Chemotherapy and radiotherapy in locally advanced head and neck cancer: an individual patient data network meta-analysis

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Summary

Background Randomised, controlled trials and meta-analyses have shown the survival benefit of concomitant chemoradiotherapy or hyperfractionated radiotherapy in the treatment of locally advanced head and neck cancer. However, the relative efficacy of these treatments is unknown. We aimed to determine whether one treatment was superior to the other.

Methods We did a frequentist network meta-analysis based on individual patient data of meta-analyses evaluating the role of chemotherapy (Meta-Analysis of Chemotherapy in Head and Neck Cancer [MACH-NC]) and of altered fractionation radiotherapy (Meta-Analysis of Radiotherapy in Carcinomas of Head and Neck [MARCH]). Randomised, controlled trials that enrolled patients with non-metastatic head and neck squamous cell cancer between Jan 1, 1980, and Dec 31, 2016, were included. We used a two-step random-effects approach, and the log-rank test, stratified by trial to compare treatments, with locoregional therapy as the reference. Overall survival was the primary endpoint. The global Cochran Q statistic was used to assess homogeneity and consistency and P score to rank treatments (higher scores indicate more effective therapies).

Findings 115 randomised, controlled trials, which enrolled patients between Jan 1, 1980, and April 30, 2012, yielded 154 comparisons (28 978 patients with 19 253 deaths and 20 579 progression events). Treatments were grouped into 16 modalities, for which 35 types of direct comparisons were available. Median follow-up based on all trials was 6·6 years (IQR 5·0–9·4). Hyperfractionated radiotherapy with concomitant chemotherapy (HFCRT) was ranked as the best treatment for overall survival (P score 97%; hazard ratio 0·63 [95% CI 0·51–0·77] compared with locoregional therapy). The hazard ratio of HFCRT compared with locoregional therapy with concomitant chemoradiotherapy with platinum-based chemotherapy ($CLRT_p$) was 0·82 (95% CI 0·66–1·01) for overall survival. The superiority of HFCRT was robust to sensitivity analyses. Three other modalities of treatment had a better P score, but not a significantly better HR, for overall survival than $CLRT_p$ (P score 78%): induction chemotherapy with taxane, cisplatin, and fluorouracil followed by locoregional therapy (IC_{TaxPF}-LRT; 89%), accelerated radiotherapy with concomitant chemotherapy (82%), and IC_{TaxPF} followed by CLRT (80%).

Interpretation The results of this network meta-analysis suggest that further intensifying chemoradiotherapy, using HFCRT or IC_{TaxPF}-CLRT, could improve outcomes over chemoradiotherapy for the treatment of locally advanced head and neck cancer.

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Introduction

Advances in the treatment of locally advanced head and neck cancer have led to higher cure rates than were previously possible. The individual patient data Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) showed that the addition of concomitant chemotherapy to radiotherapy improves overall survival, progression-free survival, and locoregional control, and decreases cancer deaths.[1] In a meta-analysis of induction chemotherapy in head and neck cancer, the addition of a taxane (docetaxel or paclitaxel) to cisplatin plus fluorouracil (Tax-PF) was superior to cisplatin plus fluorouracil alone for overall survival, progression-free survival, locoregional control, and distant control.[2] The Meta-Analysis of Radiotherapy in Carcinomas of Head and Neck (MARCH) showed that altered fractionation radiotherapy was associated with a significant overall survival benefit compared with conventional fractionation.[3] However, the overall survival benefit was restricted to hyperfractionated radiotherapy. Progression-free survival was improved by

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Research in context

Evidence before this study

Individual patient data meta-analyses have shown that concomitant chemoradiotherapy and hyperfractionated radiotherapy have the best efficacy results in the treatment of locally advanced non-metastatic head and neck cancer. A mixed treatment comparison based on the second publication of the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) and on the first publication of the Meta-Analysis of Radiotherapy in Carcinomas of Head and Neck (MARCH) compared six modalities of treatment. Altered fractionation concomitant chemoradiotherapy yielded the highest probability of survival. For this network meta-analysis, trials included in the second update of MACH-NC, in the specific MACH-NC publication on induction chemotherapy with taxanes, and in the first update of MARCH were included. We searched PubMed, Scopus, Web of Science, Cochrane Controlled Trials meta-register, ClinicalTrials.gov, and meeting proceedings, without language restriction, for published and unpublished "randomized trials" of "chemotherapy" or "radiotherapy" in "head and neck cancer". Studies done up to Dec 31, 2016, were included. To improve homogeneity, studies done before Jan 1, 1980, were excluded.

Added value of this study

Network meta-analyses allow comparison of all treatment modalities with each other, using available direct and indirect comparisons (through common comparators). Hyperfractionated radiotherapy with concomitant chemotherapy had the highest efficacy for overall survival, event-free survival, locoregional control, and cancer death. For distant control, locoregional treatment with adjuvant chemotherapy had the best results. The other modalities of treatment that had good results were taxanes, cisplatin, and fluorouracil-based induction chemotherapy followed by locoregional treatment with or without concomitant chemotherapy and accelerated radiotherapy with concomitant chemotherapy.

