META-ANALYSIS OF CHEMOTHERAPY IN NASO-PHARYNX CARCINOMA

An update with trials up to 2010

Initiated by the Institut Gustave Roussy
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SECRETARIAT

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1. INTRODUCTION AND BACKGROUND

Nasopharyngeal carcinoma (NPC) is pathologically, epidemiologically and clinically distinct from other head and neck cancers. NPC is rare in USA and Western Europe. Epstein-Barr virus is strongly associated with NPC and non-keratinizing (differentiated or undifferentiated (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. NPC are commonly treated by radiation therapy and chemotherapy. Radiotherapy with a dose of 65-75 Gy in 6-7 weeks is the standard treatment. The overall survival at 5-years ranged from 32% to 52% in past series of patients with locally advanced stage treated with radiotherapy alone and is higher in more modern series, generally around 50-60%.

Chemotherapy has been proposed to improve patients’ survival, and has been used in three ways in the treatment of locally advanced NPC: as induction treatment (induction chemotherapy); concomitantly with radiotherapy; as adjuvant treatment after radiotherapy and also combinations of these approaches. In spite of more than ten randomized trials comparing radiotherapy to radiotherapy plus chemotherapy before the year 2004, the effect of chemotherapy on survival was not established. Indeed, only two trials had shown beneficial effect on survival and four on relapse-free survival. The inconstant benefit on survival was explained by the lack of power of the trials, as for the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC).

The meta-analysis of chemotherapy in nasopharyngeal carcinoma (MAC-NPC) was therefore launched to assess the impact of chemotherapy on overall survival when added to radiotherapy (RT). This international project comprised eight trials that included 1753 patients. One trial with a 2 x 2 design was counted twice in the analysis. The analysis included 11 comparisons using the data from 1975 patients. The median follow-up was 6 years. The pooled hazard
ratio of death was 0.82 (95% confidence interval, 0.71–0.94; \( p = 0.006 \)), corresponding to an absolute survival benefit of 6% at 5 years from the addition of chemotherapy (from 56% to 62%). The pooled hazard ratio of tumor failure or death was 0.76 (95% confidence interval, 0.67–0.86; \( p < 0.0001 \)), corresponding to an absolute progression-free survival benefit of 10% at 5 years from the addition of chemotherapy (from 42% to 52%). A significant interaction was observed between the timing of chemotherapy and overall survival (\( p = 0.005 \)), explaining the heterogeneity observed in the treatment effect (\( p = 0.03 \)), with the highest benefit resulting from concomitant chemotherapy\(^3\).

Since the publication of this meta-analysis, ten trials have been conducted representing 2,471 patients. Most of these trials compared radiotherapy to the same radiotherapy plus concomitant and adjuvant chemotherapy (CT)\(^6\)-\(^{10}\), as had been done in the Intergroup trial\(^11\). Two trials compared radiotherapy to concomitant CT + RT\(^12, 13\). One trial compared concomitant CT + RT to the same concomitant CT + RT plus adjuvant chemotherapy\(^14\), and three trials compared concomitant CT + RT to the same concomitant CT + RT plus induction chemotherapy\(^15\)-\(^{17}\). One previously conducted trial but never published (VUMCA II) was not included in the previous round of the meta-analysis because induction CT was administered in both arms and only the concomitant CT (hydroxyurea) component was randomized. At that time, there was no agreement on the inclusion of trials with this design. This trial (509 patients) is now eligible for the meta-analysis update, which will therefore include eleven trials and 2,980 patients.

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

- include all existing randomized trials (exhaustivity) to better evaluate the benefit of (concomitant) chemotherapy
- update the older trials to increase follow-up and gain both statistical power and information on long term survival
- try and study treatment related toxicity in order to balance the survival benefit by the increase in short and long term toxicity

The meta-analysis will be based on individual patient data\(^18, 19\) and will use a similar methodology to that used in the MACH-NC study\(^5\), the Breast Cancer Overview\(^20\) and the
Prophylactic Cranial Irradiation Overview. 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. 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. 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.

