MACH-NC

Meta-Analysis of Chemotherapy in Head & Neck Cancer

MACH-NC3-induction

Meta-analysis of Taxane-cisplatin-5FU as Induction Chemotherapy in locally advanced Head and neck squamous cell carcinoma

Initiated by the Institut Gustave Roussy

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1. INTRODUCTION AND BACKGROUND

Head and neck squamous cell carcinomas (HNSCC) are frequently occurring tumors with approximately 140 000 new cases (oral cavity, oropharynx, hypopharynx, larynx) in 2006 within Europe and 45 000 estimated new cases in 2008 within the United States[1]. Each year, more than 500 000 new cases are diagnosed worldwide[2]. 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 5-years relative survival rates in the USA in the period 1996-2003 was around 50% in patients with locally advanced disease[1]. 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 three 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 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 naso-pharyngeal carcinoma were not eligible. The overall pooled relative risk was 0.88 corresponding to an absolute benefit of 4.4% for chemotherapy, from 31.6% to 36%, 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[4]:

Chemotherapy timing	Trial Number	Patient Number	RR (95% confidence interval)	p-value	Absolute benefit (5y.)	Heterogeneity p-value
Adjuvant	8	1 854	0.98 (0.85-1.19)	0.74	1%	0.35
Induction	31	5 269	0.95 (0.88-1.01)	0.10	2%	0.38
Concomitant	26	3 727	0.81 (0.76-0.88)	<0.0001	8%	<0.0001
Total	65*	10 850*	0.90 (0.85-0.94)	<0.0001	4%	<0.0001

**Two 3-arm trials studied two chemotherapy timing.*

In the updated version of MACH-NC[5], the absolute benefit for concurrent chemoradiotherapy is 6.5% at 5 years. The difference with the above results was related to a change of method to compute absolute benefit. In the updated study, 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). Five randomized controlled trials addressing this question have been completed and for some of them recently published (appendix B) . There is across all trials a constant benefit on locoregional control and overall survival of the addition of docetaxel to induction chemotherapy. Two trials studying the addition of TPF induction chemotherapy to platinum based concomitant chemoradiotherapy has been also performed and other trials studying the addition of induction chemotherapy to platinum based concomitant chemoradiotherapy are ongoing. The total number of patients included in randomized trials addressing these questions (which were not included in the 2000 meta-analysis) is now over 1900. Nevertheless, all of these trials compared two different types of induction chemotherapy (TPF vs PF) or the addition of TPF to radiochemotherapy, which are not the standard of care in LAHNC. It is therefore difficult to draw any conclusion on the absolute benefit of TPF induction chemotherapy. Moreover, it is not possible to rull out that adding docetaxel to induction chemotherapy might jeopardize the concomitant chemoradiation therapy (CRT), thus adding only a minimal benefit to the standard treatment. Different randomized controlled trials are addressing this first question now using head to head comparisons (induction TPF + CRT *vs* CRT), but the results of only few of them is made publi. It would be of critical importance to have sooner elements of answer to that question.

Therefore, it was decided to focus the updating of the MACH-NC study on trials with induction chemotherapy, to include the trials performed between 2001 and 2006 and to update the follow-up of the most recent trials of MACH-NC. We will conduct a meta-analysis of the adjunction of taxane to cisplatin and 5-FU as induction chemotherapy, and a meta-analysis of addition of induction platin and/or taxane based chemotherapy + 5FU to platinum based

chemoradiotherapy starting by the trials comparing to cisplatin and 5-FU plus taxane followed by concomitant radiochemotherapy versus concomitant radiochemotherapy.

Besides, 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 induction 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[7] and will use a similar methodology to that used in the MACH-NC study[4], the Breast Cancer Overview[8], the Prophylactic Cranial Irradiation Overview[9], and the Non Small Cell Lung Cancer Overview[10]. 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[11]. 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[7,12]. Updated follow-up information will be sought which will enable us to report on long-term survival.

In summary, the constitution of this unique database aims to provide the most comprehensive analysis on the effect of induction chemotherapy given prior to local treatment of LAHNC (radiotherapy +/- concurrent chemotherapy). It should help to define therapeutic guidelines and to generate new hypotheses to be tested in further randomized trials.

2. OBJECTIVES

The **main objectives** are comparison 1 and 2 on **long-term overall survival** based on updated data.