Implications of all the available evidence

We confirm that altered fractionation concomitant chemoradiotherapy is the most effective treatment for locally advanced head and neck cancer and especially hyperfractionated radiotherapy with concomitant chemotherapy. Taxane-based induction chemotherapy followed by locoregional therapy, ideally with concomitant chemotherapy, is another good option in selected patients with a good performance status and minor comorbidities. Network meta-analyses have limitations due to the use of indirect information. These results would ideally be confirmed by randomised trials. Nevertheless, it could help to guide clinical decision making in locally advanced head and neck cancer with a high risk of locoregional failure, especially human papillomavirus-negative tumours.

altered fractionation radiotherapy, without a significant difference between type of fractionation, through an improvement in local and regional control. The results of these meta-analyses support the use of conventional fractionation with concomitant platinum-based chemoradiotherapy, alone or as adjuvant treatment after surgery, for the treatment of locally advanced head and neck cancer.[4]

The individual patient data network meta-analysis framework has already been applied to head and neck squamous cell cancers as a methodological proof of concept where treatments were divided into six groups, and altered fractionation with concomitant chemoradiotherapy had the highest probability of survival.[5] Since this study, the three individual patient data meta-analyses mentioned previously were updated.[2,3,6] All of those data allowed individualisation of more detailed treatment modalities. The network is now larger in terms of treatment modalities, number of trials, and number of patients, and follow-up is longer. We aimed to update the individual patient data network meta-analysis to determine relative and absolute differences among 16 treatment modalities in patients with locally advanced head and neck cancer.

Methods

Data sources

This individual patient data network meta-analysis included randomised controlled trials that enrolled patients between Jan 1, 1980, and Dec 31, 2016. We excluded trials done before Jan 1, 1980, to improve homogeneity between trials.[7] We used data from MACH-NC, evaluating the addition of chemotherapy to local treatment, and MARCH, evaluating the role of radiotherapy fractionation, in patients with locally advanced squamous cell carcinoma of head and neck. The inclusion criteria, trial searches, trial flowcharts, data collection, and data verification procedures have been detailed in previous publications along with the results of the standard meta-analysis.[1–3,6] Briefly, all trials had to include patients with non-metastatic head and neck squamous cell cancer, and randomly assign patients to either chemotherapy or altered fractionation radiotherapy in a way that would preclude previous knowledge of the assigned treatment.

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation until death from any cause. Secondary endpoints were event-free survival, defined as the time from randomisation to the first recurrence or progression (locoregional or distant), or death; locoregional and distant control, defined as the time from randomisation to the occurrence of a locoregional or distant progression, respectively (if both a locoregional progression and a distant progression occurred at the same time, patients were considered as having a distant progression only); cancer death, including deaths from

any cause in patients with a previous progression event and deaths from the treated head and neck cancer; and non-cancer death. Deaths from unknown cause without previous disease progression or recurrence were regarded as cancer deaths if they occurred within 5 years after randomisation and as non-cancer deaths otherwise.

Statistical analysis

A specific network meta-analysis statistical analysis plan was written before the analysis and is available online.

We used a two-step method. The first step was to compute hazard ratios (HRs) for each trial on the basis of individual patient data using the Peto estimator for overall survival, event-free survival, cancer death, and non-cancer death,[8] and a competing risk model for locoregional and distant control.[9] The log-rank test, stratified by trial, was used to compare treatments. The second step was to do the network meta-analysis using a frequentist approach. Input data for each trial comparison were the two treatments compared, the logarithm of the HR, and its variance.

To limit the number of tests for both heterogeneity and inconsistency, Rücker and colleagues have proposed a global test, called the Q test.[10] This test is a generalisation of Cochran's test that is used to assess heterogeneity in conventional meta-analyses. The Q statistic is the sum of a statistic for heterogeneity (within designs) and a statistic for inconsistency (between designs). Inconsistency can be defined as the variability of treatment effect between direct (eg, randomised trials) and indirect comparisons at the meta-analytical level. A random-effects model was used in case of heterogeneity ($p<0·1$ on the basis of the Q statistic).

Treatments were ranked using the P score, which measures the mean extent of certainty that a treatment is better than the competing treatments.[11] A P score of 100% indicates that a treatment is certain to be the best and 0% indicates that a treatment is certain to be the worst. We computed the 5-year absolute benefit using the survival rate at 5 years for the locoregional therapy-only groups as the reference, and we computed the HR (95% CI) using the method by Stewart and Parmar[12] for overall survival and event-free survival. Patients without locoregional and distant progression or recurrence were censored at the date of death or the last follow-up.

A priori sensitivity analyses for the main efficacy endpoints were the exclusion of the outliers in the standard meta-analysis; the exclusion of trials with non-conventional chemotherapy (without platinum salts, with polychemotherapy using more than two drugs other than TaxPF, or with only one drug as induction chemotherapy, with adjuvant chemotherapy); the exclusion of trials based on quality criteria (less than 100 patients, follow-up less than 5 years, and unknown date of randomisation); and the exclusion of MACH-NC trials with distinctive locoregional therapy—ie, where chemotherapy was randomly assigned but locoregional therapies were different in both groups (variations in radiotherapy or surgery), hence introducing a confounding factor (appendix pp 39–40). Further sensitivity analyses were done for overall survival on the cluster of patients aged younger than 70 years and after exclusion of trials with a majority of stage I or II tumours. Due to the small number of distant control events and non-cancer deaths, we did a post-hoc sensitivity analysis by combining treatments into seven modalities instead of 16, for distant control and non-cancer death.

This study was done in accordance with network meta-analysis guidelines.[13] p values of less than 0·05 were considered to be significant for the difference between treatments. All analyses were done with R software (version 3.6.1) and the R package netmeta.

