



Original Article

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group



Benjamin Lacas^{a,b}, Alexandra Carmel^a, Cécile Landais^a, Stuart J. Wong^c, Lisa Licitra^d, Jeffrey S. Tobias^e, Barbara Burtneff^f, Maria Grazia Ghi^g, Ezra E.W. Cohen^h, Cai Grauⁱ, Gregory Wolf^j, Ricardo Hitt^k, Renzo Corvò^l, Volker Budach^m, Shaleen Kumarⁿ, Sarbani Ghosh Laskar^o, Jean-Jacques Mazon^p, Lai-Ping Zhong^q, Werner Dobrowsky^r, Pirus Ghadjari^s, Carlo Fallai^t, Branko Zakotnik^u, Atul Sharma^v, René-Jean Bensadoun^w, Maria Grazia Ruo Redda^x, Séverine Racadot^y, George Fountzilas^z, David Brizel^{aa}, Paolo Rovea^{ab}, Athanassios Argiris^{ac}, Zoltán Takácsi-Nagy^{ad}, Ju-Whei Lee^{ae}, Catherine Fortpied^{af}, Jonathan Harris^{ag}, Jean Bourhis^{b,ah}, Anne Aupérin^{a,b}, Pierre Blanchard^{a,b,ai,*}, Jean-Pierre Pignon^{a,b}, on behalf of the MACH-NC Collaborative Group

^aService de Biostatistique et d'Epidémiologie, Gustave Roussy, Oncostat U1018 INSERM, labeled Ligue Contre le Cancer, Université Paris-Saclay, Villejuif; ^bGroupe d'Oncologie Radiothérapie Tête Et Cou, Tours, France; ^cDepartment of Medicine, Medical College of Wisconsin, Milwaukee, USA; ^dDepartment of Medical Oncology 3, Fondazione IRCCS-Istituto Nazionale dei Tumori, Milano and University of Milan, Italy; ^eDepartment of Radiotherapy, University College London Hospital, UK; ^fDepartment of Internal Medicine and Yale Cancer Center, Yale University, New Haven, USA; ^gOncology Unit 2, Veneto Oncology Institute-IRCCS, Padua, Italy; ^hUC San Diego, Moores Cancer Center, California, USA; ⁱDepartment of Experimental Clinical Oncology, Aarhus, Denmark; ^jDepartment of Otolaryngology, University of Michigan, Ann Arbor, USA; ^kServicio Oncología Médica, Hospital Universitario Severo Ochoa, Madrid, Spain; ^lDepartment of Radiation Oncology, Ospedale Policlinico San Martino and University of Genoa, Genoa, Italy; ^mDepartment of Radiation Oncology, Charité Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; ⁿDepartment of Radiotherapy, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow; ^oDepartment of Radiation Oncology, Tata Memorial Hospital, Homi Bhabha National Institute Mumbai, India; ^pDépartement de radiothérapie, hôpital Pitié-Salpêtrière, Paris, France; ^qDepartment of Oral and Maxillofacial-Head and Neck Oncology, Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine, Shanghai, China; ^rDept. Clinical Oncology, Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, United Kingdom; ^sDepartment of Radiation Oncology, Charité Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany and SAKK Coordinating Center, Bern, Switzerland; ^tDepartment of Radiotherapy, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; ^uDepartment of Medical Oncology, Institute of Oncology, Ljubljana, Slovenia; ^vDepartments of Medical Oncology, Dr BR Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India; ^wDepartments of Radiation Oncology, Centre Antoine Lacassagne, Nice, France; ^xDepartment of Radiation Oncology, Maurizio Umberto I Hospital, University of Turin School of Medicine, Turin, Italy; ^yDepartment of Radiation Oncology, Centre Léon Bérard, Lyon, France; ^zAristotle University of Thessaloniki School of Medicine, Thessaloniki, Greece; ^{aa}Departments of Radiation Oncology, Duke University Medical Center, Durham, USA; ^{ab}Radiation Oncology Unit, San Giovanni Antica Sede Hospital, Turin, Italy; ^{ac}Division of Hematology-Oncology, Department of Medicine, University of Pittsburgh, USA; ^{ad}Center of Radiotherapy, National Institute of Oncology, Department of Oncology, Semmelweis University, Budapest, Hungary; ^{ae}Dana Farber Cancer Institute - ECOG-ACRIN Biostatistics Center, Boston, USA; ^{af}EORTC Headquarters, Brussels, Belgium; ^{ag}NRG Oncology Statistics and Data Management Center, American College of Radiology, Philadelphia, USA; ^{ah}Department of Radiotherapy, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; ^{ai}Department of Radiation Therapy, Gustave Roussy Cancer Campus, Université Paris-Sud, Université Paris-Saclay, Villejuif, France

ARTICLE INFO

Article history:

Received 15 October 2020
Received in revised form 22 December 2020
Accepted 8 January 2021
Available online 27 January 2021

Keywords:

Meta-analysis
Review
Individual Patient Data
Randomised Clinical Trials
Chemotherapy
Radiotherapy
Head and Neck Cancer

ABSTRACT

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

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

Results: For the main question, 101 trials (18951 patients, median follow-up of 6.5 years) were analyzed. For both questions, there were 16 new (2767 patients) and 11 updated trials. Around 90% of the patients had stage III or IV disease. Interaction between treatment effect on OS and the timing of CT was significant ($p < 0.0001$), the benefit being limited to concomitant CT (HR: 0.83, 95%CI [0.79; 0.86]; 5(10)-year absolute benefit of 6.5% (3.6%)). Efficacy decreased as patients age increased ($p_{\text{trend}} = 0.03$). OS was

* Corresponding author at: Institut Gustave-Roussy, Département de Radiothérapie, 114 rue Edouard Vaillant, 94805 Villejuif cedex, France.

E-mail: pierre.blanchard@gustaveroussy.fr (P. Blanchard).

not increased by the addition of induction (HR = 0.96 [0.90; 1.01]) or adjuvant CT (1.02 [0.92; 1.13]). Efficacy of induction CT decreased with poorer performance status ($p_{\text{trend}} = 0.03$). For the secondary question, eight trials (1214 patients) confirmed the superiority of concomitant CT on OS (HR = 0.84 [0.74; 0.95], $p = 0.005$).

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

© 2021 Elsevier B.V. All rights reserved. Radiotherapy and Oncology 156 (2021) 281–293

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

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

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

Material and methods

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

Selection criteria and search strategy

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

Data extraction and checking

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

resulting survival analyses as well as data description were sent to the trialists for review.

Outcomes

The primary endpoint was overall survival (OS), defined as the time from randomization until death from any cause. As in the previous update, secondary endpoints were event-free survival (EFS), loco-regional failure (LRF), distant failure (DF), cancer and non-cancer mortality [2]. A new endpoint, 120-day mortality, was added as proxy for deaths related to treatment [8]. EFS was defined as the time from randomization to first recurrence or progression (loco-regional or distant failure) or death from any cause. Events considered were loco-regional failures without distant failure for LRF; and distant failure, either alone or combined with loco-regional failures, for DF. Non-cancer mortality was defined as deaths without previous failure and resulting from known causes other than the treated head and neck cancer. Cancer mortality included deaths from any cause with previous failure and deaths from the treated head and neck cancer. Deaths from unknown cause without previous failure were regarded as cancer mortality if they occurred within 5 years after randomization and as non-cancer mortality otherwise.

Secondary endpoints also included acute and late toxicities, and compliance; they have been collected but are not yet analysed. Those endpoints will be reported separately.

Statistical analysis

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

To study the robustness of the results several sensitivity analyses (*i.e.* analyses after exclusion of some trials) were realised (Web-Appendix 5). We performed subset analyses to study the interaction between treatment effect and trial level characteristics, using a test of heterogeneity among the different groups of trials. We estimated the interaction between treatment effect and patient subgroups (age, sex, performance status, smoking status, primary site, and overall stage) in a Cox model stratified by trial and adjusted on treatment effect, covariate effect (*e.g.* age), and treatment-covariate interaction (one-stage model method) [16]. Details about statistical methods including power estimation are available in Web-Appendix 5. Sensitivity, subset and subgroup

analyses were pre-specified in the protocol except if mentioned otherwise in this publication.

Because of findings in our previous study [4], the interaction between sex and chemotherapy effect was studied in patients treated with or without surgery. Trials were excluded if it was not possible to separate patients treated with or without surgery.

All *p* values were two-sided. Analyses were done using SAS, version 9.4 and R software (“crrSC” package for competing risk analysis), version 3.6.3.

Results

The meta-analysis included 107 randomized trials (19805 patients). Sixteen new trials (2767 patients) [1,2,17–36] (Web-Fig. 1, Web-Appendix 6) and 2327 deaths (including death from updated previous trials) were added for this update. We were able to collect data from 725 of the 867 randomized patients who had been excluded from the original published analyses. Updated follow-up was obtained for 11 trials and the median follow-up of all trials was 6.6 years (interquartile range [IQR]: 4.3; 10.6). The description of the trials included and their references can be found in Web-Tables 1, 2, 3 and 4. Some trials with multiple strata (different loco-regional treatments or chemotherapies, three-arm trial or 2 by 2 design) were duplicated (Web-Table 5, Web-Appendix 7) or divided in two strata or more. Therefore, 138 comparisons and 21,863 patients were included in the meta-analysis.

The main question on the addition of chemotherapy included 130 comparisons (20,649 patients) and the secondary question on the comparison of induction and concomitant chemotherapy included eight comparisons (1214 patients) (SECOG II unpublished) [17,23,24,37–42].

Main question: addition of chemotherapy to locoregional treatment

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

Results are summarised in Table 1.

Effect of induction chemotherapy

Forty-five induction comparisons were available to evaluate the effect of induction chemotherapy (7054 patients, 4692 deaths, cause of death in Web-Table 8) with a median follow-up of 5.7 years (IQR: 4.2;7.6) [17–19,25–30,43–74].

The HR of death (Fig. 1A, Web-Fig. 2) was 0.96 [95% confidence interval (CI): 0.90; 1.01] (*p* = 0.14) in favour of induction chemotherapy with an absolute difference of 2.2% at 5 years (Fig. 2A). Similar results were observed for event-free survival (type of EFS events in Web-Table 9), with a HR of 0.96 [0.90; 1.02] (*p* = 0.14) and an absolute difference of 1.4% at 5 years (Web-Fig. 3A). No significant effect on 120-day mortality was observed (HR = 1.07 [0.89; 1.28], *p* = 0.47; Web-Fig. 4).

There was no significant variation of the effect on OS according to the type of induction chemotherapy (interaction test: *p* = 0.22): HR = 0.97 [0.82; 1.15] for taxane plus platin plus 5-FU (TPF), 0.90 [0.82; 0.99] for platin plus 5-FU (PF), 1.00 [0.92; 1.09] for other induction regimens, nor on EFS (test of interaction: *p* = 0.20). The exclusion (unplanned analysis) of the three comparisons with major early related to treatment mortality and/or without GCSF (two TPF comparisons (Budapest 2007, TTCC 2002 TPF) and one PF comparison (TTCC 2002 PF)) led to the following results: for OS, overall HR of 0.94 [0.89; 1.00] (*p* = 0.06) and HR of 0.83 [0.67; 1.02] (*p* = 0.08) for the TPF subset (interaction test

p = 0.08); for EFS, overall HR of 0.95 [0.89; 1.01] (*p* = 0.10) and HR of 0.77 [0.64; 0.94]; *p* = 0.02) for the TPF (interaction test *p* = 0.09).

Excluding trials with more than one timing of chemotherapy, or confounded or less than 80 patients, or performed before 1980, or with a follow-up shorter than 5 years led to similar results for OS and EFS (Web-Table 10A). Analysis without arm duplication led to similar results (Web-appendix 7). In recent trials, it was possible to separate cancer and non-cancer deaths (Web-Table 8). But data were not available in 11 comparisons out of 25. Effect of chemotherapy was not significant both for deaths related to head and neck cancer (HR = 0.97 [0.86; 1.10], *p* = 0.67 and an absolute difference of 0.7% at 5 years) and non-cancer deaths (0.84 [0.67; 1.05], *p* = 0.12) (Web-Fig. 5A). The effect addition of induction chemotherapy on LRF was not significant (sub-HR = 1.07 [95% CI = 0.99; 1.15], *p* = 0.09); Web-Figs. 6 and 8-A), when a significant decrease on DF was observed (0.76 [0.66; 0.88], *p* = 0.0002; Web-Figs. 7 and 9-A).

The effect of chemotherapy on OS and EFS did not differ significantly between the groups of trials according to chemotherapy modalities, year of start of accrual, or locoregional treatment (Web-Tables 11A, 12A, 12B, and 12C). There was no clear evidence of a differential effect of induction chemotherapy on overall or event-free survival according to age, sex, stage or tumour site (Web-Table 13A). There was a decreasing effect of chemotherapy with poorer performance status on OS (test for trend: *p* = 0.03) but not on EFS (*p* = 0.07) (Fig. 3A). With adjustment on sex and age, results were still significant for OS (*p* = 0.02) and borderline for EFS (*p* = 0.05).

Effect of concomitant chemotherapy

Seventy-one concomitant comparisons were available to evaluate the effect of concomitant chemotherapy (10,680 patients, 7944 deaths, cause of death in Web-Table 8) with a median follow-up of 9.2 years (IQR: 5.2; 12.9) [17,20–22,31–34,36,56,75–123]. The HR of death (Fig. 1A, Web-Fig. 10) was 0.83 [95% CI: 0.79; 0.86] (*p* < 0.0001) in favour of concomitant chemotherapy with an absolute benefit of 6.5% at 5 years and 3.6% at 10 years (Fig. 2B). The magnitude of the benefit was similar for the trials included in the initial meta-analysis and those included in the updates (test for interaction: *p* = 0.77), without significant heterogeneity in the most recent trials (*p* = 0.30).

Similar results were observed for event-free survival (Web-Table 9, Fig. 1B), with a HR of 0.80 [0.77; 0.84] (*p* < 0.0001) and an absolute benefit of 5.8% at 5 years and 3.1% at 10 years (Web-Fig. 3B). No significant effect on 120-day mortality was observed (HR = 1.07 [0.92; 1.24], *p* = 0.37; Web-Fig. 4).

Similar results were observed with the sensitivity analyses (Web-Table 10B). The benefit of chemotherapy was due to its effect on deaths related to head and neck cancer (HR = 0.79 [0.74; 0.84], *p* < 0.0001 and an absolute benefit of 9.8% at 5 years) (Web-Fig. 5B). There was no effect on non-cancer deaths (1.01 [0.89; 1.16], *p* = 0.83). Addition of concomitant chemotherapy showed a significant decrease of LRF (sub-HR = 0.71 [0.67; 0.75], *p* < 0.0001; Web-Figs. 6 and 8-B) with a non significant effect on DF (1.04 [0.92; 1.18], *p* = 0.48; Web-Figs. 7 and 9-B).

No significant variation of chemotherapy effect on OS and EFS was observed according to year of start of accrual or locoregional treatment (Web-Tables 11B, 12B, and 12C). For EFS, treatment effect varied significantly according to chemotherapy modality (test for interaction: *p* = 0.01) with the highest effect for polychemotherapy with platin salt (HR = 0.74 [0.67; 0.82]) and the lowest for monochemotherapy without platin salt (0.86 [0.80; 0.93]). For OS, interaction was borderline (*p* = 0.06) (Web-Table 12A). The only statistically significant variation of treatment effect on survival according to patient characteristics

Table 1

Results of the addition of chemotherapy to loco-regional treatment.

	Overall survival	120-day mortality	Event-free survival	Cancer mortality [§]	Non-cancer mortality [§]	Loco-regional failure*	Distant failure*
Induction							
No. events/No. patients	4692/7054	470/7054	4556/6374	979/2031	320/2031	2574/6342	761/5582
HR of chemotherapy effect [95% CI]; <i>p</i> -value	0.96 [0.90; 1.01] <i>p</i> = 0.14	1.07 [0.89; 1.28] <i>p</i> = 0.47	0.96 [0.90; 1.02] <i>p</i> = 0.14	0.97 [0.86; 1.10] <i>p</i> = 0.67	0.84 [0.67; 1.05] <i>p</i> = 0.12	1.07 [0.99; 1.15] <i>p</i> = 0.09	0.76 [0.66; 0.88] <i>p</i> = 0.0002
Heterogeneity: <i>p</i> -value (<i>I</i> ²)	<i>p</i> = 0.63 (0%)	<i>p</i> = 0.46 (1%)	<i>p</i> = 0.25 (12%)	<i>p</i> = 0.24 (19%)	<i>p</i> = 0.28 (16%)	<i>P</i> < 0.0001 (63%)	<i>P</i> < 0.0001 (97%)
Absolute difference at 5 years [95% CI]	+2.2% [−0.2; +4.6]	NA	+1.4% [−0.9; +3.7]	−0.7% [−5.5; +4.1]	−4.8% [−0.4; −9.2]	+3.2% [+0.8; +5.7]	−4.1% [−6.0; −2.2]
Absolute difference at 10 years [95% CI]	+1.3% [−1.9; +4.5]	NA	−0.6% [−3.6; +2.4]	NA	NA	+4.6% [+1.7; +7.5]	−3.5% [−5.7; −1.3]
Concomitant							
No. events/No. patients	7944/10,680	716/10,680	8345/10,457	3730/6483	955/6483	4766/10,076	1034/9022
HR of chemotherapy effect [95% CI]; <i>p</i> -value	0.83 [0.79; 0.86] <i>p</i> < 0.0001	1.07 [0.92; 1.24] <i>p</i> = 0.37	0.80 [0.77; 0.84] <i>p</i> = 0.04 (24%)	0.79 [0.74; 0.84] <i>p</i> < 0.0001	1.01 [0.89; 1.16] <i>p</i> = 0.83	0.71 [0.67; 0.75] <i>p</i> < 0.0001	1.04 [0.92; 1.18] <i>p</i> = 0.48
Heterogeneity: <i>p</i> -value (<i>I</i> ²)	<i>p</i> = 0.0002 (42%)	<i>p</i> = 0.01 (30%)	<i>p</i> = 0.04 (24%)	<i>p</i> = 0.18 (18%)	<i>p</i> = 0.80 (0%)	<i>P</i> < 0.0001 (85%)	<i>P</i> < 0.0001 (96%)
Absolute difference at 5 years [95% CI]	+6.5% [+4.6; +8.4]	NA	+5.8% [+4.1; +7.5]	−9.8% [−12.4; −7.2]	+2.9% [+0.1; +5.7]	−9.3% [−11.3; −7.3]	+0.2% [−1.0; +1.6]
Absolute difference at 10 years [95% CI]	+3.6% [+1.8; +5.4]	NA	+3.1% [+1.5; +4.7]	NA	NA	−9.6% [−11.6; −7.5]	+0.2% [−1.2; +1.6]
Adjuvant							
No. events/No. patients	1605/2915	127/2915	1461/2416	NA	NA	571/2416	324/2224
HR of chemotherapy effect [95% CI]; <i>p</i> -value	1.02 [0.92; 1.13] <i>p</i> = 0.69	1.89 [1.33; 2.68] <i>p</i> = 0.0003	0.98 [0.88; 1.09] <i>p</i> = 0.72	NA	NA	0.84 [0.72; 1.00] <i>p</i> = 0.04	0.77 [0.62; 0.96] <i>p</i> = 0.02
Heterogeneity: <i>p</i> -value (<i>I</i> ²)	<i>p</i> = 0.21 (23%)	<i>p</i> = 0.10 (34%)	<i>p</i> = 0.03 (47%)	NA	NA	<i>p</i> = 0.16 (29%)	<i>P</i> < 0.0001 (98%)
Absolute difference at 5 years [95% CI]	−0.3% [−4.3; +3.7]	NA	−0.6% [−5.0; +3.8]	NA	NA	−3.7% [−7.2; −0.2]	−3.0% [−6.0; 0.0]
Absolute difference at 10 years [95% CI]	+1.2% [−4.1; +6.5]	NA	+3.6% [−2.7; +9.9]	NA	NA	−3.6% [−7.2; 0.0]	−3.2% [−6.5; +0.2]
Interaction test (timing × treatment effect)	<i>p</i> < 0.0001	0.01	<i>p</i> < 0.0001	<i>P</i> = 0.003	<i>P</i> = 0.15	<i>p</i> < 0.0001	<i>P</i> = 0.001

CI: Confidence Interval, HR: Hazard Ratio, NA: Not Applicable.

Absolute differences at 5 and 10 years are absolute differences of survival for overall survival, and event-free survival, absolute differences of mortality for cancer mortality and non-cancer mortality, and absolute differences of cumulative incidence for loco-regional failure and distant failure.

* HR are sub-HR estimated with Fine and Gray model. § Data on cancer/non-cancer deaths were available for only two trials (5 comparisons) for the adjuvant timing.

All patients were analysed for OS. Six comparisons (1402 patients) were excluded from the analyses of EFS, LRF and DF due to incomplete data regarding failures [33,34,44,89,126]. One additional comparison (371 patients) was excluded from the analyses of LRF and DF because of missing failure location [82,83]. Concerning cancer and non-cancer mortality and induction timing, out of 25 recent comparisons (PF/TPF subsets: 3870 patients), 11 (1839 patients) were excluded because of lack of data ([29,30,59–63,68,69,71–74] and two unpublished trials: BNH003, EORTC 24844). For concomitant timing, out of 41 recent comparisons (first and second update: 6911 patients), four (428 patients) were excluded for the same reason [22,32,33].

See Web-Appendix 8 for the study of the source of heterogeneity.

B

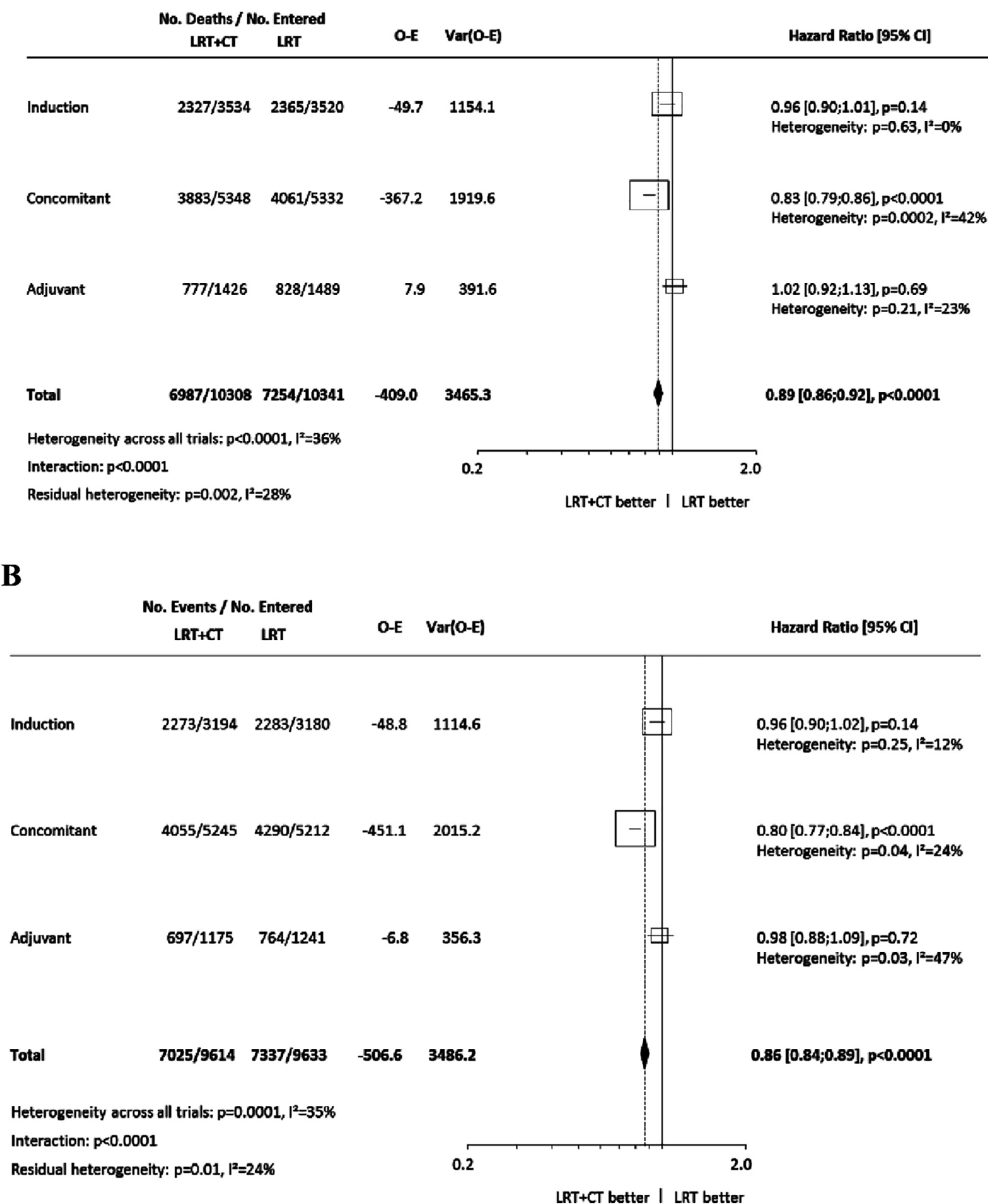


Fig. 1. Efficacy of loco-regional treatment plus chemotherapy versus loco-regional treatment alone by timing of chemotherapy. (A) Overall survival (see [web-Figure 2, 10 and 11](#) for detailed HR plot), (B) Event-free survival. Dotted line and centre of the black diamond are the overall pooled hazard ratio. Horizontal tip of the diamond is the 95% confidence interval. Centre of the squares correspond are the HR of each chemotherapy timing. Area of the square is proportional to the number of deaths in each group of trials. CI: Confidence Interval, CT: Chemotherapy, HR: Hazard Ratio, LRT: Loco-Regional Treatment, O-E: Observed minus Expected.

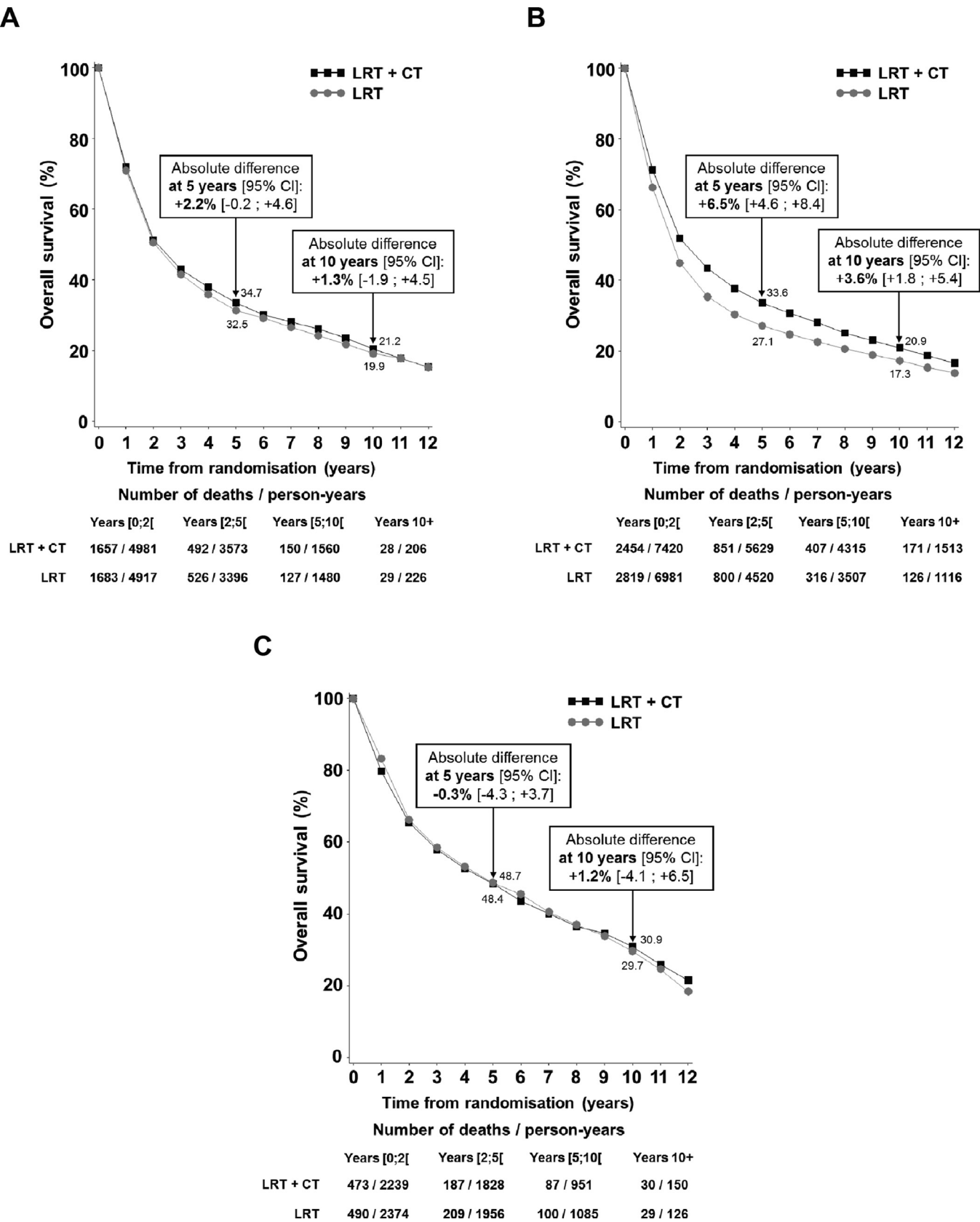


Fig. 2. Overall survival – Survival curves of loco-regional treatment plus chemotherapy and loco-regional treatment alone by timing. (A) Induction chemotherapy, (B) Concomitant chemotherapy, (C) Adjuvant chemotherapy. CI: confidence interval, CT: Chemotherapy, LRT: Loco-Regional Treatment.

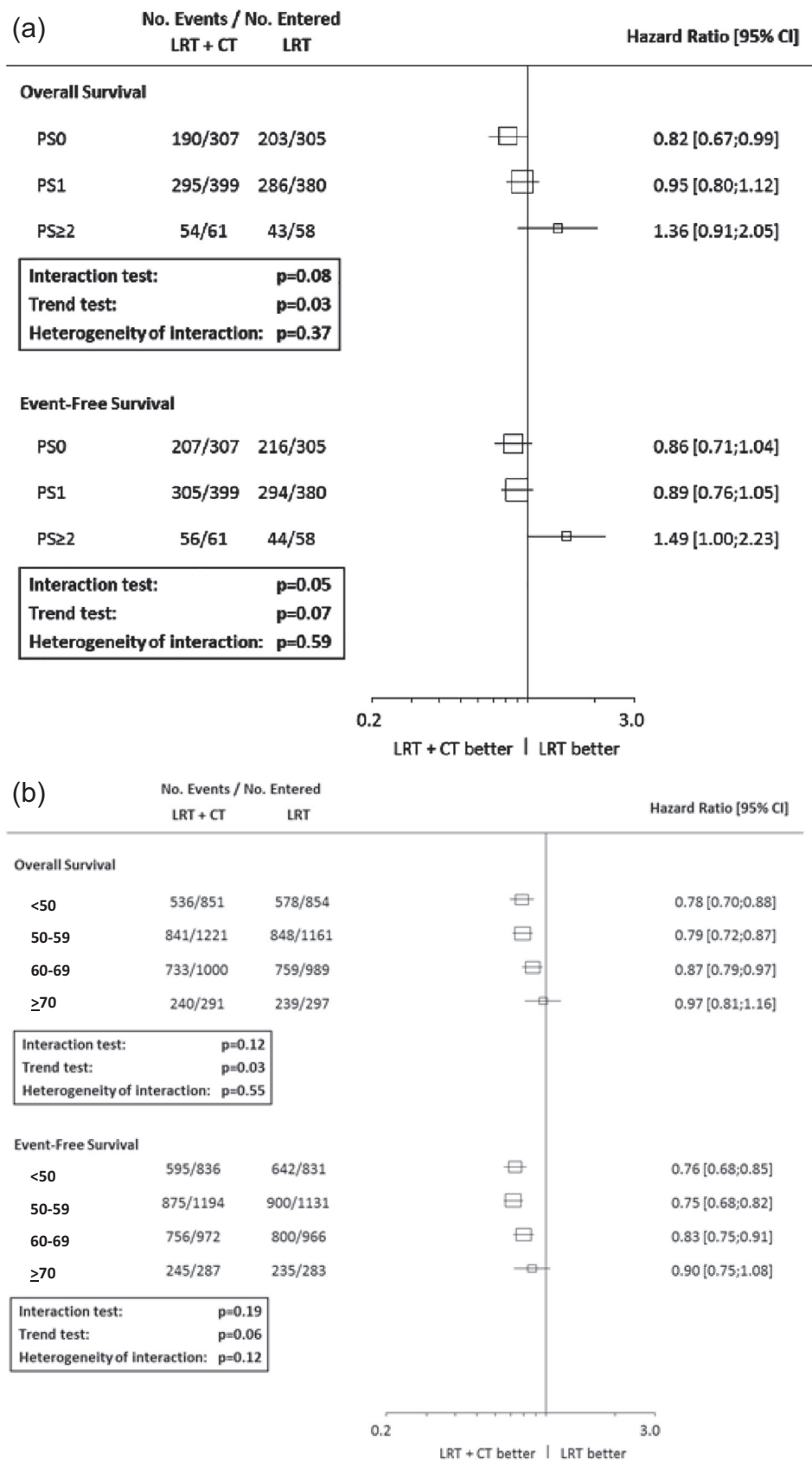


Fig. 3. Subgroup analyses for loco-regional treatment plus chemotherapy versus loco-regional treatment alone. (A) By performance status for induction chemotherapy, (B) By age for concomitant chemotherapy. CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment, PS: Performance Status.

(Web-Table 13B and Fig. 3B) was a decreasing effect of chemotherapy on OS with increasing age (test for trend: $p = 0.03$). Results were borderline for event-free survival ($p = 0.06$) (Fig. 3B). This effect could not be explained by an imbalance in the other covariates studied (data not shown). The cause of death was available only for the recent trials (1994–2010). As might be expected, the proportion of deaths not due to head and neck cancer increased with age from 18% in patients less than 50 to 37% in patients 70 and over (Web-Table 14). Adjusting on sex led to similar results for OS. Test for trend was also significant for EFS ($p = 0.04$).

Effect of adjuvant chemotherapy

Fourteen adjuvant comparisons were available to evaluate the effect of adjuvant chemotherapy (2915 patients, 1605 deaths, cause of death in Web-Table 8) with a median follow-up of 5.4 years (IQR: 3.6;8.7) [35,47,104,124–130]. The HR of death (Fig. 1A, Web-Fig. 11) was 1.02 [95% CI: 0.92; 1.13] ($p = 0.69$) with an absolute difference of -0.3% at 5 years (Fig. 2C). Similar results were observed for event-free survival (Web-Table 9, Fig. 1B), with a HR of 0.98 [0.88; 1.09] ($p = 0.72$) and an absolute difference of -0.6% at 5 years (Web-Fig. 3C). A deleterious effect on 120-day mortality was observed (HR = 1.89 [1.33; 2.68], $p = 0.0003$; Web-Fig. 4) without variation according to locoregional treatment modalities (data not shown).

Similar results were observed with the sensitivity analyses (Web-Table 10C). A significant decrease on LRF and DF was observed with the addition of adjuvant chemotherapy: sub-HR of 0.84 ([0.72; 1.00], $p = 0.04$; Web-Figs. 6 and 8-C) and of 0.77 ([0.62; 0.96], $p = 0.02$; Web-Figs. 7 and 9-C), respectively.

No significant variation of chemotherapy effect on OS and EFS was observed according to chemotherapy modalities or year of start of accrual (Web-Tables 11C, 12A, and 12B). A significant effect was observed on EFS, but not on OS for type of locoregional treatment (interaction test $p = 0.005$) with HR of 0.77 [0.62; 0.96] in the comparisons using only surgery (Web-Table 12C).

Secondary question: concomitant versus induction chemotherapy

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

Indirect comparison

Overall survival and event-free survival

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

120 days mortality

Out of 20,649 patients, 1313 (6%) died within 120-day after randomisation: 470 out of 7054 (7%), 716 out of 10,680 (7%) and 127 out of 2915 (4%) in the induction, concomitant, and adjuvant comparisons respectively. Overall, 120-day mortality increased with

chemotherapy (HR = 1.13 [1.01; 1.26], $p = 0.03$, Web-Fig. 4) with a significant variation by timing (interaction test: $p = 0.01$). This deleterious effect was significant for adjuvant timing (HR = 1.89 [1.33; 2.68], $p = 0.0003$) but not for the two other timings. The overall heterogeneity observed was mainly explained by the significant interaction between timings and the heterogeneity within concomitant group (Web-Appendix 8).

Locoregional and distant failures

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

Interaction between sex, surgery and treatment

Patients treated with surgery corresponded to 28 comparisons, 5503 patients and those treated without surgery 74 comparisons, 12,949 patients. These two populations had significantly different patient and tumour characteristics: differences were often small and, as expected, based on selection criteria for surgery (Web-Table 16). Among comparisons with surgery, a better effect of chemotherapy was observed in women compared to men: HR of 0.67 [0.54; 0.82] and 0.96 [0.89; 1.03] respectively (interaction test, $p = 0.001$) for OS with similar results for EFS. A gender effect was not significant for the comparisons without surgery: HR of 0.94 [0.85; 1.04] for women and 0.87 [0.83; 0.91] for men (interaction test, $p = 0.15$) for OS, with similar results for EFS (Web-Table 17).

Discussion

The present study provides the most comprehensive and robust analysis of the role of chemotherapy in combination with locoregional therapy for the treatment of non-metastatic HNSCC. It involved the individual data of 19,805 patients included in 107 randomized trials. Results were robust to multiple pre-specified sensitivity analyses. Given that the landscape of clinical trials has shifted from cytotoxic chemotherapy to targeted therapies and recently to immunotherapy, this analysis is likely to be the ultimate analysis on the topic. A set of major findings have been made and are discussed hereafter.

The analysis on induction chemotherapy demonstrated a survival benefit for the combination of platinum and 5FU (PF) with a HR of 0.90 [95% CI: 0.82; 0.99] but failed to show a similar benefit for the triplet containing of taxane, platinum and 5FU (TPF). This is surprising, as the superiority of TPF over PF has been demonstrated in multiple trials and meta-analyses [3]. A few important facts about induction TPF should be noticed. First, some TPF trials were not included in the meta-analysis because they were confounded due to different concomitant treatments for the TPF and no induction arms [131,132]. Second, four out of the five trials included used chemoradiation as a comparator [18,19,25–28], whereas the vast majority of PF trials had RT alone as comparator. The bar was hence higher for TPF than for PF. As shown by our analyses, TPF may be associated with a high risk of treatment related death, as shown by an excess in early death in two trials that did not appropriately select patients or use G-CSF [18,19,25]. Excluding these trials led to a significant effect of this chemotherapy on EFS, but not on overall survival. Moreover, no effect of age could be demonstrated for induction chemotherapy but there was a significant decrease of the overall survival benefit with poorer perfor-

mance status. Hence induction chemotherapy should be considered only for fit patients. To decrease TPF toxicity without changing efficacy, modified schedule of TPF has been proposed. But, data from randomized trial are currently limited and results mixed [133,134]. Better selection tools to identify patients who will benefit from TPF induction remain needed.

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

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

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

Limitations include the large time span of the randomized trials included, 1965–2012 during which time staging, treatments and supportive care have all greatly evolved. No interaction between period of accrual and overall survival or event-free survival was recorded and exclusion of the trials performed before 1980 led to similar results. Individual patient data were not available for 13 trials (1067 patients), but such trials appeared of lower quality, with fewer patients and with higher treatment effect than those included in IPD meta-analysis [136]. Three potentially eligible randomised trials (415 patients) were identified in 2019, but because of their design and size they are unexpected to have any impact on the conclusion of this work (Web-Table 18). To the best of our knowledge, no patient has been accrued in a trial eligible for this meta-analysis after 2012. For the secondary question, only few trials could be included and although they show the superiority of concomitant chemotherapy, a network meta-analysis would improve the estimation of relative treatment efficacy. No data on HPV or limited data on smoking status were available and given the timing of the trials and tumour subsites, most tumours are likely HPV-negative although this hypothesis cannot be confirmed. The superiority of concomitant cisplatin has been shown in HPV-positive oropharyngeal cancers compared to cetuximab and is in

these studies of the same magnitude as in this analysis, with a 5-year benefit for cisplatin of 6.7% in RTOG 1016 [6]. No data on treatment compliance or toxicity have been presented here. Last, there are statistical limitations. The important number of endpoints analyzed raises the question of multiplicity of testing and the inflation of type I error. However, overall survival was the primary endpoint of the meta-analysis, most secondary endpoints and analyses were pre-specified, and there is consistency between main and secondary endpoints. Also the duplication of trial arms in case of multi-arms trials could bias the results, but analyses without duplication did not alter the results (Web-Appendix 7).

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

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

Contributors

PB, JB, and JPP with the help of the steering committee members designed and supervised the study.

PB, and JPP obtained funding.

PB, JB, JPP and BL searched and selected the trials. Steering committee members contributed to the identification and selection of the trials.

PB, BL and JPP collected and checked data with the help of the investigators who validated the re-analysis of their trials.

AA, BL, PB and JPP did the statistical analyses and wrote the draft, with revisions from the other investigators.

All authors contributed to the interpretation of the results during the investigator meeting and the revision of the manuscript. All investigators listed in Web-Appendix 1 received the manuscript for revision.

Role of funding sources

The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The submission of the paper for publication was decided by the MACH-NC collaborative group. AA, PB, BL, and J-PP had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have seen and approved the final version and, after consultation with the collaborators, agreed to submit for publication.

Declaration of Competing Interest

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

Acknowledgements

We thank the trialists and the collaborative groups who agreed to share their data. The contents of this publication and methods used are solely the responsibility of the authors and do not necessarily represent the official views of the ECOG-ACRIN Cancer Research Group, and NRG Oncology. This research was funded by grants from Institut National du Cancer (Programme Hospitalier de Recherche Clinique) and Ligue Nationale Contre le Cancer.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2021.01.013>.