Comparison 1:

Assessment of the role of taxane, cisplatin and 5-FU (TPF) compared to cisplatin and 5-FU (PF) as induction chemotherapy before radiotherapy in the treatment of head and neck squamous carcinoma by studying the following comparison (direct comparison meta-analysis):

TPF + Radiotherapy [%]

↗

↘

PF + Radiotherapy [%]

[%] Only trial in which none or both arms used concomitant chemotherapy will be included for this comparison.

Comparison 2:

Assessment of the role of taxane, cisplatin and 5-FU (TPF) as induction chemotherapy before concomitant chemo-radiotherapy compared to concomitant chemo-radiotherapy in the treatment of head and neck squamous carcinoma by studying the following comparison:

TPF + Radiotherapy +concomitant chemotherapy

↗

↘

Radiotherapy + concomitant chemotherapy

Secondary objectives

- Effect of induction TPF 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).

Comparison of induction TPF to concomitant RT-CT and to modified fractionation RT

The estimation of the treatment effect of the comparison induction TPF versus none will be indirectly compared to those of:

a) the comparison cisplatin based concomitant chemotherapy versus none
b) the comparison altered fractionation radiotherapy versus standard radiotherapy

A specific protocol will be prepared.

Surrogate endpoint

The trials on TPF will be included on the study of the value of event-free survival as surrogate endpoint for overall survival (see specific protocole).

3. TRIALS SELECTION CRITERIA

All trials must satisfy the following criteria:

Trials must

- Compare taxane-based (docetaxel or paclitaxel) induction chemotherapy to a standard arm of treatment (PF induction chemotherapy or concurrent chemoradiation w/o induction chemotherapy).
- 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).
- Have completed accrual before 31st December 2006.
- Include patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx.
- Not include patients with metastatic disease.

Trial in which the same concomitant chemotherapy was used in both arms are eligible.

Patients should

- Not receive prior surgery.
- Not receive prior radiotherapy.
- Not receive prior chemotherapy.
- Undergo a potentially curative locoregional treatment.

4. TRIAL SEARCH

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 1970-2007 (Medline, Cancerlit, DARE, Embase, CCT meta-register), hand searching (review articles, meeting proceedings) and by contacting experts in the field.

The search strategy used was :
1) for MEDLINE from PubMed
("head and neck neoplasms/drug therapy"[MAJR] OR "head and neck neoplasms/radiotherapy"[MAJR]) AND ("Randomized Controlled Trials"[MESH] OR "Clinical Trials, Phase III"[MESH] OR "clinical trial, phase III"[Publication Type] OR "randomized controlled trial"[Publication Type]) NOT "Neoplasm Metastasis"[MESH]
2) for EMBASE

(Head-and-Neck-Tumor- Drug Therapy MJ. OR Head-and-Neck-Tumor- Radiotherapy MJ.) AND (Phase-3-Clinical-Trial DE OR Randomized-Controlled-Trial DE) NOT Metastasis#.W..DE.
Trials registries (PDQ, ClinProt...) will be also consulted. All trialists who take part in the meta-analysis will be asked to help to identify more trials.

5. DESCRIPTION OF THE TRIALS INCLUDED

Appendix A describes the trials comparing induction TPF to induction PF followed by radiotherapy (+/- concomitant chemotherapy) which accrued before 2007 and are potentially eligible for the meta-analysis. Six trials including 1 904 patients were identified. One trial compared TPF vs PF vs no chemotherapy. Then, five trials (1 704 patients) are available for the comparison TPF vs PF, and two for the comparison TPF vs none. The trial references are given in **appendix B**.

6. CRITERIA OF EVALUATION

6.1 ENDPOINTS

The main endpoint will be **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, 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.

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).

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).
- Allocated treatment.
- Date of randomization.
- Number of cycles of induction chemotherapy received.
- Number of cycles (or injection) of concomitant chemotherapy received.

- o Radiotherapy started / not started
- o Date first day radiotherapy
- o Date last day radiotherapy
- o Total administered dose of radiotherapy
- o Total number of fractions of radiotherapy
- o Acute toxicity (neutropenia, thrombocytopenia, anemia, kidney failure, cutaneous, need for feeding tube, mucositis, hearing loss, neurotoxicity)
  + Specification of toxicity grading system used
- o Late toxicity (cutaneous fibrosis, xerostomia, bone necrosis, persistence of feeding tube after one year of treatment)
  + specification of toxicity grading system used
- o Date of last follow-up.
- o Survival status.
- o Cause of death.
- o Date of tumor failure, date of nodal failure
- o Date of distant failure
- o Date and type of second primary
- o Whether excluded from trial analysis.
- o 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 1 750 (1 300) patients it would be possible to detect, with a power of 80%, an absolute improvement in survival from 30 % to 36 % (37%) 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[13].