Role of the funding source

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

Results

The individual patient data network meta-analysis consisted of 115 randomised, controlled trials and 28 978 patients (24 013 [82·9%] male, 4587 [15·8%] female, and 378 [1·3%] missing) enrolled between Jan 1, 1980, and April 30, 2012 (no relevant studies were done between May 1, 2012, and Dec 31, 2016). Because of a factorial or multi-arm design or distinctive locoregional treatment in 19 trials, these 115 trials were split into 154 trial comparisons. 35 types of direct comparisons were available for 16 different treatments: locoregional therapy alone (surgery, radiotherapy, or both), which was used as the reference category; locoregional therapy with concomitant chemoradiotherapy with platinum-based chemotherapy ($CLRT_P$); locoregional therapy with concomitant chemoradiotherapy without platinum-based chemotherapy ($CLRT_{noP}$); induction chemotherapy with TaxPF followed by locoregional therapy (IC_{TaxPF}-LRT); induction chemotherapy with cisplatin or carboplatin and fluorouracil followed by locoregional therapy (IC_{PF}-LRT); any other type of induction chemotherapy followed by locoregional therapy (IC_{other}-LRT); induction chemotherapy followed by CLRT (IC_{TaxPF}-CLRT, IC_{PF}-CLRT, or IC_{other}-CLRT); locoregional therapy followed by adjuvant chemotherapy (LRT-AC); $CLRT_{noP}$ followed by adjuvant chemotherapy ($CLRT_{noP}$-AC); hyperfractionated radiotherapy (HFRT); hyperfractionated radiotherapy with concomitant chemotherapy (HFCRT); moderately accelerated radiotherapy (MART); very accelerated radiotherapy (VART); and accelerated radiotherapy with concomitant chemotherapy (ACRT).

The network is presented in figure 1. A description of treatment modalities is given in the appendix (p 2), a list of trials included in each treatment comparison is given in the appendix (pp 3–4), and the main characteristics of each trial are presented in the appendix (pp 5–21). Median follow-up based on all trials was 6·6 years (IQR 5·0–9·4).

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See **Online** for appendix

For the **statistical analysis plan** see https://www.gustaveroussy.fr/fr/meta-analyses-protocoles-dessais-orl

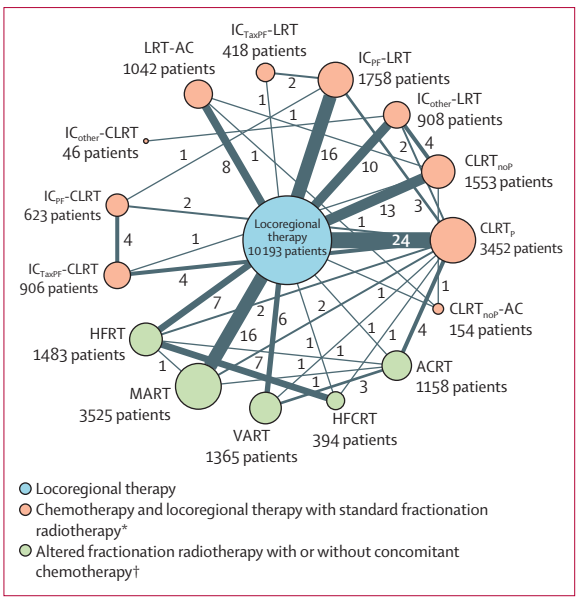


Figure 1: **Graphical representation of the trial network for overall survival**
The size of the nodes is proportional to the number of patients, which is given under each treatment category. The width of the lines is proportional to the number of comparisons, which are given on each line. The network included 154 comparisons from 115 trials (appendix pp 3–4). ACRT=accelerated radiotherapy with concomitant chemotherapy. CLRT$_{noP}$=locoregional therapy with concomitant chemoradiotherapy without platinum-based chemotherapy. CLRT$_{noP}$-AC=CLRT$_{noP}$ followed by adjuvant chemotherapy. CLRT$_{P}$=locoregional therapy with concomitant chemoradiotherapy with platinum-based chemotherapy. HFCRT=hyperfractionated radiotherapy with concomitant chemotherapy. HFRT=hyperfractionated radiotherapy. IC-CLRT=induction chemotherapy followed by locoregional therapy with concomitant chemoradiotherapy. IC-LRT=induction therapy followed by locoregional therapy. LRT-AC=locoregional therapy followed by adjuvant chemotherapy. MACH-CN=Meta-Analysis of Chemotherapy in Head and Neck Cancer. MARCH=Meta-Analysis of Radiotherapy in Carcinomas of Head and Neck. MART=moderately accelerated radiotherapy. Other=other type of induction chemotherapy. PF=cisplatin or carboplatin plus fluorouracil. TaxPF=taxane with cisplatin plus fluorouracil. VART=very accelerated radiotherapy. *Most of the trials for these comparisons were included in MACH-NC. †Most of the trials for these comparisons were included in MARCH.

