META-ANALYSIS OF CHEMOTHERAPY IN NASO-PHARYNX CARCINOMA

Second update with trials up to 2016

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SECRETARIAT

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Addendum to the statistical analysis plan prepared before the analyses for the investigator meeting (October 24th, 2019)

Because of the low number of trials studying altered fractionation with available data (2 trials, 768 patients) or the absence of trials studying anti-EGFR with available data (only 2 trials with 197 patients identified), the anti-EGFR and the altered fractionation trials will not be included in the present meta-analysis.

Data are available for 28 trials (8221 patients) for the chemotherapy question.

Two trials (NPC 9901 and 0501) had a second randomization comparing conventional fractionation (CF) radiotherapy to accelerated fractionation (AF) radiotherapy. In both cases, separate strata will be considered for each modality of radiotherapy. For the trial NPC 0501, a third stratum which corresponds to the group of patients who received CF outside of the part randomizing CF vs. AF will be considered. The NPC 0501 trial compared two induction regimens (cisplatin + 5FU and cisplatin plus capecitabine), for the purpose of this meta-analysis, the two induction arms will be pooled.

Because one trial (222 patients) with a 2x2 design allowed to perform 6 distinct comparisons, the number of patients included in the network is 8665. The corresponding network is described in figure 1. Overall, 36 strata (i.e. trials + strata of trials) will be considered.

Eight modalities of treatments are compared with 13 direct comparisons possible:
-   Radiotherapy (RT)
-   Radiotherapy + concomitant chemotherapy (CRT)
-   Radiotherapy + concomitant and adjuvant chemotherapy (CRT-AC)
-   Radiotherapy + induction chemotherapy (IC-RT)
-   Radiotherapy + adjuvant chemotherapy (RT-AC)
-   Radiotherapy + induction with taxane (e.g. TPF) and concomitant chemotherapy (IC-CRT)
-   Radiotherapy + induction (others) and concomitant chemotherapy (IC-CRT)
-   Radiotherapy + induction and adjuvant chemotherapy (IC-RT-AC)

The standard meta-analysis will be performed on 26 trials (7302 patients) and 30 strata studying the addition of chemotherapy and 10 types of comparisons (see table below) of the 8 treatments above. The two trials comparing two chemotherapy timings which performed different comparisons (induction vs. adjuvant with both arms receiving concomitant chemotherapy for one and induction vs. concomitant with both arms receiving adjuvant chemotherapy for the other) were excluded of this part of the study.

For the standard analysis, we propose to pool the 10 comparisons in 5 categories, to study the heterogeneity between these categories and within each category. We will also draw stratified survival curves by arm for each of these 5 categories.

Simplified comparison	Detailed comparison	No. patients	No. RCTs
Concomitant CT	CRT vs RT	806	4
CRT (± IC or AC) vs	CRT-AC vs RT-AC	111	1
RT(± IC or AC)	IC-CRT vs IC-RT	917	2
Subtotal		1 834	7
Induction CT in pts treated by RT	IC-RT vs RT	753	3
IC-RT(± AC) vs RT	IC-RT-AC vs RT	77	1
Subtotal		830	4
Adjuvant CT	RT-AC vs RT	267	2
(C)RT-AC vs (C)RT	CRT-AC vs CRT	725	3
Subtotal		992	3
Concomitant and adjuvant CT	CRT-AC vs RT	1 267	6
CRT-AC vs RT			
Subtotal		1 267	6
Induction CT in pts treated by CRT	IC-CRT vs CRT	1 435	3
IC-CRT vs CRT ± taxane	IC(T+)-CRT vs CRT	9442	5
Subtotal		2 379	8
Total		**7 302**	**30**

Sensitivity analyses

The analysis excluding old trials and/or trials using drugs not used anymore was **changed in excluding trials using drugs not currently used in locally advanced nasopharynx carcinoma**. The list of such drugs includes: Bleomycin, Epirubicin, Floxuridine, Hydroxyurea, Oxaliplatin, Mitomicyn, Methotrexate, Vincristine and UFT.

This group corresponds to more recent trials and to more homogenous for imaging/staging, radiotherapy practices and treatment of recurrence.

For the standard meta-analysis, 18 trials, 4530 patients and 19 "strata" will be included. **We propose to use this population instead of the overall population for the subgroup analyses (i.e. study of interaction between covariates and treatment effect), because of its relevance** to today's practices.

For the network meta-analysis (Figures 2 and 3), we should add the 4 strata (2 trials, 1141 patients) comparing two timings of chemotherapy. This leads to 20 trials, 234 strata and 5671 patients (Figure 3). But two trials (238 patients, one compared IC-RT vs. RT and the other RT-AC vs. RT) correspond to **"dead" arms** (i.e. only connected to RT alone) (Figure 3) and to **simplify the network** we propose to exclude them, leading 18 trials, 21 strata and 5 433 patients.

Fig 1 Complete network

8,220 patients
8 modalities of treatment
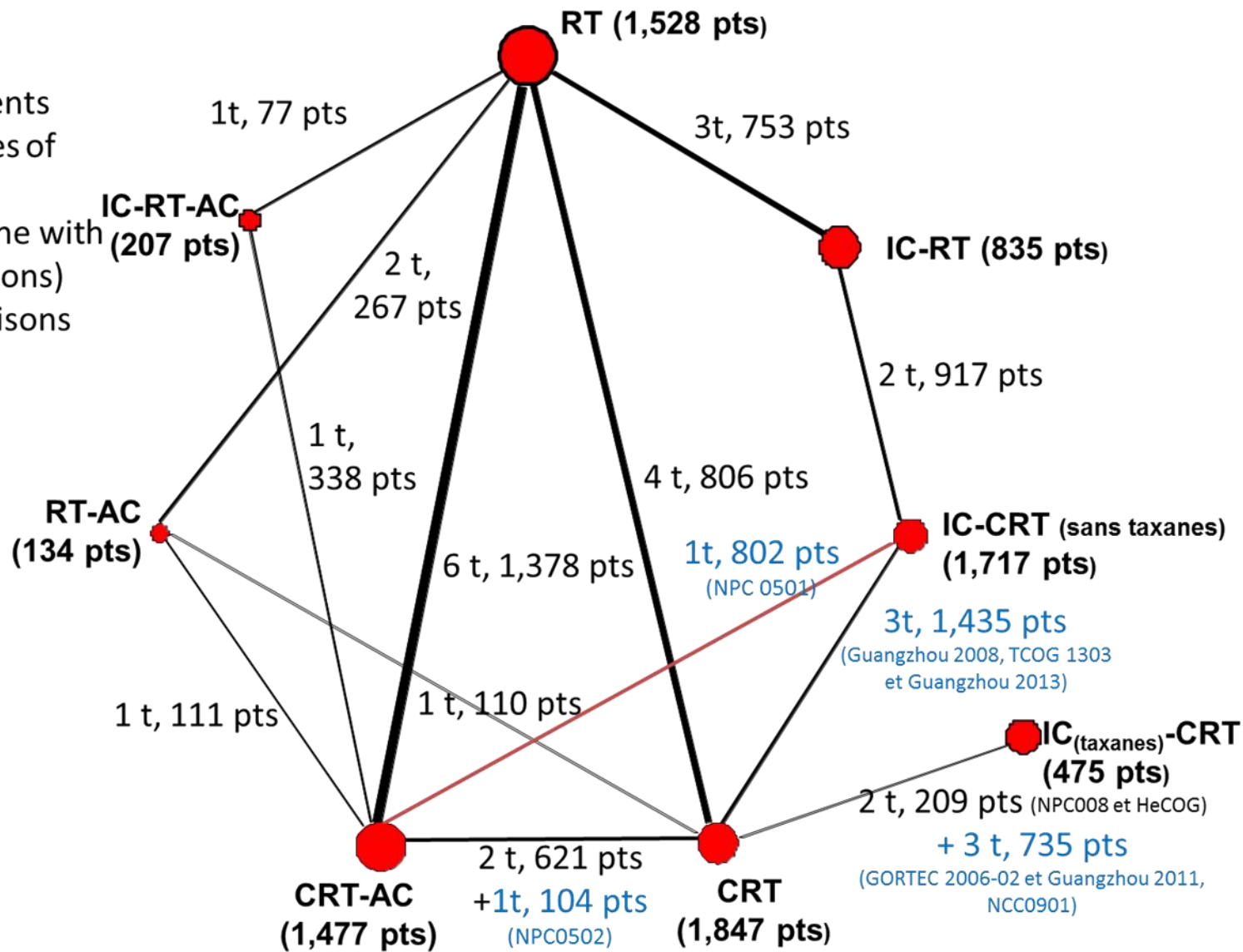28 trials (one with 6 comparisons)
13 comparisons

RT (1,528 pts)

1t, 77 pts

3t, 753 pts

IC-RT-AC (207 pts)

IC-RT (835 pts)

2 t, 267 pts

2 t, 917 pts

1 t, 338 pts

4 t, 806 pts

RT-AC (134 pts)

IC-CRT (sans taxanes) (1,717 pts)

6 t, 1,378 pts

1t, 802 pts (NPC 0501)

3t, 1,435 pts (Guangzhou 2008, TCOG 1303 et Guangzhou 2013)

1 t, 111 pts

1 t, 110 pts

IC(taxanes)-CRT (475 pts)

2 t, 209 pts (NPC008 et HeCOG)

+ 3 t, 735 pts (GORTEC 2006-02 et Guangzhou 2011, NCC0901)

CRT-AC (1,477 pts)

2 t, 621 pts
+1t, 104 pts (NPC0502)

CRT (1,847 pts)