References

- Pignon J-P, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet* 2000;355:949–55.
- Pignon J-P, le Maître A, Maillard E, Bourhis J. MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009;92:4–14. <https://doi.org/10.1016/j.radonc.2009.04.014>.
- Blanchard P, Bourhis J, Lacas B, Posner MR, Vermorken JB, Hernandez JJC, et al. Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the Meta-Analysis of Chemotherapy in Head and Neck Cancer Group. *J Clin Oncol* 2013;31:2854–60. <https://doi.org/10.1200/JCO.2012.47.7802>.
- Dauzier E, Lacas B, Blanchard P, Le Q-T, Simon C, Wolf G, et al. Role of chemotherapy in 5000 patients with head and neck cancer treated by curative surgery: A subgroup analysis of the meta-analysis of chemotherapy in head and neck cancer. *Oral Oncol* 2019;95:106–14.
- Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCaLaTe HPV): an open-label randomised controlled phase 3 trial. *Lancet* 2019;393:51–60. [https://doi.org/10.1016/S0140-6736\(18\)32752-1](https://doi.org/10.1016/S0140-6736(18)32752-1).
- Gillison ML, Trotti AM, Harris J, Eisbruch A, Harari PM, Adelstein DJ, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet* 2019;393:40–50. [https://doi.org/10.1016/S0140-6736\(18\)32779-X](https://doi.org/10.1016/S0140-6736(18)32779-X).
- Stewart LA, Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. *Cochrane Working Group. Stat Med* 1995;14:2057–79.
- Lacas B, Bourhis J, Overgaard J, Zhang Q, Grégoire V, Nankivell M, et al. Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. *Lancet Oncol* 2017;18:1221–37. [https://doi.org/10.1016/S1470-2045\(17\)30458-8](https://doi.org/10.1016/S1470-2045(17)30458-8).
- Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA* 2015;313:1657–65. <https://doi.org/10.1001/jama.2015.3656>.
- Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996;17:343–6.
- Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Progr Cardiovasc Dis* 1985;27:335–71.
- Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58. <https://doi.org/10.1002/sim.1186>.
- Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 1992;339:71–85.
- Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. *N Engl J Med* 1995;333:1444–55. <https://doi.org/10.1056/NEJM199511303332202>.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509. <https://doi.org/10.1080/01621459.1999.10474144>.
- Fisher DJ, Copas AJ, Tierney JF, Parmar MKB. A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. *J Clin Epidemiol* 2011;64:949–67. <https://doi.org/10.1016/j.ijclinepi.2010.11.016>.
- Kumar S, Datta NR, Nagar Y, Lal P, Singh S, Rastogi N, et al. A three-arm randomized trial comparing neo-adjuvant or concurrent weekly cisplatin to radiotherapy alone for locally advanced head and neck squamous cell cancer (HNSCC). *Eur J Cancer* 2011;47(S1):547.
- Hitt R, Grau J, López-Pousa A, Berrocal A, García-Girón C, Irigoyen A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. *Ann Oncol* 2014;25:216–25. <https://doi.org/10.1093/annonc/mdt461>.
- Hitt R, Iglesias L, López-Pousa A, Berrocal-Jaime A, Grau JJ, García-Girón C, et al. Long-term outcomes of induction chemotherapy followed by chemoradiotherapy vs chemoradiotherapy alone as treatment of unresectable head and neck cancer: follow-up of the Spanish Head and Neck Cancer Group (TTCC) 2503 Trial. *Clin Transl Oncol* 2020. <https://doi.org/10.1007/s12094-020-02467-8>.
- Argiris A, Karamouzis M, Johnson J, Heron D, Myers E, Eibling D, et al. Long-term results of a phase III randomized trial of postoperative radiotherapy with or without carboplatin in patients with high-risk head and neck cancer. *Laryngoscope* 2008;118:444–9. <https://doi.org/10.1097/MLG.0b013e31815b48f4>.
- Bensadoun R-J, Bénézy K, Dassonville O, Magné N, Poissonnet G, Ramaïoli, et al. French multicenter phase III randomized study testing concurrent twice-a-day radiotherapy and cisplatin/5-fluorouracil chemotherapy (BiRCF) in unresectable pharyngeal carcinoma: Results at 2 years (FNCLCC-GORTEC). *Int J Radiat Oncol Biol Phys* 2006;64:983–94. <https://doi.org/10.1016/j.ijrobp.2005.09.041>.
- Sharma A, Mohanti B, Thakar A, Bahadur S, Bhasker S. Concomitant chemoradiation versus radical radiotherapy in advanced squamous cell carcinoma of oropharynx and nasopharynx using weekly cisplatin: A phase II randomized trial. *Ann Oncol* 2010;21:2272–7. <https://doi.org/10.1093/annonc/mdq219>.
- Lefebvre J, Rolland F, Tesselaar M, Bardet E, Leemans C, Geoffrois L, et al. Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. *J Natl Cancer Inst* 2009;101:142–52. <https://doi.org/10.1093/jnci/din460>.
- Henriques De Figueiredo B, Fortpied C, Menis J, Lefebvre JL, Barzan L, de Raucourt D, et al. Long-term update of the 24954 EORTC phase III trial on larynx preservation. *Eur J Cancer* 2016;65:109–12. <https://doi.org/10.1016/j.ejca.2016.06.024>.
- Takacs-Nagy Z, Hitre E, Remenar E, Oberna F, Polgar C, Major T, et al. Docetaxel, cisplatin and 5-fluorouracil induction chemotherapy followed by chemoradiotherapy or chemoradiotherapy alone in stage III-IV unresectable head and neck cancer: Results of a randomized phase II study. *Strahlenther Onkol* 2015;191:635–41. <https://doi.org/10.1007/s00066-015-0829-z>.
- Cohen E, Karrison T, Kocherginsky M, Mueller J, Egan R, Huang CH, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. *J Clin Oncol* 2014;32:2735–43. <https://doi.org/10.1200/JCO.2013.54.6309>.
- Paccagnella A, Ghi M, Loreggian L, Buffoli A, Koussis H, Mione C, et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: A phase II randomized study. *Ann Oncol* 2010;21:1515–22. <https://doi.org/10.1093/annonc/mdp573>.
- Ghi MG, Paccagnella A, Ferrari D, Foa P, Alterio D, Codeca C, et al. Induction TPF followed by concomitant treatment versus concomitant treatment alone in locally advanced head and neck cancer. A phase II-III trial. *Ann Oncol* 2017;28:2206–12. <https://doi.org/10.1093/annonc/mdx299>.
- Zhong L-P, Zhang C-P, Ren G-X, Guo W, William WNJ, Hong C, et al. Long-term results of a randomized phase III trial of TPF induction chemotherapy followed by surgery and radiation in locally advanced oral squamous cell carcinoma. *Oncotarget* 2015;6:18707–14.
- Zhong L-P, Zhang C-P, Ren G-X, Guo W, William Jr WN, Sun J, et al. Randomized phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma. *J Clin Oncol* 2013;31:744–51. <https://doi.org/10.1200/JCO.2012.43.8820>.
- Ruo Redda MG, Ragona R, Ricardi U, Beltramo G, Rampino M, Gabriele P, et al. Radiotherapy alone or with concomitant daily low-dose carboplatin in locally advanced, unresectable head and neck cancer: definitive results of a phase III study with a follow-up period of up to ten years. *Tumori* 2010;96:246–53.
- Racadot S, Mercier M, Dussart S, Dessard-Diana B, Bensadoun R-J, Martin M, et al. Randomized clinical trial of post-operative radiotherapy versus concomitant carboplatin and radiotherapy for head and neck cancers with lymph node involvement. *Radiother Oncol* 2008;87:164–72. <https://doi.org/10.1016/j.radonc.2007.12.021>.
- Boidi Trotti A, Rovea P, Gabriele AM, Tseroni V, Fracchia F, Raiteri M, et al. The use of cisplatin as radiosensitizing agent in advanced tumors of the head and neck. *Randomized study. La Radiol Med* 1991;82:504–7.
- Haddad E, Mazeron JJ, Martin M, Vergnes L, Brun B, Piedbois P, et al. Comparison of concomitant radiotherapy and chemotherapy with radiotherapy alone in advanced cancers of the head and neck: results of a randomized trial. *Bull Cancer Radiother* 1996;83:97–103.

- [35] Ervin TJ, Clark JR, Weichselbaum RR, Fallon BG, Miller D, Fabian RL, et al. An analysis of induction and adjuvant chemotherapy in the multidisciplinary treatment of squamous-cell carcinoma of the head and neck. *J Clin Oncol* 1987;5:10–20. <https://doi.org/10.1200/JCO.1987.5.10>.
- [36] Ghosh-Laskar S, Kalyani N, Gupta T, Budrukkar A, Murthy V, Sengar M, et al. Conventional radiotherapy versus concurrent chemoradiotherapy versus accelerated radiotherapy in locoregionally advanced carcinoma of head and neck: Results of a prospective randomized trial. *Head Neck* 2016;38:202–7. <https://doi.org/10.1002/hed.23865>.
- [37] Adelstein D, Sharan V, Earle A, Shah A, Vlastou C, Haria C, et al. Simultaneous versus sequential combined technique therapy for squamous cell head and neck cancer. *Cancer* 1990;65:1685–91.
- [38] Adelstein D, Sharan V, Earle A, Shah A, Vlastou C, Haria C, et al. Long-term follow-up of a prospective randomized trial comparing simultaneous and sequential chemoradiotherapy for squamous cell head and neck cancer. Adjuvant therapy of cancer VII, Philadelphia, PA: Lippincott Company; 1993, p. 82–91.
- [39] A randomized trial of combined multidrug chemotherapy and radiotherapy in advanced squamous cell carcinoma of the head and neck. An interim report from the SECOG participants. *Eur J Surg Oncol* 1986;12:289–95.
- [40] Buffoli A, Morrica B, Frata P, La Face B. Chemo-radiotherapy in advanced head and neck tumors. Personal experience. *La Radiologia medica* 1992;83:636–40.
- [41] Taylor SG, Murthy AK, Vannetzel J-M, Colin P, Dray M, Caldarelli DD, et al. Randomized comparison of neoadjuvant cisplatin and fluorouracil infusion followed by radiation versus concomitant treatment in advanced head and neck cancer. *J Clin Oncol* 1994;12:385–95.
- [42] Merlano M, Corvo R, Margarino G, Benasso M, Rosso R, Sertoli MR, et al. Combined chemotherapy and radiation therapy in advanced inoperable squamous cell carcinoma of the head and neck. The final report of a randomized trial. *Cancer* 1991;67:915–21.
- [43] Richard JM, Sancho H, Lepintre Y, Rodary J, Pierquin B. Intra-arterial methotrexate chemotherapy and telecobalt therapy in cancer of the oral cavity and oropharynx. *Cancer* 1974;34:491–6. [https://doi.org/10.1002/1097-0142\(197409\)34:3<491::AID-CNCR2820340303.0.CO;2-G](https://doi.org/10.1002/1097-0142(197409)34:3<491::AID-CNCR2820340303.0.CO;2-G).
- [44] Fazekas J, Sommer C, Kramer S. Adjuvant intravenous methotrexate or definitive radiotherapy alone for advanced squamous cancers of the oral cavity, oropharynx, supraglottic larynx or hypopharynx. Concluding report of an RTOG randomized trial on 638 patients. *Int J Radiat Oncol Biol Phys* 1980;6:533–41. [https://doi.org/10.1016/0360-3016\(80\)90379-X](https://doi.org/10.1016/0360-3016(80)90379-X).
- [45] Jortay A, Demard F, Dalesio O, Blanchet C, Desautly A, Gehanno C, et al. A randomized EORTC study on the effect of preoperative polychemotherapy in pyriform sinus carcinoma treated by pharyngolaryngectomy and irradiation. Results from 5 to 10 years. *Acta Chirurgica Belgica* 1990;90:115–22.
- [46] Pearlman NW, Johnson FB, Braun TJ, Kennaugh RC, Spofford BF, Borlase BC, et al. A prospective study of preoperative chemotherapy and split-course irradiation for locally advanced or recurrent oral/pharyngeal squamous carcinoma. *Am J Clin Oncol* 1985;8:490–6. <https://doi.org/10.1097/0000421-198512000-00008>.
- [47] Adjuvant chemotherapy for advanced head and neck squamous carcinoma. Final report of the Head and Neck Contracts Program. *Cancer* 1987;60:301–11. [https://doi.org/10.1002/1097-0142\(19870801\)60:3<301::aid-cnrcr2820600306.0.co;2-v](https://doi.org/10.1002/1097-0142(19870801)60:3<301::aid-cnrcr2820600306.0.co;2-v).
- [48] Richard J, Kramar A, Molinari R, Lefebvre J, Blanchet F, Jortay A, et al. Randomised EORTC Head and Neck Cooperative Group trial of preoperative intra-arterial chemotherapy in oral cavity and oropharyngeal carcinoma. *Eur J Cancer* 1991;27:821–7. [https://doi.org/10.1016/0277-5379\(91\)90125-W](https://doi.org/10.1016/0277-5379(91)90125-W).
- [49] Holoye PY, Grossman TW, Toohill RJ, Kun LE, Byhardt RW, Duncavage JA, et al. Randomized study of adjuvant chemotherapy for head and neck cancer. *Otolaryngol-Head Neck Surg* 1985;93:712–7.
- [50] Kun LE, Toohill RJ, Holoye PY, Duncavage JA, Byhardt RW, Ritch PS, et al. A randomized study of adjuvant chemotherapy for cancer of the upper aerodigestive tract. *Int J Radiat Oncol Biol Phys* 1986;12:173–8. [https://doi.org/10.1016/0360-3016\(86\)90090-8](https://doi.org/10.1016/0360-3016(86)90090-8).
- [51] Schuller DE, Metch B, Stein DW, Mattox D, McCracken JD. Preoperative chemotherapy in advanced resectable head and neck cancer: final report of the Southwest Oncology Group. *Laryngoscope* 1988;98:1205–11. <https://doi.org/10.1288/00005537-198811000-00011>.
- [52] Szpirglas H, Nizri D, Marneur M, Lacoste J, Benslama L. Neoadjuvant chemotherapy. A randomized trial before radiotherapy in oral and oropharyngeal carcinomas: end results. Proceedings of the 2nd international head and neck oncology research conference. Ghedini Ed, Berkeley: Kugler Publications; 1988, p. 261–4.
- [53] Carugati A, Pradier R, De La Torre A. Combination chemotherapy pre-radical treatment for head and neck squamous cell carcinoma. *Proc Am Soc Clin Oncol* 1988;7:152.
- [54] Mazon J, Martin M, Brun B, Grimard L, Lelièvre G, Vergnes L, et al. Induction chemotherapy in head and neck cancer: Results of a phase III trial. *Head Neck* 1992;14:85–91. <https://doi.org/10.1002/hed.2880140202>.
- [55] Brunin F, Rodriguez J, Jaulerry C, Jouve M, Pontvert D, Point D, et al. Induction chemotherapy in advanced head and neck cancer. Preliminary results of a randomized study. *Acta Oncologica* 1989;28:61–5. <https://doi.org/10.3109/02841868909111183>.
- [56] Salvajoli J, Morioka H, Trippé N, Kowalski L. A randomized trial of neoadjuvant vs concomitant chemotherapy vs radiotherapy alone in the treatment of stage IV head and neck squamous cell carcinoma. *Eur Arch Oto-Rhino-Laryngol* 1992;249:211–5.
- [57] Jaulerry C, Rodriguez J, Brunin F, Jouve M, Mosseri V, Point D, et al. Induction chemotherapy in advanced head and neck tumors: Results of two randomized trials. *Int J Radiat Oncol Biol Phys* 1992;23:483–9. [https://doi.org/10.1016/0360-3016\(92\)90002-Y](https://doi.org/10.1016/0360-3016(92)90002-Y).
- [58] Maipang T, Maipang M, Geater A, Panjapayakul C, Watanaapornchai S, Punperk S. Combination chemotherapy as induction therapy for advanced resectable head and neck cancer. *J Surg Oncol* 1995;59:80–5. <https://doi.org/10.1002/jso.2930590203>.
- [59] Toohill R, Anderson T, Byhardt R, Cox J, Duncavage J, Grossman T, et al. Cisplatin and fluorouracil as neoadjuvant therapy in head and neck cancer. *Arch Otolaryngol Head Neck Surg* 1987;113:758–61.
- [60] Toohill R, Duncavage J, Thomas M, Wilson F, Anderson T, et al. The effects of delay in standard treatment due to induction chemotherapy in two randomized prospective studies. *Laryngoscope* 1987;97:407–12. <https://doi.org/10.1288/00005537-198704000-00002>.
- [61] Lewin F, Damber L, Jonsson H, Andersson T, Berthelsen A, Björklund A, et al. Neoadjuvant chemotherapy with cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the head and neck: A randomized phase III study. *Radiother Oncol* 1997;43:23–8. [https://doi.org/10.1016/S0167-8140\(97\)01922-1](https://doi.org/10.1016/S0167-8140(97)01922-1).
- [62] Martin M, Hazan A, Vergnes L, Peytral C, Mazon J, Sénéchaut JP, et al. Randomized study of 5 fluorouracil and cis platin as neoadjuvant therapy in head and neck cancer: A preliminary report. *Int J Radiat Oncol Biol Phys* 1990;19:973–5. [https://doi.org/10.1016/0360-3016\(90\)90021-B](https://doi.org/10.1016/0360-3016(90)90021-B).
- [63] Martin M, Vergnes L, Lelièvre G, Michel-Langlet P, Peytral C, Mazon J, et al. A randomized study of CDDP and 5-FU as neoadjuvant chemotherapy in head and neck cancer: an interim analysis. In: Banzet P, Holland J, Khayat D, Weil M, editors. *Cancer treatment: an update*. Springer-V, Paris: 1994, p. 214–8.
- [64] Paccagnella A, Orlando A, Marchiori C, Zorat PL, Cavaniglia G, Sileni VC, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: A study by the Gruppo di Studio sui Tumori della Testa e del Collo. *J Natl Cancer Inst* 1994;86:265–72. <https://doi.org/10.1093/jnci/86.4.265>.
- [65] Zorat PL, Paccagnella A, Cavaniglia G, Loreggian L, Gava A, Mione CA, et al. Randomized phase III trial of neoadjuvant chemotherapy in head and neck cancer: 10-year follow-up. *J Natl Cancer Inst* 2004;96:1714–7. <https://doi.org/10.1093/jnci/djh306>.
- [66] Domenge C, Hill C, Lefebvre J, De Raucourt D, Rhein B, Wibault P, et al. Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. *Br J Cancer* 2000;83:1594–8. <https://doi.org/10.1054/bjoc.2000.1512>.
- [67] Dalley D, Beller E, Aroney R, Dewar J, Page J, Philip R, et al. The value of chemotherapy (CT) prior to definitive local therapy (DTL) in patients with locally advanced squamous cell carcinoma (SCC) of the head and neck (HN). *Proc Am Soc Clin Oncol* 1995;14:297.
- [68] Tejedor M, Murias A, Soria P, Aguiar J, Salinas J, Hernandez MA, et al. Induction chemotherapy with carboplatin and ifosfamide in advanced head and neck cancer. A randomized study. *Am J Clin Oncol* 1992;15:417–21.
- [69] Gedouin D, Desprez P, Perron JJ, Fleury F, Leclech G, Miglianico L, et al. Cancers de la base de langue et de l'hypopharynx: résultats d'un essai multicentrique randomisé de chimiothérapie avant traitement locoregional. *Bull Cancer/Radiother* 1996;83:104–7. [https://doi.org/10.1016/0924-4212\(96\)85320-5](https://doi.org/10.1016/0924-4212(96)85320-5).
- [70] Di Blasio B, Barbieri W, Bozzetti A, Iotti C, Di Sarra S, Cocconi G. A prospective randomized trial in resectable head and neck carcinoma: loco-regional treatment with and without neoadjuvant chemotherapy. *Proc Am Soc Clin Oncol* 1994;13:279.
- [71] Gehanno P, Depondt J, Peynegre R, Peytral C, Martin M, Baillet F, et al. Neoadjuvant combination of carboplatin and 5-FU in head and neck cancer: A randomized study. *Ann Oncol* 1992;3:43–6.
- [72] Depondt J, Gehanno P, Martin M, Lelièvre G, Guerrier B, Peytral C, et al. Neoadjuvant chemotherapy with carboplatin/5-fluorouracil in head and neck cancer. *Oncology* 1993;50:23–7. <https://doi.org/10.1159/000227257>.
- [73] Volling P, Schroder M, Muller RP, Ebeling O, Quirin R, Stennert E. Induction chemotherapy in primary resectable head and neck tumors: A prospective randomized trial. *Int J Oncol* 1994;4:909–14. <https://doi.org/10.3892/ijo.4.4.909>.
- [74] Hasegawa Y, Matsuura H, Fukushima M, Kano M, Shimozato K. Potential suppression of distant and node metastasis by neoadjuvant chemotherapy in advanced head and neck cancer: result of a randomized trial. *Proc Am Soc Clin Oncol* 1996;15:318.
- [75] Hussey DH, Abrams JP. Combined therapy in advanced head and neck cancer: hydroxyurea and radiotherapy. *Progr Clin Cancer* 1975;6:79–86.
- [76] Eschwege F, Sancho-Garnier H, Gerard JP, Madelain M, Desautly A, Jortay A, et al. Ten-year results of randomized trial comparing radiotherapy and concomitant bleomycin to radiotherapy alone in epidermoid carcinomas of the oropharynx: experience of the European Organization for Research and Treatment of Cancer. *NCI Monographs* 1988;6:275–8.
- [77] Parvinen L-M, Parvinen M, Nordman E, Kortekangas AE. Combined bleomycin treatment and radiation therapy in squamous cell carcinoma of the head and neck region. *Acta Radiol Oncol* 1985;24:487–9. <https://doi.org/10.3109/02841868509134421>.
- [78] Vermund H, Kaalhus O, Winther F, Trausjø J, Thorud E, Harang R. Bleomycin and radiation therapy in squamous cell carcinoma of the upper aero-digestive

- tract: A phase III clinical trial. *Int J Radiat Oncol Biol Phys* 1985;11:1877-86. [https://doi.org/10.1016/0360-3016\(85\)90267-6](https://doi.org/10.1016/0360-3016(85)90267-6).
- [79] Sanchiz F, Milla A, Torner J, Bonet F, Artola N, Carreno L, et al. Single fraction per day versus two fractions per day versus radiochemotherapy in the treatment of head and neck cancer. *Int J Radiat Oncol Biol Phys* 1990;19:1347-50.
- [80] Gupta NK, Poinon RC, Wilkinson PM. A randomised clinical trial to contrast radiotherapy with radiotherapy and methotrexate given synchronously in head and neck cancer. *Clin Radiol* 1987;38:575-81.
- [81] Gupta NK, Swindell R. Concomitant methotrexate and radiotherapy in advanced head and neck cancer: 15-year follow-up of a randomized clinical trial. *Clin Oncol* 2001;13:339-44. <https://doi.org/10.1053/clon.2001.9286>.
- [82] Haselow R, Warshaw M, Oken M, Adams G, Aughey J, Cooper J, et al. Radiation alone versus radiation with weekly low dose cisplatin in unresectable cancer of the head and neck. *Head and Neck Cancer*. Vol II, Philadelphia, PA: BC Decker; 1990, p. 279-81.
- [83] Quon H, Leong T, Haselow R, Leipzig B, Cooper J, Forastiere A. Phase III study of radiation therapy with or without cis-platinum in patients with unresectable squamous or undifferentiated carcinoma of the head and neck: an intergroup trial of the Eastern Cooperative Oncology Group (E2382). *Int J Radiat Oncol Biol Phys* 2011;81:719-25. <https://doi.org/10.1016/j.ijrobp.2010.06.038>.
- [84] Browman GP, Cripps C, Hodson DI, Eapen L, Sathya J, Levine MN. Placebo-controlled randomized trial of infusional fluorouracil during standard radiotherapy in locally advanced head and neck cancer. *J Clin Oncol* 1994;12:2648-53. <https://doi.org/10.1200/JCO.1994.12.2648>.
- [85] Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: A prospective randomized trial. *Radiother Oncol* 1997;43:29-37. [https://doi.org/10.1016/S0167-8140\(97\)00048-0](https://doi.org/10.1016/S0167-8140(97)00048-0).
- [86] Wendt TG, Grabenbauer GG, Rödel CM, Thiel H-J, Aydin H, Rohloff R, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: A randomized multicenter study. *J Clin Oncol* 1998;16:1318-24.
- [87] Smid L, Lesnicar H, Zakotnik B, Soba E, Budihna M, Furlan L, et al. Radiotherapy, combined with simultaneous chemotherapy with mitomycin C and bleomycin for inoperable head and neck cancer—preliminary report. *Int J Radiat Oncol Biol Phys* 1995;32:769-75.
- [88] Shanta V, Krishnamurthi S. Combined bleomycin and radiotherapy in oral cancer. *Clin Radiol* 1980;31:617-20.
- [89] Kapstad B, Bang G, Rennaes S, Dahler A. Combined preoperative treatment with cobalt and bleomycin in patients with head and neck carcinoma—a controlled clinical study. *Int J Radiat Oncol Biol Phys* 1978;4:85-9.
- [90] Morita K. Clinical significance of radiation therapy combined with chemotherapy. *Strahlentherapie* 1980;156:228-33.
- [91] Bezwodna WR, de Moor NG, Derman DP. Treatment of advanced head and neck cancer by means of radiation therapy plus chemotherapy—a randomised trial. *Med Pediatr Oncol* 1979;6:353-8. <https://doi.org/10.1002/mpo.2950060412>.
- [92] Nissenbaum M, Browde S, Bezwodna WR, de Moor NG, Derman DP. Treatment of advanced head and neck cancer: multiple daily dose fractionated radiation therapy and sequential multimodal treatment approach. *Med Pediatr Oncol* 1984;12:204-8. <https://doi.org/10.1002/mpo.2950120312>.
- [93] Weissberg JB, Son YH, Papac RJ, Sasaki C, Fischer DB, Lawrence R, et al. Randomized clinical trial of mitomycin C as an adjunct to radiotherapy in head and neck cancer. *Int J Radiat Oncol Biol Phys* 1989;17:3-9.
- [94] Keane T, Cummings B, O'Sullivan B, Payne D, Rawlinson E, Mackenzie R, et al. A randomized trial of radiation therapy compared to split course radiation therapy combined with mitomycin C and 5 fluorouracil as initial treatment for advanced laryngeal and hypopharyngeal squamous carcinoma. *Int J Radiat Oncol Biol Phys* 1993;25:613-8. [https://doi.org/10.1016/0360-3016\(93\)90006-H](https://doi.org/10.1016/0360-3016(93)90006-H).
- [95] Bachaud J-M, Cohen-Jonathan E, Alzieu C, David J-M, Serrano E, Daly-Schweitzer N. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: Final report of a randomized trial. *Int J Radiat Oncol Biol Phys* 1996;36:999-1004. [https://doi.org/10.1016/S0360-3016\(96\)00430-0](https://doi.org/10.1016/S0360-3016(96)00430-0).
- [96] Weissler MC, Melin S, Sailer SL, Qaqish BF, Rosenman JG, Pillsbury 3rd HC. Simultaneous chemoradiation in the treatment of advanced head and neck cancer. *Arch Otolaryng Head Neck Surg* 1992;118:806-10.
- [97] Haffty BG, Son YH, Sasaki CT, Papac R, Fischer D, Rockwell S, et al. Mitomycin C as an adjunct to postoperative radiation therapy in squamous cell carcinoma of the head and neck: Results from two randomized clinical trials. *Int J Radiat Oncol Biol Phys* 1993;27:241-50. [https://doi.org/10.1016/0360-3016\(93\)90234-M](https://doi.org/10.1016/0360-3016(93)90234-M).
- [98] Merlano M, Vitale V, Rosso R, Benasso M, Corvo R, Cavallari M, et al. Treatment of advanced squamous-cell carcinoma of the head and neck with alternating chemotherapy and radiotherapy. *N Engl J Med* 1992;327:1115-21.
- [99] Merlano M, Benasso M, Corvò R, Rosso R, Vitale V, Blengio F, et al. Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck. *J Natl Cancer Inst* 1996;88:583-9. <https://doi.org/10.1093/nci/88.9.583>.
- [100] Kumar S, Datta NR, Ahuja RC, Mali HR, Agarwal GN, Ayyagari S. Feasibility of non-cisplatin-based induction chemotherapy and concurrent chemoradiotherapy in advanced head and neck cancer. *Acta Oncol* (Stockholm, Sweden) 1996;35:721-5. <https://doi.org/10.3109/02841869609084005>.
- [101] Adelstein DJ, Lavertu P, Saxton JP, Secic M, Wood BG, Wanamaker JR, et al. Mature results of a Phase III randomized trial comparing concurrent chemoradiotherapy with radiation therapy alone in patients with Stage III and IV squamous cell carcinoma of the head and neck. *Cancer* 2000;88:876-83. [https://doi.org/10.1002/\(SICI\)1097-0142\(20000215\)88:4<876::AID-CNCR19**3.0.CO;2-Y](https://doi.org/10.1002/(SICI)1097-0142(20000215)88:4<876::AID-CNCR19**3.0.CO;2-Y).
- [102] Brizel DM, Albers ME, Fisher SR, Scher RL, Richtsmeier WJ, Hars V, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 1998;338:1798-804. <https://doi.org/10.1056/NEJM199806183382503>.
- [103] Dobrowsky W, Naudé J. Continuous hyperfractionated accelerated radiotherapy with/without mitomycin C in head and neck cancers. *Radiother Oncol* 2000;57:119-24. [https://doi.org/10.1016/S0167-8140\(00\)00233-4](https://doi.org/10.1016/S0167-8140(00)00233-4).
- [104] Tobias JS, Monson K, Gupta N, Macdougall H, Glaholm J, Hutchison I, et al. Chemoradiotherapy for locally advanced head and neck cancer: 10-year follow-up of the UK Head and Neck (UKHAN1) trial. *Lancet Oncol* 2010;11:66-74. [https://doi.org/10.1016/S1470-2045\(09\)70306-7](https://doi.org/10.1016/S1470-2045(09)70306-7).
- [105] Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. *J Clin Oncol* 2000;18:1458-64. <https://doi.org/10.1200/JCO.2000.18.7.1458>.
- [106] Giglio R, Mickiewicz E, Pradier R, Roth B, Gatica G, Califano L, et al. No recurrence beyond the second year of follow-up in inoperable stage III and IV squamous cell carcinoma of the head and neck patients (IOHN). Final report of a randomized trial of alternating chemotherapy (CT) + hyperfractionated radiotherapy (RT) vs RT. *Proc Am Soc Clin Oncol* 1999;15:317.
- [107] Adelstein DJ, Li Y, Adams GL, Wagner H, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol* 2003;21:92-8. <https://doi.org/10.1200/JCO.2003.01.008>.
- [108] Forastiere AA, Goepfert H, Maor M, Pajak T, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;349:2091-8. <https://doi.org/10.1056/NEJMoa031317>.
- [109] Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol* 2013;31:845-52. <https://doi.org/10.1200/JCO.2012.43.6097>.
- [110] Olmi P, Crispino S, Fallai C, Torri V, Rossi F, Bolner A, et al. Locoregionally advanced carcinoma of the oropharynx: conventional radiotherapy vs. accelerated hyperfractionated radiotherapy vs. concomitant radiotherapy and chemotherapy—a multicenter randomized trial. *Int J Radiat Oncol Biol Phys* 2003;55:78-92.
- [111] Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol* 2004;22:69-76. <https://doi.org/10.1200/JCO.2004.08.021>.
- [112] Budach V, Stuschke M, Budach W, Baumann M, Geismar D, Grabenbauer G, et al. Hyperfractionated accelerated chemoradiation with concurrent fluorouracil-mitomycin is more effective than dose-escalated hyperfractionated accelerated radiation therapy alone in locally advanced head and neck cancer. *J Clin Oncol* 2005;23:1125-35. <https://doi.org/10.1200/JCO.2005.07.010>.
- [113] Bernier J, Dommene C, Ozsahin M, Matuszewski K, Lefebvre J-L, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945-52. <https://doi.org/10.1056/NEJMoa032641>.
- [114] Huguenin P, Beer KT, Allal A, Rufibach K, Friedli C, Davis JB, et al. Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. *J Clin Oncol* 2004;22:4665-73. <https://doi.org/10.1200/JCO.2004.12.193>.
- [115] Ghadjar P, Simcock M, Studer G, Allal AS, Ozsahin M, Bernier J, et al. Concomitant cisplatin and hyperfractionated radiotherapy in locally advanced head and neck cancer: 10-year follow-up of a randomized phase III trial (SAKK 10/94). *Int J Radiat Oncol Biol Phys* 2012;82:524-31.
- [116] Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy - Results of a multicentric randomized German trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001;50:1161-71. [https://doi.org/10.1016/S0360-3016\(01\)01544-9](https://doi.org/10.1016/S0360-3016(01)01544-9).
- [117] Fountzilas G, Ciuleanu E, Dafni U, Plataniotis G, Klogera-Fountzila A, Samantas E, et al. Concomitant radiochemotherapy vs radiotherapy alone in patients with head and neck cancer: A Hellenic Cooperative Oncology Group Phase III Study. *Med Oncol* 2004;21:95-107.
- [118] Cooper J, Pajak T, Forastiere A, Jacobs J, Campbell B, Saxman S, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004;350:1937-44. <https://doi.org/10.1056/NEJMoa032646>.

- [119] Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: Postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys* 2012;84:1198–205. <https://doi.org/10.1016/j.ijrobp.2012.05.008>.
- [120] Grau C, Prakash Agarwal J, Jabeen K, Rab Khan A, Abeyakoon S, Hadjieva T, et al. Radiotherapy with or without mitomycin c in the treatment of locally advanced head and neck cancer: results of the IAEA multicentre randomised trial. *Radiother Oncol* 2003;67:17–26. [https://doi.org/10.1016/S0167-8140\(03\)00020-3](https://doi.org/10.1016/S0167-8140(03)00020-3).
- [121] Bourhis J, Lapeyre M, Tortochaux J, Lusinchi A, Etessami A, Ducourtieux M, et al. Accelerated radiotherapy and concomitant high dose chemotherapy in non resectable stage IV locally advanced HNSCC: results of a GORTEC randomized trial. *Radiother Oncol* 2011;100:56–61. <https://doi.org/10.1016/j.radonc.2011.07.006>.
- [122] Lartigau E, Giralt J, Glassman P, Lawton A, von Roemeling R. A phase III double-blind randomized placebo controlled study of porfiromycin and radiation therapy in patients with head and neck cancer. *Int J Radiat Oncol Biol Phys* 2002;54(S2):74. [https://doi.org/10.1016/S0360-3016\(02\)03184-X](https://doi.org/10.1016/S0360-3016(02)03184-X).
- [123] Zakotnik B, Budihna M, Smid L, Soba E, Strojanc P, Fajdiga I, et al. Patterns of failure in patients with locally advanced head and neck cancer treated postoperatively with irradiation or concomitant irradiation with Mitomycin C and Bleomycin. *Int J Radiat Oncol Biol Phys* 2007;67:685–90. <https://doi.org/10.1016/j.ijrobp.2006.09.018>.
- [124] Szpirglas H, Chastang CI, Bertrand JCh. Adjuvant treatment of tongue and floor of the mouth cancers. In: Bonadonna G, Mathé G, Salmon S, editors. *Adjuvant therapies and markers of post-surgical minimal residual disease II. Adjuvant therapies of the various primary tumors*, Berlin: Springer-Verlag; 1979, p. 309–17. https://doi.org/10.1007/978-3-642-81332-0_47.
- [125] Domenge C, Marandas P, Vignoud J, Beauvillain de Montreuil C, Prevost B, Lefebvre J, et al. Post-surgical adjuvant chemotherapy in extracapsular spread invaded lymph node (N+R+) of epidermoid carcinoma of the head and neck: a randomized multicentric trial. Second international conference on head and neck cancer. American Society of Head and Neck Surgery 1988;74.
- [126] Laramore GE, Scott CB, al-Sarraf M, Haselow RE, Ervin TJ, Wheeler R, et al. Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report on Intergroup Study 0034. *International Journal of Radiation Oncology, Biology, Physics* 1992;23:705–13.
- [127] Yoshino K, Sato T, Nakai Y, Tanabe M, Matsunaga T, Kozuka T, et al. A comparative clinical study of adjuvant chemotherapy of tumors in the head and neck areas by means of HCFU. *Jap J Cancer Chemother* 1991;18:2581–8.
- [128] Rao RS, Parikh DM, Parikh HK, Bhansali MB, Deshmene VH, Fakih AR. Perioperative chemotherapy in patients with oral cancer. *Am J Surg* 1994;168:262–7.
- [129] Kotani A, Sunada O, Tamura M, Takaku S, Kobayashi A, Asakura A, et al. Multiple cooperative study of UFT-adjuvant chemotherapy for malignant tumor in the jaw and oral cavities. *Jap J Cancer Chemother* 1994;21:987–92.
- [130] Tsukuda M, Ogasawara H, Kaneko S, Komiyama S, Horiuchi M, Inuyama Y, et al. A prospective randomized trial of adjuvant chemotherapy with UFT for head and neck carcinoma. *Jap J Cancer Chemother* 1994;21:1169–77.
- [131] Haddad R, O'Neill A, Rabinowits G, Tishler R, Khuri F, Adkins D, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): A randomised phase 3 trial. *Lancet Oncol* 2013;14:257–64.
- [132] Geoffrois L, Martin L, De Raucourt D, Sun XS, Tao Y, Maingon P, et al. Induction chemotherapy followed by cetuximab radiotherapy is not superior to concurrent chemoradiotherapy for head and neck carcinomas: Results of the GORTEC 2007–02 Phase III Randomized Trial. *J Clin Oncol* 2018;36:3077–83. <https://doi.org/10.1200/JCO.2017.76.2591>.
- [133] Stromberger C, Knecht R, Raguse JD, Keilholz U, Tribius S, Busch C-J, et al. Standard or split TPF induction chemotherapy followed by bioradiation: ICRAT randomized phase II study. *JCO* 2016;34:6035–6035. https://doi.org/10.1200/JCO.2016.34.15_suppl.6035.
- [134] Tousif D, Sarathy V, Kumar R, Naik R. Randomized Controlled Study Comparing Efficacy and Toxicity of Weekly vs. 3-Weekly Induction Chemotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma. *Frontiers in Oncology* 2020;10:1284. <https://doi.org/10.3389/fonc.2020.01284>.
- [135] Blanchard P, Lee A, Marguet S, Leclercq J, Ng WT, Ma J, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. *Lancet Oncol* 2015;16:645–55. [https://doi.org/10.1016/S1470-2045\(15\)70126-9](https://doi.org/10.1016/S1470-2045(15)70126-9).
- [136] Fayard F, Petit C, Lacas B, Pignon JP. Impact of missing individual patient data on 18 meta-analyses of randomised trials in oncology: Gustave Roussy experience. *BMJ Open* 2018;8. <https://doi.org/10.1136/bmjopen-2017-020499>.
- [137] Zakeri K, Rotolo F, Lacas B, Vitzthum LK, Le Q-T, Gregoire V, et al. Predictive classifier for intensive treatment of head and neck cancer. *Cancer* 2020;126:5263–73. <https://doi.org/10.1002/cncr.33212>.

Supplementary appendix

Contents

Web-Appendix 1: MACH-NC collaborative group	3
Web-Appendix 2: Inclusion criteria	4
Web-Appendix 3: Trial search equations	4
Web-Appendix 4: Data checking and trial quality	5
Web-Appendix 5: Statistical methods	5
Web-Appendix 6: Results of trials search	7
Web-Appendix 7: Trial design, trial division and patient duplication	7
Web-Appendix 8: Heterogeneity between comparisons and sensitivity analyzes	8
Web-Table 1: Description of induction trials	9
Web-Table 2: Description of concomitant trials	16
Web-Table 3: Description of adjuvant trials	23
Web-Table 4: Description of trials comparing induction (sequential) chemotherapy plus radiotherapy to concomitant (alternating) radio-chemotherapy	25
Web-Table 5: Trial divisions in treatment comparisons	27
Web-Table 6: Characteristics of patients overall and by timing (addition of chemotherapy) ..	29
Web-Table 7: Number of comparisons and patients in trial subsets	31
Web-Table 8: Cause of death and events for cancer/non-cancer mortality	32
Web-Table 9: Events for event-free survival	33
Web-Table 10A: Sensitivity analyzes for the addition of induction chemotherapy	34
Web-Table 10B: Sensitivity analyzes for the addition of concomitant chemotherapy	35
Web-Table 10C: Sensitivity analyzes for the addition of adjuvant chemotherapy	36
Web-Table 11A: Classification of induction comparisons for subset analyzes	37
Web-Table 11B: Classification of concomitant comparisons for subset analyzes	38
Web-Table 11C: Classification of adjuvant comparisons subsets analyzes	40
Web-Table 12A: Variation of treatment effect according to the type of chemotherapy	41
Web-Table 12B: Variation of treatment effect according to the start of accrual	41
Web-Table 12C: Variation of treatment effect according to loco-regional treatment	42
Web-Table 13A: Variation of treatment effect according to patients' subgroups for induction comparisons	43
Web-Table 13B: Variation of treatment effect according to patients' subgroups for concomitant comparisons	44
Web-Table 14: Cause of death by age groups for concomitant comparison	45
Web-Table 15: Characteristics of patients (concomitant versus induction chemotherapies) ..	46
Web-Table 16: Characteristics of patients included in comparisons with or without surgery ..	47
Web-Table 17: Effect of chemotherapy according to sex in comparisons with or without	

surgery	48
Web-Table 18: Description of trials identified in 2019	49
Web-Figure 1: Flowchart	50
Web-Figure 2: Overall survival - Loco-regional treatment plus induction chemotherapy versus loco-regional treatment alone.	51
Web-Figure 3: Event-free survival - Survival curves of loco-regional treatment plus chemotherapy and loco-regional treatment alone by timing	52
Web-Figure 4: Cancer and non-cancer mortality - Survival curves of loco-regional treatment plus chemotherapy and loco-regional treatment alone by timing	54
Web-Figure 5: 120-day mortality - Loco-regional treatment plus chemotherapy versus loco-regional treatment alone	55
Web-Figure 6: Loco-regional failure - Loco-regional treatment plus chemotherapy versus loco-regional treatment alone	56
Web-Figure 7: Distant failure - Loco-regional treatment plus chemotherapy versus loco-regional treatment alone	57
Web-Figure 8: cumulative incidence of locoregional failure (LRF).....	58
Web-Figure 9: cumulative incidence of distant failure (DF)	61
Web-Figure 10: Overall survival - Loco-regional treatment plus concomitant chemotherapy versus loco-regional treatment alone. <i>See Web-Table 2 for trials abbreviations</i>	64
Web-Figure 11: Overall survival - Loco-regional treatment plus adjuvant chemotherapy versus loco-regional treatment alone.....	65
Web-Figure 12: Efficacy of concomitant versus induction chemotherapy.....	66
Web-Figure 13: Survival curves of concomitant versus induction chemotherapy	67
References	68

Web-Appendix 1: MACH-NC collaborative group

Secretariat

A. Aupérin, P. Blanchard, J. Bourhis, F. Janot, B. Lacas, J.P. Pignon

Steering Committee

C. Fortpied, J. Harris, J.A. Langendijk, Q.T. Le, L. Licitra, J. Vermorken

Investigators

Members of the MACH-NC group are listed below. Names of people who contributed to the initial meta-analysis and its first update are available in references 1 and 2.

