Meta-Analysis of Radiotherapy in Carcinomas of Head and neck

UPDATE OF A META-ANALYSIS BASED ON INDIVIDUAL PATIENT DATA EVALUATING
THE ROLE OF MODIFIED FRACTIONATION
RADIOTHERAPY IN HEAD AND NECK CARCINOMAS

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ADVISORY BOARD

Jens Overgaard, MD
Danish Cancer Society
Aarhus University Hospital
Nørrebrogade 44, Building 5
8000 Aarhus C, Denmark

Andy Trotti, MD
H Lee Moffitt Cancer Ctr
and Rsrch Inst
12902 Magnolia Drive
Mail Stop MCC—RadOnc
Tampa, Fl 33612-9416
U.S.A.

Jacques Bernier, MD
Swiss Genolier Medical Network
Dept. of Radiotherapy
Clinique de Genolier
CH-1272 Genolier, Switzerland

Masheh KB Parmar, DPhil
MRC Clinical Trials Unit
222 Euston Road
London, NW1 2DA, U.K.

Quynh-Thu Le, MD FACR
Katharine Dexter McCormick & Stanley McCormick Memorial Professor
Department of Radiation Oncology
875 Blake Wilbur Dr, MC 5847
Stanford, CA

SECRETARIAT

Statisticians

Jean-Pierre Pignon, MD, PhD
Institut Gustave Roussy
114, rue Edouard Vaillant
94 805 Villejuif Cedex,
France
Phone : 33 1 42 11 45 65
fax : 33 1 42 11 52 58 ;
e-mail : jppignon@igr.fr

Clinical Managers

Jean Bourhis, MD, PhD
Institut Gustave Roussy
114, rue Edouard Vaillant
94 805 Villejuif Cedex, France

Pierre Blanchard, MSc
Institut Gustave Roussy
114, rue Edouard Vaillant
94 805 Villejuif Cedex, France

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1. INTRODUCTION AND BACKGROUND

Head and neck squamous cell carcinomas are frequent tumours, with more than 550 000 new cases and more than 300 000 deaths from oral cavity, oropharynx, hypopharynx, and larynx cancer every year worldwide.[1] About 40% of patients have locally advanced disease at diagnosis. Surgery, radiation therapy, or both, have been used for decades to achieve locoregional control; the most commonly used schedule when radiotherapy is given alone is 2 Gy in a single fraction per day, 5 days a week, for 7 weeks. Despite these treatments, the prognosis of patients with head and neck squamous cell carcinomas with locally advanced disease remains poor, with 5-year survival rates of 30-35%.[2] In the past decade, new radiotherapy regimens for the treatment of head and neck squamous cell carcinomas have been assessed. These regimens were designed to increase the dose-intensity by delivering a higher total dose in the same time (hyperfractionated radiotherapy),[3-6] the same total dose in 5-6 weeks instead of 7 weeks (accelerated radiotherapy),[6-12] or a smaller total dose given in 3-4 weeks (accelerated radiotherapy with total dose reduction).[13-17] Reducing the total treatment time should reduce the repopulation of tumour cells between fractions, resulting in improved locoregional control. It has been shown, in previous meta-analyses of head and neck cancer or breast cancer, that improving loco-regional control could lead to an increase of overall survival. [18] In hyperfractionated regimens, two to three fractions are delivered each day, with a reduced dose per fraction equals to 1.1-1.2 Gy. Moreover, concomitant chemotherapy, which improves survival when added to standard radiotherapy[2] has recently been added to modified fractionation radiotherapy in clinical trials, to further enhance therapy. This radiation technique has also been used in the post-operative setting, alone or combined with chemotherapy.

The reduction of the dose per fraction might reduce the risk of late toxicity, despite an increased total dose. Acceleration and hyperfractionation can be combined, in particular for regimens in which overall treatment time is reduced. The use of altered fractionated radiotherapy is associated with some increase in toxicity, mostly due to mucositis,[6-9,17] and can add some

practical constraints in radiotherapy departments[3,9,11,17] that need to be balanced by substantial benefits.

A meta-analysis of updated individual patient data was undertaken by the MARCH (Meta-Analysis of Radiotherapy in Carcinomas of Head and neck) Collaborative Group[19]. Randomized trials comparing conventional radiotherapy with hyperfractionated or accelerated radiotherapy, or both, in patients with non-metastatic HNSCC were identified and updated individual patient data were obtained. Overall survival was the main endpoint. Trials were grouped in three pre-specified categories: hyperfractionated, accelerated, and accelerated with total dose reduction.

The median follow-up was 6 years. Fifteen trials with 6515 patients were included. Tumour sites were mostly oropharynx and larynx (78%); 5 221 (74%) patients had stage III–IV disease (International Union Against Cancer, 1987). There was a significant survival benefit with altered fractionated radiotherapy, corresponding to an absolute benefit of 3.4% at 5 years (hazard ratio 0.92, 95% CI 0.86–0.97; p=0.003). The benefit was significantly higher with hyperfractionated radiotherapy (8% at 5 years) than with accelerated radiotherapy (2% with accelerated fractionation without total dose reduction and 1.7% with total dose reduction at 5 years, p=0.02). There was a benefit on locoregional control in favour of altered fractionation versus conventional radiotherapy (6.4% at 5 years; p<0.0001), which was particularly efficient in reducing local failure, whereas the benefit on nodal control was less pronounced. The benefit was significantly higher in the youngest patients (hazard ratio 0.78 [0.65–0.94] for 50 year olds or less, 0.95 [0.83–1.09] for 51–60 year olds, 0.92 [0.81–1.06] for 61–70 year olds, and 1.08 [0.89–1.30] for over 70 year olds; test for trend p=0.007). Data on treatment compliance and toxicity could be helpful to understand the interaction between age and endpoints (overall survival as well as event-free survival). In brief, the MARCH meta-analysis showed that altered fractionation radiotherapy improves survival in patients with head and neck squamous cell carcinoma. Comparison of the different types of altered radiotherapy suggests that hyperfractionation provides the greatest benefit.

In addition, a separate analysis of MACH-NC and MARCH showed that EFS is better correlated 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 randomized trials of locally advanced HNSCC[18].

Since the publication of this first meta-analysis, many trials have been published about that specific topic. An update of this meta-analysis would be of great interest for many reasons. First, it would allow us to **confirm the superiority of hyperfractionation** over other fractionation schemes with a longer follow-up and a greater number of patients and events. Second, we could address other issues that were addressed in the first meta-analysis due to an insufficient number of patients and/or trials, for instance the **effect of altered fractionation radiotherapy in the post-operative setting**, or the role of altered fractionation radiotherapy in the **context of concomitant chemoradiation therapy,** or to directly **compare hyperfractionation and concomitant chemo-radiotherapy**. Third, a longer follow up would allow us to **better analyze the late adverse effects** of these therapies, and to better understand whether these regimens are associated with higher **non-cancer related death**, as was suggested in the MARCH meta-analysis. Fourth, this update could give an opportunity to validate the analysis of **surrogate endpoints in radiotherapy HNSCC trials**.

