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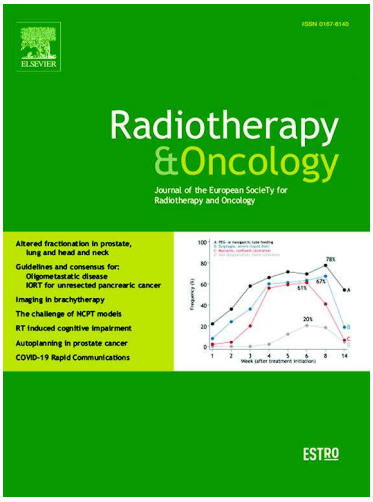

Original Article

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19805 patients, on behalf of MACH-NC group

Benjamin Lacas, Alexandra Carmel, Cécile Landais, Stuart J. Wong, Lisa Licitra, Jeffrey S. Tobias, Barbara Burtness, Maria Grazia Ghi, Ezra E.W. Cohen, Cai Grau, Gregory Wolf, Ricardo Hitt, Renzo Corvò, Volker Budach, Shaleen Kumar, Sarbani Ghosh Laskar, Jean-Jacques Mazeron, Lai-Ping Zhong, Werner Dobrowsky, Pirus Ghadjar, Carlo Fallai, Branko Zaktonik, Atul Sharma, René-Jean Bensadoun, Maria Grazia Ruo Redda, Séverine Racadot, George Fountzilas, David Brizel, Paolo Rovea, Athanassios Argiris, Zoltán Takácsi Nagy, Ju-Whei Lee, Catherine Fortpied, Jonathan Harris, Jean Bourhis, Anne Aupérin, Pierre Blanchard, Jean-Pierre Pignon, on behalf of the MACH-NC Collaborative Group,

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Short title: Meta-analysis of chemotherapy in head and neck cancer

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Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19805 patients, on behalf of MACH-NC group

Short title: Meta-analysis of chemotherapy in head and neck cancer

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Abstract

Background and purpose

The Meta-Analysis of Chemotherapy in squamous cell Head and Neck Cancer (MACH-NC) demonstrated that concomitant chemotherapy (CT) improved overall survival (OS) in patients without distant metastasis. We report the updated results.

Materials and methods Published or unpublished randomized trials including patients with non-metastatic carcinoma randomized between 1965 and 2016 and comparing curative loco-regional treatment (LRT) to LRT + CT or adding another timing of CT to LRT + CT (main question), or comparing induction CT + radiotherapy to radiotherapy + concomitant (or alternating) CT (secondary question) were eligible. Individual patient data were collected and combined using a fixed-effect model. OS was the main endpoint.

Results For the main question, 101 trials (18951 patients, median follow-up of 6.5 years) were analyzed. For both questions, there were 16 new (2767 patients) and 11 updated trials. Around 90% of the patients had stage III or IV disease. Interaction between treatment effect on OS and the timing of CT was significant (p<0.0001), the benefit being limited to concomitant CT (HR: 0.83, 95%CI [0.79; 0.86]; 5(10)-year absolute benefit of 6.5% (3.6%)). Efficacy decreased as patients age increased (p_trend=0.03). OS was not increased by the addition of induction (HR=0.96 [0.90; 1.01]) or adjuvant CT (1.02 [0.92; 1.13]). Efficacy of induction CT decreased with poorer performance status (p_trend=0.03). For the secondary question, eight trials (1214 patients) confirmed the superiority of concomitant CT on OS (HR=0.84 [0.74; 0.95], p=0.005).

Conclusion The update of MACH-NC confirms the benefit and superiority of the addition of concomitant CT for non-metastatic head and neck cancer.

Keyword: Meta-analysis, Systematic Review, Individual Patient Data, Randomised Clinical Trials, Chemotherapy, Radiotherapy, Head and Neck Cancer, Squamous Cell Carcinoma

