when prescribing a treatment. While the impact of age had not been demonstrated in previous MAC-NPC rounds, maybe due to a lack of power, it now seems clear that age is associated with treatment effect, the effect being larger in younger patients and not significant in patients older than 60 years. The cause of this age-effect is unclear, and competing causes of deaths are likely not involved as no increase in non-cancer death could be demonstrated with increasing patient age (Web table 8). Potential explanations could be related to poor tolerance, increased risk of toxicity leading to lower chemotherapy dose intensity received. There is no clear pathophysiological explanation for such a decreased efficacy in older patients. As such a finding was replicated in other head and neck cancer meta-analyses evaluating chemotherapy or radiotherapy [39,40], the effect of chance is unlikely. Due to small patient numbers above 70, it was not reasonable to further stratify between 60 and 69 and 70+. No other disease or patient related factor, such as tumor stage or performance status, was associated with treatment effect. Hence it is not possible to define which patients could be the best candidates for the addition of chemotherapy, especially before or after concomitant. Physicians will need to consider both the patient's absolute benefit and the risk of additional toxicity before prescribing.

The strengths of the present work are the use of individual patient data, updated follow up, the use of standardized endpoints and a pre-planned analysis based on the intention to treat principle. However not all data could be retrieved, although it has been shown that trials with no individual patient data available are usually smaller, more often published in national journals, of lower quality and tend to show higher treatment effect than trial with IPD available [41]. For instance, among the 11 non-included trials, ten were reported only in the Chinese medical literature and median sample size was 121 patients, compared to 273 patients for the included trials. However not including those 11 trials could have partly affected the results of the meta-analysis.

There are many unanswered questions in the management of NPC that our analysis could unfortunately not address. Our analysis does not demonstrate a significant interaction between patient stage and treatment effect, although HR for progression or death for stage II patients was only 0.98 [0.57; 1.68] in our subgroup analysis. This analysis was greatly underpowered, with only 164 patients, as trials had to have all stages represented to be included. Hence one positive trial focusing mostly on stage II patients treated with 2D radiotherapy [34] was not included in this analysis due to the absence of all stage categories. Besides stage II is a highly heterogeneous category, with some patients