The methodology will be similar to that used in the Breast Cancer Overview[20], the Small Cell Lung Cancer Meta-analysis[21], the Non Small Cell Lung Cancer Overview[22], and MACH-NC2[2]. 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[23]. Basic survival and prognostic information will be collected for all randomized patients in each study because this allows for a more reliable and flexible approach, a more sensitive analysis and avoids the potential bias of post-randomization exclusion[24,25]. Updated follow-up information will be sought to report on long-term survival.

Nineteen trials have been found eligible for this update of MARCH meta-analysis, which included more than 5 000 patients. Overall, the study will include more than 30 trials and 11 000 patients for the main comparison (modified fractionation RT *versus* standard RT). This will give a higher statistical power to the meta-analysis and allow addressing previously unanswered questions. Tables A lists the new trials and Table B in Appendix B shows the number of patients and trials for each comparison.

In brief, we believe that an update of the collaborative MARCH meta-analysis would be of great interest to further explore the question addressed in the previous meta-analysis, and to document long term survival, control, non cancer death and toxicity. We could also address the question of post-operative and concomitant chemoradiation settings.

2. OBJECTIVES

Assessment of the role of modified fractionated radiotherapy in head and neck squamous carcinoma by studying the following questions:

2.1. MAIN QUESTION

Role of modified fractionated radiotherapy on the **overall survival** of patients with HNSCC.

1st comparison

- Primary or postoperative **Conventional radiotherapy** (+/- ***same*** concomitant chemotherapy)

versus

- Primary or postoperative **Hyperfractionated and / or accelerated radiotherapy** (+/- ***same*** concomitant chemotherapy)

2nd comparison

- Conventional **radiotherapy + concomitant chemotherapy**

versus

- **Hyperfractionated radiotherapy**

2.2. SECONDARY QUESTIONS

- Impact of modified fractionation radiotherapy on distant control and loco-regional control.
- Comparison of long term toxicity and non cancer death according to fractionation regimen.
- Investigation of the interaction between the treatment effect and the prognostic factors (subgroup analysis).
- Investigation of the interaction between the treatment effect and the type of radiotherapy (indirect comparison).
- Investigate the validity of event-free survival and loco-regional control as surrogate markers for overall survival.

- Use of a bayesian network meta-analysis model to rank treatments according to the achieved overall survival and compare direct and indirect estimates.
- A second project will be performed on smoking status and HPV data.
- A third project will be performed on pathological variables of resected tumor (pT, pN, resection margins, …).

3. TRIAL SELECTION CRITERIA

3.1. INCLUSION CRITERIA

All trials must satisfy the following criteria:

Trials must

- Be randomized in a way which precludes prior knowledge of treatment assignment.
- Be unconfounded, i.e. trials should differ only on radiotherapy modalities.
- Have started randomization on or after January 1st 1970. (the trials with accrual between 1970-1999 have already been included in the MARCH study)
- Have completed accrual before December 31th, 2010
- Include patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx.
- Not include patients with metastatic disease.

Patients should

- Undergo a first line therapy.
- Not have received prior radiotherapy.
- Not have received prior chemotherapy.
- Undergo a potentially curative loco-regional treatment.

3.2. EXCLUSION CRITERIA:

- Randomized trials without a conventional radiotherapy arm;

- Randomized trials comparing hypofractionated (dose per fraction above 2.5 Gy) versus conventional radiotherapy;
- Randomized trials including mainly or exclusively nasopharyngeal carcinomas.

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 (Medline, SCOPUS), hand searching (review articles, ASCO, ASTRO, ECCO and ESTRO meeting proceedings) and by contacting experts in the field. Trials registries (PDQ, ClinProt...) will be also consulted. The final search was performed in May 2009. All trialists who take part in the meta-analysis will be asked to help to identify more trials.

The search equations used were:

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 SCOPUS :

(otolaryngolog* OR buccal OR mouth OR (oral cavity) OR lip OR hypopharynx OR oropharynx OR larynx OR “head and neck”) AND (random* OR phase 3) AND (radiation OR radiotherapy OR chemoradiotherapy)

5. DESCRIPTION OF TRIALS INCLUDED

The authors of the trials already included in the MARCH database will be contacted to provide updated information from their databases (representing 15 trials and 6 515 patients).

The references of the eligible trials are listed in section 14. **Appendix B** describes the available material to-date for the meta-analysis. Eighteen new trials (22 therapeutic comparisons as 2 trials with 3 arms contribute to two comparisons and one trials with a 2x2 design contributes to 3 comparisons) that completed their accrual before December 31th, 2010 and included approximately 5 131 patients studied the role of modified fractionation in patients with HNSCC. Overall (new and old trials together), there are 33 trials (11 646 patients) for comparison 1 and 3 trials (688 patients) for comparison 2. One other new trial compared two regimens of altered fractionation radiotherapy without a standard arm and included 69 patients. Four trials than planned to include more than one thousand of patients are ongoing.

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 will include endpoints necessary to study the secondary questions as mentioned in §2:

- time to first event
- time to local or distant failure
- head and neck cancer mortality and non-head and neck cancer mortality
- toxicity will also be considered, especially long term toxicity
- compliance will give an insight into acute toxicity
- Smoking status (never, former, current), if available
- HPV status (p16), if available
- Pathological variable of resected tumor, if available

6.2. PROGNOSTIC FACTORS

The prognostic factors that will be considered are:

- Age (50 or less, 50-59, 60-69,70+).
- Sex (male, female).
- Site of the primary tumor (oral cavity, oropharynx, larynx, hypopharynx, other).
- Stage (I-II, III, IV).
- Smoking status (never, former, current; pack-year), if available
- HPV status (p16), if available
- Performance status (WHO or equivalent, 0, 1, 2+).

