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

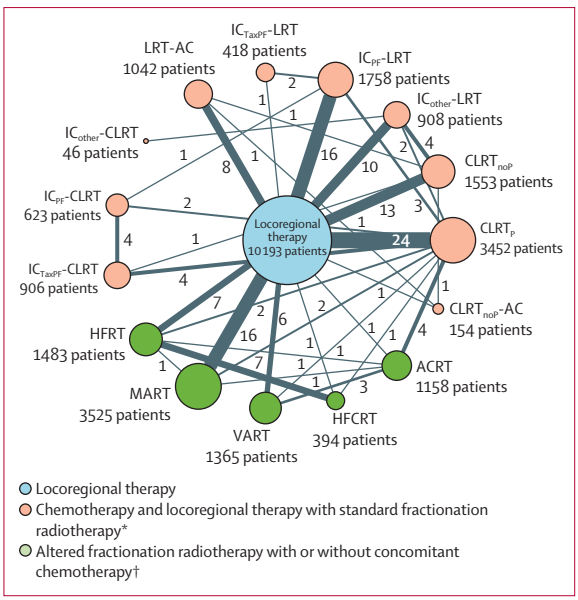


Figure 1: **Graphical representation of the trial network for overall survival**
The size of the nodes is proportional to the number of patients, which is given under each treatment category. The width of the lines is proportional to the number of comparisons, which are given on each line. The network 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**

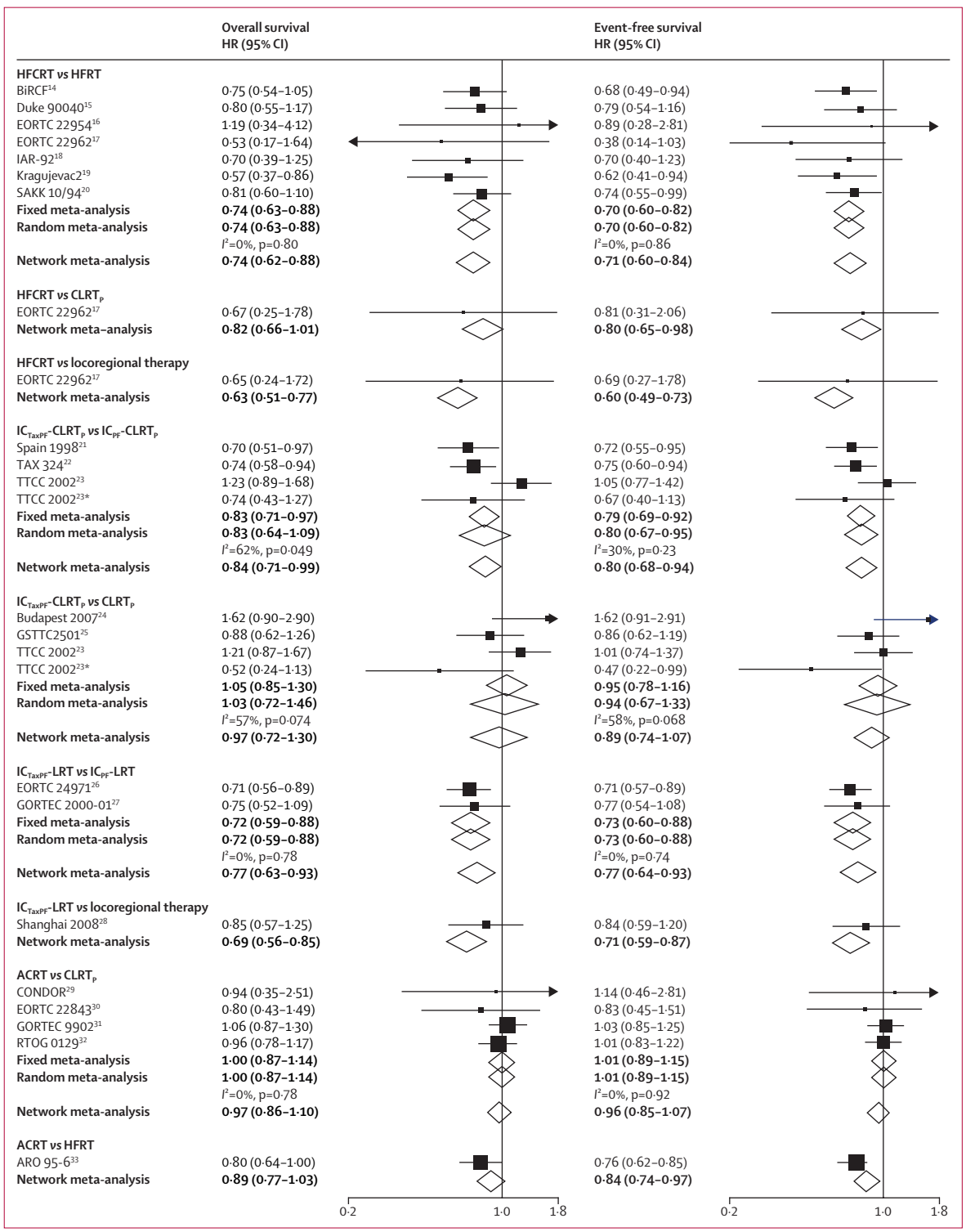
of trials with a majority of stage I or II tumours (appendix p 31). Heterogeneity was not significant after exclusion of outliers. For locoregional control and cancer death, the results were also robust to sensitivity analyses. For locoregional control, inconsistency was not significant after exclusion 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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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Appendix

Web-Table 1 – Description of the different type of chemotherapy and the different type of loco-regional treatment and their association in the treatment modalities defined for the network meta-analysis.

Web-Table 2 – List of the 35 treatment comparisons with the corresponding trial comparisons, number of comparisons and number of patients for overall survival.

Web-Table 3 – Main characteristics of trials included in the network meta-analysis

Web-Table 4 – League table presenting the results hazard ratio with their 95% confidence interval of the network meta-analysis (random effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for overall survival.

Web-Table 5 – Summary of results from direct comparisons and network meta-analysis for overall survival and event-free survival corresponding to comparisons presented in Figure 2.

Web-Table 6 – League table presenting the results hazard ratio with their 95% confidence interval of the network meta-analysis (random effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for event-free survival.

Web-Table 7 – League table presenting the results hazard ratio with their 95% confidence interval of the network meta-analysis (random effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for loco-regional control.

Web-Table 8 – League table presenting the results hazard ratio with their 95% confidence interval of the network meta-analysis (random effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for distant control.

Web-Table 9 – League table presenting the results hazard ratio with their 95% confidence interval of the network meta-analysis (random effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for cancer death.

Web-Table 10 – League table presenting the results hazard ratio with their 95% confidence interval of the network meta-analysis (random effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for non-cancer death.

Web-Table 11 – Results of main analysis and sensitivity analysis for overall survival: see web appendix 1 for the list of trial comparison excluded in each sensitivity analysis

Web-Table 12 – Results of main analysis and sensitivity analysis for event-free survival.

Web-Table 13 – Results of main analysis and sensitivity analysis for loco-regional control.

Web-Table 14 – Results of main analysis and sensitivity analysis for cancer death.

Web-Table 15 – Results of main analysis and sensitivity analysis for distant control.

Web-Table 16 – Sensitivity analysis with lumping of groups of treatment modalities for distant control and non-cancer death endpoint.

Web-Appendix 1 - MACH-NC & MARCH collaborative group

Web-Appendix 2 - Trials excluded for:
A - Secondary endpoint analysis
B - Sensitivity analysis

Web-Appendix 3 – Data sharing

Web-References

Web-Table 1 – Description of the different type of chemotherapy and the different type of loco-regional treatment and their association in the treatment modalities defined for the network meta-analysis.

Type of CT / Type of LRT	No CT	Induction CT with TaxPF (IC_{TaxPF})	Induction CT with PF (IC_{PF})	Induction CT with another regimen (IC_{other})	Concomitant platinum based CT (CT_P)	Concomitant non-platinum based CT (CT_{noP})	Adjuvant CT (AC)
LRT alone *surgery and/or RT[$]*	LRT	IC_{TaxPF}-LRT	IC_{PF}-LRT	IC_{other}-LRT			LRT-AC
Concomitant chemoradiotherapy (CLRT) *(+/- Surgery)*		IC_{TaxPF}-CLRT	IC_{PF}-CLRT	IC_{other}-CLRT	$CLRT_P$	$CLRT_{noP}$	$CLRT_{noP}$-AC
Hyperfractionated RT (HFRT) *the total radiotherapy dose was higher (~15% overall), with RT given twice a day while maintaining same overall treatment time*	HFRT				HFCRT		
Moderately accelerated RT (MART) *(+/- Surgery) the total radiotherapy dose was unchanged (±5%) but delivered more quickly (generally about 1 week faster) than in the reference group, with usually 1-2 more RT fractions per week*	MART				ACRT[*]	ACRT[*]	
Very accelerated RT (VART) *(+/- Surgery) the total radiotherapy dose was lower (about 15%) and overall treatment time was shortened by ~50% or more*	VART					ACRT[*]	

[$]standard RT: total dose varies from 60 Gy to 70 Gy, with 2 Gy per day and the corresponding overall treatment time varies from 6 to 7 weeks.
[*]these modalities are lumped together due to the small sample size

LRT=loco-regional treatment, CT=chemotherapy, RT=radiotherapy, IC=induction CT, AC=adjuvant CT, HFCRT=HFRT with concomitant CT, ACRT=accelerated (moderately or very) RT with concomitant CT, TaxPF=taxanes, platin and 5-Fluorouracil association, PF=platin and 5-Fluorouracil association.

Web-Table 2 – List of the 35 treatment comparisons with the corresponding trial comparisons, number of comparisons and number of patients for overall survival.

Treatment comparison	Number of comparisons	Number of patients	Trials
HFRT vs LRT	7	1 702	DAHANCA 9[1], EORTC 22791[2], EORTC 22962[$], PMH Toronto[3], Rio 1986[4], RTOG 9003[5], RTOG 9512[6]
MART vs LRT	16	6 472	ARTSCAN[7], BCCA 9113[8], CAIR[9], DAHANCA 6&7[10], EORTC 22851[11], IAEA-CRP-ACC[12], INRC-HN-10[13], KBN PO 79[14], KROG 0201[15], CRT 90-002[16], ORO 9301[17], Osaka 1993[18], pCAIR[19], POPART[20], RTOG 9003[5], TMH 1114[21]
VART vs LRT	6	1 879	CAIRO 1990[22], CHART[23], CHARTWEL[$], GORTEC 9402[24], TROG 9101[25], Vienna[26]
HFCRT vs LRT	1	29	EORTC 22962[$]
ACRT vs LRT	1	161	Vienna[26]
$CLRT_{noP}$-AC vs LRT	1	387	UKHAN[27]
$CLRT_{P}$ vs LRT	24	4 265	AC Camargo[28], AIIMS03[29], Bavaria89[30], CH-7401[31], FRCT 94[32], ECOG2382[33], EORTC 22931[34], EORTC 22954[$], EORTC 22962[$], GORTEC 9401[35], HeCOG 9405[36], INRC HN-8[37], Int 0126a[38], Int 0126b[38], Kragujevac1[39], Lucknow95[40], ORO 9301[17], RPC 3250[41], RTOG 9111a[42], RTOG 9501[43], THM 1114[21], Torino 92[44], Toulouse[45], UPCI 93-99[46]
$CLRT_{noP}$ vs LRT	13	2 446	IAEA-MMC[47], LOHNG91[48], LOHNG97[49], NCI-V98-1416[50], Ontario[51], PMHCGS[52], SECOGII[$], UKHAN[27], UKHANpo[27], Yale80[53], Yale80po[53], Yale86[54], Yale86po[54]
IC_{other}-LRT vs LRT	10	1 206	AC Camargo[28], BuenosAires[55], Creteil-82[56], HNCGIC02[57], HNCGIC03[58], Lucknow95[40], Pitie-81[59], SECOGII[$], Songkhla[60], SWOG8006[61]
IC_{PF}-LRT vs LRT	16	2 451	AHNTGsurg[62], AHNTG[62], BNH003[$], CFHNS[63], Cologne-88[64], Creteil-86[65], EORTC24844[$], GETTECneo1[66], GETTECneo2[66], GSTTC86[67], GSTTC86po[67], HNAP-02[68], MCW-2[69], Parma[70], Rennes-87[71], SHNG-85[72]
IC_{TaxPF}-LRT vs LRT	1	256	Shanghai 2008[73]
LRT-AC vs LRT	8	2 151	GETTECadj[74], HNU-87a[75], HNU-87b[75], Int0034[76], JHCFUS[77], KKD-86[78], TMHR-4[79], UKHAN[27]
IC_{TaxPF}-CLRT vs $CLRT_{P}$	4	584	Budapest 2007[80], GSTTC 2501[81,82], TTCC 2002[83,84], TTCC 2002+[83,84]
HFRT vs $CLRT_{P}$	2	171	EORTC 22962[$], INRC-HN-9[85]
MART vs $CLRT_{P}$	2	262	ORO 9301[17], THM 1114[21]
VART vs $CLRT_{P}$	1	560	GORTEC 9902[86]
HFCRT vs $CLRT_{P}$	1	30	EORTC 22962[$]
ACRT vs $CLRT_{P}$	4	1 405	CONDOR[87], EORTC 22843[88], GORTEC 9902[86], RTOG 0129[89]
$CLRT_{P}$ vs IC_{other}-LRT	2	260	AC Camargo[28], Lucknow95[40]
$CLRT_{P}$ vs IC_{PF}-LRT	3	416	CMGH-85[90], EORTC 24954[91], ICC-PCP[92]
IC_{PF}-CLRT vs $CLRT_{P}$	2	258	TTCC 2002[83,84], TTCC2002+[83,84]
IC_{TaxPF}-CLRT vs $CLRT_{noP}$	1	285	DeCIDE[93]
$CLRT_{noP}$-AC vs $CLRT_{noP}$	1	320	UKHAN[27]
$CLRT_{noP}$ vs IC_{other}-LRT	4	598	Brescia[94], INRC HN-7[95], SECOG I[96], SECOGII[$]
LRT-AC vs $CLRT_{noP}$	1	326	UKHAN[27]
IC_{TaxPF}-LRT vs IC_{PF}-LRT	2	578	EORTC 24971[97], GORTEC 2000-01[98]
IC_{other}-CLRT vs IC_{other}-LRT	1	108	Torino 85[99]
IC_{PF}-CLRT vs IC_{PF}-LRT	1	56	Créteil 85[100]
IC_{TaxPF}-CLRT vs IC_{PF}-CLRT	3	1 194	Spain 1998[101], TAX 324[102], TTCC 2002[83,84], TTCC 2002+[83,84]
HFRT vs MART	1	834	RTOG 9003[5]

Treatment comparison	Number of comparisons	Number of patients	Trials
HFCRT vs HFRT	7	766	BiRCF[103], Duke 90040[104], EORTC 22954[$], EORTC 22962[$], IAR 92[105], Kragujevac2[106], SAKK 10-94[107]
ACRT vs HFRT	1	384	ARO 95-6[108]
ACRT vs MART	1	263	Cologne 95[109]
ACRT vs VART	3	828	GORTEC 9601[110], GORTEC 9902[86], Vienna[26]
$CLRT_{noP}$-AC vs LRT-AC	1	314	UKHAN[27]

[$] unpublished

LRT=loco-regional treatment, CT=chemotherapy, RT=radiotherapy, CLRT=LRT with concomitant chemoradiotherapy, IC=induction CT, AC=adjuvant CT, HFRT=hyperfractionated RT, HFCRT=HFRT with concomitant CT, MART=moderately accelerated RT, VART=very accelerated RT, ACRT=accelerated (moderately or very) RT with concomitant CT, P=platin-based CT, noP=not platin-based CT, TaxPF=taxanes, platin and 5-Fluorouracile association, PF=platin and 5-Fluorouracile association.

Web-Table 3 – Main characteristics of trials included in the network meta-analysis

These tables are adapted from the tables in the articles reporting our previous meta-analyses which provided further information: MARCH[111,112] and MACH-NC[113,114–116].

