Meta-Analysis of Chemotherapy in Head & Neck Cancer

Meta-Analysis of Radiotherapy in Carcinomas of Head & neck

Network meta-analysis on treatment of non-metastatic head and neck squamous cell carcinomas: an individual patient data meta-analysis based on data from MARCH update and MACH-NC second update.

Claire Petit, Pierre Blanchard, Jean-Pierre Pignon

April 2016

CONTENTS

Abbreviation

AC= Adjuvant Chemotherapy

ACRT= Accelerated Chemo-Radiotherapy

CLRT= Concomitant chemotherapy and LRT

CT= Chemotherapy

IC= Induction Chemotherapy

LRT= Loco-Regional Treatment

MACH-NC= Meta-Analysis of Chemotherapy in Head and Neck Cancer

MARCH= Meta-Analysis of Radiotherapy in Carcinomas of Head and neck

MTC= Mixed Treatment Comparison

NMA= Network Meta-Analysis

PF= cisplatin and 5-fluorouracil

Tax-PF= taxane, cisplatin and 5-fluorouracil

RT= Radiation Therapy

Network meta-analysis (NMA), also known as mixed treatment comparisons (MTC), is a statistical method that deals with conditions where multiple treatments have been investigated that have not been compared altogether (Blanchard et al., 2011). NMA permits evaluation of all possible pair-wise comparisons based on direct and indirect evidence, and allows ranking the different treatments according to their relative efficacies. A network meta-analysis will be performed using the trials included in the second updated of MACH-NC (MACH-NC3) and the first update of MARCH (MARCH2) databases which will be divided according to the treatment compared (Pignon et al., Radiother Oncol 2009, Blanchard et al., J Clin Oncol 2013, Blanchard et al., Eur J Cancer 2013). This protocol is an addendum to the protocol of MARCH 2 and MACH-NC3.

1. DESCRIPTION OF INCLUDED STUDIES

The included studies are the same as those included in MACH-NC and MARCH meta-analysis. Relevant studies should have completed patient accrual at December 31, 2010. A detailed description of the included trials is given in the MARCH2 and MACH-NC3 respective protocols (details here: https://www.gustaveroussy.fr/node/2783/). Names of the trials are those used in the previous publications.

We decided to exclude studies or a specific arm of a study (in case of multiple arms (≥3) study) where locoregional treatments were different (ie. a strategy of organ preservation in one arm and a standard treatment in the other arm). The comparison of another treatment modality (ie. concurrent chemotherapy) in addition to a strategy of organ preservation in both arms was not excluded. Our aim was to have comparable LRT in both arms so the difference observed can be attributed to the treatment studied (which is randomized) and not to confounding differences other than the one randomized.

Due to the use of outdated chemotherapy regimens and the results of previous sensitivity analyses in MACH-NC meta-analysis (especially regarding heterogeneity) we have decided to exclude studies which began before January 1st, 1980 (Pignon et al., 2000).

DESCRIPTION OF THE NETWORK

The different nodes of the network, i.e. treatments compared, are described below.

Number	Treatment	Label	Number of patients
1	Standard radiotherapy (RT) +/- surgery	LRT	10 179
2	LRT + concomitant chemotherapy (CT) 1	CLRT1	3 640
3	LRT + concomitant CT 2	CLRT2	1 553
4	Induction CT 1 + LRT	IC1-LRT	908
5	Induction CT 2 + LRT	IC2-LRT	1 758
6	Induction CT 3 + LRT	IC3-LRT	418
7	LRT + adjuvant chemotherapy	LRT-AC	1 042
8	Induction CT 1 + LRT+ concomitant CT 1	IC1-CLRT1	46
9	Induction CT 1 + LRT+ concomitant CT 2	IC1-CLRT2	0
10	Induction CT 2 + LRT + concomitant CT 1	IC2-CLRT1	623
11	Induction CT 2 + LRT + concomitant CT 2	IC2-CLRT2	0
12	Induction CT 3 + LRT + concomitant CT 1	IC3-CLRT1	961
13	Induction CT 3 + LRT + concomitant CT 2	IC3-CLRT2	144
14	Hyperfractionated RT	HFRT	1 483
15	Moderately accelerated RT	MART	3 524
16	Very accelerated RT	VART	1 365
17	Hyperfractionated RT + concomitant CT 1	HFCRT1	394
18	Moderately accelerated RT + concomitant CT 1	MACRT1	887
19	Very accelerated RT + concomitant CT 1	VACRT1	0
20	Hyperfractionated RT + concomitant CT 2	HFCRT2	0
21	Moderately accelerated RT + concomitant CT 2	MACRT2	190
22	Very accelerated RT + concomitant CT 2	VACRT2	80
23	LRT + concomitant CT 2 + adjuvant CT	CLRT2-AC	154
			Total 29 349

Induction CT 1= other than induction CT 2 and 3, induction CT 2= PF, induction CT 3= Tax-PF; concomitant CT 1= CT with platin, concomitant CT 2= CT without platin.