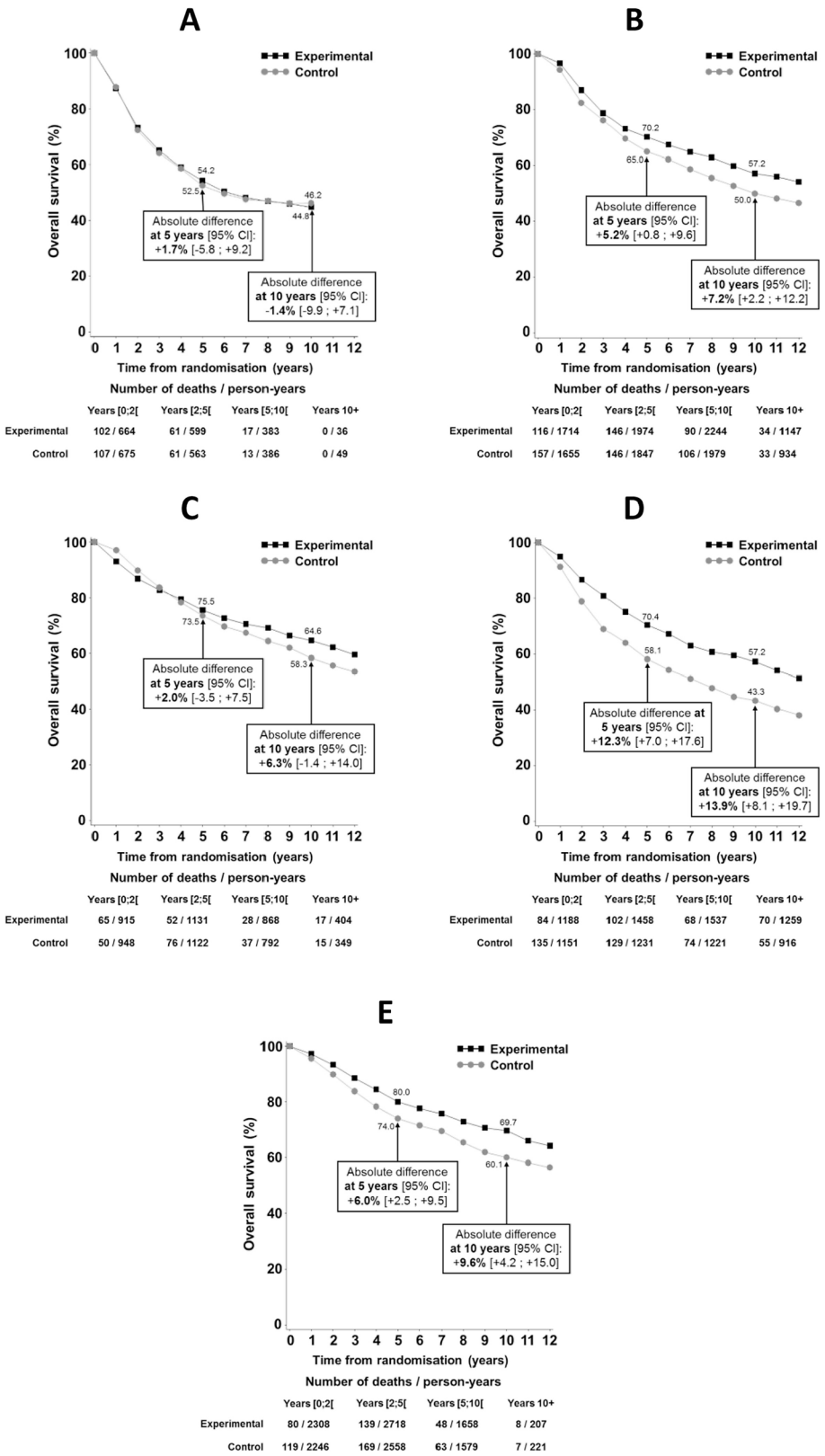


Fig. 2. Survival curves for overall survival by subsets of chemotherapy timing. A: Induction, B: Concomitant, C: Adjuvant, D: Concomitant + adjuvant, E: Induction (concomitant).

requiring CRT while others not. Another issue is the impact of EBV DNA before, during and after the course of radiotherapy and its influence on disease management. We attempted to collect EBV DNA levels pre-treatment or post-treatment, but those were missing for 3,948 patients (87%) and 4,475 patients (99%) respectively. Therefore, EBV related parameters were not analyzed. Similarly, the management of keratinizing NPC usually follows the guidelines for endemic non-keratinizing NPC although there is no specific trial in this population. According to