A- Description of trials with induction chemotherapy

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
Chemotherapy other than platin + fluorouracil or Taxane + platin + fluorouracil										
SWOG 8006[61]	1980–85	OC, OP, HP, L	II to IV	B C Mx Vc	15 U/m² $d_{1,8}$, $wks_{1,4,7}$ 50 mg/m², $wks_{1,4,7}$ 40 mg/m², $wks_{1,4,7}$ 2 mg, $wks_{1,4,7}$	S + RT	MD	167/167	13.7	IC_{other}-LRT vs LRT
Pitié-81[59]	1981–85	OC, OP, O	I to IV	A B (im) C Vc	60 mg, 3 cycles 15 mg x 3 150 mg 2 mg	RT	70 Gy/7 wks or 60 Gy/4 wks, sc, bf	112/116	11.3	IC_{other}-LRT vs LRT
Buenos Aires[55]	1981–86	OC, OP, HP, L, NP	III, IV	$\underline{Arm_1}$: C B $\underline{Arm_2}$: C B Mx	 100 mg/m², $d_{1,15}$ 40 mg/m², $d_{1,8,15,22}$ 100 mg/m², $d_{4,19}$ 40 mg/m², $d_{1,8,15,22}$ 50 mg/m², $d_{1,15}$	S or RT or S + RT	NA MD MD	120/120	7.0	IC_{other}-LRT vs LRT
Créteil-82[56]	1982–87	OC, OP	II to IV	B (ci) F Mx	10 mg/m² x 5, $wks_{1,5,9}$ 600 mg/m² d_2, $wks_{1,5,9}$ 120 mg/m² d_2, $wks_{1,5,9}$	RT or S + RT	70 Gy/7.8 wks 55 Gy/6 wks	122/131	5.0	IC_{other}-LRT vs LRT

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
				LA (po) C	10 mg x 4, d_3, $wks_{1,5,9}$ 120 mg/m² d_4, $wks_{1,5,9}$					
HNCGIC 02[57]	1983–86	OC, OP, HP, L	II to IV	B (ci) C Mi Vd	12.5 mg/m² x 4, $wks_{1,4}$ 20 mg/m² x 4, $wks_{1,4}$ 10 mg/m², $wks_{1,4}$ 2.5 mg/m², $wks_{1,4}$	RT	65-75 Gy	100/100	10.2	IC_{other}-LRT vs LRT
HNCGIC 03[58]	1986–89	OC, OP, HP, L	II to IV	C (ci) F (ci) Vd	40 mg/m² x 3, $wks_{1,4,7}$ 600 mg/m² x 5, $wks_{1,4,7}$ 3 mg/m² x 2, $wks_{1,4,7}$	RT	70 Gy	108/108	7.2	IC_{other}-LRT vs LRT
Songkhla[60]	1988–92	OC, OP, HP, O	III, IV	B (ci) C Mx	10 mg/m² d_{3-7}, $wks_{1,5}$ 20 mg/m² x 5, $wks_{1,5}$ 40 mg/m² $d_{15,22}$, $wks_{1,5}$	S + RT	≥ 60 Gy	54/54	4.1	IC_{other}-LRT vs LRT
Platin + fluorouracil only										
MCW-2[69]	1983–86	OC, OP, HP, L, NP, O	III, IV	C F (ci)	100 mg/m², $wks_{1,4,7}$ 500 mg/m² x 5, $wks_{1,4,7}$	RT + S or RT	50 Gy/5 wks 70 Gy/7 wks	63/63	8.3	IC_{PF}-LRT vs LRT
EORTC 24844 (unpublished)	1985–91	OP	II to IV	C F (ci)	100 mg/m², $wks_{1,4,7}$ 1000 mg/m² x 5, $wks_{1,4,7}$	S + RT	50 Gy/5 wks +/- 15 Gy boost	139/139	2.8	IC_{PF}-LRT vs LRT
SHNG-85[72]	1985–92	OC, OP, HP, L	II to IV	C F (ci)	100 mg/m², $wks_{1,4,7}$ 1000 mg/m² x 5, $wks_{1,4,7}$	RT	64-70 Gy/6.5-7 wks	461/461	7.2	IC_{PF}-LRT vs LRT
Créteil-86[65]	1986–89	OC, OP, HP, L	II to IV	C F (ci)	100 mg/m², $wks_{1,4,7}$ 1000 mg/m² x 5, $wks_{1,4,7}$	RT or S + RT	70 Gy/8 wks 55 Gy/6 wks	156/156	6.0	IC_{PF}-LRT vs LRT
GSTTC-86[67]	1986–90	OC, OP, HP, O	III, IV	C F (ci)	100 mg/m², $wks_{1,4,7,10}$ 1000 mg/m² x 5, $wks_{1,4,7,10}$	RT or S + RT	65-70 Gy/6.5-7wks 45-50 Gy/4.5-5wks	237/237	11.6	IC_{PF}-LRT vs LRT

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
GETTECneo1[66]	1986–91	OP	II to IV	C F (ci)	100 mg/m^2, wks$_{1,4,7}$ 1000 mg/m^2 x 5, wks$_{1,4,7}$	RT	70-75 Gy/7-7.5 wks	174/174	12.0	IC$_{PF}$-LRT vs LRT
GETTECneo2[66]	1986–92	OP	II to IV	C F (ci)	100 mg/m^2, wks$_{1,4,7}$ 1000 mg/m^2 x 5, wks$_{1,4,7}$	S + RT	50-65Gy/5-6.5 wks	144/144	12.3	IC$_{PF}$-LRT vs LRT
AHNTG[62]	1986–93	OC, OP, HP, L, NP, O	II to IV	C F (ci)	100 mg/m^2, wks$_{1,4,7}$ 1000 mg/m^2 x 4, wks$_{1,4,7}$	S or RT or S + RT	NA MD MD	280/280	7.1	IC$_{PF}$-LRT vs LRT
Rennes-87[71]	1987–90	OP, HP	I to IV	C F (ci)	100 mg/m^2, wks$_{1,3,5}$ 1000 mg/m^2 J$_{2\text{-}5}$, wks$_{1,3,5}$	RT or S + RT	68.6 Gy MD	133/133	6.4	IC$_{PF}$-LRT vs LRT
Parma[70]	1987–91	OC, OP, HP, L	II to IV	C F (ci)	100 mg/m^2, wks$_{1,4,7 \pm 10,13}$ 1000 mg/m^2 x 5, wks$_{1,4,7 \pm 10,13}$	S or RT or S + RT	NA MD MD	69/69	6.2	IC$_{PF}$-LRT vs LRT
CFHNS[63]	1988–91	OC, OP, HP, L	II to IV	Cb F (ci)	400 mg/m^2, wks$_{1,4,7}$ 1000 mg/m^2 x 5, wks$_{1,4,7}$	RT or S + RT	75 Gy 45-75 Gy	324/324	5.7	IC$_{PF}$-LRT vs LRT
Cologne 88[64]	1988–93	OC, OP, HP	II to IV	Cb F (ci)	360 mg/m^2, wks$_{1 \pm 5 \pm 9}$ 1000 mg/m^2 x 5, wks$_{1 \pm 5 \pm 9}$	S + RT	60-66 Gy/6-7 wks	97/97	2.0	IC$_{PF}$-LRT vs LRT
HNAP-02[68]	1989–92	OC, OP, HP, L	III, IV	C F	70 mg/m^2, 2 cycles 660 mg/m^2 d$_{2\text{-}6}$, 2 cycles	S or S + RT	50 Gy 50 Gy	50/50	5.2	IC$_{PF}$-LRT vs LRT
BNH 003 (unpublished)	1990–92	OC, OP, HP, O	III, IV	C F	100 mg/m^2 x 2–3 4000 mg/m^2 x 2–3	S + RT	45-60 Gy	124/124	3.7	IC$_{PF}$-LRT vs LRT
Taxane + platin + fluorouracil (second update and induction publication)										

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
GSTTC 2501[81,82]	2003–12	OC, OP, HP, O	III, IV	C Do F (ci) C (ci; 2 arms) F (ci; arms)	ind: 80 mg/m², $wks_{1,4,7}$ ind: 75 mg/m², $wks_{1,4,7}$ ind: 800 mg/m² x 4, $wks_{1,4,7}$ conco: 20 mg/m² x 4, $wks_{1,6*}$ conco: 800 mg/m² x 4, $wks_{1,6*}$ *of RT	RT	70 Gy/7 wks	261/261	3.7	IC_{TPF}-$CLRT_P$ vs $CLRT_P$
DeCIDE[93]	2004–09	OC, OP, L, NP, O, U	IV	Do C F (ci) Do (2 arms) F (ci, 2 arms) Conco in 2 arms Hu (po) Hu (po)	ind: 75 mg/m², $wks_{1,4}$ ind: 75 mg/m², $wks_{1,4}$ ind: 750 mg/m² x 5, $wks_{1,4}$ conco: 25 mg/m², $wks_{1,3,5,7,9*}$ conco: 600 mg/m² x 5, $wks_{1,3,5,7,9*}$ conco: 500 mg x 2, d_{1-5}, $wks_{1,3,5,7,9*}$ conco: 500 mg, d_6, $wks_{1,3,5,7,9*}$ * of RT	RT	75 Gy/9 wks, bid, sc	285/285	6.0	IC_{TPF}-$CLRT_{noP}$ vs $CLRT_{noP}$
Budapest 2007[80]	2007–09	OC, OP, HP, L	III, IV	Do C F (ci) C (two arms)	ind: 75 mg/m²,$wks_{1,4}$ ind: 75 mg/m², $wks_{1,4}$ ind : 750 mg/m² x 4, $wks_{1,4}$ conco: 100 mg/m², $wks_{1,4,7}$ of RT	RT	70 Gy/7 wks	66/66	6.8	IC_{TPF}-$CLRT_P$ vs $CLRT_P$
Shanghai 2008[73]	2008–10	OC	III, IVa	Do C F (ci)	75 mg/m², $wks_{1,4}$ 75 mg/m², $wks_{1,4}$ 750 mg/m² x 5, $wks_{1,4}$	S + RT	54-60 Gy/6 wks	256/256	5.6	IC_{TPF}-LRT vs LRT
Spain 1998[101]	1998-2001	OC, OP, HP, L	III-IV	$\underline{Arm_1}$: Pa C	 ind: 175 mg/m², $wks_{1,4,7}$ ind: 100 mg/m², $wks_{1,4,7}$	RT ± S	70Gy/7 wks	382	2.4	IC_{TPF}-$CLRT_P$ vs IC_{PF}-$CLRT_P$

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
				F (ci)	ind: 500 mg/m² x 5, $wks_{1,4,7}$					
				$\underline{Arm_2}$:						
				C	ind: 100 mg/m², $wks_{1,4,7}$					
				F (ci)	ind: 1000 mg/m² x 5, $wks_{1,4,7}$					
				C (2 arms)	conco: 100 mg/m², $wks_{1,4,7}$ of RT					
TAX 324[102]	1999-2003	OC, OP, HP, L	III-IV	$\underline{Arm_1}$:		RT ± S	70-74Gy/7weeks	501	6.0	IC_{TPF}-$CLRT_P$ vs IC_{PF}-$CLRT_P$
				Do	ind: 75 mg/m², $wks_{1,4,7}$					
				C	ind: 100 mg/m², $wks_{1,4,7}$					
				F (ci)	ind: 1000 mg/m² x 5, $wks_{1,4,7}$					
				$\underline{Arm_2}$:						
				C	ind: 100 mg/m², $wks_{1,4,7}$					
				F (ci)	ind: 1000 mg/m² x 5, $wks_{1,4,7}$					
				Cb (2 arms)	conco: AUC1.5, weekly during RT					
EORTC 24971[97]	1999-2002	OC, OP, HP, L	III, IV	$\underline{Arm_1}$:		RT ± S	66-74Gy/7weeks	358	8.6	IC_{TPF}-LRT vs IC_{PF}-LRT
				Do	ind: 75 mg/m², $wks_{1,4,7,10}$					
				C	ind: 75 mg/m², $wks_{1,4,7,10}$					
				F (ci)	ind: 750 mg/m² x 5, $wks_{1,4,7,10}$					
				$\underline{Arm_2}$:						
				C	ind: 100 mg/m², $wks_{1,4,7,10}$					
				F (ci)	ind: 1000 mg/m² x 5, $wks_{1,4,7,10}$					
GORTEC 2000-01[98]	2000-2005	HP, L	III, IV	$\underline{Arm_1}$:		RT ± S	70Gy/7weeks 50-66Gy/5-6.5weeks when post-operative	220	5.1	IC_{TPF}-LRT vs IC_{PF}-LRT
				Do	ind: 75 mg/m², $wks_{1,4,7}$					
				C	ind: 75 mg/m², $wks_{1,4,7}$					

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
				F (ci)	ind: 750 mg/m² x 5, $wks_{1,4,7}$					
				Arm2:						
				C	ind: 100 mg/m², $wks_{1,4,7}$					
				F (ci)	ind: 1000 mg/m² x 5, $wks_{1,4,7}$					

A: Doxorubicin; AC Camargo: Hospital AC Camargo; adj: Adjuvant; AHNTG: Australian Head and neck Trial Group; AIIMS: All India Institute of Medical Sciences; alt: alternating; ARO: Arbeitsgemeinschaft für Radio-Onkologie; ARTSCAN: Accelerated RadioTherapy of Squamous cell CArcinomas in the head and Neck; BCCA: British Columbia Cancer Agency; bid: twice daily; B: Bleomycin; BiRCF: Bifractionnated Radiotherapy and cisplatin/5-fluorouracile; BNH: B. Nanavati Hospital; b: boost; C: Cisplatin; CAIR: Continuous Accelerated IRadiation; Cb: Carboplatin; CFHNS: Carboplatin French Head and Neck Study; CH: Chapel Hill; ci: Continuous Infusion; CHART: Continuous Hyperfractionated Accelerated Radiation Therapy; CHARTWEL: Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) Week-end-Less; conco: Concomitant; Co: Control arm; CONDOR: Dutch Head and Neck Society 08-01 trial; CRT: Clinical Randomized Trial; Cy: Cyclophosphamide; conco: concomitant; d: day; DAHANCA: DAnish Head ANd Neck CAncer group; DeCIDE: Docetaxel-based Chemotherapy plus or minus Induction chemotherapy to Decrease Events; Do: Docetaxel; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; Ex: Experimental arm; F: 5-Fluorouracil; FCRT: French Carboplatine Radiotherapy Trial; GETTEC: Groupe d'Etude des Tumeurs de la Tête Et du Cou; GORTEC: Groupe d'Oncologie Radiothérapie Tête Et Cou; GSTTC: Gruppo di Studio sui Tumori della Testa et del Collo; Gy: Gray; HNAP: Head and Neck Adjuvant Project; HeCOG: Hellenic Cooperative Oncology Group; HNCGIC: Head and Neck Cancer Group of Institut Curie; HNCP: Head and Neck Contract Program; HP: Hypophraynx; Hu: Hydroxyurea; ia: intrarterial; IAEA-CRP-ACC: International Atomic Energy Agency Coordinated Research Projects ACCelerated; IAEA-MMC: International Atomic Energy Agency – Mitomycine; IAR: Instituto de Oncologia Angel H. Roffo; IGR: Institut Gustave Roussy; im: intramuscular; ind: Induction; INRC-HN: Instituto Nazionale per la Ricerca sul Cancro-Head and Neck; INT: US INTer group trial; iv: intravenous; KBN=Komiet Badan Naukowych; KROG: Korean Radiation Oncology Group; L: Larynx; LA: Leucovorin; LOHNG: Ljubljana Oncology Head and Neck Group; MCW: Medical College of Wisconsin; MD: Missing Data; MDA: MD Anderson; Mi: Mitomycin; Mp: Mercaptopurine; Mx: Methotrexate; NA: Not Applicable; NCI-V: National Cancer Institute; NP: Nasopharynx; NRH: Norwegian Radium Hospital; O: Other; OC: Oral Cavity; OP: Oropharynx; ORO: Oropharynx; Pa: Paclitaxel; pCAIR: post-operative Continuous Accelerated Irradiation (CAIR); Pm: Porfiromycin; PMH: Princess Margaret Hospital; PMHCGS: Princess Margaret Hospital Cooperative Group Study; po: per os; POPART: Post-Operative Accelerated RadioTherapy; RPC: Research Program Committee; RT: Radiotherapy; RTOG: Radiation Therapy Oncology Group; S: Surgery; SAKK: Swiss Group for Clinical Cancer Research; sc: split course; SECOG: South of England Co-operative Oncology Group; SHNG: Scandinavian Head and Neck Group; SWOG: SouthWest Oncology Group; Tg: Tegafur; TMH: Tata Memorial Hospital; TROG: Trans-Tansman Radiation Oncology Group; TTCC: Tratamiento de Tumores de Cabeza y Cuello; tid: thrice daily; U: Unknown primary; UKHAN: United Kingdom Head And Neck; UPCI: University of Pittsburgh Cancer Institute; UW: University of the Witwatersrand; Vc: Vincristine; Vd: Vindesine; Vc: Vincristine; wks: weeks