The main analysis will be performed on the endpoint of overall survival. Additional analyses will be performed on the endpoints of loco-regional failure rate, distant failure rate, head and

neck cancer mortality and non head and neck cancer mortality, if sufficient data are available. Proportion of patients who have received all the planned cycles of chemotherapy, of those receiving at least one radiotherapy fraction (radiotherapy started / not started), the percentage of the planned total dose of radiotherapy, acute and late toxicity rates will be also studied.

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 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[14] (Yusuf, Peto, Lewis, Collins, Sleight, 1985). 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 TPF induction chemotherapy compared with those who were allocated PF induction chemotherapy. 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 in Carcinoma of Head and neck[6] (MARCH; Bourhis, 2006) 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) [8]. 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, death from head and neck cancer and death from unknown cause.

The χ^2 heterogeneity tests[6,10] will be used to test for gross statistical heterogeneity, the I^2 statistic[15] will be used as a measure of consistency among trials. 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 2-years, and 5-years with their 95% confidence intervals[16]. All p-values will be two-sided.

Direct comparison of PF and TPF

In the comparison of PF vs TPF, the following sensitivity analyses will be performed: analysis without the paclitaxel trial (Hitt 2006), analysis without EORTC 24971 trial (the only trial without concomitant chemotherapy), analysis without the GORTEC 2000-01 trial, the only trial using organ preservation strategy. An indirect comparison of PF and TPF will be also performed using the two comparison PF vs none and TPF vs none.

Comparison of induction TPF vs none

An estimation of the effect of induction TPF versus none will be performed both by direct comparison (2 trials) and by indirect comparison using the two comparison PF vs none and PF vs TPF.

The following sentivity analysis will be performed: impact on the results of the indirect comparison TPF vs none of the exclusion of trials using only surgery as loco-regional treatment for the comparison PF versus none.

To study the interaction between treatment effect and covariates, e.g. sex, analyses stratified by trial will be performed for each value of this covariate. The results will be then combined to give overall hazard ratios for male and female and compared by a test for heterogeneity.

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

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-NC3 Induction 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 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-NC3 Induction 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.

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. 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-NC3 Induction Group and include a list of all collaborators.

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APPENDIX A: **Description of the trials comparing TPF to PF as induction chemotherapy prior to radiotherapy or concurrent radio-chemotherapy**

See abbreviations on pages 18-19 and references on pages 20-21.

Trial (Reference)	Inclusion period	Sites	Stages	Induction CT	Induction chemotherapy doses	RT-CT/RT	Surgery	Nb patients randomized
Hitt (Hitt, Lopez-Pousa, Martinez-Trufero et al. 2005)	12/98 - 12/01	OC, OP, HP, L	III-IV	PF vs PxPF	PF*3 / 3 weeks versus (Px 175 mg/m² at D1 + P 100mg/m² at D2 + 5FU 500mg/m² D2-6)*3 / 3 weeks	RT-CT[(1)]	Neck if PR<80% or SD on lymph nodes. Off study if no response in the primary or PD	382
Hitt (Hitt, Grau, Lopez-Pousa et al. 2006)	Unknown	OC, OP, HP, L	III-IV	PF vs DoPF vs 0	PF*3 / 3 weeks versus (Do 75 mg/m² at D1+ P 75 mg/m² + 5FU 750 mg/m² D1-5)*3 / 3 weeks versus 0	RT-CT[(1)]	+/- Neck before or after RT, +/- site after RT	310
EORTC 24971 (Vermorken, Remenar, van et al. 2007)	04/99 - 03/02	OC, OP, HP, L	III-IV	PFvsDoPF	PF*4 / 3 weeks versus (Do 75 mg/m² at D1+ P 75 mg/m²+ + 5FU 750 mg/m² D1-5)*4 / 3 weeks	RT[(2)]	+/- Neck before or after RT, +/- site after RT or before if progression	358

TPF= Taxane, Cisplatin, 5-Fluorouracil

PF= (Cisplatin 100 mg/m² at Day 1 + 5-Fluorouracil 1000 mg/m² on continuous infusion on days 1 through 5)

[(1)] RT: conventional (site: 66-70 Gy. Nodes: 60Gy). CT: Cisplatin 100 mg/m² D1, 22, 43

[(2)] RT: in the absence of progression, conventional (66-70 Gy), treatment received by the majority of patients, accelerated (max 70 Gy) or hyperfractionated (max 74 Gy) according to center.