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
- Smoking status (never, former, current; pack-year)
- HPV status (p16)
- Site of the primary.
- Stage TNM (if stage not available; information on classification used)
- Allocated treatment
- Date of randomization
- Date of last follow-up
- Survival status
- Cause of death
- Whether excluded from trial analysis

- Reason for exclusion (if available)
- Date of first event
- Type of first event (loco-regional failure, distant failure)
- *If available*
    - Date of first local failure
    - Date of first regional failure
    - Date of first distant failure
    - Type of first distant failure : location
    - Date of first second primary
    - Type of first second primary : location
- Compliance to radiotherapy
    - date of the beginning of treatment
    - date of end of treatment
    - total radiation dose received
    - total number of fraction
- Compliance to chemotherapy (if applicable)
    - number of cycles planned
    - number of cycles received
    - cycle dose reduction : yes/no
- Grade 3-4 acute toxicity
    - scale used to quantify toxicity (NCI CTC v3.0, RTOG, SOMA-LENT…)
    - mucositis
    - weight loss (weight at randomization minus weight at the end of treatment)
    - dermatitis
    - neutropenia
    - febrile neutropenia
    - renal toxicity (renal failure)
    - Thombopenia
    - Anemia

- Feeding tube

o Grade 3-4 late toxicity
  - scale used to quantify toxicity (NCI CTC v3.0, RTOG, SOMA-LENT…)
  - neck fibrosis
  - persistance of feeding tube > 1 year after end of treatment
  - weight loss (weight at randomization minus weight one year after treatment)
  - xerostomia
  - renal toxicity (renal failure)
  - bone necrosis
  - mucosal toxicity
  - hear toxicity
o For post-operative trials
  - version of the pTNM classification
  - pT
  - pN
  - pN2 details
  - resection margins
  - total number of nodes
  - number of positive lymph nodes
  - extra-capsular extension
  - presence of peri-neural invasion
  - presence of lymphovascular invasion

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 12 000 patients (and at least 7000 deaths) it would be possible to detect, with a power of 99.9 %, an absolute improvement in survival from 30 % to 33 % at 5-years (two-sided logrank test, type I error=5%). Table B-8 in appendix B shows the number of patients and trials for each comparison.

All randomized patients will be included in the analysis. The analysis will be performed on an intent-to-treat basis using the stratified (by trial) logrank test. The hazard ratio for individual trials and for each comparison will be reported. 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 altered fractionated radiotherapy compared with those who were allocated conventional radiotherapy. For comparing toxicity rates, overall pooled odds ratio stratified by trials will be calculated by a fixed-effect model. All p-values will be two-sided.

Stratified survival curves will be estimated for control and experimental groups using annual death rates and hazard ratios[26]. They will be used to calculate absolute benefit at 3-years, and 5-years with their 95% confidence intervals[26]. The overall heterogeneity between trials will be studied using hazard ratio plot and chi-square test for heterogeneity. I^2 values will be calculated[27].

All these analyses will be performed for the main endpoint, overall survival and for the secondary endpoints: event-free survival, time to loco-regional and distant failure, cancer-related death, non-cancer death, acute and late toxicities.

Head and Neck (HN) cancer and non-HN cancer mortality using method similar to that used in MACH-NC[2] and in the Lung Adjuvant Cisplatin Evaluation (LACE) [28] 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) [28]. Non-HN cancer mortality is defined as death of known cause without recurrence and not considered as a HN cancer death. HN cancer mortality included death of any cause with prior recurrence, death from HN cancer and death from unknown cause.

8.1. ANALYSES BY TRIAL LEVEL CHARACTERISTICS

The effect of altered fractionated radiotherapy may vary across trials in the meta-analysis because the treatments might be applied in different ways. To explore this further, providing that there are sufficient data available, analyses are planned in which trials, or arms within trials, will be grouped according to the type of altered fractionated radiotherapy to determine whether there is any difference in treatment effect among these groups.

Three groups of trials (appendix A) have been identified according to the type of radiotherapy. Two 3-arm trials and one 2*2 factorial trial allow us to perform 22 comparisons by counting twice the control group. The analysis will take into account these groups of trials and study the interaction between the observed effect of the treatment on survival and the type of radiotherapy. The hazard ratios of the three groups of trials will be compared by a chi-square test for heterogeneity and I^2 values will be calculated. Results of the postoperative trials and those combined with chemotherapy will be compared with those using radiotherapy alone.

The following exploratory analyses will be performed to take into account the multidimensional aspect of the difference between the trials included. A fixed-effect survival model stratified by trial will be fitted using all the trials, and an overall hazard ratio between conventional and alternative radiotherapy will be calculated. Additionally, a more detailed model will be fitted

which also includes indicator variables to represent the different aspects of the radiotherapy (acceleration, total dose, hyperfractionation) and the associated trial-level characteristics (concomitant chemotherapy, post-operative trial). Hazard ratios will be calculated from this model to assess the impact of the various methods of altering conventional radiotherapy.

8.2. ANALYSES BY PATIENT LEVEL CHARACTERISTICS

Provided that there will be sufficient data available, we will investigate whether any observed treatment effect is consistent across well-defined patient subgroups. These analyses will be carried out on all trials and will be stratified by trial. If there are substantial heterogeneity and differences of effect between treatment categories, then subgroup analyses will be done within treatment categories.

If there are insufficient numbers of patients within any patient category, categories will be combined. Chi-squared tests for interaction or trend will be used to test whether there is any evidence that a particular type of patients benefit more or less from altered fractionated radiotherapy.

8.3. SENSITIVITY ANALYSES

Hazard ratios for overall survival will also be calculated excluding any trials that are clear outliers, 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.

8.4. 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. At the individual level, the rank correlation coefficient ρ between the surrogate endpoint (loco-regional failure rate, or event-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[18].

8.5. 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[29,30]. 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 in the updated MARCH and MACH-NC studies and a specific protocol prepared.

8.6. HUMAN PAPILLOMA VIRUS

A second project will be to analyze the interaction between HPV status, smoking status, and the effect of altered fractionation radiotherapy.

A specific protocol will be written.

8.7. DATA ON RESECTED TUMOR

Finally, a third project will be to analyze the prognostic and predictive effects of pathological variables of resected tumor.

A specific protocol will be written.

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 Advisory Board 3) the MARCH Trialists' Collaborative Group (MARCH-CG).

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 patient data. The

Secretariat is also in charge of checking, processing and analyzing the data. Finally, the Secretariat is responsible for preparing reports and publications.

The Advisory Board is a small group of international experts that will support the Secretariat with medical and statistical expertise.

The Trialists' Collaborative Group (MARCH-CG) will include the investigators responsible for trials included in the meta-analysis. The members of the Secretariat and the Advisory Board will also be included in this group. They will be responsible for providing the Secretariat with data on patients and for discussing the reports prepared by the Secretariat.

10. PRACTICAL CONSIDERATIONS

The Secretariat is located in the Biostatistics Department of the Institut Gustave-Roussy (IGR). This Department will be responsible for liaising with trialists. The main database will be run by the Secretariat. All data, updates and corrections should be sent there. The protocol will be submitted to the IGR Institutional Review Board.

All supplied data will remain confidential and will be used exclusively for the meta-analysis. A meeting of all group members will be organized by the Secretariat to discuss the preliminary results. **Appendix D** provides the form to register in the meta-analysis.

Advance timetable and key steps

Protocol prepared and validated by the Advisory Board: 11-12/2009

Contact with investigators, data collection and checking: 01-12/2010

Analyses of the data by the Secretariat with the help of the Advisory Board: 01-03/2013

Discussion of the preliminary results, complementary analyses, and investigator meeting organization: 04/2013-05/2013

Investigators meeting: 06/2013

Final analyses, presentation in international meetings: 09/2013-06/2014

Manuscript(s) preparation: 07/2014-12/2014

11. PUBLICATION POLICY

The Secretariat will prepare the manuscript and will submit it for revision to all the members of the Group. Any publication arising from this project will be made in the name of the MARCH Collaborative Group and include a list of all collaborators.