B- Description of trials with concomitant chemotherapy

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
MACH-NC 1										
ECOG 2382[33]	1982–87	OC, OP, HP, L, NP, O	I-IV	C	20 mg/m^2, wks$_{1\text{-}7 \text{ or } 8}$	RT	68-76 Gy/7-8 wks	371/371	15.3	CLRT$_P$ vs LRT
Ontario[51]	1987–91	OC, OP, HP, L	III, IV	F	1200 mg/m² x 3, wks$_{1,3}$	RT	66 Gy/6.5 wks	175/175	5.7	CLRT$_{noP}$ vs LRT
Kragujevac1[39]	1988–91	OC, OP, HP, L, NP	III, IV	Arm$_1$: C Arm$_2$: Cb	6 mg/m^2 x 5, wks$_{1\text{-}7}$ 25 mg/m^2 x 5, wks$_{1\text{-}7}$	RT	70 Gy/7-7.5 wks	159/159	4.8	CLRT$_P$ vs LRT
Bavaria-89[30]	1989–93	OC, OP, HP, L	III, IV	C F LA	60 mg/m^2, wks$_{1,4,7}$ 350 mg/m^2 x 1 bolus + x 5 ci, wks$_{1,4,7}$ 50 mg/m^2 bolus +100 mg/m^2 x 5 ci, wks$_{1,4,7}$	RT	70.2 Gy/7.3 wks, bid, sc	298/298	1.6	CLRT$_P$ vs LRT
LOHNG-91[48]	1991–93	OC, OP, HP, O	III, IV	B Mi dicoumarol	5 U x 2, wks$_{1\text{-}7}$ 10-15 mg/m^2 , wks$_{1\text{-}7}$	RT	66-70 Gy/6.5-7 wks	64/64	11.0	CLRT$_{noP}$ vs LRT
Yale-80[53]	1980–86	OC, OP, HP, NP, L	II-IV	Mi	15 mg/m², wks$_{1,7}$	RT S + RT/RT + S	> 56 Gy > 50 Gy	120/120	12.9	CLRT$_{noP}$ vs LRT
PMHCGS[117]	1982–86	HP, L	I-IV	F (ci) Mi	1000 mg/m^2 d$_{1\text{-}4}$, wks$_{1,7}$ 10 mg/m^2, wks$_{1,7}$	RT	50 Gy/4 wks (Co) 50 Gy/8 wks, sc (Ex)	212/212	10.0	CLRT$_{noP}$ vs LRT
Toulouse[118]	1984–88	OC, OP, HP, L, O	I-IV	C	50 mg x 1, wks$_{1\text{-}7 \text{ or } 9}$	S + RT	54-70 Gy/6.5-8 wks	90/90	8.9	CLRT$_P$ vs LRT
CH-7401[119]	1985–90	OC, OP, HP, L, O	II-IV	F C	1000 mg/m^2 x4, wks$_{1\ 5,ci}$ 100 mg/m^2, wks$_{1,5}$	RT S + RT	≥69 Gy/≥6.5, bid, sc 54-60 Gy/5.5-6 wks, bid, sc	62/62	5.9	CLRT$_P$ vs LRT
Yale-86[54]	1986–92	OC, OP, HP, L, NP, O	I-IV	Mi dicoumarol	15 mg/m², wks$_{1,7}$	RT or S + RT or RT + S	> 56 Gy > 50 Gy	83/83	6.1	CLRT$_{noP}$ vs LRT
INRC HN-8[37]	1987–90	OC, OP, HP, L, NP	II-IV	F C	200 mg/m^2 x 5, wks$_{1,4,7,10}$ 20 mg/m^2 x 5, wks$_{1,4,7,10}$	RT alt	70 Gy/7 wks (Co) 60 Gy/8 wks, alt (Ex)	157/157	5.1	CLRT$_P$ vs LRT
MACHN-NC2										
RPC 3250[41]	1990-95	OC, OP, HP, L	III, IV	C (ci) F (ci)	20 mg/m² x 4, wks$_{1,4}$ 1000 mg/m² x 4, wks$_{1,4}$	RT	68-72 Gy/7-8 wks	100/100	8.8	CLRT$_P$ vs LRT
Duke 90040[104]	1990-96	OC, OP, HP, L, NP, O	II-IV	C F	12 mg/m² x 5, wks$_{1,6}$ 600 mg/m² x 5, wks$_{1,6}$	RT	75 Gy/6 wks, bid 70 Gy/7 wks, sc, bid (Ex)	120/122	NA	
Kragujevac2[106]	1991-93	OC, OP, HP, L, NP	III, IV	C	6 mg/m² x 5, wks$_{1\text{-}7}$	RT	77 Gy/7 wks, bid	130/130	6.5	HFCRT vs HFRT

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
IAR-92[105]	1992-95	OC, OP, HP, L, O	III, IV	C F FA	20 mg/m²x 4, $wks_{1,4,7,10}$ 300 mg/m² x 4, $wks_{1,4,7,10}$ 20 mg/m² x 4, $wks_{1,4,7,10}$		79.2 Gy/6.5 wks, bid (Co) 80 Gy/9 wks, bid, alt (Ex)	68/68	8.3	HFCRT vs HFRT
Int 0126[38]	1992-99	OC, OP, HP, L	III, IV	C (Ex1) C (Ex2) F (Ex2)	100 mg/m², $wks_{1,4,7}$ 75 mg/m², $wks_{1,5,9}$ 1000 mg/m² x 4, $wks_{1,5,9}$	RT	70 Gy /7 wks (Co, Ex 1) 60-70 Gy/11-12 wks, sc (Ex2)	295/295	11.0	$CLRT_P$ vs LRT
RTOG 9111[42]	1992-2000	OP, L, O	II-IV	C	100 mg/m², $wks_{1,4,7}$	RT	70 Gy/7 wks	366/367	12.2	$CLRT_P$ vs LRT
GORTEC 9401[35]	1994-97	OP	III, IV	Cb F	70 mg/m²x 4, $wks_{1,4,7}$ 600 mg/m²x 4, $wks_{1,4,7}$	RT	70 Gy/ 7 wks	226/226	5.3	$CLRT_P$ vs LRT
ARO 95-06[108]	1994-99	OC, OP, HP	III, IV	Mi F	10 mg/m², $wks_{1,6}$ 600 mg/m² x 5, wk_1	RT	77.6 Gy/ 6 wks, bid (Co) 70.6 Gy/ 6 wks, bid (Ex)	384 /384	8.8	ACRT vs HFRT
EORTC 22931[34]	1994-2000	OC, OP, HP, L	I-IV	C	100 mg/m² $wks_{1,4,7}$	S + RT	66 Gy/6.5 wks	334/334	5.0	$CLRT_P$ vs LRT
SAKK 10-94[107]	1994-2000	OC, OP, HP, L	II-IV	C	20 mg/m² x 5, $wks_{1,5}$	RT	74.4 Gy/6.5 wks, bid	224/224	9.7	HFCRT vs HFRT
Cologne 95[109]	1995-99	OP, HP	II-IV	Cb F	70 mg/m² x 5, $wks_{1,4}$ 600 mg/m² x 5, $wks_{1,4}$	RT	69.9 Gy / 5.5 wks, b	263/263	4.7	ACRT vs MART
HeCOG 9405[36]	1995-99	OC, OP, HP, L	II-IV	C (Ex1) Cb (Ex2)	100 mg/m², wks $_{1,4,7}$ AUC 7, wks $_{1,4,7}$	RT	70 Gy / 7.5 wks	128/128	14.4	$CLRT_P$ vs LRT
RTOG 9501[43]	1995-2000	OC, OP, HP, L, O	I-IV	C	100 mg/m² $wks_{1,4,7}$	S + RT	60 Gy/ 6 wks	459/459	10.2	$CLRT_P$ vs LRT
IAEA-MMC[47]	1996-99	OC, OP, HP, L	III, IV	Mi	15 mg/m² d_5	RT	66 Gy /6.5 wks	478/478	2.8	$CLRT_{noP}$ vs LRT
GORTEC 9601[110]	1996-2000	OC, OP, HP, L, O	IV	C F	100 mg/m², wks $_{1,3,5}$ 1000 mg/m² x 5, wks $_{1,5}$	RT	62 Gy/ 3 wks, bid (Co) 62 Gy/ 5 wks, bid, sc (Ex)	109/109	10.9	ACRT vs VART
NCI-V98-1416[50]	1997-2000	OC, OP, HP, L	II-IV	Pm	40 mg/m², $wks_{1,7}$	RT	70 Gy/ 7 wks	393/393	0.9	$CLRT_{noP}$ vs LRT
MACH-NC 3										
LOHNG-97[49]	1997-2001	OC, OP, HP, L, O	III, IV	B Mi	5 mg twice-a-week during RT 15 mg/m², wk_2	S + RT	56-70 Gy / 5.5-7 wks	114/114	15.4	$CLRT_{noP}$ vs LRT
Torino 85[99]	1985-90	OC, OP, HP, L, NP, O	III, IV	$\underline{Arm_1}$: B C Mx Vc $\underline{Arm_2}$: Arm_1 + C	ind: 10 U/m² $d_{1,8,15,22,29,36}$ ind: 50 mg/m² $d_{4,22}$ ind: 40 mg/m² $d_{1,15,22,36}$ ind: 2 mg/m² $d_{1,8,15,22,29,36}$ conco: 5 mg/m² daily during RT	RT	60 Gy/7wks	108/108	7.2	IC_{other}-$CLRT_P$ vs IC_{other}-LRT

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
Créteil 85[100]	1987-90	OC, OP, HP, L	II-IV	$\underline{Arm_1}$: C F (ci) $\underline{Arm_2}$: Arm_1 + C F (im)	ind: 100 mg/m², wks $_{1,4,7}$ ind: 1000 mg/m² x 5, wks $_{1,4,7}$ conco: 50 mg/m² $d_{1,15,29,43}$ conco: 5 mg/kg , three time a week during RT	RT	70 Gy/8 wks	56/57	5.3	IC_{PF}-$CLRT_P$ vs IC_{PF}-LRT
Torino 92[44]	1992-95	OC, OP, HP, L	III, IV	Cb	45 mg/m² x 5, $wk_{1,3,5,7}$	RT	70 Gy/7 wks	151/164	13.6	$CLRT_P$ vs LRT
AIIMS 2003[29]	2003-05	OP, NP	III, IV	C	40 mg/m², wk_{1-7}	RT	70 Gy/7 wks	176/176	3.0	$CLRT_P$ vs LRT
BiRCF[103]	1997-2002	OC, OP, HP, L	III, IV	C F F	100 mg/m², wks $_{1,4,7}$ 750 mg/m² x 5, wks $_{1}$ 430 mg/m² x 5, $wks_{4,7}$	RT	80.4 Gy/7 wks, bid	171/171	6.6	HFCRT vs HFRT
FCRT 94[32]	1994-2002	OP, HP, L	I–IV	Cb	50 mg/m² $d_{1,3}$ weekly during RT	S + RT	54 Gy/6.5 wks or 72 Gy/8 wks	144/146	8.9	$CLRT_P$ vs LRT
UPCI 93-99[46]	1994-2002	OP, HP, L	III, IV	Cb	100 mg/m² weekly during RT	S + RT	59.4 Gy/6.5 wks	76/76	6.2	$CLRT_P$ vs LRT
MARCH 2										
RTOG 0129[89]	2002-05	OC, OP, HP, L	II-IV	C	100 mg/m², wks $_{1,4\pm7}$	RT	70 Gy/7 wks 72 Gy/6 wks, bid for 12 fractions	738/743	7.9	ACRT vs $CLRT_P$
EORTC 22843[88]	1984-87	OC, OP, HP, L, O	III, IV	C	6 mg/m²/d Or 10mg/m² x 5, wks $_{1,4,7}$	RT	70 Gy/7 wks 72 Gy/7 wks, sc, three times per day on wk 1, 4 and 7	53	5.0	ACRT vs $CLRT_P$
CONDOR[87]	2009-12	OC, OP, HP, L	III, IV	C	40 mg/m², wks $_{1-6}$	RT	70 Gy/7 wks 70 Gy/6 wks, 6 times per wk	56	2.8	ACRT vs $CLRT_P$
INRC-HN-9[85]	1992-98	OC, OP, HP, L	III, IV	C	20 mg/m²/d, wks $_{1,4,7,10}$	RT	60 Gy/6 wks, sc 75 Gy/6 wks, bid for 2 wks	136	18.5	HFRT vs $CLRT_P$

Abbreviations: see under web-table 3-A.

C- Description of trials with adjuvant chemotherapy

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ Randomised	Median follow-up (years)	Treatment comparison
MACH-NC 1										
GETTECadj[74]	1982–85	OC, OP, HP, L, NP	I-IV	B B (im) C Mx	15 mg x3, $wks_{1, 4, 7}$ then 15 mg $d_{1,15}$, monthly x 5 150 mg, $wks_{1, 4, 7}$ 100 mg, $wks_{1, 4, 7}$, then monthly x 5	S + RT	50 Gy/5 wks	286/286	8.9	LRT-AC vs LRT
Int 0034[76]	1984–89	OC, OP, HP, L, NP	II- IV	C F	100 mg/m^2, $wks_{1, 4, 7}$ 1000 mg/m^2 x 5, $wks_{1, 4, 7}$	S + RT	50-54 Gy/5-6wks	499/499	8.2	LRT-AC vs LRT
JHCFUS[77]	1985–86	OC, OP, HP, L, NP, O	I-IV	Hc (po)	300–600 mg x 84 d+	S	NA	191/191	2.9	LRT-AC vs LRT
TMH R4[79]	1986–89	OC	III, IV	Mx	50 mg/m^2 $d_{3,10,17}$ post-operative	S	NA	135/135	1.3	LRT-AC vs LRT
KKD-86[78]	1986–89	OC	I-IV	U (po)	400 mg d_{1-365}	S	NA	112/112	6.9	LRT-AC vs LRT
HNU-87a[75]	1987–90	OC, OP. HP, L, NP	I-IV	U (po)	300 mg d_{1-365}	RT	MD	111/111	4.1	LRT-AC vs LRT
HNU-87b[75]	1987–90	OC, OP, HP, L, NP	II-IV	U (po)	300 mg d_{1-365}	S	NA	424/424	4.2	LRT-AC vs LRT

Abbreviations: see under web-table 3-A.

D- Description of trials with two timing of chemotherapy: induction versus concomitant

Trial	Inclusion period	Sites	Stage	Timing	Drug	Chemotherapy	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
SECOG I[96]	1980-84	OC, OP, L, O	III, IV	$\underline{Arm_1}$: CT-CT-RT-CT-CT $\underline{Arm_2}$: (CT-RT) x3 - RT	B Mx LA LA (im) Vc	30 mg 200 mg 50 mg 45 mg 2 mg	60-66 Gy/6.5 wks 60-66 Gy/8 wks alt	267/270	19.8	$CLRT_{noP}$ vs IC_{other}-LRT
Brescia[94]	1981-83	OC, OP, HP, NP	III, IV	$\underline{Arm_1}$: CT-CT-CT-CT-RT $\underline{Arm_2}$: RT1-CT-CT-CT-CT-RT2	B Hu (po) Mx LA	15 mg/m² 6000 mg/m² 50 mg/m² 45 mg/m²	64 Gy/4 wks 60 Gy sc	55/56	8.2	$CLRT_{noP}$ vs IC_{other}-LRT
INRC-HN-7[95]	1983-86	OC, OP, HP, L, NP	III, IV	$\underline{Arm_1}$: CT-CT-CT-CT-RT $\underline{Arm_2}$: CT - (CT-RT) x3	B (im) Vb Mx LA	30 U, d_1 6 mg/m², d_1 200 mg, d_2 45 mg, d_3	60-70 Gy 60 Gy, alt	116/116	4.3	$CLRT_{noP}$ vs IC_{other}-LRT
ICC-PCP[92]	1984-91	OC, OP, HP, L, NP, O	III, IV	$\underline{Arm_1}$: CT-CT-CT-RT $\underline{Arm_2}$: (CT-RT) x7	$\underline{Arm_1}$: C F $\underline{Arm_2}$: C F	100 mg/m², d_1 1000 mg/m² x 5 60 mg/m², d_1 800 mg/m² x 5	70 Gy/7 wks 70Gy/13 wks, alt	215/215	6.0	$CLRT_P$ vs IC_{PF}-LRT
CMGH-85[90]	1985-88	OC, OP, HP, NP	II-IV	$\underline{Arm_1}$: CT-CT-CT-RT $\underline{Arm_2}$: CRT-CT-CRT-CT	$\underline{Arm_1}$: C F $\underline{Arm_2}$:	100 mg/m², d_1 1000 mg/m² x 5	60 Gy 60 Gy, sc	48/48	5.8	$CLRT_P$ vs IC_{PF}-LRT

Trial	Inclusion period	Sites	Stage	Timing	Drug	Chemotherapy	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
					C F	75 mg/m², d_1 800 mg/m² x 5				
EORTC 24954[91]	1996-2004	HP, L	II-IV	Arm$_1$: CT-RT Arm$_2$: (CT-RT) x3 - CT	Arm$_1$: C F Arm$_2$: C F	 100 mg/m², d_1 1000 mg/m² x 5 20 mg/m² x 5 200 mg/m² x 5	Arm$_1$: 70 Gy/7 wks Arm$_2$: 20 Gy/2 wks x3	450/450	9.0	$CLRT_P$ vs IC_{PF}-LRT

Abbreviations: see under web-table 3-A.