For overall survival, the five treatments that had the highest effect were HFCRT (P score 97%; HR for comparison with locoregional therapy 0·63 [95% CI 0·51–0·77]), IC$_{TaxPF}$-LRT (89%; 0·69 [0·56–0·85]), ACRT (82%; 0·75 [0·66–0·85]), IC$_{TaxPF}$-CLRT (80%; 0·75 [0·62–0·92]), and CLRT$_{P}$ (78%; 0·77 [0·72–0·83]; table 1). The full results are presented in the appendix (pp 22–23). The absolute benefits at 5 years compared with locoregional therapy alone were 16·7% for HFCRT, 13·4% for IC$_{TaxPF}$-LRT, 10·4% for ACRT, 10·3% for IC$_{TaxPF}$-CLRT, and 9·5% for CLRT$_{P}$ (appendix pp 22–23). There were no significant differences between the five top-ranking treatments (appendix pp 22–25). Compared with CLRT$_{P}$, HFCRT (HR 0·82 [95% CI 0·66–1·01]), IC$_{TaxPF}$-LRT (0·90 [0·72–1·12], ACRT (0·97 [0·86–1·10]), and IC$_{TaxPF}$-CLRT (0·98 [0·81–1·19]) seemed to have superior overall survival (figure 2; appendix pp 22–25). There was significant heterogeneity (p=0·013), but no inconsistency (p=0·91; appendix pp 22–23).

Some trials had no data or events for specific secondary endpoints and were excluded from the corresponding analysis (appendix pp 39–40). The results of event-free survival are in agreement with overall survival; heterogeneity was still present (p=0·054), and no inconsistency (p=0·52) was detected for this endpoint (table 1). The five best treatments in terms of event-free survival were similar to those for overall survival, although IC$_{TaxPF}$-LRT and IC$_{TaxPF}$-CLRT swapped ranks, with HFCRT the most effective (P score 97%; table 1; figure 2; appendix p 26). Of these five treatments, only HFCRT had significantly better results than CLRT$_{P}$ (HR 0·80 [95% CI 0·65–0·98]; appendix pp 24, 26). Absolute benefit is shown in the appendix (p 26).

The results of locoregional control are also in agreement with overall survival and event-free survival results (table 1). Heterogeneity was still present (p<0·0001), and inconsistency (p=0·0008) was detected for this endpoint. Four of the best treatments were the same as for event-free survival, with HFCRT being the most effective (P score 88%); IC$_{TaxPF}$-CLRT ranked fourth but IC$_{TaxPF}$-LRT appeared to be less effective (table 1). When comparing the five top-ranking treatments between each other, the differences were not significant, even compared with CLRT$_{P}$ (appendix p 27).

The results for distant control were different from the other endpoints: LRT-AC was the most effective (P score 84%), followed by IC$_{PF}$-LRT (78%), CLRT$_{noP}$-AC (71%), HFRT (71%), and IC$_{TaxPF}$-LRT (65%; table 1). Heterogeneity and inconsistency were significant (p<0·0001) for this endpoint. Some comparisons between these treatments were significantly different (appendix p 28).

The results for cancer death are in agreement, in terms of treatments that were most effective, with overall survival, event-free survival, and locoregional control (table 2; appendix p 29). There was no heterogeneity (p=0·10) or inconsistency (p=0·80) for this endpoint. The five best treatments were HFCRT (P score 98%), IC$_{TaxPF}$-LRT (90%), CLRT$_{P}$ (81%), ACRT (80%), and IC$_{TaxPF}$-CLRT (78%; table 2). HFCRT had significantly better results than CLRT$_{P}$ (HR 0·77 [95% CI 0·62–0·97]; appendix p 29). For non-cancer death there was no heterogeneity (p=0·81) or inconsistency (p=0·17; table 2; appendix p 30). No treatment modality had a significant difference with locoregional therapy.

In sensitivity analyses of overall survival and event-free survival, the five top treatment modalities remained consistent, with HFCRT ranking first in all but one analysis (without outlier trials in conventional meta-analyses for event-free survival; appendix pp 31–32). The results of the cluster analysis of overall survival in patients younger than 70 years were similar to those of the entire population analysis, as well as after exclusion