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14. REFERENCES OF RANDOMIZED TRIALS ELIGIBLE FOR THE META-ANALYSIS

(See MARCH[19] for the list of trials already in the database or excluded)

Trials included for Comparison # 1

Ang 2001

Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, Geara FB, Klotch DW, Goepfert H, Peters LJ. Randomized trial addressing risk feature and times factors of surgery plus radiotherapy in advanced head and neck cancer. Int J Radiat Oncol Biol Phys 2001;51:571-78.

Ang 2007: RTOG H0129

Ang K, Pajak T, Rosenthal DI, et al.: A phase III trial to compare standard versus accelerated fractionation in combination with concurrent cisplatin for head and neck carcinomas (RTOG 0129): report of compliance and toxicity. Int J Radiat Oncol Biol Phys 2007;69(Suppl):S12-13. http://clinicaltrials.gov/ct2/show/NCT00047008?term=H0129&rank=1

Awwad 1992

Awwad HK, Khafagy Y, Barsoum M, Ezzat S, El-Attar I, Farag H, Akoush H, Meabid H, Zaghloul MS. Accelerated versus conventional fractionation in the postoperative irradiation of locally advanced head and neck cancer: influence of tumor proliferation. Radiother Oncol 1992;25:261-66.

Bartelink 2002

Bartelink H, Van den Bogaert W, Horiot JC, Jager J, Van Glabbeke M. Concomitant cisplatin and radiotherapy in a conventional and modified fractionation schedule in locally advanced head and neck cancer: a randomised phase II EORTC trial. Eur J Cancer 2002;38:667-73.

Bourhis 2008 : **GORTEC 99-02**

Bourhis J, Sire C, Lapeyre M, et al. Accelerated versus Conventional Radiotherapy with Concomitant Chemotherapy in Locally Advanced Head and Neck Carcinomas: Results of a Phase III Randomized Trial, Int J Radiat Oncol Biol Phys. 2008;72(Suppl):S31-32

DAHANCA 9

Randomized trial of accelerated radiotherapy versus hyperfractionated radiotherapy with nimorazole in both arms

See protocol: http://www.dahanca.dk/get_media_file.php?mediaid=40

Dische 2007

Dische S, Saunders M. Phase III randomized study of adjuvant continuous hyperfractionated accelerated radiotherapy versus conventional radiotherapy in patients with head and neck cancer. PDQ data base 2009.

See protocol :

http://clinicaltrials.gov/ct2/show/NCT00021125?cond=%22Skin+Neoplasms%22&rank=21

Ezzat 2005

Ezzat M, Shouman T, Zaza K, Safwat A, El-Khoudary A, El-Senosi M, Ezzat I. A Randomized Study of Accelerated Fractionation Radiotherapy with and Without Mitomycin C in the Treatment of Locally Advanced Head and Neck Cancer. Journal of the Egyptian Nat. Cancer Inst., Vol. 17, No. 2, June: 85-92, 2005

Ghosh 2006

Ghosh S, Agarwal J, Bhutani R, Vora A, Prabhash K, D'cruz A, Chaukar D, Shrivastava S, Dinshaw K. Randomized Trial of Conventional Fractionated RT (CFRT) vs. Concomitant Chemo Radiotherapy (CTRT) and Accelerated Radiotherapy (ACRT) in Patients with Advanced, Non Nasopharyngeal, Squamous Cell Cancers of the head and Neck Region. Int J Rad Oncol Biol Phys 2006;66(Suppl 1):S191.

Ghoshal 2008

S. Ghoshal, J. S. Goda, I. Mallick, T. S. Kehwar, S. C. Sharma. Concomitant Boost Radiotherapy Compared with Conventional Radiotherapy in Squamous Cell Carcinoma of the Head and Neck d a Phase III Trial from a Single Institution in India. Clinical Oncology (2008) 20: 212-220

Horiot 2007: **EORTC 22962**

Horiot JC. EORTC 22962: Phase III comparison study of conventional vs hyperfractioned radiotherapy in head and neck squamous cell carcinoma with or without concomitant chemotherapy. PDQ data base 2009.

See protocol : http://www.cancer.gov/clinicaltrials/EORTC-22962

Johnson 1995

Johnson CR, Schmidt-Ullrich RK, Arthur DW, Huang DT, Duffy EW. Standard once daily versus thrice-daily concomitant boost accelerated superfractionated irradiation for advanced squamous cell carcinoma of the head and neck: preliminary results of a prospective randomized trial. Int J Rad Oncol Biol Phys 1995;32 (Suppl 1):162.

Overgaard 2006

Overgaard J, Mohanti B, Bhasker S, Begum N, Ali R, Agerwal J, Kuddu M, Baeza M, Vikram B, Grau C. Accelerated Versus Conventional Fractionated Radiotherapy in Squamous Cell Carcinoma of the Head And Neck (SCCHN). A Randomized International Multicenter Trial With 908 Patients Conducted by the IAEA-ACC Study Group. Int J Rad Oncol Biol Phys 2006;66(Suppl 1):S13.

Other references:

Overgaard J, Mohanti BK, Bhasker S, Begum N, Ali R, Agerwal JP, Kuddu M, Baeza MR, Al-Amro A, Stannard C, Geara F, Vikram B, Crau C. A randomized trial with 908 patients evaluating the importance of accelerated versus conventional fractionated radiotherapy study of in squamous cell carcinoma of the head and neck. Eur J Cancer 2005; 3(Suppl):13.

Sanguineti 2005

Sanguineti G, Richetti A, Bignardi M, Corvo' R, Gabriele P, Sormani MP, Antognoni P. Accelerated versus conventional fractionated postoperative radiotherapy for advanced head and neck cancer: results of a multicenter Phase III study. Int J Radiat Oncol Biol Phys 2005;61:762-71.

Suwinski 2007

Suwinski R, Bankowska-Wozniak M, Majewski W,et al. Randomized clinical trial on 7-days-a-week postoperative radiotherapy for high-risk squamous cell head and neck cancer. Radiother Oncol. 2008;87:155-63.

Trotti 2006: RTOG 9512

Trotti A, Pajak T, Emami B, Hammond E, Jones C, Morrison W, Sagar S, Ridge J, Fu KK, Ang K. A randomized trial of hyperfractionation versus standard fractionation in T2 squamous cell carcinoma of the vocal cord. Int J Rad Oncol Biol Phys 2006;66(Suppl 1):S15.

