Hyperfractionated and/or accelerated radiotherapy versus conventional radiotherapy for head and neck cancer (Protocol)

Pignon JP, Sylvester R, Bourhis J

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Protocol]

Hyperfractionated and/or accelerated radiotherapy versus conventional radiotherapy for head and neck cancer

Jean Pierre Pignon[1], Richard Sylvester[2], Jean Bourhis[3]

[1]Service de Biostatistique et d'Epidemiologie, Institut Gustave-Roussy, Villejuif Cedex, France. [2]European Organisation for Research and Treatment of Cancer Data Center, 1200 Brussels, Belgium. [3]Département de Radiothérapie, Institut Gustave-Roussy, 94805 Villejuif Cedex, France

Contact address: Jean Pierre Pignon, Service de Biostatistique et d'Epidemiologie, Institut Gustave-Roussy, 39, rue Camille Desmoulins, Villejuif Cedex, 94805, France. jppignon@igr.fr.

Editorial group: Cochrane Ear, Nose and Throat Disorders Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

Citation: Pignon JP, Sylvester R, Bourhis J. Hyperfractionated and/or accelerated radiotherapy versus conventional radiotherapy for head and neck cancer. *Cochrane Database of Systematic Reviews* 2000, Issue 2. Art. No.: CD002026. DOI: 10.1002/14651858.CD002026.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

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

Main objective

To assess the effect of modified fractionated radiotherapy on the survival of patients with HNSCC by comparing conventional radiotherapy with hyperfractionated and / or accelerated radiotherapy.

Secondary objectives

To investigate the interaction between the treatment effect and the type of radiotherapy (indirect comparison) and to investigate the interaction between the treatment effect and the prognostic factors (subgroup analysis).

BACKGROUND

Head and neck squamous cell carcinomas (HNSCC) are frequently occurring tumors with 88,000 new cases (oral cavity, oropharynx, hypopharynx, larynx) in 1990 within the European Community (Ferlay 1996) and 41,000 new cases in 1996 within the United States (Parker 1996). In 1980, the estimated number of new cases worldwide was 477,000 (Parkin 1992). In oral cavity and pharynx carcinoma, at least 40 % of patients have locally advanced disease at diagnosis (Parker 1996). Surgery and/or radiation therapy are standard modalities used to achieve loco-regional control (Vokes 1993). Despite this therapeutic approach, the prognosis of HNSCC patients remains poor: the 5-years relative survival rates in USA for the period 1986-1996 was around 35% in locally advanced disease. The overall survival at 5-years was 32% in the control group of the meta-analysis of chemotherapy in head and neck cancer (MACH-NC), study which included more than 10,000 patients with locally advanced HNSCC (Pignon 1999).

In recent years, considerable interest has been raised about non conventional fractionation schedules in radiation therapy for HNSCC. Two types of altered fractionation have been studied (Peters 1992). The first was hyperfractionation in which the dose per fraction was decreased, two or three fractions per day were given instead of one. The reduction of the dose per fraction was supposed to decrease the probability of late radiation induced morbidity, and by this means the total dose to the tumor can be increased. A second and more recent approach consisted of reducing the overall treatment time, thus accelerating radiotherapy by delivering to the tumor a high total dose in a much shorter overall time. Accelerated radiotherapy is often combined with hyperfractionation. In both cases, the aim was to increase the loco-regional control rate, which may ultimately result in a benefit in overall survival.

In the past decades, several randomized trials have compared a conventional radiotherapy arm to hyperfractionated or accelerated radiotherapy arm(s) in HNSCC. These trials contain relatively homogeneous series of patients mostly with locally advanced HNSCC, and generally a reference arm of conventional radiotherapy alone (60-70 Gy / 6-7 weeks). In some of these trials, a significant improvement in local control was evident in favor of the modified fractionation arm, without significant gain in overall survival. Therefore, it remains controversial whether modified fractionation can improve survival for HNSCC patients. However, to distinguish between ineffective treatment and moderate effects a great number of patients must be studied. For instance, to detect a 5 to 10% reduction in mortality, more than one thousand patients have to be randomized. The size of most of the individual trials performed in HNSCC has not been large enough to detect such a moderate decrease in mortality. Only two trials included more than 300 patients per arm. Increased evidence suggests that a moderate improvement in survival is generally the best that can be expected of new cancer treatment and that it may be clinically worthwhile (Breast Cancer 1992; Pignon 1992; Lung Cancer 1995; Pignon 1999). Given the incidence of HNSCC, an improvement in survival of 5% could prolong the life of thousands of patients throughout the world, each year.