	Overall survival	Event-free survival	Locoregional control	Distant control
Randomised controlled trials	115	112	110	100
Comparisons	154	151	150	137
Patients	28 978	28 315	27 309	25 042
Events	19 253	20 579	10 882	3065
Gobal p value	0·074	0·11	<0·0001	<0·0001
p value for heterogeneity	0·013	0·054	<0·0001	<0·0001
p value for inconsistency	0·91	0·52	0·0008	<0·0001
Hazard ratio (95% CI); P score (%)				
Locoregional therapy	1 (ref); 21%	1 (ref); 12%	1 (ref); 15%	1 (ref); 33%
HFCRT	0·63 (0·51–0·77)*; 97%†	0·60 (0·49–0·73)*; 97%†	0·49 (0·30–0·78)*; 88%†	1·15 (0·15–8·99); 32%
IC_{TaxPF}-LRT	0·69 (0·56–0·85)*; 89%†	0·71 (0·59–0·87)*; 80%	0·87 (0·48–1·57); 36%	0·32 (0·03–4·01); 65%
ACRT	0·75 (0·66–0·85)*; 82%†	0·71 (0·63–0·80)*; 82%†	0·57 (0·40–0·81)*; 79%†	0·91 (0·17–5·04); 38%
IC_{TaxPF}-CLRT	0·75 (0·62–0·92)*; 80%	0·66 (0·55–0·80)*; 89%†	0·56 (0·35–0·89)*; 78%	0·60 (0·08–4·59); 51%
$CLRT_{P}$	0·77 (0·72–0·83)*; 78%	0·74 (0·70–0·79)*; 75%	0·54 (0·46–0·65)*; 84%†	1·36 (0·61–2·99); 23%
HFRT	0·85 (0·76–0·95)*; 61%	0·84 (0·76–0·93)*; 55%	0·81 (0·59–1·11); 42%	0·32 (0·08–1·27); 71%
$CLRT_{noP}$	0·89 (0·81–0·98)*; 50%	0·88 (0·81–0·97)*; 43%	0·80 (0·63–1·03); 44%	0·42 (0·13–1·43); 62%
IC_{PF}-LRT	0·90 (0·82–0·99)*; 47%	0·93 (0·85–1·02); 30%	1·04 (0·83–1·31); 13%	0·25 (0·09–0·71)*; 78%†
VART	0·90 (0·81–1·01); 47%	0·88 (0·79–0·98)*; 43%	0·83 (0·59–1·17); 39%	0·92 (0·20–4·29); 38%
IC_{PF}-CLRT	0·90 (0·72–1·13); 46%	0·83 (0·66–1·03); 55%	0·58 (0·31–1·06); 73%	1·47 (0·10–20·56); 29%
MART	0·94 (0·87–1·01); 37%	0·89 (0·83–0·96)*; 40%	0·77 (0·62–0·97)*; 48%	0·47 (0·16–1·39); 59%
LRT-AC	1·03 (0·90–1·17); 18%	0·99 (0·86–1·13); 17%	0·77 (0·53–1·13); 48%	0·16 (0·03–0·88)*; 84%†
$CLRT_{noP}$-AC	1·07 (0·84–1·36); 16%	0·95 (0·75–1·20); 28%	0·77 (0·36–1·65); 47%	0·19 (0·01–6·83); 71%†
IC_{other}-CLRT	1·15 (0·73–1·82); 16%	NA‡	NA‡	NA‡
IC_{other}-LRT	1·04 (0·93–1·16); 15%	1·05 (0·94–1·17); 6%	1·00 (0·77–1·30); 17%	2·00 (0·49–8·09); 16%

ACRT=accelerated radiotherapy with concomitant chemotherapy. $CLRT_{noP}$=locoregional therapy with concomitant chemoradiotherapy without platinum-based chemotherapy. $CLRT_{noP}$-AC=$CLRT_{noP}$ followed by adjuvant chemotherapy. $CLRT_{P}$=locoregional therapy with concomitant chemoradiotherapy with platinum-based chemotherapy. HFCRT=hyperfractionated radiotherapy with concomitant chemotherapy. HFRT=hyperfractionated radiotherapy. IC-CLRT=induction chemotherapy followed by locoregional therapy with concomitant chemoradiotherapy. IC-LRT=induction therapy followed by locoregional therapy. LRT-AC=locoregional therapy followed by adjuvant chemotherapy. MART=moderately accelerated radiotherapy. NA=not available. Other=other type of induction chemotherapy. PF=cisplatin or carboplatin plus fluorouracil. TaxPF=taxane with cisplatin plus fluorouracil. VART=very accelerated radiotherapy. *Significant. †The three modalities of treatment with the highest P score. ‡No comparison was possible as the trial with this modality of treatment did not have information for event-free survival, locoregional control, and distant control.