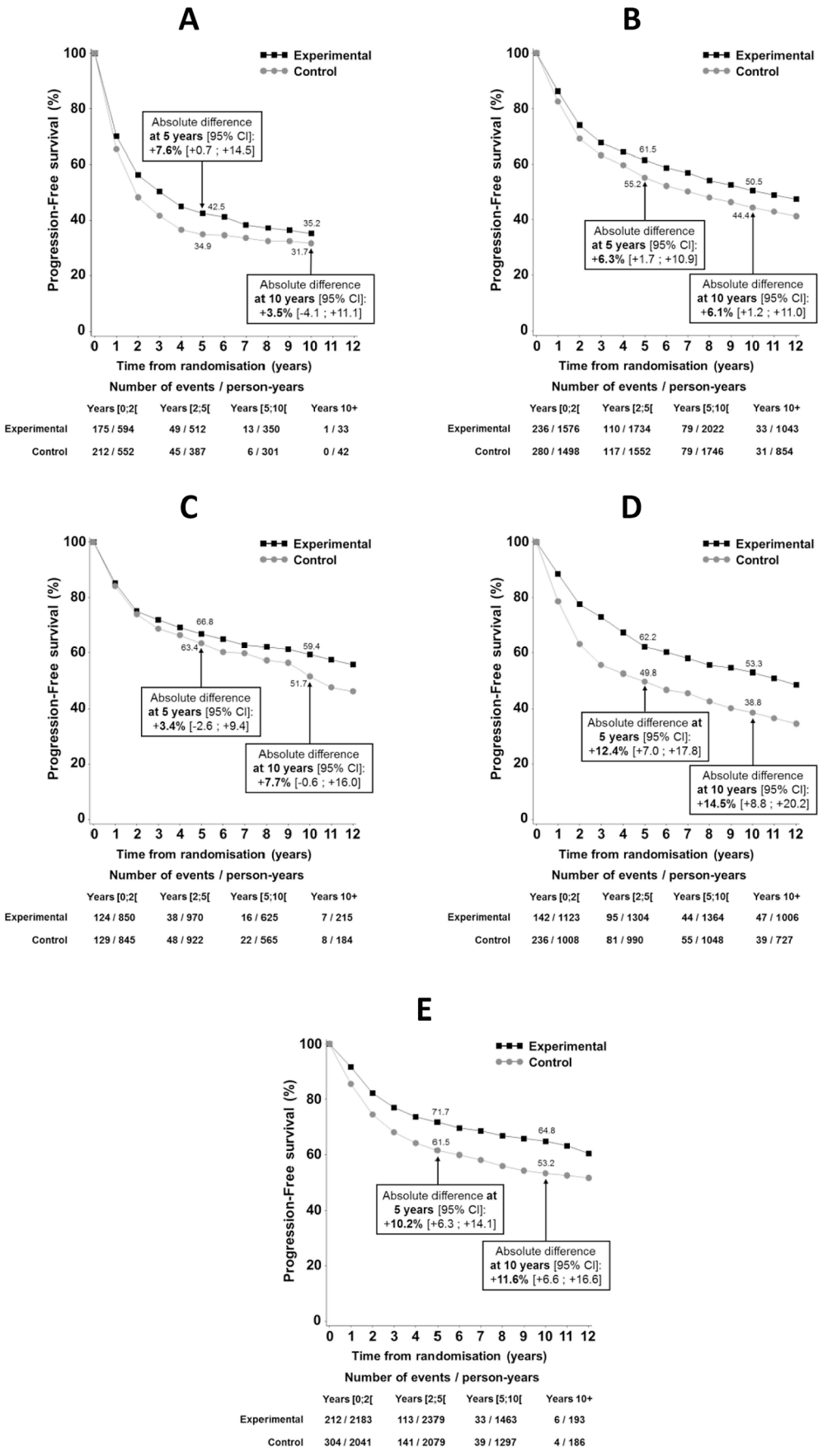


Fig. 3. Survival curves for progression-free survival by subsets of chemotherapy timing. A: Induction, B: Concomitant, C: Adjuvant, D: Concomitant + adjuvant, E: Induction (concomitant).

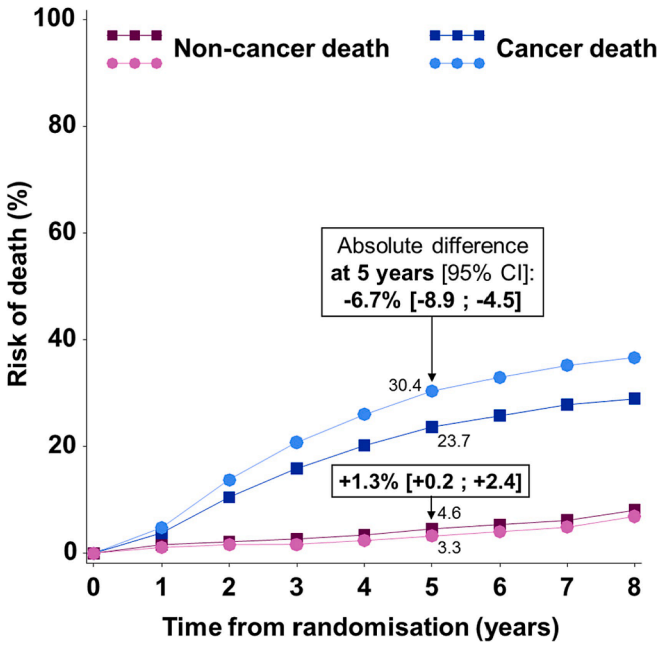


Fig. 4. Survival curves for cancer and non-cancer deaths.

the protocol, histology type was to be analyzed as "WHO type I vs. II-III" due to its clinical relevance. But only three comparisons were eligible for such a subgroup analysis, which represented too few patients. In addition, staging and toxicity scoring evolved over time; hence, there is inherent heterogeneity between trials. Last, the included trials did not prospectively compare chemotherapy regimens used at the same timing, so it was not possible to perform comparisons between different chemotherapy agents.