A meta-analysis based on individual patient data (IPD) has therefore been initiated by Institut Gustave-Roussy and the European Organization for Research and Treatment of Cancer (EORTC). 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 (Begg 1989). IPD will allow us: 1) to check the quality of each trial; 2) to collect basic survival and prognostic information for all patients randomized in each study leading to a more reliable and flexible approach, a more sensitive analysis and avoiding the potential bias of post-randomization exclusion (Stewart 1993; Pignon 1995); 3) to update follow-up which will enable us to report on long-term survival.

The main purpose of this meta-analysis is to evaluate the role of modified fractionation on the survival of patients with HNSCC. In order to answer this question, we intend to combine the data of trials comparing conventional radiotherapy to modified radiotherapy fractionation.

This meta-analysis, based on individual patient data from all available relevant randomized studies, aims to provide the most comprehensive and reliable summary of the effect of modified fractionated radiotherapy in HNSCC. It is also hoped that the meta-analysis will stimulate future international collaboration and will lead to a valuable exchange of ideas and will ultimately be of benefit to the patients.

OBJECTIVES

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

Main objective

To assess the effect of modified fractionated radiotherapy on the survival of patients with HNSCC by comparing conventional radiotherapy with hyperfractionated and / or accelerated radiotherapy.

Secondary objectives

To investigate the interaction between the treatment effect and the type of radiotherapy (indirect comparison) and to investigate the interaction between the treatment effect and the prognostic factors (subgroup analysis).

METHODS

Criteria for considering studies for this review

Types of studies

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 and have completed accrual before December 31th, 1998;
- Include patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx;
- Not include patients with distant metastatic disease.

Randomized trials without a conventional radiotherapy arm are excluded.

Types of participants

Participants must fulfil the following criteria.
They must:

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

Randomized trials including mainly or exclusively nasopharyngeal carcinomas are excluded as their epidemiology and response to radio- and chemotherapy is different from that of other head and neck cancers.

Types of interventions

Conventional radiotherapy versus hyperfractionated and / or accelerated radiotherapy.
Randomized trials comparing hypofractionated (dose per fraction above 2.5 Gy) versus conventional radiotherapy are excluded.

Types of outcome measures

The main endpoint will be survival, because of its importance and because of the reliability of the measurement. Cause of death will be studied, if possible.
Secondary endpoints such as time to first event (local or distant failure (recurrence or progression), second primary tumour) will be also considered.

Search methods for identification of studies

Data from all published and unpublished randomized trials making the above comparisons in HNSCC patients will be sought using electronic database searching (Medline, Cancerlit, Embase), hand searching (review articles, meeting proceedings) and by contacting experts in the field. Trials registries will be also consulted. All trialists who take part in the meta-analysis will be asked to help to identify more trials.

Search strategy for MEDLINE (1980-1997)

1. exp mouth neoplasms/ or exp otorhinolaryngologic neoplasms/
2. limit 1 to clinical trial
3. randomiz$.mp [mp=ti, ab, sh]
4. (phase adj ("III" or "3")).mp
5. 3 or 4
6. 2 and 5
7. (radiotherap$ or chemoradiotherap$).mp
8. 6 and 7
9. limit 8 to human

Search strategy for EMBASE (1980-1997)

1. exp *"Head and neck tumour"/rt [Radiotherapy]
2. exp *phase 3 clinical trial/ or exp *randomized controlled trial/
3. 1 and 2
4. phase 3 clinical trial/ or randomized controlled trial/
5. 1 and 4

Search strategy for CANCERLIT (1980-1997)

1. exp *"Head and neck neoplasms"/rt [Radiotherapy]
2. exp *mouth neoplasms/ or exp *otolaryngologic neoplasms/
3. exp Nasopharyngeal neoplasms/
4. 1 and 2
5. 4 not 3
6. limit 5 to (human and clinical trial)
7. (phase adj ("3" or iii)).mp [mp=ti, ab, sh]
8. randomized.mp
9. 7 or 8
10. 6 and 9
11. limit 12 to nonmedline

Search strategy for PDQ ACTIVE PROTOCOLS (1980-1997)

1. (hypopharyn$ or laryn$ or lip or oral cavity or mouth or oropharyn$).cn
2. phase III.ph
3. (radiation or radio$).tm
4. 1 and 2 and 3

Data collection and analysis

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 (using the WHO, ECOG or Karnofsky scale to estimate a patient's global fitness);
- Site of the primary tumour;
- Stage of tumour (using the TNM system - if not available, information on classification will be used);
- Allocated treatment;
- Date of randomization;
- Date of last follow-up;
- Survival status;
- Cause of death;
- Date of first event;
- Type of first event (loco-regional tumour recurrence, distant tumour recurrence, second primary tumour);
- Whether excluded from trial analysis;
- Reason for exclusion (if applicable).