Highlights

- The Individual patient data Meta-Analyses of Chemotherapy in non-metastatic Head and Neck Cancer (MACH-NC) includes 107 randomised trials that completed accrual before 2017, 19805 patients and a median follow-up of 6.6 years. It is its second update with the previous study on 92 trials, 17346 patients and a median follow-up of 5.6 years. Trial comparing curative loco-regional treatment versus loco-regional treatment + chemotherapy, and those with also another timing of chemotherapy, identical in both groups were eligible. Taxane-based induction chemotherapy trials were also included.
- There was a significant interaction (p<0.0001) between treatment effect on overall survival and the timing of CT (induction, concomitant or adjuvant), the benefit being limited to concomitant CT, with a HR of 0.83 [95% confidence interval: 0.79; 0.86] and a 5(10)-year absolute survival benefit of 6.5 (3.6)%.
- Concomitant (or alternating) radio-chemotherapy significantly was better on overall survival, event-free survival, and loco-regional failure compared to sequential (induction +/- adjuvant) radio-chemotherapy.
- This updated meta-analysis confirms the efficacy of adding chemotherapy to loco-regional treatment and the superiority of concomitant chemotherapy over induction or adjuvant chemotherapy. Taxane-based induction chemotherapy may have a role in a selected population.

Introduction

Concomitant chemoradiotherapy is the standard of care for locally advanced head and neck squamous cell carcinoma, either as definitive treatment or following surgery in case of pathological adverse features. The evidence supporting this statement comes from the multiple randomized trials, summarized in two individual patient data meta-analyses [1,2].

However, novel regimens, or combination of different chemotherapy timings such as taxane based triplet induction chemotherapy, have been tested prior to chemoradiotherapy or surgery [3], and an interaction between patient gender and chemotherapy effect was shown [4]. In addition, the importance of cytotoxic chemotherapy used in concomitance with radiotherapy has been recently reinforced by two trials that have shown the superiority of concomitant cisplatin over concomitant cetuximab in the specific population of p16-positive oropharyngeal cancers [5,6].

The second update of the meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) was performed to provide insights into long-term benefits of chemotherapy for non-metastatic locally advanced HNSCC.

Material and methods

The methods were pre-specified in a protocol (https://www.gustaveroussy.fr/fr/meta-analyses-protocoles-dessais-orl).

Selection criteria and search strategy

Trials were eligible if they had accrued previously untreated patients with HNSCC (oral cavity, oropharynx, hypopharynx and larynx) and compared curative loco-regional treatment with loco-regional treatment plus chemotherapy, the addition of another timing of chemotherapy to loco-regional treatment plus chemotherapy (main question), or compared induction chemotherapy and radiotherapy to the same concomitant (or alternating) chemoradiotherapy (secondary question). Trials were eligible if they completed accrual before December 31st, 2016 (Web-Appendix 2). To avoid publication bias, both published and unpublished trials were included. Electronic database searches (Medline, SCOPUS, CENTRAL, clinicaltrials.gov; Web-Appendix 3) were supplemented with hand searches of meeting abstracts (ASCO, ESTRO, ASTRO, ESMO, ECCO) and review articles. Experts and all trialists who took part in the meta-analysis were also asked to identify trials.

Data extraction and checking

Individual patient data (IPD) were requested for each eligible trial for all randomized patients. Data collected were patient and tumour characteristics, dates of randomisation, failures and death, treatment group allocated, details about treatments received, and acute and late toxicities. Follow-up information was updated whenever possible. All data were checked with a standard procedure [7–9] which follows the recommendations of the Cochrane working group on meta-analysis using individual patient data (Web-Appendix 4). Each trial was analysed individually, and the resulting survival analyses as well as data description were sent to the trialists for review.

Outcomes

The primary endpoint was overall survival (OS), defined as the time from randomisation until death from any cause. As in the previous update, secondary endpoints were event-free survival (EFS), loco-regional failure (LRF), distant failure (DF), cancer and non-cancer mortality [2]. A new endpoint, 120-

day mortality, was added as proxy for deaths related to treatment [8]. EFS was defined as the time from randomisation to first recurrence or progression (loco-regional or distant failure) or death from any cause. Events considered were loco-regional failures without distant failure for LRF; and distant failure, either alone or combined with loco-regional failures, for DF. Non-cancer mortality was defined as deaths without previous failure and resulting from known causes other than the treated head and neck cancer. Cancer mortality included deaths from any cause with previous failure and deaths from the treated head and neck cancer. Deaths from unknown cause without previous failure were regarded as cancer mortality if they occurred within 5 years after randomisation and as non-cancer mortality otherwise.
Secondary endpoints also included acute and late toxicities, and compliance; they have been collected but are not yet analysed. Those endpoints will be reported separately.