D.J. Adelstein (Cleveland Clinic Foundation, Ohio, USA), M. Alfonsi (Institut Saint Catherine, France), A. Argiris (Thomas Jefferson University, Pennsylvania, USA), A. Aupérin (Gustave Roussy, France), Y. Belkacemi (CHU Henri Mondor, France), R.J. Bensadoun (Centre Antoine Lacassagne, France), V. Bar-Ad (Thomas Jefferson University Hospital USA), J. Bernier (Genolier Swiss Oncology Network, Switzerland), P. Blanchard (Gustave Roussy, France), J. Bourhis (Centre Hospitalier Universitaire Vaudois, Switzerland), Å. Bratland (Oslo University Hospital, Norway), D. Brizel (Duke University Medical Center, North Carolina, USA), V. Budach (Charité Universitätsmedizin, Germany), B. Burtneß (Yale University, New Haven, Connecticut, USA), G. Calais (Centre Hospitalier Universitaire de Tours, France), B. Campbell (Medical College of Wisconsin, USA), A. Carmel (Gustave Roussy, France), J. Caudell (H. Lee Moffitt Cancer Center & Research Institute, USA), S. Chabaud (Centre Léon Bérard, France), E. Chamorey (Centre Antoine Lacassagne, France), D. Chaukar (Tata Memorial Centre Advanced Centre for Treatment, Research and Education in Cancer, India), K.N. Choi (State University of New York Downstate Medical Center, USA), O. Choussy (Institut Curie, France), E.E.W. Cohen (Moore's Cancer Center, California, USA), L. Collette (EORTC Headquarters, Belgium), R. Corvò (Ospedale Policlinico San Martino and University of Genoa, Genoa, Italy), J.J. Cruz (Spanish Head and Neck Cancer Cooperative Group, Spain), C. Dani (Ospedale Policlinico San Martino, Genoa, Italy), E. Dauter (Gustave Roussy, France), W. Dobrowsky (Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, UK), C. Fallai (Università di Firenze, Italy), A.A. Forastiere (Johns Hopkins Univ/Sidney Kimmel Cancer Center, Maryland, USA), C. Fortpied (EORTC Headquarters, Belgium), G. Fountzilas (Aristotle University of Thessaloniki, Greece), P. Garaud (Centre Hospitalier Universitaire de Tours, France), M.G. Ghi (Veneto Oncology Institute - IRCCS, Italy), P. Ghadjari (Charité Universitätsmedizin, Germany and SAKK Coordinating Center, Switzerland), S. Ghosh Laskar (Tata Memorial Hospital, Homi Bhabha National Institute, India), C. Grau (Aarhus University Hospital, Denmark), V. Gregoire (Centre Léon Bérard, France), A. Hackshaw (Cancer Research UK & UCL Cancer Trials Centre, UK), E. Haddad (Hôpital Henri Mondor, Créteil, France), B.G. Haffty (Rutgers Robert Wood Johnson and NJ Medical School, New Jersey, USA), A. Hansen (Princess Margaret Cancer Centre/University of Toronto, Ontario, Canada), J. Harris (NRG Oncology Statistics and Data Management Center, American College of Radiology, Pennsylvania, USA), S. Hayoz (SAKK Coordinating Center, Switzerland), R. Hitt (Hospital Universitario Severo Ochoa, Spain), J.C. Horiot (Centre Georges François Leclerc, France), B. Jeremic (Kragulevac University Hospital, Yugoslavia), T.G. Karrison (University of Chicago, Illinois, USA), S. Kumar (Sanjay Gandhi Post Graduate Institute of Medical Sciences, India), B. Lacas (Gustave Roussy, France), C. Landais (Gustave Roussy, France), J.A. Langendijk (University Medical Center Groningen, Netherlands), M. Lapeyre (Centre Jean Perrin, France), E. Lartigau (Centre Oscar Lambret, France), T. Leong (Rollins School of Public Health, Emory University, Georgia, USA), Q.T. Le (Stanford University School of Medicine, California, USA), J.W. Lee (Dana-Farber Cancer Institute – ECOG-ACRIN Biostatistics Center, Massachusetts, USA), P.P.Y. Lee (University of Texas-MD Anderson Cancer Center, USA), F. Lewin (Huddinge University Hospital, Sweden), L. Licitra (Fondazione IRCCS-Istituto Nazionale dei Tumori, Italy), A. Lin (University of Pennsylvania Medical Center USA), A. Lopes (Cancer Research UK & UCL Cancer Trials Centre, UK), J.J. Mazon (Hôpital Pitié-Salpêtrière, France), S. Mehta (Department of Surgery, Sarla Hospital, India), J. Moon (SWOG Statistical Center, Washington, USA), E. Moyal (IUCT Oncopole - CLCC Institut Claudius Regaud, France), B.V. Occéan (Gustave Roussy, France), P. Olmi (Università di Firenze, Italy), R. Orecchia (IRCCS Istituto Europeo di Oncologia, Italy), B. O'Sullivan (Princess Margaret Cancer Centre/University of Toronto, Ontario, Canada), J. Overgaard (Aarhus University Hospital, Denmark), C. Petit (Gustave Roussy, France), J.P. Pignon (Gustave Roussy, France), H. Quon (Johns Hopkins Univ/Sidney Kimmel Cancer Center, Maryland, USA), S. Racadot (Centre Léon Bérard, France), P. Rovea (San Giovanni Antica Sede Hospital, Italy), M.G. Ruvo Redda (Mauriziano Umberto I Hospital, University of Turin, Italy), G. Sanguineti (IRCCS Regina Elena National Cancer Institute, Rome, Italy), T. Satar (Gustave Roussy, France), J. Simes (NHMRC Clinical Trials Center, Australia), A. Sharma (All India Institute of Medical Sciences, India), C. Simon (Centre Hospitalier Universitaire Vaudois, Switzerland), C. Sire (Hôpital Bretagne Sud, France), S. Staar (University of Cologne, Germany), C. Stromberger (Charité Universitätsmedizin, Germany), P. Strojani (Institute of Oncology, Slovenia), Z. Takácsi-Nagy (National Institute of Oncology, Hungary), S. Temam (Gustave Roussy, France), D. Thomson (The Christie NHS FT, UK), A. Timochenko (CHU de St-Etienne, France), J.S. Tobias (University College London Hospital, UK), V. Torri (Mario Negri, Italy), V.

Tseroni (San Giovanni Antica Sede Hospital, Italy), J. Vermorken (Antwerp University Hospital, Belgium), E.E. Vokes (University of Chicago Medical Center, Illinois, USA), J. Waldron (Princess Margaret Cancer Centre/University of Toronto, Ontario, Canada), K.D. Wernecke (Charité Universitätsmedizin, Germany), J. Widder (Medical University of Vienna, Austria), G. Wolf (University of Michigan, USA), S.J. Wong (Medical College of Wisconsin, USA), B. Zaktonik (Institute of Oncology, Slovenia), B. Zackrisson (Umeå University, Sweden), L.P. Zhong (Shanghai Jiao Tong University School of Medicine, China)

Web-Appendix 2: Inclusion criteria

Trials were eligible if they had accrued previously untreated patients with HNSCC and compared curative loco-regional treatment with loco-regional treatment plus chemotherapy, the addition of another timing of chemotherapy to loco-regional treatment plus chemotherapy (main question), or compared induction chemotherapy and radiotherapy to the same concomitant (or alternating) chemoradiotherapy (secondary question). Chemotherapy and radiotherapy should be similar in both arms. Each trial had to be randomized it would be impossible to know in advance which treatment an individual would receive (avoiding the potential of allocation bias). Trials should be unconfounded, except changes of the radiotherapy in the experimental arm (decreased dose or increased duration without change in fractionation). Trials were eligible if accrual was completed before December 31st 2016, and if all randomized patients had undergone a potentially curative loco-regional treatment and had not been treated for another malignancy. Trials including tumors of the oral cavity, oropharynx, hypopharynx and larynx were included. Trials including only nasopharyngeal carcinomas were excluded.

Web-Appendix 3: Trial search equations

Medline (PubMed)

Search ((laryngeal neoplasms[MeSH Terms] OR mouth neoplasms[MeSH Terms] OR nose neoplasms[MeSH Terms] OR pharyngeal neoplasms[MeSH Terms] OR salivary gland neoplasms[MeSH Terms]) OR ("head and neck" OR laryngeal OR larynx OR glottis OR glottic OR subglottis OR subglottic OR supraglottis OR supraglottic OR oral OR mouth OR lip OR gingiva OR gingival OR tongue OR palate OR palatal OR buccal OR nose OR nasal OR sinonasal OR paranasal OR sinus OR pharyngeal OR pharynx OR hypopharynx* OR nasopharynx* OR oropharynx* OR pharyngeal OR pharynx OR hypopharynx* OR nasopharynx* OR oropharynx*) AND (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm*)) AND ((squamous OR epidermoid) OR "Carcinoma, Squamous Cell"[Mesh Terms]) AND (drug therapy[MeSH Subheading] OR chemotherapy OR chemoradiation OR chemoradiotherapy OR radiochemotherapy OR radio-chemotherapy OR pharmacotherapy OR taxane* OR docetaxel OR paclitaxel OR Taxoid OR taxotere OR cisplatin OR platin* OR carboplatin OR fluorouracil OR 5-fluorouracil OR fluoro-uracil OR 5FU OR hydroxyurea OR tegafur-uracil OR leucovorin OR cetuximab OR bevacizumab OR panitumumab OR tirapazamine OR gefitinib OR erlotinib OR lapatinib OR Nimotuzumab OR gemcitabine OR amifostine OR methotrexate) AND ((randomized controlled trial [pt] OR clinical trial, phase iii [pt] OR clinical trial, phase iv [pt] OR clinicaltrials.gov [si] OR isrctn [si] OR randomized controlled trials as topic [mh]) OR ((random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR single-blind OR double-blind) AND (trial OR trials OR study OR studies))) Limits: Publication Date from 2000

SCOPUS

((TITLE-ABS-KEY("head and neck" OR laryngeal OR larynx OR glottis OR glottic OR subglottis OR subglottic OR supraglottis OR supraglottic OR oral OR mouth OR lip OR gingiva OR gingival OR tongue OR palate OR palatal OR buccal OR nose OR nasal OR sinonasal OR paranasal) OR TITLE-ABS-KEY(sinus OR pharyngeal OR pharynx OR hypopharynx* OR nasopharynx* OR oropharynx* OR pharyngeal OR pharynx OR hypopharynx* OR nasopharynx* OR oropharynx*)) AND ((TITLE-ABS-KEY(chemotherapy OR chemoradiation OR chemoradiotherapy OR radiochemotherapy OR radio-chemotherapy OR pharmacotherapy OR taxane* OR docetaxel OR paclitaxel OR taxoid OR taxotere OR cisplatin OR platin* OR carboplatin OR fluorouracil OR 5-fluorouracil) OR TITLE-ABS-KEY(fluoro-uracil OR 5fu OR hydroxyurea OR tegafur-uracil OR leucovorin OR cetuximab OR bevacizumab OR panitumumab OR tirapazamine OR gefitinib OR erlotinib OR lapatinib OR nimotuzumab OR gemcitabine OR amifostine OR methotrexate))) AND ((TITLE-ABS-KEY(random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR single-blind OR double-blind) AND TITLE-ABS-KEY(trial OR trials OR study OR studies))) AND ((TITLE-ABS-KEY(cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm*) AND TITLE-ABS-KEY(squamous OR epidermoid))) AND (LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-

TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002) OR LIMIT-TO(PUBYEAR, 2001) OR LIMIT-TO(PUBYEAR, 2000))

Cochrane

"head and neck" OR laryngeal OR larynx OR glottis OR glottic OR subglottis OR subglottic OR supraglottis OR supraglottic OR oral OR mouth OR lip OR gingiva OR gingival OR tongue OR palate OR palatal OR buccal OR nose OR nasal OR sinonasal OR paranasal OR sinus OR pharyngeal OR pharynx OR hypopharynx* OR nasopharynx* OR oropharynx* OR pharyngeal OR pharynx OR hypopharynx* OR nasopharynx* OR oropharynx* in Title, Abstract or Keywords and chemotherapy OR "drug therapy" in Title, Abstract or Keywords and squamous in Title, Abstract or Keywords and randomized OR randomised in Title, Abstract or Keywords and cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* in Title, Abstract or Keywords, from 2000 to 2010 in Cochrane Central Register of Controlled Trials

Web of Science (meeting abstract)

Topic=("head and neck" OR laryngeal OR larynx OR glottis OR glottic OR subglottis OR subglottic OR supraglottis OR supraglottic OR oral OR mouth OR lip OR gingiva OR gingival OR tongue OR palate OR palatal OR buccal OR nose OR nasal OR sinonasal OR paranasal OR sinus OR pharyngeal OR pharynx OR hypopharynx* OR nasopharynx* OR oropharynx* OR pharyngeal OR pharynx OR hypopharynx* OR nasopharynx* OR oropharynx*) AND Topic=(chemotherapy OR chemoradiation OR chemoradiotherapy OR radiochemotherapy OR radiochemotherapy OR pharmacotherapy) AND Topic=(cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm) AND Topic=(squamous) AND Topic=(random*)

Refined by: Document Type=(MEETING ABSTRACT)

Timespan=2000-2010. Databases=SCI-EXPANDED.

clinicaltrials.gov

random* | Interventional Studies | head and neck cancer AND squamous | drug therapy OR chemotherapy | received on or after 01/01/2000

Web-Appendix 4: Data checking and trial quality

Internal consistency was checked (chronology of dates, extreme values, etc). Randomization validity was assessed by checking patterns of treatment allocation and balance of baseline characteristics between treatment groups. Post-randomization exclusion were systematically searched. Follow-up of patients was also compared between treatment groups. All data were compared to trial protocols and published reports. All questions raised by the checking procedure were discussed with the trialists [1].

We were able to collect data from 725 of the 867 randomized patients who had been excluded from the original published analyzes. For 89 trials out of 107, data were available for all randomized patients. Numbers of analyzed and randomized patients are available for each trial in Web-Tables 1, 2, 3, and 4. No significant difference due to randomization was observed between treatment arms, except for two trials in which follow-up was significantly different [2–4]*. In agreement with the investigators, follow-up was censored for these two trials. None of the trials identified for this update were excluded because of randomization or follow-up problem. Trials previously excluded after checking the individual patient data are available in the publications of the initial meta-analysis and its first update [5,6]. Because of the difficulty to detect quality problem in small trials, a sensitivity analysis without small trials was performed (Web-Table 10).

* Hitt R, Grau J, López-Pousa A, Berrocal A, García-Girón C, Irigoyen A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. *Annals of Oncology* 2014;25:216–25. <https://doi.org/10.1093/annonc/mdt461>. (update reference 2)

Web-Appendix 5: Statistical methods

Power of the analysis

With more than 18000 patients (and at least 12000 deaths), an absolute improvement in survival from 30% to 33% at 5 years could be detected with a power of 99.9% (two-sided log-rank test, $\alpha=5\%$). For the population included in the 4 main analyzes on OS (3 analyzes by timing for the main question and the secondary question) that ranged from 1214 to 10680 patients, this power ranged 22% from to 94% to detect a 3% difference from 30% to 33%. For the analysis with 1214 patients, the power was 82% to detect a 7.5% difference from 30% to 37.5%.

120-day mortality

Hazard ratio and Peto curves were estimated with Peto method (O-E and Var(O-E)). Patients with a follow-up longer than 120 days were censored at 120 days.

Heterogeneity

In case of significant heterogeneity ($p < 0.10$), analysis was repeated without the “outliers” defined as trials with a 95% CI that did not overlap the 95% CI of the global HR). If heterogeneity was still significant, a random-effects model was used [7]. We computed residual heterogeneity within trial subgroups by subtracting the Chi^2 statistic of the heterogeneity test between groups from the Chi^2 statistic of the overall heterogeneity test [8].

Cancer/non-cancer mortality, survival within and after 5 years

Expected (E) and observed (O) numbers of events were derived from the log-rank statistic (method developed by R Peto)[9]. Cancer mortality was obtained indirectly by subtracting (O-E) and its variance (Var(O-E)) of non-cancer mortality from (O-E) and Var(O-E) of overall survival [10]. Cancer/non-cancer mortality was studied only for the induction and concomitant timings, and was restricted to recent and more homogenous trials: for induction comparisons, only trials using PF or TPF schedules; for concomitant comparison, only trials included in the updates. Moreover, only trials with data on tumour failures and cause of death were included.

Overall survival after 5 (10) years was obtained indirectly by subtracting (O-E) and Var(O-E) of overall survival within 5 (10) years from (O-E) and Var(O-E) of overall survival on the whole period of time [10].

Competing risk

Only the first type of failure (loco-regional or distant) were collected. Fine and Gray model stratified on trial comparisons was used with three types of event: loco-regional failure, distant failure, and death without failure [11]. Each type of event was successively analyzed as the main event. The others were considered as competing events. Patients alive without failure were censored at the date of last follow-up. Results of the “death without failure” analysis are not presented in this publication but are available on request. Cumulative incidence curves were drawn according to the Aalen Johanssen method and were not stratified.

Analyzes were performed with R software (version 3.3.2, R foundation for Statistical Computing, Vienna, Austria). Sub-distribution HR were estimated in each trial with the “cmprsk” package and global sub-distribution HR were estimated with the “crrSC” package.

Sensitivity, subset and subgroup analyzes

Sensitivity, subset and subgroup analyzes were pre-specified in the protocol except if mentioned otherwise in this publication.

Six sensitivity analyzes (i.e. analysis after exclusion of some comparisons) were performed for each timing: a) without comparisons with two timing (e.g. concomitant radio-chemotherapy vs. induction chemotherapy plus concomitant radio-chemotherapy); b) without confounded comparisons; c) without trials starting accrual before 1980; d) without trial including 80 patients or less or 40 patients or less by arm; e) without trials with a median follow-up of 5 years or less; d) after exclusion of duplicated patients. For the induction timing, because of the apparent contradiction between the previous meta-analysis comparing PF and TPF induction chemotherapy [12] and the current results, unplanned analyzes were performed after exclusion of the 3 comparisons with major early related to treatment mortality and/or without GCSF (Budapest 2007, TTCC 2002 PF and TPF without GCSF) [12,13].

Subgroup analyzes (i.e. interaction between patient characteristics and treatment effect) were performed only for the induction and concomitant timings, and were restricted to recent and more homogeneous trials: for induction comparisons, only trials using PF and TPF schedules; for concomitant comparisons, only trials included in the updates. Only trials with all categories of the studied characteristic were included. For instance, if age is analyzed in four categories (<50 , 50-59, 60-69, ≥ 70), trials without patients 70 or older were excluded. Between trials heterogeneity was studied using the Fisher et al method [14]. As in MARCH, subgroup analyzes with adjustment on covariables available for most of the patient (age, sex) were performed as sensitivity (unplanned) analyzes. In the absence of recent trial, no subgroup analysis was performed for the adjuvant comparisons and the secondary question (see text below Web-Table 12-B).

Web-Appendix 6: Results of trials search

Following trial search, 16 new trials were identified as potentially eligible for this meta-analysis. Four of those trials were excluded: a three-arm trial was considered too small (N=60)[15], one investigator reported his trial as not suitable enough for publication (N=275)[16], data of one trial were lost (N=105)[17], one trial was excluded after data collection because it compared two larynx preservation approaches (N=75)[18].

Data of three trials were collected at the time of the initial meta-analysis but were not included back then because they studied the addition of a second timing of chemotherapy to another timing plus loco-regional treatment. They were included in this second update (N=210)[19–21].

One trial, INRC-HN-9 [22] included in the first update was transferred to the MARCH meta-analysis (N=143)[23]. One trial, TMH 1114 identified for the MARCH meta-analysis was also eligible for MACH-NC (N=131)[24].

Trials not available or excluded in the initial meta-analysis or in the first update are described in the corresponding publications [5,6].

Among the 107 trials included in the second update of the meta-analysis, five were unpublished: BNH 003 (N=124), EORTC 24844 (N=139), EORTC 22954 (N=59), EORTC 22962 (N=54), SECOG II (N=239).

Web-Appendix 7: Trial design, trial division and patient duplication

Trial design

Three trials were analyzed as several independent randomized trials since the initial meta-analysis. Among those three trials, two were divided into two independent randomized trials based on their loco-regional treatments: GETTEC neo1 and GETTEC neo2 [25], HNU-87a and HNU-87b [26]. The third trial was analyzed as three independent randomized trials because the route of drug administration differed: WIA-OC5a, WIA-OC5b and WIA-OC5c [27].

Out of the 107 randomized trials included in the second update of the meta-analysis, 15 were three-arm trials (SECOG II unpublished)[2,24,28–40]. They were analyzed as follows:

- Third arm was not eligible in six trials: TMH 1114, Barcelona, Vienna, RTOG 9111, Oro 9301, Pité 74 [24,28–33];
- The two experimental arms were pooled in three trials: Buenos Aires, Kragejuvac 1, HeCOG 9405 [34–36].

The three arms were taken into account for the six other trials: Lucknow 95, TTCC 2002, HNCP, AC Camargo, Int 126, SECOG II (unpublished) [2,37–40].

Design was a 2x2 factorial plan in six trials. In three of those trials, factorial plan applied only on a part of the population (SECOG II unpublished; GSTTC 2501 [41,80], UKHAN [42]); in one trial, a second randomization was performed (+/- G-CSF; Cologne 95)[43]; in two trials, a second randomization was performed (+/- radiotherapy) (EORTC 22962 unpublished, Pitié 81)[44]. Second randomization was not taken into account for two trials (Cologne 95, Pitié 81) and led to the exclusion of a part of the trial in GSTTC 2501 trial in which the second randomization was between cetuximab and cisplatin [41,80].

There was an imbalanced randomization in five trials: SECOG II (unpublished), TTCC 2002, MDA-70, UKHAN, IAR-92 [2,42,45,46].

Trial division

To study treatment effect according to chemotherapy timing, loco-regional treatment and type of chemotherapy drug, some trials were divided into several comparisons because of their designs. In some cases, it led to patient duplication. Details of these divisions are available in Web-Table 5.

Patient duplication

According to the analysis performed, duplicated patients were:

- 1/ Main question (addition of chemotherapy, 130 comparisons): 8.2% (1698/20649)
 - Induction chemotherapy (45 comparisons): 4.7% (330/7054)
 - Concomitant chemotherapy (71 comparisons): 1.3% (144/10680)
 - Adjuvant chemotherapy (14 comparisons): 0% (0/2915)
- 2/ Secondary question (direct comparison of induction and concomitant chemotherapies, 8 comparisons): 0% (0/1214).

Re-analysis with correction for duplication [47], led to similar results (data not shown).

Web-Appendix 8: Heterogeneity between comparisons and sensitivity analyzes

Induction comparisons

No significant heterogeneity was observed, except for loco-regional ($p < 0.0001$; $I^2 = 63\%$) and distant failure ($p < 0.0001$; $I^2 = 97\%$). After the exclusion of outliers (3 comparisons for LRF and 7 for DF), heterogeneity became non-significant. The sub-hazard ratio was 0.99 [0.91; 1.08], $p = 0.88$ for LRF and similar for DF (data not shown).

Concomitant comparisons

Significant heterogeneity was observed both for overall ($p = 0.0002$; 42%) and event-free survival ($p < 0.01$; 30%). In both cases, the heterogeneity was observed only among the comparison of the initial meta-analysis which have been explored previously [48] and the hazard ratios were not significantly different between the initial meta-analysis and the updates (Web-Figure 10 for OS; data not shown for EFS).

For 120-day mortality, the heterogeneity observed ($p = 0.01$, $I^2 = 30\%$; Web-Figure 5) was not significant anymore after exclusion of six outliers ($p = 0.45$, $I^2 = 1\%$): UW-77 [49], UW-79 [50], CH-7401 [51], ORO 9301 [28], UKHAN1po1 [42] and Lucknow 90 [52] (5% of Var(O-E) for this timing). Without those outliers, HR was 1.12 [0.96; 1.31].

A significant heterogeneity was observed for loco-regional ($p < 0.0001$; $I^2 = 85\%$) and for distant failure ($p < 0.0001$; $I^2 = 96\%$). After the exclusion of outliers (5 comparisons for LRF and 6 for DF), heterogeneity became non-significant with similar results in both cases (data not shown).

Adjuvant comparison

For event-free survival, a significant heterogeneity was observed ($p = 0.03$, 47%; Figure 1). After the exclusion of the outlier (one comparison), heterogeneity became not significant with similar results (data not shown).

For 120-day mortality, a borderline heterogeneity was observed ($p = 0.10$, $I^2 = 34\%$). After the exclusion of UKHAN1a1 [42] (9% of Var(O-E) for this timing), heterogeneity became non-significant ($p = 0.48$, $I^2 = 0\%$) but the deleterious effect was still significant (HR=1.61 [1.12; 2.33]).

A significant heterogeneity was observed for distant failure ($p < 0.0001$; $I^2 = 98\%$). After the exclusion of outliers (4 comparisons), heterogeneity became non-significant. Sub-hazard ratio was equal to 0.81 [0.65; 1.02], $p = 0.07$.

Secondary question

For the secondary question (concomitant [or alternating] radio-chemotherapy versus induction [+/- adjuvant] chemotherapy and radiotherapy), no significant heterogeneity was observed (Web-Figure 12).

Web-Table 1: Description of induction trials

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized ^a	Median follow-up [95% CI] (years)
Chemotherapy other than platin + fluorouracil or Taxane + platin + fluorouracil									
IGR-65[53]	1965–67	OC, OP	IV	Mx (ia) LA (im)	50 mg x 6–12 15 mg x 6–12	RT	30-60 Gy	36/39 ^a	NA [†]
RTOG 6801[54]	1968–73	OC, OP, HP, L	III, IV	Mx	25 mg x 5	RT	55-80/5-10 wks	680/712 ^b	4.3 [4.0 ; 4.8]
EORTC 24771[55]	1977–82	HP	II to IV	B Mx Vc	15 mg 20 mg/m ² x 4 1.5 mg/m ²	S + RT	50-65 Gy /≤10 wks	231/231 ^c	5.9 [4.9 ; 6.6]
Denver 77[56]	1977–83	OC, OP, HP, O	III, IV	B C Mx	10 U/m ² x 4, wks _{1,4} or 5 50 mg/m ² , wks _{1,4} or 5 30 mg/m ² x 2, wks _{1,4} or 5	RT	60-70 Gy, alt	59/59 ^d	NA [†]
						or S + RT	50-60 Gy, alt		
HNCP[38]	1978–82	OC, HP, L	II to IV	<u>Arm₁</u> : B (bolus) B (ci) C <u>Arm₂</u> : Arm ₁ + C	ind: 15 mg/m ² d ₃ ind: 15 mg/m ² d _{3,7} ind: 100 mg/m ² d ₁ adj : 80 mg/m ² monthly x 6	S + RT	50 Gy/5-5.5wks	462/462 ^e	5.3 [5.1 ; 5.5]
EORTC 78-OCP[57]	1978–84	OC, OP	I to IV	B (ia) Vc (ia)	15 mg d ₁₋₁₂ 1 mg, d _{1,5,9}	S	NA	225/225 ^f	4.9 [4.5 ; 5.3]
						or S + RT	MD		
MCW-1[58,59]	1979–82	OC, OP, HP, L, NP, O	III, IV	B Cy F Mx	30 U x 4, wks _{1,4} 200 mg/m ² x 5, wks _{1,4} 400 mg/m ² x 5, wks _{1,4} 30 mg/m ² x 5, wks _{1,4}	RT	70 Gy/7wks	83/83 ^g	5.9 [3.3 ; 17.1]
						or RT + S	50 Gy/5wks		
SWOG 8006[60]	1980–85	OC, OP, HP, L	II to IV	B C Mx Vc	15 U/m ² d _{1,8} , wks _{1,4,7} 50 mg/m ² , wks _{1,4,7} 40 mg/m ² , wks _{1,4,7} 2 mg, wks _{1,4,7}	S + RT	MD	167/167	13.7 [11.6 ; 14.5]
Pitié-81[44]	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 ^h	11.3 [4.4 ; 12.9]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized ^a	Median follow-up [95% CI] (years)
Buenos Aires[34]	1981–86	OC, OP, HP, L, NP	III, IV	<u>Arm₁</u> : C B	100 mg/m ² , d _{1,15} 40 mg/m ² , d _{1,8,15,22}	S	NA	120/120 ⁱ	7.0 [6.1 ; 8.9]
				<u>Arm₂</u> : C B	100 mg/m ² , d _{4,19} 40 mg/m ² , d _{1,8,15,22}	or RT	MD		
				Mx	50 mg/m ² , d _{1,15}	or S + RT	MD		
Créteil-82[61]	1982–87	OC, OP	II to IV	B (ci) F Mx LA (po) C	10 mg/m ² x 5, wks _{1,5,9} 600 mg/m ² d ₂ , wks _{1,5,9} 120 mg/m ² d ₂ , wks _{1,5,9} 10 mg x 4, d ₃ , wks _{1,5,9} 120 mg/m ² d ₄ , wks _{1,5,9}	RT	70 Gy/7.8 wks	122/131 ^j	5.0 [4.2 ; 5.7]
						or S + RT	55 Gy/6 wks		
HNCGIC 02[62]	1983–86	OC, OP, HP, L	II to IV	B (ci) C Mi Vd	12.5 mg/m ² x 4, wks _{1,4} 20 mg/m ² x 4, wks _{1,4} 10 mg/m ² , wks _{1,4} 2.5 mg/m ² , wks _{1,4}	RT	65-75 Gy	100/100 ^k	10.2 [9.8 ; 12.3]
AC Camargo[39]	1984–86	OC, OP, HP	III, IV	B C Mi Vb	10 mg/m ² , wks _{1 ± 2} 30 mg/m ² x 2, wks _{1 ± 2} 8 mg/m ² , wks _{1 ± 2} 4 mg/m ² , wks _{1 ± 2}	RT	70 Gy/7 wks (Co) or 8 wks (Ex)	60/60 ^l §	6.5 [3.6 ;]*
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	60-66 Gy/6.5 wks	163/163 ^m	12.5 [12.1 ; 15.0]
HNCGIC 03[63]	1986–89	OC, OP, HP, L	II to IV	C (ci) F (ci) Vd	40 mg/m ² x 3, wks _{1,4,7} 600 mg/m ² x 5, wks _{1,4,7} 3 mg/m ² x 2, wks _{1,4,7}	RT	70 Gy	108/108 ⁿ	7.2 [6.7 ; 7.5]
Songkhla [64]	1988–92	OC, OP, HP, O	III, IV	B (ci) C Mx	10 mg/m ² d _{3,7} , wks _{1,5} 20 mg/m ² x 5, wks _{1,5} 40 mg/m ² d _{15,22} , wks _{1,5}	S + RT	≥ 60 Gy	54/54 ^o	4.1 [2.8 ; 5.3]
Lucknow 95[37]	1995–99	OC, OP, HP, L, O	III, IV	C	35 mg/m ² d ₁ , wks ₁₋₇	RT	70 Gy/7 wks	200/200 ^{p,§}	13.0 [10.4 ; 14.5]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized ^a	Median follow-up [95% CI] (years)
Platin + fluorouracil only									
MCW-2[65,66]	1983–86	OC, OP, HP, L, NP, O	III, IV	C F (ci)	100 mg/m ² , wks _{1,4,7} 500 mg/m ² x 5, wks _{1,4,7}	RT + S or RT	50 Gy/5 wks 70 Gy/7 wks	63/63 ^q	8.3 [5.6 ; 11.0]
EORTC 24844 (unpublished)	1985–91	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}	S + RT	50 Gy/5 wks +/- 15 Gy boost	139/139 ^r	2.8 [2.2 ; 3.8]
SHNG-85[67]	1985–92	OC, OP, HP, L	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	64-70 Gy/6.5-7 wks	461/461 ^s	7.2 [6.9 ; 7.5]
Créteil-86[68,69]	1986–89	OC, OP, HP, L	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 or S + RT	70 Gy/8 wks 55 Gy/6 wks	156/156 ^t	6.0 [5.3 ; 6.0]
GSTTC-86[70,71]	1986–90	OC, OP, HP, O	III, IV	C F (ci)	100 mg/m ² , wks _{1,4,7,10} 1000 mg/m ² 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 ^u	11.3 [10.2 ; 11.6]
GETTECneo1[25]	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 ^v	12.0 [11.0 ; 12.8]
GETTECneo2[25]	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 ^w	12.3 [11.1 ; 12.8]
AHNTG[72]	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 ^x	7.1 [6.7 ; 7.7]
Las Palmas[73]	1987–89	OC, OP, HP, L, NP	III, IV	Cb Tg (po)	400 mg/m ² , wks _{1,5,9} 1000 mg/m ² x 14, wks _{1,5,9}	RT	66-74 Gy/6.5-7.5 wks	36/42 ^y	3.2 [2.6 ; 4.0]
Rennes-87[74]	1987–90	OP, HP	I to IV	C F (ci)	100 mg/m ² , wks _{1,3,5} 1000 mg/m ² J ₂₋₅ , wks _{1,3,5}	RT or S + RT	68.6 Gy MD	133/133 ^z	6.4 [5.5 ; 7.4]
Parma[75]	1987–91	OC, OP, HP, L	II to IV	C F (ci)	100 mg/m ² , wks _{1,4,7 ± 10,13} 1000 mg/m ² x 5, wks _{1,4,7 ± 10,13}	S or RT or S + RT	NA MD MD	69/69 ^{aa}	6.2 [5.6 ; 6.8]
CFHNS[76,77]	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 ^{bb}	5.7 [5.3 ; 6.0]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized ^u	Median follow-up [95% CI] (years)
Cologne 88[78]	1988–93	OC, OP, HP	II to IV	Cb F (ci)	360 mg/m ² , wks _{1 ± 5 ± 9} 1000 mg/m ² x 5, wks _{1 ± 5 ± 9}	S + RT	60-66 Gy/6-7 wks	97/97 ^{cc}	2.0 [1.6 ; 2.5]
HNAP-02[79]	1989–92	OC, OP, HP, L	III, IV	C F	70 mg/m ² , 2 cycles 660 mg/m ² d ₂₋₆ , 2 cycles	S or S + RT	50 Gy 50 Gy	50/50 ^{dd}	5.2 [4.1 ; 5.6]
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 [3.4 ; 4.0]
Taxane + platin + fluorouracil (second update)^s									
TTCC 2002[2]	2002–07	OC, OP, HP, L	III, IV	<u>Arm₂</u> : Do C F (ci) <u>Arm₃</u> : C F (ci) C (3 arms)	ind: 75 mg/m ² , wks _{1,4,7} ind: 75 mg/m ² , wks _{1,4,7} ind: 750 mg/m ² x 5, wks _{1,4,7} ind: 100 mg/m ² , wks _{1,4,7} ind: 1000 mg/m ² x 5, wks _{1,4,7} conco: 100 mg/m ² , wks _{1,4,7} of RT	RT	70 Gy/7 wk	387/387 ^{cc}	5.0 [5.0 ; 5.0]
GSTTC 2501[41,80]	2003–12	OC, OP, HP, O	III, IV	C Do F (ci) C (ci; 2 arms) F (ci; arms)	ind: 80 mg/m ² , wks _{1,4,7} ind: 75 mg/m ² , wks _{1,4,7} ind: 800 mg/m ² x 4, wks _{1,4,7} conco: 20 mg/m ² x 4, wks _{1,6*} conco: 800 mg/m ² x 4, wks _{1,6*} of RT	RT	70 Gy/7 wks	261/261 ^{ff}	3.7 [3.4 ; 3.9]
DeCIDE[81]	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/m ² , wks _{1,4} ind: 75 mg/m ² , wks _{1,4} ind: 750 mg/m ² x 5, wks _{1,4} conco: 25 mg/m ² , wks _{1,3,5,7,9*} conco: 600 mg/m ² 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 ^{gg}	6.0 [5.6 ; 6.4]
Budapest 2007[13]	2007–09	OC, OP, HP, L	III, IV	Do C F (ci) C (two arms)	ind: 75 mg/m ² , wks _{1,4} ind: 75 mg/m ² , wks _{1,4} ind : 750 mg/m ² x 4, wks _{1,4} conco: 100 mg/m ² , wks _{1,4,7} of RT	RT	70 Gy/7 wks	66/66 ^{hh}	6.8 [6.1 ; 7.6]
Shanghai 2008 [82,83]	2008–10	OC	III, IVa	Do C F (ci)	75 mg/m ² , wks _{1,4} 75 mg/m ² , wks _{1,4} 750 mg/m ² x 5, wks _{1,4}	S + RT	54-60 Gy/6 wks	256/256 ⁱⁱ	5.6 [5.4 ; 5.8]

* Upper value not reached. [†] Median follow-up and 95% confidence interval not available for two trials because of high rate of mortality. ^u Number of patients analyzed in the meta-analysis and corresponding number of patient randomized. ^s Trial not included in initial MACH-NC or its first update.

A: Doxorubicin ; AC Camargo: Hospital AC Camargo ; Adj: Adjuvant ; AHNTG: Australian Head and neck Trial Group ; B: Bleomycin ; BNH: B. Nanavati Hospital ; C: Cisplatin ; Cb: Carboplatin ; CFHNS: Carboplatin French Head and Neck Study ; ci: Continuous Infusion ; conco: Concomitant ; Co: Control arm ; DeCIDE: Docetaxel-based Chemotherapy plus or minus Induction chemotherapy to Decrease Events ; Do: Docetaxel ; EORTC: European Organisation for Research and Treatment of Cancer ; Ex: Experimental arm ; F: 5-Fluorouracil ; GETTEC: Groupe d'Etude des Tumeurs de la Tête Et du Cou ; GSTTC: Gruppo di Studio sui Tumori della Testa et del Collo ; Gy: Gray ; HNAP: Head and Neck Adjuvant Project ; HNCGIC: Head and Neck Cancer Group of Institut Curie ; HNCP: Head and Neck Contract Program ; HP: Hypopharynx ; Hu: Hydroxyurea ; ia: intrarterial ; IGR: Institut Gustave Roussy ; im: intramuscular ; ind: Induction ; iv: intravenous ; L: Larynx ; LA: Leucovorin ; MCW: Medical College of Wisconsin ; MD: Missing Data ; Mi: Mitomycin ; Mx: Methotrexate ; NA: Not Applicable ; NP: Nasopharynx ; NR: not reached ; O : Other ; OC: Oral Cavity ; OP: Oropharynx ; po: per os ; RT: Radiotherapy ; RTOG: Radiation Therapy Oncology Group ; S: Surgery ; SECOG: South of England Co-operative Oncology Group ; SHNG: Scandinavian Head and Neck Group ; SWOG: SouthWest Oncology Group ; Tg: Tegafur ; TTCC: Tratamiento de Tumores de Cabeza y Cuello ; U : Unknown primary ; Vd: Vindesine ; Vc: Vincristine ; wks: weeks

^a Radiotherapy started 2 weeks after the end of ia infusion. 30 Gy was administered over 2 week period. Radiotherapy was stopped if progression was observed; it could be continued up to 60 Gy or followed by curietherapy or even surgery. 16 pts (8 in each arm) received at least 50 Gy.

^b Mx every third day for 5 injections. Surgical intervention (either resection of the primary or radical neck dissection) was permitted after radiotherapy provided that the some policy was carried out in both arms. Surgery was also permitted as part of an integrated combined treatment regimen.

^c Only one cycle of chemotherapy, postoperative radiotherapy within the 3 months, 50 Gy plus 15 Gy in limited area in case of unclear tumour margins, not to exceed 10 weeks.

^d For the operable patients of the control arm, radiotherapy dose was 50 Gy followed by surgery if patient seemed resectable, patients who remained inoperable or refused surgery received another 15-20 Gy. In the experimental arm, after the first cycle of CT on week 2-3, patients received 20 Gy in 10 fractions, a second cycle on wks 4/5, and if resectable, surgery on wks 6-7 plus 40 Gy in 20 fractions when healing seemed complete; those who remained inoperable received another 40-50 Gy. At randomization, 31 were considered as inoperable and 28 as operable.

^e Three-arm trial with one induction and one induction plus adjuvant.

^f In the floor of mouth group, postoperative radiotherapy was delivered depending upon the lymph node involvement and the completeness of tumor resection. In this group, tumor bed was irradiated in 68% in chemotherapy arm and 55% in control arm. Irradiation was systematically applied in the posterior oral cavity or oropharynx group.

^g 2 Gy/fraction. Irradiation was initiated 3 weeks after the last cycle of chemotherapy. Radiotherapy alone was delivered for 46 patients and preoperative radiotherapy plus surgery 36 patients. One additional patient expired in the experimental arm prior the planned irradiation. Initially, responders to induction chemotherapy were scheduled to receive two post-operative cycles of B-CMF using 50% of the induction bleomycin dose. Toxicities and poor compliance with postoperative B-CMF led to discontinue postoperative chemotherapy, testing only induction chemotherapy as outlined.

^h 3 cycles of chemotherapy planned. Duration of cycle, 3 or 4 weeks? There was a second randomization between standard radiotherapy and bi or tri-fractionated radiotherapies. Standard radiotherapy: 2 Gy/ fraction, 5 fractions a week on 7 wks. Bi-fractionated RT: 1.5 Gy x 2 (4 hours between sessions) , 10 sessions in 5 days, 2 weeks break, similar one week session.

ⁱ Three-arm trial with 2 chemotherapy arms (A1, A2), BC, BCMx, two 2-wks cycles.

^j Radiotherapy only (51 patients out of 116 eligible patients), 70 Gy, 1.8 Gy/fraction, 5 fraction by week ; Surgery + radiotherapy (65 patients out of 116 patients), 55 Gy in 6 wks, boost to 70 Gy if incomplete resection. Locoregional treatment decided before randomization.

^k Two cycles of chemotherapy. Tumor response was evaluated after 50-55 Gy. Surgical excision was performed if the response was < 50% (6 pts). Otherwise the radiotherapy was completed to 65-75 Gy in 1.8 -2.2 Gy per fraction. Mean tumor dose was 69 and 70.3 Gy in the chemotherapy + radiotherapy and radiotherapy arm respectively with mean overall duration of 49 and 49.7 days and mean number of fraction of 34.8 and 34.5 respectively.

^{1f} Three-arm trial with a concomitant arm and 90 patients overall. Same total dose was delivered in both arms: 2 Gy/fraction over 7 weeks in control arm; 1.8 Gy/fraction over 8 weeks in the experimental arm. Second cycle was given 3 weeks later to the patients in partial response. Patients stable or progressing started radiotherapy immediately. In this group 6 patients did not start RT.

^m Three-arm trial with a concomitant arm and 239 patients overall; patients allocated to the chemotherapy arms were randomized to receive B/Mx/Vb or same chemotherapy plus F. Two cycles of chemotherapy before radiotherapy and two after. Radiotherapy starting on weeks 5.

ⁿ Three cycles of chemotherapy. Tumor response was evaluated after 55 Gy. Surgical excision was performed if the response was < 50% (10 patients). Otherwise the radiotherapy was completed to 70 Gy. Mean tumor dose was 68 and 66.6 Gy in the chemotherapy + radiotherapy and radiotherapy arm respectively with mean overall duration of 47.4 and 47.7 days and mean number of fraction of 33 Gy in both arms.

^o Radiotherapy started within 6 weeks, minimum 60 Gy.

^p Three-arm trial with 300 patients overall: radiotherapy, induction chemotherapy and radiotherapy, radiotherapy and concomitant chemotherapy. Same chemotherapy in both experimental arms.