Looking at the absolute benefit of treatments at 5–10 years, a greater magnitude was achieved by Adjuvant + concomitant, followed by Induction (with concomitant in both arms). However, there are three reasons that can explain this difference. First, the induction (concomitant) group was more heterogeneous in terms of chemotherapy drugs. Second, the control arms were different: RT alone in the concomitant + adjuvant group and concomitant chemoradiation in the induction (concomitant) group, hence the control arm in the induction group did much better than in adjuvant + concomitant trials (5-year OS of 74% vs 58%). Last, the relative benefits of these two schedules appear similar, with respective HR for CRT-AC and IC-(CRT) of 0.68 [0.59; 0.79], 0.73 [0.63; 0.86] for death and 0.64 [0.56; 0.75] and 0.68 [0.60; 0.78] for progression or death.

Comparison of induction and adjuvant chemotherapy, both combined with concomitant chemoradiation, could not be performed in the setting of this meta-analysis, because we focused on the addition of a chemotherapy timing. While induction is easier to deliver than adjuvant, proponents of adjuvant claim that delivery of induction will impair the proper delivery of the concomitant phase, which is considered the cornerstone of treatment. The NPC-0501 trial has compared directly induction and adjuvant chemotherapy and suggests that induction could be associated with improved outcomes, especially when using conventionally fractionated radiotherapy [42]. Another way to perform such a comparison would be to conduct a network meta-analysis, which is planned as part of this update.

Even if outcomes are improved with the use of chemotherapy, a significant number of the patients will still relapse after treatment. In our report there are as many locoregional relapses as there are distant relapses. There is currently a lot of enthusiasm in the NPC community for checkpoint inhibitors, due to positive signals from two phase III

Table 1
Summary of the results, overall and by chemotherapy timing for all endpoints.

	Overall Survival	Progression-Free Survival	Cancer death	Loco-regional Failure	Distant Failure
All chemotherapy timings	HR: 0.79 [0.73; 0.85] AB5: 6.1% [+3.9; +8.3] AB10: +8.4% [+5.7 ; +11.1]	HR: 0.75 [0.70; 0.80] AB5: +8.5% [+6.2 ; +10.8] AB10: +9.3% [+6.7 ; +11.9]	HR: 0.74 [0.68; 0.81] AB5:+6.7% [+4.5; +8.9]	sHR: 0.79 [0.70; 0.89] AB5: −3.4% [-5.2; −1.6] AB10: −3.7% [-5.8; −1.6]	sHR: 0.70 [0.62; 0.78] AB5: −6.8% [-8.8; −4.8] AB10: −6.7% [-8.9; −4.5]
p-value	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p = 0.0001$	$p < 0.0001$
Interaction test	$p = 0.03$	$p = 0.03$	$p = 0.255$	$p = 0.77$	$p = 0.55$
Residual heterogeneity	$p = 0.24$	$p = 0.27$	NR	NR	NR
Induction	HR: 0.99 [0.80; 1.21] AB5: +1.7% [-5.8; +9.2] AB10: −1.4% [-9.9; +7.1]	HR: 0.82 [0.68; 0.97] AB5:+7.6% [+0.7; +14.5] AB10: +3.5% [-4.1; +11.1]	HR: 0.89 [0.71; 1.11]	sHR: 0.86 [0.67; 1.11]	sHR: 0.68 [0.52; 0.90]
Concomitant	HR: 0.81 [0.70; 0.92]AB5: +5.2% [+0.8; +9.6] AB10: +7.2% [+2.2; +12.2]	HR: 0.83 [0.73; 0.94] AB5: +6.3% [+1.7; +10.9] AB10: +6.1% [+1.2; +11.0]	HR: 0.72 [0.61; 0.87]	sHR: 0.82 [0.65; 1.03]	sHR: 0.76 [0.59; 0.97]
Adjuvant	HR: 0.90 [0.72; 1.11]AB5: +2.0% [-3.5; +7.5] AB10: +6.3% [-1.4; +14.0]	HR: 0.86 [0.71; 1.05] AB5: +3.4% [-2.6; +9.4] AB10: +7.7% [-0.6; +16.0]	HR: 0.82 [0.64; 1.04]	sHR: 0.73 [0.52; 1.04]	sHR: 0.84 [0.63; 1.11]
Concomitant and adjuvant	HR:0.68 [0.59; 0.79] AB5: +12.3% [+7.0;+17.6] AB10: +13.9% [+8.1; +19.7]	HR: 0.64 [0.56; 0.75] AB5: +12.4% [+7.0; +17.8] AB10: +14.5% [+8.8; +20.2]	HR: 0.65 [0.54; 0.78]	sHR: 0.66 [0.49; 0.90]	sHR: 0.65 [0.51; 0.83]
Induction (concomitant)	HR: 0.73 [0.63; 0.86] AB5: +6.0% [+2.5; +9.5] AB10: +9.6% [+4.2; +15.0]	HR: 0.68 [0.60;0.78] AB5: +10.2 [+6.3; +14.1] AB10: +11.6% [+6.6; +16.6]	HR: 0.72 [0.61; 0.85]	sHR: 0.81 [0.64; 1.02]	sHR: 0.63 [0.52; 0.77]