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Fig 2: Exclusion of trial with "old" drug and without two isolated modalities
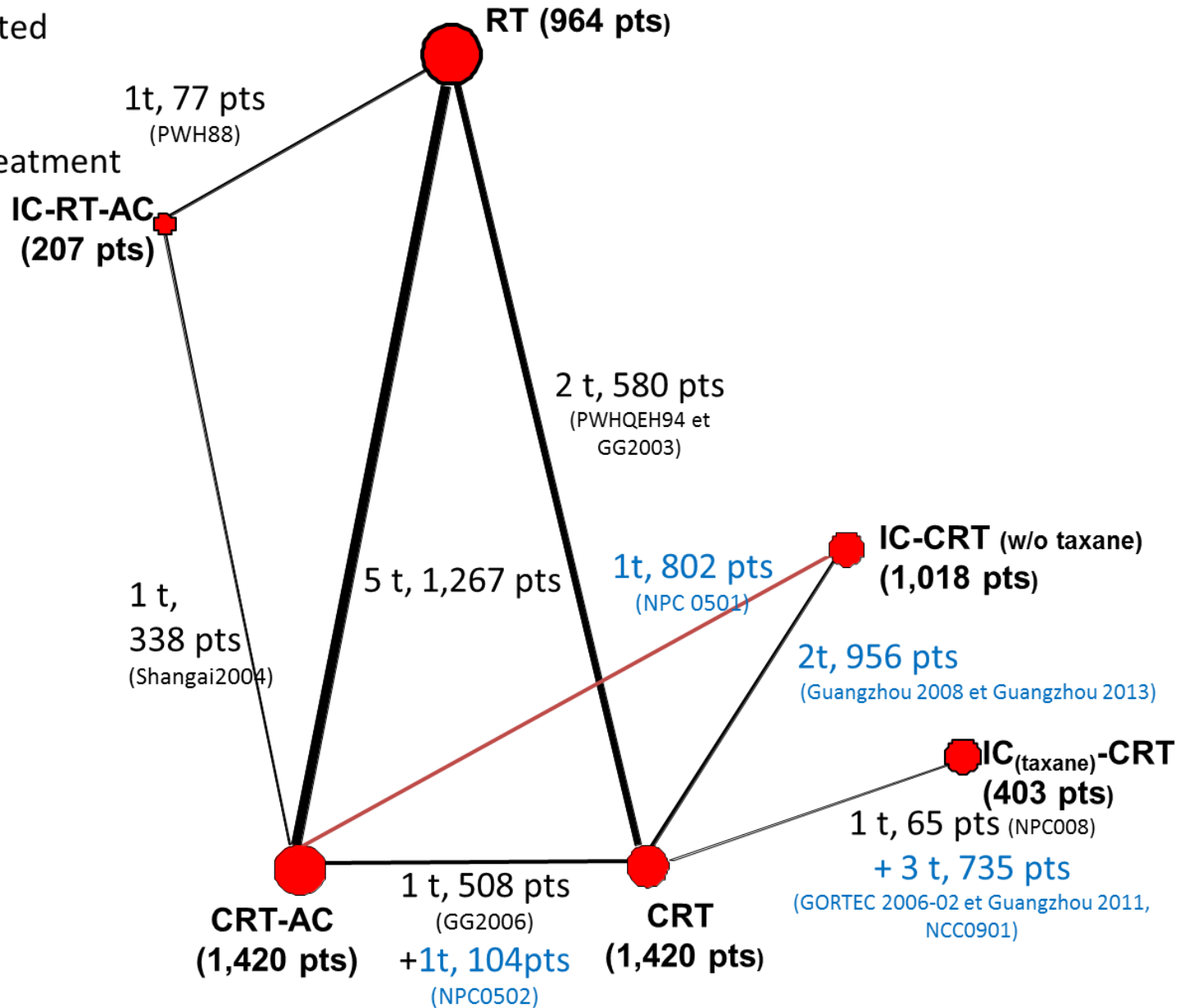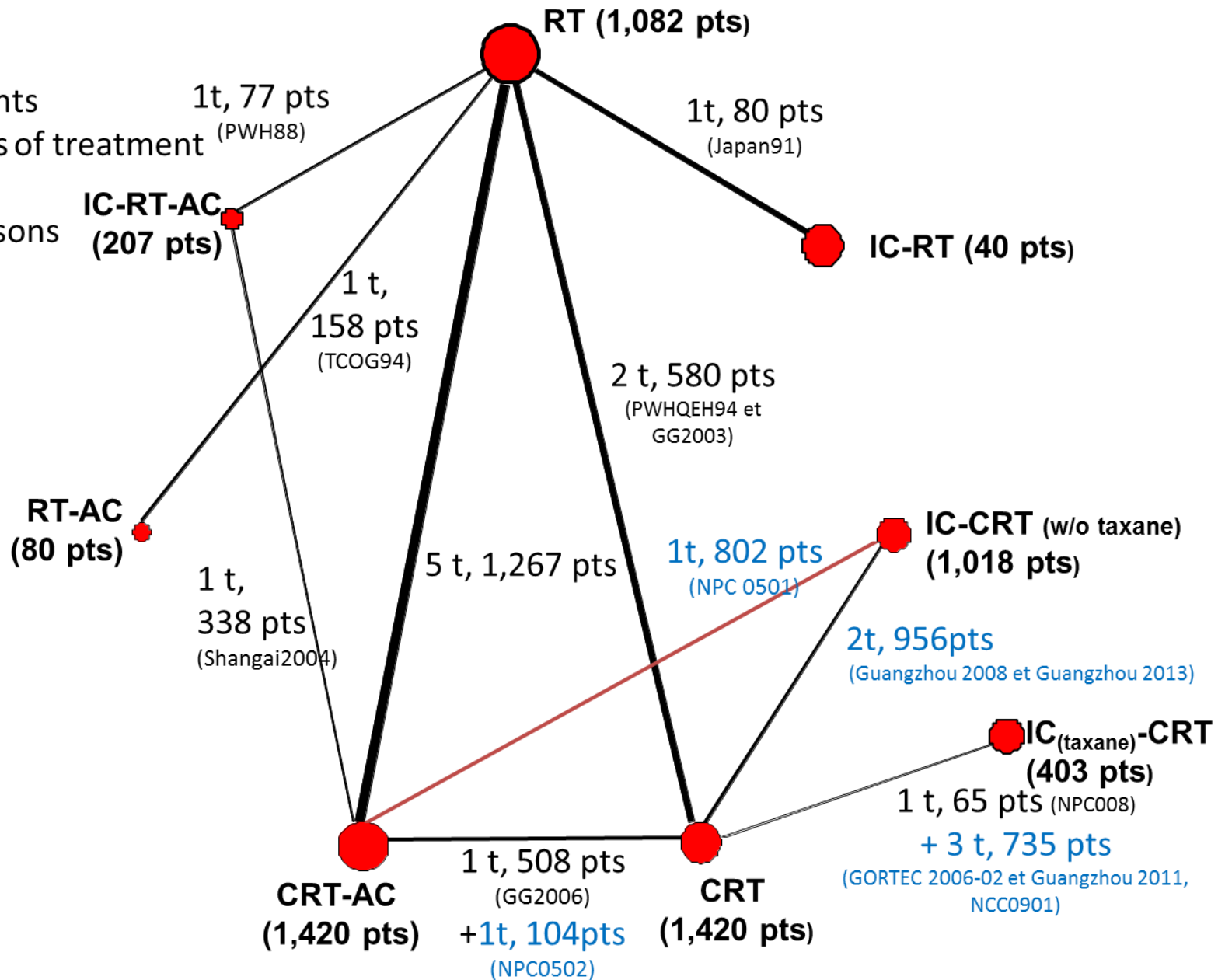5,432 patients
6 modalities of treatment
18 trials
8 comparisons

RT (964 pts)

1t, 77 pts (PWH88)

IC-RT-AC (207 pts)

2 t, 580 pts (PWHQEH94 et GG2003)

5 t, 1,267 pts

1t, 802 pts (NPC 0501)

IC-CRT (w/o taxane) (1,018 pts)

1 t, 338 pts (Shangai2004)

2t, 956 pts (Guangzhou 2008 et Guangzhou 2013)

IC(taxane)-CRT (403 pts)

1 t, 65 pts (NPC008)

+ 3 t, 735 pts (GORTEC 2006-02 et Guangzhou 2011, NCC0901)

CRT-AC (1,420 pts)

1 t, 508 pts (GG2006)

+1t, 104pts (NPC0502)

CRT (1,420 pts)

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Fig 3: exclusion of trials with old drug

5,670 patients
8 modalities of treatment
20 trials
10 comparisons

RT (1,082 pts)

1t, 77 pts (PWH88)

1t, 80 pts (Japan91)

IC-RT-AC (207 pts)

IC-RT (40 pts)

1 t, 158 pts (TCOG94)

2 t, 580 pts (PWHQEH94 et GG2003)

RT-AC (80 pts)

5 t, 1,267 pts

1t, 802 pts (NPC 0501)

IC-CRT (w/o taxane) (1,018 pts)

1 t, 338 pts (Shangai2004)

2t, 956pts (Guangzhou 2008 et Guangzhou 2013)

IC(taxane)-CRT (403 pts)

1 t, 65 pts (NPC008)

CRT-AC (1,420 pts)

1 t, 508 pts (GG2006)

+1t, 104pts (NPC0502)

CRT (1,420 pts)

+ 3 t, 735 pts (GORTEC 2006-02 et Guangzhou 2011, NCC0901)

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CONTENTS

1. INTRODUCTION AND BACKGROUND

Nasopharyngeal carcinoma (NPC) is pathologically, epidemiologically and clinically distinct from other head and neck cancers [1]. NPC is rare in USA and Western Europe. Epstein-Barr virus is strongly associated with NPC and non-keratinizing (differentiated or undifferentiated, i.e. WHO type II or III by past system) carcinomas are the most common forms of the disease. In addition to the Epstein-Barr virus, specific environmental (nitrosamine) and genetic factors are involved in the carcinogenesis of NPC. Most of the patients with NPC present with locally advanced stage, and a higher incidence of bilateral nodal involvement is observed as compared to patients with other head and neck cancers [1]. NPC are commonly treated by radiation therapy and chemotherapy. The meta-analysis of chemotherapy in nasopharyngeal carcinoma (MAC-NPC) has demonstrated the benefit of chemotherapy on overall survival when given concomitantly to radiotherapy (RT). This international project comprised eight trials initially and a total of 1 753 patients. With a median follow-up of 6 years, the pooled hazard ratio of death was 0.82 (95% confidence interval, 0.71– 0.94; $p = 0.006$), and a significant interaction was observed between the timing of chemotherapy and overall survival ($p = 0.005$), with the highest benefit resulting from concomitant chemotherapy [2].

A first update was done with trials up to 2010 [3] and included 4 806 patients from 19 trials, including one unpublished trial (VUMCA-95: International Nasopharynx Cancer Study Group, NCT00180973). One 2×2 design trial (222 patients) was counted twice (four comparisons) and another was split into two comparisons, leading to a total of 23 comparisons and 5 028 patients. The median follow-up was 7·7 years. The pooled hazard ratio of death was 0.79 (95% confidence interval, 0.73– 0.86; $p<0.0001$), corresponding to an absolute survival benefit of 6.3% at 5 years (95% confidence interval, 3.5– 9.1) The pooled hazard ratio of progression-free survival was 0.75 (95% confidence interval, 0.69– 0.81; $p<0.0001$). Statistical heterogeneity was observed among trials for overall survival ($p=0.087$, $I^2=30\%$), which was mainly related to the timing of chemotherapy ($p_{interaction}=0.012$) and no heterogeneity remained after taking this into account ($p=0.36$). The interaction between chemotherapy timing and chemotherapy effect was also significant for progression-free survival ($p_{interaction}=0.041$). The two regimen that yielded the largest benefit in terms of

survival were concomitant chemoradiotherapy and concomitant chemoradiotherapy followed by adjuvant chemotherapy.

Two ancillary projects were planned with this meta analysis: a network meta analysis and an analysis of surrogate markers for overall survival. The surrogate analysis demonstrated that PFS was a valid surrogate for overall survival [5].

Network-based meta-analysis, also known as mixed treatment comparisons (MTC), is a statistical method that deals with conditions where multiple treatments have been investigated that have not been compared altogether [4,6,7]. It permits evaluation of all possible pair-wise comparisons based on direct and indirect evidence, and ranking of the different treatments according to their relative efficacies. With the first MAC-NPC update data, a network meta-analysis was performed [4]. Overall 20 trials and 5,144 patients were included and seven treatment modalities were analysed. This study showed that the addition of adjuvant chemotherapy to CRT achieved the highest survival benefit and consistent improvement for all endpoints and showed that the addition of induction chemotherapy to CRT achieved the highest effect on distant control.

Since the publication of this meta-analysis, 21 additional trials have been identified, representing 4 582 patients. Ten trials (3 072 patients) [8–16] including one unpublished compared induction chemotherapy (CT) to none or to another type of induction CT or to other timing of CT with concomitant chemo-radiotherapy in most of them. Six other trials, all published in the Chinese literature, compared radiotherapy (RT) to the same RT plus concomitant CT. These trials should have been included in the previous meta-analysis but were not identified at that time [17–22]. One trial compared addition of both concomitant and adjuvant CT to RT [23]. The 7 trials investigating concomitant CT represent 913 patients. Two trials (197 patients) have focused on anti-EGFR therapies [23,47], and three trials (1°203 patients) on altered fractionation radiotherapy +/- chemotherapy (one unpublished trial) [12, 24], including one trial also included in the evaluation of induction CT (803 patients) [13]. One trial already included in the meta-analysis will also be considered (NPC9902, 189 patients) [26] in this comparison.

An update of the meta-analysis is therefore needed in order to :

- include all existing randomized trials (exhaustivity) to better evaluate the benefit of chemotherapy, especially looking at new induction CT regimens
- update the older trials to increase follow-up and gain both statistical power and information on long term survival
- study treatment related toxicity in order to balance the survival benefit by the increase in short and long term toxicity
- include other randomized trial such those trials evaluating anti-EGFR therapy or comparing radiotherapy fractionation to perform a network meta-analysis of all treatment options used in non metastatic disease.

The meta-analysis will be based on individual patient data [27,28] and will use a similar methodology to that used in the MACH-NC study [29,30], the Breast Cancer Overview [31] and the MARCH study [32,33]. A similar collaborative group comprising those involved in trials included in the project will be established and the meta-analysis will be conducted and reported on its behalf.

Both published and unpublished studies will be included in the meta-analysis since there is evidence that both investigators and journal editors are more likely to publish trials with positive results [34]. Basic survival and prognostic information will be collected for all patients randomized in each study because this allows a more reliable and flexible approach, a more sensitive analysis and avoids the potential bias of post-randomization exclusion [27,28]. Updated follow-up information will be sought which will enable us to report on long-term survival.

In summary, the update of this unique database aims to provide the most comprehensive and up-to-date analysis on the effect of chemotherapy in nasopharyngeal carcinoma. It should contribute to define therapeutic guidelines and to generate new hypotheses to be tested in further randomized trials. This update was registered on PROSPERO International prospective register of systematic reviews on July 8, 2016 under number CRD42016042524.

2. OBJECTIVES

The main objective of the present analysis is to assess the effect of treatment modifications (chemotherapy, EGFR inhibitor, altered fractionation) on overall survival in patients with nasopharyngeal carcinoma. The primary analysis will be a network meta-analysis that will combine the different trials using direct and indirect comparisons.

For the trials on target therapy and altered fractionation, the first step will be to perform standard meta-analysis (i.e one meta-analysis by treatment comparison). Then, based on the amount and quality of the data available, the corresponding trials will be included or not in the network meta-analysis.