^{q2} 2 Gy per fraction; 70 Gy in favorable tumor site: 7 patients in chemotherapy group and 5 in control;

^r Surgery + radiotherapy in case of progression after first cycle of chemotherapy or progression or stable disease after the second cycle. Radiotherapy started as soon as possible after complete wound healing. If delayed for more than 10 days, radiotherapy is not mandatory anymore. Dose of 50 Gy in 25 fractions, 5 times a week plus 14 Gy in 7 fractions if the excision was irradical.

^s 2 Gy by fraction, 5 times a weeks.

^t Operable patient: 55 Gy over 6 weeks, 1.8 Gy per fraction, 5 days a week, boosted to 70 Gy in residual disease; Inoperable patients: 70 Gy over 8 wks in 1.8 Gy per fraction. Non responding patients were switched to definitive local treatment after 1-2 cycles. Locoregional treatment was decided before randomization.

^u For operable patients (n=66), 45-50 Gy of adjuvant radiotherapy was planned. Modality of surgery was decided before randomization: 5 patients had no surgery of incomplete surgery. For the inoperable patients (n=171), the planned dose was 65-70 Gy with 2 Gy per fraction and 5 fractions per week. A two-week break was allowed after 40 Gy or in case of grade 3-4 mucositis. Patient level information on planned locoregional treatment was available and the trial was split in two strata: GSTCC 86 and GSTTC 86po (n=66), po for post-operative radiotherapy.

^v Radiotherapy began 2-3 wks after chemotherapy completion: 70 Gy in 7 weeks with 5 Gy added in case of residual disease

^w Radiotherapy began within 10 weeks after surgery that was performed 2-3 after chemotherapy completion: 50 Gy in 5 weeks with 2 Gy fraction in patients with free surgical marginal and 65 Gy in 6.5 weeks in case of positive margins.

^x 36/280 (24%) patients were treated by surgery, 113/280 (76%) patients were treated by surgery and radiotherapy, 118/280 patients by radiotherapy alone, 10 patients had no locoregional treatment, one mixed locoregional treatment and for 2 patients, locoregional treatment was unknown. Protocol mentioned "Radiotherapy should be given in radical doses. In general, fields for DLT (radiotherapy and surgery) should be based upon the original tumour extent, not on its extent following chemotherapy".

^y 2 Gy by day, 5 days a week. Surgery was performed after radiotherapy, if disease persisted or recurred (9 patients). Tg daily 1000 mg/m² dose was fractioned into two

^z 28 patients had surgery plus postoperative and 90 only radiotherapy. Mean dose of radiotherapy was 68.6 Gy+/-6 without difference between the two arms. For the 15 other patients, 5 were ineligible (associated diseases), 4 had protocol violation (chemotherapy dose), 3 refused treatment and for 3 died during chemotherapy.

^{aa} Patients achieving complete or partial responses > 80% received two further cycles.

^{bb} For radiotherapy alone, a dose of 75 Gy was used. For basilingual and T2 tonsillar tumors a dose of 45-50 Gy was used followed by brachytherapy 30-35 Gy. Post-operative dose ranged from 45 to 75 Gy depending of the degree of resection. Patients showing complete tumor regression switched to radiotherapy alone. Out of the 34 patients in complete response, 29 switched to radiotherapy alone, the other being planned to receive radiotherapy alone. Of the 143 evaluable patients who underwent chemotherapy, 37 out of 90 with primary indication of locoregional surgery qualified for treatment modification, including 21 out of 73 with primary indication of mutilating surgery. Confounded trial (see definition in WEB-Table 3.

^{cc} Patients without response after the first cycle were operated immediately. Only patient with patient response after two cycles received the third one. Radiotherapy started at least 6 weeks after surgery. In case of insufficient wound healing at 6 weeks, no RT was performed. Daily fraction was 2 Gy, with 5 fractions a week.

^{dd} When nodes metastases were found to be multiple or extracapsular, or surgical margin were insufficient, radiotherapy of 50 Gy was administered post-operatively

^{ee} Three-arm trial: CF, DoPF, no induction, with concomitant cisplatin in the three arms and 439 patients overall. Dose of C and F were higher in the CF arm than in the DoCF arm. G-CSF administration from the first cycle to patients assigned to TPF, was implemented in the protocol, by amendment, to prevent neutropenia, after the inclusion of 338 patients. Once the planned 128 patients at the CCRT-alone arm were recruited, the last 52 patients were only randomly assigned to DoCF -CCRT and PF-CCRT arms. Significant unbalance between arms on the median of follow-up was observed, mostly due to difference in the follow-up after 5 years. For this meta-analysis, the last 52 patients were excluded and the follow-up censored to 5 years.

^{ff} Two by two design: addition of induction DoCF to radiotherapy plus concomitant treatment; radiotherapy + cisplatin vs radiotherapy + cetuximab. The two cetuximab arms were not eligible for this meta-analysis. Then, only 261 patients out of 421 were included. The trial was a phase II/III that started by the randomized phase II (XRP 6976) comparing induction DoCF to radiotherapy + concomitant cisplatin vs. radiotherapy + concomitant cisplatin. Antibiotic prophylaxis was administrated after each TPF cycle.

^{gg} Radiotherapy: 1.5 Gy/fraction, bid, 5 days per week, 5 two-week cycles (one week on/one week off). White blood cell growth factor support was administered with each cycle of IC. Three-dimensional conformal radiotherapy or intensity-modulated radiation therapy were used.

^{hh} Phase 2 on the addition of induction CT to concomitant radio-chemotherapy with sample size of 92 and tumor response after radiotherapy as main endpoint. Recruitment was stopped prematurely because of 3 deaths due to febrile neutropenia in the experimental arm. Radiotherapy schedule was 2 Gy per day, 5 days per week. Granulocyte colony-stimulating factor (G-CSF) was administered in febrile and grade 4 neutropenia.

ⁱⁱ 1.8-2 Gy/fraction, 5 days a week

Web-Table 2: Description of concomitant trials

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized ^μ	Median follow-up [95% CI] (years)
Initial meta-analysis									
MDA-70[45]	1970–72	OC, OP, HP, L, NP, O	III, IV	Hu (po)	81 mg/kg x 3, weekly during RT	RT	45-75 Gy/4.5-9.5 wks	36/42 ^a	NA [†]
EORTC73-OC[84]	1973–75	OP	II-IV	B (im or iv)	15 mg x 2, wks _{1,2,3,4,5}	RT	70 Gy/7-8.5 wks	199/226	7.0 [5.7 ; 7.5]
Turku[85]	1975–79	OC, HP, L, O	I-IV	B (im)	7–15 mg x 5, wks _{1,3}	RT	55-60Gy /9 wks, sc	46/46 ^b	18.1 [17.7 ; 21.3]
						RT + S	30-32 Gy/3 wks		
NRH-78[86]	1978–81	OC, OP, HP, L, NP, O	II-IV	B (im)	5 mg x 2–35	RT, RT+ S	65 Gy/6-7 wks +/- curietherapy	222/222 ^c	14.5 [14.1 ; 14.7]
Barcelona[30]	1978–88	OC, HP, L, NP, O	III, IV	F	250 mg/m ² every 2d, wks ₁₋₆	RT	60 Gy/6 wks	573/600 ^d	12.8 [12.3 ; 13.8]
Manchester[87,88]	1979–84	OC, OP, HP, NP, L	I-IV	Mx	100 mg/m ² , wks _{1,3}	RT	45-55 Gy/3 wks	313/313 ^e	13.9 [12.5 ; 15.0]
ECOG 2382 [89,90]	1982–87	OC, OP, HP, L, NP, O	I-IV	C	20 mg/m ² , wks ₁₋₇ or 8	RT	68-76 Gy/7-8 wks	371/371 ^f	15.3 [14.3 ; 16.0]
AC Camargo[39]	1984–86	OC OP, HP	IV	B C	5 mg x 2, wks _{1,4,7} 20 mg/m ² x 2, wks _{1,4,7}	RT	70 Gy/ 7 wks (Co) or 8 wks (Ex)	60/60 ^g	9.6 [2.4 ;]*
Ontario[91]	1987–91	OC, OP, HP, L	III, IV	F	1200 mg/m ² x 3, wks _{1,3}	RT	66 Gy/6.5 wks	175/175 ^h	5.7 [5.3 ; 6.0]
Kragujevac1[35]	1988–91	OC, OP, HP, L, NP	III, IV	<u>Arm₁</u> : C <u>Arm₂</u> : Cb	6 mg/m ² x 5, wks ₁₋₇ 25 mg/m ² x 5, wks ₁₋₇	RT	70 Gy/7-7.5 wks	159/159 ⁱ	4.8 [4.3 ; 5.0]
Bavaria-89[92]	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 ^j	1.6 [1.4 ; 2.1]
LOHNG-91[93]	1991–93	OC, OP, HP, O	III, IV	B Mi dicoumarol	5 U x 2, wks ₁₋₇ 10-15 mg/m ² , wks ₁₋₇	RT	66-70 Gy/6.5-7 wks	64/64 ^k	11.0 [9.3 ; 11.9]
WIA-0C5a[27]	1971–72	OC	III, IV	B (ia)	10–15 mg x 2-3, wks _{1,2,3,4,5,6,7}	RT	65 Gy/6.5 wks (Co) 55-60 Gy/6.5-7 wks (Ex)	50/50 ^l	23.9 [23.6 ; 23.9]
WIA-0C5b[27]	1972–73	OC	III, IV	B (ia or iv)	10–15 mg x 2-3, wks _{1,2,3,4,5,6,7}	RT	65 Gy/6.5wks (Co) 55-60 Gy/6.5-7 wks (Ex)	79/79 ^l	21.4 [17.0 ; 22.5]
Bergen[94]	1973–75	OC, OP, L, NP, O	I-IV	B (im)	15 mg d _{1,3,5} , wks _{1,2,3,5}	RT + S	30 Gy /5 wks, sc	32/32 ^m	21.1 [12.0 ; 21.8]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized ^μ	Median follow-up [95% CI] (years)
RT-BLM-73[95]	1973–76	OC	II, III	B (im)	5 mg x 3, wks _{1,2,3}	RT	40-50 Gy/4-5 wks (Co) 30 Gy/3 wks (Ex)	46/46 ⁿ	10.7 [10.3 ; 10.8]
WIA-OC5c[27]	1974–75	OC	III, IV	B (im)	10–15 mg x 3, wks _{1,2,3,4,5+6,7}	RT	65 Gy/6.5 wks (Co) 55-60 Gy/6.5-7 wks (Ex)	40/40 ^l	19.3 [11.7 ; 20.7]
UW-77[49]	1977–78	OC, OP, HP, NP, L	III, IV	A B F Hu (po) Mx (po) Mp (po) Vc	40 mg, wks _{1,5,10} 60 mg, wks _{1,5,10} 500 mg, wks _{1,5,10} 2000 mg, wks _{1,5,10} 30 mg x 3, wks _{1,5,10} 200 mg, wks _{1,5,10} 2 mg, wks _{1,5,10}	RT alt	65 Gy/8 wks, sc	58/58 ^o	NA [†]
UW-79[50]	1979–80	OC, OP, HP, L, NP	III, IV	B C	10 mg/m ² days _{1,3,5,7} , wks _{1, 5} , 9+13,17,21,25,29,33 20 mg/m ² days _{1,3,5} , wks _{1, 5} , 9+13,17,21,25,29,33	RT alt	48 Gy/5 wks, bid, sc	27/27 ^p	NA [†]
Yale-80[96]	1980–86	OC, OP, HP, NP, L	II-IV	Mi	15 mg/m ² , wks _{1,7}	RT S + RT/RT + S	> 56 Gy > 50 Gy	120/120 ^a	12.9 [11.7 ; 14.1]
PMHCGS[97]	1982–86	HP, L	I-IV	F (ci) Mi	1000 mg/m ² d ₁₋₄ , wks _{1,7} 10 mg/m ² , wks _{1,7}	RT	50 Gy/4 wks (Co) 50 Gy/8 wks, sc (Ex)	212/212 ^r	10.0 [9.2 ; 10.8]
Toulouse[98]	1984–88	OC, OP, HP, L, O	I-IV	C	50 mg x 1, wks _{1-7 or 9}	S + RT	54-70 Gy/6.5-8 wks	90/90 ^s	8.9 [7.3 ; 9.0]
SECOG II (unpublished)	1984–89	OC, OP, HP, L, NP, O	III, IV	<u>Arm₁</u> : B (im) Mx LA (iv) LA (im) Vc <u>Arm₂</u> : Arm ₁ + F	30 mg, wks _{1,3,6,9} 200 mg, wks _{1,3,6,9} 50 mg, wks _{1,3,6,9} 15 mg x 6, wks _{1,4,6,9} 1.5-2 mg, wks _{1,4,6,9} 500 mg, wks _{1,4,6,9}	RT alt	60-66 Gy/6.5 wks (Co) 60-66 Gy/8 wks, sc (Ex)	155/155 ^t	12.5 [12.1 ; 15.0]
CH-7401[51]	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 ^u	5.9 [5.0 ; 7.6]
Yale-86[99]	1986–92	OC, OP, HP, L, NP, O	I-IV	Mi dicoumarol	15 mg/m ² , wks _{1,7}	RT or S + RT or RT + S	> 56 Gy > 50 Gy	83/83 ^a	6.1 [5.0 ; 6.4]
INRC HN-8 [100,101]	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 ^v	5.1 [4.2 ; 5.8]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized ^μ	Median follow-up [95% CI] (years)
First update									
Lucknow 90[52]	1990-91	OC, OP, HP, L	III, IV	Cy Mx F	600 mg/m ² , wks _{1,3} 60 mg/m ² , wks _{1,3} 600 mg/m ² , wks _{5,6,7,8}	RT	70 Gy/7 wks starting wk ₅	38/38 ^ε	4.8 [4.6 ; 5.0]
RPC 3250[102]	1990-95	OC, OP, HP, L	III, IV	C (ci) F (ci)	20 mg/m ² x 4, wks _{1,4} 1000 mg/m ² x 4, wks _{1,4}	RT	68-72 Gy/7-8 wks	100/100 ^{εε}	8.9 [8.2 ; 9.5]
Duke 90040[103]	1990-96	OC, OP, HP, L, NP, O	II-IV	C F	12 mg/m ² x 5, wks _{1,6} 600 mg/m ² x 5, wks _{1,6}	RT	75 Gy/6 wks, bid 70 Gy/7 wks, sc, bid (Ex)	120/122 ^w	NA [†]
Vienna[29]	1990-97	OC, OP, HP, L	II-IV	Mi	20 mg/m ² d ₅	RT	55 Gy/2.5 wks, bid(Co)	158/158 ^x	7.9 [6.5 ; 8.9]
UKHAN[42]	1990-2000	OC, OP, HP, L, NP, O	I-IV	Vc B (im) Mx F, alt Mx	1.4 mg/m ² , wks _{1,3 ± 5,7 or 8,10} 30 mg, wks _{1,3 + 5,7 or 8,10} 100 mg/m ² , wks _{1,3 ± 5,7 or 8,10} 500 mg/m ² , wks _{1,3 + 5,7 or 8,10} 100 mg/m ² , wks _{1,3}	RT	60 Gy/6 wks, alt	966/970 ^y	10.1 [9.8 ; 10.5]
						S + RT	50-55 Gy/3-4 wks		
Kragujevac2[104]	1991-93	OC, OP, HP, L, NP	III, IV	C	6 mg/m ² x 5, wks ₁₋₇	RT	77 Gy/7 wks, bid	130/130	6.5 [6.2 ; 6.7]
IAR-92[46]	1992-95	OC, OP, HP, L, O	III, IV	C F FA	20 mg/m ² x 4, wks _{1,4,7,10} 300 mg/m ² x 4, wks _{1,4,7,10} 20 mg/m ² x 4, wks _{1,4,7,10}		79.2 Gy/6.5 wks, bid (Co) 80 Gy/9 wks, bid, alt (Ex)	68/68 ^z	8.3 [3.9 ; 8.9]
Int 0126[40]	1992-99	OC, OP, HP, L	III, IV	C (Ex1) C (Ex2) F (Ex2)	100 mg/m ² , wks _{1,4,7} 75 mg/m ² , wks _{1,5,9} 1000 mg/m ² x 4, wks _{1,5,9}	RT	70 Gy /7 wks (Co, Ex 1) 60-70 Gy/11-12 wks, sc (Ex2)	295/295 ^{aa}	11.0 [9.4 ; 11.6]
RTOG 9111 [31,32]	1992-2000	OP, L, O	II-IV	C	100 mg/m ² , wks _{1,4,7}	RT	70 Gy/7 wks	366/367 ^{bb}	12.2 [11.2 ; 12.9]
ORO-9301[28]	1993-98	OP	II-IV	Cb F	75 mg/m ² x 4, wks _{1,5,9} 1000 mg/m ² x 4, wks _{1,5,9}	RT	66-70 Gy/7 wks	127/127 ^{cc}	7.0 [5.7 ; 8.1]
GORTEC 9401 [105]	1994-97	OP	III, IV	Cb F	70 mg/m ² x 4, wks _{1,4,7} 600 mg/m ² x 4, wks _{1,4,7}	RT	70 Gy/ 7 wks	226/226	5.3 [4.7 ; 5.7]
ARO 95-06[106]	1994-99	OC, OP, HP	III, IV	Mi F	10 mg/m ² , wks _{1,6} 600 mg/m ² x 5, wk ₁	RT	77.6 Gy/ 6 wks, bid (Co) 70.6 Gy/ 6 wks, bid (Ex)	384 /384 ^{dd}	8.8 [7.8 ; 9.4]
EORTC 22931 [107]	1994-2000	OC, OP, HP, L	I-IV	C	100 mg/m ² wks _{1,4,7}	S + RT	66 Gy/6.5 wks	334/334	5.0 [4.7 ; 5.4]
SAKK 10-94 [108,109]	1994-2000	OC, OP, HP, L	II-IV	C	20 mg/m ² x 5, wks _{1,5}	RT	74.4 Gy/6.5 wks, bid	224/224	9.7 [8.4 ; 11.4]
Cologne 95[43]	1995-99	OP, HP	II-IV	Cb F	70 mg/m ² x 5, wks _{1,4} 600 mg/m ² x 5, wks _{1,4}	RT	69.9 Gy / 5.5 wks, b	263/263 ^{cc}	4.7 [4.0 ; 5.0]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized ^μ	Median follow-up [95% CI] (years)
HeCOG 9405[36]	1995-99	OC, OP, HP, L	II-IV	C (Ex1) Cb (Ex2)	100 mg/m ² , wks _{1,4,7} AUC 7, wks _{1,4,7}	RT	70 Gy / 7.5 wks	128/128 ^{ff}	14.4 [11.7 ; 14.8]
RTOG 9501 [110,111]	1995-2000	OC, OP, HP, L, O	I-IV	C	100 mg/m ² wks _{1,4,7}	S + RT	60 Gy/ 6 wks	459/459 ^{gg}	10.2 [9.6 ; 10.8]
EORTC 22954 (unpublished)	1996-99	L, HP	II-IV	C	100 mg/m ² , wks _{1,4,7}	RT	70 Gy/ 7 wks 70 Gy/ 7 wks, bid	59/59 ^{hh}	4.5 [4.1 ; 4.9]
EORTC-22962 (unpublished)	1996-99	OC, OP, HP, L	II-IV	C	100 mg/m ² , wks _{1,4,7}	RT	70 Gy/ 7 wks 80.5 Gy/ 7 wks, bid	57/57 ⁱⁱ	4.4 [3.6 ; 4.8]
IAEA-MMC[112]	1996-99	OC, OP, HP, L	III, IV	Mi	15 mg/m ² d ₅	RT	66 Gy /6.5 wks	478/478	2.8 [2.3 ; 3.2]
GORTEC 9601 [113]	1996-2000	OC, OP, HP, L, O	IV	C F	100 mg/m ² , wks _{1,3,5} 1000 mg/m ² x 5, wks _{1,5}	RT	62 Gy/ 3 wks, bid (Co) 62 Gy/ 5 wks, bid, sc (Ex)	109/109 ^{jj}	10.9 [6.5 ; 13.3]
NCI-V98-1416 [114]	1997-2000	OC, OP, HP, L	II-IV	Pm	40 mg/m ² , wks _{1,7}	RT	70 Gy/ 7 wks	393/393	0.9 [0.7 ; 1.0]
LOHNG-97[115]	1997-2001	OC, OP, HP, L, O	III, IV	B Mi	5 mg twice-a-week during RT 15 mg/m ² , wk ₂	S + RT	56-70 Gy / 5.5-7 wks	114/114	15.4 [14.4 ; 16.2]
Second update									
Torino 85[19]	1985-90	OC, OP, HP, L, NP, O	III, IV	<u>Arm₁</u> : B C Mx Vc <u>Arm₂</u> : Arm ₁ + C	ind: 10 U/m ² d _{1,8,15,22,29,36} ind: 50 mg/m ² d _{4,22} ind: 40 mg/m ² d _{1,15,22,36} ind: 2 mg/m ² d _{1,8,15,22,29,36} conco: 5 mg/m ² daily during RT	RT	60 Gy/7wks	108/108 ^{kk}	7.2 [6.5 ; 7.9]
Créteil 85[20]	1987-90	OC, OP, HP, L	II-IV	<u>Arm₁</u> : C F (ci) <u>Arm₂</u> : Arm ₁ + C F (im)	ind: 100 mg/m ² , wks _{1,4,7} ind: 1000 mg/m ² x 5, wks _{1,4,7} conco: 50 mg/m ² d _{1,15,29,43} conco: 5 mg/kg , three time a week during RT	RT	70 Gy/8 wks	56/57 ^{ll}	5.3 [4.3 ; 6.5]
Torino 92[116]	1992-95	OC, OP, HP, L	III, IV	Cb	45 mg/m ² x 5, wk _{1,3,5,7}	RT	70 Gy/7 wks	151/164	13.6 [12.9; 19.8]
Lucknow 95[37]	1995–99	OC, OP, HP, L, O	III, IV	C	35 mg/m ² , wks _{1,7}	RT	70 Gy/7 wks	200/200 ^{mm}	13.0 [10.4; 14.5]
AIIMS 2003[117]	2003-05	OP, NP	III, IV	C	40 mg/m ² , wk _{1,7}	RT	70 Gy/7 wks	176/176	3.0 [2.4 ; 4.8]
BiRCF[118]	1997-2002	OC, OP, HP, L	III, IV	C F F	100 mg/m ² , wks _{1,4,7} 750 mg/m ² x 5, wks ₁ 430 mg/m ² x 5, wks _{4,7}	RT	80.4 Gy/7 wks, bid	171/171 ^{mm}	6.6 [6.0 ; 7.1]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized ^μ	Median follow-up [95% CI] (years)
FCRT 94[119]	1994-2002	OP, HP, L	I–IV	Cb	50 mg/m ² d _{1,3} weekly during RT	S + RT	54 Gy/6.5 wks or 72 Gy/8 wks	144/146 ⁿⁿ	8.9 [7.4 ; 10.0]
UPCI 93-99[120]	1994-2002	OP, HP, L	III, IV	Cb	100 mg/m ² weekly during RT	S + RT	59.4 Gy/6.5 wks	76/76 ^{oo}	6.2 [5.2 ; 9.9]
TMH 1114[24]	2000–2008	OP, HP, L	II–IV	C	30 mg/m ² wks ₁₋₇	RT	66-70 Gy/6-7 wks	131/NA ^{pp}	4.5 [2.0 ;7.8]

* Upper value not reached

† Median follow-up and 95% confidence interval not available of high rate of mortality.

^μ Number of patients analyzed in the meta-analysis and corresponding number of patient randomized.

A: Doxorubicin ; AC Camargo: Hospital AC Camargo ; AIIMS: All India Institute of Medical Sciences ; alt: alternating ; ARO: Arbeitsgemeinschaft für Radio-Onkologie ; b: boost ; B: Bleomycin ; bid: twice daily ; BiRCF: Bifractionated Radiotherapy and cisplatin/5-fluorouracile ; C: Cisplatin ; Cb: Carboplatin ; CH: Chapel Hill ; ci: continuous infusion ; Cy: Cyclophosphamide ; conco: concomitant ; Co: Control arm ; d: day ; ECOG: Eastern Cooperative Oncology Group ; EORTC: European Organisation for Research and Treatment of Cancer ; F: 5-Fluorouracil ; Ex: Experimental arm; FCRT: French Carboplatine Radiotherapy Trial ; GORTEC: Groupe d'Oncologie Radiothérapie Tête Et Cou ; HeCOG: Hellenic Cooperative Oncology Group ; HP: Hypopharynx ; Hu: Hydroxyurea ; ia: intrarterial ; IAEA-MMC: International Atomic Energy Agency – Mitomycin ; IAR: Instituto de Oncologia Angel H. Roffo ; im: intramuscular ; ind: induction ; INRC-HN: Instituto Nazionale per la Ricerca sul Cancro-Head and Neck ; INT: US INTER group trial ; iv: intravenous ; L: Larynx ; LA: Leucovorina Acid ; LOHNG: Ljubljana Oncology Head and Neck Group ; MDA: MD Anderson ; Mi: Mitomycin ; Mp: Mercaptopurine ; Mx: Methotrexate ; NA: Not Available ; NCI-V: National Cancer Institute ; NP: Nasopharynx ; NRH: Norwegian Radium Hospital ; O: Other ; OC: Oral Cavity ; OP: Oropharynx ; ORO: Oropharynx ; Pm: Porfiromycin ; po: per os ; PMHCGS: Princess Margaret Hospital Cooperative Group Study ; RPC: Research Program Committee ; RT: Radiotherapy ; RTOG: Radiation Therapy Oncology Group ; RT-BLM: Radiotherapy – Bleomycin ; S: Surgery ; SAKK: Swiss Group for Clinical Cancer Research ; sc: split course ; SECOG: South of England Co-operative Oncology Group ; TMH: Tata Memorial Hospital ; UKHAN: United Kingdom Head And Neck ; UPCI: University of Pittsburgh Cancer Institute ; UW: University of the Witwatersrand ; Vc: Vincristine ; WIA-OC: Cancer Institute (WIA) Oral Cavity ; wks: weeks

^a Randomization 3:2. For patients with extensive disease, treatment duration was 8-9 weeks with 8.5 Gy by week. There were 10 patients (4 and 6 in control and experimental arm respectively), with recurrence after surgery or radiotherapy, who were treated by 50-60 Gy in 5-6 weeks.

^b Preoperative radiotherapy and decision about surgery after 30 Gy. Surgery omitted in 21 patients (advanced age: 11; poor general condition: 6; refusal: 4). After an interval of 3 weeks, they received an additional course of radiotherapy up to a total dose of 55-60 Gy.

^c Average dose for external radiotherapy, dose was superior to 70 Gy in 145 patients (74 in control arm and 71 in the experimental arm). Curietherapy using Iridium 192 was given to 46 patients with residual tumour after radiotherapy (27 in control arm and 19 in the experimental arm, average dose 26 and 23 Gy respectively). Surgery was performed after radiotherapy was in 102 patients with residual tumour (55 in control arm and 47 in the experimental arm; including neck dissection only in 10 and 6 patients respectively). Four patients had surgery before radiotherapy (2 in each arm). Bleomycin was injected before each irradiation treatment but was discontinued frequently because of excessive mucositis or other reaction, average dose 104 mg (range 10-175).

^d Third-arm not eligible (bifractional radiotherapy) with 859 patients overall.

^e 45-55 Gy (87% ≥ 50Gy) in 15-16 fractions over 3 weeks. Methotrexate d_{0,14} with folinic acid rescue if methotrexate concentration greater than 0.4 μmol/L.

^f 68-78 Gy with fraction of 1.8-2Gy, 5 days a week. In the experimental arm, only 1.8 Gy/fraction.

^g Three-arm trial with an induction arm and 90 patients overall, see table on induction trial for detail.

^h Saline infusion in control arm.

ⁱ Three-arm trial with two chemotherapy arms.

^j Three series of 23.4 Gy in 13 fractions twice daily (1.8 Gy/fractions) separated by a rest period of 11 days, total dose of 70.2 Gy in 51 days.

^k Bleomycin: 5 units twice a week with the planned total dose of 70 units; mitomycin: 15 mg/m² after 9-10 Gy and 10 mg/m² on the last day of radiotherapy.

^l In control arm, radiotherapy of 65 Gy in 6.6-7 weeks with 10 Gy in 5 day a week; in experimental, the severity of mucosal reaction compelled into 3 day a week with 6-7.5 Gy, the total dose was 55-60 Gy in 6.5-7 weeks. The ia and iv cases received 10-15mg of the bleomycin twice or three times a week, depending upon the intensity of the oral mucosal reaction to a total dose of 150-250 mg. The im cases received 30 mg of bleomycin twice a week for two weeks, the radiation commencing two weeks after the first injection on a three fraction per week basis. Another 30 mg were injected during radiation to a total dose of 150 mg. The control arm received a placebo (distilled water).

^m 30 Gy preoperative, 1.5 Gy (5 days a week) on weeks_{1,2,4,5}, one week rest on week₃; bleomycine or placebo intramuscular during radiotherapy.

ⁿ 2 Gy per fraction, 5 times a week: total dose 40-50 Gy in control arm and 30 Gy in experimental arm. Dose of bleomycin was usually 45-60 mg.

^o 2.5 Gy/fraction, two series of 32.5 Gy in 17 days with 3 weeks rest; in the experimental arm, radiotherapy stated at d₇ with first cycle of chemotherapy at day₀, second cycle at day₂₈ (midway rest period) and third one at day₆₃ one week after the end of radiotherapy.

^p 2.4 Gy twice a day for 5 days, two series separated by 24 days rest period, same in both arms; chemotherapy: 3 cycles plus 6 other cycles if responding or stable disease.

^q In excess of 56 Gy for radical radiotherapy (mean dose received 68 Gy) or postoperative radiotherapy with residual disease (mean dose received 60 Gy) with one injection of mitomycin C in day₅ and another 6 weeks later in the experimental arm; in excess of 50 Gy (mean dose received 58 Gy) for preoperative radiotherapy (n=3) or postoperative radiotherapy without residual disease with one injection of mitomycin C in day₅ in the experimental arm; 1.8-2 Gy/fraction, 5 days a weeks.

^r In control arm: 50 Gy in 20 fractions over 4 weeks; in experimental arm: 25 Gy in 10 fractions over 2 weeks, rest of 4 weeks, and a second series of 25 Gy in 10 fractions over 2 weeks.

^s In case of negative margin: 54 Gy, 1.7 Gy/fraction, 5 days a week; in case of positive margin: 65-70 Gy with fraction of 1.8/2 Gy after 54 Gy; 7 to 9 weekly cisplatin injection in the experimental arm.

^t Three-arm trial with an induction arm and 239 patients overall; in the control arm: radiotherapy of 60-66 Gy, 5 days a week with fraction of 1.8-2 Gy (recommended fractionation); in the experimental arm: one cycle of chemotherapy on days_{1,2,3}, two weeks of radiotherapy (starting at day₄), second cycle of chemotherapy, one week rest, two weeks of radiotherapy, third cycle of chemotherapy, one week rest, two weeks of radiotherapy, fourth cycle of chemotherapy. Patients allocated to the chemotherapy arms were also randomized initially to receive B/Mx/Vb or the same chemotherapy plus F, and after July 1st, 1986 received all B/Mx/Vb/F.

^u For the resectable group, 1.5 Gy twice a day for 10 days, 2 weeks rest, 1.5 Gy for 8-13 days, 5 days a week; 54 Gy for resected group with negative margin, and 60 Gy for resected group with positive margin. The minimum dose was 69 Gy for the unresectable group.

^v In the experimental arm, Three series of 20 Gy, 2 Gy/fraction, 5 days a week, during weeks_{2,3,5,6,8,9} alternating with 4 cycles of chemotherapy during weeks_{1, 4,7,10}.

[£] Short induction chemotherapy followed by concomitant chemotherapy. Trial classified as concomitant in all the analyzes.

^{££} After 55 Gy, patients were reevaluated. Those with a clinical response completed radiotherapy. Radiation was discontinued in case of non-response or progression. Surgical resection was recommended for those patients.

^w Seven-day interruption in the experimental arm after 40 Gy and lower total dose to the primary tumor. Two other cycles after of all local therapy: same dose of 5-Fluorouracil, 80 mg/m²/weeks of cisplatin for the third cycle, and 100/m²/weeks for the fourth.

^x Three-arm trial and 239 patients overall, third arm excluded (conventional radiotherapy).

^y Trial originally designed for stages II-IV but a few (n<10) T1N0 patients were included. 2x2 factorial design with randomization 3:2:2:2 for patients without previous surgery (n=713): radiotherapy alone, radiotherapy + simultaneous chemotherapy, radiotherapy followed by subsequent chemotherapy, radiotherapy + both. If prior surgery (n=253 patients), patients randomized (3:2) to radiotherapy alone vs. radiotherapy + simultaneous chemotherapy. Each centre chose one option from the following: radiotherapy at 50-55 Gy over 3 weeks with methotrexate alone; radiotherapy at 60 Gy over 6 weeks with either methotrexate alone or VBMF. Another regimen was also used: 55 Gy given in 20 fractions (2.75 Gy per fraction) over 4 weeks. 50 Gy given in 20 fractions (2.5 Gy per fraction) was given postoperatively. Chemotherapy was given on weeks_{1,3} in the

simultaneous arm. For the subsequent arm, chemotherapy was given on weeks_{2,4} after the end of radiotherapy (weeks_{5,7} for 50-55 Gy over 3 weeks; or weeks_{8,10} for 60 Gy over 6 weeks). The VBMF regimen includes vincristine, bleomycin, 5-fluorouracil, methotrexate with folinic acid rescue.

^z Radiotherapy alternating with chemotherapy: 80 Gy, 2 Gy/day on weeks_{2,3}, 1.5 Gy twice a day on weeks_{5,6,8,9}; randomization 2:1.

^{aa} Three-arm trial: conventional radiotherapy, conventional radiotherapy + cisplatin (100 mg/m², Ex1), split course radiotherapy (5 weeks rest) with cisplatin (75 mg/m²) + 5-Fluorouracil (Ex2).

^{bb} Three-arm trial with 547 patients overall: conventional radiotherapy, radiotherapy + concomitant cisplatin, larynx preservation arm with first 2-3 cycles of cisplatin + 5-Fluorouracil and then, according to the tumor response, radiotherapy or radiotherapy + surgery; the third arm was not eligible for this meta-analysis.

^{cc} Three-arm trial and 192 patients overall, third arm excluded (hyperfractionated radiotherapy).

^{dd} Experimental arm.

^{ee} Second randomization, prophylactic G-CSF or not; weeks_{1,2,3}, 1.8 Gy daily, weeks_{4,5,6} bid, 1.8/1.5 Gy daily.

^{ff} Three-arm trial: radiotherapy alone, radiotherapy + cisplatin, radiotherapy + carboplatin.

^{gg} With a boost of 6 Gy in 3 fractions over a period of three days to high-risk sites.

^{hh} Centers chose between conventional or bifractionated radiotherapy, and between evaluation at 2 months after completion of radiotherapy with salvage surgery if patients were not complete responders (option 1) or evaluation after 40-50 Gy (4-5 weeks). In this second case (option 2), the radiotherapy was complete up to 70 Gy if partial response or complete response. If not, surgery was performed. As in option 1, an evaluation was planned 2 months after completion of radiotherapy with salvage surgery if no complete response.

ⁱⁱ 2x2 factorial design.

^{jj} One week rest after each week of radiotherapy (2 breaks of one week); concomitant arm 2 more cycles (PF) after radio-chemotherapy if complete response.

^{kk} 2 Gy /fraction, 10 Gy/wk

^{ll} 1.8 Gy fraction

^{mm} Three-arm trial with an induction arm and 300 patients overall

ⁿⁿ 1.2 Gy/fraction

^{oo} This study included patients who had received chemotherapy before surgery: 18 patients in the control arm and 25 in the experimental arm. The type of induction chemotherapy was left to the physician's discretion. Patients were randomized after surgery. For patients with negative resection margins, 54 Gy, 1.8 Gy by fraction, in 30 fractions, and for patients with positive margins 72 Gy. The trial was stopped prematurely after publication of the preliminary results of the EORTC 22931 trial.

^{pp} For clinically uninvolved areas, the dose delivered was 50.4 Gy in 28 fractions of 1.80 Gy per day. Regions that were at high risk received additional boost, usually 9 Gy (total tumor bed dose, 59.4 Gy) in five fractions, but higher boost doses were allowed at the radiation oncologist's discretion. The trial stopped early because of low accrual.

^{qq} 2 Gy per fraction once daily, five times per week (total 33–35 fractions). Three-arm trial with 199 overall and a third arm evaluating moderately accelerated radiotherapy: same dose and number of fraction, but 6 fractions a week instead of 5. The trial was stopped early because of poor accrual.

Web-Table 3: Description of adjuvant trials

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ Randomized ^a	Median follow-up [95% CI] (years)
Initial meta-analysis									
Pitié 74[33]	1974–77	OC	II-IV	B (im) Mx LA (im)	15 mg x2, weekly x 15 400 mg, monthly x 24 100 mg, monthly x 24	S or S + RT	MD MD	96/96 ^a	5.6 [4.5 ; 6.5]
GETTECadj [121]	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 ^b	8.9 [8.3 ; 9.2]
Int 0034[122]	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 ^c	8.2 [7.9 ; 8.8]
JHCFUS[123]	1985–86	OC, OP, HP, L, NP, O	I-IV	Hc (po)	300–600 mg x 84 d+	S	NA	191/191	2.9 [2.8 ; 3.0]
TMH R4[124]	1986–89	OC	III, IV	Mx	50 mg/m ² d _{3,10,17} post-operative	S	NA	135/135	1.3 [1.1 ; 1.6]
KKD-86[125]	1986–89	OC	I-IV	U (po)	400 mg d ₁₋₃₆₅	S	NA	112/112	6.9 [6.4 ; 7.3]
HNU-87a[26]	1987–90	OC, OP, HP, L, NP	I-IV	U (po)	300 mg d ₁₋₃₆₅	RT	MD	111/111	4.1 [3.8 ; 4.4]
HNU-87b[26]	1987–90	OC, OP, HP, L, NP	II-IV	U (po)	300 mg d ₁₋₃₆₅	S	NA	424/424	4.2 [4.0 ; 4.3]
First update									
UKHAN[42]	1990-2000	OC, OP, HP, L, NP, O	I-IV	Vc B Mx F, alt Mx	1.4 mg/m ² , wks _{1,3,+5,7,or 8,10} 30 mg im, wks _{1,3,+5,7,or 8,10} 100 mg/m ² , wks _{1,3,+5,7,or 8,10} 500 mg/m ² , wks _{1,3,+5,7,or 8,10} 100 mg/m ² , wks _{1,3,+5,7,or 8,10}	RT	60 Gy/6 wks, alt 50-55Gy/3-4 wks	966/970 ^d	10.1 [9.8 ; 10.5]
Second update									
HNCP[38]	1978–82	OC, HP, L	II- IV	B (bolus) B (ci) C C	ind: 15 mg/m ² d ₃ ind: 15 mg/m ² d _{3,7} ind: 100 mg/m ² d ₁ adj: 80 mg/m ² monthly, x 6	S + RT	50 Gy/5-5.5wks	302/302 ^e	5.3 [5.1 ; 5.5]
DFCI[21]	1980-83	OC, OP, HP, L, NP, O	III, IV	B (ci) C Mx LA	ind: 10 U/m ² d _{3,7} , wks _{1,5} ind: 20 mg/m ² x 5, wks _{1,5} ind: 200 mg/m ² d _{15,22} , wks _{1,5} ind: 80 mg po, d _{16-18,23-25} , wks _{1,5}	RT	68 Gy/8wks	46/46 ^f	9.9 [8.3 ; 10.7]

Trial	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ Randomized ^a	Median follow-up [95% CI] (years)
				B C Mx LA	adj: 10 U/m ² d ₂₋₄ , three 42-days cycles adj: 20 mg/m ² d ₁₋₃ , 3 cycles adj: 200 mg/m ² d _{15,22,29,36} , 3 cycles adj: oral rescue	or S + RT	60 Gy		

adj : Adjuvant ; alt: alternating ; B: Bleomycin ; C: Cisplatin ; d: Day ; DFCI: Dana–Farber Cancer Institute ; DM: Data Missing; F: 5-Fluorouracil ; GETTEC: Groupe d'Etude des Tumeurs de la Tête Et du Cou ; Gy: Gray ; Hc: Hexycarbanoyl 5-fluorouracil ; HNCP: Head and Neck Contract Program ; HNU: Head and Neck UFT ; HP: Hypopharynx ; im: Intramuscular ; ind: Induction ; INT: US INTER group trial ; JHCFUS: Japanese H C F U Study ; KKD: Kanto Koshinetsu District ; L: Larynx ; LA: leucovorin ; Mx: Methotrexate ; NA: Not Applicable ; NP: Nasopharynx ; O: Other ; OC: Oral Cavity ; OP: Oropharynx ; po: per-os ; RT: Radiotherapy ; S: Surgery ; TMH: Tata Memorial Hospital ; U: UFT (tegafur + uracil) ; UKHAN: United Kingdom Head And Neck ; Vc: vincristine ; wks: weeks

^a Third arm with immunotherapy ineligible. 23 patients were treated by surgery + radiotherapy. Data on the modality of radiotherapy are not available.

^b All patients had positive nodes and capsular rupture, 50 Gy on node with overdosage of 15 Gy on area with capsular rupture. CT started 8 weeks after radiotherapy.

^c 50-54 Gy for low risk and 60 Gy for high risk, 1.8-2 Gy per fraction, 5 days a week.

^d Four-arm trial for patients without previous surgery (n=713): radiotherapy alone, radiotherapy + simultaneous chemotherapy, radiotherapy followed by subsequent chemotherapy, radiotherapy + both (2x2 factorial design). If prior surgery (n=253 patients), randomized to radiotherapy alone vs. radiotherapy + simultaneous chemotherapy. Only patients receiving subsequent chemotherapy are included in the adjuvant timing part. Each center chose one option from the following: radiotherapy 50-55 Gy/3 weeks with Mx alone; radiotherapy 60 Gy/6 weeks with either Mx alone or VBMF. Another regimen was also used: 55 Gy given in 20 fractions (2.75 Gy per fraction) over 4 weeks. Chemotherapy is given at weeks 1 and 3 for the simultaneous arm. For the subsequent arm, chemotherapy is given weeks 2 and 4 after end of radiotherapy (weeks 5 and 7 for 50-55 Gy/3 weeks; or weeks 8 and 10 for 60 Gy/6 weeks). The VBMF regimen includes Vc, B, F, Mx with FA rescue.

^e Induction chemotherapy in both arms and adjuvant radiotherapy randomized: 302 patients included in this comparison. Third arm (160 patients) with loco-regional treatment only not included here. Dose increase to 60 Gy for any area of suspected microscopic residual disease and 70 Gy in know areas of gross residual disease.

