MACH-NC

Meta-Analysis of Chemotherapy in Head & Neck Cancer

Meta-Analysis of Chemotherapy in Head and Neck Cancers

An update with the addition of the trials of the period 2000-2010

Initiated by the Institut Gustave Roussy

Villejuif, France

Amendment #1 dated of November 15, 2019

(see three next pages)

Protocol **June 2012**

Amendment #1 dated of November 15, 2019
to the MACH-NC protocol dated of March 2012

Background

With the publication of MACH-NC first update in 2009 (1) and of two other articles since (2,3), new endpoints and methods have been introduced in our meta-analyses, as well as new hypotheses to validate. Therefore, the points described below are added to the protocol.

Accrual period

Date of completion of accrual was changed from "before 31st December 2010" et "before 31st December 2016" to take into account update trials search and data collection.

Endpoints

Addition of the 120-days mortality as proxy for treatment related mortality (2).

Statistical methods

The same methods will be used for 120-days mortality as for overall survival.

For the study of loco-regional and distant failures, the Fine and Gray model (4) will be used as in MARCH and the subgroup of MACH-NC patients treated by surgery (2,3,5). Three types of event will be analysed: loco-regional failure only, distant failure (with or without loco-regional failure) and death without failure. For each of them, the studied type of event will be analysed as the main event. The others will be analyzed as competing events. Alive patients without failure will be censored. The fixed-effect model using the log-rank expected number of events and variance will be also used for comparison with the previous work (1).

The restricted mean survival time difference (rmstD) between two arms will be computed to supplement the results based on hazard ratio. It is a clinically relevant absolute effect estimator with interesting statistical characteristics (5,6). The methods proposed by Lueza et al will be used (6).

<u>Analysis of subgroups of trials (subset analyses)</u>

As for the previous analysis (1), one main subset analysis will be defined for each timing group. Updated version of the previous subsets will be:

- Three categories for induction: neither PF nor TPF; PF; TPF.
  Previous categories were PF; other.
- Two categories for concomitant based on when the trials were included in the meta-analysis: initial meta-analysis; first and second updates.
  Previous categories were initial meta-analysis; first update.
- Four categories for adjuvant based on the locoregioal treatment used in the trials: surgery; radiotherapy; surgery + radiotherapy; other (mixed loco-regional treatment).

Previous categories were surgery; radiotherapy; surgery + radiotherapy.

- For the secondary question (sequential vs. concomitant radio-chemotherapy): platin based; other.
  No previous categories.

The subset analysis according to loco-regional treatment has been modified based on a detailed description of the old trials: a third category of radiotherapy alone (radiotherapy other) was added because several old trials did not correspond to the groups proposed in the protocol: standard radiotherapy, hyperfractionated or accelerated radiotherapy.

A subset analysis according to the type of chemotherapy has been added to allow indirect comparison between induction and concomitant trials. A subset analysis for these two timings will be performed according to four categories defined in the previous analysis (1): polychemotherapy with platin; polychemotherapy without platin; monochemotherapy with platin; monochemotherapy without platin.
For the concomitant group, an analysis in five categories will be performed to allow the comparison with previous analysis (1): polychemotherapy with platin (i.e. cisplatin or carboplatin) and 5FU; polychemotherapy with platin or 5FU; polychemotherapy without platin and 5FU; monochemotherapy with platin; monochemotherapy without platin. This corresponds to the categories proposed in the current protocol. All these analyses are exploratory.

Subgroup Analyses of subgroups of patients (subgroup analysis)

A previous analysis using the data of the first update of MACH-NC has shown an interaction between sex and chemotherapy effect in patients with surgery as (part of) their loco-regional treatment: higher effect was observed in women (3). Such analysis will be repeated on the data of the second update. This interaction will be studied in the group of patients treated by radical radiotherapy and the 3-level interaction sex*surgery*chemotherapy will be tested.

Modification of the list of the steering committee members

Two persons are leaving the committee: Ed Zhang and Jean-Louis Lefebvre. Two are joining it:

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1. INTRODUCTION AND BACKGROUND

Head and neck squamous cell carcinomas (HNSCC) are frequently occurring tumors with approximately 103 000 new cases (oral cavity, oropharynx, hypopharynx, larynx) in 2008 within Europe [1] and 52 000 estimated new cases in 2011 within the United States [2]. Each year, more than 500 000 new cases are diagnosed worldwide[1]. In oral cavity and pharynx carcinoma, at least 50 % of patients have locally advanced disease at diagnosis [3]. Surgery and/or radiation therapy were standard modalities used to achieve loco-regional control, but since the publication of the first Meta-Analysis on Chemotherapy in Head and Neck Cancers (MACH-NC)[4], platinum-based concurrent chemoradiotherapy has largely replaced radiotherapy alone in the treatment of unresectable squamous-cell carcinoma of the head and neck. Despite this therapeutic approach, the prognosis of HNSCC patients remains poor: the overall survival at 5-years was around 32% in the control group of the update of MACH-NC, a study which included 87 trials and more than 16 000 patients with locally advanced HNSCC[5].

In the past four decades, numerous randomized clinical trials have investigated the efficacy of chemotherapy in HNSCC, as an adjunct to surgery and/or radiotherapy. These trials have mainly included patients with locally advanced disease. Chemotherapy has been used in three ways in the treatment of locally advanced HNSCC: as induction treatment (neoadjuvant chemotherapy) ; concomitantly with radiotherapy ; as adjuvant treatment after radiotherapy and/or surgery. The MACH-NC study[4], a meta-analysis based on individual patients data which pooled the results of the randomized trials performed between 1965 and 1993 and compared loco-regional treatment to loco-regional treatment plus chemotherapy, has been updated recently to include trials performed between 1994 and 2000[5]. Trials including only nasopharyngeal carcinoma were not eligible. The overall pooled hazard ratio (HR) was 0.88 corresponding to an absolute benefit of 4.5% for chemotherapy, from 31.1% to 35.6%, at 5 years (5y.). There was a significant interaction (p<0.0001) between chemotherapy timing and treatment. The treatment according to chemotherapy timing is summarized below[5]:

Chemotherapy timing	Trial Number	Patient Number	HR (95% confidence interval)	p-value	Absolute benefit (5y.)	Heterogeneity p-value
Adjuvant	12	2567	1.06 (0.95-1.18)	0.31	-1%	0.35
Induction	34	5 311	0.96 (0.90-1.02)	0.18	2.4%	0.59
Concomitant	62	9 615	0.81 (0.78-0.86)	<0.0001	6.5%	0.0001
Total	108*	17 493*	0.88 (0.85-0.92)	<0.0001	4.5%	<0.0001

* some trials (and patients) with more than two arms were counted twice

In the updated version of MACH-NC[5], an indirect comparison between induction and concurrent chemotherapy was also undertaken. It showed that the effect of concomitant chemotherapy compared with no chemotherapy on survival was significantly higher than the effect of induction chemotherapy compared with no chemotherapy (p = 0.0001).