Statistical analysis

All analyses were done on an intention-to-treat basis. Median follow-ups were estimated with the reverse Kaplan-Meier method [10]. Analyses were stratified by trial. We calculated individual and overall pooled hazard ratios (HRs) with 95% CIs through a fixed-effects model using the method developed by Peto (*i.e.* log-rank expected number of events and variance) [11]. The Chi^2 heterogeneity test and I^2 statistic were used to investigate the overall heterogeneity between trials [12]. Methods used to estimate cancer and non-cancer mortality, to draw stratified curves and estimate 5-year and 10-year absolute differences were similar to the ones used in the previous meta-analyses: annual actuarial survival rates were computed on all patients and the HR at the corresponding time period was used to compute survival in each group [2,8,13,14]. A competing risk model was used for loco-regional and distant failure [15].

To study the robustness of the results several sensitivity analyses (i.e. analyses after exclusion of some trials) were realised (Web-appendix 5). We performed subset analyses to study the interaction between treatment effect and trial level characteristics, using a test of heterogeneity among the different groups of trials. We estimated the interaction between treatment effect and patient subgroups (age, sex, performance status, smoking status, primary site, and overall stage) in a Cox model stratified by trial and adjusted on treatment effect, covariate effect (*e.g.* age), and treatment-covariate interaction (one-stage model method)[16]. Details about statistical methods including power estimation are available in Web-appendix 5. Sensitivity, subset and subgroup analyses were pre-specified in the protocol except if mentioned otherwise in this publication.
Because of findings in our previous study [4], the interaction between sex and chemotherapy effect was studied in patients treated with or without surgery. Trials were excluded if it was not possible to separate patients treated with or without surgery.
All p values were two-sided. Analyses were done using SAS, version 9.4 and R software ("crrSC" package for competing risk analysis), version 3.6.3.

Results

The meta-analysis included 107 randomised trials (19805 patients). Sixteen new trials (2767 patients)[1,2,17–36] (Web-Figure 1, Web-Appendix 6) and 2327 deaths (including death from updated previous trials) were added for this update. We were able to collect data from 725 of the 867 randomised patients who had been excluded from the original published analyses. Updated follow-up was obtained for 11 trials and the median follow-up of all trials was 6.6 years (interquartile range [IQR]: 4.3; 10.6). The description of the trials included and their references can be found in Web-Tables 1, 2, 3 and 4. Some trials with multiple strata (different loco-regional treatments or chemotherapies, three-

arm trial or 2 by 2 design) were duplicated (Web-Table 5, Web-Appendix 7) or divided in two strata or more. Therefore, 138 comparisons and 21863 patients were included in the meta-analysis.
The main question on the addition of chemotherapy included 130 comparisons (20649 patients) and the secondary question on the comparison of induction and concomitant chemotherapy included eight comparisons (1214 patients) (SECOG II unpublished)[17,23,24,37–42].

Main question: addition of chemotherapy to locoregional treatment

Results will be presented by timing of chemotherapy. Patients are described in Web-Table 6. The distribution of the treatment comparison according to timing of chemotherapy, type of loco-regional treatment, type of chemotherapy and period of accrual is given in Web-Table 7.
Results are summarised in Table 1.