Abbreviations: AB5, absolute benefit at 5 years; AB10, absolute benefit at 10 years: HR, hazard ratio; NR, not relevant; sHR, subdistribution hazard ratio
Absolute benefits at 5 and 10 years were not calculated for each timing for cancer death, loco-regional failures or distant failures because interaction was not significant between treatment effect and chemotherapy timing.

Table 2
Efficacy of chemotherapy on overall and progression -free survival according to patient age.

	Overall Survival				Progression-Free Survival			
	No. deaths / No. patients		HR [95% CI]	AB5	No. events / No. patients		HR [95% CI]	AB5
	Control	Experimental			Control	Experimental		
<40	183/590	123/636	0.60 [0.48 ; 0.75]	+8.5%	231/590	159/636	0.58 [0.48 ; 0.71]	+12.3%
40–49	302/820	254/821	0.72 [0.61 ; 0.85]	+7.1%	366/820	298/821	0.70 [0.60 ; 0.81]	+10.0%
50–59	258/592	221/595	0.79 [0.66 ; 0.95]	+6.1%	288/592	255/595	0.80 [0.68 ; 0.95]	+6.9%
≥60	172/262	140/214	0.89 [0.71 ; 1.12]	+3.9%	178/262	137/214	0.89 [0.71 ; 1.12]	+4.1%
Interaction test			p = 0.08				p = 0.02	
Trend test			p = 0.01				p = 0.003	
Heterogeneity test (for interaction/trend)			p = 0.67/p = 0.23				p = 0.62/p = 0.19	

Subgroup analysis performed on the subset of trials using "modern" chemotherapy regimens (see Web table 9 for the definition of "old" drugs)
Abbreviations: AB5, Absolute benefit at 5 years; HR, Hazard Ratio

Table 3
Acute and late severe toxicities.