The trials included will compare:

- Radiotherapy (RT) to radiotherapy + chemotherapy (CT)
- Radiotherapy + chemotherapy to radiotherapy + chemotherapy delivered at another timing
- RT + induction CT1 compared to RT + induction CT1 + taxane
- Radiotherapy to radiotherapy + EGFR inhibitor
- Radiotherapy + CT to radiotherapy + same CT + EGFR inhibitor
- Radiotherapy to radiotherapy using altered fractionation RT
- Radiotherapy + CT to radiotherapy + same CT using altered fractionation RT

Secondary objectives

- Effect of different treatments on time to loco-regional control, time to distant control, time to overall failure or death (progression-free survival), to nasopharynx cancer mortality and non-nasopharynx cancer mortality
- Comparison of observance, acute toxicity and late toxicity between treatment modalities

For the standard meta-analysis:

- Investigation of the interaction between the treatment effect and the type of treatment (subset analyses).
- Investigation of the interaction between the treatment effect and the prognostic factors and patient characteristics (subgroup analyses).

3. TRIALS SELECTION CRITERIA

All trials must satisfy the following criteria:

Trials must

o   Evaluate one of the 7 treatment comparisons mentioned above (cf. main objective).

o   Be randomized in a way which precludes prior knowledge of treatment assignment.

o   Have completed accrual before 31st December 2015 (amendment 1: 2016).

o   Include patients with nasopharynx carcinoma (WHO grade 1, 2 or 3).

o   Include at least 60 patients (30 patients per arm for trials with more than 2 arms).

o   Not include patients with distant metastatic disease.

Patients should

o   Not have received prior radiotherapy.

o   Not have received prior chemotherapy, except in trials with induction CT in both arms that randomized after induction phase the addition or not of another timing of chemotherapy.

o   Undergo a potentially curative locoregional treatment.

4. TRIALS SEARCH

Data from all published and unpublished randomized trials making the above comparison in NPC patients will be sought using electronic database searching for the period 2009-2016 to

avoid publication bias [34] (Medline, Scopus, Web of Science, Cochrane, Clinicaltrials.gov, Embase), hand searching (review articles, meeting proceedings) and by contacting experts in the field. All trialists who take part in the meta-analysis will be asked to help to identify more trials. An initial search was performed in July 2015 on all head and neck cancers (not only nasopharynx). Search was initially performed for any head and neck sites and NPC trials selected in a second step. The same search was repeated in July 2016 (on a restricted period 2015-2016) and the final search was performed in August 2016. The search strategy is described in **Appendix A**.

5. DESCRIPTION OF THE TRIALS INCLUDED

Appendix B describes the trials comparing radiotherapy versus radio-chemotherapy which ended accrual before 2015 and are potentially eligible for this update of the meta-analysis. Seventeen new trials (3°985 patients) were identified. They will add to the 15 trials (3596 patients) included in the previous update that satisfy the current inclusion criteria (exclusion of some chemotherapy drugs). According to the timing of chemotherapy (CT), four categories of new trials have been identified:

Category of trial (table) (in bold is the randomized treatment)	Number of trials (patients)	Comments
Concomitant +/- adjuvant (table 1)	7 (913)	one trial evaluated concomitant + adjuvant CT (200 patients), six trials randomized only concomitant CT (713 patients)
Induction (concomitant in both arms) (table 2 and 3)	7 (2 089)	Six trials evaluated induction CT compared to no induction (1 811 patients) and one trial compared different types of induction CT (278 patients)
Induction and Adjuvant CT (table 4)	1 (86)	one trial evaluated induction and adjuvant CT without concomitant CT vs no chemotherapy
Induction versus Adjuvant CT (table 5)	2 (897)	two trials evaluated induction versus adjuvant CT with concomitant CT in both arms

Appendix C describes the trials comparing EGFR inhibitors with radiotherapy versus radiotherapy which accrued during the period 2010-2015 and are potentially eligible for this update of the meta-analysis. Two trials (197 patients) were identified. Other trials are ongoing. It is likely that these trials will not be included in this update of the meta-analysis due to the small number of studies. Nevertheless there are ongoing trials on this topic.

Appendix D describes the trials comparing altered fractionation radiotherapy versus standard radiotherapy (+/- chemotherapy) which accrued during the period 2010-2015 and are potentially eligible for this update of the meta-analysis. Three new trials (1°203 patients) were identified. One of these trials (NPC0501) is also presented in the Appendix B (Table 5) as it also compared different timing of chemotherapy. One trial was already included in the meta-analysis (NPC9902) and figured in this table because part of the patients had altered fractionation radiotherapy.

Appendix E describes the network of treatment modalities for locally advanced nasopharyngeal carcinomas.

Appendix F describes the ongoing trials.

6. ENDPOINTS

The primary endpoint will be **overall survival**, because of its clinical importance and robustness. It is defined as the time from randomization until death due to any cause; patients remaining alive and those lost to follow-up will be censored on the date of last follow-up

Secondary endpoints such as time to locoregional progression, distant progression, progression-free survival (PFS) and cause specific survival (nasopharynx cancer mortality and non nasopharynx cancer mortality), treatment compliance, early and late toxicity will be also considered.

PFS is defined as the time from randomization until first event including local or distant progression or death from any cause; patients alive without progression will be censored on the date of last follow-up

To estimate the respective contribution of local progression and distant progression, in the progression-free survival, the cumulative incidences of these two types of events will be calculated within a competing risk framework (Fine and Gray 1999):

Cumulative incidence of loco-regional progression

Cumulative incidence of distant progression: patients who experienced a distant progression and loco-regional progression on the same date will be counted in distant progression.

Nasopharynx cancer specific survival is defined as the time from randomization until death from nasopharynx cancer, deaths from unknown causes (with or without recurrence) or from any cause after recurrence. It is assumed that nasopharynx cancer is the most likely cause of death in these latter cases.

Non- nasopharynx cancer specific survival is defined as the time from randomization until death from treatment-related causes, from a second primary cancer or any other non-nasopharynx cancer causes with no reported recurrence.

Severe (grade $\geq$3) acute toxicity: neutropenia, thrombocytopenia, anemia, febrile neutropenia, kidney failure, cutaneous, need for feeding tube, weight loss, mucositis, hearing loss, acneiform rash, infusion related reaction, neurotoxicity (highest grade), including death related to treatment. Toxicity will be studied on globally and not for each timing of treatment (e.g. induction nand concomitant).

Severe (grade $\geq$3) late toxicity (between 1 year and 5 years after randomization): cutaneous fibrosis, xerostomia, bone necrosis, persistence of feeding tube after one year of treatment, endocrine dysfunction, hearing deficit, cranial nerve palsy, stroke, symptomatic and asymptomatic temporal lobe necrosis, trismus, visual deficit, massive bleeding (if possible). For late toxicity, the main criteria will be defined as occurrence of at least one severe toxicity.

Compliance for chemotherapy is based on the number of cycles of chemotherapy received and for radiotherapy on the dose received: good complianc for chemotherapy is defined as at least 2/3 of the number of cycles and for radiotherapy as at least 90% of the total dose.

7. DATA COLLECTION AND QUALITY CONTROL

For each eligible trial, the main investigator will be asked to provide the following basic data for survival and prognostic factors for **all** randomized patients.

- o Date of birth or age.
- o Sex.
- o Performance status.
- o Smoking status, if available (current, former or never smoker)
- o Histology (WHO type).
- o TNM staging (if not available other staging ; in any case, provide information on classification used) – name of classification system and edition used.
- o Imaging methods used for evaluation of local extension: x-ray, CT scan, MRI
- o EBV data if available (pretreatment EBV DNA and/or posttreatment EBV DNA), if possible the number of copies/mL, otherwise low/high value, specify the unit used, the cut-off if any
- o Allocated treatment.
- o Date of randomization.
- o Number of cycles of induction chemotherapy regimen received overall, and if possible, if dose reduction occured or if one drug was stopped before the other.
- o Number of cycles (or injection) of concomitant chemotherapy regimen received, and if possible, if dose reduction occured or if one drug was stopped before the other.
- o Number of cycles of adjuvant chemotherapy regimen received, and if possible, for if dose reduction occured or if one drug was stopped before the other.
- o Radiotherapy started / not started
- o Radiotherapy technique: conventional 2D / 3D conformal/ IMRT
- o Date first day radiotherapy
- o Date last day radiotherapy
- o Total administered dose of radiotherapy
- o Total number of fractions of radiotherapy

- o Worst acute toxicity (neutropenia, thrombocytopenia, anemia, febrile neutropenia, kidney failure, cutaneous, need for feeding tube, weight loss, mucositis, hearing loss, acneiform rash, infusion related reaction, neurotoxicity) + Specification of toxicity grading system used
- o Late toxicity (cutaneous fibrosis, xerostomia, bone necrosis, persistence of feeding tube after one year of treatment, endocrine dysfunction, hearing deficit, cranial nerve palsy, stroke, symptomatic and asymptomatic temporal lobe necrosis, trismus, visual deficit, massive bleeding) + specification of toxicity grading system used
- o Date of last follow-up.
- o Survival status.
- o Cause of death.
- o Date of tumor failure,
- o Date of nodal failure
- o Date of distant failure
- o Date and type of second primary (within or outside irradiation field, if available)
- o Whether excluded from trial analysis.
- o Reason for exclusion (if applicable).

Appendix G gives the suggested format and coding to send the data to the Secretariat. All data will be checked for internal consistency and consistency with trial protocol and published report. Range checks will be performed and extreme values will be checked with the trialists. Each trial will be analyzed individually, and the resulting survival analyses and trial data will be sent to the trialists for verification.

8. STATISTICAL ANALYSIS PLAN

With around 4 500 patients it would be possible to detect, with a power exceeding 90%, an absolute improvement in survival from 40% to 45% at 5-years. Therefore, the study will have enough power to detect small but clinically important differences. Before analyzing the data,

the analysis plan will be finalized following discussion between the members of the secretariat and the steering committee.

The main analysis will be performed on the endpoint of overall survival. Additional analyses will be performed on the endpoints of progression-free survival, loco-regional progression, distant progression, nasopharynx cancer mortality and non nasopharynx cancer mortality, if sufficient data are available.

Fine and Gray modelization will be used for loco-regional progression and distant progression (Fine and Gray 1999). For each of these endpoints, the studied type of progression will be analyzed as the main event. The other types of progression and death without progression will be analyzed as competing events. Alive patients without progression will be censored. Competing risk analyses will be performed with R software (R foundation for Statistical Computing, Vienna, Austria). Sub-distribution hazard ratios will be estimated in each trial with the "cmprsk" package and global sub-distribution hazard ratios will be estimated with the "crrSC" package. Cumulative incidences will also be computed using the same packages.

All analyses will include all randomized patients and will be carried out on an **intention-to-treat basis** that is patients will be analyzed according to the treatment allocated, irrespective of whether they have actually received that treatment. **Survival analyses** will be use the log-rank expected number of deaths and variance to calculate individual and overall pooled hazard ratios by the fixed-effect model [31]. Thus, the time to death for individual patients will be used within trials to calculate the hazard ratio, representing the overall risk of death for patients who were allocated new treatment compared with those who were allocated reference treatment.

Nasopharynx cancer and non-nasopharynx cancer mortality using methods similar to that used in the Meta-Analysis of Radiotherapy in Carcinoma of Head and neck [33] will be studied. An unbiased, although potentially diluted, logrank analysis of nasopharynx cancer mortality was obtained indirectly by subtracting the logrank statistic for non-nasopharynx cancer mortality from the logrank statistic for mortality from all causes (i.e., the two observed values, the two expected values, and the two variances are each subtracted from each other). Survival curves will be estimated for both treatment groups using annual death rates and hazard ratio

(Early Breast Cancer Trialists Collaborative Group 1995). They will be used to calculate absolute benefit at 2-years, 5-years and 10-years with their 95% confidence intervals [31]. Restricted mean survival time difference at 5 and 10 years will also be used as an absolute effect endpoint and will be considred a s secondary analysis [35]. All p-values will be two-sided. In case of important and unexplained heterogeneity, DerSimonian-Laird random effects will be used to take this heterogeneity into account.

Acute toxicity will be studied globally for all the treatment. For long-term toxicity, according to the data availability, we will try to study toxicity between 1 and 5 years after randomization. For dichotomous outcomes such as toxicity (grade 3-4 versus grade 0-2), the number of events and numbers of patients will be used to calculate Peto odds ratio estimates of treatment effect. These odds ratios will be generated for individual trials and pooled across trials, using the fixed effects model. In case of heterogeneity, Der Simonian-Laird random effects models will be used. Similar approach will be used for compliance.