In addition, numerous other trials have investigated the role of altered fractionation compared to conventional radiotherapy in advanced HNSCC. A meta-analysis of these trials showed a survival benefit in favour of altered fractionation, which was highest for hyperfractionated RT without dose reduction (absolute benefit in overall survival: 8% at 5 years)[6]. Therefore it remains unclear which fractionation regimen or concurrent chemotherapy is the best for patients with locally advanced HNSCC.

Recently, there has been renewed interest for investigations on induction chemotherapy in locally advanced head and neck cancer (LAHNC), especially with the addition of taxane to platinum-5FU based induction regimen (TPF *vs* PF). The MACH-NC Group has conducted and presented a meta-analysis of these TPF trials, which shows that the addition of TPF provides a significant benefit over PF in terms of overall survival, progression-free survival, locoregional control and distant control[7].

Meta-analysis of individual patient data are important databases, providing unique information about treatment outcomes. As clinical trials keep being conducted, it is of the utmost importance to conduct regular updates of meta-analyses. This update will collect trials conducted in the last ten years in HNSCC field, and is therefore warranted. Regarding concomitant trials there are other relevant points in favour of an update of the meta-analysis.

- Firstly, fifteen **trials have been conducted and published since 2000** (see Appendix A) to investigate the role of chemotherapy, mostly delivered concomitantly to radiotherapy in HNSCC. The inclusion of these trials will **increase the power of the meta-analysis, allow more detailed subgroup analyses, and keep the database up-to-dat**e.
- Second, an **update of the follow-up of the older trials is needed** in order to evaluate long term benefit of therapy.
- Third, **the collection of data on both acute and long term toxicity and compliance to treatment** will be crucial to investigate long term quality of life associated with these more aggressive therapies. This could help better explain the interaction between age and treatment effect seen in the previous round of the meta-analysis.
- Fourth, **new prognostic factors such as HPV infection** are becoming increasingly important, and gathering the data available on this topic would allow a wider view[8].

- Fifth, the new trials included will allow to validate the **surrogate endpoints** that have been determined in an earlier study (progression-free survival and event-free survival)[9] on an external population.
- Last, this update goes along with an **update of the fractionation** meta-analysis (ongoing) and an **update of the induction** meta-analysis including TPF trials[7]. This final update will **allow a detailed and complete analysis of treatments in locally advanced HNSCC**, and will be included in a large network meta-analysis (see below).

It was therefore decided to update the MACH-NC meta-analysis in order to include the most recent trials and to obtain a longer follow-up for the most recent trials of MACH-NC. The marked increase in statistical power due to the increased number of patients will now allow to better analyze questions which were addressed in the previous MACH-NC project: the impact of chemotherapy separately on distant metastases and local-regional control; which type of chemotherapy can offer the best effect; which population is more likely to benefit from the use of each type of chemotherapy. The database will also provide the opportunity to evaluate the adverse effects due to the different chemotherapy regimens.

The meta-analysis will be based on individual patient data[10, 11] and will use a similar methodology to that used in the MACH-NC study[4, 5], the Breast Cancer Overview[12] and the Prophylactic Cranial Irradiation Overview[13]. 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[14]. 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[10, 11]. Updated follow-up information will be sought which will enable us to report on long-term survival. New data on compliance and toxicity will be collected for the new trials and the trials included in the MACH-NC update[5]. Eventually, all these trials will be included in a large network meta-analysis to try and rank treatments according to their efficacy[15].

In summary, the update of this unique database aims to provide the most comprehensive analysis on the effect of chemotherapy locally advanced HNSCC. It should help to define therapeutic guidelines and to generate new hypotheses to be tested in further randomized trials.

2. OBJECTIVES

The **main objective** is to assess **the addition of chemotherapy in the treatment of HNSCC** on **long-term overall survival** based on updated individual data from randomized trials.

First comparison

Local treatment (radiotherapy and/or surgery)

↗

↘

Local treatment (radiotherapy and/or surgery) **+ chemotherapy**

Trials comparing the same treatment strategy +/- the addition of chemotherapy will also be included. These trials are mostly trials of

- induction chemotherapy followed by radiotherapy with/without concomitant chemotherapy (included in the concomitant analysis)
- concomitant chemoradiotherapy with/without induction chemotherapy (included in the induction analysis)
- induction chemotherapy followed by radiotherapy with/without adjuvant chemotherapy (included in the adjuvant analysis)
- concomitant chemoradiotherapy with/without adjuvant chemotherapy (included in the adjuvant analysis)

Second comparison

Sequential chemotherapy and radiotherapy

↗

↘

Concomitant (or alternating) chemoradiotherapy

Secondary objectives

- Effect of Chemotherapy on time to loco-regional failure, time to distant failure, head and neck cancer mortality and non-head and neck cancer mortality
- Comparison of observance, acute toxicity and late toxicity between the two treatment modalities.

- Investigation of the interaction between the treatment effect and the type of chemotherapy (indirect comparison).
- Investigation of the interaction between the treatment effect and the prognostic factors and patient characteristics (subgroup analyses).
- Consitution of a large network based meta-analysis to compare the different treatment strategies and rank them in terms of efficacy
- The trials will be included on the study of the value of event-free survival[1] as surrogate endpoint for overall survival.

3. TRIALS SELECTION CRITERIA

All trials must satisfy the following criteria:

Trials must

- Compare local treatment (LT) plus chemotherapy to LT alone OR sequential versus concomitant chemoradiotherapy.
- Be randomized in a way which precludes prior knowledge of treatment assignment.
- Be unconfounded, except changes of the radiotherapy in the experimental arm (decreased dose or increased duration without change in fractionation).
- Have completed accrual before 31st December 2010.
- Include patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx.
- Not include patients with metastatic disease.