E- Description of trials without chemotherapy

Trial	Inclusion period	Sites	Stage	Locoregional treatment	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
MARCH 1								
BCCA 9113[8]	1991-95	OC, OP, HP, L	III-IV	RT	66 Gy/6.5 wks 66 Gy/3.5 wks, bid	82/82	18.4	MART vs LRT
CAIR[9]	1994-96	OC, OP, HP, L	II-IV	RT	70 Gy/7wks 66-70 Gy/4.7-5 wks, 7 times per wk	100/100	5.7	MART vs LRT
CHART[23]	1990-95	OC, OP, HP, L, O	I-IV	RT	66 Gy/6.5 wks 54 Gy/1.7 wks, tid	918/918	8.2	VART vs LRT
DAHANCA 6&7[10]	1991-99	OC, OP, HP, L, O	I-IV	RT	66-70 Gy/6.5-7 wks 66-70 Gy/5.5-6 wks, 6 times per wk	1481/1485	14.6	MART vs LRT
EORTC 22791[2]	1980-87	OP	II-IV	RT	70 Gy/7 wks 80.5 Gy/7 wks, bid	356/356	10.3	HFRT vs LRT
EORTC 22851[11]	1985-95	OC, OP, L, O	II-IV	RT	70 Gy/7 wks 72 Gy/5 wks, sc	512/512	4.9	MART vs LRT
GORTEC 9402[24]	1994-98	OC, OP, HP, L	III-IV	RT	70 Gy/7wks 62-67 Gy/3-3.4 wks, bid	268/268	8.8	VART vs LRT
KBN PO 79[14]	1995-98	L	I-III	RT	66 Gy/6.5 wks 66 Gy/5.5 wks,6 times per wk	395/395	4.2	MART vs LRT
PMH-Toronto[3]	1988-95	OP, HP, L	II-IV	RT	51 Gy/4 wks 58 Gy/4 wks, bid	336/336	17.5	HFRT vs LRT
Rio 1986[4]	1986-89	OC, OP, L	III-IV	RT	66 Gy/6.6 wks 70.4 Gy/6.4 wks, bid	103/112	8.8	HFRT vs LRT
TROG 9101[25]	1991-98	OC, OP, HP, L	III-IV	RT	70 Gy/7 wks 59.4 Gy/3.3 wks, bid	350/350	6.6	VART vs LRT

Trial	Inclusion period	Sites	Stage	Locoregional treatment	Radiotherapy	Patients analysed/ randomised	Median follow-up (years)	Treatment comparison
MARCH 2								
Cairo 1990[22]	1990-97	OC, OP, HP, L	II-IV	S + RT	60 Gy/6 wks 46.2 Gy/2 weeks, tib, 6 times per wk	70/70	3.8	VART vs LRT
CRT 90-002[16]	1991-96	OC, OP, HP, L	II-IV	S + RT	63 Gy/7 wks 63 Gy/5 wks, bid 2 wks	151/151	13.8	MART vs LRT
Osaka 1993[18]	1993-2000	L	I	RT	60-66 Gy/6-6.6 wks 56.25-63 Gy/5-5.6 wks	189/189	5.9	MART vs LRT
INRC-HN-10[13]	1994-2001	OC,OP,HP,L	I-IV	S + RT	60 Gy/6 wks 64Gy/5 wks, bid 2 wks	226/226	4.5	MART vs LRT
RTOG 9512[6]	1996-2003	L	II-IV	RT	70 Gy/7 wks 79.2 Gy/6.5 wks, bid	249/250	8.5	HFRT vs LRT
ARTSCAN[7]	1998-2006	OC,OP,HP,L	I-IV	RT	68 Gy/6.5-7 wks 68 Gy/4.5 wks, bid 4 wks	750/750	9.1	MART vs LRT
IAEA-CRP-ACC[12]	1999-2004	OC,OP,HP,L	I-IV	RT	66-70 Gy/6.5-7 wks 66-70 Gy/5.5-6 wks, 6 times per wk	906/908	5.9	MART vs LRT
DAHANCA 9[1]	2000-06	OP,HP,L	I-IV	RT	66 Gy/5.5 wks 76 Gy/5.5 wks, bid	77/77	4.2	HFRT vs LRT
CHARTWEL (unpublished)	2001-05	OC,OP,HP,L,O	I-IV	S + RT	60-64 Gy/6-6.5 wks 51-54 Gy/2.4 wks, tid	114/NA	4.8	VART vs LRT
pCAIR[19]	2001-04	OC,OP,L	I-IV	S + RT	63 Gy/7 wks 63 Gy/5 wks, 7 times per wk	279/279	7.2	MART vs LRT
KROG 0201[15]	2002-10	L	I-II	RT	66-70 Gy/6.5-7 wks 63-67.5 Gy/5.5-5 wks	156/156	5.3	MART vs LRT
POPART[20]	2003-08	OC,OP,HP,L,O	I-IV	S + RT	66 Gy/6.5 wks 66 Gy/5 wks, bid 3 wks	148/148	6.3	MART vs LRT

Abbreviations: see under web-table 3-A.

F- Description of multi-arm trials

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ Randomised	Median follow-up (years)	Treatment comparison
AC Camargo[28]	1984–86	OC, OP, HP	III, IV	B C Mi Vb B C	10 mg/m², $wks_{1 \pm 2}$ 30 mg/m² x 2, $wks_{1 \pm 2}$ 8 mg/m², $wks_{1 \pm 2}$ 4 mg/m², $wks_{1 \pm 2}$ 5 mg x 2, $wks_{1,4,7}$ of RT 20 mg/m² x 2, $wks_{1,4,7}$ of RT	RT	70 Gy/7 wks (Co) or 8 wks (Ex)	90/90	6.5	IC_{other}-LRT vs $CLRT_P$ vs LRT
EORTC 22954 (unpublished)	1996-99	L, HP	II-IV	C	100 mg/m², $wks_{1,4,7}$	RT	70 Gy/7 wks 70 Gy/7 wks, bid	59/59	4.5	CLRTP vs LRT HFCRT vs HFRT
EORTC-22962 (unpublished)	1996-99	OC, OP, HP, L	II-IV	C	100 mg/m², $wks_{1,4,7}$	RT	70 Gy/ 7 wks 80.5 Gy/ 7 wks, bid	57/57	4.4	$CLRT_P$ vs LRT vs HFCRT vs HFRT
GORTEC 9902[86]	2000-07	OC, OP, HP, L, O	III, IV	Cb F	10 mg/m² x 4, $wks_{1,4,7}$ 600 mg/m² x 4, $wks_{1,4,7}$	RT	70 Gy/7 wks 70 Gy/7 wks, bid(2wks) 64.8 Gy/3.5 wks, bid	840/840	5.2	ACRT vs VART vs $CLRT_P$
Lucknow 95[40]	1995–99	OC, OP, HP, L, O	III, IV	C	35 mg/m² d_1, wks_{1-7}	RT	70 Gy/7 wks	300/300	13.0	IC_{other}-LRT vs $CLRT_P$ LRT
ORO-9301[17]	1993-98	OP	II-IV	Cb F	75 mg/m2x 4, wks1,5,9 1000 mg/m²x 4, $wks_{1,5,9}$	RT	66-70 Gy/6.6-7 wks 64-67.2 Gy/6.5 wks, bid, sc	192/192	6.9	$CLRT_P$ vs MART vs LRT

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ Randomised	Median follow-up (years)	Treatment comparison
RTOG 9003[5]	1991-97	OC, OP, HP, L, O	II-IV	/	/	RT	70 Gy/7 wks 81.6 Gy/6.8 wks, bid 67.2 Gy/6 wks, bid, sc 72 Gy/6 wks, bid (12 fractions)	1113/1113	16.7	HFRT vs MART vs LRT
SECOG II (unpublished)	1984–89	OC, OP, HP, L, NP, O	III, IV	B (im) Mx LA (iv) LA (im) Vc Or the same + F	30 mg, $wks_{1,3,13,15}$ 200 mg, $wks_{1,3,13,15}$ 50 mg, $wks_{1,3,13,15}$ 15 mg x 6, $wks_{1,3,13,15}$ 1.5-2 mg, $wks_{1,3,13,15}$ 500 mg, $wks_{1,4,6,9}$	RT alt	60-66 Gy/6.5 wks (Co) 60-66 Gy/8 wks, sc (Ex)	239/239	12.5	IC_{other}-LRT vs $CLRT_{noP}$ LRT
TMH 1114[21]	2000–2008	OP, HP, L	II–IV	C	30 mg/m² wks_{1-7}	RT	66-70 Gy/6-7 wks 66-70 Gy/5.5-6 wks, 6 times per wk	199/NA	4.5	$CLRT_P$ vs MART vs LRT
TTCC 2002[83,84]	2002–07	OC, OP, HP, L	III, IV	Arm2: Do C F (ci) Arm3: C F (ci) C (3 arms)	 ind: 75 mg/m², $wks_{1,4,7}$ ind: 75 mg/m², $wks_{1,4,7}$ ind: 750 mg/m² x 5, $wks_{1,4,7}$ ind: 100 mg/m², $wks_{1,4,7}$ ind: 1000 mg/m² x 5, $wks_{1,4,7}$ conco: 100 mg/m², $wks_{1,4,7}$ of RT	RT	70 Gy/7 wk	387/387	5.0	IC_{TPF}-$CLRT_P$ vs IC_{PF}-$CLRT_P$ vs $CLRT_P$
UKHAN[27]	1990-2000	OC, OP, HP, L, NP, O	I-IV	Vc	1.4 mg/m², $wks_{1,3,+5,7,or\ 8,10}$ 30 mg im, $wks_{1,3,+5,7,or\ 8,10}$	RT	60 Gy/6 wks, alt	966/970	10.1	LRT-AC vs

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analysed/ Randomised	Median follow-up (years)	Treatment comparison
				B (im) Mx F, alt Mx	100 mg/m², $wks_{1,3,+5,7,or\ 8,10}$ 500 mg/m², $wks_{1,3,+5,7,or\ 8,10}$ 100 mg/m², $wks_{1,3,+5,7,or\ 8,10}$	S + RT	50-55Gy/3-4 wks			$CLRT_{noP}$-AC vs $CLRT_{noP}$ vs LRT
Vienna[26]	1990-97	OC, OP, HP, L	II-IV	Mi	20 mg/m² d_5	RT	55 Gy/2.5 wks, bid(Co)	239/239	7.9	ACRT vs VART vs LRT

Abbreviations: see under web-table 3-A.

Web-Table 4 – League table presenting the results hazard ratio with their 95% confidence interval of the network meta-analysis (random effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for overall survival.

HFCRT (1) 5y-AB: 16.7%				0.67* [0.25-1.78]	0.74 [0.63-0.88]						0.65* [0.24-1.72]				
0.91 [0.68-1.22]	**IC_{TaxPF}-LRT (2)** 5y-AB: 13.4%						0.72 [0.59-0.88]				0.85* [0.57-1.25]				
0.84 [0.67-1.05]	0.92 [0.72-1.17]	**ACRT (3)** 5y-AB: 10.4%		1.00 [0.87-1.14]	0.80* [0.64-1.00]			0.91 [0.78-1.06]		0.75* [0.56-1.00]	0.76* [0.54-1.08]				
0.83 [0.63-1.11]	0.92 [0.69-1.22]	1.00 [0.79-1.25]	**IC_{TaxPF}-CLRT (4)** 5y-AB: 10.3%	1.03 [0.72-1.46]		0.84* [0.56-1.26]			0.83 [0.64-1.09]						
0.82 [0.66-1.01]	0.90 [0.72-1.12]	0.97 [0.86-1.10]	0.98 [0.81-1.19]	**$CLRT_P$ (5)** 5y-AB: 9.5%	0.82 [0.58-1.16]		0.91 [0.73-1.15]	0.86* [0.71-1.05]	1.01 [0.75-1.36]	0.72 [0.52-0.99]	0.75 [0.68-0.84]				0.78 [0.51-1.20]
0.74 [0.62-0.88]	0.82 [0.64-1.03]	0.89 [0.77-1.03]	0.89 [0.71-1.11]	0.91 [0.80-1.03]	**HFRT (6)** 5y-AB: 6.1%					0.95* [0.82-1.10]	0.83 [0.74-0.93]				
0.70 [0.56-0.88]	0.77 [0.61-0.98]	0.84 [0.72-0.98]	0.85 [0.68-1.04]	0.86 [0.77-0.97]	0.95 [0.82-1.10]	**CLRTnoP (7)** 5y-AB: 4.2%					0.90 [0.82-0.99]	0.74* [0.58-0.96]	0.77* [0.60-1.00]		0.84 [0.66-1.08]
0.70 [0.56-0.87]	0.77 [0.63-0.93]	0.83 [0.71-0.97]	0.84 [0.67-1.04]	0.85 [0.76-0.95]	0.94 [0.81-1.09]	0.99 [0.86-1.13]	**IC_{PF}-LRT (8)** 5y-AB: 3.8%		1.07* [0.58-1.99]		0.90 [0.81-0.99]				
0.70 [0.55-0.88]	0.77 [0.60-0.97]	0.83 [0.72-0.96]	0.83 [0.67-1.04]	0.85 [0.75-0.96]	0.94 [0.80-1.09]	0.99 [0.85-1.15]	1.00 [0.86-1.16]	**VART (9)** 5y-AB: 3.7%			0.95 [0.85-1.07]				
0.70 [0.51-0.94]	0.77 [0.57-1.04]	0.83 [0.65-1.07]	0.84 [0.71-0.99]	0.85 [0.69-1.07]	0.94 [0.73-1.21]	0.99 [0.78-1.26]	1.00 [0.79-1.27]	1.00 [0.78-1.29]	**IC_{PF}-CLRT (10)** 5y-AB: 3.8%						
0.67 [0.54-0.83]	0.74 [0.59-0.92]	0.80 [0.70-0.92]	0.80 [0.65-0.99]	0.82 [0.74-0.90]	0.90 [0.80-1.02]	0.95 [0.84-1.07]	0.96 [0.85-1.08]	0.96 [0.84-1.10]	0.96 [0.76-1.22]	**MART (11)** 5y-AB: 2.3%	0.93 [0.85-1.03]				
0.63 [0.51-0.77]	0.69 [0.56-0.85]	0.75 [0.66-0.85]	0.75 [0.62-0.92]	0.77 [0.72-0.83]	0.85 [0.76-0.95]	0.89 [0.81-0.98]	0.90 [0.82-0.99]	0.90 [0.81-1.01]	0.90 [0.72-1.13]	0.94 [0.87-1.01]	**LRT (12)** 5y-AB: ref	0.99 [0.86-1.14]	0.94* [0.74-1.18]		0.97 [0.86-1.10]
0.61 [0.48-0.78]	0.67 [0.53-0.87]	0.73 [0.61-0.88]	0.74 [0.58-0.93]	0.75 [0.65-0.87]	0.83 [0.69-0.98]	0.87 [0.74-1.02]	0.88 [0.75-1.04]	0.88 [0.74-1.05]	0.88 [0.68-1.14]	0.92 [0.79-1.07]	0.97 [0.85-1.11]	**LRT-AC (13)** 5y-AB: -0.9%	1.04* [0.81-1.33]		
0.59 [0.43-0.81]	0.65 [0.47-0.90]	0.71 [0.54-0.93]	0.71 [0.52-0.97]	0.72 [0.56-0.93]	0.80 [0.61-1.04]	0.84 [0.65-1.08]	0.85 [0.65-1.10]	0.85 [0.65-1.11]	0.85 [0.61-1.18]	0.88 [0.69-1.14]	0.94 [0.74-1.20]	0.96 [0.75-1.24]	**$CLRT_{noP}$-AC (14)** 5y-AB: -2.3%		
0.55 [0.33-0.90]	0.60 [0.36-0.99]	0.65 [0.41-1.05]	0.66 [0.40-1.08]	0.67 [0.42-1.06]	0.74 [0.46-1.18]	0.78 [0.49-1.23]	0.78 [0.49-1.25]	0.79 [0.49-1.26]	0.78 [0.47-1.30]	0.82 [0.51-1.30]	0.87 [0.55-1.37]	0.89 [0.55-1.43]	0.93 [0.55-1.55]	**IC_{other}-CLRT (15)** 5y-AB: -5.1%	1.11* [0.73-1.68]
0.61 [0.48-0.77]	0.67 [0.52-0.85]	0.72 [0.61-0.85]	0.73 [0.58-0.91]	0.74 [0.65-0.85]	0.82 [0.70-0.96]	0.86 [0.76-0.98]	0.87 [0.75-1.01]	0.87 [0.74-1.02]	0.87 [0.68-1.12]	0.91 [0.79-1.04]	0.96 [0.86-1.08]	0.99 [0.83-1.18]	1.03 [0.79-1.34]	1.11 [0.71-1.72]	**IC_{other}-LRT (16)** 5y-AB: -1.4%

* comparison with only one trial

As a convention the cells contain the hazard ratio of the treatment with the lower number compared to the treatment with the higher number. For example the cell that joins treatments 1 (HFCRT) and 5 ($CLRT_P$) gives the hazard ratio of treatment 1 vs. 5 (HFCRT vs. $CLRT_P$).

Hazard ratio: global Cochran Q statistic p=0.07, heterogeneity (within design) p=0.01, inconsistency (between designs) p=0.91.

Results are highlighted in grey if they are statistically significant.

LRT=loco-regional treatment, CT=chemotherapy, RT=radiotherapy, CLRT=LRT with concomitant chemoradiotherapy, IC=induction CT, AC=adjuvant CT, HFRT=hyperfractionated RT, HFCRT=HFRT with concomitant CT, MART=moderately accelerated RT, VART=very accelerated RT, ACRT=accelerated RT with concomitant CT, P=platin-based CT, noP=not platin-based CT, TaxPF=taxanes, platin and 5-Fluorouracile association, PF=platin and 5-Fluorouracile association, 5y-AB=5 years – Absolute Benefit compared to RT alone

Web-Table 5 – Summary of results from direct comparisons and network meta-analysis for overall survival and event-free survival corresponding to comparisons presented in Figure 2.