2. OBJECTIVES

Assessment of the effect of chemotherapy on overall survival in patients with nasopharynx carcinoma by studying the following comparison:

Radiotherapy

Radiotherapy + chemotherapy

Trials comparing the same treatment strategy (concomitant RT+CT or induction CT + RT) +/- the addition of chemotherapy (in another timing) will also be included:
• radiotherapy + concomitant chemotherapy versus the same radiotherapy + concomitant chemotherapy + adjuvant chemotherapy
• radiotherapy + concomitant chemotherapy versus the same radiotherapy + concomitant chemotherapy + induction chemotherapy
• induction chemotherapy followed by radiotherapy +/- concomitant chemotherapy

Secondary objectives

• Effect of chemotherapy on time to local, regional and loco-regional failure, time to distant failure, time to overall failure (at any site), nasopharynx cancer mortality and non-nasopharynx 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).
• The trials will be included in the study of the value of progression-free survival (time to failure at any site or death due to any cause) 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 compare the same treatment strategy (concomitant RT+CT or induction CT + RT) +/- the addition of chemotherapy (in another timing).
• Be randomized in a way which precludes prior knowledge of treatment assignment.
• Have completed accrual before 31st December 2010.
Include patients with nasopharynx carcinoma (WHO grade 1, 2 or 3)
Include at least 60 patients (30 patients per arm for trials with more than 2 arms)
Not include patients with distant metastatic disease.

Patients should
- Not receive prior radiotherapy.
- Not receive prior chemotherapy.
- 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 2000-2011 to avoid publication bias (Medline, Scopus, CCT meta-register, Web of Science), 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. Final search was performed in June 2011. The search in Chinese papers is still ongoing and could add new trials to the list, which will be modified accordingly.

The search strategy used was:
1) for MEDLINE from PubMed
   (((nasopharyngeal neoplasms/drug therapy[MAJR] OR nasopharyngeal neoplasms/radiotherapy[MAJR]) AND (clinical trial[Publication Type] AND (random* OR (Phase III)Fields: Title Word))) OR ((nasopharyngeal neoplasms/drug therapy[MAJR] OR nasopharyngeal neoplasms/radiotherapy[MAJR]) AND (clinical trial, phase III[Publication Type] OR randomized controlled trial[Publication Type] OR meta-analysis[Publication Type])))
2) For Web of Science
Appendix A describes the trials comparing radiotherapy versus radio-chemotherapy which accrued during the period 2000-2010 and are potentially eligible for this update of the meta-analysis. Ten new trials (2,471 patients) were identified. According to the timing of chemotherapy (CT), four categories of eligible trials have been identified:

<table>
<thead>
<tr>
<th>Category of trial (in bold is the randomized treatment)</th>
<th>Number of trials (patients)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant +/- adjuvant</td>
<td>6 (1,419)</td>
<td>four trials evaluated concomitant + adjuvant CT (1,074 patients), two trials randomized only concomitant CT (345 patients)</td>
</tr>
<tr>
<td>Induction (concomitant in both arms)</td>
<td>2 (206)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant (concomitant in both arms)</td>
<td>1 (508)</td>
<td></td>
</tr>
<tr>
<td>Concomitant (induction in both arms)</td>
<td>1 (509)</td>
<td>Trial (VUMCA II) not included in the previous meta-analysis due to the presence of induction CT in both arms.</td>
</tr>
</tbody>
</table>

A fifth category with one trial (Xu et al\(^7\)) that will be eligible for the network meta-analysis was identified: trials comparing induction chemotherapy + radiotherapy versus concomitant radio-chemotherapy with adjuvant chemotherapy in both arms.
When adding the new trials with the trials previously included in the first round of the meta-analysis, the description of the trials becomes as follows.

<table>
<thead>
<tr>
<th>Category of trial</th>
<th>First round of the meta-analysis*</th>
<th>New trials</th>
<th>Total Meta-analysis update</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant +/- adjuvant or induction</td>
<td>Number of trials (patients)</td>
<td>Number of trials (patients)</td>
<td>Number of trials (patients)</td>
</tr>
<tr>
<td></td>
<td>4 (765)</td>
<td>7 (1,928)</td>
<td>11 (2,693)</td>
</tr>
<tr>
<td>Induction (+/- concomitant in both arms)</td>
<td>4 (830)</td>
<td>2 (206)</td>
<td>6 (1,036)</td>
</tr>
<tr>
<td>Adjuvant (+/- concomitant in both arms)</td>
<td>3 (380)</td>
<td>1 (508)</td>
<td>4 (888)</td>
</tr>
<tr>
<td>Total*</td>
<td>8 (1,753)</td>
<td>10 (2,642)</td>
<td>18 (4,395)</td>
</tr>
</tbody>
</table>