Patients should

- Not have a second tumor.
- Not receive prior surgery, except for those enrolled in trials of postoperative treatment.
- Not receive prior radiotherapy.
- Not receive prior chemotherapy.
- Undergo a potentially curative locoregional treatment.

4. TRIAL SEARCH

[1] Event-free survival is a mixt of disease-free survival for the patients who have complete (R0) surgery and progression-free survival for those who have incomplete surgery or radical radiotherapy.

Data from all published and unpublished randomized trials making the above comparisons in HNSCC patients will be sought using electronic database searching for the period 2000-2010 (trials previously published or presented were included in the previous rounds of the meta-analysis) (Medline, Cancerlit, DARE, Embase, CCT meta-register), hand searching (review articles, meeting proceedings) and by contacting experts in the field.

The search strategy and trials flow chart are detailed in **Appendix A.**

5. DESCRIPTION OF THE TRIALS INCLUDED

Appendix B1 describes the trials comparing local treatment +/- chemotherapy in HNSCC which accrued before 2010 and are potentially eligible for the meta-analysis. In all the trials except one, the local treatment was radiotherapy. Overall fifteen trials representing 2996 patients have been identified.

- Six trials (750 patients) compared concomitant chemotherapy to no chemotherapy (table 1, appendix B1)
- Seven trials (1 725 patients) compared induction chemotherapy to no chemotherapy (all having concomitant chemoradiotherapy as the local treatment except one for which the local treatment is radiotherapy alone). Six of these trials use docetaxel-cisplatinum-5FU chemotherapy (table 2, appendix B1)
- Two trials (521 patients) compared induction chemotherapy to concomitant or alternating chemotherapy, both in the laryngeal preservation setting (table 3, appendix B1)
- Four trials (467 patients) have been excluded because they did not fulfil the inclusion criteria (table 4, appendix B1).

Table: Number of new trials, patients and of updated trials and patients

	Number of patients (trials)			
CT timing	**MACH-NC (before 1993)[4, **]**	**MACH-NC update (1993-2000)[5, %]**	**MACH-NC update (2000-2010) [%%]**	**Total**
Concomitant*	3 891 (28)	5 704 (24)	750 (6)	10 345 (58)
Neoadjuvant*	5 269 (31)	0	1 725 (7)	6 994 (38)
Adjuvant	2 202 (10)	713 (1)	0	2 915 (11)
Sequential versus concomitant radio-chemotherapy	861 (6)		521 (2)	1 382 (8)
Total	12 223 (75)	6 417 (25)	2 996 (15)	21 636 (115)

***** include trials combining two timings of chemotherapy; ** Including four new trials, see next page
[%] updated follow-up and new data (toxicity, compliance, HPV) will be sought; [%%] New trials
References of the new trials can be found in **the reference section**, and in the published reports of the first two rounds of the meta-analysis for the older trials[4, 5].

The trials comparing the same treatment strategy (combining radiotherapy and chemotherapy) +/- the addition of another chemotherapy timing will also be included. The data of five trials has been already collected, but their results were not included in the previous meta-analyses (except UKHAN trial) which did not include such type of trials (**appendix B2** provides a description of these trials). A sensitivity analysis with and without these trials will be performed. These trials compared:

- concomitant chemoradiotherapy with/without induction chemotherapy (included in the induction analysis): six trials (1469 patients – appendix B1, table 2).
- induction chemotherapy followed by radiotherapy with/without concomitant chemotherapy (included in the concomitant analysis): two trials (165 patients - appendix B2)
- induction chemotherapy followed by radiotherapy with/without adjuvant chemotherapy (included in the adjuvant analysis): two trials (348 patients - appendix B2)
- concomitant chemoradiotherapy with/without adjuvant chemotherapy (included in the adjuvant analysis): one trial (UKHAN 320 patients - appendix B2).
- adjuvant chemoradiotherapy with/without concomitant chemotherapy (included in the concomitant analysis): one trial (UKHAN 314 patients - appendix B2).

6. CRITERIA OF EVALUATION

6.1 ENDPOINTS

The main endpoint will be **overall survival**, because of its importance and because of the reliability of the measurement. Cause of death will be studied, if possible.
Secondary endpoints such as time to local failure, regional failure, distant failure, or second primary, as well as event-free survival and specific survival (head and neck cancer mortality and non head and neck cancer mortality), treatment compliance, early and late toxicity will be also considered. Event-free survival is defined as the time from randomization to local, regional or distant failure or death from any cause. Ssecond primary are not considered an event for this endpoint.

6.2 PROGNOSTIC FACTORS

The prognostic factors (groups) that will be considered are :

- Age (50 or less, 51-60, 61-70, 71+).
- Sex (male, female).
- Performance status (WHO or equivalent, 0, 1, 2+).
- Site of the primary tumor (oral cavity, oropharynx, larynx, hypopharynx, other).
- Stage (I-II, III, IV).
- HPV status, when available

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.

- Date of birth or age.
- Sex.
- Performance status
- Site of the primary.
- TNM staging (if not available stage ; in any case, provide information on classification used).
- Smoking status (never, former, current; pack-year)
- HPV status (when available)
- Type of HPV test (p16, ISH,…)
- Allocated treatment.
- Date of randomization.
- Number of cycles of induction chemotherapy received.
- Number of cycles (or injection) of concomitant chemotherapy received.
- Tumor surgery before RT (no/yes)
- Radiotherapy started / not started
- Date first day radiotherapy
- Date last day radiotherapy
- Total administered dose of radiotherapy
- Total number of fractions of radiotherapy
- Type of radiotherapy (2D, 3D, IMRT)

- Acute toxicity (neutropenia, thrombocytopenia, anemia, kidney failure, cutaneous, need for feeding tube, mucositis, hearing loss, neurotoxicity)
  + Specification of toxicity grading system used (if NCI-CTC specify the version)
- Late toxicity (cutaneous fibrosis, xerostomia, bone necrosis, persistence of feeding tube after one year of treatment)
  + specification of toxicity grading system used
- Date of last follow-up.
- Survival status.
- Cause of death.
- Date of tumor failure, date of nodal failure
- Date of distant failure
- Date and type of second primary
- Whether excluded from trial analysis.
- Reason for exclusion (if applicable).