See protocol : http://clinicaltrials.gov/ct2/show/NCT00002727?term=RTOG+9512&rank=1

Zackrisson 2007: ARTSCAN

Zackrisson B, Kjellén E, Björk-Eriksson T, Friesland S, Reizenstein J, Lagerlund M, Ekberg L, Lödén B, Ahlgren J, Adell G, Björnlinger K, Johansson KA. Preliminary results from a Swedish study of conventional versus accelerated fractionated of squamous carcinoma of the head and neck (ARTSCAN). Radiother Oncol 2007;82(Suppl 1):S1-S2.

Other publications:

Johansson KA, Nilsson P, Zackrisson B, et al. The quality assurance process for the ARTSCAN head and neck study - a practical interactive approach for QA in 3DCRT and IMRT. Radiother Oncol. 2008;87:290-9.

Trials included for Comparison # 2

Bourhis 2008: **GORTEC 99-02**

Bourhis J, Sire C, Lapeyre M, et al. Accelerated versus Conventional Radiotherapy with Concomitant Chemotherapy in Locally Advanced Head and Neck Carcinomas: Results of a Phase III Randomized Trial, Int J Radiat Oncol Biol Phys. 2008;72(Suppl):S31-32

Ghosh 2006

Ghosh S, Agarwal J, Bhutani R, Vora A, Prabhash K, D'cruz A, Chaukar D, Shrivastava S, Dinshaw K. Randomized Trial of Conventional Fractionated RT (CFRT) vs. Concomitant Chemo Radiotherapy (CTRT) and Accelerated Radiotherapy (ACRT) in Patients with Advanced, Non Nasopharyngeal, Squamous Cell Cancers of the head and Neck Region. Int J Rad Oncol Biol Phys 2006;66(Suppl 1):S191.

Horiot 2007: **EORTC 22962**

Horiot JC. EORTC 22962: Phase III comparison study of conventional vs hyperfractioned radiotherapy in head and neck squamous cell carcinoma with or without concomitant chemotherapy. PDQ data base 2009.

See protocol : http://www.cancer.gov/clinicaltrials/EORTC-22962

To be included in the network meta-analysis but not in the standard meta-analysis (do not compare altered fractionation RT with standard RT but two different regimens of altered fractionation RT):

Krstevska 2006

Krstevska V, Crvenkova S. Altered and conventional fractionated radiotherapy in locoregional control and survival of patients with squamous cell carcinoma of the larynx, oropharynx, and hypopharynx. Croat Med J 2006;47:42-52.

This trial used standard RT between 1999-2001, and then randomized patients during the period 2001-2004 between accelerated and hyperfractionated RT. This is not a properly randomized three-arm trial as the standard RT arm is an historical control arm.

Ongoing trials

Langendijk 2007a: POPART (Randomized trial on the role of accelerating overall treatment time for high risk head and neck cancer)

Langendijk J, on behalf of the NWHHT-SG. The Dutch head and neck cancer cooperative study group (NWHHT-SG). Radiother Oncol 2007;82(Suppl 1):S1.

Langendijk 2007b: PARTIR (Terhaard) (Randomized trial on the role of accelerating overall treatment time for intermediate risk head and neck cancer)

Langendijk J, on behalf of the NWHHT-SG. The Dutch head and neck cancer cooperative study group (NWHHT-SG). Radiother Oncol 2007;82(Suppl 1):S1.

JCOG 0701

Nakamura1 K, Kodaira T, Shikama N, Kagami Y, Ishikura S, Shibata T, Hiraoka M. Accelerated Fractionation versus Conventional Fractionation Radiation Therapy for Glottic Cancer of T1-2N0M0 Phase III Study: Japan Clinical Oncology Group Study (JCOG 0701) Jpn J Clin Oncol 2008 Advance Access published April 3, 2008 doi:10.1093

Van Herpen 2009 (Rabdoud University)

- TPF induction followed by cisplatinum-CRT, either standard fractionation or accelerated RT : 5 or 6 fractions per week
- Start date : 2008
- Planned recruitment : 70 (35 in each arm)
- Web link : http://clinicaltrials.gov/ct2/show/NCT00774319?term=%22head+and+neck+cancer%22+AND+radiotherapy+AND+random*&type=Intr&age=12&phase=12&rank=8

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
sc	split course,
po	post-operative,
b	boost.
ARTSCAN	Accelerated Radiotherapy for squamous cell Cancer of the head and neck
CHARTWEL	Continuous Hyperfractionated Accelerated Radiation Therapy schedule
DAHANCA	Danish Head and Neck Cancer Study Group
EORTC	European Organisation for Research and Treatment of CancerGORTEC Groupe Oncologie Radiothérapie Tête et Cou
IAEA-CRP-ACC	International Atomic Energy Agency - Clinical Research Project, Accelerated radiotherapy
POPART	Post operative accelerated radiotherapy
PARTIR	Post operative accelerated radiotherapy in Intermediate risk patients
RTOG	Radiation Therapy Oncology Group

15. APPENDIX

APPENDIX A: CLASSIFICATION OF THE TRIALS COMPARING CONVENTIONAL RADIOTHERAPY TO RADIOTHERAPY WITH MODIFIED FRACTIONATION

1) Definition

A suggestion was made by Pr. Horiot to provide more accurate definition of acceleration and hyperfractionation. This was done according to the publication Horiot et al (Radiother Oncol, 1997 :73 ;1455).

Conventional radiotherapy for definitive radiotherapy in HNSCC = 60 Gy (UK, Canada) to 70 Gy (USA, France), 2 Gy / fraction, 5 fractions per week for 6 to 7 weeks.
For post operative radiotherapy the total dose is generally 50 to 66 Gy using the same fractionation

There are two main possibilities for increasing the dose intensity of radiotherapy by modifying the fractionation, with the goal of improving the tumor control :

a) Accelerated radiotherapy = decrease of the overall treatment time, compared to conventional radiotherapy

b) Hyperfractionation (pure) = the use of smaller dose per fraction, a higher number of fraction in the same overall time than conventional radiotherapy, usually associated with an increase in dose of radiation.

Acceleration is often combined with hyperfractionation

APPENDIX B: DESCRIPTION OF THE TRIALS COMPARING CONVENTIONAL RADIOTHERAPY TO RADIOTHERAPY WITH MODIFIED FRACTIONATION

See abbreviations on previous page and new trials references in section 14. See Reference 18 (section 13) for a list of trials included in the previous meta-analysis.