Based on this description and due to the small sample size in some trial subgroups, we have decided to merge groups 8 and 9, 10 and 11, 12 and 13, 17 and 20 and 18-19-21-22 respectively. The respective labels of treatment modalities became: IC1-CLRT, IC2-CLRT, IC3-CLRT, HFCRT and ACRT, as described below.

Number				New Number	Treatment	Label	Number of patients
8		9		8.5	Induction CT 1 + CLRT	IC1-CLRT	46
10		11		10.5	Induction CT 2 + CLRT	IC2-CLRT	623
12		13		12.5	Induction CT 3 + CLRT	IC3-CLRT	1 105
17		20		17.5	Hyperfractionated RT + concomitant CT	HFCRT	394
18	19	21	22	18.5	Accelerated RT + concomitant CT	ACRT	1 157

Our aim is to rank the probability of each treatment to be the best. Our hypothesis is that hyperfractionated RT + concomitant CT 1 or induction CT 3 + CLRT might be the most efficient treatments.

Based on the results of the analyses to be carried out, treatment modalities could be merged ("lumping") and the reason will be clearly justified.

The network based on the identified trials is presented thereafter. A total of 119 trials are selected including 20 multi-arm trials. A total of 155 comparisons have been directly explored through randomized trials, corresponding to 35 different treatment comparisons. The other comparisons will be evaluated through indirect estimation. With the 16 treatment modalities, in theory, 120 different treatment comparisons are possible. Due to the selection criteria of MACH-NC and MARCH meta-analyses, we may have a maximum of 65 different treatment comparisons and in fact, we have 35 different treatment comparisons.

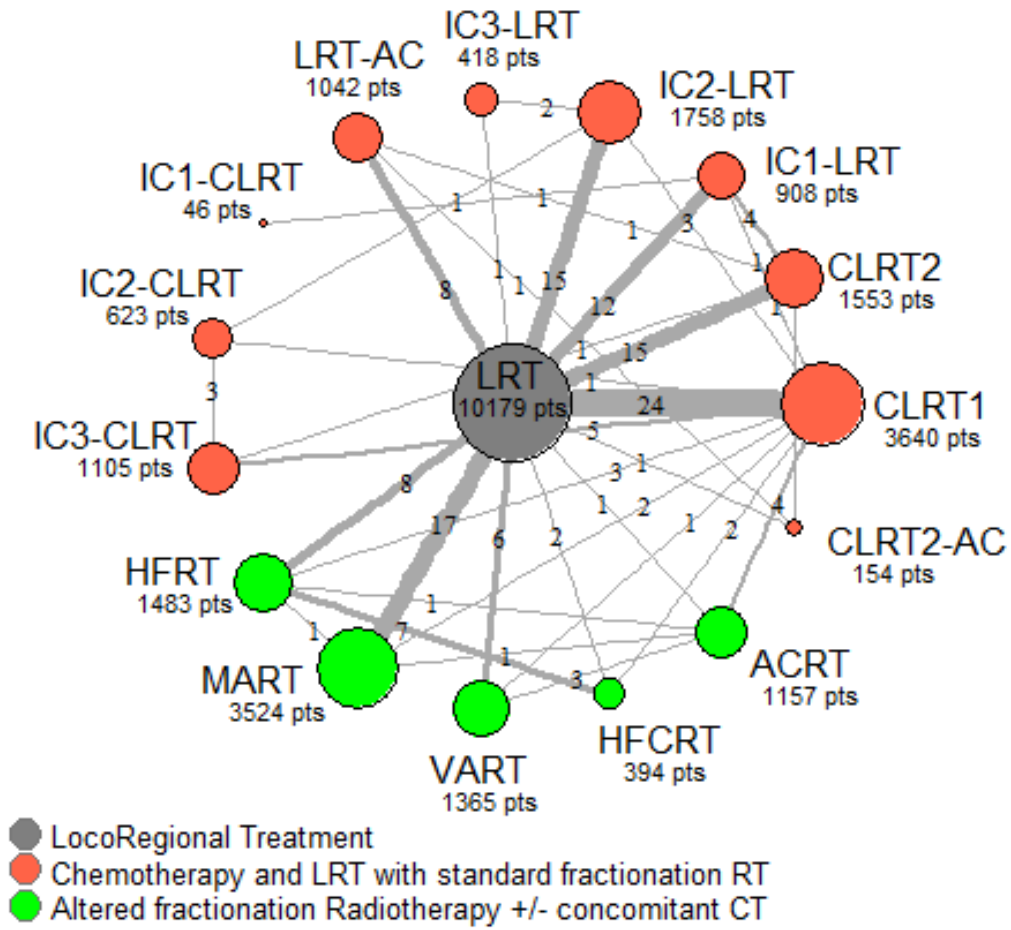
A graphical representation of the trial network is presented on the next page.

2. ENDPOINTS

The endpoints that will be evaluated in this NMA are those determined in the standard meta-analysis (MA): overall survival, progression-free survival, loco-regional failures and distant failure. The primary endpoint will be overall survival (OS), defined as the time from randomization until death from any cause. The secondary endpoints will be progression-free survival (PFS), loco-regional failures (LRF) and distant failure (DF) rates. PFS is defined as the time from randomization to first progression (loco-regional or distant) or death from any cause. Events that will be considered are local failure, regional failure or concomitant regional and local failure for LRF. Distant failure either alone or combined with a local or regional failure will be considered for DF. Only the first event will be taken into account, meaning that patients with a failure event are censored at that time for the other failure analyses. Living patients without the events corresponding to each endpoint will be censored at their date of last follow-up.