Appendix C 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 more than 18 000 patients it would be possible using a two-sided test at a 5% significance level to detect, with a power exceeding 99.9%, an absolute improvement in survival from 30 % to 35 % at 5-years. Therefore, the study will have enough power to detect the small but clinically important difference which is likely to occur in clinical oncology.

Trial characteristics will be reported in tabular form, information will include patient numbers, period of recruitment, population description, treatment details and median follow-up. Median follow-up will be computed using the reverse Kaplan-Meier method[16].

SURVIVAL ANALYSIS

The main analysis will be performed separately for each timing of chemotherapy on the endpoint of overall survival for the comparison of local treatment (radiotherapy and/or surgery) ± chemotherapy. A separate analysis for the trials comparing sequential radio-chemotherapy to concomitant radio-chemotherapy will be performed. Additional analyses will be performed on the endpoints of event-free survival, loco-regional failure rate, distant failure

rate, head and neck cancer mortality and non head and neck cancer mortality, if sufficient data are available.

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 stratified by trial**, and the log-rank expected number of deaths and variance will be used to calculate individual and overall pooled hazard ratios by the fixed-effect model[12]. 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 chemotherapy compared with those who were not. For comparing compliance or toxicity rates, overall pooled odds ratio stratified by trials will be calculated by a fixed-effect model.

Head and neck cancer and non-head and neck cancer mortality using method similar to that used in the Meta-Analysis of Radiotherapy in Carcinoma of Head and neck (MARCH) [6] will be studied. An unbiased, although potentially diluted, logrank analysis of head and neck cancer mortality was obtained indirectly by subtracting the logrank statistic for non-head and neck 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). Non-head and neck cancer mortality was defined as death of known cause without recurrence and not considered as a head and neck cancer death. Head and neck cancer mortality included death of any cause with prior recurrence or progression, death from head and neck cancer and death from unknown cause.

The χ^2 heterogeneity tests will be used to test for gross statistical heterogeneity, the I^2 statistic[17] will be used as a measure of consistency among trials. In case of important and unexplained heterogeneity, a random effects meta-analysis will be performed to take this heterogeneity into account. Stratified survival curves will be estimated for control and experimental groups using annual death rates and hazard ratios. They will be used to calculate absolute benefit at 5-years with its 95% confidence intervals[12]. All p-values will be two-sided A test with a value inferrior to 5% will be considered significant, except for the test of between trial heterogeneity for which a 10 % threshold will be used.

SUBGROUP AND SUBSET ANALYSES

To explore whether the treatment effect varies according to trial (e.g. timing of chemotherapy, type of drug…) or patient (e.g. age, performance status, HPV status…) characteristics, 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 [18].

Several comparisons of the results of chemotherapy in **groups of trials** classified according to the type of chemotherapy and radiotherapy are planned as exploratory analyses for each group of trials defined by chemotherapy timing:

- Different types of chemotherapy
    - Platinum compounds +/- 5-FU
    - Platinum polychemotherapy (other than Platinum 5-FU)
    - Other mono or polychemotherapy
- Different types of locoregional treatment
    - Standard radiotherapy
    - Hyperfractionated and/or accelerated radiotherapy
    - Postoperative radiotherapy (surgery + radiotherapy)
    - Surgery
    - Others

Among chemotherapy regimens, indirect comparisons will be used to compare:

- Cisplatin versus Cisplatin-5FU as concomitant chemotherapy
- Cisplatin based versus carboplatin based chemotherapy, adjusted for the use of 5-FU.

Lastly, an indirect comparison of the trials according to timing of chemotherapy will be performed.

SENSITIVITY ANALYSES

Hazard ratios for overall survival will also be calculated excluding any trials that are clear outliers or particular, e.g. trials that are confounded (for instance addition of chemotherapy but lower dose of radiation or hyperfractionation using split course resulting in the same total time). The impact of the exclusion of these trials on the results will be studied, as in the previous analyses[4, 5]. The following sensitivity will be performed:

- Exclusion of trials of local treatment and chemotherapy +/- another chemotherapy timing (appendix B2)
- exclusion of old trials
- exclusion of small trials
- exclusion of confounded trials
- exclusion of trials with a follow-up shorter than 5 years
- exclusion of trials for which date of randomization and events are not available, as data checking will be incomplete in this case.

SURROGATE ENDPOINT VALIDATION

The study of the usefulness of loco-regional failure rate, and event-free survival as surrogate endpoints of overall survival will imply to analyze the data at the individual and trial levels. Such an analysis has been performed and has shown that event-free survival is a better correlate with overall survival than locoregional control and could be used as a surrogate for overall survival to assess the treatment effect of radiotherapy and chemotherapy in randomised trials of locally advanced HNSCC[9]. The inclusion of new trials will be used as an external validation of this finding. A specific protocol will be prepared for this study based on the new trials included in MACH-NC and MARCH.

NETWORK META-ANALYSIS

Network-based meta-analysis, also known as mixed treatment comparisons (MTC), is a recently developed statistical method that deals with conditions where multiple treatments have been investigated that have not been compared altogether[15, 19]. It allows to evaluate all possible pair-wise comparisons based on direct and indirect evidence, and to rank the different treatments according to their relative efficacies. A network meta-analysis will be performed using the trials included based on the updated MARCH and MACH-NC studies and a specific protocol prepared.

IMPACT OF COMPLIANCE ON TREATMENT EFFECT

A separate analysis plan will be prepared to study the impact of non compliance on treatment effect.

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 MACH-NC Trialists' Collaborative 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 close collaboration with the Steering Committee.

The Steering Committee will include international experts in the field of medical oncology, radiotherapy, and surgery involved in head and neck 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 MACH-NC Trialists' Collaborative 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.

An investigator meeting will be organized by the Secretariat to discuss the preliminary results of the meta-analysis and to plan additional analyses.

10. PRACTICAL CONSIDERATIONS

The Secretariat, located in the Biostatistics Department at Institut 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.