Effect of induction chemotherapy

Fourty-five induction comparisons were available to evaluate the effect of induction chemotherapy (7054 patients, 4692 deaths, cause of death in Web-Table 8) with a median follow-up of 5.7 years (IQR: 4.2;7.6)[17-19,25–30,43–74].
The HR of death (Figure 1A, Web-Figure 2) was 0.96 [95% confidence interval (CI): 0.90; 1.01] (p=0.14) in favour of induction chemotherapy with an absolute difference of 2.2% at 5 years (Figure 2A). Similar results were observed for event-free survival (type of EFS events in Web-Table 9), with a HR of 0.96 [0.90; 1.02] (p=0.14) and an absolute difference of 1.4% at 5 years (Web-Figure 3A). No significant effect on 120-day mortality was observed (HR=1.07 [0.89; 1.28], p=0.47; Web-Figure 4).
There was no significant variation of the effect on OS according to the type of induction chemotherapy (interaction test: p=0.22): HR=0.97 [0.82; 1.15] for taxane plus platin plus 5-FU (TPF), 0.90 [0.82; 0.99] for platin plus 5-FU (PF), 1.00 [0.92; 1.09] for other induction regimens, nor on EFS (test of interaction: p=0.20). The exclusion (unplanned analysis) of the three comparisons with major early related to treatment mortality and/or without GCSF (two TPF comparisons (Budapest 2007, TTCC 2002 TPF) and one PF comparison (TTCC 2002 PF)) led to the following results: for OS, overall HR of 0.94 [0.89; 1.00] (p=0.06) and HR of 0.83 [0.67; 1.02] (p=0.08) for the TPF subset (interaction test p=0.08); for EFS, overall HR of 0.95 [0.89; 1.01] (p=0.10) and HR of 0.77 [0.64; 0.94]; p=0.02) for the TPF (interaction test p=0.09).
Excluding trials with more than one timing of chemotherapy, or confounded or less than 80 patients, or performed before 1980, or with a follow-up shorter than 5 years led to similar results for OS and EFS (Web-Table 10A). Analysis without arm duplication led to similar results (Web-appendix 7). In recent trials, it was possible to separate cancer and non-cancer deaths (Web-Table 8). But data were not available in 11 comparisons out of 25. Effect of chemotherapy was not significant both for deaths related to head and neck cancer (HR=0.97 [0.86; 1.10], p=0.67 and an absolute difference of 0.7% at 5 years) and non-cancer deaths (0.84 [0.67; 1.05], p=0.12) (Web-Figure 5A). The effect addition of induction chemotherapy on LRF was not significant (sub-HR=1.07 [95%CI=0.99; 1.15], p=0.09); Web-Figure 6 and 8-A), when a significant decrease on DF was observed (0.76 [0.66; 0.88], p=0.0002; Web-Figure 7 and 9-A).
The effect of chemotherapy on OS and EFS did not differ significantly between the groups of trials according to chemotherapy modalities, year of start of accrual, or locoregional treatment (Web-Tables 11A, 12A, 12B, and 12C). There was no clear evidence of a differential effect of induction chemotherapy on overall or event-free survival according to age, sex, stage or tumour site (Web-Table 13A). There was a decreasing effect of chemotherapy with poorer performance status on OS (test for trend: p=0.03) but not on EFS (p=0.07) (Figure 3A). With adjustment on sex and age, results were still significant for OS (p=0.02) and borderline for EFS (p=0.05).

Effect of concomitant chemotherapy

Seventy-one concomitant comparisons were available to evaluate the effect of concomitant chemotherapy (10680 patients, 7944 deaths, cause of death in Web-Table 8) with a median follow-up of 9.2 years (IQR: 5.2; 12.9)[17,20–22,31–34,36,56,75–123]. The HR of death (Figure 1A, Web-Figure 10) was 0.83 [95% CI: 0.79; 0.86] (p<0.0001) in favour of concomitant chemotherapy with an absolute benefit of 6.5% at 5 years and 3.6% at 10 years (Figure 2B). The magnitude of the benefit was similar for the trials included in the initial meta-analysis and those included in the updates (test for interaction: p=0.77), without significant heterogeneity in the most recent trials (p=0.30).
Similar results were observed for event-free survival (Web-Table 9, Figure 1B), with a HR of 0.80 [0.77; 0.84] (p<0.0001) and an absolute benefit of 5.8% at 5 years and 3.1% at 10 years (Web-Figure 3B). No significant effect on 120-day mortality was observed (HR=1.07 [0.92; 1.24], p=0.37; Web-Figure 4).
Similar results were observed with the sensitivity analyses (Web-Table 10B). The benefit of chemotherapy was due to its effect on deaths related to head and neck cancer (HR=0.79 [0.74; 0.84], p<0.0001 and an absolute benefit of 9.8% at 5 years) (Web-Figure 5B). There was no effect on non-cancer deaths (1.01 [0.89; 1.16], p=0.83).Addition of concomitant chemotherapy showed a significant decrease of LRF (sub-HR=0.71 [0.67; 0.75], p<0.0001; Web-Figure 6 and 8-B) with a non significant effect on DF (1.04 [0.92; 1.18], p=0.48; Web-Figure 7 and 9-B).
No significant variation of chemotherapy effect on OS and EFS was observed according to year of start of accrual or locoregional treatment (Web-Tables 11B, 12B, and 12C). For EFS, treatment effect varied significantly according to chemotherapy modality (test for interaction: p=0.01) with the highest effect for poly-chemotherapy with platin salt (HR=0.74 [0.67; 0.82]) and the lowest for monochemotherapy without platin salt (0.86 [0.80; 0.93]). For OS, interaction was borderline (p=0.06) (Web-table 12A).The only statistically significant variation of treatment effect on survival according to patient characteristics (Web-Table 13B and Figure 3B) was a decreasing effect of chemotherapy on OS with increasing age (test for trend: p=0.03). Results were borderline for event-free survival (p=0.06) (Figure 3B). This effect could not be explained by an imbalance in the other covariates studied (data not shown). The cause of death was available only for the recent trials (1994–2010). As might be expected, the proportion of deaths not due to head and neck cancer increased with age from 18% in patients less than 50 to 37% in patients 70 and over (Web-Table 14). Adjusting on sex led to similar results for OS. Test for trend was also significant for EFS (p=0.04).