^f Induction chemotherapy in both arms. Patients were randomized after loco-regional treatment. ut of 46 patients, 29 were treated by surgery and radiotherapy and 17 by radiotherapy alone. For postoperative radiotherapy, a minimum of 60 Gy were delivered. For radical radiotherapy, a minimum of 68 Gy in 1.8 to 2.0 Gy fractions were delivered. Radiotherapy was usually completed within 8 weeks.

Web-Table 4: Description of trials comparing induction (sequential) chemotherapy plus radiotherapy to concomitant (alternating) radio-chemotherapy

Trial	Inclusion period	Sites	Stage	Timing	Drug	Chemotherapy	Radiotherapy	Patients analyzed/ randomized	Median follow-up [95% CI] (years)
SECOG I[126]	1980-84	OC, OP, L, O	III, IV	<u>Arm₁</u> : CT-CT-RT-CT-CT <u>Arm₂</u> : (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 [18.4;20.9]
Brescia[127]	1981-83	OC, OP, HP, NP	III, IV	<u>Arm₁</u> : CT-CT-CT-CT-RT <u>Arm₂</u> : RT1-CT-CT-CT-CT-RT2	B Hu (po) Mx LA	15 mg/m ² 6000 mg/m ² 50 mg/m ² 45 mg/m ²	64 Gy/4 wks 60 Gy sc	55/56	8.2 [6.4;8.6]
INRC-HN-7[128]	1983-86	OC, OP, HP, L, NP	III, IV	<u>Arm₁</u> : CT-CT-CT-CT-RT <u>Arm₂</u> : CT - (CT-RT) x3	B (im) Vb Mx LA	30 U, d ₁ 6 mg/m ² , d ₁ 200 mg, d ₂ 45 mg, d ₃	60-70 Gy 60 Gy, alt	116/116	4.3 [3.1;5.5]
SECOG II (unpublished)	1984-89	OC, OP, HP, L, NP, O	III, IV	<u>Arm₁</u> : CT-CT-RT-CT-CT <u>Arm₂</u> : (CT-RT) x3 - CT	B Mx LA (im) Vc F	30 mg 200 mg 90 mg 2 mg/m ² 500 mg	60-66 Gy/6.5 wks 60-66 Gy/8 wks alt	160/160*	15.0 [12.3;17.0]
ICC-PCP[129]	1984-91	OC, OP, HP, L, NP, O	III, IV	<u>Arm₁</u> : CT-CT-CT-RT <u>Arm₂</u> : (CT-RT) x7	<u>Arm₁</u> : C F <u>Arm₂</u> : C F	100 mg/m ² , d ₁ 1000 mg/m ² x 5 60 mg/m ² , d ₁ 800 mg/m ² x 5	70 Gy/7 wks 70Gy/13 wks, alt	215/215 [†]	6.0 [5.3;6.6]
CMGH-85 [130,131]	1985-88	OC, OP, HP, NP	II-IV	<u>Arm₁</u> : CT-CT-CT-RT <u>Arm₂</u> : CRT-CT-CRT-CT	<u>Arm₁</u> : C F <u>Arm₂</u> : C F	100 mg/m ² , d ₁ 1000 mg/m ² x 5 75 mg/m ² , d ₁ 800 mg/m ² x 5	60 Gy 60 Gy, sc	48/48	5.8 [5.1;6.5]

Trial	Inclusion period	Sites	Stage	Timing	Drug	Chemotherapy	Radiotherapy	Patients analyzed/ randomized	Median follow-up [95% CI] (years)
Second update									
Lucknow 95[37]	1995–99	OC, OP, HP, L, O	III, IV	<u>Arm1:</u> CT-RT <u>Arm2:</u> CRT	C C	35 mg/m ² d ₁ , wks ₁₋₇ 35 mg/m ² d ₁ , wks ₁₋₇	70 Gy/7 wks	200/200 ^{µµ}	13.0 [10.4; 14.5]
EORTC 24954[3,4]	1996-2004	HP, L	II-IV	<u>Arm1:</u> CT-RT <u>Arm2:</u> (CT-RT) x3 - CT	<u>Arm1:</u> C F <u>Arm2:</u> C F	100 mg/m ² , d ₁ 1000 mg/m ² x 5 20 mg/m ² x 5 200 mg/m ² x 5	<u>Arm1:</u> 70 Gy/7 wks <u>Arm2:</u> 20 Gy/2 wks x3	450/450 ^{††}	9.0 [8.9;9.0]

B: Bleomycin ; C: Cisplatin ; CMGH: Cleveland Metropolitan General Hospital ; CRT: Chemoradiotherapy ; CT: Chemotherapy ; d: day ; EORTC: European Organisation for Research and Treatment of Cancer ; F: 5-Fluorouracil ; Gy: Gray ; HP: Hypopharynx ; Hu: hydroxyurea; im: intramuscular ; ICC-PCP: Illinois Cancer Council - Paris-Chicago Protocol ; INRC-HN: Istituto Nazionale per la Ricerca sul Cancro-Head and Neck ; L: Larynx ; LA: Leucovorin ; Mx: Methotrexate ; NP: Nasopharynx ; O : Other ; OC: Oral Cavity ; OP: Oropharynx ; po: per os ; RT: Radiotherapy ; SECOG: South of England Co-operative Oncology Group ; Vb: Vinblastine ; Vc: Vincristine ; wks: weeks

* 3-arm trial with a third arm without chemotherapy; see tables on induction or concomitant trials for detail on treatment.

† 3 cycles of induction chemotherapy every 3 weeks; “concomitant” chemotherapy and radiation consisted of seven cycles of cisplatin and 5-FU, and radiation 2 Gy on days 1 to 5, delivered every other week.

^{µµ} Three-arm trial with an RT alone arm and 300 patients overall

†† Only 153 patients out of 450 were eligible for the present meta-analysis. Centers have the option to have an interim tumour evaluation after 50 Gy (around day 42) or only after the end of radiotherapy in the concomitant arm. In the sequential arm, an evaluation was planned at day 42 after induction chemotherapy for all patients. Only patients included in centres with tumour evaluation in both arms at 42 days were included. Because of unbalance in long-term follow-up between the two arms in the whole trial, follow-up was censored at 9 years.

Web-Table 5: Trial divisions in treatment comparisons

Trial	Comparisons	
Initial meta-analysis		
WIA-OC5[27]	WIA-OC5a	RT + concomitant CT (intra-arterial) <u>versus</u> RT + placebo
	WIA-OC5b	RT + concomitant CT (intravenous) <u>versus</u> RT + placebo
	WIA-OC5c	RT + concomitant CT (intramuscular) <u>versus</u> RT + placebo
HNCP[38] ^a	HNCPneo	Surgery e + RT + induction CT <u>versus</u> surgery + RT
	HNCPneo&adj	Surgery + RT + induction CT + adjuvant CT <u>versus</u> surgery + RT
	HNCP*	Surgery + RT + induction CT + adjuvant CT <u>versus</u> surgery + RT + induction CT
Yale-80[96]	Yale 80	RT + concomitant CT <u>versus</u> RT only
	Yale 80po	Surgery + RT + concomitant CT <u>versus</u> surgery + RT
AC Camargo[39] ^b	AC Camargo (ind)	RT + induction CT <u>versus</u> RT only
	AC Camargo (conc)	RT + concomitant CT <u>versus</u> RT only
SECOG II ^c (unpublished)	SECOG IIneo	RT + induction CT (without 5-FU, randomized) <u>versus</u> RT only
	SECOG IIneofr	RT + induction CT (with 5-FU, randomized) <u>versus</u> RT only
	SECOG IIneofnr	RT + induction CT (with 5-FU, no randomiszd) <u>versus</u> RT only
	SECOG IIconc	RT + concomitant CT (without 5-FU, randomized) <u>versus</u> RT only
	SECOG IIconcfr	RT + concomitant CT (with 5-FU, randomized) <u>versus</u> RT only
	SECOG IIconcfnr	RT + concomitant CT (with 5-FU, no randomized) <u>versus</u> RT only
	SECOG II	RT + concomitant CT (without distinction on 5-FU) <u>versus</u> RT + induction CT (without distinction on 5-FU)
GSTTC 86[70,71]	GSTTC 86	RT + induction CT <u>versus</u> RT only (non-operable patients)
	GSTTC 86po	Surgery + RT + induction CT <u>versus</u> surgery + RT (operable patients)
Yale 86[99]	Yale 86	RT + concomitant CT <u>versus</u> RT only
	Yale 86po	Surgery + RT + concomitant CT <u>versus</u> surgery + RT
AHNTG[72]	AHNTG	RT+ induction CT <u>versus</u> RT only or other locoregional treatment than surgery et surgery + RT
	AHNTGsurg	Surgery (± RT) + induction CT <u>versus</u> surgery (± RT) only
HNU-87[26]	HNU-87a	RT + adjuvant CT <u>versus</u> RT only
	HNU-87b	Surgery + adjuvant CT <u>versus</u> surgery only
First update		
UKHAN[42] ^d	UKHAN1po1	Surgery + RT + concomitant monoCT <u>versus</u> surgery + RT
	UKHAN1po2	Surgery + RT + concomitant polyCT <u>versus</u> surgery + RT
	UKHAN1npo1	RT + concomitant monoCT <u>versus</u> RT only
	UKHAN1npo2	RT + concomitant polyCT <u>versus</u> RT only
	UKHAN1npo1*	RT + concomitant monoCT + adjuvant CT <u>versus</u> RT + adjuvant CT
	UKHAN1npo2*	RT + concomitant polyCT + adjuvant CT <u>versus</u> RT + adjuvant CT
	UKHAN1a1	RT + adjuvant monoCT <u>versus</u> RT only
	UKHAN1a2	RT + adjuvant polyCT <u>versus</u> RT only
	UKHAN1a1*	RT + concomitant CT + adjuvant monoCT <u>versus</u> RT + concomitant CT
	UKHAN1a2*	RT + concomitant CT + adjuvant polyCT <u>versus</u> RT + concomitant CT

Trial	Comparisons	
Int 0126[40] ^c	Int 0126a	RT + concomitant CT (cisplatin) <u>versus</u> RT only
	Int 0126b	RT + concomitant CT (5-FU, cisplatin) <u>versus</u> RT only
EORTC 22954 (unpublished)	EORTC 22954a	Conventional RT + concomitant CT <u>versus</u> conventional RT only
	EORTC 22954b	Hyperfractionated RT + concomitant CT <u>versus</u> hyperfractionated RT only
EORTC 22962 (unpublished)	EORTC 22962a	Conventional RT + concomitant CT <u>versus</u> conventional RT only
	EORTC 22962b	Hyperfractionated RT + concomitant CT <u>versus</u> hyperfractionated RT only
Second update		
FCRT 94[119]	FCRT 94	Surgery + RT + concomitant CT <u>versus</u> surgery + RT
	FCRT 94*	Surgery + RT + induction CT + concomitant CT <u>versus</u> surgery + RT + induction CT
Lucknow 95[37] ^f	Lucknow 95 (ind)	RT + concomitant CT <u>versus</u> RT only
	Lucknow 95 (conc)	RT + concomitant CT <u>versus</u> RT only
	Lucknow 95	RT + concomitant CT <u>versus</u> RT + induction CT
TTCC 2002[2] ^g	TTCC 2002 PF-	RT + induction CT (PF) + concomitant CT <u>versus</u> RT + concomitant CT
	TTCC 2002 PF+	RT + induction CT (PF) + concomitant CT <u>versus</u> RT + concomitant CT
	TTCC 2002 TPF-	RT + induction CT (TPF, without G-CSF) + concomitant CT <u>versus</u> RT + concomitant CT
	TTCC 2002 TPF+	RT + induction CT (TPF, with G-CSF) + concomitant CT <u>versus</u> RT + concomitant CT

Stars are part of comparison names and do not correspond to footnote below the table.

5-FU: 5-fluorouracil, adj: adjuvant, conc: concomitant, CT: chemotherapy, fr: 5-FU randomized, G-CSF: Granulocyte - *Colony Stimulating Factor*, monoCT: mono chemotherapy, neo: neoadjuvant (induction), nfr: 5-FU non-randomized, npo: non post-operative, PF combination of 5-FU + platin salt, po: post-operative, polyCT: polychemotherapy, surg: *surgery*, RT: radiotherapy, TPF: combination of taxane + 5-FU + platin salt

See Web-Tables 1, 2 and 3 for trial abbreviations

^a Each arm is duplicated once as this trial is included in two timings (induction with duplication of the control arm, concomitant) (462 patients)

^b Control arm duplicated once (30 patients)

^c Each arm is duplicated once as this trial is included in two timings (induction, concomitant) and in the secondary question (239 patients). The control arm of the part that randomized addition of 5-FU is duplicated twice (84 patients, overall 323 patients)

^d Non-postoperative part of the trial with 2x2 design duplicated once as this trial is included in two timings (concomitant, adjuvant) (713 patients). Same monochemotherapy and polychemotherapy for the two timings (centre option). The concomitant polychemotherapy was alternating with radiotherapy.

^e Control arm duplicated once (102 patients)

^f Each arm is duplicated once as this trial is included in two timings (induction, concomitant) and in the secondary question (300 patients)

^g Control arm duplicated once (128 patients)

Web-Table 6: Characteristics of patients overall and by timing (addition of chemotherapy)

	Timing of chemotherapy						All timings	
	Induction		Concomitant		Adjuvant			
	N	%	N	%	N	%	N	%
Sex								
Male	5951	84.4	8663	81.1	2375	81.5	16989	82.3
Female	1056	15.0	1688	15.8	530	18.2	3274	15.9
Unknown	47	0.7	329	3.1	10	0.3	386	1.9
Age (years)								
< 50	1437	20.4	2557	23.9	566	19.4	4560	22.1
[50;60[2725	38.6	3637	34.1	1000	34.3	7362	35.7
[60;70[2157	30.6	3197	29.9	925	31.7	6279	30.4
≥ 70	564	8.0	944	8.8	376	12.9	1884	9.1
Unknown	171	2.4	345	3.2	48	1.7	564	2.7
Median (IQR)	57 (51;63)		57 (50;64)		58 (52;65)		57 (50;64)	
Performance status								
PS0	1953	27.7	3818	35.8	1434	49.2	7205	34.9
PS1	2383	33.8	3707	34.7	521	17.9	6611	32.0
PS ≥ 2	459	6.5	600	5.6	57	2.0	1116	5.4
Unknown*	2259	32.0	2555	23.9	903	31.0	5717	27.7
Primary site								
Oral cavity	2157	30.6	2121	19.9	933	32.0	5211	25.2
Oropharynx	2669	37.8	3995	37.4	504	17.3	7168	34.7
Larynx	836	11.9	2150	20.1	738	25.3	3724	18.0
Hypopharynx	1229	17.4	1700	15.9	468	16.1	3397	16.5
Others	88	1.2	634	5.9	265	9.1	987	4.8
Unknown	75	1.1	80	0.8	7	0.2	162	0.8
T-stage								
T0/Tx/Tis	39	0.6	43	0.4	34	1.2	116	0.6
T1	202	2.9	504	4.7	189	6.5	895	4.3
T2	1292	18.3	1727	16.2	885	30.4	3904	18.9
T3	2932	41.6	3808	35.7	974	33.4	7714	37.4
T4	2429	34.4	4218	39.5	588	20.2	7235	35.0
Unknown	160	2.3	380	3.6	245	8.4	785	3.8
N-stage								
N0	2504	35.5	2932	27.5	1443	49.5	6879	33.3
N1	1717	24.3	1757	16.5	431	14.8	3905	18.9
N2	1619	23.0	3754	35.2	259	8.9	5632	27.3
N3	1065	15.1	1442	13.5	218	7.5	2725	13.2
N+ (no details)	0	-	473	4.4	319	10.9	792	3.8
Nx	3	< 0.1	0	-	0	-	3	< 0.1
Unknown	146	2.1	322	3.0	245	8.4	713	3.5
Stage								

	Timing of chemotherapy						All timings	
	Induction		Concomitant		Adjuvant		N	%
	N	%	N	%	N	%		
Stage 0	0	-	0	-	2	0.1	2	< 0.1
Stage I-II	423	6.0	587	5.5	607	20.8	1617	7.8
Stage III	2393	33.9	2574	24.1	967	33.2	5934	28.7
Stage IV Low	974	13.8	2132	20.0	226	7.8	3332	16.1
Stage IV High	3072	43.6	4851	45.4	740	25.4	8663	42.0
Stage IV M+	11	0.2	14	0.1	0	-	25	0.1
Stage IV (unspecified)	32	0.5	197	1.8	125	4.3	354	1.7
Unknown	149	2.1	325	3.1	248	8.5	722	3.5
Smoking status								
Never	177	2.5	384	3.6	0	-	561	2.7
Former	267	3.8	1025	9.6	0	-	1292	6.3
Current	91	1.3	1119	10.5	0	-	1210	5.9
Unknown	6519	92.4	8152	76.3	2915	100	17586	85.2
HPV status								
Negative	8	0.1	40	0.4	0	-	48	0.2
Positive	44	0.6	3	< 0.1	0	-	47	0.2
Unknown	7002	99.3	10637	99.6	2915	100	20554	99.5
Total	7054	100	10680	100	2915	100	20649	100

* Overall rate of missing data is 5.4% after exclusion of the 40 comparisons that did not collect performance status: 17 (2070 patients) for induction, 19 (2061 patients) for concomitant and 4 (708 patients) for adjuvant
IQR: interquartile range

Web-Table 7: Number of comparisons and patients in trial subsets

	Comparisons (patients)		
	Induction	Concomitant	Adjuvant
Type of chemotherapy			
PolyCT - With platin salt	36 (5394)	15 (2042) ^b	3 (831) ^c
PolyCT - Without platin salt	6 (744)	12 (1328)	3 (295)
MonoCT - With platin salt	1 (200)	22 (3562) ^c	1 (302)
MonoCT - Without platin salt	2 (716) ^a	22 (3748) ^d	7 (1487)
Platin salt*			
Cisplatin only	1 (200)	16 (2904) ^f	0
Cisplatin and 5-FU	24 (3643)	10 (1339) ^g	1 (499)
Carboplatin only	0	4 (371)	0
Carboplatin and 5-FU	3 (457)	3 (616)	0
Locoregional treatment			
Surgery only	0	0	4 (862)
Conventional RT	15 (2253)	35 (5386) ⁱ	0
Hyperfractionated and/or accelerated RT	0	11 (1680)	0
Other RT [†]	7 (1 318) ^h	10 (1657) ^j	5 (824)
Surgery and RT	12 (2079)	11 (1595)	3 (1087) ^l
Other [‡]	11 (1404)	4 (362) ^k	2 (142)
Year of accrual start			
< 1980	8 (1936) ^m	13 (1721) ⁿ	3 (444)
1980-1993	28 (3535)	36 (4833) ^o	11 (2471) ^p
1994-2000	1 (200)	21 (4950)	0
2001-2010	8 (1383)	1 (176)	0
Total	45 (7054)^q	71 (10680)^r	14 (2915)^s

* Comparisons were excluded if neither cisplatin nor carboplatin was administrated or if platin salt was combined with drug other than 5-FU. In the induction timing, comparisons using cisplatin + 5-FU and other drug (taxane or other) were included in the cisplatin + 5-FU groups [2,13,61,63,80-83]. Comparisons were also excluded if it was not possible to separate patients treated by cisplatin and those treated carboplatin.

[†] Alternating radiotherapy, hypofractionated radiotherapy.

[‡] Mostly with several modalities of loco-regional treatments impossible to separate in distinct categories, very rare case of preoperative radiotherapy + surgery

For event-free survival, number of comparisons (number of patients):

^a 1 (36), ^b 13 (1 959), ^c 20 (3 324), ^d 21 (3 716), ^e 2 (332), ^f 14 (2 665), ^g 9 (1 283), ^h 6 (638), ⁱ 32 (5 091), ^j 9 (1 630), ^k 3 (330), ^l 2 (588), ^m 7 (1 256), ⁿ 11 (1 662), ^o 34 (4 669), ^p 10 (1 972), ^q 44 (6 426), ^r 66 (10 327), ^s 13 (2 416)

5-FU: 5-Fluorouracil, MonoCT: Monochemotherapy, PolyCT: Polychemotherapy, RT: Radiotherapy

Web-Table 8: Cause of death and events for cancer/non-cancer mortality

	Timing of chemotherapy					
	Induction		Concomitant		Adjuvant	
	LRT+CT	LRT	LRT+CT	LRT	LRT+CT	LRT
Cause of death						
Cancer	446 (12.6%)	472 (13.4%)	1422 (26.6%)	1789 (33.6%)	167 (11.7%)	203 (13.6%)
Other	297 (8.4%)	297 (8.4%)	587 (11.0%)	467 (8.8%)	77 (5.4%)	78 (5.2%)
Unknown	1584 (44.8%)	1596 (45.3%)	1874 (35.0%)	1805 (33.9%)	533 (37.4%)	547 (36.7%)
Alive	1207 (34.2%)	1155 (32.8%)	1465 (27.4%)	1271 (23.8%)	649 (45.5%)	661 (44.4%)
Events for cancer/non-cancer mortality*						
Previous failure	452 (44.4%)	444 (43.9%)	1427 (44.1%)	1650 (50.8%)	NA	NA
Death caused by cancer without previous failure	29 (2.8%)	20 (2.0%)	181 (5.6%)	238 (7.3%)	NA	NA
Death caused by unknown reason without previous failure within 5 years after randomization	19 (1.9%)	15 (1.5%)	122 (3.8%)	112 (3.4%)	NA	NA
Total (cancer deaths)	500 (49.1%)	479 (47.3%)	1730 (53.5%)	2000 (61.6%)	NA	NA
Death caused by unknown reason without previous failure after 5 years after randomization	7 (0.7%)	9 (0.9%)	100 (3.1%)	55 (1.7%)	NA	NA
Death caused by other reason without previous failure	142 (13.9%)	162 (16.0%)	444 (13.7%)	356 (11.0%)	NA	NA
Total (non-cancer deaths)	149 (14.6%)	171 (16.9%)	544 (16.8%)	411 (12.7%)	NA	NA
Patients alive	370 (36.3%)	362 (35.8%)	960 (29.7%)	838 (25.8%)	NA	NA

* Number of events was lower for cancer/non cancer deaths analyzes as several trials were excluded because the cause of death was not available. The analysis on cancer/non-cancer death was not performed for the adjuvant timing as cause of death was missing for 9 out of 14 comparisons.

NA: Not Applicable.

Cause of death is missing for all patients in the 65 following comparisons (9896 patients):

Induction comparisons : AC Camargo [39], BNH-003 (unpublished), BuenosAires [34], CFHNS [76,77], Cologne-88 [78], Creteil-82 [61], Creteil-86 [68,69], Denver-77 [56], EORTC 24771 [55], EORTC78-OCP [57], EORTC 24844 (unpublished), HNCGIC02 [62], HNCGIC03 [63], IGR-65 [53], LasPalma [73], MCW-1 [58,59], MCW-2 [65,66], Pitie-81 [44], Rennes-87 [74], RTOG 6801 [54], SHNG-85 [67], SWOG 8006 [60], Shanghai 2008 [82,83], Songkhla [64];

Concomitant comparisons : AC Camargo (included in two timings) [39], AIIMS-2003 [117], Barcelona [30], Bavaria-89 [92], Bergen [94], CH-7401 [51], FCRT 94 [119], FCRT 94* [119], ECOG 2382 [89,90], EORTC73-OC [84], HNAF-02, INRCHN-8 [100,101], Kragujevac1 [35], LOHNG-91 [93], MDA-70 [45], Manchester [87,88], NRH-78 [86], Ontario [91], PMHCGS [97], RT-BLM-73 [95], Torino-85 [19], Toulouse [98], Turku [85], UW-77 [49], UW-79 [50], WIA-OC5a [27], WIA-OC5b [27], WIA-OC5c [27], Yale-80 [96], Yale-80po [96], Yale-86 [99], Yale-86po [99];

Adjuvant comparisons: DFCI [21], GETTECadj [121], HNU-87a [26], HNU-87b [26], Int 0034 [122], JHCFUS [123], KKD-86 [125], Pitie-74 [33], TMHR-4 [124].

Web-Table 9: Events for event-free survival

	Timing of chemotherapy					
	Induction		Concomitant		Adjuvant	
	LRT+CT	LRT	LRT+CT	LRT	LRT+CT	LRT
Loco-regional failure	1355 (42.4%)	1219 (38.3%)	2154 (41.1%)	2612 (50.1%)	256 (21.8%)	315 (25.4%)
Distant failure	321 (10.1%)	413 (13.0%)	398 (7.6%)	356 (6.8%)	136 (11.6%)	172 (13.9%)
Loco-regional and distant failures	11 (0.3%)	16 (0.5%)	128 (2.4%)	152 (2.9%)	4 (0.3%)	12 (1.0%)
Death without failure*	586 (18.3%)	615 (19.3%)	1290 (24.6%)	1060 (20.3%)	301 (25.6%)	265 (21.4%)
Failure with unknown location	0	20 (0.6%)	85 (1.6%)	110 (2.1%)	0	0
Total (events)	2273 (71.2%)	2283 (71.8%)	4055 (77.3%)	4290 (82.3%)	697 (59.3%)	764 (61.6%)
Alive without failure	921 (28.8%)	897 (28.2%)	1190 (22.7%)	922 (17.7%)	478 (40.7%)	477 (38.4%)
Total	3194 (100%)	3180 (100%)	5245 (100%)	5212 (100%)	1175 (100%)	1241 (100%)

* includes patients dying from cancer, other cause (including toxicity) and of unknown causes in proportion variable according to timing and trials.

Web-Table 10A: Sensitivity analyzes for the addition of induction chemotherapy

	LRT + CT (No. events / No. patients)	LRT (No. events / No. patients)	Hazard Ratio [95% IC]
Overall survival			
Main analysis on all trials: 45 comparisons (7054 patients) ; HR=0.96 [0.90;1.01], p=0.14			
One timing of chemotherapy ^a 37 comparisons (5611 patients)	1931 / 2812	1965 / 2799	0.95 [0.89;1.01] p=0.12
No confounded ^{*b} 40 comparisons (6466 patients)	2134 / 3258	2139 / 3208	0.97 [0.91;1.03] p=0.26
First inclusion ≥ 1980 ^c 37 comparisons (5118 patients)	1705 / 2577	1713 / 2541	0.95 [0.89;1.02] p=0.13
Sample size > 80 patients ^d 36 comparisons (6561 patients)	2140 / 3278	2204 / 3283	0.95 [0.89;1.00] p=0.07
Follow-up > 5 years ^e 32 comparisons (4801 patients)	1635 / 2398	1672 / 2403	0.96 [0.90;1.03] p=0.24
Without duplicated patients ^f 39 comparisons (6687 patients)	2327 / 3534	2115 / 3153	0.96 [0.90;1.01] p=0.14
Event-free survival			
Main analysis on all trials: 44 comparisons (6374 patients) ; HR=0.96 [0.90;1.02], p=0.14			
One timing of chemotherapy 36 comparisons (4931 patients)	1831 / 2472	1 819 / 2459	0.97 [0.91;1.03] p=0.32
No confounded [*] 39 comparisons (5786 patients)	2052 / 2918	2039 / 2868	0.96 [0.90;1.02] p=0.16
First inclusion ≥ 1980 37 comparisons, (5118 patients)	1855 / 2577	1847 / 2541	0.95 [0.89;1.02] p=0.15
Sample size > 80 patients 35 comparisons (5881 patients)	2074 / 2938	2109 / 2943	0.95 [0.89;1.00] p=0.07
Follow-up > 5 years 32 comparisons (4801 patients)	1770 / 2398	1791 / 2403	0.97 [0.91;1.03] p=0.33
Without duplicated patients 39 comparisons (6007 patients)	2273 / 3194	2004 / 2813	0.96 [0.90;1.02] p=0.19

* Trial with a lower dose of radiotherapy or the same dose delivered in a longer time in the chemotherapy arm than in the control arm

^a Eight comparisons excluded: HNCPneo&adj [38], Budapest 2007 [13], DeCIDE [81], GSTTC 2501 [41,80], TTCC 2002 PF- [2], TTCC 2002 PF+ [2], TTCC 2002 TPF- [2], TTCC 2002 TPF+ [2]

^b Five comparisons excluded: Denver 77 [56], SECOG IIneo (unpublished), SECOG IIneofr (unpublished), SECOG IIneofnr (unpublished), CFHNS [76,77]

^c Eight comparisons excluded: IGR-65 [53], RTOG 6801 [54], EORTC 24771 [55], Denver-77 [56], HNCPneo [38], HNCPneo&adj [38], EORTC78-OCP [57], MCW-1 [58,59]

^d Nine comparisons excluded because sample size of trials less than or equal to 80 patients (40 patients per arm): IGR-65 [53], Denver 77 [56], MCW-2 [65,66], AC Camargo [39], Las Palmas [73], Parma [75], Songkhla [64], HNAP-02 [79], Budapest 2007 [13]

^e Ten comparisons excluded: RTOG 6801 [54], LasPalmas [73], EORTC78-OCP [57], Créteil-82 [61], EORTC 24844 (unpublished), BNH-003 (unpublished), Songkhla [64], Cologne-88 [78], TTCC 2002 [2], GSTTC 2501 [41,80]

^f Five control arms excluded: HNCPneo [38], SECOG IIneofr (unpublished), SECOG IIneofnr (unpublished), TTCC 2002 TPF- [2], TTCC 2002 TPF+ [2]

CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Table 10B: Sensitivity analyzes for the addition of concomitant chemotherapy

	LRT + CT (No. events / No. patients)	LRT (No. events / No. patients)	Hazard Ratio [95% IC]
Overall survival			
Main analysis on all trials: 71 comparisons (10680 patients) ; HR=0.83 [0.79;0.86], p<0.0001			
One timing of chemotherapy^a 65 comparisons (10121 patients)	3664 / 5074	3836 / 5047	0.81 [0.78;0.85] p<0.0001
No confounded^{* b} 54 comparisons (8759 patients)	3124 / 4416	3228 / 4343	0.83 [0.79;0.88] p<0.0001
First inclusion ≥ 1980^c 58 comparisons (8959 patients)	3137 / 4464	3348 / 4495	0.83 [0.79;0.87] p<0.0001
Sample size > 80 patients^d 51 comparisons (9726 patients)	3506 / 4851	3710 / 4875	0.84 [0.80;0.88] p<0.0001
Follow-up > 5 years^e 60 comparisons (8294 patients)	3252 / 4116	3405 / 4178	0.83 [0.79;0.87] p<0.0001
Without duplicated patients^f 68 comparisons (10499 patients)	3883 / 5348	3901 / 5151	0.83 [0.79;0.87] p<0.0001
Event-free survival			
Main analysis on all trials: 67 comparisons (10457 patients) ; HR=0.80 [0.77;0.84], p<0.0001			
One timing of chemotherapy 63 comparisons (10062 patients)	3896 / 5045	4127 / 5017	0.80 [0.76;0.83] p<0.0001
No confounded[*] 50 comparisons (8536 patients)	3260 / 4313	3410 / 4223	0.80 [0.76;0.84] p<0.0001
First inclusion ≥ 1980 56 comparisons (8795 patients)	3325 / 4390	3579 / 4405	0.79 [0.76;0.83] p<0.0001
Sample size > 80 patients 50 comparisons (9618 patients)	3717 / 4805	3951 / 4813	0.81 [0.77;0.85] p<0.0001
Follow-up > 5 years 56 comparisons (8071 patients)	3280 / 4013	3463 / 4058	0.81 [0.77;0.85] p<0.0001
Without duplicated patients 64 comparisons (10276 patients)	4055 / 5245	4123 / 5031	0.80 [0.76;0.84] p<0.0001

* Trial with a lower dose of radiotherapy or the same dose delivered in a longer time in the chemotherapy arm than in the control arm

^a Six comparisons excluded: Torino 85 [19], Creteil 85 [20], Lucknow 90 [52], UKHAN1np01* [42], UKHAN1np02* [42], FCRT 94* [119]

^b Seventeen comparisons excluded: WIA-OCa [27], WIA-OCb [27], WIA-OCc [27], RT-BLM73 [95], PMHCGS [97], SECOG IIconc (unpublished), SECOG IIconcfr (unpublished), SECOG IIconcfnr (unpublished), INRC HN-8 [100,101], Duke 90040 [103], UKHAN1np02 [42], UKHAN1np02* [42], UKHAN1po2 [42], IAR 92 [46], Int 0126b [40], ARO 95-6 [106], GORTEC 9601 [113]

^c Twelve comparisons excluded: MDA-70 [45], WIA-OC5a [27], WIA-OC5b [27], EORTC73-OC [84], Bergen [94], RT-BLM-73 [95], WIA-OC5c [27], Turku [85], UW-77 [49], NRH-78 [86], Barcelona [30], UW-79 [50], Manchester [87,88]

^d Twenty comparisons excluded because sample size of trials less than or equal to 80 patients (40 patients per arm): MDA-70 [45], WIA-OC5a [27], WIA-OC5b [27], Bergen [94], RT-BLM-73 [95], WIA-OC5c [27], Turku [85], UW-77 [49], UW-79 [50], AC Camargo [39], CH-7401 [51], LOHNG-91 [93], Creteil-85 [20], Lucknow-90 [52], IAR-92 [46], UPCI 93-99 [120], EORTC 22954a (unpublished), EORTC 22954b (unpublished), EORTC 22962a (unpublished), EORTC 22962b (unpublished)

^e Eleven comparisons excluded: TMH 1114 [24], Cologne-95 [43], Bavaria-89 [92], Kragujevac1 [35], IAEA-MMC [112], EORTC 22931 [107], NCI-V98-1416 [114], Lucknow-90 [52], AIIMS 2003 [117], EORTC 22954 (unpublished), EORTC 22962 (unpublished)

^f Three control arms excluded: SECOG IIconcfr (unpublished), SECOG IIconcfnr (unpublished), Int 0126a [40]

CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Table 10C: Sensitivity analyzes for the addition of adjuvant chemotherapy

	LRT + CT (No. events / No. patients)	LRT (No. events / No. patients)	Hazard Ratio [95% IC]
Overall survival			
Main analysis on all trials: 14 comparisons (2915 patients), HR=1.02 [0.92;1.13] ; p=0.69			
One timing of chemotherapy^a 10 comparisons (2247 patients)	551 / 1090	607 / 1157	1.01 [0.90;1.13] p=0.92
No confounded^{*,b} 13 comparisons (2824 patients)	742 / 1382	791 / 1442	1.01 [0.91;1.12] p=0.84
First inclusion ≥ 1980^c 11 comparisons (2471 patients)	642 / 1196	691 / 1275	1.06 [0.95;1.18] p=0.32
Sample size > 80 patients^d 13 comparisons (2869 patients)	762 / 1400	812 / 1469	1.03 [0.94;1.14] p=0.50
Follow-up > 5 years^e 10 comparisons (2054 patients)	684 / 994	720 / 1060	1.05 [0.95;1.17] p=0.35
Event-free survival			
Main analysis on all trials: 13 comparisons (2416 patients), HR=0.98 [0.88;1.09] ; p=0.72			
One timing of chemotherapy 9 comparisons (1748 patients)	458 / 839	532 / 909	0.97 [0.85;1.10] p=0.60
No confounded* 12 comparisons (2325 patients)	662 / 1131	726 / 1194	0.98 [0.88;1.09] p=0.66
First inclusion ≥ 1980 10 comparisons (1972 patients)	545 / 945	616 / 1027	1.01 [0.90;1.14] p=0.82
Sample size > 80 patients 12 comparisons (2370 patients)	682 / 1149	748 / 1221	1.00 [0.90;1.11] p=0.96
Follow-up > 5 years 9 comparisons (1555 patients)	551 / 743	591 / 812	1.03 [0.92;1.16] p=0.58

* Trial with a lower dose of radiotherapy or the same dose delivered in a longer time in the chemotherapy arm than in the control arm

^a Four comparisons excluded: DFCI [21], HNCP* [38], UKHAN1a1* [42], UKHAN1a2* [42]

^b One comparison excluded: UKHAN1a2* [42]

^c Three comparisons excluded: Pitie-74 [33], DFCI [21], HNCP* [38]

^d One comparison excluded because sample size of trials less than or equal to 80 patients (40 patients per arm): DFCI [21]

^e Four comparisons excluded: HNU-87a [26], HNU-87b [26], TMHR-4 [124], JHCFUS [123]

Patients were not duplicated for the analysis of the addition of adjuvant chemotherapy.

CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Table 11A: Classification of induction comparisons for subset analyzes

Comparison	Start of accrual	Type of chemotherapy	Loco-regional treatment
IGR-65[53]	< 1980	MonoCT without platin	Radiotherapy other*
RTOG 6801[54]	< 1980	MonoCT without platin	Radiotherapy other*
EORTC 24771[55]	< 1980	PolyCT without platin	Surgery and radiotherapy
Denver 77[56]	< 1980	PolyCT with platin	Other**
HNCpneo[38]	< 1980	PolyCT with platin	Surgery and radiotherapy
HNCpneo&adj[38]	< 1980	PolyCT with platin	Surgery and radiotherapy
EORTC 78-OCP[57]	< 1980	PolyCT without platin	Other**
MCW-1[58,59]	< 1980	PolyCT without platin	Other**
SWOG 8006[60]	1980-1993	PolyCT with platin	Surgery and radiotherapy
Pitié-81[44]	1980-1993	PolyCT with platin	Radiotherapy other*
Buenos Aires[34]	1980-1993	PolyCT with platin	Other**
Créteil-82[61]	1980-1993	PolyCT with platin	Other**
HNCGIC 02[62]	1980-1993	PolyCT with platin	Conventional radiotherapy
MCW-2[65,66]	1980-1993	PolyCT with platin	Other**
AC Camargo[39]	1980-1993	PolyCT with platin	Conventional radiotherapy
SECOG IIneo (unpublished)	1980-1993	PolyCT without platin	Radiotherapy other*
SECOG IIneofr (unpublished)	1980-1993	PolyCT without platin	Radiotherapy other*
SECOG IIneofnr (unpublished)	1980-1993	PolyCT without platin	Radiotherapy other*
EORTC 24844 (unpublished)	1980-1993	PolyCT with platin	Surgery and radiotherapy
SHNG-85[67]	1980-1993	PolyCT with platin	Conventional radiotherapy
Créteil-86[68,69]	1980-1993	PolyCT with platin	Other**
HNCGIC 03[63]	1980-1993	PolyCT with platin	Conventional radiotherapy
GSTTC-86[70,71]	1980-1993	PolyCT with platin	Conventional radiotherapy
GSTTC-86po[70,71]	1980-1993	PolyCT with platin	Surgery and radiotherapy
GETTECneo 1[25]	1980-1993	PolyCT with platin	Conventional radiotherapy
GETTECneo 2[25]	1980-1993	PolyCT with platin	Surgery and radiotherapy
AHNTG[72]	1980-1993	PolyCT with platin	Conventional radiotherapy
AHNTGsurg[72]	1980-1993	PolyCT with platin	Surgery and radiotherapy
Las Palmas[73]	1980-1993	PolyCT with platin	Conventional radiotherapy
Rennes-87[74]	1980-1993	PolyCT with platin	Other**
Parma[75]	1980-1993	PolyCT with platin	Other**
CFHNS[76,77]	1980-1993	PolyCT with platin	Other**
Songkhla[64]	1980-1993	PolyCT with platin	Surgery and radiotherapy
Cologne 88[78]	1980-1993	PolyCT with platin	Surgery and radiotherapy
HNAP 02[79]	1980-1993	PolyCT with platin	Other**
BNH 003 (unpublished)	1980-1993	PolyCT with platin	Surgery and radiotherapy
Lucknow 95[37]	1994-2000	MonoCT with platin	Conventional radiotherapy

Comparison	Start of accrual	Type of chemotherapy	Loco-regional treatment
TTCC 2002 PF -[2]	2001-2010	PolyCT with platin	Conventional radiotherapy
TTCC 2002 PF +[2]	2001-2010	PolyCT with platin	Conventional radiotherapy
TTCC 2002 TPF -[2]	2001-2010	PolyCT with platin	Conventional radiotherapy
TTCC 2002 TPF + [2]	2001-2010	PolyCT with platin	Conventional radiotherapy
GSTTC 2501[41,80]	2001-2010	PolyCT with platin	Conventional radiotherapy
DeCIDE[81]	2001-2010	PolyCT with platin	Radiotherapy other*
Budapest 2007[13]	2001-2010	PolyCT with platin	Conventional radiotherapy
Shanghai 2008 [82,83]	2001-2010	PolyCT with platin	Surgery and radiotherapy

* Alternating hypofractionated, radiotherapy ...

** Mostly with several modalities of loco-regional treatments impossible to separate in distinct categories, very rare case of preoperative radiotherapy + surgery.

5-FU: 5-Fluorouracil, MonoCT: Monochemotherapy, PolyCT: Polychemotherapy

See Web-Table 1 for trials abbreviations.