11. PUBLICATION POLICY

Any publication arising from this project will be made on behalf of the MACH-NC Collaborative Group and include a list of all collaborators.

APPENDIX A: **Trial search strategy**

Search Equations

Database	Search Equation	Limits	Réf.	Date of Search
PubMed MEDLINE	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 hypopharyn* OR nasopharyn* OR oropharyn* OR pharyngeal OR pharynx OR hypopharyn* OR nasopharyn* OR oropharyn*) 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	2010-2000	538	23 nov. 2010
SCOPUS (Elsevier)	Your query: ((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 **hypopharyn*** OR **nasopharyn*** OR **oropharyn*** OR **pharyngeal** OR **pharynx** OR **hypopharyn*** OR **nasopharyn*** OR **oropharyn***))) 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	2010-2000	578	26 nov 2010

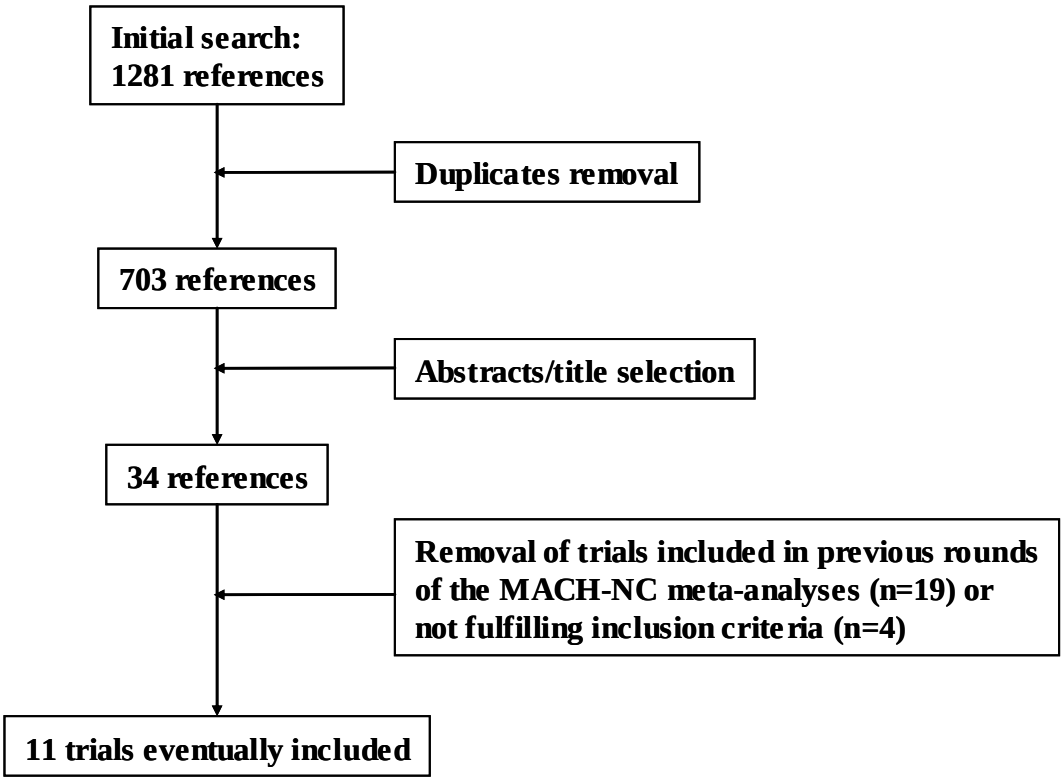
	tirapazamine OR **gefitinib** OR **erlotinib** OR **lapatinib** OR **nimotuzumab** OR **gemcitabine** OR **amifostine** OR **methotrexate**))) AND ((TITLE-ABS-KEY(**random** OR **randomise** OR **randomize** OR **randomised** OR **randomized** OR **rct** OR **rcts** OR **single-blind** OR **double-blind**) 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 Central Register of Controlled Trials	There are **155** results out of **635167 records** for: "**"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* OR pharyngeal OR pharynx OR hypopharyn* OR nasopharyn* OR oropharyn*** 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**"	2000-2010	155	29 nov 2010
Web Of Science Meeting Abstracts	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 hypopharyn* OR nasopharyn* OR oropharyn* OR pharyngeal OR pharynx OR hypopharyn* OR nasopharyn* OR oropharyn*) AND Topic=(chemotherapy OR chemoradiation OR chemoradiotherapy OR radiochemotherapy OR radio-chemotherapy 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.	2000-2010	10	29 nov 2010

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Found 131 studies with search of: random* | Interventional Studies | head and neck cancer AND squamous | drug therapy OR chemotherapy | received on or after 01/01/2000

http://clinicaltrials.gov/ct2/results?term=squamous+AND+random*&recr=&rslt=&type=Intr&cond=head+and+neck+cancer&intr=drug+therapy+OR+chemotherapy&outc=&lead=&spons=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&gndr=&rcv_s=01%2F01%2F2000&rcv_e=&lup_s=&lup_e=

Trial Flow Chart (2012 initial search)



APPENDIX B1: Description of the trials comparing local treatment with or without chemotherapy

Table 1: Trials of Concomitant chemotherapy vs none

Trial (ref)	Inclusion period	Sites	Stage	Drug	Chemotherapy dose (mg/m²)	Radiotherapy dose (Gray) /duration (weeks)	Patients analyzed /randomized	Median follow-up (years)
Concomitant vs none								
Ruo Redda[20]	1992-1995	OC, OP, HP, L	III, IV	Cb	45 mg/m² d_{1-5}, $wk_{1,3,5,7}$	70 Gy, 2 Gy/fraction	164	NA
Sharma[21]	2003-2005	OP, NP	III, IV	C	40 mg/m² d_1, wk_{1-7}	70 Gy, 2 Gy/fraction	153	1.8
Ezzat[22]*	1998-2001	OC, OP, HP, L	III, IV	MMC	15 mg/m² d_5	64.8 Gy, 2 Gy/F, 6F/wk (5.5 wks OTT)	40	0.9
Bensadoun[23]	1997-2002	OC, OP, HP, L	III, IV	C F F	100 mg/m², $d_{1, 22, 43}$ 750 mg/m²/d, d_{1-5} 430 mg/m² $d_{22-26, 43-47}$	80.4 Gy 1.2 Gy/fraction bid	163/171	3.8
Racadot[24]	1994-2002	**Post-op** OP, HP, L	NA	Cb	50 mg/m² $d_{1,3}$ weekly	54 Gy (R0) or 72 (R1-2) Gy, 1.8 Gy/fraction	144/146	8.8
Argiris[25]	1994-2002	**Post-op** OP, HP, L	NA	Cb	100 mg/m² weekly	59.4, 1.8 Gy/fraction	72/76	5.3