8.1. Standard meta-analysis

A standard meta-analysis will be performed for radiotherapy with altered fractionation to know if we need to separate standard fractionation and altered fractionation in the network meta-analysis. Indeed, if a difference is shown in the standard meta-analysis, several treatment modalities will be created in the network meta-analysis to individualize the modalities with altered fractionation radiotherapy. With 1 400 patients (497 deaths), it would be possible using a two-sided test at a 5% significance level to detect, with a 87% power, an absolute improvement in overall survival from 60 % to 68 % at 5-years.

Survival analyses will be stratified by trial, and the log-rank expected number of deaths and variance will be used to calculate overall pooled hazard ratios by the fixed-effect model [31]. The χ^2 heterogeneity tests will be used to test for gross statistical heterogeneity, the I^2 statistic will be used as a measure of consistency among trials [36]. Stratified survival curves will be estimated for control and experimental groups using annual death rates and hazard ratios.

8.2. Network meta-analysis

A new network meta-analysis will be performed using the trials included based on the updated MAC-NPC database and the addition of other trials (anti-EGFR therapies and RT with altered fractionation) which will be divided according to the treatment compared:

- radiotherapy

- radiotherapy + concomitant chemotherapy

- radiotherapy + concomitant and adjuvant chemotherapy

- radiotherapy + induction chemotherapy

- radiotherapy + adjuvant chemotherapy

- radiotherapy + induction with taxane (e.g. TPF) and concomitant chemotherapy

- radiotherapy + induction (others) and concomitant chemotherapy

- radiotherapy + induction and adjuvant chemotherapy

- radiotherapy + EGFR inhibitor (+/- chemotherapy in both arms)

- radiotherapy with altered fractionation (+/- chemotherapy in both arms)

The two last modalities of treatment are not yet included in the figure of the network as we are not sure to have enough material for anti-EGFR therapy and because we will perform a standard meta-analysis for radiotherapy with altered fractionation to know if we need to separate standard fractionation and altered fractionation, and to separate standard radiotherapy versus altered fractionation from separate standard radiotherapy + chemotherapy versus altered fractionation + chemotherapy (same modalities) in the network meta-analysis.

Statistical methods

A two-step method will be used, the first step being the computation of hazard ratios (HRs) on the basis of the IPD gathered by the MAC-NPC Collaborative Group, using the Peto estimator for OS and PFS, and a competing risk model for locoregional and distant control. The proportional hazards assumption will be checked at each meta-analysis level for OS and PFS [35,37]. The second step is the actual NMA, using as input data for each trial the two treatments compared, the logarithm of the HRs, which is usually normally distributed and its variance. Therefore, all the analyses will be stratified by trial. The transitivity hypothesis and

the consistency hypothesis state that: logHR(B vs C) = logHR(A vs C) − logHR(A vs B). Moreover the consistency hypothesis assumes that there is no discrepancies between direct and indirect estimates into a closed loop. The final analysis will be performed using a frequentist approach and the R package netmeta [38,39]. Heterogeneity will be quantified using the I², which represents the proportion of total variation in study estimates that is due to heterogeneity. To limit the number of tests for both heterogeneity and inconsistency, Rücker has proposed a global test, called Q test [39]. This test is a generalization of Cochran's test that is used to assess heterogeneity in conventional meta-analysis. The Q statistic is the sum of a statistic for heterogeneity and a statistic for inconsistency, which represents the variability of treatment effect between direct and indirect comparisons at the meta-analytic level. A fixed-effects model will be used first and in case of significant heterogeneity ($P < .1$), two solutions would be investigated: the use of random-effects models and the performance of sensitivity analyses after the exclusion of trials that are considered as outliers in the standard meta-analysis. The netmeta package allows identifying in which closed loop the inconsistency is located. The trials responsible for inconsistency could be determined by comparing direct and indirect estimates and trial forest plots within the inconsistent closed loop; the effect of trial removal on the network consistency and estimation could therefore be investigated. Within the Bayesian framework, the treatments are ranked using the surface under the cumulative ranking curve. Rücker and Schwarzer have proposed a frequentist analog to surface under the cumulative ranking curve, which is named P-score, that works without resampling and measures the mean extent of certainty that a treatment is better than the competing treatments [40]. P-score would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. Five-year absolute benefit will be computed using the survival rate at 5 years for the RT-only arms in MAC-NPC1 and the HR using the method by Stewart and Parmar. P values $< .05$ will be considered significant for the difference between treatments. All analyses will be performed using the R software (version 3.4.0; R Foundation, Vienna, Austria).

The reporting of the results will include a description of the networks (princeps and for each sensitivity analysis), effect sizes from direct evidence, indirect evidence, and the network meta-analysis (at least for the primary analysis, through a comparative HR plot for each comparison of interest), a ranking of the treatment that includes the uncertainty of the ranking estimates. All endpoints mentioned above will be studied in the network meta-analysis. If

meanwhile the PRISMA guidelines extended to network meta-analyses are published, they will be followed for the reporting of the meta-analysis [41].

8.3. Validation of the model hypothesis and sensitivity analyses

The proportional hazards assumption will be checked for each trial comparison and each endpoint based on the Grambsch-Therneau test [42]. Heterogeneity will be checked in standard meta-analysis and in network meta-analysis as detailed in previous paragraphs. Inconsistency will be checked for network meta-analysis as detailed proviously.

Clinical sensitivity analyses will be performed in coherence with the standard meta-analysis, either by excluding a certain category of patients or a certain category of trials.

Main sensitivity analyses will be analysis restricted to:

- trials that are considered outliers on the overall survival analysis in the standard MA

Secondary sensitivity analyses will be included analyses with exclusion of:

- trials including less than 100 patients,
- trials with a median follow-up shorter than five years
- old trials and/or trials using drugs not use any more
- trials for which dates of randomization are not available.
- trials using sealed envelopes for randomization
- patients with stage I/II tumors
- patients with WHO type I disease

Another sensitivity analysis will be performed using HR adjusted on patient sex, age, performance status, and stage using Cox model.

8.4. Subgroup analyses

At this point, subgroup analysis could be performed for standard meta-analysis and not for network meta-analysis.

To study the interaction between treatment effect and covariates, e.g. sex, an analysis of the interaction (or trend) between these characteristics and the treatment effect will be conducted.

To avoid bias, only within trial information will be used for subgroup analyses, as described by Fisher et al [43].

Main subgroup analyses:

- Age (50 or less vs 51-60 vs 61+)
- Sex
- Performance status (WHO or equivalent, 0 vs 1 vs 2+)
- T stage (T1-2 vs T3 vs T4)
- N stage (N0 vs N+; N0 vs N1-2 vs N3)
- Overall stage (I-II vs III vs IVa vs IVb)
- WHO histology type (I vs II-III, i.e. keratinizing versus non-keratinizing)
- Imaging methods for evaluation of local extension: X-ray, CT scan, MRI[1]
- Radiotherapy technique (IMRT vs 3D-CRT vs 2D-RT) [2]
- Number/ratio of chemotherapy cycles received, if possible. This analysis will be exploratory and will use a 12 months landmark.
- EBV markers if available

9. WORKING PARTIES IN THE META-ANALYSIS

In order to complete the meta-analysis successfully, three groups with specific functions have been created : 1) the Secretariat 2) the Steering Committee 3) the MAC-NPC Trialists' Group.

The Secretariat is in charge of the coordination of the meta-analysis. It is responsible for completing the trial register and for inviting investigators to provide data available on patients. The Secretariat is also in charge of checking, processing and analyzing the data. Finally, the Secretariat is responsible for preparing reports, publications and works in very close collaboration with the Steering Committee.

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[1] Depending on the distribution of the type of imaging in each trial, a subgroup or a subset analysis will be performed.

[2] Depending of the distribution of the type of radiotherapy technique in each trial, a subgroup or a subset analysis will be performed.

The Steering Committee will include international experts in the field of oncology, radiotherapy, and surgery involved in nasopharyngeal cancer, and experts in meta-analysis. The list of its members is given on the following page. The Steering Committee will support the Secretariat with medical and methodological expertise, help determine trials relevant to the overview, and promote contact between investigators and all the collaborators.

The MAC-NPC trialists' group will include the investigators responsible for trials included in the meta-analysis. The members of the Secretariat and the Steering Committee will also be included in this group. It will be responsible for providing the Secretariat with data on patients and for discussing the reports prepared by the Steering Committee and the Secretariat.

10. PRACTICAL CONSIDERATIONS

The Secretariat, located in the Meta-Analysis Unit of the Biostatistics Department at Gustave Roussy, will be responsible for liaising with trialists. The main database will be run by the Secretariat. All data, updating and correction should be sent there. All supplied data will remain confidential and used exclusively for the meta-analysis.

A meeting of all group members will be organized by the Secretariat to discuss the preliminary results.

11. PUBLICATION POLICY

Any publication arising from this project will be made in the name of the MAC-NPC Group and include a list of all collaborators.

The meta-analysis funding grant will also be acknowledged on each publication (Ligue Nationale contre le Cancer: PLRC2015.LNCC/JPP, and PHRC-K15-189).

List of the members of the steering committee

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Appendix A: Description of the trials search strategy

The search strategy used in July 2015 and repeated in August 2016 was :

1) for MEDLINE from PubMed

(((((((((((((((((((((((((((((((((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 hypopharyn*) OR nasopharyn*) OR oropharyn*)) AND (((((((((cancer*) OR carcinom*) OR adenocarcinom*) OR malignan*) OR tumor*) OR tumour*) OR neoplasm*) OR (squamous OR epidermoid OR undifferentiated carcinoma)) OR Carcinoma, squamous cell[MeSH Terms])) AND (((((((((((((((((((((((((((((((((((drug therapy[MeSH Subheading]) OR chemotherapy) OR chemoradiation) OR chemoradiotherapy) OR radiochemotherapy) OR radio-chemotherapy) OR radiation*) OR radiotherap*) 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 target therapy) OR anti-egfr) OR egfr-inhibitors) OR egfr) OR EGF) OR zalutumumab) OR cetuximab) OR bevacizumab) OR panitumumab) OR gefitinib) OR erlotinib) OR lapatinib) OR nimotuzumab) OR gemcitabine) OR mitomycin) OR methotrexate)) AND ((((((((randomized controlled trial[Publication Type]) OR clinical trial, phase iii[Publication Type]) OR clinical trial, phase iv[Publication Type]) OR clinicaltrials.gov[Secondary Source ID]) OR isrctn[Secondary Source ID]) OR randomized controlled trials as topic[MeSH Terms])) AND ((((random OR randomised OR randomized OR rct OR rcts OR single-blind OR double-blind)) AND (trial* OR study OR studies)))))))) AND ("2009"[Date - Publication] : "2015"[Date - Publication]))

2) For Web of Science

#6	#5 AND #4 AND #3 AND #2 AND #1 *DocType=All document types; Language=All languages;*
#5	(TS=(random*)) *AND* **DOCUMENT TYPES:** (Article) *DocType=All document types; Language=All languages;*
#4	(TS=(squamous)) *AND* **DOCUMENT TYPES:** (Article) *DocType=All document types; Language=All languages;*
#3	(TS=(chemotherapy OR chemoradiation OR chemoradiotherapy OR radiochemotherapy OR radio-chemotherapy OR pharmacotherapy)) *AND* **DOCUMENT TYPES:** (Article) *DocType=All document types; Language=All languages;*
#2	(TS=(cancer* OR carcinoma* OR adenocarinoma* OR malignan* OR tumor* OR tumour* OR neoplasm)) *AND* **DOCUMENT TYPES:** (Article) *DocType=All document types; Language=All languages;*
#1	(TS=((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 hypopharyn* OR nasopharyn* OR oropharyn*)) *AND* **DOCUMENT TYPES:** (Article) *DocType=All document types; Language=All languages;*

3) For 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 **sinus** OR **pharyngeal** OR **pharynx** OR **hypopharyn*** OR **nasopharyn*** OR **orophayn***) AND TITLE-ABS-

KEY (**cancer*** OR **carcinoma*** OR **adenocarcinoma*** OR **malignan*** OR **tumor*** OR **tumour*** OR **ne oplasm***) AND TITLE-ABS-KEY (**squamous** OR **epidermoid** OR "**undifferentiated carcinoma**") 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 **taxot ere** OR **cisplatin** OR **platin*** OR **carboplatin** OR **fluorouracil** OR **5-fluorouracil** OR **fluoro- uracil** OR **5fu** OR **hydroxyuera** OR **tegarfur-uracil** OR **leucovorin** OR "**target therapy**" OR **anti- egfr** OR "**EGFR inhibitors**" OR **egfr** OR **egf** OR **zalutumumab** OR **cetuximab** OR **bevacizumab** OR **panitumumab** OR **gefitinib** OR **erlotinib** OR **lapatinib** OR **nimotuzumab** OR **gemcitabine** OR **mitomycin** OR **met hotrexate**) 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 (LIMIT-TO (PUBYEAR , **2015**) OR LIMIT-TO (PUBYEAR , **2014**) OR LIMIT-TO (PUBYEAR , **2013**) OR LIMIT-TO (PUBYEAR , **2012**) OR LIMIT-TO (PUBYEAR , **2011**) OR LIMIT-TO (PUBYEAR , **2010**) OR LIMIT-TO (PUBYEAR , **2009**))