	Availability*		Incidence		OR [95% CI]	Efficacy	Heterogeneity	Interaction†
	No. comparisons	No. patients	CT‡	Control				
Acute								
Neutropenia	24	5,776	33.2%	7.3%	6.32 [5.50 ; 7.27]	p < 0.001	I^2 = 82%, p < 0.001[a]	p = 0.002
Febrile neutropenia	14	3,253	2.0%	1.8%	1.09 [0.68 ; 1.75]	p = 0.72	I^2 = 7%, p = 0.38	p = 0.29
Thrombocytopenia	23	5,423	6.2%	1.6%	4.08 [3.16 ; 5.26]	p < 0.001	I^2 = 62%, p < 0.001[b]	p < 0.001
Anemia	24	5,776	5.8%	1.9%	3.17 [2.46 ; 4.08]	p < 0.001	I^2 = 50%, p = 0.003[c]	p = 0.047
Dermatitis	20	5,328	11.4%	9.3%	1.25 [1.04 ; 1.50]	p = 0.02	I^2 = 35%, p = 0.06	p = 0.08
Weight loss	15	3,466	10.6%	6.1%	1.83 [1.43 ; 2.36]	p < 0.001	I^2 = 45%, p = 0.03[d]	p < 0.001
Mucositis	23	5,576	39.2%	33.5%	1.28 [1.15 ; 1.44]	p < 0.001	I^2 = 61%, p < 0.001[e]	p < 0.001
Hearing loss	19	4,633	1.9%	0.9%	2.16 [1.41 ; 4.14]	p < 0.001	I^2 = 21%, p = 0.20	p < 0.001
Neurotoxicity	18	4,201	0.4%	0.3%	1.35 [0.67 ; 2.71]	p = 0.40	I^2 = 0%, p > 0.99	p = 0.55
Nausea and vomiting	21	5,186	15.6%	8.6%	1.96 [1.65 ; 2.32]	p < 0.001	I^2 = 63%, p < 0.001[f]	p < 0.001
Late§								
Cutaneous fibrosis	15	4,064	2.2%	1.8%	1.24 [0.81 ; 1.90]	p = 0.32	I^2 = 10%, p = 0.34	p = 0.18
Xerostomia	20	4,454	5.5%	4.5%	1.23 [0.94 ; 1.62]	p = 0.14	I^2 = 0%, p = 0.86	p = 0.25
Bone necrosis	22	4,557	0.5%	0.6%	0.91 [0.50 ; 1.66]	p = 0.76	I^2 = 0%, p > 0.99	p = 0.68
Hearing deficit	19	3,547	19.8%	16.0%	1.30 [1.08 ; 1.55]	p = 0.005	I^2 = 0%, p = 0.28	p = 0.28
Cranial nerve palsy	18	3,483	4.6%	3.6%	1.28 [0.92 ; 1.79]	p = 0.14	I^2 = 0%, p = 0.56	p = 0.78
Symptomatic temporal lobe necrosis	18	3,570	1.4%	1.5%	0.91 [0.55 ; 1.50]	p = 0.70	I^2 = 0%, p = 0.97	p = 0.99
Brainstem or spinal cord damage	19	3,896	0.6%	0.5%	1.21 [0.64 ; 2.27]	p = 0.56	I^2 = 0%, p = 0.98	p = 0.57
Trismus	21	4,341	4.2%	4.5%	0.93 [0.69 ; 1.25]	p = 0.61	I^2 = 0%, p = 0.98	p = 0.31
Visual deficit	19	3,942	1.1%	1.1%	1.04 [0.60 ; 1.78]	p = 0.90	I^2 = 0%, p = 0.99	p = 0.65
Massive bleeding	12	2,249	1.0%	1.2%	0.82 [0.40 ; 1.67]	p = 0.58	I^2 = 0%, p = 0.98	p = 0.68

Toxicity was scored locally according to the scale used at the time of the trial and hence only graded according to NCI CTCAE v4 as severe (grade ≥ 3 for all except xerostomia where it was grade ≥ 2) vs not.
CI: Confidence Interval, CT: Chemotherapy, OR: Odds Ratio
* Only trials with available data for at least 60% of patients were included in the analyses
‡ Estimated with the Stewart et al method based on the toxicity rate in control arm and the odds ratio12
† Interaction between subsets of trials: induction, concomitant, adjuvant, concomitant + adjuvant, and induction (concomitant)
§ Only patients with a follow-up greater or equal to one year were included in the analyses
Residual heterogeneity:
aI2 = 82%, p < 0.001; b I2 = 9%, p = 0.34; c I2 = 48%, p = 0.009; d I2 = 0%, p = 0.77; e I2 = 9%, p = 0.35; f I2 = 0%, p = 0.58.

randomized trials of checkpoint inhibitors in combination with first line chemotherapy in recurrent or metastatic nasopharyngeal cancer [43–44]. Whether this will translate in an improvement for locally advanced disease is unknown. Indeed the recent trials of immunotherapy in head and neck squamous cell cancers have had disappointing results in the setting of chemoradiation [45].

In conclusion, this updated meta-analysis confirms the benefit of concomitant chemoradiation in locoregionally advanced NPC, especially with the addition of adjuvant or induction chemotherapy. The benefit of treatment decreases with increasing patient age.

Previous presentation

This work has not been presented at any meeting prior to this submission.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article and the protocol of the meta-analysis can be found online at https://doi.org/10.1016/j.ctro.2021.11.007.

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