* total may be lower than the sums of the lines because of trials with 3-arms or 2x2 design that can be counted twice.
6. ENDPOINTS

The main endpoint will be **overall survival**, because of its importance and because of the reliability of the data. Cause of death will be also studied, if possible. Secondary endpoints such as time to local failure, regional failure (or locoregional failure according to available data), distant failure, overall failure, as well as progression-free survival and specific survival (nasopharynx cancer mortality and non nasopharynx cancer mortality), treatment compliance, early and late toxicity will be also considered.

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.
- Histology (WHO type).
- TNM staging (if not available other staging; in any case, provide information on classification used) – name of classification system and edition used.
- Imaging methods used for evaluation of local extension (bone structure): standard radiography, CT scan, MRI
- Allocated treatment.
- Date of randomization.
- Number of cycles of induction chemotherapy received.
- Number of cycles (or injection) of concomitant chemotherapy received.
- Number of cycles of adjuvant chemotherapy received.
- Radiotherapy started / not started
Radiotherapy technique: conventional 2D / 3D conformal/ IMRT
Date first day radiotherapy
Date last day radiotherapy
Total administered dose of radiotherapy
Total number of fractions of radiotherapy
Worst acute toxicity (neutropenia, thrombocytopenia, anemia, febrile neutropenia, kidney failure, cutaneous, need for feeding tube, weight loss, mucositis, hearing loss, neurotoxicity)
+ Specification of toxicity grading system used
Late toxicity (cutaneous fibrosis, xerostomia, bone necrosis, persistence of feeding tube after one year of treatment, endocrine dysfunction, hearing deficit, cranial nerve palsy, symptomatic and asymptomatic temporal lobe necrosis), trismus, visual deficit, massive bleeding
+ 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 (within or outside irradiation field, if available)
Whether excluded from trial analysis.
Reason for exclusion (if applicable).

Appendix B 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.

ANALYSIS ON THE OVERALL POPULATION

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 failure rate, distant failure rate, nasopharynx cancer mortality and non-nasopharynx 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\(^\text{20}\). 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.

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\(^\text{23}\) 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). Non-nasopharynx cancer mortality was defined as death of known cause without recurrence and not considered as a nasopharynx cancer death. Nasopharynx cancer mortality included death of any cause with prior recurrence, death from nasopharynx cancer and death from unknown cause.

The $\chi^2$ heterogeneity tests will be used to test for gross statistical heterogeneity, the $I^2$ statistic\textsuperscript{24} 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\textsuperscript{20}. All p-values will be two-sided. In case of important and unexplained heterogeneity, a random effects meta-analysis will be performed to take this heterogeneity into account.

**SUBGROUP AND SUBSET ANALYSES**

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 then be combined to give overall hazard ratios for male and female and compared by a test for heterogeneity (or trend if appropriate). To avoid bias, only within trial information will be used for subgroup analyses, as described by Fisher et al\textsuperscript{25}.

Main subgroup analyses:

- Age (50 or less vs 51-60 vs 61+. See if a trend exists as in the squamous cell carcinoma meta-analyses\textsuperscript{5,23})
- 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 IV)
- WHO histology type; (keratinizing versus non-keratinizing, i.e.WHO I, vs II-III by past system), probably not possible due to the very low prevalence of WHO type I patients in the trials
- Imaging methods for evaluation of local extension (bone structure): X-ray, CT scan, MRI\(^1\)
- Radiotherapy technique (IMRT vs 3D-CRT vs 2D-RT) \(^2\)

To study the interaction between treatment effect and trial level covariates, subset analyses will be performed. The methods used is a heterogeneity test between the HR for the different subsets of trials. Main subset analysis will be:

- Adjuvant versus induction versus concomitant versus concomitant + adjuvant
- Cisplatin-based chemotherapy versus nonplatin-based chemotherapy.
- Trial size
- Sealed envelop versus other method of randomization.