OP=oropharynx ; OC= oral cavity ; HP= hypopharynx ; L= Larynx ; CT= chemotherapy ; RT= radiotherapy ; TPF= taxane+platin+5-fluorouracil ; CisP= cisplatin ; 5-FU= 5 Fluorouracil ; D=day ; TL= total laryngectomy ; PR= partial response ; PD= progressive disease ; CR= complete response

Trial (Reference)	Inclusion period	Sites	Stages	Induction CT	Induction chemotherapy doses	RT-CT/RT	Surgery	Nb patients randomized
TAX324 (Posner, Hershock, Blajman et al. 2007)	05/99 - 12/03	OC, OP, HP, L	III-IV	PF vs DoPF	PF*3 / 3 weeks versus (Do 75 mg/m² at D1 + P 100 mg/m² + + 5FU 1000 mg/m² D1-4)*3 / 3 weeks	RT-CT[3]	+/- Neck after RT	538
Paccagnella (Paccagnella, Buffoli, Koussis et al. 2008)	Unknown	OC, OP, HP, L	III-IV	DoPF vs 0	(Do 75 mg/m² at D1 + P 80 mg/m² at D1 + 5FU 800 mg/m² D1-4)*3 / 3 sem versus (0)	RT-CT[4]	Neck in N2-3 patients with pathological CR on primary site	96
GORTEC 2000-01 (Calais, Pointreau, Alfonsi et al. 2006)	Unknown	HP, L	III-IV	PF vs DoPF	PF*3 / 3 weeks versus (Do 75mg/m² at D1P 75mg/m²+ + 5FU 750mg/m² D1-5)*3 / 3 weeks	RT[5] or TL+RT	TL+Neck before RT unless CR or PR+laryngeal mobility	220

[3] RT: conventional (70 Gy); CT: weekly carboplatin AUC 1.5

[4] RT: conventional 66-70 Gy. CT: (Cisplatin 20 mg/m² day 1 and 4; 5-FU 800 mg/m² 96 hours c.i.) weeks 1 and 6 during RT

[5] RT: conventional (70 Gy)

OP=oropharynx ; OC= oral cavity ; HP= hypopharynx ; L= Larynx ; CT= chemotherapy ; RT= radiotherapy ; TPF= taxane+platin+5-fluorouracil ; P= cisplatin ; 5-FU= 5 C = Cispaltine, Do = Docetaxel, Fluorouraci,Px = Paclitaxel ;D=day ; TL= total laryngectomy ; PR= partial response ; PD= progressive disease ; CR= complete response

List of abbreviations

CT	Chemotherapy
RT	Radiotherapy
Nb	Number
wks	weeks
OC	Oral cavity
OP	Oropharynx
HP	Hypopharynx
NP	Nasopharynx
L	Larynx
S	Sinus
O	Other
HNSCC	Head and Neck Squamous Cell Carcinoma
N+	Positive node
M+	Surgical margin positive
R+	Extra nodal capsular spread
EORTC	European Organisation for Research and Treatment of Cancer
GORTEC	Groupe d'Oncologie Radiothérapie Tête et Cou
NCI	National Cancer Institute
RTOG	Radiation Therapy Oncology Group
P	Cisplatin
Cb	Carboplatin
F	5-Fluorouracil
Px	Paclitaxel

APPENDIX B : References of the eligible trials

Calais G, Pointreau Y, Alfonsi M et al. Randomized phase III trial comparing induction chemotherapy using cisplatin fluorouracil with or without docetaxel for organ preservation in hypopharynx and larynx cancer. Preliminary results of GORTEC 2000-01. *Proc Am Soc Clin Oncol* 2006 part 1, vol 24 (suppl 18S) : 5506.

Hitt R, Lopez-Pousa A, Martinez-Trufero J, Escrig V, Carles J, Rizo A, Isla D, Eugenia Vega M, Martý´JL, Lobo F, Pastor P, Valentý´V, Belon J, Miguel A, Sanchez MA, Chaib C, Pallarés C, Anton A, Cervantes A, Luis Paz-Ares, Cortés-Funes H. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol* 2005;23:8636-45.

Hitt R, Grau JJ, Lopez-Pousa A et al. Randomized Phase II/III trial of induction Chemotherapy (ICT) with Cisplatin/5-Fluorouracil (PF) vs. Docetaxel (T) plus PF (TPF) followed by chemoradiotherapy (CRT) vs. CRT for unresectable locally advanced head and neck cancer. *Proc Am Soc Clin Oncol* 2006 part 1, vol 24 (suppl 18S) : 55.