TABLE B-1: RANDOMIZED TRIALS OF HYPERFRACTIONATED VERSUS CONVENTIONAL RADIOTHERAPY IN HNSCC

Reference	**Inclusion period**	**Sites**	**Stage**	**Arm compared dose (Gray)/ duration**	**Nb of daily (or wk) fractions**	**Dose per fraction (Gray)**	**Number of fractions**	**Nb of patients randomized**
Johnson 1995	1992-1994	HNSCC	III/IV	70 Gy / 47 days 74.8 Gy / 33 days **b**	1/day 1/day then 3/day	2 1.8 + 1.5	35 ??	34
RTOG 9512 (Trotti 2006)	1996-2001	L	II	70 Gy / 7 wks 79.2 Gy / 6.5 wks	1/day 2/day	2 1.2	35 66	250
EORTC-22962[£] (Horiot JC 2007)	1996-1999	OC, OP, HP, L	II/III/IV	70 Gy / 7 wks 80.5 Gy / 7 wks	1/day 2/day	2 1.15	35 70	27
DAHANCA 9	2000-2006	OP, HP, L	I-IV	66 Gy / 38 days 76 Gy / 38 days	1/day 10/wk	2 1.35	33 56	77*

po= post-operative, **b**= boost.

[£] 2x2 factorial design, two arms with and two arms without cisplatin, inclusion closed after December 31th, 1998. 57 patients included out of 994 planned

* Accrual stopped (based on personal communication by Pr Overgaard). Patients in both arms were taking oral nimorazole daily.

TABLE B-2: RANDOMIZED TRIALS OF ACCELERATED WITHOUT TOTAL DOSE REDUCTION versus CONVENTIONAL RADIOTHERAPY IN HNSCC

Reference	**Inclusion period**	**Sites**	**Stage**	**Arm compared dose (Gray)/ duration**	**Nb of daily (or wk) fractions**	**Dose per fraction (Gray)**	**Number of fractions**	**Nb of patients randomized**
Sanguineti 2005	1994-2000	OC, OP, HP, L	NA	60 Gy / 6 wks 64 Gy / 5 wks **b**	1/day 2/day	2 2	30 32	226
IAEA-CRP-ACC (Overgaard 2006)	1999-2004	OC, OP, HP, L	I/II/III/IV	66-70 Gy / ≥ 6.5 wks 66-70 Gy / ≥ 5.5 wks	5/wk 6/wk	2 2	33-35 33-35	908[$$]
Ang 2001	1991-1997	OC, OP, HP, L	III/IV	63 Gy / 7 wks **po** 63 Gy / 5 wks **b**, **po**	1/day 1/day/3wks +2/day/2wks	1.8 1.8 +1.8	35 15 +20=35	151
ARTSCAN (Zackrisson 2007)	1998-2006	OC, OP, HP, L	I-IV	68 Gy / 6.5-7 wks 68 Gy / 5 wks **b**	1/day 2/day	2 2 + 1.1	34 43	750
p-CAIR (Suwinski 2007)	2001-2004	OC, OP, L	NA	63 Gy / 7 wks **po** 63 Gy / 5 wks **po**	1/day (5/wk) 1/day (7/wk)	1.8 1.8	35 35	279
Ghoshal 2008	1998-2004	HNSCC	III/IV	66 Gy / 6.5 wks 67.5 Gy / 5 wks **b**	1/day 1/day on PTV1 2/day on boost	2 1.8 + 1.5	33 40	290
Ezzat 2005	1998-2001	OP, HP, L, OC	III/IV	68 Gy / 6.5 wks 68 Gy / 5.5 wks	5/wk 6/wk	2 2	34 34	40
Ghosh 2006§	2000-2004	OP, HP, L	III/IV	66-70 Gy / 7 wks 66-70 Gy / 6 wks	5/wk 6/wk	2 2	30-35 39	150 *2/3

po= post-operative, **b**= boost.

[$$] 5 fractions a week (control arm) versus 6 fractions a week (experimental arm), given either in 6 days, one fraction a day, or in 5 days including one day with 2 fractions (DAHANCA schedule). § 3 arms trial allowing 2 comparisons (third arm with weekly concomitant cisplatin and standard fractionation RT). The altered fractionated radiotherapy arm will thus be counted twice once in comparison 1 and once in comparison 2)

TABLE B-3: RANDOMIZED TRIALS OF ACCELERATED WITH TOTAL DOSE REDUCTION versus CONVENTIONAL RADIOTHERAPY IN HNSCC

Reference	**Inclusion period**	**Sites**	**Stage**	**Arm compared dose (Gray)/ duration**	**Nb of daily (or wk) fractions**	**Dose per fraction (Gray)**	**Number of fractions**	**Nb of patients randomized**
CHARTWEL (Dische 2001)	2001-2004	OC, OP, HP, L,O	II-IV	60-64 Gy / 6-6.5 wks **po**	1/day	2	30-32	460
				51-54Gy / 2.5 wks (16 days) **b**, **po**	3/day	1.5	34-36	
Awwad 1992	1987-1989	OC, OP, HP, L,O	III/IV	50 Gy / 5 wks **po**	1/day	2	25	56
				42 Gy / 2.5 wks (11 days) **po**	3/day	1.4	30	
Awwad 2002	1995-1997	OC, HP, L	T2/N1-N2 T3-4/anyN	60 Gy / 6 wks **po**	1/day	2	30	70
				46.2 Gy / 12 days **po**	3/day	1.4	33	

po= post-operative, **b**= boost.

TABLE B-4: RANDOMIZED TRIALS OF CHEMOTHERAPY + ALTERED FRACTIONATION RADIOTHERAPY VERSUS CHEMOTHERAPY +CONVENTIONAL RADIOTHERAPY IN HNSCC

Reference	**Inclusion period**	**Sites**	**Stage**	**Arm compared dose (Gray)/ duration**	**Nb of daily (or wk) fractions**	**Dose per fraction (Gray)**	**Number of fractions**	**Chemotherapy drug/dose (mg/m²)**	**Cumulative dose of Platin** (mg/m²)	**Nb of patients randomized**
EORTC-22962[£] (Horiot JC 2007)	1996-1999	OC, OP, HP, L	II/III/IV	70 Gy / 7 wks	1/day	2	35	C: 100 mg/m², wks 1,4,7	300	30
				80.5 Gy / 7 wks	2/day	1.15	70	C: 100 mg/m², wks 1,4,7	300	
EORTC (Bartelink 2002)	NA	OC, OP, HP, L, O		70 Gy / 7 wks	1/day	2	35	C: 6 mg/m²/day during 35 days	210	53
				72 Gy / 7 wks (wk 1,4,7) **sc**	3/day	1.6	45	C: 10 mg/m²/day d1-5 on wk 1,4,7	150	
GORTEC 99-02§ (Bourhis 2008)	2000-2007	OC, OP, HP, L	III/IV	70 Gy / 7 wks	5/wk (i.e 1/day)	2	35	5FU : 600 mg/m²/day Cb: 70 mg/m²/day d1-4 on wk 1,4,7	840	840 *2/3
				70 Gy / 6 wks **b**	1/day/4wks 2/day/2wks	2 + 1.5	20 + 20	5FU: 600 mg/m²/day Cb: 70 mg/m²/day d1-5 on wk 1,4	700	
RTOG H0129 (Ang 2007)	NA	OC, OP, HP, L	III/IV	70 Gy / 7 wks	1/day	2	35	C: 100 mg/m², wks 1,4,7	300	720
				72 Gy / 6 wks **b**	1/day 2/day	1.8+ 1.5	30 + 12	C: 100 mg/m² 1,4		

C: cisplatin; Cb: Carboplatin; 5FU: 5-fluorouracile

sc= split course, **b**= boost.