**SENSITIVITY ANALYSES**

Hazard ratios for overall survival will also be calculated excluding any trials that are clear outliers. The impact of the exclusion of these trials on the results will be studied. The main sensitivity analyses will be:

- Exclusion of trials comparing concomitant chemotherapy plus radiotherapy +/- induction/adjuvant chemotherapy or trials comparing induction CT plus RT +/- concomitant CT (i.e. trials including two different CT timings but only one being randomized)
- Exclusion of trials with a short follow-up
- Exclusion of patients with keratinizing (WHO type 1) cancer
- Exclusion of confounded trials (for instance addition of chemotherapy but lower dose of radiation or hyperfractionation using split course resulting in the same total time)
- Exclusion of the trials including less than 100 patients;
- Exclusion of the trials for which dates of randomization are not available (and then only delay of survival available).

\(^1\) 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.
SURROGATE ENDPOINT VALIDATION

As clinical research goes faster, it is important to determine surrogate endpoints for important clinical endpoints, which could help investigators and patients to have earlier the results of ongoing research. In oncology overall survival (OS) is the most clinically relevant endpoint, but some other endpoints, such as loco-regional failure rate, and progression-free survival (PFS) could serve as surrogate for overall survival. It has been shown in Head and Neck Squamous Cell Carcinoma based on the MACH-NC and MARCH databases that PFS was a good surrogate endpoint for OS especially in trials investigating the role of chemotherapy\textsuperscript{26}. A similar analysis could be conducted for nasopharyngeal carcinoma.

To study the usefulness of loco-regional failure rate, and progression-free survival as surrogate endpoints of overall survival, it is necessary to analyze the data at the individual and trial levels. At the individual level, the rank correlation coefficient $\rho$ between the surrogate endpoint (loco-regional failure rate, or progression-free survival) and overall survival will be estimated from the bivariate distribution of these endpoints. At the trial level, the correlation coefficient $R$ between treatment effects (estimated by log hazard ratios) on the surrogate endpoint and overall survival will be estimated from a linear regression\textsuperscript{26}.

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\textsuperscript{27, 28}. 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. A network meta-analysis will be performed using the trials included based on the updated MAC-NPC database 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 and concomitant chemotherapy

The network based on the identified trials is presented on next page.

Note: the Xu trial is comparing induction chemotherapy + radiotherapy versus concomitant radio-chemotherapy with adjuvant chemotherapy in both arms, and not induction chemotherapy versus none with concomitant radio-chemotherapy in both arms.
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.

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 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-NPC Group and include a list of all collaborators.

Acknowledgments

We are grateful to Francine Courtial for assistance in preparing the literature search.
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Appendix A: Description of the trials comparing radiotherapy to radio-chemotherapy in locally advanced nasopharyngeal carcinoma

See abbreviations on page14 and references in the references section (for trials included in the first round of the meta-analysis, see paper by Baujat et al).

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

<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>Inclusion period</th>
<th>Stage</th>
<th>Histologic type</th>
<th>RT Dose &amp; Duration</th>
<th>Chemotherapy timing</th>
<th>Chemotherapy Dose</th>
<th>Number of cycles</th>
<th>Patients randomized-analyzed</th>
<th>Median FU (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPC 9901</td>
<td>1999-2004</td>
<td>III-IV</td>
<td>WHO II-III</td>
<td>≥66 Gy, 2Gy/F,5F/wk</td>
<td>Concomitant</td>
<td>C: 100 mg/m² d₁,22,43 C: 80 mg/m² d₇₁-99,127 Fu: 1000 mg/m²/d d₁-71-74,99-102,127-130</td>
<td>3</td>
<td>348/348</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjuntive</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCCS01</td>
<td>1997-2003</td>
<td>III-IV</td>
<td>WHO II-III</td>
<td>70 Gy, 2Gy/F, 5F/wk</td>
<td>Concomitant</td>
<td>C: 25 mg/m²/d d₁-4,22-25,43-46 C: 20 mg/m²/d d₇₁-74,99-102,127-130 Fu: 1000 mg/m²/d d₁-71-74,99-102,127-130</td>
<td>3</td>
<td>221/221</td>
<td>3.2</td>
</tr>
<tr>
<td>Guangzhou</td>
<td>2001-2003</td>
<td>III-IV</td>
<td>WHO II-III</td>
<td>≥70 Gy, 2Gy/F,5F/wk</td>
<td>Concomitant</td>
<td>Ox: 70 mg/m² d₁,8,15,22,29,36</td>
<td>6</td>
<td>115/115</td>
<td>2</td>
</tr>
<tr>
<td>NPC 9902</td>
<td>1999-2004</td>
<td>III-IV</td>
<td>WHO II-III</td>
<td>≥66 Gy, 2Gy/F,5F/wk</td>
<td>Concomitant</td>
<td>C: 100 mg/m² d₁,22,43 C: 80 mg/m² d₇₁-99,127 Fu: 1000 mg/m²/d d₁-71-74,99-102,127-130</td>
<td>3</td>
<td>189/189</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥66 Gy, 2Gy/F,6F/wk</td>
<td>Adjuntive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SKLOSC</td>
<td>2002-2005</td>
<td>III-IV</td>
<td>WHO II-III</td>
<td>70 Gy, 2Gy/F, 5F/wk</td>
<td>Concomitant</td>
<td>C: 40 mg/m² d₁,8,15,22,29,36,43 C: 80 mg/m² d₇₁-99,127 Fu: 800 mg/m²/d d₁-71-75,99-103,127-131</td>
<td>7</td>
<td>316/316</td>
<td>2.4</td>
</tr>
<tr>
<td>Guangzhou-early stage</td>
<td>2003-2007</td>
<td>II</td>
<td>WHO II-III</td>
<td>70 Gy, 2Gy/F, 5F/wk</td>
<td>Concomitant</td>
<td>C: 30 mg/m² d₁,8,15,22,29,36,43</td>
<td>7</td>
<td>230/230</td>
<td>5</td>
</tr>
</tbody>
</table>