Web-Table 11B: Classification of concomitant comparisons for subset analyzes

Comparison	Start of accrual	Type of chemotherapy	Loco-regional treatment
MDA-70[45]	< 1980	MonoCT without platin	Radiotherapy other*
WIA-0C5a[27]	< 1980	MonoCT without platin	Conventional radiotherapy
WIA-0C5b[27]	< 1980	MonoCT without platin	Conventional radiotherapy
Bergen[94]	< 1980	MonoCT without platin	Other**
EORTC73-OC[84]	< 1980	MonoCT without platin	Conventional radiotherapy
RT-BLM-73[95]	< 1980	MonoCT without platin	Conventional radiotherapy
WIA-OC5c[27]	< 1980	MonoCT without platin	Conventional radiotherapy
Turku[85]	< 1980	MonoCT without platin	Other**
UW-77[49]	< 1980	PolyCT without platin	Radiotherapy other*
NRH-78[86]	< 1980	MonoCT without platin	Other**
Barcelona[30]	< 1980	MonoCT without platin	Conventional radiotherapy
UW-79[50]	< 1980	PolyCT with platin	Radiotherapy other*
Manchester[87,88]	< 1980	MonoCT without platin	Radiotherapy other*
Yale-80np[96]	1980-1993	MonoCT without platin	Conventional radiotherapy
Yale-80po[96]	1980-1993	MonoCT without platin	Surgery and radiotherapy
PMHCGS[97]	1980-1993	PolyCT without platin	Radiotherapy other*
ECOG 2382[89,90]	1980-1993	MonoCT with platin	Conventional radiotherapy
AC Camargo[39]	1980-1993	PolyCT with platin	Conventional radiotherapy
Toulouse[98]	1980-1993	MonoCT with platin	Surgery and radiotherapy
SECOG Ilconc (unpublished)	1980-1993	PolyCT without platin	Conventional radiotherapy
SECOG Ilconcfr (unpublished)	1980-1993	PolyCT without platin	Conventional radiotherapy
SECOG Ilconcfnr (unpublished)	1980-1993	PolyCT without platin	Conventional radiotherapy

Comparison	Start of accrual	Type of chemotherapy	Loco-regional treatment
CH-7401[51]	1980-1993	PolyCT with platin	Other**
Torino 85[19]	1980-1993	MonoCT with platin	Conventional radiotherapy
Yale-86npo[99]	1980-1993	MonoCT without platin	Conventional radiotherapy
Yale-86po[99]	1980-1993	MonoCT without platin	Surgery and radiotherapy
Ontario[91]	1980-1993	MonoCT without platin	Conventional radiotherapy
Kragujevac1[35]	1980-1993	MonoCT with platin	Conventional radiotherapy
LOHNG-91[93]	1980-1993	PolyCT without platin	Conventional radiotherapy
Créteil 85[20]	1980-1993	PolyCT with platin	Conventional radiotherapy
INRC HN-8[100,101]	1980-1993	PolyCT with platin	Conventional radiotherapy
Bavaria-89[92]	1980-1993	PolyCT with platin	Radiotherapy other*
Lucknow 90[52]	1980-1993	PolyCT without platin	Conventional radiotherapy
RPC 3250[102]	1980-1993	PolyCT with platin	Conventional radiotherapy
Duke 90040[103]	1980-1993	PolyCT with platin	HF or Acc radiotherapy
Vienna[29]	1980-1993	MonoCT without platin	HF or Acc radiotherapy
UKHAN1npo1[42]	1980-1993	MonoCT without platin	Radiotherapy other*
UKHAN1npo1*[42]	1980-1993	MonoCT without platin	Radiotherapy other*
UKHAN1po1[42]	1980-1993	MonoCT without platin	Surgery and radiotherapy
UKHAN1npo2[42]	1980-1993	PolyCT without platin	Radiotherapy other*
UKHAN1npo2*[42]	1980-1993	PolyCT without platin	Radiotherapy other*
UKHAN1po2[42]	1980-1993	PolyCT without platin	Surgery and radiotherapy
Kragujevac 2[104]	1980-1993	MonoCT with platin	HF or Acc radiotherapy
IAR-92[46]	1980-1993	PolyCT with platin	HF or Acc radiotherapy
Torino 92[116]	1980-1993	MonoCT with platin	Conventional radiotherapy
Int 0126a[40]	1980-1993	MonoCT with platin	Conventional radiotherapy
Int 0126b[40]	1980-1993	PolyCT with platin	Conventional radiotherapy
RTOG 9111[31,32]	1980-1993	MonoCT with platin	Conventional radiotherapy
ORO-9301[28]	1980-1993	PolyCT with platin	Conventional radiotherapy
GORTEC 9401[105]	1994-2000	PolyCT with platin	Conventional radiotherapy
ARO 95-06[106]	1994-2000	PolyCT without platin	HF or Acc radiotherapy
EORTC 22931[107]	1994-2000	MonoCT with platin	Surgery and radiotherapy
SAKK 10-94 [108,109]	1994-2000	MonoCT with platin	HF or Acc radiotherapy
FCRT 94[119]	1994-2000	MonoCT with platin	Surgery and radiotherapy
FCRT 94*[119]	1994-2000	MonoCT with platin	Surgery and radiotherapy
UPCI 93-99[120]	1994-2000	MonoCT with platin	Surgery and radiotherapy
Cologne 95[43]	1994-2000	PolyCT with platin	HF or Acc radiotherapy
HeCOG 9405[36]	1994-2000	MonoCT with platin	Conventional radiotherapy
Lucknow 95[37]	1994-2000	MonoCT with platin	Conventional radiotherapy
RTOG 9501[110,111]	1994-2000	MonoCT with platin	Surgery and radiotherapy
EORTC 22954a (unpublished)	1994-2000	MonoCT with platin	Conventional radiotherapy

Comparison	Start of accrual	Type of chemotherapy	Loco-regional treatment
EORTC 22954b (unpublished)	1994-2000	MonoCT with platin	HF or Acc radiotherapy
EORTC-22962a (unpublished)	1994-2000	MonoCT with platin	Conventional radiotherapy
EORTC-22962b (unpublished)	1994-2000	MonoCT with platin	HF or Acc radiotherapy
IAEA-MMC[112]	1994-2000	MonoCT without platin	Conventional radiotherapy
GORTEC 9601[113]	1994-2000	PolyCT with platin	HF or Acc radiotherapy
NCI-V98-1416[114]	1994-2000	MonoCT without platin	Conventional radiotherapy
LOHNG-97[115]	1994-2000	PolyCT without platin	Surgery and radiotherapy
BiRCF[118]	1994-2000	PolyCT with platin	HF or Acc radiotherapy
AIIMS 2003[117]	2001-2010	MonoCT with platin	Conventional radiotherapy
TMH 1114[24]	1994-2000	MonoCT with platin	Conventional radiotherapy

* Alternating hypofractionated, radiotherapy. ** Mostly with several modalities of loco-regional treatments impossible to separate in distinct categories, very rare case of preoperative radiotherapy + surgery.

5-FU: 5-Fluorouracil, Acc: Accelerated, HF: Hyperfractionated, MonoCT: Mono chemotherapy, PolyCT: Polychemotherapy. See Web-Table 2 for trials abbreviations.

Web-Table 11C: Classification of adjuvant comparisons subsets analyzes

Comparison	Start of accrual	Type of chemotherapy	Loco-regional treatment
Pitié-74[33]	< 1980	PolyCT sans platine	Other**
HNCP*[38]	< 1980	MonoCT avec platine	Surgery and radiotherapy
DFCI[21]	< 1980	PolyCT avec platine	Other**
GETTECadj[121]	1980-1993	PolyCT avec platine	Surgery and radiotherapy
Int 0034[122]	1980-1993	PolyCT avec platine	Surgery and radiotherapy
JHCFUS[123]	1980-1993	MonoCT sans platine	Surgery
TMHR-4[124]	1980-1993	MonoCT sans platine	Surgery
KKD-86[125]	1980-1993	MonoCT sans platine	Surgery
HNU-87a[26]	1980-1993	MonoCT sans platine	Radiotherapy other*
HNU-87b[26]	1980-1993	MonoCT sans platine	Surgery
UKHAN1a1[42]	1980-1993	MonoCT sans platine	Radiotherapy other*
UKHAN1a1*[42]	1980-1993	MonoCT sans platine	Radiotherapy other*
UKHAN1a2[42]	1980-1993	PolyCT sans platine	Radiotherapy other*
UKHAN1a2*[42]	1980-1993	PolyCT sans platine	Radiotherapy other*

* Alternating hypofractionated, radiotherapy. ** Mostly with several modalities of loco-regional treatments impossible to separate in distinct categories, very rare case of preoperative radiotherapy + surgery.

MonoCT: Mono chemotherapy, PolyCT: Polychemotherapy

See Web-Table 3 for trials abbreviations.

Web-Table 12A: Variation of treatment effect according to the type of chemotherapy

	Hazard Ratio [95% CI]		
	Induction	Concomitant	Adjuvant
Overall survival			
PolyCT with platin salt	0.95 [0.89;1.01]	0.76 [0.69;0.84]	0.99 [0.84;1.17]
PolyCT without platin salt	0.98 [0.82;0.17]	0.82 [0.73;0.92]	1.13 [0.86;1.48]
MonoCT with platin salt	0.97 [0.73;1.29]	0.80 [0.74;0.86]	0.94 [0.70;1.26]
MonoCT without platin salt	0.99 [0.84;1.18]	0.90 [0.83;0.97]	1.04 [0.88;1.22]
Interaction	p=0.96	p=0.06*	p=0.80
Event-free survival			
PolyCT with platin salt	0.96 [0.90;1.02]	0.74 [0.67;0.82]	1.08 [0.85;1.38]
PolyCT without platin salt	0.97 [0.82;1.15]	0.85 [0.76;0.96]	0.98 [0.75;1.27]
MonoCT with platin salt	0.88 [0.67;1.17]	0.75 [0.69;0.81]	1.00 [0.76;1.33]
MonoCT without platin salt	0.96 [0.49;1.90]	0.86 [0.80;0.93]	0.94 [0.82;1.09]
Interaction	p=0.95	p=0.01*	p=0.81

* Analysis performed in two categories (with and without platin salt): p=0.02 for overall survival and p=0.001 for event-free survival

CI: Confidence interval, MonoCT: Monotherapy, PolyCT: Polychemotherapy

Web-Table 12B: Variation of treatment effect according to the start of accrual

	Hazard Ratio [95% IC]		
	Induction	Concomitant	Adjuvant
Overall survival			
< 1980	0.98 [0.88;1.10]	0.82 [0.74;0.91]	0.86 [0.67;1.09]
1980-1993	0.94 [0.87;1.02]	0.85 [0.79;0.90]	1.06 [0.95;1.18]
1994-2000	0.97 [0.73;1.29]	0.81 [0.75;0.87]	NA
2001-2010	0.98 [0.84;1.13]	0.63 [0.41;0.97]	NA
Interaction	p=0.92	p=0.48	p=0.12
Event-free survival			
< 1980	0.98 [0.85;1.12]	0.83 [0.75;0.93]	0.87 [0.69;1.09]
1980-1993	0.98 [0.91;1.06]	0.81 [0.76;0.86]	1.01 [0.90;1.14]
1994-2000	0.88 [0.67;1.17]	0.78 [0.72;0.84]	NA
2001-2010	0.89 [0.78;1.03]	0.66 [0.45;0.97]	NA
Interaction	p=0.66	p=0.53	p=0.23

CI: Confidence interval, NA: Not Applicable

Period of accrual was different for the trials included in the 3 timing trial subsets of the main question and for the secondary question: 37 trials between 1965 and 2012 for induction timing; 58 trials between 1970 and 2008 concomitant for timing with one trial ending accrual in 2008 and another in 2005, three in 2002 and the other before 2001; 11 trials between 1974 and 2000 for adjuvant timing with 10 trials between 1974 and 1990 and one between 1990 and 2000 [42] between 1980 and 2004 for the secondary question. For the induction trials, trials with TPF accrued between 2002 and 2012, those with PF between 1983 and 1993 (one TPF trial had also a PF arm, (TTCC 2002) [2] and the others between 1965 and 1999 (one trial accrued between 1995 and 1999 and the others before 1993).

Web-Table 12C: Variation of treatment effect according to loco-regional treatment

	Hazard Ratio [95% IC]		
	Induction	Concomitant	Adjuvant
Overall survival			
Surgery only	NA	NA	0.87 [0.67;1.14]
Conventional RT	0.96 [0.87;1.05]	0.83 [0.78;0.89]	NA
Hyperfractionated and/or accelerated RT	NA	0.78 [0.70;0.87]	NA
Other RT *	0.96 [0.84;1.10]	0.83 [0.74;0.93]	1.17 [0.99;1.38]
Surgery and RT	0.95 [0.85;1.07]	0.83 [0.73;0.93]	1.01 [0.87;1.17]
Other **	0.97 [0.85;1.11]	0.96 [0.77;1.21]	0.71 [0.47;1.10]
Interaction	p=0.99 [†]	p=0.59 [‡]	p=0.09 [§]
Event-free survival			
Surgery only	NA	NA	0.77 [0.62;0.96]
Conventional RT	0.91 [0.83;1.00]	0.78 [0.73;0.83]	NA
Hyperfractionated and/or accelerated RT	NA	0.73 [0.66;0.81]	NA
Other RT *	0.83 [0.69;1.00]	0.88 [0.79;0.98]	1.10 [0.93;1.30]
Surgery and RT	1.02 [0.92;1.43]	0.83 [0.74;0.94]	1.11 [0.92;1.34]
Other **	1.04 [0.91;1.18]	0.97 [0.76;1.23]	0.64 [0.43;0.95]
Interaction	p=0.09 [†]	p=0.06 [‡]	p=0.005 [§]

* Alternating radiotherapy, hypofractionated RT ...

** Mainly trials with several types of loco-regional treatment impossible to separate in distinct categories, very rare case of preoperative radiotherapy + surgery.

[†] Afters exclusion of the « other » category: p=0.99 for overall survival and p=0.10 for event-free survival.

[‡] Afters exclusion of the « other » category: p=0.80 for overall survival and p=0.09 for event-free survival.

[§] Afters exclusion of the « other » category: p=0.16 for overall survival and p=0.02 for event-free survival.

CI: Confidence interval, NA: Not Applicable, RT: Radiotherapy

Web-Table 13A: Variation of treatment effect according to patients' subgroups for induction comparisons
see Figure 3 for performance status subgroups

		LRT + CT (No. events / No. patients)	LRT (No. events / No. patients)	Hazard Ratio [95% IC]	Interaction	Heterogeneity of interaction
Overall survival						
Sex 24 comparisons 3830 patients	Male	1024 / 1628	1041 / 1613	0.91 [0.83;0.99]	p=0.58	p=0.77
	Female	142 / 297	147 / 292	0.98 [0.77;1.23]		
Age 20 comparisons 3493 patients	< 50	234 / 383	200 / 359	1.06 [0.88;1.28]	p=0.09	p=0.59
	[50;60[374 / 655	437 / 683	0.81 [0.71;0.93]		
	[60;70[374 / 580	356 / 543	0.93 [0.80;1.08]		
	≥70	99 / 138	115 / 152	1.06 [0.81;1.39]		
Tumour site 14 comparisons 2184 patients	Oral cavity	212 / 323	181 / 292	0.99 [0.81;1.21]	p=0.32	p=0.89
	Oropharynx	251 / 428	251 / 416	1.02 [0.85;1.21]		
	Hypopharynx	140 / 188	172 / 214	0.80 [0.64;1.01]		
	Larynx	91 / 164	84 / 159	1.09 [0.81;1.46]		
Stage* 21 comparisons 3084 patients	III	350 / 590	356 / 600	0.96 [0.83;1.11]	p=0.28	p=0.16
	IV-low	168 / 256	164 / 260	1.05 [0.84;1.30]		
	IV-high	493 / 700	496 / 678	0.87 [0.76;0.98]		
Event-free survival						
Sex 24 comparisons 3830 patients	Male	1125 / 1628	1122 / 1613	0.91 [0.84;0.99]	p=0.38	p=0.91
	Female	162 / 297	171 / 292	0.98 [0.79;1.21]		
Age 20 comparisons patients	< 50	261 / 383	223 / 359	1.08 [0.90;1.28]	p=0.12	p=0.79
	[50;60[425 / 655	482 / 683	0.83 [0.72;0.94]		
	[60;70[399 / 580	378 / 543	0.94 [0.82;1.09]		
	≥70	101 / 138	121 / 152	0.89 [0.68;1.56]		
Tumour site 14 comparisons 2184 patients	Oral cavity	229 / 323	204 / 292	0.94 [0.78;1.14]	p=0.38	p=0.67
	Oropharynx	272 / 428	280 / 416	0.98 [0.83;1.16]		
	Hypopharynx	152 / 188	178 / 214	0.83 [0.66;1.03]		
	Larynx	110 / 164	92 / 159	1.12 [0.85;1.48]		
Stage* 20 comparisons 3 168 patients	III	393 / 590	384 / 600	1.01 [0.88;1.16]	p=0.17	p=0.06
	IV-low	183 / 256	184 / 260	0.99 [0.81;1.22]		
	IV-high	522 / 700	529 / 678	0.85 [0.76;0.96]		

* Stage III: T3N0 or T1-3N1, stage IV-low: T0-3N2, stage IV-high: T4 or N3

CI: Confidence interval, CT: Chemotherapy, LRT: Loco-Regional Control

Web-Table 13B: Variation of treatment effect according to patients' subgroups for concomitant comparisons *see Figure 3 for age subgroups*

		LRT + CT (No. events / No. patients)	LRT (No. events / No. patients)	Hazard Ratio [95% CI]	Interaction	Heterogeneity of interaction
Overall survival						
Sex 34 comparisons 6788 patients	Male	2042 / 2902	2107 / 2836	0.83 [0.78;0.89]	p=0.82	p=0.21
	Female	350 / 523	363 / 527	0.82 [0.71;0.95]		
Performance status 25 comparisons 5450 patients	PS0	926 / 1384	958 / 1365	0.83 [0.76;0.91]	p=0.52	p=0.21
	PS1	914 / 1200	897 / 1129	0.81 [0.73;0.88]		
	PS≥2	131 / 179	147 / 193	0.93 [0.74;1.19]		
Tumour site 24 comparisons 4650 patients	Oral cavity	359 / 537	366 / 531	0.82 [0.71;0.95]	p=0.85	p=0.93
	Oropharynx	697 / 990	665 / 909	0.82 [0.73;0.91]		
	Hypopharynx	293 / 376	299 / 380	0.88 [0.75;1.04]		
	Larynx	305 / 464	324 / 463	0.81 [0.69;0.95]		
Stage* 33 comparisons 6145 patients	III	526 / 829	564 / 827	0.86 [0.76;0.97]	p=0.50	p=0.0006
	IV-low	512 / 767	521 / 748	0.85 [0.75;0.96]		
	IV-high	1161 / 1523	1149 / 1451	0.80 [0.73;0.86]		
Smoking status 10 comparisons 2427 patients	Never	133 / 204	112 / 176	0.95 [0.74;1.22]	p=0.38	p=0.11
	Former / Current	844 / 1107	718 / 940	0.84 [0.76;0.93]		
Event-free survival						
Sex 32 comparisons 6624 patients	Male	2136 / 2835	2225 / 2753	0.79 [0.75;0.84]	p=0.73	p=0.13
	Female	382 / 516	404 / 520	0.77 [0.67;0.89]		
Performance status 24 comparisons 5342 patients	PS0	980 / 1368	1030 / 1341	0.77 [0.70;0.84]	p=0.41	p=0.86
	PS1	963 / 1174	943 / 1093	0.79 [0.72;0.86]		
	PS≥2	142 / 175	166 / 191	0.90 [0.72;1.13]		
Tumour site 22 comparisons 4509 patients	Oral cavity	413 / 521	430 / 518	0.78 [0.68;0.89]	p=0.45	p=0.25
	Oropharynx	712 / 963	675 / 877	0.80 [0.72;0.89]		
	Hypopharynx	292 / 361	307 / 361	0.90 [0.77;1.05]		
	Larynx	327 / 457	333 / 451	0.76 [0.65;0.89]		
Stage* 31 comparisons 5989 patients	III	552 / 783	602 / 783	0.76 [0.68;0.85]	p=0.65	p=0.001
	IV-low	529 / 733	545 / 716	0.82 [0.73;0.92]		
	IV-high	1193 / 1467	1193 / 1388	0.77 [0.71;0.84]		
Smoking status 10 comparisons 2427 patients	Never	168 / 204	148 / 176	0.84 [0.67;1.05]	p=0.69	p=0.006
	Former / Current	915 / 1107	796 / 940	0.80 [0.72;0.88]		

* Stage III: T3N0 or T1-3N1, stage IV-low: T0-3N2, stage IV-high: T4 or N3

For these analyzes, the following comparisons were pooled: EORTC 22962a and EORTC 22962b, EORTC 22954a and EORTC 22954b, Int 0126a and Int 0126b [40], UKHAN1np01 and UKHAN1np01* and UKHAN1np02 and UKHAN1np02*, UKHAN1po1 and UKHAN1po2 [42].

CI: Confidence interval, CT: Chemotherapy, LRT: Loco-Regional Control

Web-Table 14: Cause of death by age groups for concomitant comparison

148 dead patients excluded as age was missing.

	< 50 years				[50-60[[60-70[≥ 70			
	LRT		LRT + CT		LRT		LRT + CT		LRT		LRT + CT		LRT		LRT + CT	
Cancer	448	48.5%	356	42.0%	625	44.9%	517	38.9%	563	44.4%	420	33.8%	152	38.5%	125	31.1%
Other	80	8.7%	92	10.8%	156	11.2%	189	14.2%	156	12.3%	216	17.4%	74	18.7%	89	22.1%
Unknown	395	42.8%	400	47.2%	610	43.9%	622	46.8%	548	43.4%	606	48.8%	169	42.8%	188	46.8%

Web-Table 15: Characteristics of patients (concomitant versus induction chemotherapies)

	Concomitant		Induction		Total	
	N	%	N	%	N	%
Sex						
Male	496	81.9	492	80.9	988	81.4
Female	110	18.1	116	19.1	226	18.6
Age (years)						
<50	119	19.6	113	18.6	232	19.1
50-59	205	33.8	197	32.4	402	33.1
60-69	208	34.3	203	33.4	411	33.9
≥70	74	12.2	95	15.6	169	13.9
Median [IQR]	59 [52;65]		59 [51;66]		59 [52;66]	
Performance status						
PS 0	163	26.9	150	24.7	313	25.8
PS 1	189	31.2	194	31.9	383	31.5
PS ≥2	17	2.8	22	3.6	39	3.2
Unknown*	237	39.1	242	39.8	479	39.5
Tumour site						
Oral cavity	105	17.3	111	18.3	216	17.8
Oropharynx	228	37.6	221	36.4	449	37.0
Larynx	93	15.4	103	16.9	196	16.1
Hypopharynx	96	15.8	87	14.3	183	15.1
Others	84	13.9	86	14.1	170	14.0
T (TNM)						
T0	6	1	2	0.3	8	0.7
T1	18	3.0	21	3.5	39	3.2
T2	76	12.5	58	9.5	134	11.0
T3	281	46.4	305	50.2	586	48.3
T4	224	37.0	221	36.4	445	36.7
Tx	1	0.2	1	0.2	2	0.2
N (TNM)						
N0	179	29.5	204	33.6	383	31.5
N1	156	25.7	147	24.2	303	25.0
N2	133	22.0	124	20.4	257	21.2
N3	138	22.8	133	21.9	271	22.3
Stage (TNM)						
Stage II	5	0.8	8	1.3	14	1.2
Stage III	209	34.5	221	36.4	429	35.3
Stage IV	392	64.7	379	62.3	771	63.5
Total	606	100	608	100	1214	100

* Information not collected in three comparisons (475 patients)

Web-Table 16: Characteristics of patients included in comparisons with or without surgery

	Without surgery (N=12949)		With surgery (N=5503)		p-value
	N	%	N	%	
Sex					p=0.0006
Male	10447	80.7	4663	84.7	
Female	2138	16.5	818	14.9	
Unknown*	364	2.8	22	0.4	
Age (years)					p < 0.0001
<50	2832	21.9	1303	23.7	
50-59	4424	34.2	2054	37.3	
60-69	4033	31.2	1550	28.2	
≥70	1279	9.9	423	7.7	
Unknown*	381	2.9	173	3.1	
Performance status					p < <0.0001
PS0	4497	34.7	2068	37.6	
PS1	5002	38.6	1130	20.5	
PS≥2	947	7.3	116	2.1	
Unknown*	2503	19.3	2189	40.0	
Tumour site					p < 0.0001
Oral cavity	2612	20.2	1903	34.6	
Oropharynx	5249	40.5	1439	26.2	
Larynx	2330	18.0	906	16.5	
Hypopharynx	1952	15.1	1017	18.5	
Other	674	5.2	219	4.0	
Unknown*	132	1.1	19	0.4	
T (TNM)					p < 0.0001
T0-1	523	4.0	367	6.7	
T2	2122	16.4	1339	24.3	
T3	4616	35.7	2282	41.5	
T4	5245	40.5	1227	22.3	
Tx*	37	0.3	0	-	
Tis*	0	-	2	< 0.1	
Unknown*	406	3.1	286	5.2	
N (TNM)					p < 0.0001
N0	3722	28.7	2042	37.1	
N1	2219	17.1	1284	23.3	
N2	3932	30.4	1310	23.8	
N3	2074	16.0	439	8.0	
N+*	638	4.9	154	2.8	
Nx (without detail)*	3	< 0.1	0	-	
Unknown*	361	2.8	274	5.0	
Stage (TNM)					p < 0.0001
Stage 0*	0	-	2	< 0.1	
Stage I-II	784	6.1	548	10.0	
Stage III	3138	24.2	2035	37.0	
Stage IV	8655	66.8	2620	47.6	
Unknown*	372	2.9	300	5.5	

* Excluded from the estimation of p-value

Web-Table 17: Effect of chemotherapy according to sex in comparisons with or without surgery

		LRT + CT (No. events / No. patients)	LRT (No. events / No. patients)	Hazard Ratio [95% CI]	Interaction
Overall Survival					
101 comparisons (18055 patients)†					
With surgery	Male	1417 / 2377	1373 / 2286	0.96 [0.89;1.03]	p=0.001
	Female	162 / 415	208 / 403	0.67 [0.54;0.82]	
Without surgery	Male	3940 / 5277	3992 / 5170	0.87 [0.83;0.91]	p=0.15
	Femme	728 / 1042	755 / 1096	0.94 [0.85;1.04]	
Interaction chemotherapy*sex*surgery : p=0.0004					
Event-free survival					
96 comparisons (16691 patients)†					
With surgery	Male	1400 / 2169	1345 / 2080	0.97 [0.90;1.05]	p=0.0021
	Female	174 / 375	218 / 364	0.69 [0.57;0.85]	
Without surgery	Male	3919 / 4936	4012 / 4815	0.83 [0.79;0.87]	p=0.47
	Female	723 / 956	778 / 1007	0.86 [0.78;0.96]	
Interaction chemotherapy*sex*surgery : p=0.002					

† Exclusion of two comparisons with missing sex for all patients.

CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Table 18: Description of trials identified in 2019

Trial (year of publication)	Inclusion period	Sites	Stage	Drug	Chemotherapy	Locoregional treatment	Radiotherapy	Patients analyzed/ randomized	Median follow-up [range] (years)
Yi J et al (2017) ^a [x]	2002-12	OC, OP, HP, L	III, IV	C (concomitant)	30 mg/m ² weekly	RT +S	50-70 Gy/5-7 wks	222/240	4.9 [5.8 ; 6.25]
Huang PW et al (2018) ^b [y]	2006-11	OP, HP, L	III, IV	C U (po) LA (po)	50 mg/m ² d ₁ , wks _{1,3,5,7,9,11} 300 mg/m ² d ₁₋₁₄ , wks _{1,3,5,7,9,11} 60 mg/m ² d ₁₋₁₄ , wks _{1,3,5,7,9,11}	RT	70-76/7-7.5 wks	151/151	4.5 [0.25 ; 6.25]
Sadighi S et al (2015) ^c [z]	2009-11	OC	III, IVa	Induction Do C F	70-80 mg/m ² , 60 mg/m ² , 750 mg/m ² x 5,	S + RT	DM	24/24	1.3 [NA]

C: Cisplatin ; d: day ; Do: Docetaxel ; DM : data missing ; F: 5-Fluorouracil ; Gy: Gray ; HP: Hypopharynx ; L: Larynx ; LA: Leucovorin ; NA: Not available ; NP: Nasopharynx ; O : Other ; OC: Oral Cavity ; OP: Oropharynx ; po: per os ; U=Tegafur-Uracil ; wks: weeks

^a After 50 Gy, tumor evaluation was performed. Responders (>80% reduction of the primary tumor) received an overall dose of 70 Gy with modified neck dissection for N2/N3 patients, non-responders underwent resection of the primary and modified neck dissection. For OS, the HR was 0.74 [0.50-1.10; p0.13].

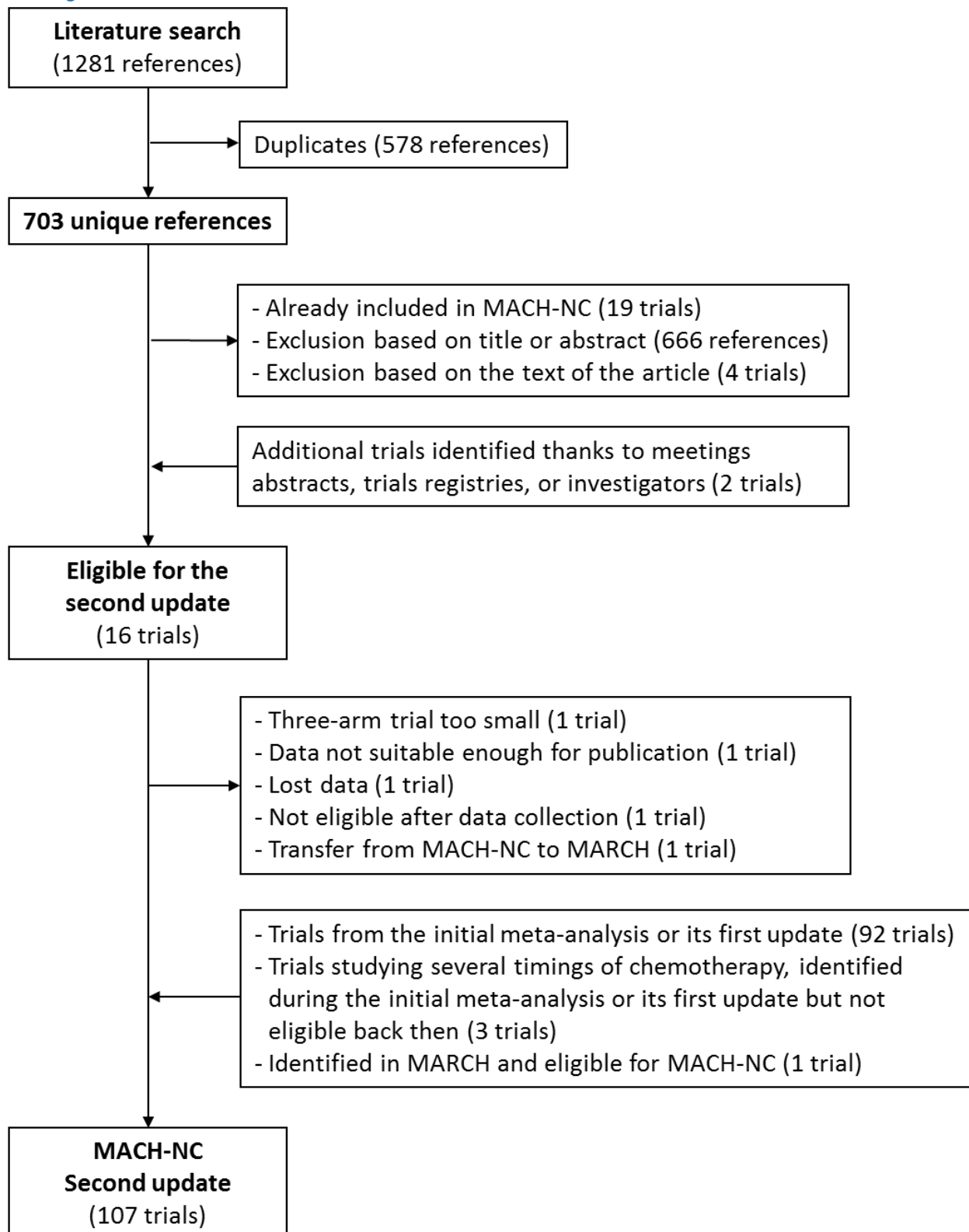
^b 151 out of the 200 planned patients were included. “The study was suspended because of slow accrual and poor end points in the ICT/CCRT arm during interim analysis. With insufficient statistical power, the OS in the ICT/CCRT arm was not poorer than that in the CCRT arm.” “in patients with advanced PLSCC. However, patients treated with ICT/CCRT had poorer PFS and LRC. The higher prevalence of hypopharynx cancer (57.1% vs 40.5%, p ¼ 0.09) and N2 or N3 disease (85.7% vs. 74.4%, p ¼ 0.02) in the ICT/CCRT arm may account for the poorer PFS and LRC.” The same chemotherapy regimen was given in both arms concurrently with radiotherapy. Median follow-up time was only for surviving patients. No value of hazard ratio for overall or progression-free survival was reported.

^c After two cycles of chemotherapy, tumor response was evaluated with a third cycle in case of objective response. No value of hazard ratio for overall or progression-free survival was reported.

References:

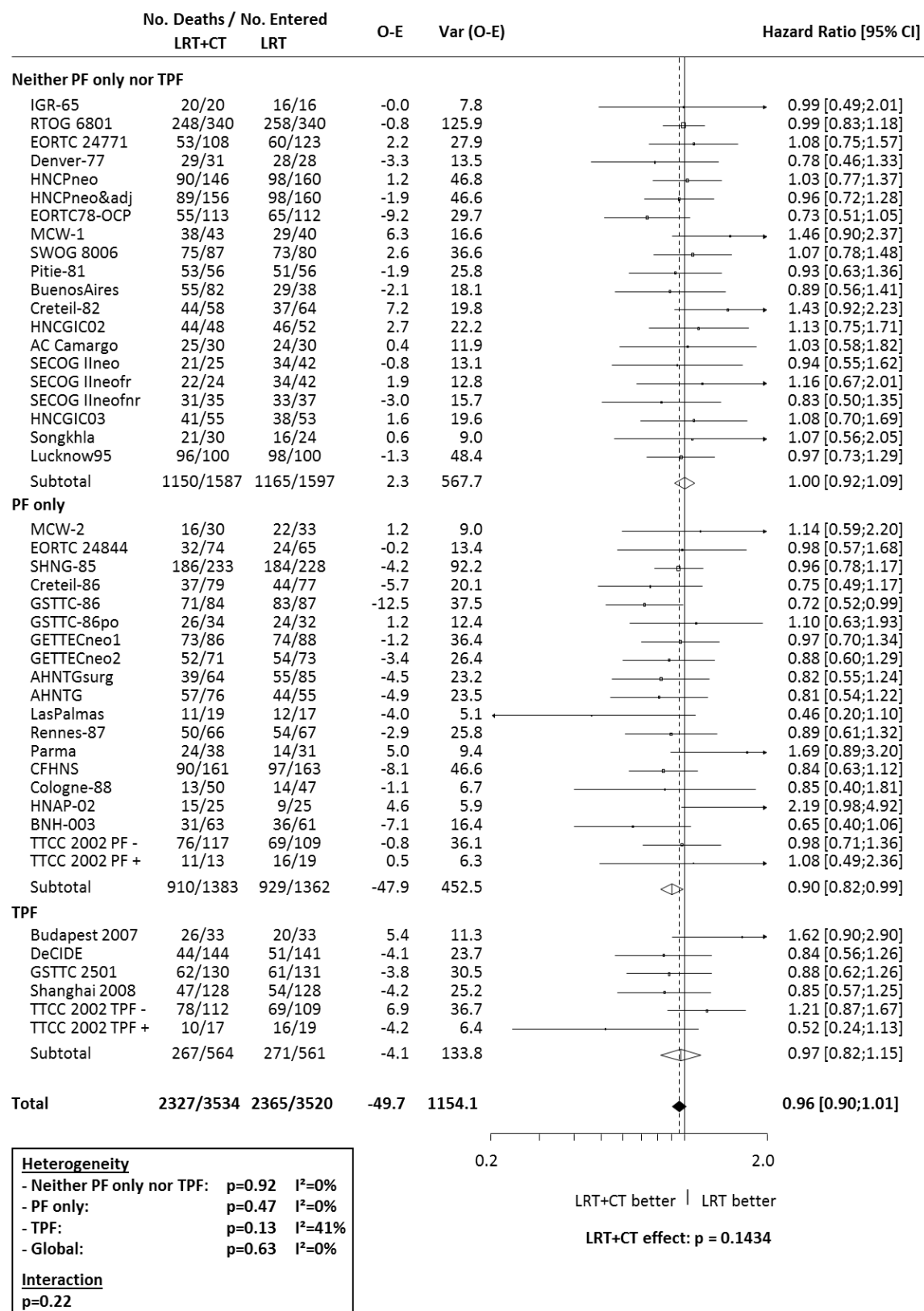
- [x] Yi J, Huang X, Xu Z, Liu S, et al. Phase III randomized trial of preoperative concurrent chemoradiotherapy versus preoperative radiotherapy for patients with locally advanced head and neck squamous cell carcinoma. *Oncotarget*. 2017;8:44842-44850.
- [y] Huang PW, Lin CY, Hsieh CH, et al. A phase II randomized trial comparing neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in advanced squamous cell carcinoma of the pharynx or larynx. *Biomed J*. 2018 ;41:129-136.
- [z] Sadighi S, Keyhani A, Harirchi I, et al. Neoadjuvant Chemotherapy for Locally Advanced Squamous Carcinoma of Oral Cavity: a Pilot Study. *Acta Med Iran*. 2015;53:380-6.

Web-Figure 1: Flowchart



MACH-NC: Meta-Analysis of Chemotherapy in Head and Neck Cancer, MARCH: Meta-Analysis of Radiotherapy in Head and Neck cancer

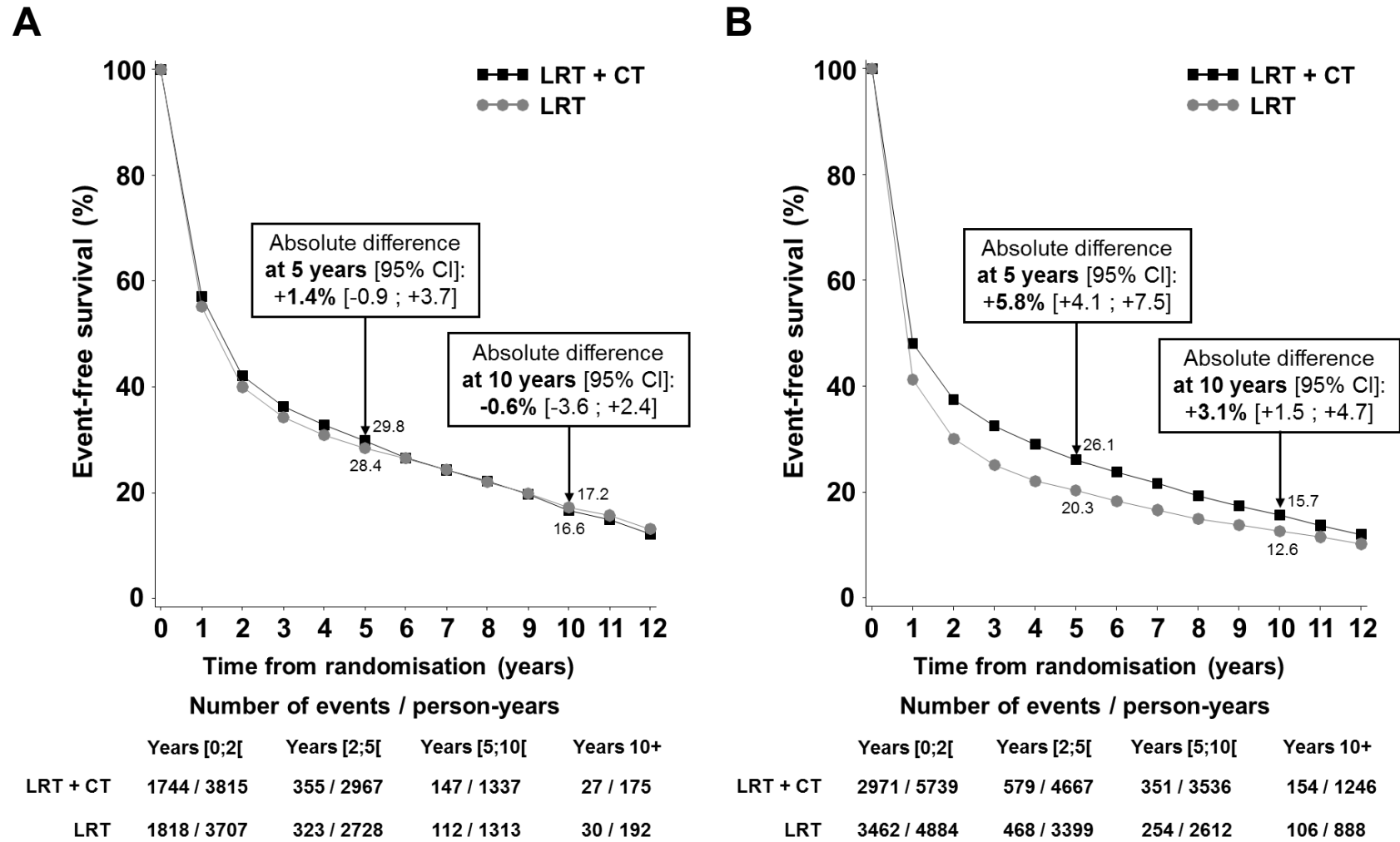
Web-Figure 2: Overall survival - Loco-regional treatment plus induction chemotherapy versus loco-regional treatment alone. See Web-Table1 for trials abbreviations



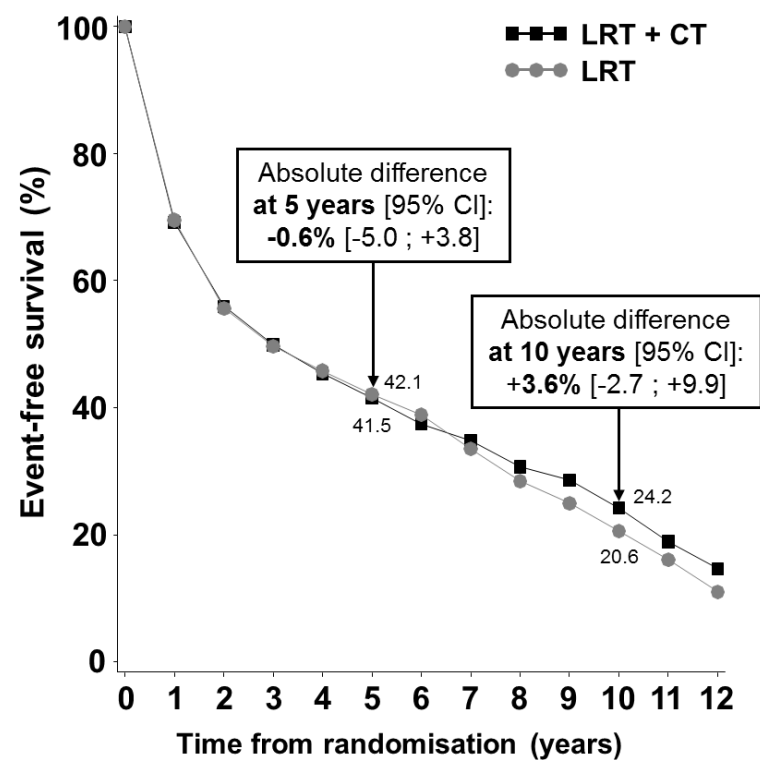
CI: Confidence Interval, CT: Chemotherapy, E: Expected, LRT: Loco-Regional Treatment, O: Observed, PF: 5-Fluorouracil + platin salt, TPF: 5-Fluorouracil + platin salt + taxane

Web-Figure 3: Event-free survival - Survival curves of loco-regional treatment plus chemotherapy and loco-regional treatment alone by timing

A: Induction chemotherapy, B: Concomitant chemotherapy, C: Adjuvant chemotherapy.