[£] 2x2 factorial, two arms with and two arms without cisplatin, inclusion closed after December 31th, 1998. 57 patients included out of 994 planned

§ 3 arms trial allowing 2 comparisons (third arm with concomitant 5FU/carboplatin, see table A-5). The altered fractionated radiotherapy arm will thus be counted twice once in comparison 1 and once in comparison 2)

TABLE B-5: RANDOMIZED TRIALS OF ALTERED FRACTIONATION RADIOTHERAPY VERSUS CHEMOTHERAPY + CONVENTIONAL RADIOTHERAPY IN HNSCC, corresponding to COMPARISON 2

Reference	**Inclusion period**	**Sites**	**Stage**	**Arm compared dose (Gray)/ duration**	**Nb of daily (or wk) fractions**	**Dose per fraction (Gray)**	**Number of fractions**	**Chemotherapy drug/dose (mg/m²)**	**Nb of patients randomized**
EORTC-22962[£] (Horiot JC 2007)	1996-1999	OC, OP, HP, L	II/III/IV	70 Gy / 7 wks	1/day	2	35	C: 100 mg/m², wks 1,4,7	28
				80.5 Gy / 7 wks	2/day	1.15	70	No CT	
Ghosh 2006§	2000-2004	OP, HP, L	III/IV	66-70 Gy / 6-7 wks	5/wk	2	30-35	C: 30 mg/m²/wk, wk 1-7	150 *2/3
				66-70 Gy / 6.5 wks	6/wk	2	33-35	No CT	
GORTEC 99-02§ (Bourhis 2008)	2000-2007	OC, OP, HP, L	III/IV	70 Gy / 7 wks	5/wk (i.e 1/day)	2	35	5FU : 600 mg/m²/day Cb: 70 mg/m²/day d1-4 on wk 1,4,7	840 *2/3
				64.8 Gy / 3.5 wks	2/day	1.8	36	No CT	

[£] two arms with and two arms without cisplatin, inclusion closed after December 31th, 1998. 57 patients included out of 994 planned

$ Number of patients expected.

§ 3 arms trial allowing 2 comparisons. The altered fractionated radiotherapy arm will thus be counted twice once in comparison 1 and once in comparison 2)

TABLE B-6: TRIALS COMPARING TWO DIFFERENT REGIMENS OF ALTERED FRACTIONATION RADIOTHERAPY

Reference	**Inclusion period**	**Sites**	**Stage**	**Arm compared dose (Gray)/ duration**	**Nb of daily (or wk) fractions**	**Dose per fraction (Gray)**	**Number of fractions**	**Nb of patients randomized**
Krstevska 2006	1999-2004	OP, HP, L	I/II/III/IV	66 to 70 Gy / 6.5-7 wks 74.4 to 79.2 Gy / 6.2-7 wks 68.7 to 72 Gy / 6 wks **b**	1/day 2/day 1/day 2/day	2 1.2 1.8 1.8+1.5	33-35 NA NA	152*
DAHANCA 9	2000-?	OP, HP, L	I/II/III/IV	66 Gy /5.5 wk 76 Gy/5.5wk	1/day (6/wk) 2/day (10/wk)	2 1.35	33 56	70-80 **

* The standard radiotherapy arm is an historical arm, randomization is between the two experimental arms.
** Accrual stopped (based on personal communication by Pr Overgaard). Patients in both arms were taking oral nimorazole daily.

TABLE B-7: ONGOING TRIALS

Reference	**Inclusion period**	**Sites**	**Stage**	**Arm compared dose (Gray)/ duration (weeks)**	**Nb of daily (or wk) fractions**	**Dose per fraction (Gray)**	**Number of fractions**	**Nb of patients randomized**
POPART (Langendijk 2007a)	2003	HNSCC	High risk	66 Gy / 7 wks**, po**	5/wk	2	33	104/350
				66 Gy / 5 wks**, po**	7/wk	2	33	
PARTIR (Langendijk2007b)	2006	HNSCC	Intermediate risk	56 Gy / 6 wks**, po**	5/wk	2	28	12/360
				56 Gy / 4 wks**, po**	7/wk	2	28	
JCOG 0701	2007	Larynx	T1-2 N0	66-70 Gy / 7 wks	5/wk	2	33-35	??/360
				60-64.8 Gy / 5.5 wks	5/wk	2.4	25-27	
Rabdoud University	2008	HNSCC	Stage III-IV	70 Gy / 7 wks	5/wk	2	35	??/70
				70 Gy / 6 wks	6/wk	2	35	

TABLE B-8 : Number of trials and participants for each comparison (trials included in MARCH; new trials and total) ; and power to detect a 5% difference in OS in the updated meta-analysis (all trials together)

	MARCH*		New Trials*		Total (Update of MARCH)	
	Trial #	**Patient #**	**Trial #**	**Patient #**	**Trial #**	**Patient #**
COMPARISON # 1						
Altered fractionation RT *versus* conventional RT (+/- same concomitant CT / primary or post-op RT)	15	6515	18	5131	33	11646
SUB-GROUPS OF COMPARISON # 1						
HFRT *versus* conventional RT	4	1350	4	388	8	1738
AccRT w/o dose reduction *versus* conventional RT	8	3818	8**	2744	16	6562
AccRT with dose reduction *versus* conventional RT	5	1905	3***	586	8	2491
Altered fractionation RT *versus* conventional RT Post-operative setting$	NA	NA	5$	1016$	5$	1016$
Altered fractionation CRT *versus* conventional CRT	NA	NA	4$$	1363	4	1363
COMPARISON # 2						
HFRT *versus* concomitant CRT	NA	NA	3	688	3	688

* Some trials are counted twice because they have three arms or more and contribute to more than one comparison.
RT: radiotherapy; CRT: chemoradiation therapy; HFRT: hyperfractionated RT; CT: chemotherapy; AccRT: Accelerated RT; dose red : dose reduction;
** 2 of these 8 trials are post-operative trials;*** all these 3 trials are post-operative trials;
$ this sub-group consists in the three trials in the accelerated with dose reduction category and the two trials in the accelerated w/o dose reduction category and are accounted for in the above lines;
$$ Trials of Altered fractionation CRT include two trials with AccRT w/o dose reduction (Brouhis, Ang), one trial with HFRT (Horiot) and one trial with accelerated split course RT (Bartelink).