*: 2x2 trial comparing two types of fractionation (5/week vs 6/week) and the addition of concomitant/adjuvant chemo
NPC 9901 included only N2N3 tumors while NPC 9902 included only T3-4 N0-1 tumors
| Trial (ref) | Inclusion period | Stage | Histologic type | RT Dose & Duration | Chemotherapy timing | Chemotherapy Dose | Number of cycles | Patients randomized-analyzed | Median FU (years) |
|------------|------------------|-------|-----------------|-------------------|---------------------|------------------|------------------|------------------------|----------------|------------------|
| VUMCA II*  | 1996-2000        | III-IV| WHO II-III      | 70 Gy, 2 Gy/F, 5F/wk | Induction           | B: 10 mg         | 3                | 509/509               | NA             |
|            |                  |       |                 |                   |                     | B: 48 mg/m²       |                  |                        |                |
|            |                  |       |                 |                   |                     | E: 70 mg/m²       |                  |                        |                |
|            |                  |       |                 |                   |                     | C: 100 mg/m²      |                  |                        |                |
|            |                  |       |                 |                   |                     | Concomitant (R)   | Hu: 500-1000 mg/d, po |                        |                |

* unpublished data
(R): randomized arm
VUMCA II: The patients were all treated by induction chemotherapy and randomized to received or not concomitant chemotherapy. The randomization was performed before the start of induction chemotherapy.
Table 3. Trials of induction chemotherapy versus None (followed by concomitant CT+RT in both arms)

<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>Inclusion period</th>
<th>Stage</th>
<th>Histologic type</th>
<th>RT Dose &amp; Duration</th>
<th>Chemotherapy timing</th>
<th>Chemotherapy Dose</th>
<th>Number of cycles</th>
<th>Patients randomized-analyzed</th>
<th>Median FU (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeCOG\textsuperscript{15}</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Induction (R)</td>
<td>C: 75 mg/m\textsuperscript{2} \textsubscript{d1,22,43}</td>
<td>3</td>
<td>141/NA</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E: 75 mg/m\textsuperscript{2} \textsubscript{d1,22,43}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P: 175 mg/m\textsuperscript{2} \textsubscript{d1,22,43}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concomitant</td>
<td>C: 40 mg/m\textsuperscript{2} \textsubscript{d1,8,15,22,29,36,43}</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hui\textsuperscript{16}</td>
<td>2002-2004</td>
<td>III-IV</td>
<td>WHO II-III</td>
<td>70 Gy, 2Gy/F, 5F/wk</td>
<td>Induction (R)</td>
<td>Do: 75 mg/m\textsuperscript{2} \textsubscript{d1,22}</td>
<td>2</td>
<td>65/65</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C: 75 mg/m\textsuperscript{2} \textsubscript{d1,22}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concomitant</td>
<td>C: 40 mg/m\textsuperscript{2} \textsubscript{d1,8,15,22,29,36,43}</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(R) : randomized arm
Table 4. Trials of adjuvant chemotherapy versus none (Preceded by concomitant CT+RT in both arms)