C

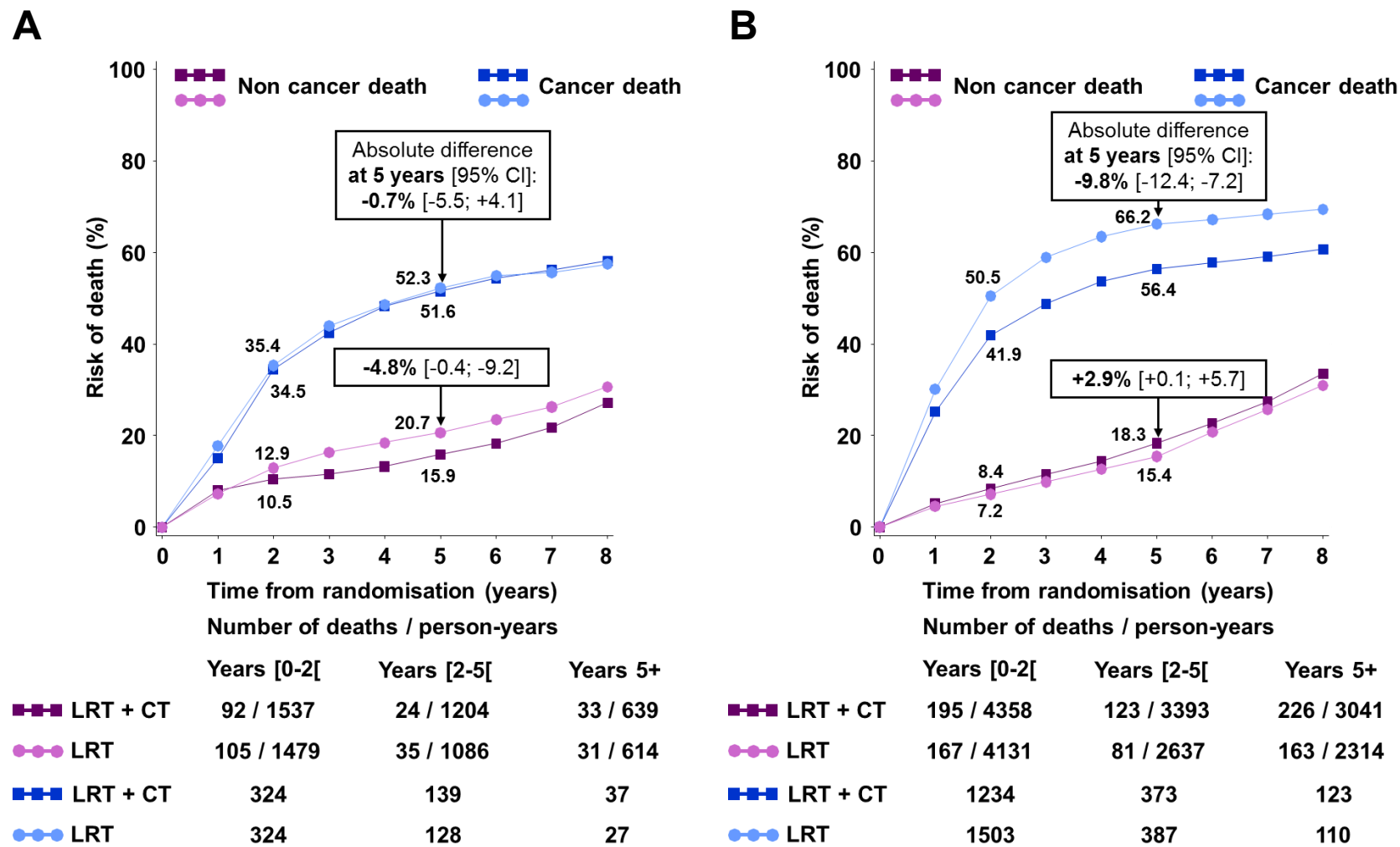


Number of events / person-years

	Years [0;2[Years [2;5[Years [5;10[Years 10+
LRT + CT	497 / 1659	123 / 1226	50 / 512	27 / 109
LRT	543 / 1752	131 / 1331	69 / 532	21 / 58

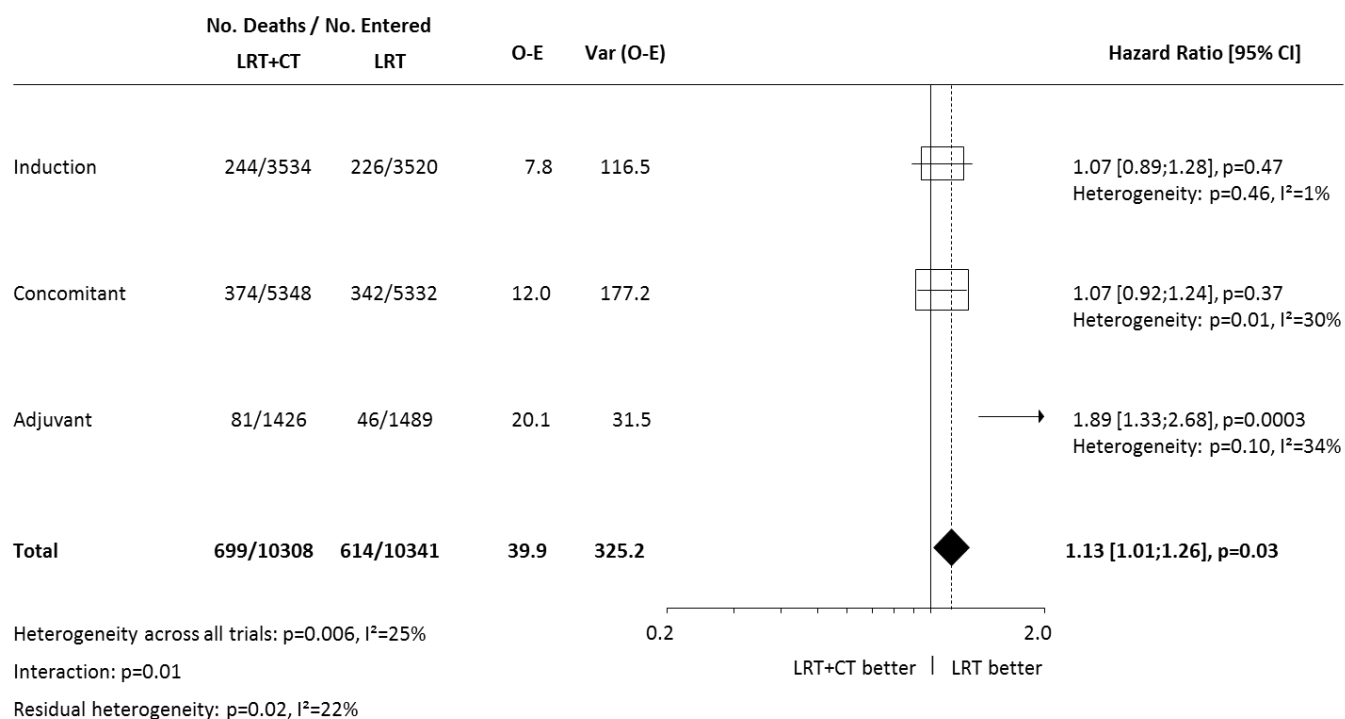
CI: confidence interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Figure 4: Cancer and non-cancer mortality - Survival curves of loco-regional treatment plus chemotherapy and loco-regional treatment alone by timing
A: Induction chemotherapy, B: Concomitant chemotherapy.



CI: confidence interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Figure 5: 120-day mortality - Loco-regional treatment plus chemotherapy versus loco-regional treatment alone



CI: Confidence Interval, CT: Chemotherapy, HR: Hazard Ratio, LRT: Loco-Regional Treatment, O-E: Observed minus Expected

	No. Events / No. Entered		Sub-HR [95% CI]
	LRT + CT	LRT	
Induction	1355/3194	1219/3148	1.07 [0.99;1.15], p=0.09 Heterogeneity: p<0.0001, I ² =63%
Concomitant	2154/5059	2612/5017	0.71 [0.67;0.75], p<0.0001 Heterogeneity: p<0.0001, I ² =85%
Adjuvant	256/1175	315/1241	0.84 [0.72;1.00], p=0.04 Heterogeneity: p=0.16, I ² =29%
Total	3765/9428	4146/9406	0.82 [0.78;0.86], p<0.0001

Heterogeneity across all trials: p < 0.0001, I²=81%

Interaction: p < 0.0001

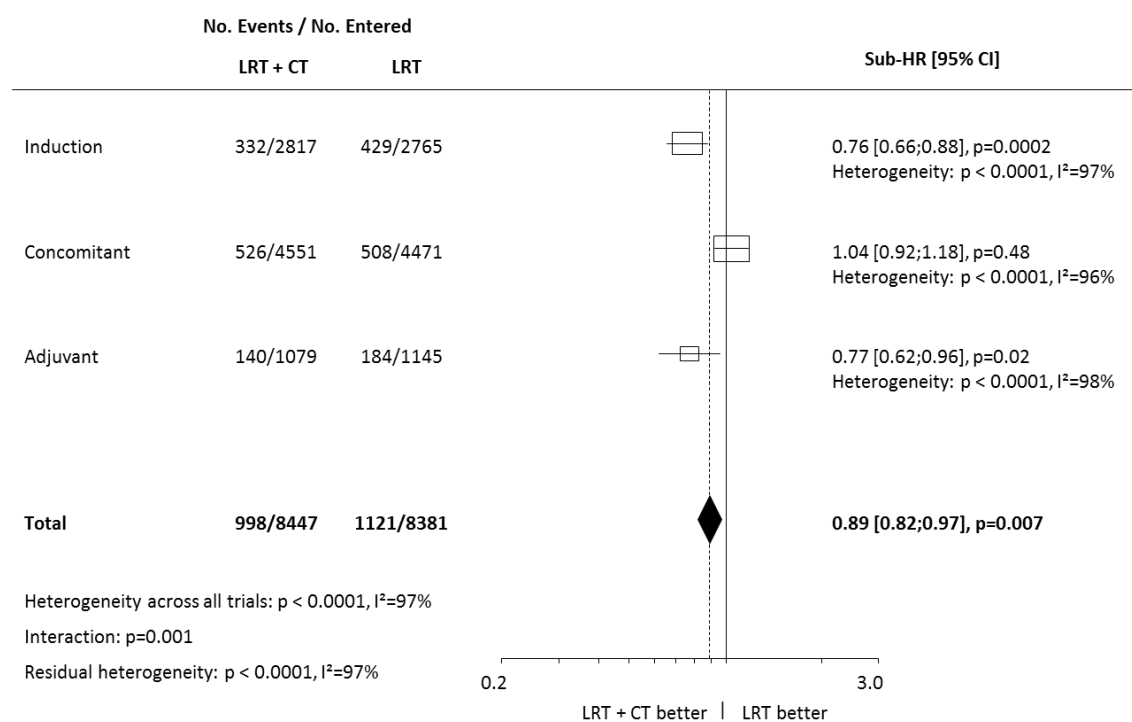
Residual heterogeneity: p < 0.0001, I²=78%

0.2 3.0

LRT + CT better | LRT better

56

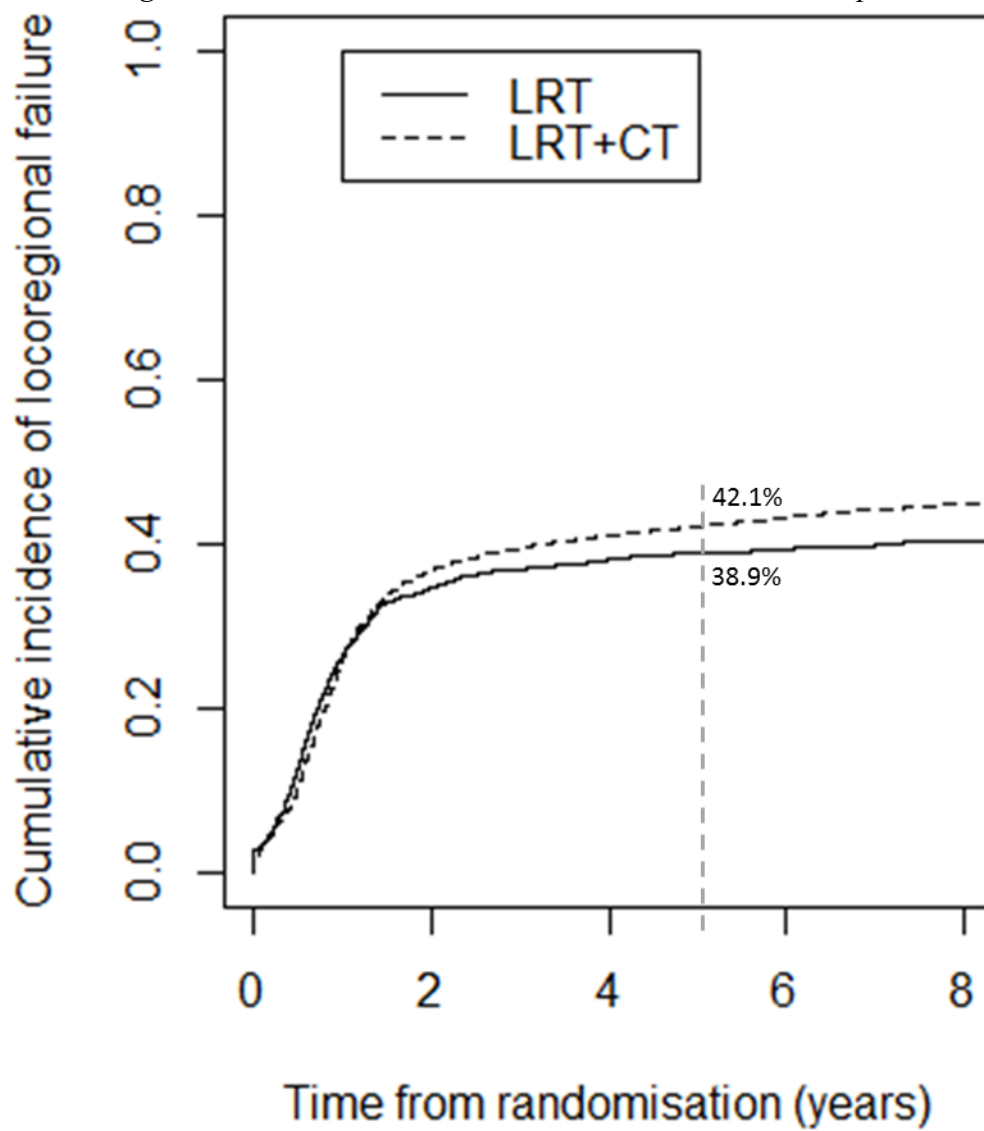
Web-Figure 7: Distant failure - Loco-regional treatment plus chemotherapy versus loco-regional treatment alone



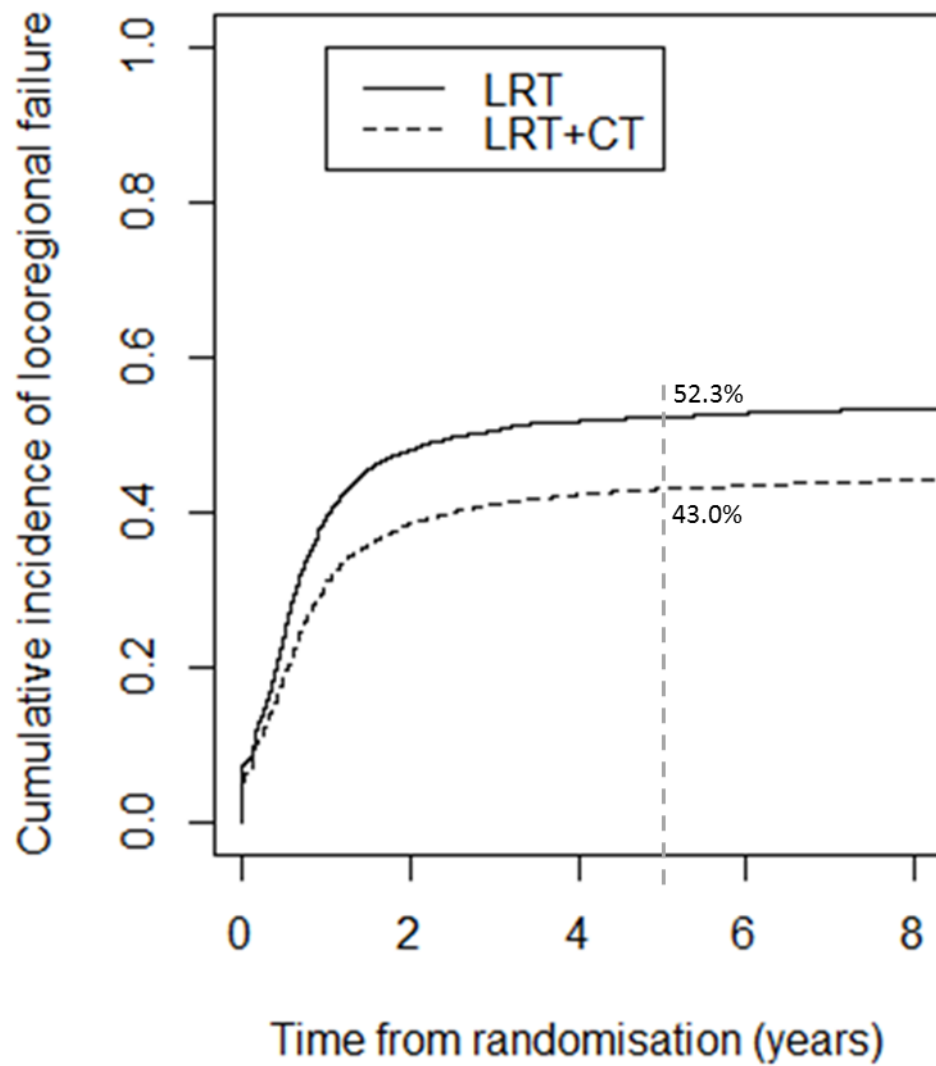
CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment, sub-HR: Sub-distribution Hazard Ratio

Similar results were observed after excluding the comparisons with a rate of distant failure inferior to 5% (data not shown)

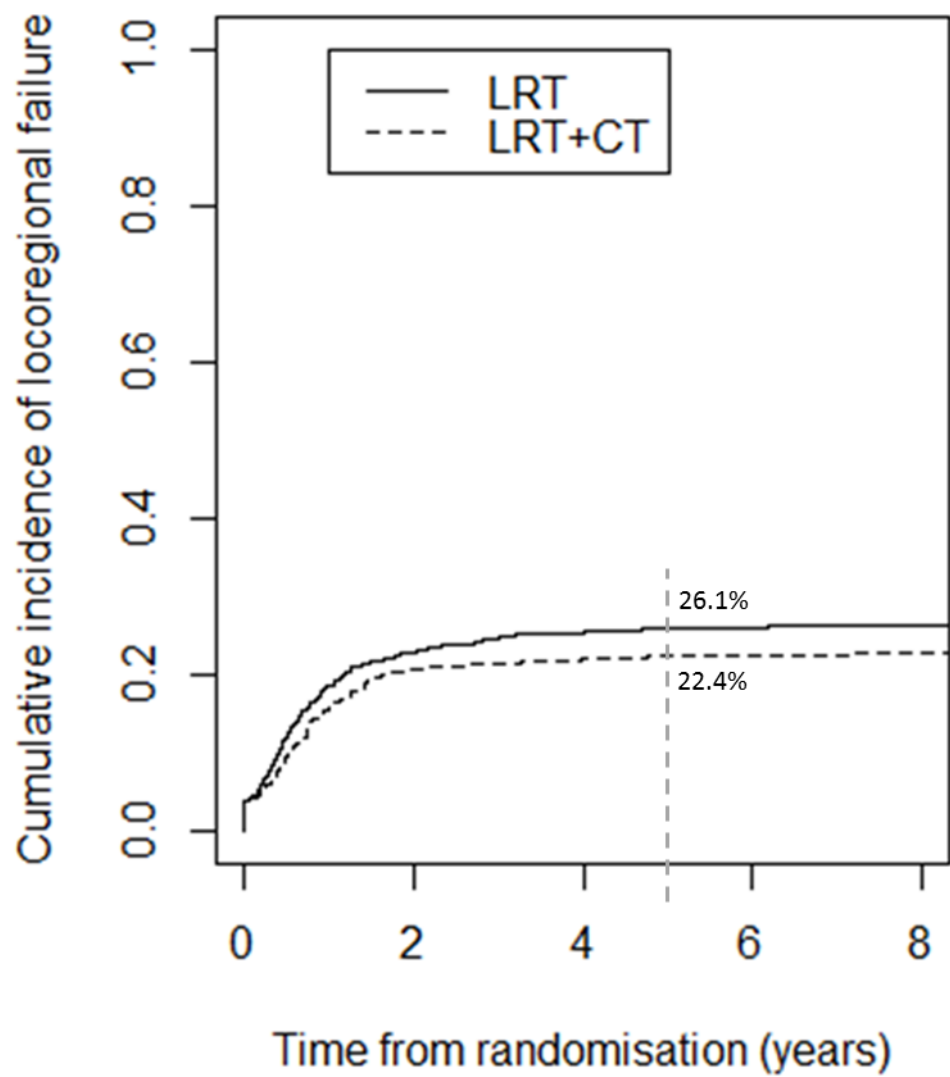
Web-Figure 8-A: LRF - Cumulative incidence in induction comparisons



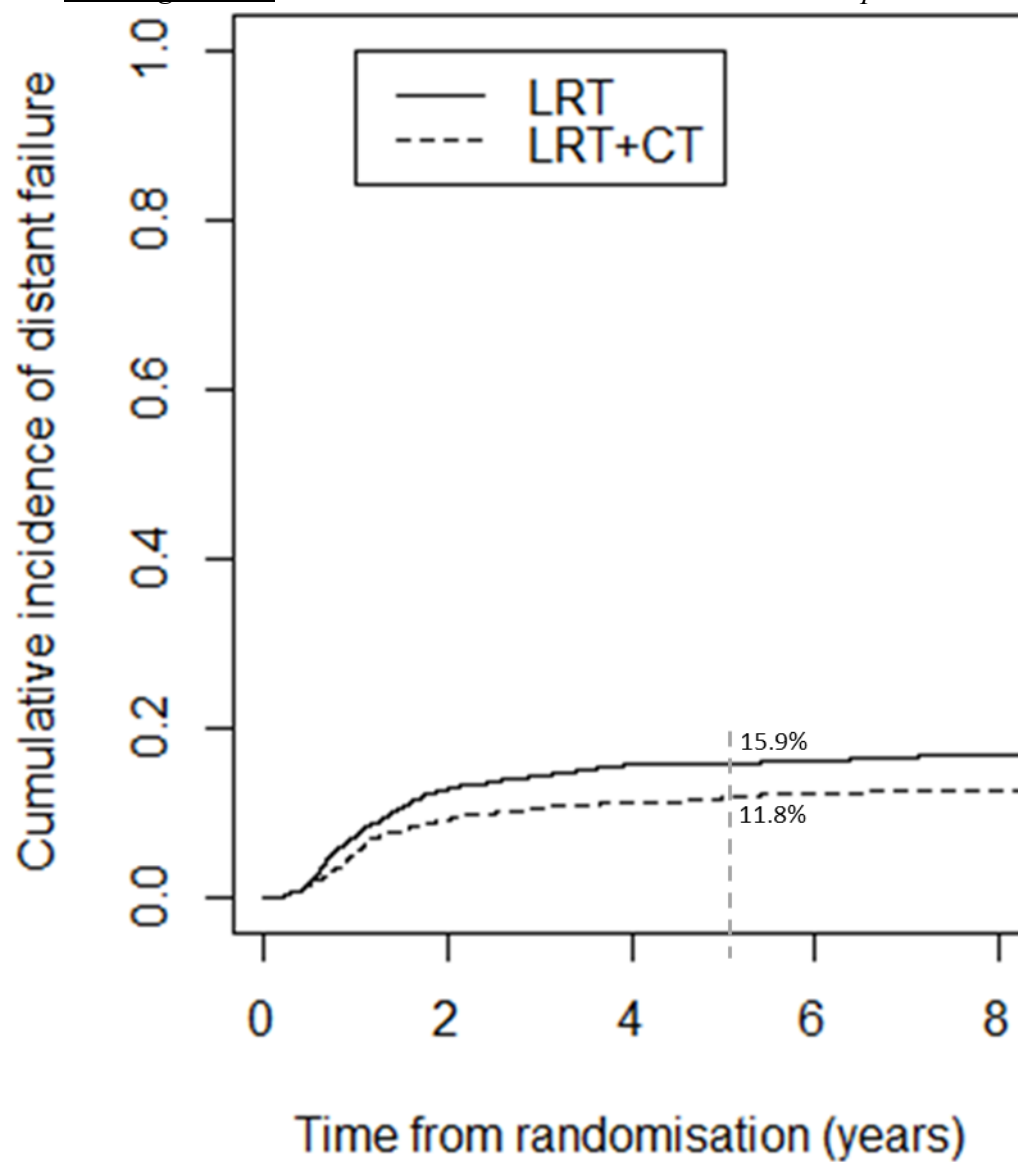
Web-Figure 8-B: LRF - Cumulative incidence in concomitant comparisons



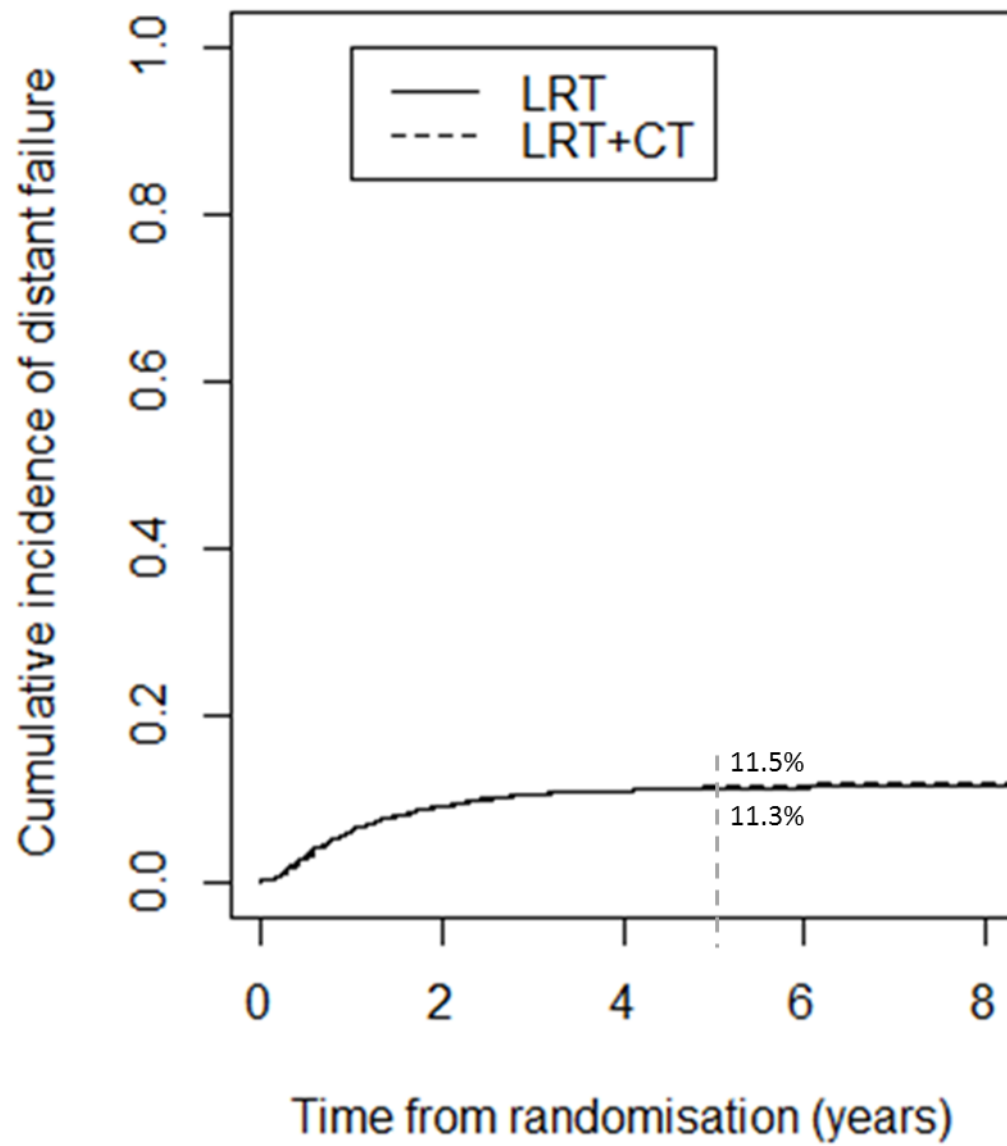
Web-Figure 8-C: LRF - Cumulative incidence in adjuvant comparisons



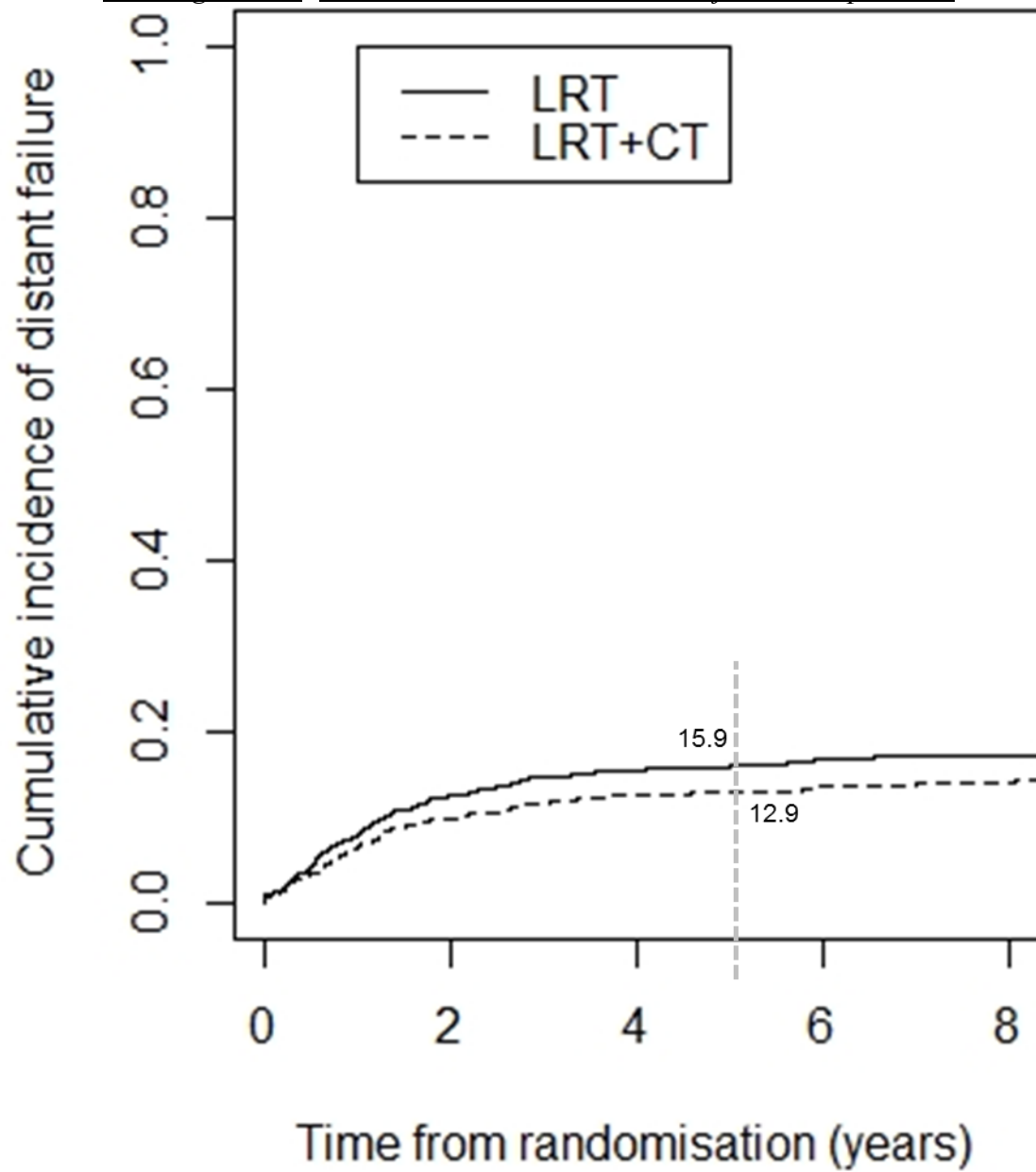
Web-Figure 9-A: DF - Cumulative incidence in induction comparisons



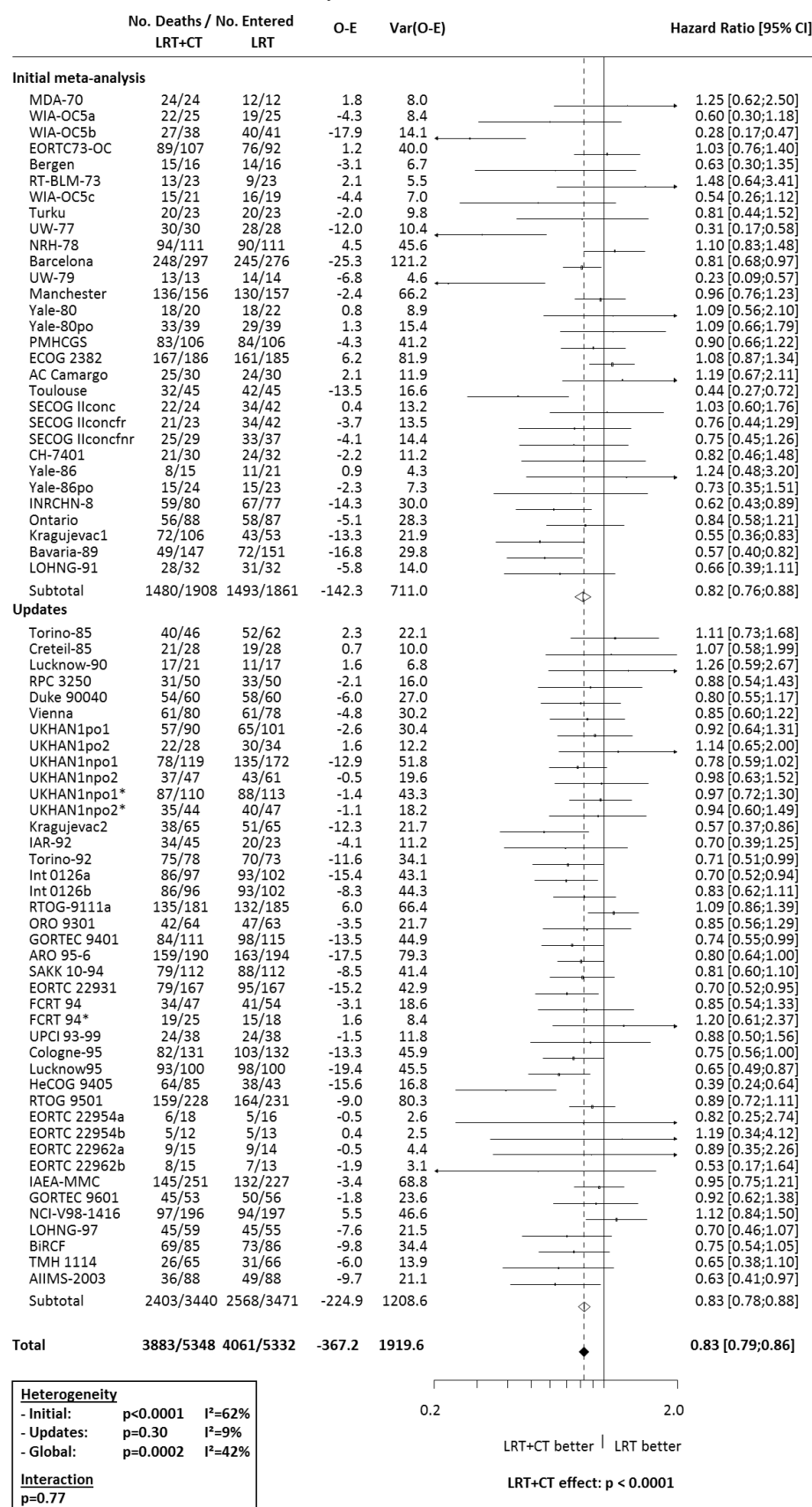
Web-Figure 9-B: DF - Cumulative incidence in concomitant comparisons



Web-Figure 9-C: DF - Cumulative incidence in adjuvant comparisons



Web-Figure 10: Overall survival - Loco-regional treatment plus concomitant chemotherapy versus loco-regional treatment alone. See Web-Table 2 for trials abbreviations



CI: confidence interval,

CT: Chemotherapy, LRT: Loco-Regional Treatment

Web-Figure 11: Overall survival - Loco-regional treatment plus adjuvant chemotherapy versus loco-regional treatment alone

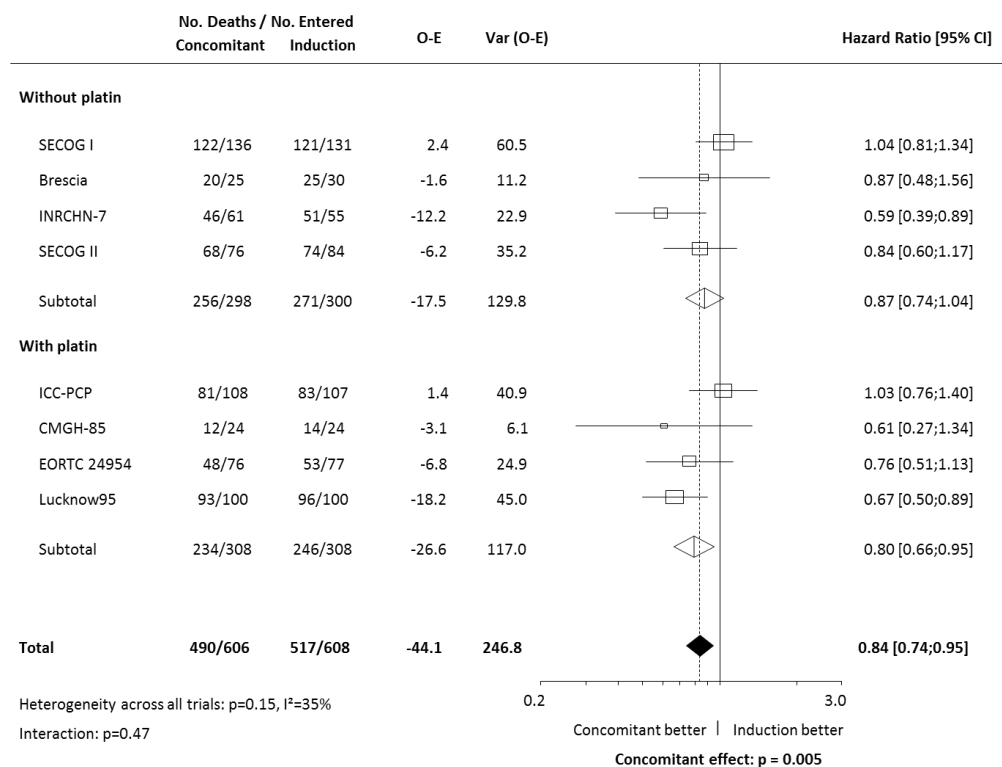
	No. Events / No. Entered LRT+CT	No. Events / No. Entered LRT	O-E	Var(O-E)		Hazard Ratio [95% CI]
Surgery						
Pitie-74	31/48	31/48	-1.8	14.5		0.88 [0.53;1.48]
JHCFUS	12/96	22/95	-5.6	8.5		0.52 [0.26;1.02]
TMHR-4	13/65	13/70	0.4	6.4		1.06 [0.49;2.29]
KKD-86	18/56	17/56	1.8	8.7		1.23 [0.63;2.40]
HNU-87b	58/213	63/211	-3.9	30.2		0.88 [0.62;1.26]
Subtotal	132/478	146/480	-9.1	68.3		0.88 [0.69;1.11]
Radiotherapy						
HNU-87a	10/58	10/53	-0.2	5.0		0.97 [0.40;2.32]
UKHAN1a1	88/113	135/172	2.5	51.8		1.05 [0.80;1.38]
UKHAN1a2	40/47	43/61	4.1	19.7		1.23 [0.79;1.91]
Subtotal	138/218	188/286	6.4	76.5		1.09 [0.87;1.36]
Surgery and Radiotherapy						
GETTECadj	120/143	110/143	11.8	57.1		1.23 [0.95;1.59]
Int 0034	161/251	163/248	-7.4	80.6		0.91 [0.73;1.14]
Subtotal	281/394	273/391	4.4	137.7		1.03 [0.87;1.22]
Other CT and Adjuvant CT						
DICI	15/26	16/20	-5.3	6.6		0.45 [0.21;0.96]
HNCP*	89/156	90/146	-2.9	44.6		0.94 [0.70;1.26]
UKHAN1a1*	87/110	78/119	10.5	40.6		1.29 [0.95;1.76]
UKHAN1a2*	35/44	37/47	4.0	17.3		1.26 [0.79;2.02]
Subtotal	226/336	221/332	6.2	109.1		1.06 [0.88;1.28]
Total	777/1426	828/1489	7.9	391.6		1.02 [0.92;1.13]

CI: confidence interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

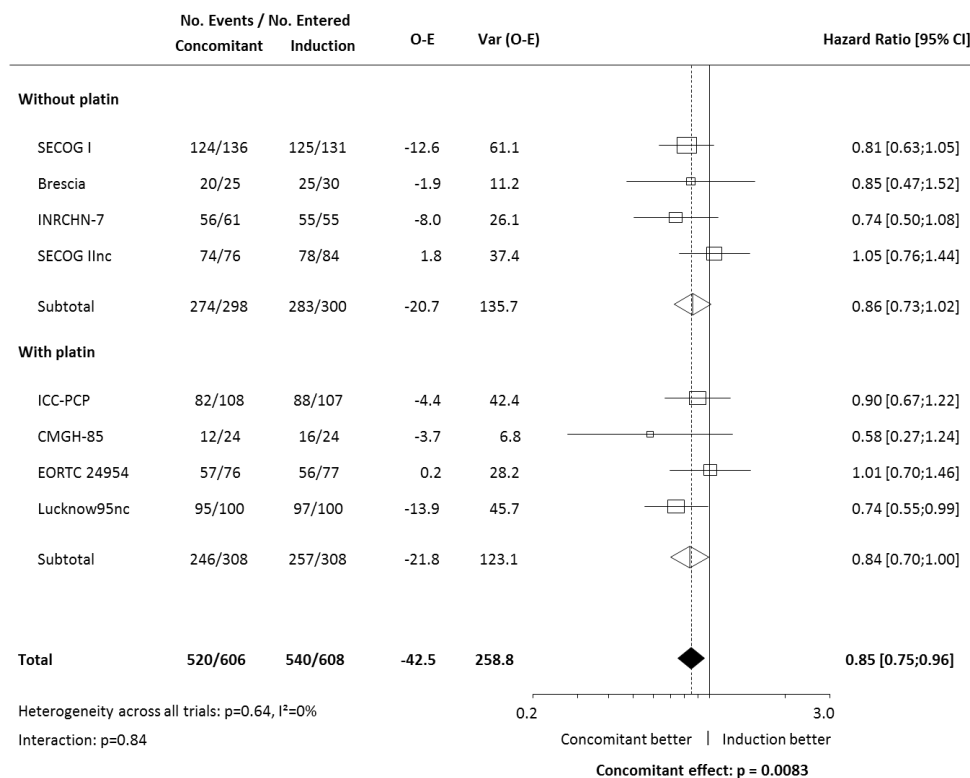
Web-Figure 12: Efficacy of concomitant versus induction chemotherapy.

A: Overall survival, B: Event-free survival. See Web-Table-4 for trials abbreviations.