* : 3-arm trial (RT, accelerated RT, accelerated RT + concomitant MMC)

OP=oropharynx; OC=oral cavity; HP=hypopharynx; L=Larynx; CT=chemotherapy; NA=not available RT=radiotherapy; F=Fluorouracile; C=Cisplatin, Cb=carboplatin; d=day; OTT=Overall Treatment Time; wk=week

Table 2: Trials of induction chemotherapy

Trial (ref)	Inclusion period	Sites	Stage	Drug	Chemotherapy dose (mg/m²)	Radiotherapy dose (Gray)/duration (weeks)	Patients analyzed /randomized	Median follow-up (years)
Induction vs none (conco in both arms)								
Gupta[26]	2005-07	OP	III, IV	C F C	75 mg/m² $d_{1,22,43\ (induction)}$ 800 mg/m², $d_{1\text{-}3,\ 22\text{-}24,\ 43\text{-}45\ (induction)}$ 35mg/m² $wks_{1\text{-}7\ (concomitant)}$	66-70 Gy, 2 Gy/fraction	105/?	2
Paccagnella[27]	2003-2006	OC, OP, HP	III, IV	Do C F C F	75 mg/m² $d_{1,22,43\ (induction)}$ 75 mg/m² $d_{1,22,43\ (induction)}$ 800 mg/m² $d_{1\text{-}4,\ 22\text{-}25,\ 43\text{-}46\ (induction)}$ 20 mg/m² $d_{1\text{-}4}$ $wks_{1\text{-}6\ (concomitant)}$ 800 mg/m² $d_{1\text{-}4}$ $wks_{1\text{-}6\ (concomitant)}$	70 Gy, 2 Gy/fraction	101/101	3.5
Hitt[43,£]	2002-2007	OC, OP, HP, L	III, IV	Do C F C	75 mg/m² $d_{1,22,43\ (induction)}$ 75 or 100 mg/m² $d_{1,22,43\ (induction)}$ 750 or 1000mg/m² $d_{1\text{-}5,\ 22\text{-}26,\ 43\text{-}47}$ (induction) 100 mg/m² $d_{1,22,43\ (concomitant)}$	70 Gy, 2 Gy/fraction	439/439	4.6
Cohen[40]	2004-2009	OC, OP, L	IVa, IVb	Do C F Do F Hu Hu	75 mg/m² $d_{1,\ 22\ (induction)}$ 75 mg/m² $d_{1,\ 22\ (induction)}$ 750 mg/m² $d_{1\text{-}5,\ 22\text{-}26\ (induction)}$ 25 mg/m² $d_1 wks_{1,3,5,7,9\ (concomitant)}$ 600 mg/m²/day $d_{1\text{-}5} wks_{1,3,5,7,9\ (concomitant)}$ 500 mg × 2 PO $d_{1\text{-}5}$ $wks_{1,3,5,7,9\ (concomitant)}$ 500 mg PO d_6 $wks_{1,3,5,7,9\ (concomitant)}$	75 Gy, 1.5 Gy/fraction, bid	273/285	Not available
Knecht[42]	Not available	L, HP	III, IV	C Do C F	100 mg/m² $d_{1,\ 22,\ 43\ (concomitant)}$ 75 mg/m² $d_{1,\ 22,\ 43\ (induction)}$ 100 mg/m² $d_{1,\ 22,\ 43\ (induction)}$ 1000 mg/m² $d_{1\text{-}4,\ 22\text{-}25,\ 43\text{-}46\ (induction)}$	70 Gy, 2 Gy/fraction	278(?)/278	Not available
Ghi[41]	Not available	OC, OP, HP	III, IV	C Do F	80 mg/m² $d_{1,22\ (induction)}$ 75 mg/m² $d_{1,22\ (induction)}$ 800mg/m² $d_{1\text{-}4,\ 22\text{-}25\ (induction)}$	70 Gy, 2 Gy/fraction (5 days per week for 7 weeks)	258/261[*]	Not available

Trial (ref)	Inclusion period	Sites	Stage	Drug	Chemotherapy dose (mg/m²)	Radiotherapy dose (Gray)/duration (weeks)	Patients analyzed /randomized	Median follow-up (years)
				C F	20 mg/m² $d_{1\text{-}4}$ $wks_{1,6\ (concomitant)}$ 800 mg/m² $d_{1\text{-}4}$ $wks_{1,6\ (concomitant)}$			
Induction vs none (without concomitant chemotherapy)								
Zhong[39, **]	2008-2010	OC	III, IVA	Do C F	75 mg/m² $d_{1,\ 22\ (induction)}$ 75 mg/m² $d_{1,\ 22\ (induction)}$ 750 mg/m² $d_{1\text{-}5,\ 22\text{-}26\ (induction)}$	54-60 Gy, 1.8-2 Gy/fraction (5 days per week for 6 weeks)	256/256	2.5

OP=oropharynx ; OC=oral cavity ; HP=hypopharynx ; L=Larynx ; CT=chemotherapy ; RT=radiotherapy ; C=cisplatin ; Do=docetaxel ; F=Fluorouracil ; Hu=hydroxyurea ; d=day; wk=week

£ Three-arm trial: CF, DoPF, no induction with concomitant cisplatin in the 3-arms. Dose of C and F were higher in the CF arm than in the DoCF arm.