<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>Inclusion period</th>
<th>Stage</th>
<th>Histologic type</th>
<th>RT Dose &amp; Duration</th>
<th>Chemotherapy timing</th>
<th>Chemotherapy Dose</th>
<th>Number of cycles</th>
<th>Patients randomized-analyzed</th>
<th>Median FU (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma\textsuperscript{14}</td>
<td>2006-2010</td>
<td>III-IV</td>
<td>WHO II-III</td>
<td>≥66 Gy, 2Gy/F, 5F/wk</td>
<td>Concomitant in both arms Adjuvant (R)</td>
<td>C: 40 mg/m\textsuperscript{2} d\textsubscript{1,8,15,22,29,36,43} C: 80 mg/m\textsuperscript{2} d\textsubscript{71,99,127} Fu: 800 mg/m\textsuperscript{2}/d d\textsubscript{71-75,99-103,127-131}</td>
<td>7</td>
<td>508/508</td>
<td>3.1</td>
</tr>
</tbody>
</table>

(R) : randomized arm

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

<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>Inclusion period</th>
<th>Stage</th>
<th>Histologic type</th>
<th>RT Dose &amp; Duration</th>
<th>Chemotherapy timing</th>
<th>Chemotherapy Dose</th>
<th>Number of cycles</th>
<th>Patients randomized-analyzed</th>
<th>Median FU (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu\textsuperscript{17}</td>
<td>2004-2007</td>
<td>III-IV</td>
<td>WHO II-III</td>
<td>70 Gy, 2 Gy/F, 5F/wk</td>
<td>Induction concomitant</td>
<td>C: 30 mg/m\textsuperscript{2} d\textsubscript{1-3,28-30} Fu: 500 mg/m\textsuperscript{2} d\textsubscript{1-3,28-30} C: 30 mg/m\textsuperscript{2} d\textsubscript{1-3,22-24} Fu: 500 mg/m\textsuperscript{2} d\textsubscript{1-3,22-24}</td>
<td>2</td>
<td>338/338</td>
<td>NA</td>
</tr>
</tbody>
</table>

Adjuvant

C: 30 mg/m\textsuperscript{2} d\textsubscript{1-3,28-30} Fu: 500 mg/m\textsuperscript{2} d\textsubscript{1-3,28-30}
List of abbreviations

CT       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

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)
APPENDIX B: 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. We should be able to read any standard CD/DVD 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.

------------------

1 Our e-mail address is : jppignon@igr.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 floppy disk**

<table>
<thead>
<tr>
<th>Column</th>
<th>Variable</th>
<th>Format/Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-11</td>
<td>Patient identifier</td>
<td>10 characters</td>
</tr>
<tr>
<td>13-20</td>
<td>Date of birth or age</td>
<td>dd/mm/yyyy, 99999999=Unknown, 6 blanks (columns 13-18), 2 digits (columns 19-20), 99=Unknown</td>
</tr>
<tr>
<td>22</td>
<td>Sex</td>
<td>1=Male, 2=Female, 9=Unknown</td>
</tr>
<tr>
<td>24-26</td>
<td>Performance Status</td>
<td>For Karnofsky index use 3 digits, for WHO or ECOG index use 2 blanks (column 24-25) and one digit (column 26)</td>
</tr>
<tr>
<td>28</td>
<td>Histology</td>
<td>1= WHO grade 1, 2= WHO grade 2, 3=WHO grade 3, 4= other, 9=Unknown</td>
</tr>
<tr>
<td>30</td>
<td>T</td>
<td>0=T0, 1=T1, 2=T2, 3=T3, 4=T4, 5=TX, 6=TI5, 9=Unknown</td>
</tr>
<tr>
<td>32</td>
<td>N</td>
<td>0=N0, 1=N1, 2=N2, 3=N3, 4=NX, 9=Unknown</td>
</tr>
<tr>
<td>34</td>
<td>M</td>
<td>0=M0, 1=M1, 9=Unknown</td>
</tr>
<tr>
<td>36-37</td>
<td>Stage group</td>
<td>2 digits needed (1, 2, 3, 4A, 4B), 1 digit (column 37) with blanks in columns 36, 9=Unknown</td>
</tr>
<tr>
<td>39</td>
<td>Imaging method</td>
<td>1= Standard X-Ray, 2= CT scan, 3= MRI, 9= Unknown</td>
</tr>
<tr>
<td>41</td>
<td>Treatment allocated</td>
<td>1=No Chemotherapy, 2=Chemotherapy</td>
</tr>
<tr>
<td>43</td>
<td>Induction chemotherapy – cycles</td>
<td>No. of cycles received</td>
</tr>
<tr>
<td>45-46</td>
<td>concomitant chemotherapy – cycles*</td>
<td>2 digits, No. of cycles/injections received</td>
</tr>
</tbody>
</table>