	Overall survival				Event-free survival			
Comparison	**Nb of event/Nb of patients**		**HR**	**95% CI**	**Nb of event/Nb of patients**		**HR**	**95% CI**
	experimental	**control**			**experimental**	**control**		
HFCRT vs HFRT								
BiRCF	69/85	73/86	0.75	[0.54-1.05]	71/85	77/86	0.68	[0.49-0.94]
Duke 90040	54/60	58/60	0.80	[0.55-1.17]	54/60	58/60	0.79	[0.54-1.16]
EORTC 22954	5/12	5/13	1.19	[0.34-4.12]	5/12	7/13	0.89	[0.28-2.81]
EORTC 22962	8/15	7/13	0.53	[0.17-1.64]	9/15	10/13	0.38	[0.14-1.03]
IAR 92	34/45	20/23	0.70	[0.39-1.25]	37/45	22/23	0.70	[0.40-1.23]
Kragujevac2	38/65	51/65	0.57	[0.37-0.86]	38/65	51/65	0.62	[0.41-0.94]
SAKK 10-94	79/112	88/112	0.81	[0.60-1.10]	84/112	97/112	0.74	[0.55-0.99]
Fixed meta-analysis	287/394	302/372	0.74	[0.63-0.88]	298/394	322/372	0.70	[0.60-0.82]
Random meta-analysis			0.74	[0.63-0.88]			0.70	[0.60-0.82]
				I^2=0%, p=0.80				I^2=0%, p=0.86
Network meta-analysis			**0.74**	**[0.62-0.88]**			**0.71**	**[0.60-0.84]**
HFCRT vs $CLRT_P$								
EORTC 22962	8/15	9/15	0.67	[0.25-1.78]	9/15	9/15	0.81	[0.31-2.06]
Network meta-analysis			**0.82**	**[0.66-1.01]**			**0.80**	**[0.65-0.98]**
HFCRT vs LRT								
EORTC 22962	8/15	9/14	0.65	[0.24-1.72]	9/15	9/14	0.69	[0.27-1.78]
Network meta-analysis			**0.63**	**[0.51-0.77]**			**0.60**	**[0.49-0.73]**
IC_{TaxPF}-$CLRT_P$ vs IC_{PF}-$CLRT_P$								
Spain 1998	66/189	85/193	0.70	[0.51-0.97]	92/189	112/193	0.72	[0.55-0.95]
TAX 324	124/255	145/246	0.74	[0.58-0.94]	140/255	162/246	0.75	[0.60-0.94]
TTCC 2002	78/112	76/117	1.23	[0.89-1.68]	80/112	87/117	1.05	[0.77-1.42]
TTCC 2002+	28/43	27/39	0.74	[0.43-1.27]	30/43	30/39	0.67	[0.40-1.13]
Fixed meta-analysis	296/599	333/595	0.83	[0.71-0.97]	342/599	391/595	0.79	[0.69-0.92]
Random meta-analysis			0.83	[0.64-1.09]			0.80	[0.67-0.95]
				I^2=62%, p=0.05				I^2=30%, p=0.23
Network meta-analysis			**0.84**	**[0.71-0.99]**			**0.80**	**[0.68-0.94]**
IC_{TaxPF}-$CLRT_P$ vs $CLRT_P$								
Budapest 2007	26/33	20/33	1.62	[0.90-2.90]	26/33	20/33	1.62	[0.91-2.91]
GSTTC2501	62/130	61/131	0.88	[0.62-1.26]	71/130	72/131	0.86	[0.62-1.19]
TTCC 2002	78/112	69/109	1.21	[0.87-1.67]	80/112	81/109	1.01	[0.74-1.37]
TTCC 2002+	10/17	16/19	0.52	[0.24-1.13]	12/17	17/19	0.47	[0.22-0.99]
Fixed meta-analysis	176/292	166/292	1.05	[0.85-1.30]	189/292	190/292	0.95	[0.78-1.16]
Random meta-analysis			1.03	[0.72-1.46]			0.94	[0.67-1.33]
				I^2=57%, p=0.07				I^2=58%, p=0.07
Network meta-analysis			**0.97**	**[0.72-1.30]**			**0.89**	**[0.74-1.07]**

IC_{TaxPF}-LRT vs IC_{PF}-LRT								
EORTC 24971	139/177	160/181	0.71	[0.56-0.89]	145/177	165/181	0.71	[0.57-0.89]
GORTEC 2000-01	52/113	63/107	0.75	[0.52-1.09]	60/113	70/107	0.77	[0.54-1.08]
Fixed meta-analysis	191/290	223/288	0.72	[0.59-0.88]	205/290	235/288	0.73	[0.60-0.88]
Random meta-analysis			0.72	[0.59-0.88]			0.73	[0.60-0.88]
				I^2=0%, p=0.78				I^2=0%, p=0.74
Network meta-analysis			**0.77**	**[0.63-0.93]**			**0.77**	**[0.64-0.93]**
IC_{TaxPF}-LRT vs LRT								
Shanghai 2008	47/128	54/128	0.85	[0.57-1.25]	55/128	64/128	0.84	[0.59-1.20]
Network meta-analysis			**0.69**	**[0.56-0.85]**			**0.71**	**[0.59-0.87]**
ACRT vs $CLRT_P$								
CONDOR	8/29	8/27	0.94	[0.35-2.51]	10/29	9/27	1.14	[0.46-2.81]
EORTC 22843	20/27	21/26	0.80	[0.43-1.49]	21/27	22/26	0.83	[0.45-1.51]
GORTEC 9902	198/280	196/279	1.06	[0.87-1.30]	206/280	207/279	1.03	[0.85-1.25]
RTOG 0129	186/368	189/370	0.96	[0.78-1.17]	209/368	209/370	1.01	[0.83-1.22]
Fixed meta-analysis	412/704	414/702	1.00	[0.87-1.14]	446/704	447/702	1.01	[0.89-1.15]
Random meta-analysis			1.00	[0.87-1.14]			1.01	[0.89-1.15]
				I^2=0%, p=0.78				I^2=0%, p=0.92
Network meta-analysis			**0.97**	**[0.86-1.10]**			**0.96**	**[0.85-1.07]**
ACRT vs HFRT								
ARO 95-6	159/190	163/194	0.80	[0.64-1.00]	166/190	173/194	0.76	[0.62-0.85]
Network meta-analysis			**0.89**	**[0.77-1.03]**			**0.84**	**[0.74-0.97]**

HR= Hazard Ration, CI= Confidence Interval, LRT=loco-regional treatment, CT=chemotherapy, RT=radiotherapy, CLRT=LRT with concomitant chemoradiotherapy, IC=induction CT, HFRT=hyperfractionated RT, HFCRT=HFRT with concomitant CT, ACRT=accelerated RT with concomitant CT, P=platin-based CT, TaxPF=taxanes, platin and 5-Fluorouracile association, PF=platin and 5-Fluorouracile association

Web-Table 6 – League table presenting the results hazard ratio with their 95% confidence interval of the network meta-analysis (random effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for event-free survival.

Hazard ratio: global Cochran Q statistic p=0.11, heterogeneity (within design) p=0.05, inconsistency (between designs) p=0.52.

HFCRT (1) 5y-AB: 18.6%				0.81* [0.31-2.06]	0.70 [0.60-0.82]						0.69* [0.27-1.78]			
0.83 [0.63-1.10]	**IC_{TaxPF}-LRT (2)** 5y-AB: 12.2%						0.73 [0.60-0.88]				0.84* [0.59-1.20]			
0.84 [0.67-1.04]	1.01 [0.80-1.27]	**ACRT (3)** 5y-AB: 12.5%		1.01 [0.89-1.15]	0.76* [0.62-0.95]			0.84 [0.72-0.98]		0.73* [0.55-0.97]	0.72* [0.51-1.03]			
0.90 [0.69-1.18]	1.08 [0.82-1.42]	1.07 [0.87-1.33]	**IC_{TaxPF}-CLRT (4)** 5y-AB: 14.9%	0.94 [0.67-1.33]		0.71* [0.50-1.01]			0.80 [0.67-0.95]					
0.80 [0.65-0.98]	0.96 [0.78-1.18]	0.96 [0.85-1.07]	0.89 [0.74-1.07]	**$CLRT_P$ (5)** 5y-AB: 10.8%	0.76 [0.52-1.12]		0.90 [0.73-1.13]	0.86* [0.71-1.05]	1.04 [0.78-1.38]	0.67 [0.50-0.90]	0.75 [0.70-0.81]			0.78 [0.60-1.00]
0.71 [0.60-0.84]	0.85 [0.68-1.06]	0.84 [0.74-0.97]	0.79 [0.64-0.98]	0.88 [0.79-0.99]	**HFRT (6)** 5y-AB: 6.4%					0.98* [0.85-1.14]	0.82 [0.74-0.91]			
0.67 [0.54-0.84]	0.81 [0.65-1.00]	0.80 [0.69-0.93]	0.75 [0.61-0.91]	0.84 [0.75-0.94]	0.95 [0.83-1.09]	**$CLRT_{noP}$ (7)** 5y-AB: 4.5%					0.89 [0.81-0.97]	0.81* [0.63-1.04]	0.88* [0.68-1.13]	0.86 [0.73-1.02]
0.64 [0.52-0.80]	0.77 [0.64-0.93]	0.76 [0.66-0.88]	0.71 [0.58-0.88]	0.80 [0.72-0.89]	0.90 [0.79-1.04]	0.95 [0.84-1.08]	**IC_{PF}-LRT (8)** 5y-AB: 2.7%				0.94 [0.85-1.03]			
0.67 [0.54-0.84]	0.81 [0.65-1.01]	0.80 [0.70-0.92]	0.75 [0.61-0.93]	0.84 [0.75-0.95]	0.95 [0.82-1.10]	1.00 [0.87-1.15]	1.05 [0.92-1.21]	**VART (9)** 5y-AB: 4.6%			0.90 [0.80-1.02]			
0.72 [0.54-0.97]	0.87 [0.64-1.17]	0.86 [0.67-1.10]	0.80 [0.68-0.94]	0.90 [0.73-1.12]	1.02 [0.80-1.30]	1.07 [0.85-1.35]	1.13 [0.89-1.43]	1.07 [0.84-1.36]	**IC_{PF}-CLRT (10** 5y-AB: 7.0%					
0.67 [0.54-0.82]	0.80 [0.65-0.99]	0.80 [0.70-0.91]	0.74 [0.61-0.91]	0.83 [0.76-0.91]	0.94 [0.84-1.06]	0.99 [0.89-1.11]	1.04 [0.93-1.17]	0.99 [0.87-1.12]	0.93 [0.73-1.17]	**MART (11)** 5y-AB: 4.2%	0.87 [0.79-0.96]			
0.60 [0.49-0.73]	0.71 [0.59-0.87]	0.71 [0.63-0.80]	0.66 [0.55-0.80]	0.74 [0.70-0.79]	0.84 [0.76-0.93]	0.88 [0.81-0.97]	0.93 [0.85-1.02]	0.88 [0.79-0.98]	0.83 [0.66-1.03]	0.89 [0.83-0.96]	**LRT (12)** 5y-AB: ref	1.08 [0.86-1.36]	1.06* [0.84-1.33]	0.96 [0.81-1.13]
0.60 [0.47-0.77]	0.73 [0.57-0.93]	0.72 [0.60-0.86]	0.67 [0.53-0.85]	0.75 [0.65-0.88]	0.85 [0.72-1.02]	0.90 [0.77-1.05]	0.94 [0.80-1.12]	0.90 [0.75-1.07]	0.84 [0.64-1.09]	0.91 [0.77-1.06]	1.02 [0.88-1.17]	**LRT-AC (13)** 5y-AB: 0.6%	1.09* [0.85-1.40]	
0.63 [0.46-0.85]	0.75 [0.56-1.02]	0.75 [0.58-0.97]	0.70 [0.52-0.94]	0.78 [0.62-1.00]	0.89 [0.69-1.14]	0.93 [0.73-1.19]	0.98 [0.76-1.26]	0.93 [0.72-1.20]	0.87 [0.63-1.20]	0.94 [0.74-1.20]	1.05 [0.84-1.33]	1.04 [0.81-1.33]	**$CLRT_{noP}$-AC (14)** 5y-AB: 2.0%	
0.57 [0.45-0.71]	0.68 [0.54-0.86]	0.68 [0.58-0.79]	0.63 [0.51-0.78]	0.71 [0.63-0.80]	0.80 [0.69-0.93]	0.84 [0.75-0.96]	0.89 [0.77-1.02]	0.84 [0.72-0.98]	0.79 [0.62-1.01]	0.85 [0.75-0.97]	0.95 [0.86-1.07]	0.94 [0.79-1.12]	0.91 [0.70-1.17]	**IC_{other}-LRT (16)** 5y-AB: -1.7%

* comparison with only one trial; results are highlighted in grey if they are statistically significant, see web-table 2 for abbreviations and how to read this table

Web-Table 7 – League table presenting the results hazard ratio with their 95% confidence interval of the network meta-analysis (random effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for loco-regional control.

As a convention the cells contain the hazard ratio of the treatment with the lower number compared to the treatment with the higher number. For example the cell that joins treatments 1 (HFCRT) and 5 ($CLRT_P$) gives the hazard ratio of treatment 1 vs. 5 (HFCRT vs. $CLRT_P$).

Hazard ratio: global Cochran Q statistic p<0.0001, heterogeneity (within design) p <0.0001, inconsistency (between designs) p=0.0008.

HFCRT (1)				0.67* [0.19-2.36]	0.63 [0.52-0.76]						0.49* [0.15-1.65]			
0.56 [0.26-1.20]	**IC_{TaxPF}-LRT (2)**						0.78 [0.61-0.99]				1.06* [0.41-2.76]			
0.85 [0.49-1.50]	1.53 [0.77-3.03]	**ACRT (3)**		1.03 [0.74-1.45]	0.79* [0.57-1.08]			0.67 [0.52-0.87]		0.81* [0.56-1.17]	0.61* [0.43-0.86]			
0.86 [0.45-1.66]	1.54 [0.73-3.25]	1.01 [0.58-1.77]	**IC_{TaxPF}-CLRT (4)**	1.22 [0.91-1.64]		0.50* [0.25-0.99]			0.96 [0.67-1.39]					
0.89 [0.54-1.47]	1.59 [0.87-2.93]	1.04 [0.73-1.49]	1.03 [0.67-1.60]	**$CLRT_P$ (5)**	0.78 [0.48-1.27]		0.70 [0.41-1.17]	0.86* [0.65-1.14]	1.13 [0.36-3.58]	0.61 [0.43-0.85]	0.45 [0.31-0.66]			1.17 [0.90-1.52]
0.60 [0.41-0.88]	1.07 [0.55-2.08]	0.70 [0.46-1.08]	0.69 [0.40-1.20]	0.67 [0.48-0.94]	**HFRT (6)**					0.93* [0.73-1.19]	0.82 [0.71-0.95]			
0.60 [0.35-1.03]	1.08 [0.57-2.05]	0.71 [0.46-1.08]	0.70 [0.43-1.15]	0.68 [0.50-0.91]	1.01 [0.68-1.50]	**$CLRT_{noP}$ (7)**					0.83 [0.74-0.93]	0.88* [0.58-1.33]	1.02* [0.66-1.57]	0.85 [0.74-0.99]
0.47 [0.28-0.79]	0.83 [0.47-1.47]	0.55 [0.36-0.83]	0.54 [0.33-0.90]	0.52 [0.40-0.69]	0.78 [0.53-1.14]	0.77 [0.55-1.08]	**IC_{PF}-LRT (8)**				1.06 [0.88-1.28]			
0.58 [0.33-1.04]	1.04 [0.53-2.05]	0.68 [0.45-1.03]	0.67 [0.38-1.18]	0.65 [0.45-0.94]	0.97 [0.62-1.52]	0.96 [0.63-1.46]	1.25 [0.83-1.87]	**VART (9)**			0.84 [0.65-1.07]			
0.84 [0.39-1.82]	1.51 [0.65-3.52]	0.99 [0.50-1.96]	0.98 [0.57-1.66]	0.95 [0.52-1.71]	1.41 [0.71-2.77]	1.40 [0.73-2.66]	1.81 [0.95-3.45]	1.45 [0.73-2.90]	**IC_{PF}-CLRT (10)**					
0.63 [0.37-1.05]	1.12 [0.60-2.11]	0.74 [0.50-1.09]	0.73 [0.44-1.21]	0.70 [0.54-0.92]	1.05 [0.73-1.51]	1.04 [0.75-1.45]	1.34 [0.98-1.85]	1.08 [0.72-1.61]	0.74 [0.39-1.42]	**MART (11)**	0.80 [0.71-0.92]			
0.49 [0.30-0.78]	0.87 [0.48-1.57]	0.57 [0.40-0.81]	0.56 [0.35-0.89]	0.54 [0.46-0.65]	0.81 [0.59-1.11]	0.80 [0.63-1.03]	1.04 [0.83-1.31]	0.83 [0.59-1.17]	0.58 [0.31-1.06]	0.77 [0.62-0.97]	**LRT (12)**	1.27 [0.96-1.68]	1.15* [0.78-1.71]	0.86 [0.58-1.26]
0.63 [0.34-1.15]	1.12 [0.56-2.26]	0.73 [0.44-1.23]	0.73 [0.40-1.31]	0.70 [0.47-1.06]	1.05 [0.64-1.70]	1.04 [0.67-1.60]	1.34 [0.87-2.08]	1.08 [0.65-1.79]	0.74 [0.36-1.52]	1.00 [0.65-1.55]	1.29 [0.89-1.88]	**LRT-AC (13)**	1.15* [0.76-1.76]	
0.63 [0.26-1.54]	1.12 [0.43-2.94]	0.74 [0.32-1.70]	0.73 [0.30-1.76]	0.70 [0.32-1.53]	1.05 [0.46-2.38]	1.04 [0.48-2.25]	1.35 [0.61-2.97]	1.08 [0.47-2.48]	0.75 [0.28-1.97]	1.00 [0.45-2.21]	1.29 [0.61-2.77]	1.00 [0.46-2.20]	**$CLRT_{noP}$-AC (14)**	
0.49 [0.28-0.84]	0.87 [0.46-1.66]	0.57 [0.37-0.88]	0.56 [0.34-0.95]	0.54 [0.40-0.74]	0.81 [0.54-1.22]	0.80 [0.59-1.09]	1.04 [0.74-1.47]	0.84 [0.54-1.28]	0.58 [0.30-1.11]	0.77 [0.55-1.09]	1.00 [0.77-1.30]	0.77 [0.49-1.22]	0.77 [0.35-1.71]	**IC_{other}-LRT (16)**

* comparison with only one trial

Results are highlighted in grey if they are statistically significant.

LRT=loco-regional treatment, CT=chemotherapy, RT=radiotherapy, CLRT=LRT with concomitant chemoradiotherapy, IC=induction CT, AC=adjuvant CT, HFRT=hyperfractionated RT, HFCRT=HFRT with concomitant CT, MART=moderately accelerated RT, VART=very accelerated RT, ACRT=accelerated RT with concomitant CT, P=platin-based CT, noP=not platin-based CT, TaxPF=taxanes, platin and 5-Fluorouracile association, PF=platin and 5-Fluorouracile association

Web-Table 8 – League table presenting the results hazard ratio with their 95% confidence interval of the network meta-analysis (random effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for distant control.

As a convention the cells contain the hazard ratio of the treatment with the lower number compared to the treatment with the higher number. For example the cell that joins treatments 1 (HFCRT) and 5 ($CLRT_P$) gives the hazard ratio of treatment 1 vs. 5 (HFCRT vs. $CLRT_P$).