4) For Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Laryngeal Neoplasms] explode all trees	283 / 304
#2	MeSH descriptor: [Mouth Neoplasms] explode all trees	513 / 553
#3	MeSH descriptor: [Nose Neoplasms] explode all trees	34 / 36
#4	MeSH descriptor: [Pharyngeal Neoplasms] explode all trees	510 / 559
#5	MeSH descriptor: [Salivary Gland Neoplasms] explode all trees	67 / 74
#6	#1 or #2 or #3 or #4 or #5	1125 / 1229
#7	cancer*:ti,ab,kw (Word variations have been searched)	68705 / 76662
#8	carcinoma*:ti,ab,kw (Word variations have been searched)	20974 / 22905
#9	adenocarcinoma*:ti,ab,kw (Word variations have been searched)	4051 / 4571
#10	malignan*:ti,ab,kw (Word variations have been searched)	8939 / 9850
#11	tumor*:ti,ab,kw (Word variations have been searched)	24326 / 27941
#12	tumour*:ti,ab,kw (Word variations have been searched)	5329 / 5954
#13	neoplasm*:ti,ab,kw (Word variations have been searched)	51357 / 56767
#14	squamous:ti,ab,kw (Word variations have been searched)	4597 / 5053
#15	epidermoid:ti,ab,kw (Word variations have been searched)	140 / 144
#16	undifferentiated carcinoma:ti,ab,kw (Word variations have been searched)	108 / 128
#17	squamous cell carcinoma:ti,ab,kw (Word variations have been searched)	3881 / 5
#18	{or #7-#17}	101793 / 112526
#19	"drug therapy":ti,ab,kw (Word variations have been searched)	98573 / 110975
#20	chemotherapy:ti,ab,kw (Word variations have been searched)	35299 / 38588
#21	chemoradiation:ti,ab,kw (Word variations have been searched)	762 / 881
#22	chemoradiotherapy:ti,ab,kw (Word variations have been searched)	1703 / 2081
#23	radiochemotherapy:ti,ab,kw (Word variations have been searched)	407 / 449
#24	radio-chemotherapy:ti,ab,kw (Word variations have been searched)	132 / 139
#25	radiation*:ti,ab,kw (Word variations have been searched)	11244 / 14964
#26	radiotherap*:ti,ab,kw (Word variations have been searched)	13630 / 14964
#27	pharmacotherapy:ti,ab,kw (Word variations have been searched)	4882 / 5170
#28	taxane:ti,ab,kw (Word variations have been searched)	707 / 842
#29	docetaxel:ti,ab,kw (Word variations have been searched)	2545 / 3023
#30	paclitaxel:ti,ab,kw (Word variations have been searched)	3842 / 4392
#31	taxoid:ti,ab,kw (Word variations have been searched)	20 / 25
#32	taxotere:ti,ab,kw (Word variations have been searched)	181 / 185
#33	cisplatin:ti,ab,kw (Word variations have been searched)	7709 / 8275
#34	platin*:ti,ab,kw (Word variations have been searched)	2340 / 2674
#35	carboplatin*:ti,ab,kw (Word variations have been searched)	2896 / 3197
#36	fluorouracil:ti,ab,kw (Word variations have been searched)	6971 / 7500
#37	5-fluorouracil:ti,ab,kw (Word variations have been searched)	3416 / 3599
#38	fluoro-uracil:ti,ab,kw (Word variations have been searched)	29 / 31

#39   5FU:ti,ab,kw (Word variations have been searched) 488 / 533
#40   hydroxyuera:ti,ab,kw (Word variations have been searched) 0 / 0
#41   tegafur-uracil:ti,ab,kw (Word variations have been searched) 46 / 49
#42   leucovorin:ti,ab,kw (Word variations have been searched)   1682 / 1812
#43   "target therapy":ti,ab,kw (Word variations have been searched)   509 / 20
#44   anti-egfr:ti,ab,kw (Word variations have been searched)   129 / 169
#45   egfr-inhibitors:ti,ab,kw (Word variations have been searched)   78 / 55
#46   egfr:ti,ab,kw (Word variations have been searched) 1612 / 2155
#47   egf:ti,ab,kw (Word variations have been searched) 203 / 237
#48   zalutumumab:ti,ab,kw (Word variations have been searched) 13 / 14
#49   cetuximab:ti,ab,kw (Word variations have been searched)   694 / 852
#50   bevacizumab:ti,ab,kw (Word variations have been searched) 1572 / 2048
#51   panitumumab:ti,ab,kw (Word variations have been searched) 169 / 230
#52   gefitinib:ti,ab,kw (Word variations have been searched)   300 / 357
#53   erlotinib:ti,ab,kw (Word variations have been searched)   498 / 0
#54   lapatinib:ti,ab,kw (Word variations have been searched)   273 / 357
#55   nimotuzumab:ti,ab,kw (Word variations have been searched) 33 / 44
#56   gemcitabine:ti,ab,kw (Word variations have been searched) 1987 / 2303
#57   mitomycin:ti,ab,kw (Word variations have been searched)   2088 / 2184
#58   methotrexate:ti,ab,kw (Word variations have been searched) 6159 / 6593
#59   {or #19-#58}   152970 / 169601
#60   clinical trial phase3:ti,ab,kw or clinical trial phase 4:ti,ab,kw Publication Year from 2009 to 2015 (Word variations have been searched)   8333 / 42255 (without date restriction)
#61   random*:ti,ab,kw or rct:ti,ab,kw or rcts:ti,ab,kw or single-blind:ti,ab,kw or double-blind:ti,ab,kw (Word variations have been searched)   542986 / 597096
#62   trial*:ti,ab,kw or study:ti,ab,kw or studies:ti,ab,kw Publication Year from 2009 to 2015 (Word variations have been searched)   235645 / 744675 (without date restriction)
#63   {and #61-#62}   192923 / 556878
#64   #60 or #63   193602 / 563387
#65   #6 and #18 and #59 and #64   91 / 42 (Publication Year from 2014 to 2016)

5) Embase

#70   ('larynx tumor'/exp OR 'mouth tumor'/exp OR 'nose tumor'/exp OR 'pharynx cancer'/exp OR 'salivary gland tumor'/exp OR 'head cancer'/exp OR 'neck cancer'/exp) AND (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR ((squamous OR 'epidermoid'/exp OR epidermoid OR 'undifferentiated carcinoma'/exp OR 'undifferentiated carcinoma') OR ('squamous cell carcinoma'/exp OR 'squamous cell carcinoma'))) AND (('drug therapy'/exp OR 'drug therapy') OR ('chemotherapy'/exp OR 'chemotherapy') OR ('chemoradiation'/exp OR 'chemoradiation') OR ('chemoradiotherapy'/exp OR 'chemoradiotherapy') OR ('radiochemotherapy'/exp OR 'radiochemotherapy') OR 'radio chemotherapy' OR ('pharmacotherapy'/exp OR pharmacotherapy) OR 'taxane' OR 'docetaxel'/exp OR 'paclitaxel'/exp OR 'taxoid'/exp OR 'taxotere'/exp OR 'cisplatin'/exp OR platin* OR 'carboplatin'/exp OR 'fluorouracil'/exp OR '5 fluorouracil':ab,ti OR 'fluoro uracil':ab,ti OR 5fu:ab,ti OR 'hydroxyurea'/exp OR 'tegafur uracil'/exp OR 'leucovorin'/exp OR 'targeted therapy' OR 'anti egfr':ab,ti OR (egfr AND inhibitors:ab,ti) OR 'egfr' OR 'egf' OR 'zalutumumab'/exp OR 'cetuximab'/exp OR 'bevacizumab'/exp OR 'panitumumab'/exp OR 'gefitinib'/exp OR 'erlotinib'/exp OR 'lapatinib'/exp OR 'nimotuzumab'/exp OR 'gemcitabine'/exp OR 'mitomycin'/exp OR 'methotrexate'/exp) AND (('randomized controlled trial'/exp OR 'randomized controlled trial') OR ('phase 3 clinical trial'/exp OR 'phase 3 clinical trial') OR ('phase 4 clinical trial'/exp OR 'phase 4 clinical trial') OR 'clinicaltrials gov' OR 'isrctn' OR ('randomized controlled trial (topic)'/exp OR 'randomized controlled trial (topic)') OR ((random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR 'single blind' OR 'double blind':ab,ti) AND (trial OR trials OR 'study'/exp OR study OR studies:ab,ti))) AND [2009-2015]/py   1088
#69   ('larynx tumor'/exp OR 'mouth tumor'/exp OR 'nose tumor'/exp OR 'pharynx cancer'/exp OR 'salivary gland tumor'/exp OR 'head cancer'/exp OR 'neck cancer'/exp) AND (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR ((squamous OR 'epidermoid'/exp OR epidermoid OR 'undifferentiated carcinoma'/exp OR 'undifferentiated carcinoma') OR ('squamous cell carcinoma'/exp OR 'squamous cell carcinoma'))) AND (('drug therapy'/exp OR 'drug therapy') OR ('chemotherapy'/exp OR 'chemotherapy') OR ('chemoradiation'/exp OR 'chemoradiation') OR

('chemoradiotherapy'/exp OR 'chemoradiotherapy') OR ('radiochemotherapy'/exp OR 'radiochemotherapy') OR 'radio chemotherapy' OR ('pharmacotherapy'/exp OR pharmacotherapy) OR 'taxane' OR 'docetaxel'/exp OR 'paclitaxel'/exp OR 'taxoid'/exp OR 'taxotere'/exp OR 'cisplatin'/exp OR platin* OR 'carboplatin'/exp OR 'fluorouracil'/exp OR '5 fluorouracil':ab,ti OR 'fluoro uracil':ab,ti OR 5fu:ab,ti OR 'hydroxyurea'/exp OR 'tegafur uracil'/exp OR 'leucovorin'/exp OR 'targeted therapy' OR 'anti egfr':ab,ti OR (egfr AND inhibitors:ab,ti) OR 'egfr' OR 'egf' OR 'zalutumumab'/exp OR 'cetuximab'/exp OR 'bevacizumab'/exp OR 'panitumumab'/exp OR 'gefitinib'/exp OR 'erlotinib'/exp OR 'lapatinib'/exp OR 'nimotuzumab'/exp OR 'gemcitabine'/exp OR 'mitomycin'/exp OR 'methotrexate'/exp) AND (('randomized controlled trial'/exp OR 'randomized controlled trial') OR ('phase 3 clinical trial'/exp OR 'phase 3 clinical trial') OR ('phase 4 clinical trial'/exp OR 'phase 4 clinical trial') OR 'clinicaltrials gov' OR 'isrctn' OR ('randomized controlled trial (topic)'/exp OR 'randomized controlled trial (topic)') OR ((random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR 'single blind' OR 'double blind':ab,ti) AND (trial OR trials OR 'study'/exp OR study OR studies:ab,ti)))   1839

#68   ('randomized controlled trial'/exp OR 'randomized controlled trial') OR ('phase 3 clinical trial'/exp OR 'phase 3 clinical trial') OR ('phase 4 clinical trial'/exp OR 'phase 4 clinical trial') OR 'clinicaltrials gov' OR 'isrctn' OR ('randomized controlled trial (topic)'/exp OR 'randomized controlled trial (topic)') OR ((random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR 'single blind' OR 'double blind':ab,ti) AND (trial OR trials OR 'study'/exp OR study OR studies:ab,ti))   957672

#67   (random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR 'single blind' OR 'double blind':ab,ti) AND (trial OR trials OR 'study'/exp OR study OR studies:ab,ti)   910989

#66   trial OR trials OR 'study'/exp OR study OR studies:ab,ti   13502644

#65   random OR randomise OR randomize OR randomised OR randomized OR rct OR rcts OR 'single blind' OR 'double blind':ab,ti   982118

#64   'randomized controlled trial (topic)'/exp OR 'randomized controlled trial (topic)'   76318

#63   'isrctn'   7506

#62   'clinicaltrials gov'70044

#61   'phase 4 clinical trial'/exp OR 'phase 4 clinical trial'   2440

#60   'phase 3 clinical trial'/exp OR 'phase 3 clinical trial'   36071

#59   'randomized controlled trial'/exp OR 'randomized controlled trial'   457044