Table 1: **Summary of efficacy endpoints**

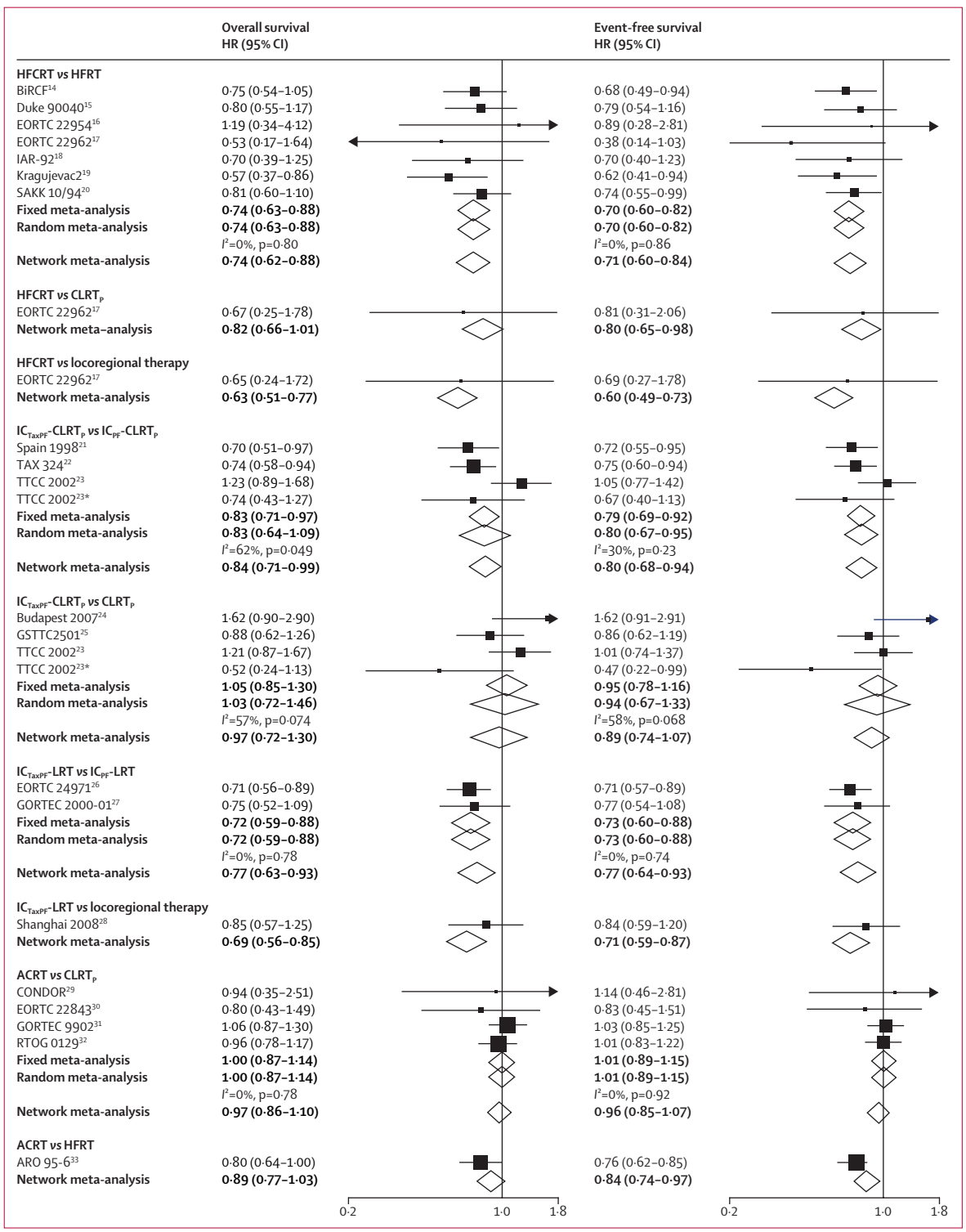
of trials with a majority of stage I or II tumours (appendix p 31). Heterogeneity was not significant after exclusion of outliers. For locoregional control and cancer death, the results were also robust to sensitivity analyses. For locoregional control, inconsistency was not significant after exclusion of trials with non-conventional chemotherapy, and the three best treatments remained unchanged. HFCRT always ranked first, except in the sensitivity analysis excluding trials with distinctive locoregional therapies (appendix pp 33–34). Conversely, for distant control, there was more variation in the ranking, but very few comparisons were significant (appendix p 35). In a post-hoc analysis of distant control using seven treatment modalities instead of 16, LRT-AC (with or without concomitant chemotherapy) ranked first (P score 89%) followed by altered fractionation radiotherapy (71%) and IC-LRT (64%); only the two first modalities had significant results compared with locoregional therapy (appendix p 36). In a similar post-hoc analysis for non-cancer death, there were no significant differences compared with locoregional therapy.

Discussion

In this individual patient data network meta-analysis, HFCRT ranked first overall survival, event-free survival, locoregional control, and cancer-specific death, and the results were robust following sensitivity analyses. IC_{TaxPF}-LRT and ACRT were also found to rank high.

This work has several strengths. First, data used as input to the network meta-analysis are individual patient data, which were verified and re-analysed by our team, with competing risks for locoregional and distant control accounted for. Second, the two-step frequentist network meta-analysis is a validated method,[10] previously used by our group[34] and others.[35–38] The network meta-analysis approach is also used by institutions.[39] Third, the assumptions of the network meta-analysis were met. There was no inconsistency for overall survival and event-free survival, and the heterogeneity was not significant after exclusion of the main outliers of the standard meta-analysis, without major changes in the conclusions. The transitivity assumption (ie, that there are no systematic differences between the available comparisons other than the treatments being compared) was

theoretically met thanks to well defined selection criteria of studies included in the network, allowing studies to be sufficiently similar in all respects other than the treatments compared. Moreover, the difference in stage or tumour site distribution from one trial to the other is not expected to affect the results, and the standard meta-analysis did not detect variation of effect according to these tumour characteristics.[6] However, this important hypothesis cannot be formally tested. Fourth, the main results were robust to predefined sensitivity analyses.



This work has limitations. First, given that trials' accrual spanned decades, it was impossible to ensure that patients were comparable between trials. Moreover, some important data, such as human papillomavirus (HPV) status or smoking status, were not available. Interaction between treatment and covariates is difficult to take into account in such a large network. As age is the most important predictive factor for chemotherapy and fractionation modifications, and the benefit of concomitant chemotherapy or altered fractionation was not significant in patients aged 70 years or older,[1] we did a sensitivity analysis only including patients younger than 70 years that showed similar results. Although the patient population included in the network meta-analysis is large, the number of events for distant control and non-cancer death were small as only the first event in these analyses was included. As a result, the analyses of these endpoints lack power even when combining treatment modalities. Moreover, the ranking of a network meta-analysis should be examined carefully, because it tends to overestimate the effect of treatment modalities with fewer trials.[40] Consideration must be given to HRs comparing modalities with each other. Here, there was no significant difference between the top five treatments for overall survival.

A few small recent trials[6] and trials with anti-EGFR therapy or immunotherapy were not included, which could limit the policy implications of this network meta-analysis. Besides, as Hu and colleagues stated: "the role of a network meta-analysis is not to provide recommendations but rather to synthesize the research in a manner that facilitates interpretation. The results of network meta-analyses are a decision-supporting tool rather than a decision-making tool".[41] We used a two-step frequentist model with individual patient data, but one-step models are currently being developed, especially for Bayesian network meta-analysis.[42] The use of Bayesian modelling could help to provide credible intervals for ranking. Finally, we have not analysed toxicity data because the data available in MACH-NC and MARCH were different, with very few toxicities in common. Thus, the toxicity networks were not considered relevant. Nevertheless, it is important to put the efficacy of treatment modalities in perspective with their toxicity profile, especially because HFRT and induction chemotherapy based on taxane, cisplatin, and fluorouracil are known to be toxic.