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. Randomization procedure (distribution of date of randomization by arm, covariate balance) and quality of follow-up (distribution of date of last follow-up among alive patients by arm) will be also checked. Each trial will be analyzed individually, and the resulting survival analyses and trial data will be sent to the trialists for verification.

Statistical analysis plan

With 2500 patients (or 1700 deaths) it would be possible to detect, with a power of 80%, an absolute improvement in survival from 30% to 35% at 5-years (two-sided logrank test, type I error=5%). The power to detect the same difference with 4000 patients (or 2800 deaths) will be close to 95%.

The methodology used will be similar to that used in the previous IPD meta-analyses (Pignon 1992; Lung Cancer 1995; Pignon 1999). 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. The overall heterogeneity between trials will be studied using hazard ratio plot and chi-square test for heterogeneity. Survival difference between treatment arms (absolute benefit) at 2 and 5-years will be calculated from baseline survival and hazard ratio (Stewart 1993). All p values will be two-sided.

Survival curves will be simple non-stratified Kaplan-Meier curve for the control group and for the experimental group, the survival curves will be obtained by adding to the control group survival rate the survival difference between treatments at given time points (6 months, 12 months, 18 months etc...).

The analysis will study the interaction between the observed effect of treatment on survival and the type of radiotherapy. Groups of trials according to the type of radiotherapy will be defined and the hazard ratios of the corresponding groups will be compared by a chi-square test for heterogeneity.

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

These analyses will be performed for the main endpoint, overall survival and for the secondary endpoint : event-free survival.

The prognostic factors that will be considered are :

- Age;
- Sex;
- Site of the primary tumour;
- Stage;
- Performance status.

ACKNOWLEDGEMENTS

We are grateful to Sylvianne Iacobelli, Denise Avenell and Michael Ghez for assistance in preparing the protocol.

REFERENCES

Additional references

Begg 1989
Begg CB, Berlin A. Publication bias and the dissemination of clinical research. *Journal of the National Cancer Institute* 1989;**18**: 107–15.

Breast Cancer 1992
Early Breast Cancer Trialists Collaborative Group. Effect of Systemic treatment of early breast cancer by hormonal, cytotoxic, or immunotherapy therapy: 133 randomized trials involving 31000 recurrences and 24000 deaths among 75000 women. *Lancet* 1992; **339**(8784):1–15.

Ferlay 1996
Ferlay J, Black RJ, Pisani P, Valdivieso MT, Parkin DM. *EUCAN 1990: Cancer in the European Union*. Lyon: IARC, 1996.

Lung Cancer 1995
Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in Non Small Cell Lung Cancer: a meta-analysis using updated data on individual patient from 52 randomized clinical trials. *British Medical Journal* 1995;**311**:899–909.

Parker 1996
Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1996. *CA: A Cancer Journal for Clinicians* 1996;**65**:5–27.

Parkin 1992
Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J. *Cancer Incidence in Five Continents*. Vol. **6**, Lyon: IARC, 1992.

Peters 1992
Peters L, Ang K. The role of altered fractionation in head and neck cancer. *Seminars in Radiation Oncology* 1992;**2**:45–7.

Peto 1987
Peto R. Why do we need systematic overviews of randomized trials?. *Statistics in Medicine* 1987;**6**:233–40.

Pignon 1992
Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, et al.A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *New England Journal of Medicine* 1992;**327**: 1618–24.

Pignon 1995
Pignon JP, Bourhis J, Domenge C, on behalf of the MACH-NC Secretariat. Meta-analysis of chemotherapy in head and neck cancer: individual patient data vs literature data. *British Journal of Cancer* 1995;**72**:1062.

Pignon 1999
Pignon J-P, Bourhis J, Domenge C, Désigné L, on behalf of the MACH-NC Collaborative Group. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet* 2000;**355**(9208):949–55.

Stewart 1993
Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual data: is there a difference?. *Lancet* 1993;**341**:418–22.

Vokes 1993
Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. *New England Journal of Medicine* 1993;**328**:184–94.

* *Indicates the major publication for the study*

WHAT'S NEW

30 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2000

CONTRIBUTIONS OF AUTHORS

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.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Institut Gustave-Roussy, France.
- European Organisation for Research and Treatment of Cancer (EORTC), Belgium.

External sources

- Programme Hospitalier de Recherche Clinique AOM 98 083, France.

NOTES

Note on the timescale for completion of Cochrane individual patient data review 'Hyperfractionated and/or accelerated radiotherapy versus conventional radiotherapy for head and neck cancer'.

'Hyperfractionated and/or accelerated radiotherapy versus conventional radiotherapy for head and neck cancer' is a meta-analysis of individual patient data which is still being collected. To date (February 2001) the authors have collected data on 7500 patients and 20 trials. Preliminary results are anticipated at the end of 2001 and it is hoped that the review will be available during 2002.