* Two by two design: addition of induction DoCF to RT plus concomitant treatment; RT + cisplatin vs RT + cetuximab. The two cetuximab arms were not eligible for his meta-analysis

** Locoregional treatment is surgery plus postoperative radiotherapy.

Table 3: Trials of inductionchemoterapy plus radiotherapy versus concomitant (or alternating) chemo-radiotherapy

Trial (ref)	Inclusion period	Sites	Stage	Drug	Chemotherapy dose (mg/m²)	Radiotherapy dose (Gray) / duration (weeks)	Patients analyzed /randomized	Median follow-up (years)
Induction vs concomitant (laryngeal preservation setting)								
Prades[28]	2001-05	HP	III,IV	C F C	100 mg/m², $d_{1, 22, 43\ (induction)}$ 1000 mg/m², $d_{1\text{-}5, 22\text{-}26, 43\text{-}47\ (induction)}$ 100 mg/m², $d_{1, 22, 43\ (concomitant)}$	70 Gy, 2 Gy/fraction	71	2
Lefebvre[29]	1996-2004	L, HP	III,IV	C F	100 mg/m², $d_{1, 22, 43, 64}$ 1000 mg/m², $d_{1\text{-}5, 22\text{-}26, 43\text{-}47, 64\text{-}68}$	70 Gy, 2 Gy/fraction after CT 60 Gy, 2 Gy/fraction between CT cycles ($wk_{2\text{-}3, 5\text{-}6,8\text{-}9}$)	450/450	6.5

OP=oropharynx ; OC= oral cavity ; HP= hypopharynx ; L= Larynx ; CT= chemotherapy ; RT= radiotherapy ;C=cisplatin; F=Fluorouracile; d=day ; wk=week

Table 4: Excluded trials and reason for exclusion

Trial (ref)	Inclusion period	Sites	Stage	Drug	Chemotherapy dose (mg/m²)	Radiotherapy dose (Gray) / duration (weeks)	Patients analyzed/ randomized	Median follow-up (years)
Reason for exclusion: CT1 vs CT2								
Fonsecca[30]	2000-01	OC, OP, HP, L	III, IV	Do C F	Arm 1: DoC $d_{1,22,43}$ Arm 1: CF $d_{1,22,43}$	NA (surgery or RT allowed according to local policy)	82/84	NA
Rewari (Yale 92-99)[31]*	1992-1999	**Post op** OC, OP, HP, L, Sinus, CUP	III, IV	Pf MMC	Arm 1: 40 mg/m² $d_{5,47}$ Arm 2: 15 mg/m² $d_{5,47}$	? In general 60 Gy for post-op patients	205	NA
Haffty[32]*	1992-1999	OC, OP, HP, L, NP, S	III-IV	Pf MMC	Arm 1: 40 mg/m² $d_{5,47}$ Arm 2: 15 mg/m² $d_{5,47}$	64 Gy, 2 Gy / fraction	121/128	6.3
Reason for exclusion: CT in both arms, fractionation trial								
Katori[33]	2001-2004	OC, OP, HP, L, NP, S	III-IV	Do C F	50 mg/m² $d_{1,29}$ 60 mg/m² $d_{4,32}$ 600 mg/m² $d_{1\text{-}5,29\text{-}33}$	Arm 1: 76.8 Gy 1.2Gy / fraction bid Arm 2: 70 Gy, 2Gy / fraction	50/50	NA

CUP= Carcinoma of Unknown Primary; OP=oropharynx ; OC= oral cavity ; HP= hypopharynx ; L= Larynx ; NP= Nasopharynx ; S= Paranasal Sinus; CT= chemotherapy ; RT= radiotherapy ; Do=Docetaxel; MMC= mitomycin C= Cisplatin; Pf= Porfiromycin; F= Fluorouracile, d=day ; *: two reports of the same trial: one is post-operative and the other is of definitive radiotherapy

APPENDIX B2: Description of the trials comparing local treatment + chemotherapy +/- another chemotherapy timing performed before 2001. The first four trials were not included in the previous meta-analyses.

First author	Inclusion period	Sites	Stage	Drugs*	Chemotherapy dose /cycle or day (mg/m²)		Loco-regional treatment	Patients analyzed/ randomized	Comments
					Randomized chemotherapy : Adjuvant or concomitant	Chemotherapy given in both arms: Neoadjuvant or adjuvant			
HNCP[34]	1978-82	OC,HP,L	II to IV			**Neoadjuvant**			
				B		90 mg/m² x 1	S + RT	302/302	Three-arm trial with one arm without CT see table 1.2
				C	Adj: 80 mg/m² x 6	100 mg/m² x 1			
				C					
DFCI[35]	1979-83	OC,OP,HP,NP,L,O	III,IV	B	Adj: 30 U/m² x 3	50 U/ m² x 2	RT or S + RT	46/46	
				C	Adj: 60 mg/m² x 3	100 mg/m² x 2			
				Mx	Adj: 800 mg/m² x 3	400 mg/m² x 2			
				LA (po)	Adj: 960 mg x 3	480 mg x 2			
Torino 85[36]	1985-90	OC,OP,HP,NP,L,O	III,IV	B		30 U/m² x 2	RT	108/108	
				C	Conc: 5 mg/m² x 30	50 mg/m² x 2			
				Mx		80 mg/m² x 2			
				Vc		6 mg/m² x 2			
Créteil 85[37]	1987-90	OC,OP,HP,L	II to IV	C	Conc: 50 mg/m² x 4	100 mg/m² x 3	RT	56/57	
				F (im)	Conc: 15 mg/kg x 8	5 000 mg/m² x 3			
UKHAN[38]	1991-2000	OC,OP,HP,L	II to IV			**Adjuvant**			
					Conc: Mx or VBMF $d_{1,14}$ of RT	Mx or VBMF $d_{14,28}$ post RT	RT	320/320	
						Concomitant	RT	314/314	
					Adj: Mx or VBMF $d_{14,2}$	Mx or VBMF $d_{1,14}$ of RT			

* iv, unless otherwise specified.

§ 4 arms-trial for patients without previous surgery (n=713): RT alone, RT + simultaneous CT, RT followed by CT, both: only the arm RT + simultaneous CT and .and the one with both CT timing are eligible. If prior surgery (n=255 patients), randomized to RT vs RT + simultaneous CT (not eligible for this comparison). Two options according to center: RT 50-55 Gy/ 3 wks ±

Mx or RT 60 Gy/ 6 wks alternating with VBMF. Mx dose is 100 mg/m² with FA rescue at wks 1 and 3 for the simultaneous arm. For the simultaneous part, 2 cycles of VBMF are given at wks 1, 3. For the adjuvant part, 2 cycles of VBMF are given at wks 3, 5 post RT. The VBMF regimen includes Vc (1.4 mg/m²), B (30 mg im), F (500 mg/m²), Mx (100 mg/m²) with FA rescue.