Hazard ratio: global Cochran Q statistic p <0.0001, heterogeneity (within design) p <0.0001, inconsistency (between designs) p <0.0001.

HFCRT (1)				0.40* [0.04-4.16]	3.48 [0.43-27.93]						0.79* [0.06-10.76]			
3.61 [0.14-93.89]	**IC_{TaxPF}-LRT (2)**						0.82 [0.49-1.36]				0.79* [0.54-1.17]			
1.26 [0.10-15.92]	0.35 [0.02-7.34]	**ACRT (3)**		0.96 [0.70-1.31]	1.20* [0.82-1.75]			1.20 [0.59-2.44]			1.61* [0.46-5.65]			
1.92 [0.11-32.89]	0.53 [0.02-13.50]	1.52 [0.12-19.38]	**IC_{TaxPF}-CLRT (4)**	0.55 [0.35-0.87]		0.66* [0.37-1.18]			0.57 [0.26-1.23]					
0.85 [0.10-7.09]	0.24 [0.02-3.28]	0.67 [0.13-3.63]	0.44 [0.06-3.07]	**$CLRT_P$ (5)**	0.89 [0.37-2.11]		0.95 [0.46-1.95]	1.23* [0.84-1.80]	0.90 [0.13-6.19]	1.20 [0.54-2.67]	2.91 [1.03-8.18]			0.002 [0.00-26.25]
3.63 [0.70-18.78]	1.00 [0.06-17.96]	2.88 [0.38-21.75]	1.89 [0.17-21.07]	4.27 [0.96-19.06]	**HFRT (6)**					1.19* [0.84-1.68]	0.23 [0.03-1.92]			
2.72 [0.25-29.42]	0.75 [0.05-12.46]	2.15 [0.27-17.30]	1.42 [0.15-13.03]	3.20 [0.78-13.18]	0.75 [0.12-4.71]	**$CLRT_{noP}$ (7)**					0.41 [0.09-1.87]	1.84* [0.94-3.59]	2.88* [1.30-6.40]	0.27* [0.06-1.28]
4.60 [0.46-45.74]	1.27 [0.11-14.93]	3.65 [0.50-26.46]	2.40 [0.25-22.99]	5.42 [1.55-18.96]	1.27 [0.23-7.13]	1.69 [0.34-8.39]	**IC_{PF}-LRT (8)**				0.18 [0.03-1.14]			
1.25 [0.10-15.60]	0.35 [0.02-6.67]	0.99 [0.15-6.69]	0.65 [0.05-7.96]	1.47 [0.28-7.60]	0.34 [0.05-2.59]	0.46 [0.07-3.25]	0.27 [0.04-1.73]	**VART (9)**			1.01 [0.80-1.26]			
0.79 [0.03-21.30]	0.22 [0.01-8.34]	0.62 [0.03-13.08]	0.41 [0.04-4.36]	0.92 [0.07-11.83]	0.22 [0.01-4.08]	0.29 [0.02-4.88]	0.17 [0.01-2.86]	0.63 [0.03-12.79]	**IC_{PF}-CLRT (10)**					
2.44 [0.25-23.91]	0.68 [0.04-10.58]	1.93 [0.26-14.27]	1.27 [0.13-12.46]	2.87 [0.79-10.48]	0.67 [0.12-3.69]	0.90 [0.18-4.56]	0.53 [0.12-2.37]	1.95 [0.30-12.66]	3.10 [0.18-52.90]	**MART (11)**	0.47 [0.19-1.17]			
1.15 [0.15-8.99]	0.32 [0.03-4.01]	0.91 [0.17-5.04]	0.60 [0.08-4.59]	1.36 [0.61-2.99]	0.32 [0.08-1.27]	0.42 [0.13-1.43]	0.25 [0.09-0.71]	0.92 [0.20-4.29]	1.47 [0.10-20.56]	0.47 [0.16-1.39]	**LRT (12)**	5.64 [1.27-25.12]	2.03* [0.91-4.51]	1.86 [0.08-42.63]
7.35 [0.50-107.49]	2.03 [0.09-43.56]	5.83 [0.52-65.97]	3.83 [0.27-54.37]	8.65 [1.30-57.53]	2.03 [0.22-18.53]	2.71 [0.35-20.65]	1.60 [0.21-12.00]	5.88 [0.58-59.25]	9.35 [0.40-217.50]	3.01 [0.39-23.07]	6.38 [1.14-35.83]	**LRT-AC (13)**	1.57* [0.65-3.78]	
5.93 [0.10-361.68]	1.64 [0.02-129.70]	4.71 [0.09-243.57]	3.09 [0.05-181.03]	6.98 [0.18-266.66]	1.64 [0.04-74.59]	2.18 [0.06-81.06]	1.29 [0.03-52.70]	4.75 [0.10-229.22]	7.55 [0.09-623.63]	2.43 [0.06-100.45]	5.15 [0.15-181.31]	0.81 [0.02-32.18]	**$CLRT_{noP}$-AC (14)**	
0.58 [0.05-6.83]	0.16 [0.01-2.87]	0.46 [0.05-4.04]	0.30 [0.03-3.38]	0.68 [0.15-3.16]	0.16 [0.02-1.12]	0.21 [0.04-1.24]	0.13 [0.02-0.71]	0.46 [0.06-3.64]	0.73 [0.04-14.01]	0.24 [0.04-1.37]	0.50 [0.12-2.02]	0.08 [0.01-0.72]	0.10 [0.00-4.38]	**IC_{other}-LRT (16)**

* comparison with only one trial

Results are highlighted in grey if they are statistically significant.

LRT=loco-regional treatment, CT=chemotherapy, RT=radiotherapy, CLRT=LRT with concomitant chemoradiotherapy, IC=induction CT, AC=adjuvant CT, HFRT=hyperfractionated RT, HFCRT=HFRT with concomitant CT, MART=moderately accelerated RT, VART=very accelerated RT, ACRT=accelerated RT with concomitant CT, P=platin-based CT, noP=not platin-based CT, TaxPF=taxanes, platin and 5-Fluorouracile association, PF=platin and 5-Fluorouracile association

Web-Table 9 – League table presenting the results hazard ratio with their95% confidence interval of the network meta-analysis (fixed effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for cancer death.

As a convention the cells contain the hazard ratio of the treatment with the lower number compared to the treatment with the higher number. For example the cell that joins treatments 1 (HFCRT) and 5 ($CLRT_P$) gives the hazard ratio of treatment 1 vs. 5 (HFCRT vs. $CLRT_P$).

Hazard ratio: global Cochran Q statistic p= 0.25, heterogeneity (within design) p=0.10, inconsistency (between designs) p=0.80.

HFCRT (1)				0.48* [0.16-1.44]	0.65 [0.54-0.78]						0.45* [0.15-1.39]			
0.88 [0.63-1.25]	**IC_{TaxPF}-LRT (2)**						0.67 [0.54-0.83]							
0.77 [0.61-0.97]	0.87 [0.65-1.17]	**ACRT (3)**		1.01 [0.87-1.18]	0.78* [0.62-0.98]			0.89 [0.75-1.06]		0.76* [0.56-1.02]	0.66* [0.45-0.96]			
0.76 [0.57-1.01]	0.86 [0.61-1.19]	0.98 [0.79-1.23]	**IC_{TaxPF}-CLRT (4)**	1.04 [0.76-1.42]		0.75* [0.48-1.20]			0.78 [0.59-1.03]					
0.77 [0.62-0.97]	0.88 [0.66-1.16]	1.00 [0.89-1.13]	1.02 [0.84-1.24]	**$CLRT_P$ (5)**	0.81 [0.53-1.22]		0.68* [0.41-1.13]	0.88* [0.71-1.10]	0.87 [0.64-1.19]	0.68 [0.48-0.96]	0.69 [0.62-0.77]			0.64* [0.47-0.87]
0.65 [0.54-0.78]	0.73 [0.55-0.98]	0.84 [0.74-0.96]	0.86 [0.68-1.07]	0.84 [0.74-0.95]	**HFRT (6)**					0.97* [0.82-1.16]	0.82 [0.72-0.93]			
0.57 [0.44-0.72]	0.64 [0.47-0.87]	0.73 [0.62-0.87]	0.75 [0.60-0.94]	0.73 [0.63-0.84]	0.87 [0.74-1.03]	**$CLRT_{noP}$ (7)**					0.95 [0.83-1.09]	0.75* [0.56-1.00]	0.87* [0.64-1.18]	0.86 [0.62-1.21]
0.59 [0.45-0.78]	0.67 [0.54-0.83]	0.77 [0.63-0.94]	0.78 [0.61-1.01]	0.77 [0.64-0.92]	0.91 [0.75-1.11]	1.05 [0.85-1.29]	**IC_{PF}-LRT (8)**		0.89* [0.47-1.70]		0.91 [0.73-1.13]			
0.61 [0.49-0.77]	0.69 [0.52-0.93]	0.80 [0.70-0.91]	0.81 [0.65-1.01]	0.79 [0.70-0.89]	0.94 [0.82-1.09]	1.08 [0.92-1.28]	1.04 [0.85-1.26]	**VART (9)**			0.91 [0.79-1.05]			
0.61 [0.45-0.82]	0.69 [0.49-0.97]	0.79 [0.62-1.00]	0.80 [0.68-0.94]	0.78 [0.63-0.97]	0.93 [0.73-1.19]	1.07 [0.84-1.37]	1.02 [0.78-1.34]	0.99 [0.77-1.26]	**IC_{PF}-CLRT (10)**					
0.61 [0.49-0.75]	0.68 [0.52-0.91]	0.78 [0.69-0.89]	0.80 [0.65-0.99]	0.78 [0.70-0.87]	0.93 [0.83-1.05]	1.07 [0.92-1.24]	1.02 [0.85-1.23]	0.99 [0.87-1.12]	1.00 [0.79-1.26]	**MART (11)**	0.88 [0.78-1.00]			
0.54 [0.43-0.66]	0.61 [0.46-0.80]	0.70 [0.62-0.78]	0.71 [0.58-0.87]	0.69 [0.64-0.75]	0.83 [0.74-0.92]	0.95 [0.84-1.08]	0.91 [0.77-1.08]	0.88 [0.79-0.97]	0.89 [0.71-1.11]	0.89 [0.83-0.95]	**LRT (12)**	0.88* [0.67-1.15]	1.02* [0.77-1.34]	
0.45 [0.33-0.63]	0.51 [0.35-0.74]	0.59 [0.45-0.77]	0.60 [0.44-0.82]	0.59 [0.45-0.76]	0.70 [0.53-0.91]	0.80 [0.62-1.03]	0.77 [0.57-1.03]	0.74 [0.56-0.97]	0.75 [0.54-1.04]	0.75 [0.58-0.97]	0.84 [0.66-1.08]	**LRT-AC (13)**	1.15* [0.86-1.53]	
0.52 [0.37-0.73]	0.59 [0.41-0.86]	0.68 [0.51-0.90]	0.69 [0.50-0.96]	0.68 [0.52-0.89]	0.81 [0.61-1.07]	0.93 [0.71-1.21]	0.88 [0.65-1.20]	0.85 [0.65-1.13]	0.86 [0.61-1.21]	0.87 [0.66-1.13]	0.97 [0.75-1.26]	1.15 [0.86-1.55]	**$CLRT_{noP}$-AC (14)**	
0.50 [0.37-0.67]	0.57 [0.40-0.80]	0.65 [0.52-0.81]	0.66 [0.50-0.87]	0.65 [0.53-0.79]	0.77 [0.61-0.97]	0.88 [0.73-1.07]	0.84 [0.65-1.10]	0.82 [0.65-1.02]	0.83 [0.62-1.10]	0.83 [0.67-1.02]	0.93 [0.76-1.14]	1.10 [0.81-1.50]	0.96 [0.70-1.31]	**IC_{other}-LRT (16)**

* comparison with only one trial

Results are highlighted in grey if they are statistically significant.

LRT=loco-regional treatment, CT=chemotherapy, RT=radiotherapy, CLRT=LRT with concomitant chemoradiotherapy, IC=induction CT, AC=adjuvant CT, HFRT=hyperfractionated RT, HFCRT=HFRT with concomitant CT, MART=moderately accelerated RT, VART=very accelerated RT, ACRT=accelerated RT with concomitant CT, P=platin-based CT, noP=not platin-based CT, TaxPF=taxanes, platin and 5-Fluorouracile association, PF=platin and 5-Fluorouracile association

Web-Table 10 – League table presenting the results hazard ratio with their 95% confidence interval of the network meta-analysis (fixed effects, lower triangle) and of the conventional meta-analysis (random effects, upper triangle) for non-cancer death.

As a convention the cells contain the hazard ratio of the treatment with the lower number compared to the treatment with the higher number. For example the cell that joins treatments 1 (HFCRT) and 5 ($CLRT_P$) gives the hazard ratio of treatment 1 vs. 5 (HFCRT vs. $CLRT_P$).

Hazard ratio: global Cochran Q statistic p= 0.57, heterogeneity (within design) p=0.81, inconsistency (between designs) p=0.17.

HFCRT (1)				2.14* [0.28-16.24]	1.16 [0.81- 1.65]						2.06* [0.27-15.63]			
1.24 [0.66-2.35]	**IC_{TaxPF}-LRT (2)**						1.00 [0.64- 1.56]							
0.98 [0.62-1.55]	0.79 [0.45-1.40]	**ACRT (3)**		0.96 [0.69- 1.34]	1.20* [0.52- 2.74]			1.21 [0.62- 2.35]		0.68* [0.25- 1.86]	1.86* [0.73- 4.74]			
1.23 [0.67-2.25]	0.99 [0.50-1.97]	1.25 [0.74-2.11]	**IC_{TaxPF}-CLRT (4)**	1.00 [0.49- 2.07]		1.19* [0.52- 2.69]			1.26 [0.31- 5.09]					
0.98 [0.65-1.48]	0.79 [0.47-1.34]	1.00 [0.78-1.29]	0.80 [0.50-1.27]	**$CLRT_P$ (5)**	0.81* [0.43- 1.55]		0.90* [0.49- 1.66]	0.80* [0.53- 1.20]	5.70* [1.75-18.62]	1.01 [0.37- 2.77]	1.27 [1.03- 1.56]			1.00* [0.38- 2.66]
1.20 [0.85-1.69]	0.97 [0.57-1.66]	1.23 [0.90-1.66]	0.98 [0.59-1.62]	1.22 [0.97-1.54]	**HFRT (6)**					0.88* [0.66- 1.18]	0.86 [0.70- 1.07]			
1.36 [0.86-2.14]	1.10 [0.62-1.92]	1.39 [0.97-1.97]	1.11 [0.68-1.81]	1.38 [1.05-1.83]	1.13 [0.83-1.53]	**$CLRT_{noP}$ (7)**					0.81 [0.60- 1.08]	0.72* [0.42- 1.22]	0.56* [0.35- 0.92]	1.28 [0.83- 1.97]
1.24 [0.79-1.94]	1.00 [0.64-1.56]	1.26 [0.89-1.79]	1.01 [0.60-1.70]	1.26 [0.96-1.65]	1.03 [0.76-1.39]	0.91 [0.65-1.28]	**IC_{PF}-LRT (8)**		1.62* [0.17-15.90]		0.86 [0.66- 1.11]			
0.98 [0.63-1.53]	0.79 [0.46-1.38]	1.00 [0.76-1.32]	0.80 [0.48-1.34]	1.00 [0.79-1.27]	0.82 [0.62-1.08]	0.72 [0.52-1.00]	0.79 [0.58-1.09]	**VART (9)**			1.08 [0.83- 1.42]			
1.27 [0.60-2.70]	1.02 [0.45-2.32]	1.30 [0.65-2.57]	1.04 [0.62-1.73]	1.29 [0.68-2.46]	1.06 [0.54-2.07]	0.93 [0.48-1.82]	1.03 [0.52-2.03]	1.29 [0.66-2.55]	**IC_{PF}-CLRT (10)**					
1.05 [0.71-1.56]	0.85 [0.51-1.42]	1.07 [0.81-1.42]	0.86 [0.53-1.39]	1.07 [0.89-1.29]	0.87 [0.72-1.06]	0.77 [0.59-1.01]	0.85 [0.66-1.10]	1.07 [0.84-1.36]	0.83 [0.43-1.60]	**MART (11)**	1.07 [0.96-1.19]			
1.13 [0.77-1.66]	0.91 [0.55-1.52]	1.15 [0.89-1.50]	0.92 [0.57-1.48]	1.15 [0.98-1.35]	0.94 [0.78-1.13]	0.83 [0.65-1.06]	0.91 [0.72-1.16]	1.15 [0.92-1.43]	0.89 [0.46-1.70]	1.08 [0.97-1.19]	**LRT (12)**	1.00 [0.63- 1.59]	0.76* [0.49- 1.18]	
1.06 [0.59-1.91]	0.86 [0.44-1.68]	1.08 [0.65-1.81]	0.87 [0.46-1.64]	1.08 [0.68-1.73]	0.88 [0.55-1.43]	0.78 [0.49-1.24]	0.86 [0.52-1.42]	1.08 [0.66-1.77]	0.84 [0.38-1.82]	1.01 [0.64-1.59]	0.94 [0.60-1.46]	**LRT-AC (13)**	0.80* [0.50- 1.28]	
0.83 [0.47-1.45]	0.67 [0.35-1.28]	0.84 [0.52-1.37]	0.67 [0.37-1.25]	0.84 [0.55-1.30]	0.69 [0.44-1.08]	0.61 [0.40-0.93]	0.67 [0.42-1.07]	0.84 [0.53-1.34]	0.65 [0.31-1.39]	0.79 [0.52-1.20]	0.73 [0.49-1.10]	0.78 [0.49-1.25]	**$CLRT_{noP}$-AC (14)**	
1.59 [0.88-2.85]	1.28 [0.65-2.51]	1.62 [0.97-2.69]	1.29 [0.70-2.40]	1.61 [1.02-2.55]	1.32 [0.82-2.13]	1.17 [0.78-1.73]	1.28 [0.78-2.12]	1.61 [0.99-2.64]	1.25 [0.58-2.68]	1.51 [0.95-2.38]	1.40 [0.90-2.19]	1.49 [0.82-2.72]	1.91 [1.08-3.39]	**IC_{other}-LRT (16)**

* comparison with only one trial

Results are highlighted in grey if they are statistically significant.