#58   ('drug therapy'/exp OR 'drug therapy') OR ('chemotherapy'/exp OR 'chemotherapy') OR ('chemoradiation'/exp OR 'chemoradiation') OR ('chemoradiotherapy'/exp OR 'chemoradiotherapy') OR ('radiochemotherapy'/exp OR 'radiochemotherapy') OR 'radio chemotherapy' OR ('pharmacotherapy'/exp OR pharmacotherapy) OR 'taxane' OR 'docetaxel'/exp OR 'paclitaxel'/exp OR 'taxoid'/exp OR 'taxotere'/exp OR 'cisplatin'/exp OR platin* OR 'carboplatin'/exp OR 'fluorouracil'/exp OR '5 fluorouracil':ab,ti OR 'fluoro uracil':ab,ti OR 5fu:ab,ti OR 'hydroxyurea'/exp OR 'tegafur uracil'/exp OR 'leucovorin'/exp OR 'targeted therapy' OR 'anti egfr':ab,ti OR (egfr AND inhibitors:ab,ti) OR 'egfr' OR 'egf' OR 'zalutumumab'/exp OR 'cetuximab'/exp OR 'bevacizumab'/exp OR 'panitumumab'/exp OR 'gefitinib'/exp OR 'erlotinib'/exp OR 'lapatinib'/exp OR 'nimotuzumab'/exp OR 'gemcitabine'/exp OR 'mitomycin'/exp OR 'methotrexate'/exp   4525373

#57   'methotrexate'/exp   139830

#56   'mitomycin'/exp   39805

#55   'gemcitabine'/exp 36918

#54   'nimotuzumab'/exp   745

#53   'lapatinib'/exp   8088

#52   'erlotinib'/exp   18149

#51   'gefitinib'/exp   17208

#50   'panitumumab'/exp   5360

#49   'bevacizumab'/exp   36023

#48   'cetuximab'/exp   18631

#47   'zalutumumab'/exp   181

#46   'egf'   34410

#45   'egfr'   57733

#44   egfr AND inhibitors:ab,ti 10653

#43   'anti egfr':ab,ti   3568

#42   'targeted therapy' 28851

#41   'leucovorin'/exp   28441

#40   'tegafur uracil'/exp   3359

#39   'hydroxyurea'/exp   20970

#38   5fu:ab,ti 3364

#37   'fluoro uracil':ab,ti   263

#36   '5 fluorouracil':ab,ti   31473

#35   'fluorouracil'/exp 110836

#34   'carboplatin'/exp 48312

#33   platin* 69141

#32   'cisplatin'/exp   134660

#31   'taxotere'/exp 38592

#30   'taxoid'/exp   2041

#29   'paclitaxel'/exp 73159

#28   'docetaxel'/exp 38592

#27   'taxane' 15350

#26   'pharmacotherapy'/exp OR pharmacotherapy   2014742

#25   'radio chemotherapy'   1656

#24   'radiochemotherapy'/exp OR 'radiochemotherapy'   22577

#23   'chemoradiotherapy'/exp OR 'chemoradiotherapy'   28139

#22   'chemoradiation'/exp OR 'chemoradiation'   25876

#21   'chemotherapy'/exp OR 'chemotherapy'   683524

#20   'drug therapy'/exp OR 'drug therapy'   4190081

#19   cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm* OR ((squamous OR 'epidermoid'/exp OR epidermoid OR 'undifferentiated carcinoma'/exp OR 'undifferentiated carcinoma') OR ('squamous cell carcinoma'/exp OR 'squamous cell carcinoma'))   4283987

#18   (squamous OR 'epidermoid'/exp OR epidermoid OR 'undifferentiated carcinoma'/exp OR 'undifferentiated carcinoma') OR ('squamous cell carcinoma'/exp OR 'squamous cell carcinoma') 182590

#17   'squamous cell carcinoma'/exp OR 'squamous cell carcinoma' 135872

#16   squamous OR 'epidermoid'/exp OR epidermoid OR 'undifferentiated carcinoma'/exp OR 'undifferentiated carcinoma'   181974

#15   neoplasm*   755811

#14   tumour* 285768

#13   tumor* 2307642

#12   malignan*   619565

#11   adenocarcinoma*194843

#10   carcinoma*   911655

#9   cancer* 2860570

#8   'larynx tumor'/exp OR 'mouth tumor'/exp OR 'nose tumor'/exp OR 'pharynx cancer'/exp OR 'salivary gland tumor'/exp OR 'head cancer'/exp OR 'neck cancer'/exp   134269

#7   'neck cancer'/exp 3106

#6   'head cancer'/exp 1439

#5   'salivary gland tumor'/exp 17411

#4   'pharynx cancer'/exp   27451

#3   'nose tumor'/exp 18351

#2   'mouth tumor'/exp   90913

#1   'larynx tumor'/exp   30481

The resulting flow chart is:
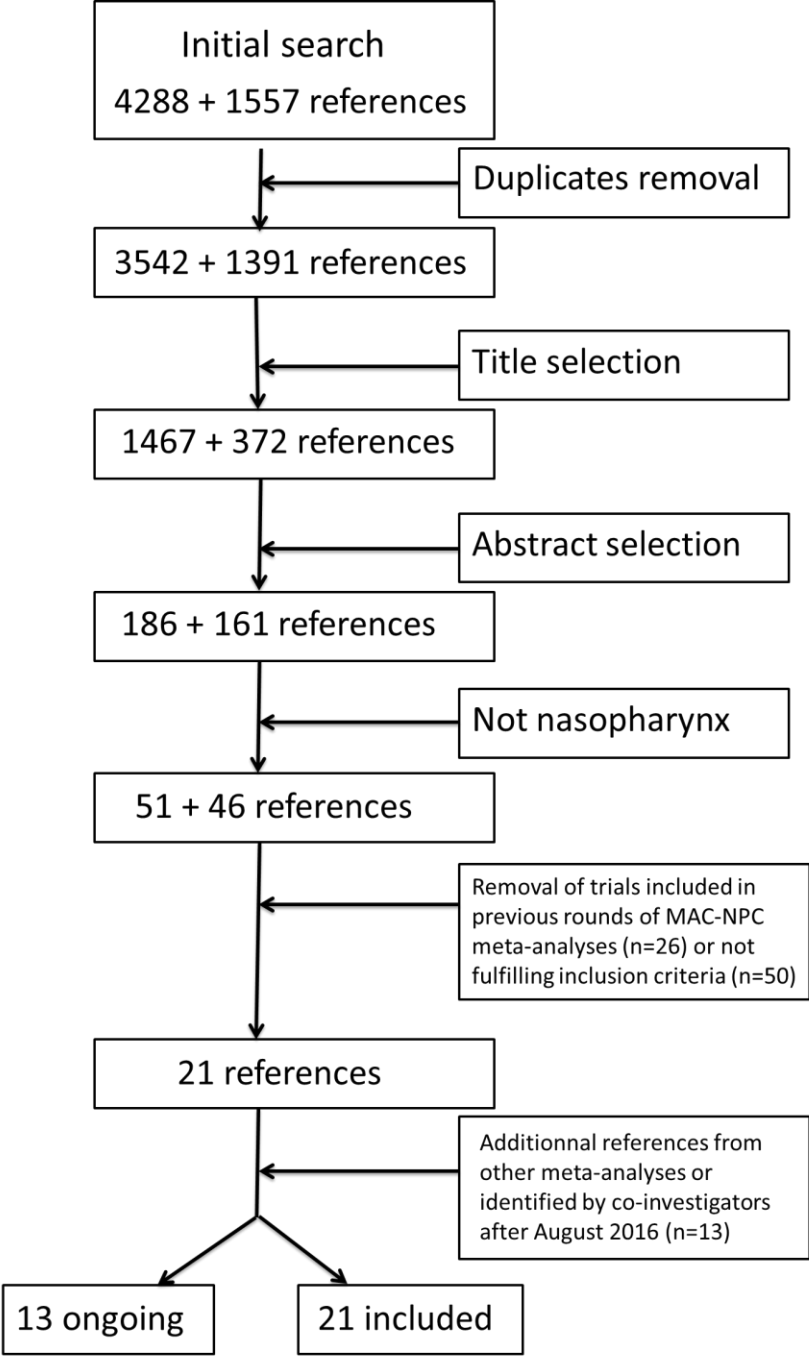
When two numbers are added: the first number correspond to the first round of research and the second one to the second round of research.

For the initial search, references are spead as follow: Pubmed = 2771, Embase = 1088, Scopus = 906, Wef Of Science = 758, Cochrane = 120, Clinical trials = 165, Meeting = 37.

Appendix B: Description of the trials comparing radiotherapy to radio-chemotherapy in locally advanced nasopharyngeal carcinoma

See abbreviations on page 44 and references in the references section (for older trials see previous MAC-NPC publications).

Table 1. Trials of concomitant (+/- adjuvant) chemotherapy versus none

Trial (ref)	Inclusion period	Patients randomized-analyzed	Stage	Histologic type	RT Dose & Duration	Chemotherapy timing	Chemotherapy Dose	Number of cycles	Median FU (years)
Kong F.[23]	2006 - 2006	200/ 200	III-IV	NA	66-75 Gy, 1.8-2 Gy/F, 5F/wk	Concomitant and adjuvant	Cisplatin 20mg/m², d $_{1-5}$ 5-FU 750mg/m²	3-5	NA
Zhou XF [17]	1994 - 1998	105	III-IV	WHO II/ III	70-76 Gy 2 Gy/F, 5F/wk	Concomitant	Cisplatin 100mg/m², d $_1$ 5-FU 750mg/m² d $_{1-4}$	2	NA
Xiong Q [18]	1996 - 1999	128	III-IVa	NA	68-70 Gy 2 Gy/F, 5F/wk	Concomitant	Cisplatin 30mg/m², d $_{1-5}$ 5-FU 750mg/m² d $_{1-5}$ CF 200mg d $_{1-5}$	2	NA
Chen CB [19]	1997 - 2000	130	III-IV	NA	68-72 Gy 2 Gy/F, 5F/wk	Concomitant	Cisplatin 10mg/m², d $_{1-5}$ 5-FU 250mg/m²/d; d $_{1-5}$	Last 2wk of RT	3.6
Fu JZ [20]	2003 - 2005	115	III-IV	NA	70 Gy 5fr/wk	Concomitant	Cisplatin 20mg/m² x2/w	7w	3.6
Du MJ [21]	2000 - 2004	80	III-IV	WHO II or III	70-76 Gy 2 Gy/F, 5F/wk	Concomitant	Cisplatin 30mg/m²	weekly x 8	5
Cai K [22]	2004 - 2010	155	III-IVa	NA	70-74 Gy 2 Gy/F, 5F/wk	Concomitant	Cisplatin 30mg/m², d $_{1-3}$ 5-FU 500mg/m² d $_{1-5}$	3	2.1

Table 2. Trials of induction chemotherapy versus None (followed by concomitant CT+RT in both arms)

Trial (ref)	Inclusion period	Patients randomized-analyzed	Stage	Histologic type	RT Dose & Duration	Chemotherapy timing	Chemotherapy Dose	Number of cycles	Median FU (years)
Tan T.[8]	2004 - 2012	180/ 172	III-IV	WHO II-III	2D: 70 Gy, 2 Gy/F, IMRT: 69.96 Gy, 2.12 Gy/F	Induction (R)	Gemcitabine 1000 mg/m² $d_{1,8}$ Carboplatin AUC 2.5 $d_{1,8}$ Paclitaxel 70 mg/m² $d_{1,8}$	3	3.3
						Concomitant	Cisplatin 40 mg/m²/wk	8	
Daoud J. GORTEC NPC 2006 [9]	2009 - 2012	83	II-IVa	NA	70 Gy, 2 Gy/F, 5F/w	Induction (R)	Docetaxel 75 mg/m² Cisplatin 75 mg/m² 5-FU 750 mg/m²/d, d_{1-5}	3	
						Concomitant	Cisplatin 40 mg/m²	7	
Sun Y.[10]	2011 - 2013	480/ 476	III-IVb	WHO II-III	NA	Induction (R)	Docetaxel 60 mg/m² Cisplatin 60 mg/m² 5-FU 600 mg/m²/d, d_{1-5}	3	1.5
						Concomitant	Cisplatin 100 mg/m²	3	
Gao J.[11]	2008 - 2009	112/ 112	III-IV	WHO II-III	70-74 Gy, 2 Gy/F, 5F/wk	Induction (R)	Cisplatin 30 mg/m², d_{1-3} 5-FU 450 mg/m², d_{1-3}	2	3.5
						Concomitant	Cisplatin 40 mg/m²/wk		
Cao SM [12]	2008-2015	476/476	III-IVB		2-2.33 Gy/F	Induction (R)	Cisplatin 80 mg/m²/3 wks 5-FU 800 mg/m²/d, $d_{1-5/3wks}$	2	4.2
						Concomitant	Cisplatin 80 mg/m²/3 wks		
NCT00201396 (Unpublished)	2003-2009	480	IV	NA	NA	Induction (R)	Mitomycin C Epirubicin Cisplatin 5-Fluorouracil Leucovorin	3	NA
						Concomitant	Weekly Cisplatin		