Effect of adjuvant chemotherapy

Fourteen adjuvant comparisons were available to evaluate the effect of adjuvant chemotherapy (2915 patients, 1605 deaths, cause of death in Web-Table 8) with a median follow-up of 5.4 years (IQR: 3.6;8.7).[35,47,104,124–130] The HR of death (Figure 1A, Web-Figure 11) was 1.02 [95% CI: 0.92; 1.13] (p=0.69) with an absolute difference of -0.3% at 5 years (Figure 2C). Similar results were observed for event-free survival (Web-Table 9, Figure 1B), with a HR of 0.98 [0.88; 1.09] (p=0.72) and an absolute difference of -0.6% at 5 years (Web-Figure 3C). A deleterious effect on 120-day mortality was observed (HR=1.89 [1.33; 2.68], p=0.0003; Web-Figure 4) without variation according to locoregional treatment modalidies (data not shown).
Similar results were observed with the sensitivity analyses (Web-Table 10C). A significant decrease on LRF and DF was observed with the addition of adjuvant chemotherapy: sub-HR of 0.84 ([0.72; 1.00], p=0.04); Web-Figure 6 and 8-C) and of 0.77 ([0.62; 0.96], p=0.02; Web-Figure 7 and 9-C), respectively.
No significant variation of chemotherapy effect on OS and EFS was observed according to chemotherapy modalities or year of start of accrual (Web-Tables 11C and 12A, and 12B). A significant effect was observed on EFS, but not on OS for type of loco-regional treatment (interaction test p=0.005) with HR of 0.77 [0.62; 0.96] in the comparisons using only surgery (Web-Table 12C).

Secondary question: concomitant versus induction chemotherapy

Eight comparisons used the same drugs in both arms, and compared the timing of their use relative to radiotherapy. They included 1214 patients (1007 deaths, Web-Table 15) with a median follow-up of 9.0 years (IQR: 7.0; 17.0)[17,23,24,37–42]. The analysis of DF was not performed because data were missing for half of the comparisons. All endpoints showed results in favour of the concomitant group: HR=0.84 [95% CI: 0.74; 0.95] (p=0.005) for OS (absolute benefit of 6.2% at 5 years, (Web-Figures 12A, 13A), 0.85 [0.75; 0.96] (p=0.008) for EFS (absolute benefit of 3.7% at 5 years) (Web-Figure 12B, 13B), and 0.86 [0.76; 0.97] (p=0.01) (absolute benefit of 5.8% at 5 years) for LRF. Results were not significantly different for the trials with or without platin.

Indirect comparison

Overall survival and event-free survival
The benefit of chemotherapy was significantly greater in the concomitant group than in the induction and adjuvant groups both for OS and EFS (interaction test: p<0.0001 for both endpoints, Figure 1).

120 days mortality
Out of 20649 patients, 1313 (6%) died within 120-day after randomisation: 470 out of 7054 (7%), 716 out of 10680 (7%) and 127 out of 2915 (4%) in the induction, concomitant, and adjuvant comparisons respectively. Overall, 120-day mortality increased with chemotherapy (HR=1.13 [1.01; 1.26], p=0.03, Web-Figure 4) with a significant variation by timing (interaction test: p=0.01). This deleterious effect was significant for adjuvant timing (HR=1.89 [1.33; 2.68], p=0.0003) but not for the two other timings. The overall heterogeneity observed was mainly explained by the significant interaction between timings and the heterogeneity within concomitant group (Web-Appendix 8).