LRT=loco-regional treatment, CT=chemotherapy, RT=radiotherapy, CLRT=LRT with concomitant chemoradiotherapy, IC=induction CT, AC=adjuvant CT, HFRT=hyperfractionated RT, HFCRT=HFRT with concomitant CT, MART=moderately accelerated RT, VART=very accelerated RT, ACRT=accelerated RT with concomitant CT, P=platin-based CT, noP=not platin-based CT, TaxPF=taxanes, platin and 5-Fluorouracile association, PF=platin and 5-Fluorouracile association

Web-Table 11 – Results of main analysis and sensitivity analysis for overall survival.
See web appendix 2B for the list of trial comparison excluded in each sensitivity analysis

Treatment data	**Overall survival**		**Sensitivity analysis for outliers**		**Sensitivity analysis for chemotherapy**		**Sensitivity analysis for quality**		**Sensitivity analysis for distinctive loco-regional treatment**		**Sensitivity analysis with exclusion of patients aged more than 70 years**		**Sensitivity analysis with exclusion of trials with a majority of stage I/II tumours**	
	115 trials 154 comparisons 28,978 patients 19,253 events		113 trials 150 comparisons 28,700 patients 19,073 events		85 trials 108 comparisons 22,168 patients 14,793 events		71 trials 98 comparisons 21,922 patients 15,785 events		62 trials 85 comparisons 18,173 patients 12,157 events		115 trials 154 comparisons 26,077 patients 17,049 events		107 trials 146 comparisons 26,128 patients 17,774 events	
P value global	0.07		0.60		0.02		0.04		0.01		0.12		0.05	
P value heterogeneity	0.01		0.23		0.01		0.02		0.01		0.02		0.01	
P value inconsistency	0.91		0.98		0.64		0.52		0.78		0.97		0.89	
	HR (95% CI)	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**
LRT	ref	21	ref	21	ref	4	ref	22	ref	20	ref	23	ref	22
HFCRT	**0.63 [0.51-0.77]**	97	**0.64 [0.53-0.77]**	94	**0.61 [0.49-0.77]**	96	**0.67 [0.53-0.86]**	92	**0.60 [0.46-0.78]**	95	**0.63 [0.51-0.78]**	96	**0.63 [0.51-0.78]**	97
IC_{TaxPF}-LRT	**0.69 [0.56-0.85]**	89	**0.69 [0.57-0.83]**	89	**0.70 [0.56-0.87]**	83	**0.68 [0.55-0.84]**	91.8	**0.63 [0.46-0.86]**	92	**0.69 [0.56-0.86]**	89	**0.69 [0.56-0.86]**	89
ACRT	**0.75 [0.66-0.85]**	82	**0.77 [0.69-0.85]**	78	**0.76 [0.65-0.89]**	68.7	**0.78 [0.68-0.90]**	78	**0.77 [0.65-0.91]**	74.4	**0.73 [0.65-0.83]**	84	**0.75 [0.66-0.85]**	82
IC_{TaxPF}-CLRT	**0.75 [0.62-0.92]**	80	**0.64 [0.52-0.80]**	93.5	**0.75 [0.60-0.95]**	70	0.76 [0.55-1.05]	76	**0.76 [0.61-0.95]**	74.5	**0.76 [0.62-0.93]**	78	**0.75 [0.62-0.92]**	80
$CLRT_P$	**0.77 [0.72-0.83]**	78	**0.79 [0.74-0.84]**	74	**0.77 [0.71-0.83]**	68.8	**0.80 [0.74-0.86]**	75	**0.77 [0.69-0.86]**	74.6	**0.76 [0.71-0.81]**	79	**0.77 [0.72-0.83]**	78
HFRT	**0.85 [0.76-0.95]**	61	**0.86 [0.79-0.95]**	58	**0.83 [0.73-0.94]**	51	**0.85 [0.76-0.95]**	60	**0.82 [0.71-0.94]**	63	**0.84 [0.75-0.94]**	61	**0.85 [0.75-0.95]**	61
$CLRT_{noP}$	**0.89 [0.81-0.98]**	50	**0.89 [0.82-0.97]**	52	/	/	0.89 [0.79-1.01]	49	0.94 [0.79-1.13]	33	**0.88 [0.79-0.97]**	53	**0.89 [0.81-0.99]**	49
IC_{PF}-LRT	**0.90 [0.82-0.99]**	47	**0.90 [0.83-0.98]**	48	0.90 [0.82-1.00]	29.2	**0.88 [0.79-0.98]**	53	0.86 [0.72-1.04]	52	**0.90 [0.81-0.99]**	47	**0.90 [0.82-1.00]**	46.8
VART	0.90 [0.81-1.01]	46.5	0.92 [0.84-1.02]	42	0.90 [0.80-1.02]	29.3	0.92 [0.81-1.04]	42	0.91 [0.79-1.05]	40	0.91 [0.81-1.02]	45	0.90 [0.80-1.01]	46.8
IC_{PF}-CLRT	0.90 [0.72-1.13]	45.5	0.86 [0.69-1.06]	57	0.90 [0.70-1.16]	31	0.88 [0.64-1.20]	51	0.90 [0.70-1.16]	42	0.91 [0.72-1.15]	44	0.90 [0.72-1.13]	45.7
MART	0.94 [0.87-1.01]	37	0.96 [0.91-1.02]	32	0.94 [0.86-1.02]	20	**0.91 [0.83-1.00]**	**44**	0.92 [0.82-1.03]	38	**0.91 [0.84-0.99**]	43	0.93 [0.85-1.01]	40
LRT-AC	1.03 [0.90-1.17]	18	1.03 [0.92-1.16]	17	/	/	1.09 [0.93-1.27]	12	1.09 [0.81-1.47]	16	1.06 [0.92-1.22]	14.9	1.05 [0.91-1.21]	15.4
$CLRT_{noP}$-AC	1.07 [0.84-1.36]	16	1.06 [0.86-1.31]	14.9	/	/	1.09 [0.85-1.40]	15	/	/	1.10 [0.85-1.43]	14.4	1.07 [0.84-1.37]	16.0
IC_{other}-CLRT	1.15 [0.73-1.82]	15.8	1.15 [0.75-1.76]	15.1	/	/	1.13 [0.71-1.80]	18	1.16 [0.69-1.94]	17	1.19 [0.74-1.93]	14.3	1.15 [0.73-1.83]	16.2
IC_{other}-LRT	1.04 [0.93-1.16]	15.2	1.03 [0.93-1.15]	15.4	/	/	1.02 [0.90-1.16]	20	1.04 [0.84-1.29]	18	1.06 [0.94-1.20]	14.2	1.04 [0.93-1.17]	15.8

Results are in bold if they are statistically significant and the three modalities of treatment with the highest p-score are highlighted in grey.

See web-table 1 for abbreviations.

Web-Table 12 – Results of main analysis and sensitivity analysis for event-free survival.
See web appendix 2B for the list of trial comparison excluded in each sensitivity analysis

Treatment data	**Event-free survival**		**Sensitivity analysis for outliers**		**Sensitivity analysis for chemotherapy**		**Sensitivity analysis for quality**		**Sensitivity analysis for distinctive loco-regional treatment**	
	112 trials 151 comparisons 28,315 patients 20,579 events		110 trials 147 comparisons 28,037 patients 20,389 events		84 trials 107 comparisons 22,112 patients 16,035 events		69 trials 96 comparisons 21,315 patients 16,414 events		60 trials 83 comparisons 18,009 patients 13,278 events	
P value global	0.11		0.58		0.20		0.12		0.19	
P value heterogeneity	0.05		0.43		0.15		0.06		0.08	
P value inconsistency	0.52		0.65		0.51		0.51		0.65	
	HR (95% CI)	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**
LRT	ref	12	ref	12	ref	1	ref	16	ref	10
HFCRT	**0.60 [0.49-0.73]**	**97**	**0.60 [0.50-0.72]**	**94**	**0.59 [0.49-0.71]**	**97**	**0.61 [0.49-0.77]**	**94**	**0.57 [0.45-0.71]**	**96**
IC_{TaxPF}-LRT	**0.71 [0.59-0.87]**	**80**	**0.71 [0.59-0.85]**	**80**	**0.71 [0.59-0.85]**	**76**	**0.70 [0.58-0.86]**	**83**	**0.63 [0.48-0.82]**	**88**
ACRT	**0.71 [0.63-0.80]**	**82**	**0.72 [0.65-0.80]**	**79**	**0.74 [0.66-0.84]**	**69**	**0.74 [0.65-0.84]**	**79**	**0.73 [0.63-0.83]**	**73.3**
IC_{TaxPF}-CLRT	**0.66 [0.55-0.80]**	**89**	**0.58 [0.48-0.71]**	**96**	**0.68 [0.55-0.83]**	**84**	**0.65 [0.49-0.87]**	**89**	**0.65 [0.54-0.79]**	**87**
$CLRT_P$	**0.74 [0.70-0.79]**	**75**	**0.75 [0.71-0.80]**	**72**	**0.75 [0.71-0.80]**	**67**	**0.77 [0.72-0.83]**	**71**	**0.73 [0.67-0.79]**	**73.3**
HFRT	**0.84 [0.76-0.93]**	**54.5**	**0.85 [0.78-0.93]**	**53**	**0.83 [0.75-0.91]**	**46**	**0.84 [0.76-0.94]**	**54**	**0.82 [0.74-0.92]**	**51**
$CLRT_{noP}$	**0.88 [0.81-0.97]**	**42.7**	**0.88 [0.81-0.96]**	**45**	/	/	0.90 [0.80-1.01]	39	0.89 [0.78-1.03]	33
IC_{PF}-LRT	0.93 [0.85-1.02]	30	0.93 [0.85-1.01]	31	0.93 [0.85-1.01]	18	0.91 [0.82-1.00]	37	0.86 [0.73-1.01]	41
VART	**0.88 [0.79-0.98]**	**42.8**	**0.90 [0.82-0.98]**	**40**	**0.90 [0.82-0.98]**	**25.9**	**0.90 [0.80-1.00]**	**40**	**0.88 [0.79-0.99]**	**36**
IC_{PF}-CLRT	0.83 [0.66-1.03]	54.8	**0.78 [0.63-0.96]**	**66**	0.85 [0.68-1.06]	40	0.79 [0.59-1.06]	61	0.81 [0.65-1.02]	52
MART	**0.89 [0.83-0.96]**	**40**	**0.91 [0.86-0.96]**	**36**	**0.90 [0.85-0.95]**	**26**	**0.87 [0.80-0.94]**	**48**	**0.88 [0.81-0.95]**	**36**
LRT-AC	0.99 [0.86-1.13]	17	1.00 [0.88-1.13]	15	/	/	1.10 [0.92-1.31]	6	1.09 [0.86-1.38]	6
$CLRT_{noP}$-AC	0.95 [0.75-1.20]	28	0.95 [0.77-1.17]	27	/	/	0.99 [0.78-1.25]	23	/	/
IC_{other}-CLRT	/	/	/	/	/	/	/	/	/	/
IC_{other}-LRT	1.05 [0.94-1.17]	6	1.05 [0.94-1.16]	31	/	/	1.05 [0.93-1.19]	9	0.97 [0.80-1.16]	19

Results are in bold if they are statistically significant and the three modalities of treatment with the highest p-score are highlighted in grey.

See web-table 1 for abbreviations

Web-Table 13 – Results of main analysis and sensitivity analysis for loco-regional control.
See web appendix 2B for the list of trial comparison excluded in each sensitivity analysis

Treatment data	**Loco-regional control**		**Sensitivity analysis for outliers**		**Sensitivity analysis for chemotherapy**		**Sensitivity analysis for quality**		**Sensitivity analysis for distinctive loco-regional treatment**	
	110 trials 150 comparisons 27,309 patients 10,882 events		80 trials 113 comparisons 21,767 patients 8,071 events		81 trials 105 comparisons 21,049 patients 8,113 events		68 trials 96 comparisons 20,717 patients 8,197 events		58 trials 81 comparisons 17,026 patients 7,141 events	
P value global	<0.0001		0.09		<0.0001		<0.0001		<0.0001	
P value heterogeneity	<0.0001		0.27		<0.0001		<0.0001		<0.0001	
P value inconsistency	0.0008		0.07		0.18		0.01		<0.0001	
	HR (95% CI)	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**
LRT	ref	15	ref	2	ref	13	ref	15	ref	13
HFCRT	**0.49 [0.30-0.78]**	**88**	**0.49 [0.38-0.63]**	**98**	**0.49 [0.29-0.82]**	**83**	**0.47 [0.30-0.72]**	**97**	**0.45 [0.25-0.80]**	**75**
IC_{TaxPF}-LRT	0.87 [0.48-1.57]	36	**0.71 [0.54-0.93]**	**66**	0.87 [0.46-1.62]	32	0.81 [0.54-1.22]	49	0.74 [0.30-1.87]	41
ACRT	**0.57 [0.40-0.81]**	**79**	**0.64 [0.56-0.75]**	**81**	**0.53 [0.34-0.83]**	**77**	**0.63 [0.48-0.82]**	**83**	**0.50 [0.31-0.82]**	**68**
IC_{TaxPF}-CLRT	**0.56 [0.35-0.89]**	**78**	**0.60 [0.45-0.79]**	**86**	**0.57 [0.33-0.98]**	**70**	0.78 [0.48-1.26]	54	**0.37 [0.22-0.63]**	**85**
$CLRT_P$	**0.54 [0.46-0.65]**	**84**	**0.65 [0.59-0.72]**	**80**	**0.51 [0.42-0.63]**	**82**	**0.67 [0.58-0.77]**	**79**	**0.34 [0.26-0.45]**	**90**
HFRT	0.81 [0.59-1.11]	42	**0.80 [0.71-0.91]**	**45**	0.82 [0.58-1.16]	35.52	**0.80 [0.64-1.00]**	**50**	0.85 [0.57-1.25]	28
$CLRT_{noP}$	0.80 [0.63-1.03]	44	**0.77 [0.68-0.88]**	**54**	/	/	**0.77 [0.62-0.96]**	**56**	0.72 [0.47-1.10]	42
IC_{PF}-LRT	1.04 [0.83-1.31]	13	0.89 [0.77-1.02]	23	1.04 [0.81-1.32]	11	0.98 [0.82-1.19]	19	0.93 [0.55-1.60]	22
VART	0.83 [0.59-1.17]	39	**0.87 [0.77-0.97]**	**28**	0.82 [0.57-1.18]	35.50	0.87 [0.70-1.09]	37	0.74 [0.47-1.18]	39
IC_{PF}-CLRT	0.58 [0.31-1.06]	73	0.81 [0.60-1.08]	42	0.56 [0.29-1.10]	69	0.82 [0.50-1.34]	46	**0.33 [0.17-0.67]**	**88**
MART	**0.77 [0.62-0.97]**	**48.3**	**0.84 [0.77-0.92]**	**34**	**0.76 [0.60-0.97]**	**43**	**0.77 [0.64-0.92]**	**57**	**0.69 [0.50-0.95]**	**46**
LRT-AC	0.77 [0.53-1.13]	47.5	0.83 [0.67-1.03]	38	/	/	0.83 [0.55-1.25]	46	1.14 [0.53-2.44]	14
$CLRT_{noP}$-AC	0.77 [0.36-1.65]	47.2	0.79 [0.55-1.13]	47	/	/	0.78 [0.46-1.32]	52	/	/
IC_{other}-CLRT	/	/	/	/	/	/	/	/	/	/
IC_{other}-LRT	1.00 [0.77-1.30]	17	0.88 [0.77-1.01]	25	/	/	1.05 [0.86-1.28]	11	0.68 [0.41-1.12]	22

Results are in bold if they are statistically significant and the three modalities of treatment with the highest p-score are highlighted in grey.