TABLE B-9: Classification of the old trials according to the total dose and dose/fraction in the experimental arm (see reference 19)

TOTAL DOSE IN THE EXPERIMENTAL ARM

ACCELERATION	LOWER	IDENTICAL (+/- 5%)	HIGHER
0-13%		Oro 9301	EORTC-22791 Rio PMH-Toronto RTOG-9003 HF*
14-49%	RTOG-7913	EORTC 22851 RTOG 9003* RTOG 9003* CAIR DAHANCA KBN P0 79	
≥ 50%	CHART Vienna GORTEC 9402 TROG 9101	BCCA 9113	
	Hyperfractionated **Normal** **< 1.25 Gy** **1.25-1.75 Gy** **1.8-2 Gy**	**Hyperfractionated** **Normal** **< 1.25 Gy** **1.25-1.75 Gy** **1.8-2 Gy**	**Hyperfractionated** **Normal** **< 1.25 Gy** **1.25-1.75 Gy** **1.8-2 Gy**

DOSE / FRACTION IN THE EXPERIMENTAL ARM

***** *the RTOG 9003 is a 4-arm trial*

TABLE B-10: Classification of the new trials according to the total dose and dose/fraction in the experimental arm

TOTAL DOSE IN THE EXPERIMENTAL ARM

ACCELERATION	LOWER	IDENTICAL (+/- 5%)	HIGHER
0-13%		EORTC (Bartelink)	RTOG 9512, EORTC 22962, DAHANCA 9
14-49%		GORTEC 99-02, ARTSCAN, Sanguineti, IAEA-CRP-ACC, Ang, p-CAIR, Goshal, Ezzat, Gosh, RTOG H0129	Johnson
≥ 50%	CHARTWEL, Awwad 1992, Awwad 2002, GORTEC 99-02		

	Hyperfractionated		Normal	Hyperfractionated		Normal	Hyperfractionated		Normal
	< 1.25 Gy	**1.25-1.75 Gy**	**1.8-2 Gy**	**< 1.25 Gy**	**1.25-1.75 Gy**	**1.8-2 Gy**	**< 1.25 Gy**	**1.25-1.75 Gy**	**1.8-2 Gy**

DOSE / FRACTION IN THE EXPERIMENTAL ARM

APPENDIX C: SUGGESTED FORMAT AND CODING TO SEND THE DATA TO THE SECRETARIAT

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	Smoking status	0=Never, 1=Former, 2=Current, 9=Unknown
38-40	*if yes, pack-years*	3 digits, 999=Unkown
42	HPV status	0=Negative, 1=Positive
44	Treatment allocated	1=Standard radiotherapy, 2=Modified fractionation radiotherapy
46-53	Date of randomization	dd/mm/yyyy, 99999999=Unknown
55-62	Date of last follow-up	dd/mm/yyyy, 99999999=Unknown

Column	Variable	Format/Coding
64	Survival status	0=Alive, 1=Dead
66	Cause of death	0=Cancer, 1=Toxicity of radiotherapy, 2=Other, 9=Unknown
68	Whether excluded from your analysis	0=No, 1=Yes
70-81	Reasons for exclusion	12 characters
83	Failure[1]	0=No, 1=Yes
85-92	Date of first failure	dd/mm/yyyy, 99999999=Unknown
94	Type of first failure	1=Loco-regional failure(T or N), 2=Distant failure, 3= Both, 9=Unknown
96	Type of first failure (if available, provide detail)	1 = T failure, 2 = T failure + distant failure, 3 = N failure ; 4 = N failure + distant failure, 5 = T + N failure, 6 = T + N + distant failure, 7 = Distant failure only
98-105	Date of first local (T) failure	dd/mm/yyyy, 99999999=Unknown, 0 if no event
107-114	Date of first regional (N) failure	dd/mm/yyyy, 99999999=Unknown, 0 if no event
116-123	Date of first distant (M) failure	dd/mm/yyyy, 99999999=Unknown, 0 if no event
125-132	Date of first second primary	dd/mm/yyyy, 99999999=Unknown, 0 if no event
134	Type of first second primary	Lung=1, Esophagus=2, Stomach=3, Colorectal=4, Liver=5, Head& neck=6, Other=7 (specify) 9=Unknown

[1] A failure correspond to a recurrence if the patient achieved a complete response, or a progression if the patient did not achieve a complete response.

Column	Variable	Format/Coding
	Compliance to radiotherapy	
136-143	Date of the beginning of treatment	dd/mm/yyyy, 99999999=Unknown
145-152	Date of end of treatment	dd/mm/yyyy, 99999999=Unknown
154-155	Total radiation dose received (Gy)	2 digits
157-158	Total number of fraction	2 digits
	Compliance to chemiotherapy (if applicable)	
160	Number of cycles planned	1 digit
162	Number of cycles received	1 digit
164	Cycle dose reduction	0=No, 1=Yes, 9=Unknown
	Acute Toxicity (grade 3-4)	
166-177	Scale used to quantify toxicity	12 characters
179	Neutropenia	1 digit, 9=Unknown
181	Mucositis	1 digit, 9=Unknown
183	Weight loss	1 digit, 9=Unknown
185	Dermatitis	1 digit, 9=Unknown
187	Febrile neutropenia	1 digit, 9=Unknown
189	Renal toxicity	1 digit, 9=Unknown
191	Thrombopenia	1 digit, 9=Unknown

193	Anemia	1 digit, 9=Unknown
195	Feeding tube	0=No, 1=Yes, 9=Unknown

Column	Variable	Format/Coding
	Late Toxicity (grade 3-4)	
197-208	Scale used to quantify toxicity	12 characters
210	Neck fibrosis	1 digit, 9=Unknown
212	Persistence of feeding tube after one year of treatment	0=No, 1=Yes, 9=Unknown
214	Weight loss	1 digit, 9=Unknown
216	Xerostomia	1 digit, 9=Unknown
218	Renal toxicity	1 digit, 9=Unknown
220	Bone necrosis	1 digit, 9=Unknown
222	Mucosal toxicity	1 digit, 9=Unknown
224	Hear toxicity	1 digit, 9=Unknown
	For post-operative trials	
226	Edition of the TNM classification	1 digit, 9=Unknown
228	pT	0=T_0, 1=T_1, 2=T_2, 3=T_3, 4=T_4, 5=T_X, 6=T_{is}, 9=Unknown
230	pN	0=N_0, 1=N_1, 2=N_2, 3=N_3, 4=N_X, 9=Unknown

Column	Variable	Format/Coding
232	pN2 details	0=Ipsilateral single >3-6cm, 1=Ipsilateral multiple, 2=Bilateral, 3=Contralateral
234	Resection margins	1=Sufficient, 2=Positive, 9=Unknown
236	Total number of nodes	2 digits
238	Number of positive lymph nodes	2 digits
240	Extra-capsular extension	0=No, 1=Yes
242	Presence of peri-neural invasion	0=No, 1=Yes
244	Presence of lymphovascular invasion	0=No, 1=Yes

APPENDIX D: REGISTRATION FORM

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 |__|__| |__|__| |__|__|__|__|

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? no ☐ yes ☐

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

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