Locoregional and distant failures
The analysis of LRF was based on 123 comparisons (18834 patients). The benefit of chemotherapy was significantly greater in the concomitant and adjuvant groups than in the induction group (interaction test: p<0.0001; (Web-Figure 6 and 8). The analysis of DF was based on 108 comparisons (16828 patients). The benefit of chemotherapy was significantly greater in the induction and adjuvant groups than in the concomitant group (interaction test: p=0.001; (Web-Figure 7 and 9).

Interaction between sex, surgery and treatment
Patients treated with surgery corresponded to 28 comparisons, 5503 patients and those treated without surgery 74 comparisons, 12949 patients. These two populations had significantly different patient and tumour characteristics: differences were often small and, as expected, based of selection criteria for surgery (Web-Table 16). Among comparisons with surgery, a better effect of chemotherapy was observed in women compared to men: HR of 0.67 [0.54; .82] and 0.96 [0.89; 1.03] respectively (interaction test, p=0.001) for OS with similar results for EFS. A gender effect was not significant for the comparisons without surgery: HR of 0.94 [0.85; 1.04] for women and 0.87 [0.83; 0.91] for men (interaction test, p=0.15) for OS, with similar results for EFS (Web-Table 17).

Discussion

The present study provides the most comprehensive and robust analysis of the role of chemotherapy in combination with locoregional therapy for the treatment of non-metastatic HNSCC. It involved the individual data of 19805 patients included in 107 randomised trials. Results were robust to multiple pre-specified sensitivity analyses. Given that the landscape of clinical trials has shifted from cytotoxic chemotherapy to targeted therapies and recently to immunotherapy, this analysis is likely to be the ultimate analysis on the topic. A set of major findings have been made and are discussed hereafter.

The analysis on induction chemotherapy demonstrated a survival benefit for the combination of platin and 5FU (PF) with a HR of 0.90 [95% CI: 0.82; 0.99] but failed to show a similar benefit for the triplet containing of taxane, platin and 5FU (TPF). This is surprising, as the superiority of TPF over PF has been demonstrated in multiple trials and meta-analyses [3]. A few important facts about induction TPF should be noticed. First, some TPF trials were not included in the meta-analysis because they were confounded due to different concomitant treatments for the TPF and no induction arms [131,132]. Second, four out of the five trials included used chemoradiation as a comparator [18,19,25–28], whereas the vast majority of PF trials had RT alone as comparator. The bar was hence higher for TPF than for PF. As shown by our analyses, TPF may be associated with a high risk of treatment related death, as shown by an excess in early death in two trials that did not appropriatly select patients or use G-CSF [18,19,25]. Excluding these trials led to a significant effect of this chemotherapy on EFS, but not on overall survival. Moreover, no effect of age could be demonstrated for induction chemotherapy but there was a significant decrease of the overall survival benefit with poorer performance status. Hence induction chemotherapy should be considered only for fit patients. To decrease TPF toxicity without changing efficacy, modified schedule of TPF has been proposed. But, data from randomized trial are currently limited and results mixed [133,134]. Better selection tools to identify patients who will benefit from TPF induction remain needed.

Concomitant chemoradiotherapy is the mainstay of treatment for locally advanced HNSCC whether as sole treatment or given as adjuvant after surgery, and this analysis confirms, with a much longer follow-up of 9.2 years, the OS benefit of 0.83 [0.79;0.86] with an absolute benefit of 6.5% and 3.6% at 5 and 10 years respectively. The decreasing effect of concomitant chemotherapy with increasing patient age is reinforced; thus, the use of concomitant chemotherapy should be carefully weighed after 70 years. As expected, concomitant chemotherapy mostly decreases locoregional failures, which are the first site of recurrence in HNSCC. Further, both direct and indirect comparisons demonstrated that concomitant chemotherapy yielded a greater survival advantage than induction. The subset analysis confirmed as well that platin-containing mono or polychemotherapy is the standard of care due to higher OS or EFS benefit. No comparison between three-weekly or weekly schedules of cisplatin could be performed as such trials were out of the scope of the meta-analysis.

Adjuvant chemotherapy after surgery or radiotherapy did not have significant effect on OS and EFS in spite of a significant beneficial effect on loco-regional and distant failure. Increase in 120-mortality, likely to be related to treatment may explain these results (Table 1). The adjuvant trials are old and used outdated systemic therapies. Their results are difficult to apply to current loco-regional treatment. However, in the light of the benefit of adjuvant chemotherapy after radiotherapy in nasopharyngeal cancer [135], adjuvant therapy might deserve further testing.