A



B

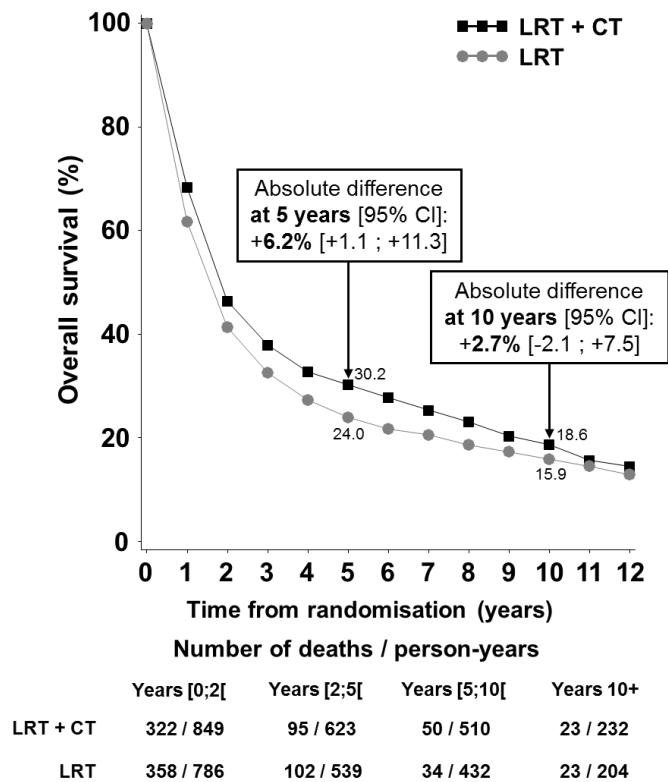


CI: Confidence Interval, CT: Chemotherapy, HR: Hazard Ratio, LRT: Loco-Regional Treatment, O-E: Observed minus Expected.

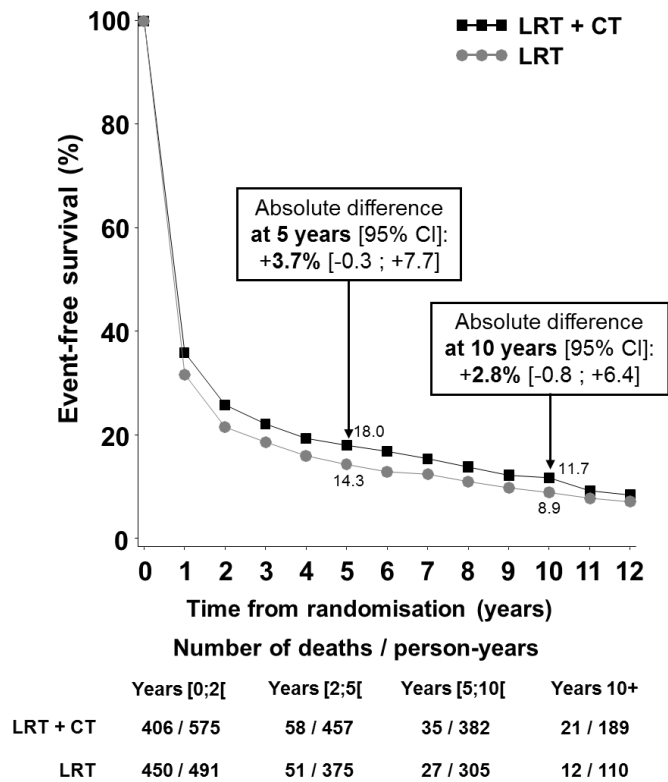
Web-Figure 13: Survival curves of concomitant versus induction chemotherapy

A: Overall survival, B: Event-free survival

A



B



CI: Confidence Interval, CT: Chemotherapy, LRT: Loco-Regional Treatment

References

- [1] Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet* 2006;368:843–54. [https://doi.org/10.1016/S0140-6736\(06\)69121-6](https://doi.org/10.1016/S0140-6736(06)69121-6).
- [2] Hitt R, Grau J, López-Pousa A, Berrocal A, García-Girón C, Irigoyen A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. *Annals of Oncology* 2014;25:216–25. <https://doi.org/10.1093/annonc/mdt461>.
- [3] Lefebvre J, Rolland F, Tesselaar M, Bardet E, Leemans C, Geoffrois L, et al. Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. *Journal of the National Cancer Institute* 2009;101:142–52. <https://doi.org/10.1093/jnci/djn460>.
- [4] Henriques De Figueiredo B, Fortpied C, Menis J, Lefebvre JL, Barzan L, de Raucourt D, et al. Long-term update of the 24954 EORTC phase III trial on larynx preservation. *European Journal of Cancer* 2016;65:109–12. <https://doi.org/10.1016/j.ejca.2016.06.024>.
- [5] Pignon J-P, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. *Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet* 2000;355:949–55.
- [6] Pignon J-P, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiotherapy and Oncology : Journal of the European Society for Therapeutic Radiology and Oncology* 2009;92:4–14. <https://doi.org/10.1016/j.radonc.2009.04.014>.
- [7] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;7:177–88.
- [8] Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in Non-Small Cell Lung Cancer: A Meta-Analysis Using Updated Data on Individual Patients From 52 Randomised Clinical Trials. *BMJ* 1995;311:909. <https://doi.org/10.1136/bmj.311.7010.889>.
- [9] Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Progress in Cardiovascular Diseases* 1985;27:335–71.
- [10] Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. *The New England Journal of Medicine* 1995;333:1444–55. <https://doi.org/10.1056/NEJM199511303332202>.
- [11] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* 1999;94:496–509. <https://doi.org/10.1080/01621459.1999.10474144>.
- [12] Blanchard P, Bourhis J, Lacas B, Posner MR, Vermorken JB, Hernandez JJC, et al. Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the Meta-Analysis of Chemotherapy in Head and Neck Cancer Group. *Journal of Clinical Oncology* 2013;31:2854–60. <https://doi.org/10.1200/JCO.2012.47.7802>.
- [13] Takacs-Nagy Z, Hitre E, Remenar E, Oberna F, Polgar C, Major T, et al. Docetaxel, cisplatin and 5-fluorouracil induction chemotherapy followed by chemoradiotherapy or chemoradiotherapy alone in stage III-IV unresectable head and neck cancer: Results of a randomized phase II study. *Strahlenther Onkol* 2015;191:635–41. <https://doi.org/10.1007/s00066-015-0829-z>.
- [14] Fisher DJ, Copas AJ, Tierney JF, Parmar MKB. A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. *Journal of Clinical Epidemiology* 2011;64:949–67. <https://doi.org/10.1016/j.jclinepi.2010.11.016>.
- [15] Ezzat M, Shouman T, Zaza K, Safwat A, El-Khoudary A, El-Senosi M, et al. A randomized study of accelerated fractionation radiotherapy with and without mitomycin C in the treatment of locally advanced head and neck cancer. *Journal of the Egyptian National Cancer Institute* 2005;17:85–92.
- [16] Knecht R. Induction chemotherapy (IC) followed by radiochemotherapy (RCT) versus radiochemotherapy alone as treatment in advanced laryngeal (LC)/hypopharyngeal cancer (HC): Phase IIb. *JCO* 2014;32:6015–6015. https://doi.org/10.1200/jco.2014.32.15_suppl.6015.
- [17] Shukla P, Gupta D. A prospective comparison of sequential chemoradiation vs concurrent chemoradiation in locally advanced oropharyngeal carcinomas. *Cancer Biology and Therapy* 2009;8:209–13.

- [18] Prades JM, Lallemand B, Garrel R, Rey E, Righini C, Schmitt T, et al. Randomized phase III trial comparing induction chemotherapy followed by radiotherapy to concomitant chemoradiotherapy for laryngeal preservation in T3M0 pyriform sinus carcinoma. *Acta Oto-Laryngologica* 2010;130:150–5.
- [19] Boidi Trotti A, Rovea P, Gabriele AM, Tseroni V, Fracchia F, Raiteri M, et al. The use of cisplatin as radiosensitizing agent in advanced tumors of the head and neck. Randomized study. *La Radiologia medica* 1991;82:504–7.
- [20] Haddad E, Mazon JJ, Martin M, Vergnes L, Brun B, Piedbois P, et al. Comparison of concomitant radiotherapy and chemotherapy with radiotherapy alone in advanced cancers of the head and neck: results of a randomized trial. *Bulletin Du Cancer Radiotherapie* 1996;83:97–103.
- [21] Ervin TJ, Clark JR, Weichselbaum RR, Fallon BG, Miller D, Fabian RL, et al. An analysis of induction and adjuvant chemotherapy in the multidisciplinary treatment of squamous-cell carcinoma of the head and neck. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 1987;5:10–20. <https://doi.org/10.1200/JCO.1987.5.1.10>.
- [22] Corvò R, Benasso M, Sanguineti G, Lionetto R, Bacigalupo A, Margarino G, et al. Alternating chemoradiotherapy versus partly accelerated radiotherapy in locally advanced squamous cell carcinoma of the head and neck: results from a phase III randomized trial. *Cancer* 2001;92:2856–67.
- [23] Lacas B, Bourhis J, Overgaard J, Zhang Q, Grégoire V, Nankivell M, et al. Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. *The Lancet Oncology* 2017;18:1221–37. [https://doi.org/10.1016/S1470-2045\(17\)30458-8](https://doi.org/10.1016/S1470-2045(17)30458-8).
- [24] Ghosh-Laskar S, Kalyani N, Gupta T, Budrukhar A, Murthy V, Sengar M, et al. Conventional radiotherapy versus concurrent chemoradiotherapy versus accelerated radiotherapy in locoregionally advanced carcinoma of head and neck: Results of a prospective randomized trial. *Head & Neck* 2016;38:202–7. <https://doi.org/10.1002/hed.23865>.
- [25] Domenge C, Hill C, Lefebvre J, De Raucourt D, Rhein B, Wibault P, et al. Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. *British Journal of Cancer* 2000;83:1594–8. <https://doi.org/10.1054/bjoc.2000.1512>.
- [26] Tsukuda M, Ogasawara H, Kaneko S, Komiya S, Horiuchi M, Inuyama Y, et al. A prospective randomized trial of adjuvant chemotherapy with UFT for head and neck carcinoma. *Japanese Journal of Cancer and Chemotherapy* 1994;21:1169–77.
- [27] Shanta V, Krishnamurthi S. Combined bleomycin and radiotherapy in oral cancer. *Clinical Radiology* 1980;31:617–20.
- [28] Olmi P, Crispino S, Fallai C, Torri V, Rossi F, Bolner A, et al. Locoregionally advanced carcinoma of the oropharynx: conventional radiotherapy vs. accelerated hyperfractionated radiotherapy vs. concomitant radiotherapy and chemotherapy--a multicenter randomized trial. *International Journal of Radiation Oncology, Biology, Physics* 2003;55:78–92.
- [29] Dobrowsky W, Naudé J. Continuous hyperfractionated accelerated radiotherapy with/without mitomycin C in head and neck cancers. *Radiotherapy and Oncology* 2000;57:119–24. [https://doi.org/10.1016/S0167-8140\(00\)00233-4](https://doi.org/10.1016/S0167-8140(00)00233-4).
- [30] Sanchiz F, Milla A, Torner J, Bonet F, Artola N, Carreno L, et al. Single fraction per day versus two fractions per day versus radiochemotherapy in the treatment of head and neck cancer. *International Journal of Radiation Oncology, Biology, Physics* 1990;19:1347–50.
- [31] Forastiere AA, Goepfert H, Maor M, Pajak T, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *New England Journal of Medicine* 2003;349:2091–8. <https://doi.org/10.1056/NEJMoa031317>.
- [32] Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *Journal of Clinical Oncology* 2013;31:845–52. <https://doi.org/10.1200/JCO.2012.43.6097>.
- [33] Szpirglas H, Chastang Cl, Bertrand JCh. Adjuvant treatment of tongue and floor of the mouth cancers. In: Bonadonna G, Mathé G, Salmon S, editors. *Adjuvant therapies and markers of post-surgical minimal residual disease II. Adjuvant therapies of the various primary tumors*, Berlin: Springer-Verlag; 1979, p. 309–17. https://doi.org/10.1007/978-3-642-81332-0_47.
- [34] Carugati A, Pradier R, De La Torre A. Combination chemotherapy pre-radical treatment for head and neck squamous cell carcinoma. *Proc Am Soc Clin Oncol* 1988;7:152.
- [35] Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable

- squamous cell carcinoma of the head and neck: A prospective randomized trial. *Radiotherapy and Oncology* 1997;43:29–37. [https://doi.org/10.1016/S0167-8140\(97\)00048-0](https://doi.org/10.1016/S0167-8140(97)00048-0).
- [36] Fountzilas G, Ciuleanu E, Dafni U, Plataniotis G, Kalogera-Fountzila A, Samantas E, et al. Concomitant radiochemotherapy vs radiotherapy alone in patients with head and neck cancer: A Hellenic Cooperative Oncology Group Phase III Study. *Medical Oncology* 2004;21:95–107.
 - [37] Kumar S, Datta NR, Nagar Y, Lal P, Singh S, Rastogi N, et al. A three-arm randomized trial comparing neo-adjuvant or concurrent weekly cisplatin to radiotherapy alone for locally advanced head and neck squamous cell cancer (HNSCC). *European Journal of Cancer* 2011;47 (S1):547.
 - [38] Adjuvant chemotherapy for advanced head and neck squamous carcinoma. Final report of the Head and Neck Contracts Program. *Cancer* 1987;60:301–11. [https://doi.org/10.1002/1097-0142\(19870801\)60:3<301::aid-cnrcr2820600306>3.0.co;2-v](https://doi.org/10.1002/1097-0142(19870801)60:3<301::aid-cnrcr2820600306>3.0.co;2-v).
 - [39] Salvajoli J, Morioka H, Trippe N, Kowalski L. A randomized trial of neoadjuvant vs concomitant chemotherapy vs radiotherapy alone in the treatment of stage IV head and neck squamous cell carcinoma. *European Archives of Oto-Rhino-Laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : Affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery* 1992;249:211–5.
 - [40] Adelstein DJ, Li Y, Adams GL, Wagner H, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *Journal of Clinical Oncology* 2003;21:92–8. <https://doi.org/10.1200/JCO.2003.01.008>.
 - [41] Ghi MG, Paccagnella A, Ferrari D, Foa P, Alterio D, Codeca C, et al. Induction TPF followed by concomitant treatment versus concomitant treatment alone in locally advanced head and neck cancer. A phase II-III trial. *Annals of Oncology* 2017;28:2206–12. <https://doi.org/10.1093/annonc/mdx299>.
 - [42] Tobias JS, Monson K, Gupta N, Macdougall H, Glaholm J, Hutchison I, et al. Chemoradiotherapy for locally advanced head and neck cancer: 10-year follow-up of the UK Head and Neck (UKHAN1) trial. *The Lancet Oncology* 2010;11:66–74. [https://doi.org/10.1016/S1470-2045\(09\)70306-7](https://doi.org/10.1016/S1470-2045(09)70306-7).
 - [43] Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy - Results of a multicentric randomized German trial in advanced head-and-neck cancer. *International Journal of Radiation Oncology Biology Physics* 2001;50:1161–71. [https://doi.org/10.1016/S0360-3016\(01\)01544-9](https://doi.org/10.1016/S0360-3016(01)01544-9).
 - [44] Szpirglas H, Nizri D, Marneur M, Lacoste J, Benslama L. Neoadjuvant chemotherapy. A randomized trial before radiotherapy in oral and oropharyngeal carcinomas: end results. *Proceedings of the 2nd international head and neck oncology research conference*. Ghedini Ed, Berkeley: Kugler Publications; 1988, p. 261–4.
 - [45] Hussey DH, Abrams JP. Combined therapy in advanced head and neck cancer: hydroxyurea and radiotherapy. *Progress in Clinical Cancer* 1975;6:79–86.
 - [46] Giglio R, Mickiewicz E, Pradier R, Roth B, Gatica G, Califano L, et al. No recurrence beyond the second year of follow-up in inoperable stage III and IV squamous cell carcinoma of the head and neck patients (IOHN). Final report of a randomized trial of alternating chemotherapy (CT) + hyperfractionated radiotherapy (RT) vs RT. *Proc Am Soc Clin Oncol* 1999;15:317.
 - [47] Soria JC, Mauguén A, Reck M, Sandler AB, Saijo N, Johnson DH, et al. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. *Annals of Oncology* 2013;24:20–30. <https://doi.org/10.1093/annonc/mds590>.
 - [48] Baujat B, Mahé C, Pignon J-P, Hill C. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. *Stat Med* 2002;21:2641–52. <https://doi.org/10.1002/sim.1221>.
 - [49] Bezwoda WR, de Moor NG, Derman DP. Treatment of advanced head and neck cancer by means of radiation therapy plus chemotherapy--a randomised trial. *Medical and Pediatric Oncology* 1979;6:353–8. <https://doi.org/10.1002/mpo.2950060412>.
 - [50] Nissenbaum M, Browde S, Bezwoda WR, de Moor NG, Derman DP. Treatment of advanced head and neck cancer: multiple daily dose fractionated radiation therapy and sequential multimodal treatment approach. *Medical and Pediatric Oncology* 1984;12:204–8. <https://doi.org/10.1002/mpo.2950120312>.
 - [51] Weissler MC, Melin S, Sailer SL, Qaqish BF, Rosenman JG, Pillsbury HC 3rd. Simultaneous chemoradiation in the treatment of advanced head and neck cancer. *Archives of Otolaryngology--Head & Neck Surgery* 1992;118:806–10.

- [52] Kumar S, Datta NR, Ahuja RC, Mali HR, Agarwal GN, Ayyagari S. Feasibility of non-cisplatin-based induction chemotherapy and concurrent chemoradiotherapy in advanced head and neck cancer. *Acta Oncologica* (Stockholm, Sweden) 1996;35:721–5. <https://doi.org/10.3109/02841869609084005>.
- [53] Richard JM, Sancho H, Lepintre Y, Rodary J, Pierquin B. Intra-arterial methotrexate chemotherapy and telecobalt therapy in cancer of the oral cavity and oropharynx. *Cancer* 1974;34:491–6. [https://doi.org/10.1002/1097-0142\(197409\)34:3<491::AID-CNCR2820340303>3.0.CO;2-G](https://doi.org/10.1002/1097-0142(197409)34:3<491::AID-CNCR2820340303>3.0.CO;2-G).
- [54] Fazekas J, Sommer C, Kramer S. Adjuvant intravenous methotrexate or definitive radiotherapy alone for advanced squamous cancers of the oral cavity, oropharynx, supraglottic larynx or hypopharynx. Concluding report of an RTOG randomized trial on 638 patients. *International Journal of Radiation Oncology, Biology, Physics* 1980;6:533–41. [https://doi.org/10.1016/0360-3016\(80\)90379-X](https://doi.org/10.1016/0360-3016(80)90379-X).
- [55] Jortay A, Demard F, Dalesio O, Blanchet C, Desautly A, Gehanno C, et al. A randomized EORTC study on the effect of preoperative polychemotherapy in pyriform sinus carcinoma treated by pharyngolaryngectomy and irradiation. Results from 5 to 10 years. *Acta Chirurgica Belgica* 1990;90:115–22.
- [56] Pearlman NW, Johnson FB, Braun TJ, Kennaugh RC, Spofford BF, Borlase BC, et al. A prospective study of preoperative chemotherapy and split-course irradiation for locally advanced or recurrent oral/pharyngeal squamous carcinoma. *American Journal of Clinical Oncology* 1985;8:490–6. <https://doi.org/10.1097/00000421-198512000-00008>.
- [57] Richard J, Kramer A, Molinari R, Lefebvre J, Blanchet F, Jortay A, et al. Randomised EORTC Head and Neck Cooperative Group trial of preoperative intra-arterial chemotherapy in oral cavity and oropharynx carcinoma. *European Journal of Cancer* 1991;27:821–7. [https://doi.org/10.1016/0277-5379\(91\)90125-W](https://doi.org/10.1016/0277-5379(91)90125-W).
- [58] Holoye PY, Grossman TW, Toohill RJ, Kun LE, Byhardt RW, Duncavage JA, et al. Randomized study of adjuvant chemotherapy for head and neck cancer. *Otolaryngology--Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery* 1985;93:712–7.
- [59] Kun LE, Toohill RJ, Holoye PY, Duncavage JA, Byhardt RW, Ritch PS, et al. A randomized study of adjuvant chemotherapy for cancer of the upper aerodigestive tract. *International Journal of Radiation Oncology*Biological*Physics* 1986;12:173–8. [https://doi.org/10.1016/0360-3016\(86\)90090-8](https://doi.org/10.1016/0360-3016(86)90090-8).
- [60] Schuller DE, Metch B, Stein DW, Mattox D, McCracken JD. Preoperative chemotherapy in advanced resectable head and neck cancer: final report of the Southwest Oncology Group. *The Laryngoscope* 1988;98:1205–11. <https://doi.org/10.1288/00005537-198811000-00011>.
- [61] Mazon J, Martin M, Brun B, Grimard L, Lelièvre G, Vergnes L, et al. Induction chemotherapy in head and neck cancer: Results of a phase III trial. *Head & Neck* 1992;14:85–91. <https://doi.org/10.1002/hed.2880140202>.
- [62] Brunin F, Rodriguez J, Jaulerry C, Jouve M, Pontvert D, Point D, et al. Induction chemotherapy in advanced head and neck cancer. Preliminary results of a randomized study. *Acta Oncologica* 1989;28:61–5. <https://doi.org/10.3109/02841868909111183>.
- [63] Jaulerry C, Rodriguez J, Brunin F, Jouve M, Mosseri V, Point D, et al. Induction chemotherapy in advanced head and neck tumors: Results of two randomized trials. *International Journal of Radiation Oncology*Biological*Physics* 1992;23:483–9. [https://doi.org/10.1016/0360-3016\(92\)90002-Y](https://doi.org/10.1016/0360-3016(92)90002-Y).
- [64] Maipang T, Maipang M, Geater A, Panjapiyakul C, Watanaarepornchai S, Punperk S. Combination chemotherapy as induction therapy for advanced resectable head and neck cancer. *Journal of Surgical Oncology* 1995;59:80–5. <https://doi.org/10.1002/jso.2930590203>.
- [65] Toohill R, Duncavage J, Malin Thomas, Wilson F, Haas Judith, ANDERSON T, et al. The effects of delay in standard treatment due to induction chemotherapy in two randomized prospective studies. *The Laryngoscope* 1987;97:407–12. <https://doi.org/10.1288/00005537-198704000-00002>.
- [66] Toohill R, Anderson T, Byhardt R, Cox J, Duncavage J, Grossman T, et al. Cisplatin and fluorouracil as neoadjuvant therapy in head and neck cancer. *Archives of Otolaryngology - Head and Neck Surgery* 1987;113:758–61.
- [67] Lewin F, Damber L, Jonsson H, Andersson T, Berthelsen A, Biörklund A, et al. Neoadjuvant chemotherapy with cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the head and neck: A randomized phase III study. *Radiotherapy and Oncology* 1997;43:23–8. [https://doi.org/10.1016/S0167-8140\(97\)01922-1](https://doi.org/10.1016/S0167-8140(97)01922-1).
- [68] Martin M, Hazan A, Vergnes L, Peytral C, Mazon JJ, S  n  chaut JP, et al. Randomized study of 5 fluorouracil and cis platin as neoadjuvant therapy in head and neck cancer: A preliminary report. *International Journal of Radiation Oncology*Biological*Physics* 1990;19:973–5. [https://doi.org/10.1016/0360-3016\(90\)90021-B](https://doi.org/10.1016/0360-3016(90)90021-B).

- [69] Martin M, Vergnes L, Lelièvre G, Michel-Langlet P, Peytral C, Mazon J, et al. A randomized study of CDDP and 5-FU as neoadjuvant chemotherapy in head and neck cancer: an interim analysis. In: Banzet P, Holland J, Khayat D, Weil M, editors. *Cancer treatment: an update*. Springer-V, Paris: 1994, p. 214–8.
- [70] Paccagnella A, Orlando A, Marchiori C, Zorat PL, Cavaniglia G, Sileni VC, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: A study by the Gruppo di Studio sui Tumori della Testa e del Collo. *Journal of the National Cancer Institute* 1994;86:265–72. <https://doi.org/10.1093/jnci/86.4.265>.
- [71] Zorat PL, Paccagnella A, Cavaniglia G, Loreggian L, Gava A, Mione CA, et al. Randomized phase III trial of neoadjuvant chemotherapy in head and neck cancer: 10-year follow-up. *Journal of the National Cancer Institute* 2004;96:1714–7. <https://doi.org/10.1093/jnci/djh306>.
- [72] Dalley D, Beller E, Aroney R, Dewar J, Page J, Philip R, et al. The value of chemotherapy (CT) prior to definitive local therapy (DTL) in patients with locally advanced squamous cell carcinoma (SCC) of the head and neck (HN). *Proc Am Soc Clin Oncol* 1995;14:297.
- [73] Tejedor M, Murias A, Soria P, Aguiar J, Salinas J, Hernandez MA, et al. Induction chemotherapy with carboplatin and fluorouracil in advanced head and neck cancer. A randomized study. *American Journal of Clinical Oncology* 1992;15:417–21.
- [74] Gedouin D, Desprez P, Perron JJ, Fleury F, Leclech G, Miglianico L, et al. Cancers de la base de langue et de l'hypopharynx: résultats d'un essai multicentrique randomisé de chimiothérapie avant traitement locoregional. *Bulletin Du Cancer/Radiothérapie* 1996;83:104–7. [https://doi.org/10.1016/0924-4212\(96\)85320-5](https://doi.org/10.1016/0924-4212(96)85320-5).
- [75] Di Blasio B, Barbieri W, Bozzetti A, Iotti C, Di Sarra S, Cocconi G. A prospective randomized trial in resectable head and neck carcinoma: loco-regional treatment with and without neoadjuvant chemotherapy. *Proc Am Soc Clin Oncol* 1994;13:279.
- [76] Gehanno P, Depondt J, Peynegre R, Peytral C, Martin M, Baillet F, et al. Neoadjuvant combination of carboplatin and 5-FU in head and neck cancer: A randomized study. *Annals of Oncology* 1992;3:43–6.
- [77] Depondt J, Gehanno P, Martin M, Lelièvre G, Guerrier B, Peytral C, et al. Neoadjuvant chemotherapy with carboplatin/5-fluorouracil in head and neck cancer. *Oncology* 1993;50:23–7. <https://doi.org/10.1159/000227257>.
- [78] Volling P, Schroder M, Muller RP, Ebeling O, Quirin R, Stennert E. Induction chemotherapy in primary resectable head and neck tumors: A prospective randomized trial. *International Journal of Oncology* 1994;4:909–14. <https://doi.org/10.3892/ijo.4.4.909>.
- [79] Hasegawa Y, Matsuura H, Fukushima M, Kano M, Shimozato K. Potential suppression of distant and node metastasis by neoadjuvant chemotherapy in advanced head and neck cancer: result of a randomized trial. *Proc Am Soc Clin Oncol* 1996;15:318.
- [80] Paccagnella A, Ghi M, Loreggian L, Buffoli A, Koussis H, Mione C, et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: A phase II randomized study. *Annals of Oncology* 2010;21:1515–22. <https://doi.org/10.1093/annonc/mdp573>.
- [81] Cohen E, Karrison T, Kocherginsky M, Mueller J, Egan R, Huang CH, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. *Journal of Clinical Oncology* 2014;32:2735–43. <https://doi.org/10.1200/JCO.2013.54.6309>.
- [82] Zhong L-P, Zhang C-P, Ren G-X, Guo W, William Jr. WN, Sun J, et al. Randomized phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma. *Journal of Clinical Oncology* 2013;31:744–51. <https://doi.org/10.1200/JCO.2012.43.8820>.
- [83] Zhong L-P, Zhang C-P, Ren G-X, Guo W, William WN J, Hong C, et al. Long-term results of a randomized phase III trial of TPF induction chemotherapy followed by surgery and radiation in locally advanced oral squamous cell carcinoma. *Oncotarget* 2015;6:18707–14.
- [84] Eschwege F, Sancho-Garnier H, Gerard JP, Madelain M, DeSaulty A, Jortay A, et al. Ten-year results of randomized trial comparing radiotherapy and concomitant bleomycin to radiotherapy alone in epidermoid carcinomas of the oropharynx: experience of the European Organization for Research and Treatment of Cancer. *NCI Monographs* 1988;6:275–8.
- [85] Parvonen L-M, Parvonen M, Nordman E, Kortekangas AE. Combined bleomycin treatment and radiation therapy in squamous cell carcinoma of the head and neck region. *Acta Radiologica Oncology* 1985;24:487–9. <https://doi.org/10.3109/02841868509134421>.
- [86] Vermund H, Kaalhus O, Winther F, Trausjø J, Thorud E, Harang R. Bleomycin and radiation therapy in squamous cell carcinoma of the upper aero-digestive tract: A phase III clinical trial. *International Journal*

- of Radiation Oncology, Biology, Physics 1985;11:1877–86. [https://doi.org/10.1016/0360-3016\(85\)90267-6](https://doi.org/10.1016/0360-3016(85)90267-6).
- [87] Gupta NK, Pointon RC, Wilkinson PM. A randomised clinical trial to contrast radiotherapy with radiotherapy and methotrexate given synchronously in head and neck cancer. *Clinical Radiology* 1987;38:575–81.
 - [88] Gupta NK, Swindell R. Concomitant methotrexate and radiotherapy in advanced head and neck cancer: 15-year follow-up of a randomized clinical trial. *Clinical Oncology* 2001;13:339–44. <https://doi.org/10.1053/clon.2001.9286>.
 - [89] Haselow R, Warshaw M, Oken M, Adams G, Aughey J, Cooper J, et al. Radiation alone versus radiation with weekly low dose cisplatin in unresectable cancer of the head and neck. *Head and Neck Cancer*. Vol II, Philadelphia, PA: BC Decker; 1990, p. 279–81.
 - [90] Quon H, Leong T, Haselow R, Leipzig B, Cooper J, Forastiere A. Phase III study of radiation therapy with or without cis-platinum in patients with unresectable squamous or undifferentiated carcinoma of the head and neck: an intergroup trial of the Eastern Cooperative Oncology Group (E2382). *International Journal of Radiation Oncology, Biology, Physics* 2011;81:719–25. <https://doi.org/10.1016/j.ijrobp.2010.06.038>.
 - [91] Browman GP, Cripps C, Hodson DI, Eapen L, Sathya J, Levine MN. Placebo-controlled randomized trial of infusional fluorouracil during standard radiotherapy in locally advanced head and neck cancer. *Journal of Clinical Oncology* 1994;12:2648–53. <https://doi.org/10.1200/jco.1994.12.12.2648>.
 - [92] Wendt TG, Grabenbauer GG, Rödel CM, Thiel H-J, Aydin H, Rohloff R, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: A randomized multicenter study. *Journal of Clinical Oncology* 1998;16:1318–24.
 - [93] Smid L, Lesnicar H, Zakotnik B, Soba E, Budihna M, Furlan L, et al. Radiotherapy, combined with simultaneous chemotherapy with mitomycin C and bleomycin for inoperable head and neck cancer--preliminary report. *International Journal of Radiation Oncology, Biology, Physics* 1995;32:769–75.
 - [94] Kapstad B, Bang G, Rennaes S, Dahler A. Combined preoperative treatment with cobalt and bleomycin in patients with head and neck carcinoma--a controlled clinical study. *International Journal of Radiation Oncology, Biology, Physics* 1978;4:85–9.
 - [95] Morita K. Clinical significance of radiation therapy combined with chemotherapy. *Strahlentherapie* 1980;156:228–33.
 - [96] Weissberg JB, Son YH, Papac RJ, Sasaki C, Fischer DB, Lawrence R, et al. Randomized clinical trial of mitomycin C as an adjunct to radiotherapy in head and neck cancer. *International Journal of Radiation Oncology, Biology, Physics* 1989;17:3–9.
 - [97] Keane T, Cummings B, O'Sullivan B, Payne D, Rawlinson E, Mackenzie R, et al. A randomized trial of radiation therapy compared to split course radiation therapy combined with mitomycin C and 5 fluorouracil as initial treatment for advanced laryngeal and hypopharyngeal squamous carcinoma. *International Journal of Radiation Oncology, Biology, Physics* 1993;25:613–8. [https://doi.org/10.1016/0360-3016\(93\)90006-H](https://doi.org/10.1016/0360-3016(93)90006-H).
 - [98] Bachaud J-M, Cohen-Jonathan E, Alzieu C, David J-M, Serrano E, Daly-Schveitzer N. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: Final report of a randomized trial. *International Journal of Radiation Oncology Biology Physics* 1996;36:999–1004. [https://doi.org/10.1016/S0360-3016\(96\)00430-0](https://doi.org/10.1016/S0360-3016(96)00430-0).
 - [99] Haffty BG, Son YH, Sasaki CT, Papac R, Fischer D, Rockwell S, et al. Mitomycin C as an adjunct to postoperative radiation therapy in squamous cell carcinoma of the head and neck: Results from two randomized clinical trials. *International Journal of Radiation Oncology, Biology, Physics* 1993;27:241–50. [https://doi.org/10.1016/0360-3016\(93\)90234-M](https://doi.org/10.1016/0360-3016(93)90234-M).
 - [100] Merlano M, Vitale V, Rosso R, Benasso M, Corvo R, Cavallari M, et al. Treatment of advanced squamous-cell carcinoma of the head and neck with alternating chemotherapy and radiotherapy. *New England Journal of Medicine* 1992;327:1115–21.
 - [101] Merlano M, Benasso M, Corvò R, Rosso R, Vitale V, Blengio F, et al. Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck. *J Natl Cancer Inst* 1996;88:583–9. <https://doi.org/10.1093/jnci/88.9.583>.
 - [102] Adelstein DJ, Lavertu P, Saxton JP, Secic M, Wood BG, Wanamaker JR, et al. Mature results of a Phase III randomized trial comparing concurrent chemoradiotherapy with radiation therapy alone in patients with Stage III and IV squamous cell carcinoma of the head and neck. *Cancer* 2000;88:876–83. [https://doi.org/10.1002/\(SICI\)1097-0142\(20000215\)88:4<876::AID-CNCR19>3.0.CO;2-Y](https://doi.org/10.1002/(SICI)1097-0142(20000215)88:4<876::AID-CNCR19>3.0.CO;2-Y).

- [103] Brizel DM, Albers ME, Fisher SR, Scher RL, Richtsmeier WJ, Hars V, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *The New England Journal of Medicine* 1998;338:1798–804. <https://doi.org/10.1056/NEJM199806183382503>.
- [104] Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. *Journal of Clinical Oncology* 2000;18:1458–64. <https://doi.org/10.1200/JCO.2000.18.7.1458>.
- [105] Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *Journal of Clinical Oncology* 2004;22:69–76. <https://doi.org/10.1200/JCO.2004.08.021>.
- [106] Budach V, Stuschke M, Budach W, Baumann M, Geismar D, Grabenbauer G, et al. Hyperfractionated accelerated chemoradiation with concurrent fluorouracil-mitomycin is more effective than dose-escalated hyperfractionated accelerated radiation therapy alone in locally advanced head and neck cancer. *Journal of Clinical Oncology* 2005;23:1125–35. <https://doi.org/10.1200/JCO.2005.07.010>.
- [107] Bernier J, Dometge C, Ozsahin M, Matuszewska K, Lefèbvre J-L, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *New England Journal of Medicine* 2004;350:1945–52. <https://doi.org/10.1056/NEJMoa032641>.
- [108] Huguenin P, Beer KT, Allal A, Rufibach K, Friedli C, Davis JB, et al. Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. *Journal of Clinical Oncology* 2004;22:4665–73. <https://doi.org/10.1200/JCO.2004.12.193>.
- [109] Ghadjar P, Simcock M, Studer G, Allal AS, Ozsahin M, Bernier J, et al. Concomitant cisplatin and hyperfractionated radiotherapy in locally advanced head and neck cancer: 10-year follow-up of a randomized phase III trial (SAKK 10/94). *International Journal of Radiation Oncology Biology Physics* 2012;82:524–31.
- [110] Cooper J, Pajak T, Forastiere A, Jacobs J, Campbell B, Saxman S, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *New England Journal of Medicine* 2004;350:1937–44. <https://doi.org/10.1056/NEJMoa032646>.
- [111] Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: Postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *International Journal of Radiation Oncology Biology Physics* 2012;84:1198–205. <https://doi.org/10.1016/j.ijrobp.2012.05.008>.
- [112] Grau C, Prakash Agarwal J, Jabeen K, Rab Khan A, Abeyakoon S, Hadjieva T, et al. Radiotherapy with or without mitomycin c in the treatment of locally advanced head and neck cancer: results of the IAEA multicentre randomised trial. *Radiotherapy and Oncology* 2003;67:17–26. [https://doi.org/10.1016/S0167-8140\(03\)00020-3](https://doi.org/10.1016/S0167-8140(03)00020-3).
- [113] Bourhis J, Lapeyre M, Tortochaux J, Lusinchi A, Etessami A, Ducourtieux M, et al. Accelerated radiotherapy and concomitant high dose chemotherapy in non resectable stage IV locally advanced HNSCC: results of a GORTEC randomized trial. *Radiotherapy and Oncology : Journal of the European Society for Therapeutic Radiology and Oncology* 2011;100:56–61. <https://doi.org/10.1016/j.radonc.2011.07.006>.
- [114] Lartigau E, Giralt J, Glassman P, Lawton A, von Roemeling R. A phase III double-blind randomized placebo controlled study of porfiromycin and radiation therapy in patients with head and neck cancer. *International Journal of Radiation Oncology*Biophysics* 2002;54 (S2):74. [https://doi.org/10.1016/S0360-3016\(02\)03184-X](https://doi.org/10.1016/S0360-3016(02)03184-X).
- [115] Zakotnik B, Budihna M, Smid L, Soba E, Strojanc P, Fajdiga I, et al. Patterns of failure in patients with locally advanced head and neck cancer treated postoperatively with irradiation or concomitant irradiation with Mitomycin C and Bleomycin. *International Journal of Radiation Oncology, Biology, Physics* 2007;67:685–90. <https://doi.org/10.1016/j.ijrobp.2006.09.018>.
- [116] Ruo Redda MG, Ragona R, Ricardi U, Beltramo G, Rampino M, Gabriele P, et al. Radiotherapy alone or with concomitant daily low-dose carboplatin in locally advanced, unresectable head and neck cancer: definitive results of a phase III study with a follow-up period of up to ten years. *Tumori* 2010;96:246–53.
- [117] Sharma A, Mohanti B, Thakar A, Bahadur S, Bhasker S. Concomitant chemoradiation versus radical radiotherapy in advanced squamous cell carcinoma of oropharynx and nasopharynx using weekly cisplatin: A phase II randomized trial. *Annals of Oncology* 2010;21:2272–7. <https://doi.org/10.1093/annonc/mdq219>.

- [118] Bensadoun R-J, Bénézy K, Dassonville O, Magné N, Poissonnet G, Ramaïoli, et al. French multicenter phase III randomized study testing concurrent twice-a-day radiotherapy and cisplatin/5-fluorouracil chemotherapy (BiRCF) in unresectable pharyngeal carcinoma: Results at 2 years (FNCLCC-GORTEC). *International Journal of Radiation Oncology Biology Physics* 2006;64:983–94.
<https://doi.org/10.1016/j.ijrobp.2005.09.041>.
- [119] Racadot S, Mercier M, Dussart S, Dessard-Diana B, Bensadoun R-J, Martin M, et al. Randomized clinical trial of post-operative radiotherapy versus concomitant carboplatin and radiotherapy for head and neck cancers with lymph node involvement. *Radiotherapy and Oncology* 2008;87:164–72.
<https://doi.org/10.1016/j.radonc.2007.12.021>.
- [120] Argiris A, Karamouzis M, Johnson J, Heron D, Myers E, Eibling D, et al. Long-term results of a phase III randomized trial of postoperative radiotherapy with or without carboplatin in patients with high-risk head and neck cancer. *Laryngoscope* 2008;118:444–9.
<https://doi.org/10.1097/MLG.0b013e31815b48f4>.
- [121] Domenge C, Marandas P, Vignoud J, Beauvillain de Montreuil C, Prevost B, Lefebvre J, et al. Post-surgical adjuvant chemotherapy in extracapsular spread invaded lymph node (N+R+) of epidermoid carcinoma of the head and neck: a randomized multicentric trial. *Second international conference on head and neck cancer. American Society of Head and Neck Surgery* 1988;74.
- [122] Laramore GE, Scott CB, al-Sarraf M, Haselow RE, Ervin TJ, Wheeler R, et al. Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report on Intergroup Study 0034. *International Journal of Radiation Oncology, Biology, Physics* 1992;23:705–13.
- [123] Yoshino K, Sato T, Nakai Y, Tanabe M, Matsunaga T, Kozuka T, et al. A comparative clinical study of adjuvant chemotherapy of tumors in the head and neck areas by means of HCFU. *Jap J Cancer & chemotherapy* 1991;18:2581–8.
- [124] Rao RS, Parikh DM, Parikh HK, Bhansali MB, Deshmene VH, Fakih AR. Perioperative chemotherapy in patients with oral cancer. *American Journal of Surgery* 1994;168:262–7.
- [125] Kotani A, Sunada O, Tamura M, Takaku S, Kobayashi A, Asakura A, et al. Multiple cooperative study of UFT-adjuvant chemotherapy for malignant tumor in the jaw and oral cavities. *Jap J Cancer & chemotherapy* 1994;21:987–92.
- [126] A randomized trial of combined multidrug chemotherapy and radiotherapy in advanced squamous cell carcinoma of the head and neck. An interim report from the SECOG participants. *European Journal of Surgical Oncology : The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 1986;12:289–95.
- [127] Buffoli A, Morrica B, Frata P, La Face B. Chemo-radiotherapy in advanced head and neck tumors. Personal experience. *La Radiologia medica* 1992;83:636–40.
- [128] Merlano M, Corvo R, Margarino G, Benasso M, Rosso R, Sertoli MR, et al. Combined chemotherapy and radiation therapy in advanced inoperable squamous cell carcinoma of the head and neck. The final report of a randomized trial. *Cancer* 1991;67:915–21.
- [129] Taylor SG, Murthy AK, Vannetzel J-M, Colin P, Dray M, Caldarelli DD, et al. Randomized comparison of neoadjuvant cisplatin and fluorouracil infusion followed by radiation versus concomitant treatment in advanced head and neck cancer. *Journal of Clinical Oncology* 1994;12:385–95.
- [130] Adelstein D, Sharan V, Earle A, Shah A, Vlastou C, Haria C, et al. Simultaneous versus sequential combined technique therapy for squamous cell head and neck cancer. *Cancer* 1990;65:1685–91.
- [131] Adelstein D, Sharan V, Earle A, Shah A, Vlastou C, Haria C, et al. Long-term follow-up of a prospective randomized trial comparing simultaneous and sequential chemoradiotherapy for squamous cell head and neck cancer. *Adjuvant therapy of cancer VII, Philadelphia, PA: Lippincott Company; 1993, p. 82–91.*