Despite limiting the network meta-analysis to trials done between 1980 and 2016, some trials were still done nearly four decades ago. The locoregional therapy used in the oldest trials is likely to be less optimal than that used nowadays, since surgery, anaesthesia, radiotherapy techniques, and supportive care have all improved over time. Imaging has also improved, and patients in older trials might have been understaged whereby even an experimental local therapy would be less effective.

	Cancer death	Non-cancer death
Randomised controlled trials	73	70
Comparisons	104	96
Patients	21753	21533
Events	11039	3645
Gobal p value	0·25	0·57
p value for heterogeneity	0·10	0·81
p value for inconsistency	0·80	0·17
Hazard ratio (95% CI); P score		
Locoregional therapy	1 (ref); 20%	1 (ref); 54%
HFCRT	0·54 (0·43–0·66)*; 98%*†	1·13 (0·77–1·66); 33%
IC_{TaxPF}–LRT	0·61 (0·46–0·80)*; 90%*†	0·91 (0·55–1·52); 62%
ACRT	0·70 (0·62–0·78)*; 80%*	1·15 (0·89–1·50); 28%
IC_{TaxPF}–CLRT	0·71 (0·58–0·87)*; 78%*	0·92 (0·57–1·48); 62%
$CLRT_{P}$	0·69 (0·64–0·75)*; 81%*†	1·15 (0·98–1·35); 26%
HFRT	0·83 (0·74–0·92)*; 58%*	0·94 (0·78–1·13); 65%†
$CLRT_{noP}$	0·95 (0·84–1·08); 31%	0·83 (0·65–1·06); 80%†
IC_{PF}–LRT	0·91 (0·77–1·08); 40%	0·91 (0·72–1·16); 67%
VART	0·88 (0·79–0·97)*; 48%*	1·15 (0·92–1·43); 28%
IC_{PF}–CLRT	0·89 (0·71–1·11); 44%	0·89 (0·46–1·70); 63%
MART	0·89 (0·83–0·95)*; 45%*	1·08 (0·97–1·19); 38%
LRT–AC	1·19 (0·93–1·52); 5%	1·07 (0·68–1·66); 43%
$CLRT_{noP}$–AC	1·03 (0·79–1·33); 21%	1·37 (0·91–2·06); 13%
IC_{other}–CLRT	NA‡	NA‡
IC_{other}–LRT	1·07 (0·88–1·32); 13%	0·71 (0·46–1·11); 89%†

ACRT=accelerated radiotherapy with concomitant chemotherapy. $CLRT_{noP}$=locoregional therapy with concomitant chemoradiotherapy without platinum-based chemotherapy. $CLRT_{noP}$-AC=$CLRT_{noP}$ followed by adjuvant chemotherapy. $CLRT_{P}$=locoregional therapy with concomitant chemoradiotherapy with platinum-based chemotherapy. HFCRT=hyperfractionated radiotherapy with concomitant chemotherapy. HFRT=hyperfractionated radiotherapy. IC-CLRT=induction chemotherapy followed by locoregional therapy with concomitant chemoradiotherapy. IC-LRT=induction therapy followed by locoregional therapy. LRT-AC=locoregional therapy followed by adjuvant chemotherapy. MART=moderately accelerated radiotherapy. NA=not available. Other=other type of induction chemotherapy. PF=cisplatin or carboplatin plus fluorouracil. TaxPF=taxane with cisplatin plus fluorouracil. VART=very accelerated radiotherapy. *Significant. †The three modalities of treatment with the highest P score. ‡No comparison was possible as the trial with this modality of treatment did not have information for event-free survival, locoregional control, and distant control.

Table 2: **Summary of cancer deaths and non-cancer death endpoints**

Figure 2: **Forest plot for overall survival and event-free survival, showing results from direct comparisons and network meta-analysis**
An HR of less than 1 is in favour of the first treatment mentioned in the heading (ie, HFCRT for the comparison: HFCRT *vs* HFRT). Detailed information about studies presented in this forest plot are available in the appendix (pp 5–21). For standard meta-analysis, results are presented with fixed and random effects, to study the effect of the heterogeneity on the choice of the model. The number of events and patients for each study are available in the appendix (pp 24–25). ACRT=accelerated radiotherapy with concomitant chemotherapy. $CLRT_{noP}$=locoregional therapy with concomitant chemoradiotherapy without platinum-based chemotherapy. $CLRT_{noP}$-AC=$CLRT_{noP}$ followed by adjuvant chemotherapy. $CLRT_{P}$=locoregional therapy with concomitant chemoradiotherapy with platinum-based chemotherapy. HFCRT=hyperfractionated radiotherapy with concomitant chemotherapy. HFRT=hyperfractionated radiotherapy. IC-CLRT=induction chemotherapy followed by locoregional therapy with concomitant chemoradiotherapy. IC-LRT=induction therapy followed by locoregional therapy. LRT-AC=locoregional therapy followed by adjuvant chemotherapy. MART=moderately accelerated radiotherapy. Other=other type of induction chemotherapy. PF=cisplatin or carboplatin plus fluorouracil. TaxPF=taxane with cisplatin plus fluorouracil. VART=very accelerated radiotherapy. *Data after evolution during the study with the systematic use of granulocyte colony-stimulating factor to prevent toxic death due to neutropenia.