* or injections, specify
<table>
<thead>
<tr>
<th>Column</th>
<th>Variable</th>
<th>Format/Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>Adjuvant chemotherapy – cycles</td>
<td>No. of cycles received</td>
</tr>
<tr>
<td>50</td>
<td>Radiotherapy – technique</td>
<td>1 = 2D, 2 = 3D, 3 = IMRT, 9 = unknown</td>
</tr>
<tr>
<td></td>
<td>(PS: for patients treated with mixed externalbeam techniques – enter the technique used for major part of the course)</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>Radiotherapy – boost</td>
<td>0=no, 1= brachytherapy, 2= stereotactic radiosurgery/radiotherapy, 3= others, 9= unknown</td>
</tr>
<tr>
<td>54-57</td>
<td>Radiotherapy – total dose</td>
<td>No. of Gy, e.g. 50.4 or 60.0</td>
</tr>
<tr>
<td>59-60</td>
<td>Radiotherapy – fractionation</td>
<td>2 digits, No. of fractions received</td>
</tr>
<tr>
<td>62</td>
<td>Radiotherapy – fractionation</td>
<td>1 = conventional fractionation, 2 = accelerated fractionation</td>
</tr>
<tr>
<td>64-71</td>
<td>Radiotherapy – Date commenced</td>
<td>dd/mm/yyyy, 99999999=Unknown</td>
</tr>
<tr>
<td>73-80</td>
<td>Radiotherapy – Date completed</td>
<td>dd/mm/yyyy, 99999999=Unknown</td>
</tr>
<tr>
<td>82-89</td>
<td>Date of randomization</td>
<td>dd/mm/yyyy, 99999999=Unknown</td>
</tr>
<tr>
<td>91-98</td>
<td>Date of last follow-up or death</td>
<td>dd/mm/yyyy, 99999999=Unknown</td>
</tr>
<tr>
<td>100</td>
<td>Survival status</td>
<td>0= Alive, 1= Dead</td>
</tr>
<tr>
<td>102</td>
<td>Cause of death</td>
<td>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</td>
</tr>
<tr>
<td>104</td>
<td>Tumor failure*,</td>
<td>0= No, 1= Yes</td>
</tr>
<tr>
<td>106-113</td>
<td>Date of tumor failure</td>
<td>dd/mm/yyyy, 99999999=Unknown</td>
</tr>
<tr>
<td>115</td>
<td>Nodal failure*,</td>
<td>0= No, 1= Yes</td>
</tr>
<tr>
<td>117-124</td>
<td>Date of nodal failure</td>
<td>dd/mm/yyyy, 99999999=Unknown</td>
</tr>
</tbody>
</table>