Paccagnella A, Buffoli A, Koussis H et al. Concomitant chemoradiotherapy (CT/RT) vs neoadjuvant chemotherapy with docetaxel/cisplatin/5-fluorouracil (TPF) followed by CT/RT in locally advanced head and neck cancer. Final results of a phase II randomized study. *J Clin Oncol* 2008;26:6000.

Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, Tjulandin S, Shin DM, Kevin Cullen K, Ervin TJ, Murphy BA, Raez LE, Cohen RB, Spaulding M, Tishler RB, Roth B, del Carmen Viroglio R, Venkatesan V, Romanov I, Agarwala S, William Harter WK, Dugan M, Cmelak A, Markoe AM, Read PW, Steinbrenner L, Colevas DA, Norris Jr CM, Robert I. Haddad RI, for the TAX 324 Study Group. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med* 2007;357:1705-15.

Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, Stewart JS, Jelic S, Jan Betka, Preiss JH, van den Weyngaert D Awada A, Cupissol D, Kienzer HR, Rey A, Desaunois I, Bernier J, Lefebvre JL, for the EORTC 24971/TAX 323 Study Group. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med* 2007;357:1695-704

MACH-NC
Meta-Analysis of Chemotherapy in Head & Neck Cancer

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

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 the secretariat (tel: 33 1 42 11 45 65 ; fax: 33 1 42 11 52 58) and a pad of them will be sent to 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.

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[1] Our e-mail address is : jppignon@igr.fr

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

Meta-Analysis of Chemotherapy in Head and neck Cancer

Suggested coding and format for sending data by network mail or floppy disk

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	Treatment allocated	1=No Chemotherapy, 2=Chemotherapy
40-47	Date of randomization	dd/mm/yyyy, 99999999=Unknown
49	Number of cycles of induction CT received	1 digit
51	Number of cycles of concomitant CT received	1 digit
53	Radiotherapy started	0=No, 1=Yes, 9=Unknown
55-62	Date of first day of radiotherapy	dd/mm/yyyy, 99999999=Unknown
64-71	Date of last day of radiotherapy	dd/mm/yyyy, 99999999=Unknown

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

Column	Variable	Format/Coding
73-74	Total administered dose of radiotherapy (Gy)	2 digits + 1 digit separated by a coma (example: 72,2), 99=Unknown
77-78	Total number of fractions of radiotherapy	2 digits, 99=Unknown
	Acute Toxicity	
80	Neutropenia	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
82	Thrombocytopenia	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
84	Anemia	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
86	Kidney failure	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
88	Cutaneous	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
90	Mucositis	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
92	Hearing loss	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknown
94	Neurotoxicity	1 digit, 0 to 5 if WHO or NCI-CTC scoring system, 9=Unknwon
96	Need for feeding tube	0=No, 1=Yes, 9 =Unknown.
	Late Toxicity	
98	Cutaneous fibrosis	1 digit, 0 to 5 according to EORTC-RTOG scale, 9=Unknown
100	Xerostomia	1 digit, 0 to 5 according to EORTC-RTOG scale, 9=Unknown
102	Bone necrosis	1 digit, 0 to 5 according to EORTC-RTOG scale, 9=Unknown
104	Persistence of feeding tube after one year of treatment	0=No, 1=Yes, 9=Unknown
106-113	Date of last follow-up or death	dd/mm/yyyy, 99999999=Unknown
115	Survival status	0=Alive, 1=Dead

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

Column	Variable	Format/Coding
117	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
119	Tumor failure*,	0=No, 1=Yes
121-128	Date of tumor failure	dd/mm/yyyy, 99999999=Unknown
130	Nodal failure*,	0=No, 1=Yes
132-139	Date of nodal failure	dd/mm/yyyy, 99999999=Unknown
141	Distant failure (metastasis)	0=No, 1=Yes
143-150	Date of distant failure (metastasis)	dd/mm/yyyy, 99999999=Unknown
152	Second primary	0=No, 1=Yes
154-161	Date of second primary	dd/mm/yyyy, 99999999=Unknown
163	Type of second primary	Lung=1, Esophagus=2, Stomach=3, Colorectal=4, Liver=5, Head& neck=6, Other=7 (specify) 9=Unknown
165	Excluded from your analysis	0=No, 1=Yes
167-178	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 the data.*