APPENDIX C: 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

As long as it will not cause delay, **the easiest way for us to receive the data is by e-mail**[1]. If sending data via email, please encrypt the data and let us know how it has been encrypted in a separate email. 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.

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 doing so will not delay the sending of the data. If it will cause a delay, then, please 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 : jppignon@igr.fr

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

Suggested coding and format for sending data

Column	Variable	Format/Coding
2-11	Patient identifier	10 characters
13-20	Date of birth	dd/mm/yyyy, 99999999=Unknown
	or age	6 blanks (columns 13-18), 2 digits (columns 19-20), 99=Unknown
22	Sex	1=Male, 2=Female, 9=Unknown
24-26	Performance Status	For Karnofsky index use 3 digits, for WHO or ECOG index use 2 blanks (column 24-25) and one digit (column 26)
28	Site of primary	1=Oral cavity, 2=Oropharynx, 3=Larynx, 4=Hypopharynx, 5=Nasopharynx, 6=Cervical node(s) without primary, 7=Others, 9=Unknown
30	T	0=T_0, 1=T_1, 2=T_2, 3=T_3, 4=T_4, 5=T_X, 6=T_{is}, 9=Unknown
32	N	0=N_0, 1=N_1, 2=N_2, 3=N_3, 4=N_X, 9=Unknown
34	M	0=M_0, 1=M_1, 9=Unknown
	or Stage	1 digit (column 34) with blanks in columns 30 & 32, 9=Unknown
36	Squamous cell	0=No, 1=Yes
38	Smoking status	0=Never, 1=Former, 2=Current, 9=Unknown
40-42	*if yes, pack-years*	3 digits, 999=Unkown
44	HPV status	0=Negative, 1=Positive*
46	Treatment allocated	1=No Chemotherapy, 2=Chemotherapy
47-54	Date of randomization	dd/mm/yyyy, 99999999=Unknown
56	Number of cycles of induction CT received	1 digit
58	Number of cycles of concomitant CT received	1 digit

* Specify the methods used (p16, ISH,…) in the documents accompagning the data.

Suggested coding for sending data (followed) **Meta-Analysis of Chemotherapy in Head and neck Cancer**

Column	Variable	Format/Coding
60	Tumor surgery	0=No, 1=Yes before RT, 2= yes after RT, 4=yes without timing information
62	Radiotherapy started	0=No, 1=Yes, 9=Unknown
64-71	Date of first day of radiotherapy	dd/mm/yyyy, 99999999=Unknown
73-80	Date of last day of radiotherapy	dd/mm/yyyy, 99999999=Unknown
82-85	Total administered dose of radiotherapy (Gy)	2 digits + 1 digit separated by a coma (example: 72,2), 99=Unknown
87-88	Total number of fractions of radiotherapy	2 digits, 99=Unknown
90	Radiotherapy – technique	1 = 2D, 2 = 3D, 3 = IMRT, 9 = unknown
	Acute Toxicity	
92	Neutropenia	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
94	Thrombocytopenia	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
96	Anemia	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
98	Kidney failure	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
100	Cutaneous	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
102	Mucositis	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
104	Hearing loss	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
106	Neurotoxicity	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknwon
108	Need for feeding tube	0=No, 1=Yes, 9 =Unknown.
	Late Toxicity	
110	Cutaneous fibrosis	1 digit, 0 to 5 according to EORTC-RTOG scale, 9=Unknown
112	Xerostomia	1 digit, 0 to 5 according to EORTC-RTOG scale, 9=Unknown

Column	Variable	Format/Coding
114	Bone necrosis	1 digit, 0 to 5 according to EORTC-RTOG scale, 9=Unknown
116	Persistence of feeding tube after one year of treatment	0=No, 1=Yes, 9=Unknown
118-125	Date of last follow-up or death	dd/mm/yyyy, 99999999=Unknown
127	Survival status	0=Alive, 1=Dead
129	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
131	Tumor failure*,	0=No, 1=Yes
133-140	Date of tumor failure	dd/mm/yyyy, 99999999=Unknown
142	Nodal failure*,	0=No, 1=Yes
144-151	Date of nodal failure	dd/mm/yyyy, 99999999=Unknown
153	Distant failure (metastasis)	0=No, 1=Yes
155-162	Date of distant failure (metastasis)	dd/mm/yyyy, 99999999=Unknown
164	Second primary	0=No, 1=Yes
166-173	Date of second primary	dd/mm/yyyy, 99999999=Unknown
175	Type of second primary	Lung=1, Esophagus=2, Stomach=3, Colorectal=4, Liver=5, Head& neck=6, Other=7 (specify) 9=Unknown
177	Excluded from your analysis	0=No, 1=Yes
179-190	Reasons for exclusion	12 characters

** A loco-regional failure corresponds either to a patient who never achieved a complete remission or to a patient who relapsed after an initial complete remission. In the first case, the date of first event should be the date of randomization and in the second case the date of occurrence of the relapse. If T and N failures are not available separately, please provide loco-regional failures and specify it when sending out the data.*

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MACH-NC

Meta-Analysis of Chemotherapy in Head & Neck Cancer

Meta-Analysis of Chemotherapy in Head and Neck Cancer

NEW TRIALS

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 _____

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 Head and Neck Cancer

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: _____

_____

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 Gustave Roussy
39, rue Camille Desmoulins – 94805 Villejuif cedex France
- Fax 33 1 42 11 52 58 – e-mail : jpignon@igr.fr

MACH-NC

Meta-Analysis of Chemotherapy in Head & Neck Cancer

Meta-Analysis of Chemotherapy in Head and Neck Cancer

TRIALS INCLUDED IN MACH-NC2 - UPDATED

Trial / Protocol number _____

Trial Publication _____

_____

Name of Investigator _____

Address _____

Telephone _____ Fax _____

Email _____

Are you willing to take part in the Meta-analysis? 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 _____

Has the trial been updated ? yes ☐ no ☐

Can you provide new data for this meta-analysis (HPV, toxicity, compliance) ? yes ☐ no ☐

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: _____

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Signed _____ Date _____

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