* 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.
<table>
<thead>
<tr>
<th>Column</th>
<th>Variable</th>
<th>Format/Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>126</td>
<td>Distant failure (metastasis)</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>128-135</td>
<td>Date of distant failure (metastasis)</td>
<td>dd/mm/yyyy, 99999999=Unknown</td>
</tr>
<tr>
<td>137</td>
<td>Second primary</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>139-146</td>
<td>Date of second primary</td>
<td>dd/mm/yyyy, 99999999=Unknown</td>
</tr>
<tr>
<td>148</td>
<td>Type of second primary</td>
<td>Lung=1, Esophagus=2, Stomac=3, Colorectal=4, Liver=5, Head&amp; neck=6, Other=7 (specify) 9=Unknown</td>
</tr>
<tr>
<td>150</td>
<td>Localisation of second primary</td>
<td>0= within, 1=outside the irration field (if available)</td>
</tr>
<tr>
<td>152</td>
<td>Excluded from your analysis</td>
<td>0=No, 1=Yes</td>
</tr>
<tr>
<td>154-165</td>
<td>Reasons for exclusion</td>
<td>12 characters</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Column</th>
<th>Variable</th>
<th>Format/Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>167</td>
<td>Neutropenia</td>
<td>0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing</td>
</tr>
<tr>
<td>169</td>
<td>Febrile neutropenia</td>
<td>0=No, 1=Yes, 9=missing (or grade)</td>
</tr>
<tr>
<td>171</td>
<td>Thrombocytopenia</td>
<td>0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing</td>
</tr>
<tr>
<td>173</td>
<td>Anemia</td>
<td>0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing</td>
</tr>
<tr>
<td>175</td>
<td>Kidney failure</td>
<td>0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing</td>
</tr>
<tr>
<td>177</td>
<td>Cutaneous</td>
<td>0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing</td>
</tr>
<tr>
<td>179</td>
<td>Need for feeding tube</td>
<td>0=No, 1=Yes, 9=missing</td>
</tr>
<tr>
<td>181</td>
<td>Weight loss</td>
<td>0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 9=missing</td>
</tr>
<tr>
<td>183</td>
<td>Mucositis</td>
<td>0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing</td>
</tr>
<tr>
<td>185</td>
<td>Hearing loss</td>
<td>0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing</td>
</tr>
<tr>
<td>187</td>
<td>Neurotoxicity</td>
<td>0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing</td>
</tr>
<tr>
<td>189-200</td>
<td>Specify</td>
<td>12 characters</td>
</tr>
<tr>
<td>Column</td>
<td>Variable</td>
<td>Format/Coding</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Worst late toxicity (Specification of toxicity grading system used for each factor)</td>
<td></td>
</tr>
<tr>
<td>202</td>
<td>Cutaneous fibrosis</td>
<td>0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing</td>
</tr>
<tr>
<td>204</td>
<td>Xerostomia</td>
<td>0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing</td>
</tr>
<tr>
<td>206</td>
<td>Bone necrosis</td>
<td>0=grade 0, 1=grade1, 2=grade 2, 3=grade 3, 4=grade 4, 5=grade 5, 9=missing</td>
</tr>
<tr>
<td>208</td>
<td>Persistence of feeding tube after one year of treatment</td>
<td>0=No, 1=Yes, 9=missing</td>
</tr>
<tr>
<td>210</td>
<td>Endocrine dysfunction**</td>
<td>0=No, 1=Yes, 9=missing</td>
</tr>
<tr>
<td>212-223</td>
<td>Specify</td>
<td>12 characters</td>
</tr>
<tr>
<td>225</td>
<td>Hearing deficit**</td>
<td>0=No, 1=Yes, 9=missing (give grade if available)</td>
</tr>
<tr>
<td>227</td>
<td>Cranial nerve palsy**</td>
<td>0=No, 1=Yes, 9=missing</td>
</tr>
<tr>
<td>229</td>
<td>Asymptomatic temporal lobe necrosisµ</td>
<td>0=No, 1=Yes, 9=missing</td>
</tr>
<tr>
<td>231</td>
<td>Symptomatic temporal lobe necrosisµ</td>
<td>0=No, 1=Yes, 9=missing</td>
</tr>
<tr>
<td>233</td>
<td>Brainstem / Spinal cord damage</td>
<td>0=No, 1=Yes, 9=missing</td>
</tr>
<tr>
<td>235</td>
<td>Trismus**</td>
<td>0=No, 1=Yes, 9=missing</td>
</tr>
<tr>
<td>237</td>
<td>Visual deficit**</td>
<td>0=No, 1=Yes, 9=missing</td>
</tr>
<tr>
<td>239</td>
<td>Massive bleeding</td>
<td>0=No, 1=Yes, 9=missing</td>
</tr>
</tbody>
</table>

** give grade if available ; µ 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
114, rue Edouard Vaillant – 94805 Villejuif cedex France
- Fax 33 1 42 11 52 58 – e-mail: jpignon@igr.fr
REFERENCES


8. Lee AW, Tung SY, Chan AT et al. Preliminary results of a randomized study (NPC-9902 Trial) on therapeutic gain by concurrent chemotherapy and/or accelerated fractionation


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