See web-table 1 for abbreviations

Web-Table 14 – Results of main analysis and sensitivity analysis for cancer death.
See web appendix 2B for the list of trial comparison excluded in each sensitivity analysis

Treatment data	**Cancer death**		**Sensitivity analysis for chemotherapy**		**Sensitivity analysis for quality**		**Sensitivity analysis for distinctive loco-regional treatment**	
	73 trials 104 comparisons 21,753 patients 11,039 events		64 trials 87 comparisons 18,526 patients 9,269 events		49 trials 72 comparisons 17,326 patients 9,160 events		49 trials 69 comparisons 16,120 patients 8,061 events	
P value global	0.25		0.14		0.05		0.05	
P value heterogeneity	0.10		0.09		0.02		0.01	
P value inconsistency	0.80		0.56		0.59		0.69	
	HR (95% CI)	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**
LRT	ref	20	ref	3	ref	17	ref	16.3
HFCRT	**0.54 [0.43-0.66]**	**98**	**0.52 [0.41-0.66]**	**97**	**0.54 [0.41-0.73]**	**94**	**0.51 [0.38-0.67]**	**95**
IC_{TaxPF}-LRT	**0.61 [0.46-0.80]**	**90**	**0.61 [0.45-0.83]**	**85**	**0.58 [0.42-0.81]**	**89**	**0.51 [0.35-0.74]**	**94**
ACRT	**0.70 [0.62-0.78]**	**80**	**0.71 [0.60-0.83]**	**69**	**0.69 [0.59-0.81]**	**76.8**	**0.71 [0.60-0.85]**	**70**
IC_{TaxPF}-CLRT	**0.71 [0.58-0.87]**	**78**	**0.71 [0.56-0.90]**	**68**	**0.67 [0.47-0.95]**	**77.3**	**0.70 [0.55-0.89]**	**72**
$CLRT_{P}$	**0.69 [0.64-0.75]**	**81**	**0.69 [0.63-0.76]**	**74**	**0.67 [0.61-0.75]**	**80**	**0.69 [0.61-0.78]**	**76**
HFRT	**0.83 [0.74-0.92]**	**58**	**0.80 [0.70-0.92]**	**47**	**0.81 [0.71-0.93]**	**54**	**0.80 [0.68-0.93]**	**54**
$CLRT_{noP}$	0.95 [0.84-1.08]	31	/	/	0.90 [0.73-1.11]	37	1.00 [0.79-1.25]	20
IC_{PF}-LRT	0.91 [0.77-1.08]	40	0.91 [0.76-1.09]	22	0.87 [0.71-1.05]	42	0.75 [0.57-0.99]	61
VART	**0.88 [0.79-0.97]**	**48**	**0.87 [0.76-0.98]**	**31**	**0.86 [0.75-0.99]**	**43**	0.87 [0.75-1.01]	40
IC_{PF}-CLRT	0.89 [0.71-1.11]	44	0.89 [0.68-1.15]	26.9	0.80 [0.57-1.13]	52	0.87 [0.66-1.14]	39
MART	**0.89 [0.83-0.95]**	**45**	**0.88 [0.81-0.97]**	**26.7**	**0.86 [0.77-0.96]**	**44**	**0.88 [0.78-0.99]**	**37**
LRT-AC	1.19 [0.92-1.52]	5	/	/	1.16 [0.85-1.59]	7	1.14 [0.81-1.60]	10
$CLRT_{noP}$-AC	1.03 [0.79-1.33]	21	/	/	1.01 [0.73-1.39]	22	/	/
IC_{other}-CLRT	/	/	/	/	/	/	/	/
IC_{other}-LRT	1.07 [0.88-1.32]	13	/	/	1.04 [0.80-1.34]	16	1.07 [0.73-1.59]	15.7

Results are in bold if they are statistically significant and the three modalities of treatment with the highest p-score are highlighted in grey.

See web-table 1 for abbreviations

Web-Table 15 – Results of main analysis and sensitivity analysis for distant control.
See web appendix 2B for the list of trial comparison excluded in each sensitivity analysis

Treatment data	**Distant control**		**Sensitivity analysis for outliers**		**Sensitivity analysis for chemotherapy**		**Sensitivity analysis for quality**		**Sensitivity analysis for distinctive loco-regional treatment**	
	100 trials 137 comparisons 25,042 patients 3,065 events		72 trials 103 comparisons 19,740 patients 2,848 events		77 trials 101 comparisons 20,054 patients 2,500 events		64 trials 90 comparisons 19,518 patients 2,631 events		54 trials 76 comparisons 15,677 patients 1,679 events	
P value global	<0.0001		0.65		<0.0001		<0.0001		<0.0001	
P value heterogeneity	<0.0001		0.98		<0.0001		<0.0001		<0.0001	
P value inconsistency	<0.0001		0.04		<0.0001		<0.0001		<0.0001	
	HR (95% CI)	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**	**HR (95% CI)**	**p-score (%)**
LRT	ref	33	ref	42	ref	42	ref	53	ref	41
HFCRT	1.15 [0.15-8.99]	32	0.79 [0.49-1.28]	70	1.15 [0.15-8.62]	39	1.02 [0.11-9.33]	50	1.29 [0.10-16.32]	37
IC_{TaxPF}-LRT	0.32 [0.03-4.01]	65	0.79 [0.57-1.09]	74	0.33 [0.03-3.74]	72	0.90 [0.13-6.15]	54.5	0.72 [0.01-52.63]	49
ACRT	0.91 [0.17-5.04]	38.1	1.10 [0.88-1.36]	24	1.21 [0.17-8.67]	38	1.78 [0.40-7.93]	32	1.38 [0.12-15.73]	36
IC_{TaxPF}-CLRT	0.60 [0.08-4.59]	51	**0.66 [0.43-1.00]**	**87**	1.08 [0.12-9.87]	43	1.16 [0.10-13.03]	48	0.53 [0.05-5.72]	57
$CLRT_{P}$	1.36 [0.61-2.99]	23	1.05 [0.90-1.22]	31	1.99 [0.90-4.38]	18	2.77 [1.31-5.87]	15	1.48 [0.42-5.20]	31
HFRT	0.32 [0.08-1.27]	70.9	1.07 [0.85-1.34]	29	0.31 [0.08-1.26]	80	1.18 [0.35-3.95]	46	0.21 [0.04-1.15]	76
$CLRT_{noP}$	0.42 [0.13-1.43]	62	1.10 [0.82-1.49]	26	/	/	1.30 [0.38-4.46]	42	0.16 [0.02-1.23]	78
IC_{PF}-LRT	0.25 [0.09-0.71]	78	0.97 [0.73-1.27]	47.1	**0.26 [0.10-0.72]**	**85**	1.19 [0.46-3.11]	45	0.90 [0.06-13.83]	45
VART	0.92 [0.20-4.29]	37.6	0.97 [0.80-1.18]	47.4	1.07 [0.24-4.76]	41	1.24 [0.32-4.80]	44	0.92 [0.12-7.35]	44
IC_{PF}-CLRT	1.47 [0.10-20.56]	29	0.89 [0.54-1.46]	56	2.43 [0.17-33.87]	23	2.81 [0.27-29.04]	23	1.41 [0.07-29.10]	37
MART	0.47 [0.16-1.39]	59	0.99 [0.83-1.18]	44	0.49 [0.17-1.38]	68	0.41 [0.15-1.12]	81	0.30 [0.06-1.42]	69
LRT-AC	**0.16 [0.03-0.88]**	**84**	0.85 [0.66-1.10]	67	/	/	0.90 [0.16-5.14]	54.5	**0.01 [0.00-0.14]**	**99**
$CLRT_{noP}$-AC	0.19 [0.01-6.83]	71.3	**0.46 [0.22-0.96]**	**95**	/	/	0.50 [0.03-7.75]	67	/	/
IC_{other}-CLRT	/	/	/	/	/	/	/	/	/	/
IC_{other}-LRT	2.00 [0.49-8.09]	16	1.38 [0.84-2.28]	10	/	/	**0.17 [0.05-0.60]**	**94**	51.44 [6.07-436.16]	1

Results are in bold if they are statistically significant and the three modalities of treatment with the highest p-score are highlighted in grey.

See web-table 1 for abbreviations

Web-Table 16 – Sensitivity analysis with lumping of groups of treatment modalities for distant control and non-cancer death endpoint.

Treatment data	**Distant control**[$]		**Non-cancer death**[£]	
	97 trials 130 comparisons 24,052 patients 2,967 events		66 trials 89 comparisons 20,073 patients 3,524 events	
P value global	<0.0001		0.53	
P value heterogeneity	<0.0001		0.44	
P value inconsistency	<0.0001		0.65	
	HR (95% CI)	**p-score (%)**	**HR (95% CI)**	**p-score (%)**
LRT	ref	22	ref	61
AF-CRT	0.99 (0.30-3.27)	27	1.12 (0.91-1.38)	28
IC-LRT	0.52 (0.23-1.14)	64	0.88 (0.72-1.09)	85
IC-CLRT	0.64 (0.12-3.42)	50	0.84 (0.54-1.31)	81
CLRT	0.95 (0.51-1.78)	26	1.03 (0.91-1.17)	48
AF-RT	**0.46 (0.22-0.94)**	**71**	1.04 (0.96-1.13)	43
(C)LRT-AC	**0.23 (0.06-0.92)**	**89**	**1.35 (1.05-1.72)**	**3**

[$] main analysis of distant control endpoint includes 100 trials; 137 comparisons; 25,042 patients; and 3,065 events but 7 trial comparisons were excluded for this analysis because for some trial comparisons the two modalities of treatment became confused with the lumping (for TAX 324, Spain 1998, and TTCC2002-, IC_{taxPF}-CLRT and IC_{PF}-CLRT became IC-CLRT; for GORTEC 2000-01, and EORTC 24971, IC_{taxPF}-LRT and IC_{PF}-LRT became IC-LRT; for UKHAN1npo*, CLRTnoP-AC and LRT-AC became (C)LRT-AC and for RTOG9003, HFRT and MART became AF-RT).

[£] main analysis of non cancer death endpoint includes 70 trials; 96 comparisons;21,533 patients; and 3,645 events but 8 trial comparisons were excluded for this analysis because for some trial comparisons the two modalities of treatment became confused with the lumping.

HR=hazard ratio, CI=Confidence Interval, LRT=loco-regional treatment, CT=chemotherapy, RT=radiotherapy, CLRT=LRT with concomitant chemoradiotherapy, IC=induction CT, AC=adjuvant CT, AF=altered fractionation RT.

Web-Appendix 1: MACH-NC & MARCH collaborative group

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Web-Appendix 2 - Trials excluded for:

A - Secondary endpoint analysis

1/ Trials excluded for event-free survival:

Créteil 85[100], Int 0034[76], Torino-85[99]

2/ Trials excluded for loco-regional control:

Créteil 85[100], Int 0034[76], Torino-85[99], ECOG 2382[33], Spain 1998[101]

3/ Trials excluded for distant control:

Créteil 85[100], Int 0034[76], Torino-85[99], Songhkla[60], SHNG-85[72], SECOG II[$], NCI-V98-1416[50], JHCFUS[77], ECOG 2382[33], Cologne 95[109], Spain 1998[101], Osaka 1993[18], CMGH-85[90], INRC HN-7[95], SECOG I[96]

[$] unpublished

4/ Trials excluded for cancer death:

AC Camargo[28], AIIMS03[29], Bavaria 89[30], BNH003[$], Brescia[94], BuenosAires[55], CFHNS[63], CH-7401[31], FRCT 94[32], CMGH-85[90], Cologne-88[64], Créteil-82[56], Créteil-86[65], ECOG2382[33], EORTC 24844[$], GETTECadj[74], HNAP-02[68], HNCGIC02[57], HNCGIC03[58], HNU-87[75], ICC-PCP[92], INRC HN-7[95], INRC HN-8[37], Int0034[76], JHCFUS[77], KKD-86[78], Kragujevac1[39], LOHNG91[48], Lucknow 95*[40], MCW-2[69], Ontario[51], Pitié-81[59], PMHCGS[52], Rennes-87[71], SECOG II*[$], Shanghai 2008[73], SHNG-85[72], Songkhla[60], SWOG8006[61], TMHR-4[79], Torino 85[99], Toulouse[45], Yale80[53], Yale86[54]

* multi-arm trial where one comparison was not excluded.
[$] unpublished

5/ Trials excluded for non cancer death:

AC Camargo[28], AIIMS03[29], Bavaria 89[30], BNH003[$], Brescia[94], BuenosAires[55], CFHNS[63], CH-7401[31], FRCT 94[32], CMGH-85[90], Cologne-88[64], Créteil-82[56], Créteil-86[65], ECOG2382[33], EORTC 24844[$], GETTECadj[74], HNAP-02[68], HNCGIC02[57], HNCGIC03[58], HNU-87[75], ICC-PCP[92], INRC HN-7[95], INRC HN-8[37], Int0034[76], JHCFUS[77], KKD-86[78], Kragujevac1[39], LOHNG91[48], Lucknow 95*[40], MCW-2[69], Ontario[51], Pitié-81[59], PMHCGS[52], Rennes-87[71], SECOG II*[$], Shanghai 2008[73], SHNG-85[72], Songkhla[60], SWOG8006[61], TMHR-4[79], Torino 85[99], Toulouse[45], Yale80[53], Yale86[54], CAIRO 1990[22], CONDOR[87], IAR 92[105], TTCC 2002*[83,84], EORTC22962*[$]

* multi-arm trial where one comparison was not excluded.
[$] unpublished

B - Sensitivity analysis

1/ Outliers:

- **For OS and EFS:** Cair[9], Budapest 2007[80] and TTCC2002[83,84] without GCSF use in the TaxPF induction arm
- **For loco-regional control and distant control :** EORTC 22954[$], CMGH-85[90], CFHNS[63], CAIRO 1990[22], Cair[9], Osaka 1993[18], SWOG 8006[61], HeCOG 9405[36,] INRC HN-8[37], DAHANCA 9[1], Yale 86[54], HNAP-02[68], Parma[70], KROG 0201[15], HNU-87a[75], AC Camargo[28], Buenos Aires[55], Bavaria89[30], BNH003[$], Cologne-88[64], Creteil-86[65], IAEA-CRP-ACC[12], IAEA-MMC[47], IAR 92[105], ICC-PCP[92], KBN PO 79[14], Kragujevac1[39], LOHNG91[48], Pitie-81[59], PMHCGS[52], TMHR-4[79]

[$] unpublished

2/ Trials with non-conventional chemotherapy

- **Without platin-based chemotherapy:** HNU-87[#75], JHCFUS[#77], KKD-86[#78], TMHR-4[#79], LOHNG91[48], Ontario[51], PMHCGS[52], SECOGII[$], Yale80[53], Yale86[54], ARO 95-06[108], IAEA-MMC[47], LOHNG97[49], NCI-V98-1416[50], UKHAN[#27], UKHANpo[27], Vienna*[26], SECOG I[96], Brescia[94], INRC HN-7[95], Decide[93].

- **With polychemotherapy ≥3drugs other than TaxPF or with only one drug as induction chemotherapy:** AC Camargo*[28], Lucknow95*[40], Torino 85[99], BuenosAires[55], Creteil-82[56], HNCGIC02[57], HNCGIC03[58], Pitie-81[59], Songkhla[60], SWOG8006[61].
- **With adjuvant chemotherapy:** GETTECadj[74], Int0034[76].

[#] trial or part of trials with adjuvant chemotherapy
* multi-arm trial where one comparison was not excluded.
[$] unpublished

3/ Trials with quality control limited by the trial size or date of randomisation not available or short follow-up

NCI-V98-1416[50], HNAP-02[68], MCW-2[69], Parma[70], TMH R-4[79], Budapest 2007[80], CH-7401[31], LOHNG91[48], AC Camargo*[28], Toulouse[45], Yale86[54], Bavaria89[30], Cologne 88[64], IAR 92[105], UPCI 93-99[46], Créteil 85[100], Brescia[94], CMGH-85[90], Spain 1998[101], CONDOR[87], EORTC 22843[88], BCCA 9113[8], EORTC 24844[$], IAEA-MMC[47], JHCFUS[77], AIIMS03[29], BNH003, GSTTC 2501[81,82], Cairo 1990[22], Songkhla[60], HNU-87[75], DAHANCA 9[1], KBN PO 79[14], INRCHN-7[95], EORTC 22962[$]*, TMH 1114*[21], INRC-HN-10[13], Cologne 95[109], EORTC 22954[$]*, CHARTWEL[$], Kragujevac1[39], EORTC 22851[11], Decide[93], Kragujevac2[106].

*multi-arm trials
[$] unpublished

4/ Trials with distinctive loco-regional treatments

- **Surgery (alone or with radiotherapy):** GETTECadj[74], Int0034[76], JHCFUS[77], TMHR-4[79], KKD-86[78], HNU-87[£75], Yale80[£53], Yale86[£54], Toulouse[45], UKHANpo[27], EORTC22931[34], RTOG9501[43], LOHNG97[49], SWOG8006[61], Buenos Aires[55], Créteil-82[56], Créteil-86[65], EORTC24844[$], GSTTC86[£67], GETTECneo2[66], AHNTG[£62], Cologne 88[64], BNH003[$], pCAIR[19], CHARTWEL[$], POPART[20], INRC-HN-10[13], CRT 90-002[16], Cairo1990[22], FRCT 94[32], HNAP-02[68], Shanghai 2008[73], Songkhla[60], UPCI 93-99[46], MCW-2[69], Rennes-87[71], Parma[70], CFHNS[63], CH-7401[31]
- **Alternating/Split/Confounded radiotherapy:** SECOG II[$], PMHCGS[52], INRC HN-8[37], Duke 90040[104], IAR 92[105], Int 0126[£38], ARO 95-06[108], GORTEC 9601[110], EORTC 24954[91], INRC HN-7[95], SECOG I[96], Brescia[94], ICC-PCP[92], CMGH-85[90], UKHAN[£27], INRC-HN9[85], EORTC 22843[88], RTOG 9003[£5], EORTC 22851[11], ORO 9301*[17], Bavaria-89[30], Pitié-81[59], RPC 3250[41]

*multi-arm trials
[£] part of the trial excluded
[$] unpublished

5/ Trials with a majority of patients with stage I/II tumours

- MACH-NC: JHCFUS[77] and KKD-86[78]
- MARCH: RTOG 9512[6], DAHANCA 9[1], DAHANCA 6&7[10,] Osaka 1993[18], KBN PO 79[14], KROG 0201[15].

Web-Appendix 3 – Data sharing

Will individual participant data be available (including data dictionaries)?	No
What data in particular will be shared?	Not available
What other documents will be available?	Study protocol is available here: https://www.gustaveroussy.fr/fr/meta-analyses-protocoles-dessais-orl. Large appendix are provided in all our publications, including this one.
When will data be available (start and end dates)?	Not applicable
With whom?	Not applicable
For what types of analyses?	Not applicable
By what mechanism will data be made available?	Not applicable

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