The major strengths of the meta-analysis are well-known. It followed a rigorous process, was overseen by a steering committee and involved the investigators of the included trials. For each trial, the IPD were collected and the data quality was checked and reanalyzed prior to inclusion in the final analysis. Unpublished trials were included. All analyses based on intent-to-treat principle were preplanned according to a protocol, unless explicitly specified. The high number of patients allowed rigorous assessment with adequate power association for subgroups with treatment effect. Update allowed to increase the median follow-up of one-year from 5.6 to 6.6 years.

Limitations include the large time span of the randomized trials included, 1965 to 2012 during which time staging, treatments and supportive care have all greatly evolved. No interaction between period of accrual and overall survival or event-free survival was recorded and exclusion of the trials performed before 1980 led to similar results. Individual patient data were not available for 13 trials (1067 patients), but such trials appeared of lower quality, with fewer patients and with higher treatment effect than those included in IPD meta-analysis [136]. Three potentially eligible randomised trials (415 patients) were identified in 2019, but because of their design and size they are unexpected to have any impact on the conclusion of this work (Web-Table 18). To the best of our knowledge, no patient has been accrued in a trial eligible for this meta-analysis after 2012. For the secondary question, only

few trials could be included and although they show the superiority of concomitant chemotherapy, a network meta-analysis would improve the estimation of relative treatment efficacy. No data on HPV or limited data on smoking status were available and given the timing of the trials and tumour subsites, most tumours are likely HPV-negative although this hypothesis cannot be confirmed. The superiority of concomitant cisplatin has been shown in HPV-positive oropharyngeal cancers compared to cetuximab and is in these studies of the same magnitude as in this analysis, with a 5-year benefit for cisplatin of 6.7% in RTOG 1016 [6]. No data on treatment compliance or toxicity have been presented here. Last, there are statistical limitations. The important number of endpoints analyzed raises the question of multiplicity of testing and the inflation of type I error. However, overall survival was the primary endpoint of the meta-analysis, most secondary endpoints and analyses were pre-specified, and there is consistency between main and secondary endpoints. Also the duplication of trial arms in case of multi-arms trials could bias the results, but analyses without duplication did not alter the results (Web-Appendix 7).

Practical implications of the meta-analysis are numerous. Firstly, they provide an accurate estimation of the effect of chemotherapy for each timing and regimen, which is essential for treatment personalization and patient counselling. In this res-pect, the interaction between patient performance status or age and the effect of induction or concomitant chemotherapy respectively are crucial, as could be the interaction between gender and the effect of chemotherapy in the postoperative setting [4]. This last interaction may be explained by a lower rate of co-morbidities among women compared to men[4]. It needs to be confirmed in more recent trials. Predictive models to select treatments have been developed based on this dataset [137]. Secondly, these data are important to design future randomized trials as they can help define credible statistical hypotheses, potentially taking advantage of the multiple subgroup analyses that can help adapt calculation to the structure of the populations.

In conclusion, the present IPD meta-analysis clearly evaluates the benefit of induction and concomitant chemotherapy for the treatment of non-metastatic HNSCC, using data of all randomized trials published up to 2019. Given the many potential combinations of systemic therapy and radiotherapy, a network meta-analysis could be helpful to rank treatments and suggest large-scale trials. In the current context, these data are invaluable for the selection of regimens to be tested with the combination of immunotherapy.

Contributors

PB, JB, and JPP with the help of the steering committee members designed and supervised the study.
PB, and JPP obtained funding.
PB, JB, JPP and BL searched and selected the trials. Steering committee members contributed to the identification and selection of the trials.
PB, BL and JPP collected and checked data with the help of the investigators who validated the re-analysis of their trials.
AA, BL, PB and JPP did the statistical analyses and wrote the draft, with revisions from the other investigators.
All authors contributed to the interpretation of the results during the investigator meeting and the revision of the manuscript. All investigators listed in Web-Appendix 1 received the manuscript for revision.

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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 MACH-NC collaborative group. AA, PB, BL, and J-PP had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for

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publication. All authors have seen and approved the final version and, after consultation with the collaborators, agreed to submit for publication.

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