(R) : randomized arm

Table 3. Trials with comparison of two types of induction chemotherapy (followed by concomitant CT+RT in both arms)

Trial (ref)	Inclusion period	Patients randomized-analyzed	Stage	Histologic type	RT Dose & Duration	Chemotherapy timing	Chemotherapy Dose	Number of cycles	Median FU (years)
Jin T. [14]	2012 - 2014	278/ 276	III-IV	WHO II-III	69-70.4 Gy in 30-32 fractions over 6 weeks	Induction (1)	Docetaxel 75 mg/m² Cisplatin 75 mg/m² 5-FU 600 mg/m²/d, d1-4	3	3
						Induction (2)	Cisplatin 100 mg/m² 5-FU 800 mg/m²/d, d_{1-5}		
						Concomitant	Cisplatin 80 mg/m², q3w		

Table 4. Trials of induction and adjuvant chemotherapy versus None (with RT in both arms)

Trial (ref)	Inclusion period	Patients randomized-analyzed	Stage	Histologic type	RT Dose & Duration	Chemotherapy timing	Chemotherapy Dose	Number of cycles	Median FU (years)
Ying HM [16]	1995 - 1997	86/84	III-IV	NA	65.1-70.3 Gy, 1.85-1.9 Gy/F	Induction Adjuvant	Cisplatin 20 mg/m², d_{1-3} 5-FU 500 mg/m²/d, d_{1-3}	2 3	5.04

Table 5. Trials of induction versus adjuvant chemotherapy (with concomitant CT+RT in both arms)

Trial (ref)	Inclusion period	Patients randomized-analyzed	Stage	Histologic type	RT Dose & Duration	Chemotherapy timing	Chemotherapy Dose	Number of cycles	Median FU (years)
Lee A.[3] NPC 05-01 [13]	2006 - 2012	803/ 706	III-IVb	WHO II-III	Conventionnal RT: 66-70Gy, 5F/w Accelerated RT: 66-70Gy, 6F/w	Induction (1)	Cisplatin 100 mg/m² 5-FU 1000 mg/m²/d, d_{1-5}	3	3.3
						Induction (2)	Cisplatin 100 mg/m² Capecitabine 2000 mg/m²/d, d_{1-14}	3	
						Concomitant Adjuvant	Cisplatin 100 mg/m² Cisplatin 80 mg/m² 5-FU 1000 mg/m²/d, d_{1-4}	3 3	
Chakrabandhu S. [15]	2009 - 2013	94	Locally advanced	WHO II-III	70 Gy, 2.12Gy/F	Induction (1)	Docetaxel 75 mg/m² Cisplatin 75 mg/m² 5-FU 750 mg/m²/d, d_{1-4}	3	2.1
						Concomitant (1) Concomitant (2) Adjuvant (2)	Carboplatin AUC 1.5 Cisplatin 100 mg/m² Cisplatin 80 mg/m² 5-FU 1000 mg/m²/d, d_{1-4}	6 3 3	

---

[3] Design 3(CT)*2(RT) : CT 1 = concomitant + adjuvant ; CT 2 = induction (1) + concomitant ; CT 3 = induction (2) + concomitant. RT 1 = conventional RT ; RT 2 = accelerated RT.

Appendix C: Description of the trials comparing EGFR inhibitors with radiotherapy versus radiotherapy in locally advanced nasopharyngeal carcinoma.

Trial (ref)	Inclusion period	Patients randomized-analyzed	Stage	Histologic type	RT Dose & Duration	Chemotherapy timing	Chemotherapy Dose	Number of cycles	Median FU (years)
Huang XD [24]*		137/130	Locally advanced		Conventionnal RT: 70-76Gy	Concomitant	h-R3 100 mg IV/w	8	
Chen X [44]		60				Concomitant	Nimotuzumab		

* this trial will be excluded because hR3 is not a commonly studied anti-EGFR treatment
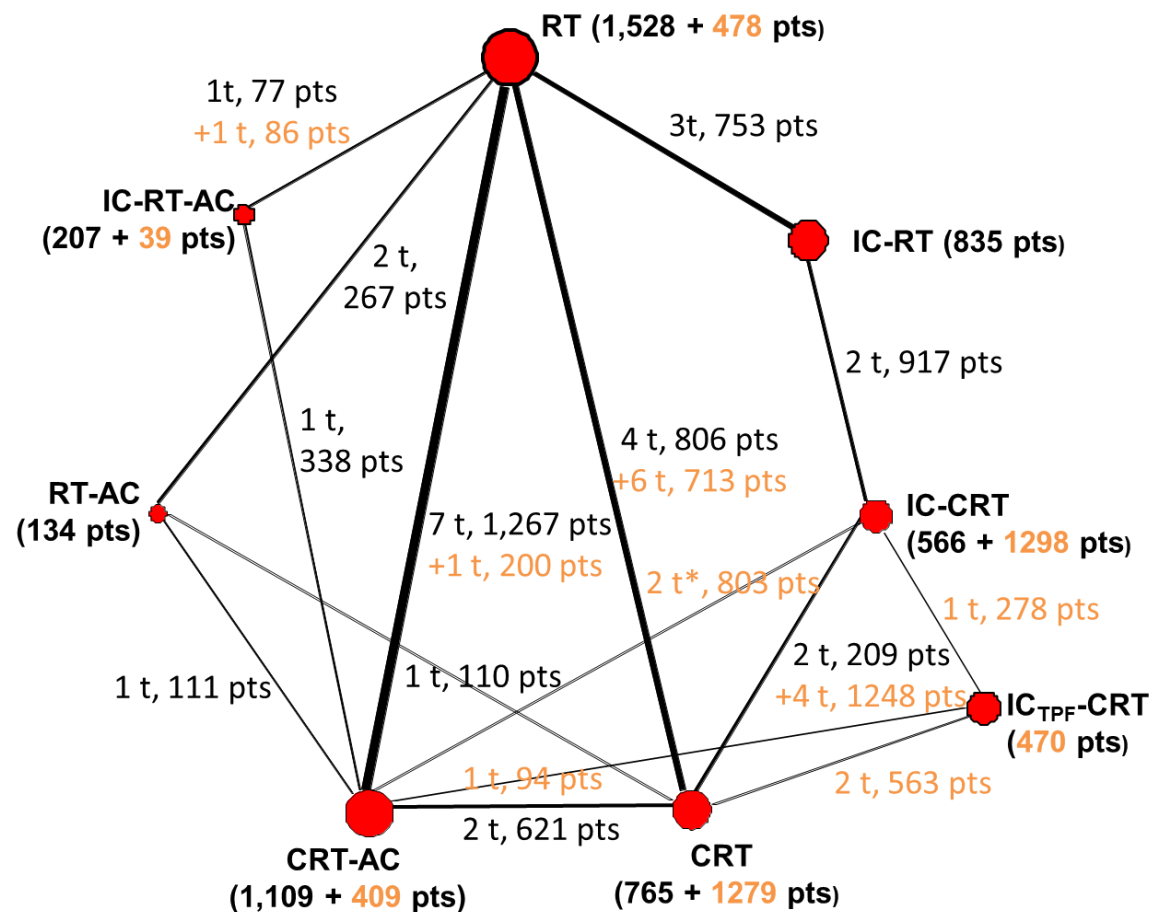
Appendix D: Description of the trials comparing altered fractionation radiotherapy versus radiotherapy (+/- chemotherapy) in locally advanced nasopharyngeal carcinoma.

Trial (ref)	Inclusion period	Patients randomized-analyzed	Stage	Histologic type	RT Dose & Duration	Chemotherapy timing	Chemotherapy Dose	Number of cycles	Median FU (years)
Lee A.[4] NPC 05-01 [13]	2006 - 2012	803/ 706	III-IVb	WHO II-III	Conventionnal RT: 66-70Gy, 5F/w Accelerated RT: 66-70Gy, 6F/w	Induction (1) Induction (2) Concomitant Adjuvant	Cisplatin 100 mg/m² 5-FU 1000 mg/m²/d, d_{1-5} Cisplatin 100 mg/m² Capecitabine 2000 mg/m²/d, d_{1-14} Cisplatin 100 mg/m² Cisplatin 80 mg/m² 5-FU 1000 mg/m²/d, d_{1-4}	3 3 3 3	3.3
Pan Z-Q.[25]	1998-2002	200	I-IV	NA	Conventional RT: 70Gy in 35 F (5F/w) Hyperfractionated RT: 78Gy in 60F (10F/w)	none	-	-	6.9
King Faisal Hospital (unpublished) NCT00535795	2007-?	200	NA	NA	Conv RT vs. Conv RT + accelerated boost	NA	NA	NA	NA
Lee A. NPC 9902[5] [26]	1999-2004	94	III-IV	WHO II-III	Conv RT (2Gy/F; 5F/w) Acc RT (2Gy/F ; 6F/w)	none	-	-	10.6
		95	III-IV	WHO II-III	Conv RT (2Gy/F; 5F/w) Acc RT (2Gy/F ; 6F/w)	Concomitant Adjuvant	Cisplatin 100mg/m² Cisplatin 80mg/m² 5-FU 1000mg/m²/d, d_{1-4}	2-3 3	

[4] Design 3(CT)*2(RT) : CT 1 = concomitant + adjuvant ; CT 2 = induction (1) + concomitant ; CT 3 = induction (2) + concomitant. RT 1 = conventional RT ; RT 2 = accelerated RT.
[5] Already included in the meta-analysis (second update).

Appendix E: Description of the network of treatment modalities in locally advanced nasopharyngeal carcinoma (see page 44 for abbreviations): in brown new trials (t).

RT (1,528 + 478 pts)

1t, 77 pts
+1 t, 86 pts

3t, 753 pts

IC-RT-AC
(207 + 39 pts)

IC-RT (835 pts)

2 t, 267 pts

2 t, 917 pts

1 t, 338 pts

4 t, 806 pts
+6 t, 713 pts

RT-AC
(134 pts)

IC-CRT
(566 + 1298 pts)

7 t, 1,267 pts
+1 t, 200 pts

2 t*, 803 pts

1 t, 278 pts

2 t, 209 pts
+4 t, 1248 pts

IC_{TPF}-CRT
(470 pts)

1 t, 111 pts

1 t, 110 pts

1 t, 94 pts

2 t, 621 pts

2 t, 563 pts

CRT-AC
(1,109 + 409 pts)

CRT
(765 + 1279 pts)

* NPC 0501 with lumping for induction chemotherapy PF et PX but divided according to RT modality (CF or AF)

Appendix F: Ongoing trials

Authors	Estimated completion date	No. patients	Treatment	Comment
Anti-EGFR : monoclonal antibody				
<u>Addition to RT ± CT</u>				
Biotech Pharmaceutical	Aug 2016	480	RT + conco cisplatin + placebo <u>vs.</u> RT + conco cisplatin + nimotuzumab	NCT01074021
<u>CT vs. anti-EGFR</u>				
Fudan University	Jun 2016 (Jun 2016)	320	TPF + RT + conco cisplatin <u>vs.</u> TPF + RT + nimotuzumab	NCT02012062 IMRT
Cytotoxic chemotherapy				
<u>Induction CT</u>				
Sun Yat-sen University	Nov 2018 (Nov 2020)	476	RT + conco cisplatin <u>vs.</u> Induction gemcitabine + cisplatin + RT + conco cisplatin	NCT01872962
Sun Yat-sen University			RT + conco cisplatin <u>vs.</u> Induction docetaxel + cisplatin + RT + conco cisplatin	NCT02512315
National Cancer Centre, Singapore	Jul 2018 (Jul 2023)	172	RT + conco cisplatin vs. Induction Gemcitabine, Carboplatin, Paclitaxel + RT + conco cisplatin	NCT00997906 Abstract ASCO 2014 ; 6003
Sun Yat-sen University	Aug 2018	235	3 arms but one outside randomization (Nomogram-predicted low risk) RT + conco cisplatin <u>vs.</u> Induction docetaxel/xeloda/cisplatin + RT + conco cisplatin	NCT02786641 Randomization for Nomogram-predicted high risk