Additionally, the epidemiology of head and neck cancer has evolved over time, with a decrease in cancers related to tobacco and alcohol and an increase in HPV-related cancers. The challenges and outcomes of these two types of cancers are quite different. Indeed, treatment for HPV-related cancers has better locoregional tumour control, disease-specific survival, and overall survival than HPV-unrelated cancers.[43] Hence, de-escalation is currently being studied for HPV-related tumours, although early results have been disappointing.[44–46] The results of our network meta-analysis suggest better outcomes with an intensification of treatment (eg, HFCRT), and this strategy could be used for HPV-negative tumours, although toxicity remains an important consideration because these patients might be less tolerant of intensification through this strategy due to associated comorbidities, especially related to smoking. Although there were no significant differences among the HRs of the top five modalities for overall survival, the HR comparing HFCRT and conventional $CLRT_p$, which is the accepted standard of care worldwide, was 0·82 (95% CI 0·66–1·01) and the corresponding HR for event-free survival, a validated surrogate,[47] was significant (0·80 [0·65–0·98]). Moreover, the patients included in our meta-analyses have characteristics that are more consistent with patients who have HPV-negative tumours. For example, in the second publication of MARCH,[3,48] with more recent studies, HPV-status was known for 2080 (17·4%) of 11 981 patients and was positive in only 645 (31·0%) patients with known status. Therefore, our results would probably be applicable to patients with locally advanced HPV-negative tumours.

HFCRT has been evaluated directly in seven trials included in our network meta-analysis (BiRCF,[14] Duke 90040,[15] EORTC 22954,[16] EORTC 22962,[17] IAR-92,[18] Kragujevac2,[19] and SAKK 10/94[20]). All of these trials compared HFCRT with HFRT, but one of them had a two-by-two design with a small number of patients (EORTC 22962,[17] closed early due to slow accrual), thus HFCRT was also compared with locoregional therapy and $CLRT_p$. None of the trials studying HFCRT were in a postoperative setting. These trials included 816 patients with only 384 patients treated in the HFCRT modality, which is a clear weakness of our analysis. A recent trial (DAHANCA 28) evaluated this modality of treatment in a phase 1/2 study of 50 patients with locally advanced HPV-negative head and neck cancer, treated with hyper-fractionated, accelerated radiotherapy with concomitant weekly cisplatin and nimorazole.[49] 3-year actuarial loco-regional recurrence was 21% (95% CI 11–33), and overall survival was 74% (59–84). Acute toxicity was high, with 38 (78%) of 49 patients requiring a feeding tube. When compared with historical trials,[50,51] this protocol appears to have higher rates of late toxicity, especially with respect to feeding tube dependency and osteoradionecrosis. However, this trial was not randomised and the toxicity rate could be partly due to patient selection. It can also be argued that HFRT is difficult to implement in the era of intensity modulated radiotherapy for head and neck cancer (none of the seven studies used this technique), but it has been done in a phase 2 trial with 1·25 Gy per fraction given twice a day up to 70 Gy.[52] HFCRT is technically feasible with modern radiotherapy delivery, with an acute toxicity profile that would require adapted patient management, but with acceptable long-term toxicity. It could be considered as an option for tertiary centres with a high throughput of patients with head and neck cancer.

Induction chemotherapy, especially regimens that included taxane, cisplatin, and fluorouracil, followed by locoregional therapy and concomitant chemotherapy also yielded good results, with IC_{TaxPF}-CLRT ranking fourth for overall survival. We believe that toxic deaths that occurred before the systematic use of granulocyte colony-stimulating factor contributed to this ranking. In the sensitivity analysis restricted to trials mandating the use of granulocyte colony-stimulating factor (ie, in the sensitivity analysis excluding outlier study protocols), IC_{TaxPF}-CLRT ranked second after HFCRT for overall survival, and first for event-free survival. Strategies with induction chemotherapy are more commonly used in clinical practice than HFCRT, and this analysis partly supports this practice for advanced disease.

In conclusion, this network meta-analysis allowed evaluation of many treatment modalities, and suggests the superiority of HFCRT over other treatments. This treatment, which can be difficult to implement in daily practice, could however be suitable for the treatment of HPV-negative head and neck cancers. Induction chemotherapy based on taxanes followed with ideally concomitant chemoradiotherapy is another strategy that has good results for selected patients with good performance status and minor comorbidities. These treatments should ideally be further investigated in clinical trials. However, in the absence of additional randomised studies our findings can help to inform current clinical decision making.

Contributors

CP, PB, and J-PP, with the help of the steering committee members, designed and supervised the study. PB and J-PP obtained funding. PB, JB, J-PP, and BL searched for and selected the trials. Steering committee members contributed to the identification and selection of the trials. CP, BL, PB, and J-PP did the statistical analyses and wrote the draft, with revisions from the other authors. All authors contributed to the interpretation of the results during the investigator meeting and the revision of the manuscript. All investigators listed in the appendix (pp 37–38) received the manuscript for revision. The corresponding author and the first author had full access to all the data in the study and had final responsibility for the decision to submit for publication. CP, BL, J-PP, and PB have accessed and verified the data.

Declaration of interests

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Data sharing

Individual patient data are not available for sharing (appendix p 41).

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