Authors	Estimated completion date	No. patients	Treatment	Comment
Concomitant CT				
Sun Yat-sen University	Dec 2016	300	Induction gemcitabine + cisplatin + RT <u>vs.</u> Induction gemcitabine + cisplatin + RT + conco cisplatin	NCT01854203
Wei Jiang	Mar 2017 (Mar 2020)	360	TPF + RT <u>vs.</u> TPF + RT + conco cisplatin	NCT02434614
Sun Yat-sen University / Guangzhou	Nov 2022	462	RT vs. RT + conco cisplatin	NCT02610010 IMRT, stade II
Chinese Academy of Medical Sciences Li Gao	April 2018	590	RT vs. RT + conco cisplatin	NCT01817023 IMRT
Adjuvant CT				
Chinese University of Hong Kong	Dec 2018	150	RT +/- conco cisplatin <u>vs.</u> RT +/- conco cisplatin + adjuvant gemcitabine and cisplatin	NCT00370890 Randomization if relevated EBV DNA Abstract ASCO 2012; 5511
National Health Research Institutes, Taiwan	Dec 2019 (Dec 2022)	147	RT $\geqq$ 66 Gy (± induction and/or concurrent chemotherapy) <u>vs.</u> RT $\geqq$ 66 Gy (± induction and/or concurrent chemotherapy) + adjuvant mitomycin, epirubicin and cisplatine + oral Tegafur	NCT02363400 Randomization if relevated EBV DNA
NRG Oncology	April 2014 to Jun 2021	924	**Phase III:** no detectable EBV DNA post RTCT RT + conco cisplatin <u>vs.</u> RT + conco cisplatine + adjuvant PF **Phase II:** detectable EBV DNA post RTCT RT + conco cisplatin + adjuvant PF <u>vs.</u> RT + conco cisplatin + adjuvant gemcitabine/placlitaxel	NCT02135042 Phase II –III Uniquement phase III pour la MA

Specially for network meta-analysis

Authors	Estimated completion date	No. patients	Treatment	Comment
Guangzhou	Jan 2022	534	Induction TP + RT + conco cisplatin + xeloda + adjuvant xeloda <u>vs.</u> RT + conco cisplatin	NCT02621970

List of abbreviations

AC	Adjuvant chemotherapy
AF	Altered fractionation
CF	Conventional fractionation
CT	Chemotherapy
CRT	Concomitant chemoradiotherapy
IC	Induction chemotherapy
RT	Radiotherapy
NA	Not available
UICC	International Union Against Cancer
AJCC	American Joint Committee on Cancer
NPC	Naso-Pharynx Cancer
T	Tumor
N-	Negative node
N+	Positive node
wks	weeks
d	day
ci	continuous infusion
po	per oral
pts	patients
t	trial
B	Bleomycin
C	Cisplatin
Do	Docetaxel
E	Epirubicin
Fu	5-Fluorouracil
Hu	Hydroxyurea
Ox	Oxaliplatin
P	Paclitaxel
NCCS	National Cancer Center of Singapore
SKLOSC	State Key Laboratory of Oncology in Southern China
VUMCA	cavum (with letters in the opposite order)

**Meta-Analysis of Chemotherapy
in NasoPharynx Cancer**

APPENDIX G: How to send data to the Secretariat?

FORMAT FOR THE DATA

The preferred format for the information is described on the following pages. However, if a different format is more convenient for you, this should cause no great difficulty as long as it is clearly specified.

WAYS OF SENDING THE DATA

EITHER: 1. As long as it will not cause delay, **the easiest way for us to receive the data is by e-mail**[1]. We should be able to read any standard CD/DVD[2] if you let us know its specification. Please accompany disk with a printout of its contents.

OR: 2. Send a printout of from your database, (preferably with blank lines between each line of data to help us avoid punching errors), giving as much as possible of the information requested on the form.

OR: 3. If you would prefer to enter the individual patient data onto forms, please contact us and we wil prepare some for you.

It is important when trying to achieve a synthesis of the results of many different trials to **include all patients ever randomized**, whether eligible or not, whether or not they received their allocated treatment, whether properly followed up or not. Please try to get as near as possible to that ideal (or, at least please indicate where post randomization exclusions or losses have occurred), as long as to do so will not delay you sending us data. If it will cause a delay, then send us what you can now, and send the extra information later.

Please, fill out and mail (or fax) the enclosed form to the secretariat to facilitate data processing.

----

[1] Our e-mail address is :   jean-pierre.pignon@gustaveroussy.fr

Encrypted data or password protected database are highly recommended

[2] The preferred specification would be PC compatible, CD, ASCII Format.

Meta-Analysis of Chemotherapy in Naso-Pharynx Cancer

Suggested coding and format for sending data by network mail or usb-disk or CD

Variable	Format/Coding
Patient identifier	10 characters
Date of birth	dd/mm/yyyy, 99999999=Unknown
or age	6 blanks (columns 13-18), 2 digits (columns 19-20), 99=Unknown
Sex	1=Male, 2=Female, 9=Unknown
Performance Status	For Karnofsky index use 3 digits, for WHO or ECOG index use 2 blanks and one digit
Histology	1= WHO grade 1, 2= WHO grade 2, 3=WHO grade 3, 4= other, 9=Unknown
T	0=T_0, 1=T_1, 2=T_2, 3=T_3, 4=T_4, 5=T_X, 6=T_{is}, 9=Unknown
N	0=N_0, 1=N_1, 2=N_2, 3=N_3, 4=N_X, 9=Unknown
M	0=M_0, 1=M_1, 9=Unknown
Stage group	2 digits needed (1, 2, 3, 4A, 4B)
	Or 1 digit with blanks, 9=Unknown
Imaging method	1= Standard X-Ray, 2= CT scan, 3= MRI, 4= TEP-scanner, 9= Unknown
Treatment allocated (specify)	1= Control (e.g. No Chemotherapy), 2= Experimental (e.g Chemotherapy)
Induction chemotherapy (CT) – cycles* If treatment started	No. of cycles received 1= Full per protocol treatment received, 2= Dose reduction, 3= In case of poly-CT (or CT + anti-EGFR), one drug stopped before the other. 4=Both (2 and 3)

* or anti-EGFR, specify if number of cycles or injections,if anti-EGFR per oral give the duration of treatment in days

Variable	Format/Coding
concomitant chemotherapy – cycles*	2 digits, No. of cycles/injections received
If treatment started	coding, same as above for induction chemotherapy
Adjuvant chemotherapy (CT) – cycles*	No. of cycles received
If treatment started	coding, same as above for induction chemotherapy
Radiotherapy – technique	1 = 2D, 2 = 3D, 3 = IMRT, 9 = unknown

(PS: for patients treated with mixed externalbeam techniques – enter the technique used for major part of the course)

Variable	Format/Coding
Radiotherapy – boost	0=no, 1= brachytherapy, 2=stereotactic radiosurgery/radiotherapy, 3=others, 9=unknown
Radiotherapy – total dose	No. of Gy, e.g. 50.4 or 60.0
Radiotherapy – fractionation	2 digits, No. of fractions received
Radiotherapy – fractionation	1 = conventional fractionation, 2 = altered fractionation
Radiotherapy – Date commenced	dd/mm/yyyy, 99999999=Unknown
Radiotherapy – Date completed	dd/mm/yyyy, 99999999=Unknown
Date of randomization	dd/mm/yyyy, 99999999=Unknown
Date of last follow-up or death	dd/mm/yyyy, 99999999=Unknown
Survival status	0=Alive, 1=Dead
Cause of death	0=Alive, Cancer=1, Toxicity of chemotherapy=2, Toxicity of radiotherapy=3, Complication of surgery=4, Other=5 (including death related to second line treatment), 9=Unknown
Tumor failure[$],	0=No, 1=Yes
Date of tumor failure	dd/mm/yyyy, 99999999=Unknown
Nodal failure[$],	0=No, 1=Yes
Date of nodal failure	dd/mm/yyyy, 99999999=Unknown

[$] *A loco-regional failure corresponds either to a patient who never achieved a complete remission and had a T or N progression or to a patient who relapsed after an initial complete remission. If T and N failures are not available separately, please provide loco-regional failures and specify it when sending the data*

Variable	Format/Coding
Distant failure (metastasis)	0=No, 1=Yes
Date of distant failure (metastasis)	dd/mm/yyyy, 99999999=Unknown
Second primary	0=No, 1=Yes
Date of second primary	dd/mm/yyyy, 99999999=Unknown
Type of second primary	Lung=1, Esophagus=2, Stomac=3, Colorectal=4, Liver=5, Head& neck=6, Other=7 (specify), 9=Unknown
Localisation of second primary	0= within, 1=outside the irration field (if available)
Excluded from your analysis	0=No, 1=Yes
Reasons for exclusion	12 characters

Worst acute toxicity (Specification of toxicity grading system used for each factor)

Neutropenia	0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing
Febrile neutropenia	0=No, 1=Yes, 9=missing (or grade)
Thrombocytopenia	0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing
Anemia	0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing
Kidney failure	0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing
Dermatitis radiation	0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing
Rash acneiform	0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing
Infusion related reaction	0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing
Need for feeding tube	0=No, 1=Yes, 9=missing
Weight loss	0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 9=missing
Mucositis	0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing
Hearing loss	0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing
Neurotoxicity	0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing
Specify	12 characters

Variable   Format/Coding

Worst late toxicity (Specification of toxicity grading system used for each factor)

Cutaneous fibrosis   0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing

Xerostomia   0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing

Bone necrosis   0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing

Persistence of feeding tube after one year of treatment   0=No, 1=Yes, 9=missing

Endocrine dysfunction**   0=No, 1=Yes, 9=missing

Specify   12 characters

Hearing deficit**   0=No, 1=Yes, 9=missing (give grade if available)

Cranial nerve palsy**   0=No, 1=Yes, 9=missing

Asymptomatic temporal lobe necrosis$^{\mu}$ 0=No, 1=Yes, 9=missing

Symptomatic temporal lobe necrosis$^{\mu}$ 0=No, 1=Yes, 9=missing

Brainstem / Spinal cord damage   0=No, 1=Yes, 9=missing

Trismus**   0=No, 1=Yes, 9=missing

Visual deficit**   0=No, 1=Yes, 9=missing

Massive bleeding   0=No, 1=Yes, 9=missing

Stroke   0=No, 1=Yes, 9=missing

** give grade if available ; $^{\mu}$ or other classification with grade

.

Meta-Analysis of Chemotherapy in Nasopharynx Cancer

Trial / Protocol number_____

Trial Publication_____

_____

Name of Investigator_____

Address _____

_____

Telephone _____Fax _____

Email_____

Are you willing to take part in the Meta-analysis?   yes ☐   no ☐

Are the details of your trial correct?   yes ☐   no ☐

Is the most recent publication cited in the publication list?   yes ☐   no ☐

If no, please give correct details _____

Do you know of any other relevant trials not listed in the protocol?   yes ☐ no ☐

If yes, please provide details _____

_____

Is a copy of the trial protocol enclosed?   yes ☐ no ☐

If different from above, please give details of the appropriate contact for the collection of trial data:

Name_____

Address _____

Telephone _____Fax _____

Email_____

Was the trial approved by an ethics committee?   yes ☐   no ☐   If yes, please provide a copy

Did the trial have a target for patient accrual?   yes ☐   no ☐   Target: _____

Did the trial reach its target accrual?   yes ☐ no ☐

Date trial opened |__|__| |__|__| |__|__|__|__| Date trial closed |__|__| |__|__| |__|__|__|__|

Meta-Analysis of Chemotherapy in Nasopharynx Cancer (MAC-NPC)

What method was used to conceal randomisation?

Sealed envelope ☐   Central telephone ☐   Other ☐

What method of randomisation was used in this trial?

   Simple ☐   Permuted Blocks ☐   Minimisation ☐   Other ☐

What, if any, stratification factors were used? _____

What proportions was the trial designed to have in each arm? (e.g.1:1) _____

Please list treatments used in the arms of your trial (including local treatment and drugs given):

Arm 1: _____

Arm 2: _____

Arm 3: _____

Arm 4: _____

Which TNM or staging classification was used? _____

Which performance status was used?   WHO ☐   ECOG ☐   Karnofsky ☐   Other ☐

Which classification was used for toxicity?

Acute: WHO ☐   NCI-CTC ☐   Other ☐ Specify: _____

Late: RTOG/EORTC ☐   Other ☐ Specify: _____

Do some of the data requested be never available?

yes ☐   no ☐

If yes, please specify: _____

_____

What was the method used for patient follow-up?   Physical consultation ☐   phone call ☐   both ☐

If both, , please specify: _____

Any data supplied will remain the property of the trialist(s) who supplied it. These data will remain confidential and will

not be used, circulated or distributed in any way that allows access to individual patient data.

Permission for use of the IPD for methodological Research
I agree that an anonymised version of the trial data that I supplied for the meta-analysis can be used in other methodological research projects:

☐ Yes   ☐ No

Signed _____   Date _____

Please return to Jean-Pierre Pignon – Institut de Cancérologie Gustave Roussy
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