A selection of acute toxicities and late toxicities (based on the amount of evidence and clinical relevance), and non-cancer mortality will be included if the rate of events allows the performance of a NMA.

Network MACH NC3 and MARCH2, in theory with lumping



Label	Description
LRT	Standard RT +/- surgery
CLRT1	LRT + concomitant CT 1
CLRT2	LRT + concomitant CT 2
IC1-LRT	Induction CT 1 + LRT
IC2-LRT	Induction CT 2 + LRT
IC3-LRT	Induction CT 3 + LRT
LRT-AC	LRT + adjuvant CT
IC1-CLRT	Induction CT 1 + LRT+ concomitant CT
IC2-CLRT	Induction CT 2 + LRT + concomitant CT
IC3-CLRT	Induction CT 3 + LRT + concomitant CT
HFRT	Hyperfractionnated RT
MART	Moderately accelerated RT
VART	Very accelerated RT
HFCRT	Hyperfractionnated RT + concomitant CT
ACRT	Accelerated RT + concomitant CT
CLRT2-AC	CLRT2 + adjuvant CT

Induction CT 1= other than induction CT 2 and 3, induction CT 2= PF, induction CT 3= Tax-PF; concomitant CT 1= CT with platin, concomitant CT 2= CT without platin.

3. STATISTICAL ANALYSIS PLAN

3.1. DESCRIPTION OF THE MODELS

For each trial, we will use the relative overall survival estimated by the logarithm of the hazard-ratio (HR) and its variance, which will be determined using the log-rank observed minus the expected number of deaths (O - E) and its variance calculated in the standard MA. LRF and DF rates will be estimated using a competing risk model. For toxicity, we will use odds ratios (OR). Unless specified, all models of the NMA are based on 2 hypotheses:

- the transitivity hypothesis, which assumes that the logarithm of the hazard ratio (logHR) can be used to estimate relative treatment effects indirectly. For instance if we have three treatments named A, B and C, the consistency hypothesis states that:

  logHR(B vs C) = logHR(A vs C) – logHR(A vs B).

- the consistency hypothesis which assumes that there is no discrepancies between direct and indirect estimates into a closed loop.

Models include

- a fixed-effects model (model 1) , which will be used first.
- a “standard” random effects model (model 2), which could be used in case of unexplained heterogeneity.

3.2. STATISTICAL METHODS

A two-step method will be used, the first step is the computation of hazard ratios or odds ratios based on the individual patient data gathered by the MACH-NC and MARCH collaborative groups. The second step is the actual network meta-analysis, using as input data for each trial the two treatments compared, the logarithm of the hazard ratios and its standard deviation.

All analyses will be performed under a frequentist approach with the R package netmeta. This package is based on graph theory methodology to model the relative treatment effects of multiple treatments under a frequentist framework. The R netmeta package will be used to provide the estimation of Q test for inconsistency (Krahn et al., 2013; Rücker et al., 2012, Rücker et al., 2015).

The reporting of the results will include a description of the networks (primary and for each sensitivity analysis), effect sizes from direct evidence, indirect evidence, and the network meta-analysis (at least for the primary analysis, through a comparative HR plot for each comparison of interest), a ranking of the treatment that includes the uncertainty of the ranking estimates. Ranking will be performed by P-score.

The forced consistency in multi-arms trials will be handled specifically. Heterogeneity will be quantified using the I^2, which represents the proportion of total variation in study estimates that is due to heterogeneity (Higgins et al., 2012). Inconsistency in the network can be assessed globally or for each closed loops. In order to limit the number of tests for both heterogeneity and inconsistency, Rücker et al have proposed a global test, called Q test (Rücker et al., 2012). This test is a generalization of Cochran's test that is used to assess heterogeneity in conventional meta-analysis. The Q statistic is the sum of a Q statistic for heterogeneity (within designs) and a Q statistic for inconsistency (between designs).

A fixed effects model will be used first. In case of unexplained heterogeneity ($p<0.1$) two solutions will be investigated: the use of random effects models and the performance of sensitivity analyses after the exclusion of trials that are considered as outliers in the standard meta-analysis. This latter method of conducting sensitivity analyses will be used in case of significant network inconsistency ($p<0.1$). The Netmeta package allows identifying in which closed loop the inconsistency is located (Rücker et al., 2015). The trials responsible for inconsistency will be determined by comparing direct and indirect estimates and trial forest plots within the inconsistent closed loop. The effect of trial removal on the network overall consistency and estimation will be investigated.

Within the bayesian framework, the treatments are ranked using the surface under the cumulative ranking curve (SUCRA) (Salanti et al., 2011). Rücker and Schwarzer have proposed a frequentist analogue to SUCRA called P-Score that works without resampling, and measures the mean extent of certainty that a treatment is better than the competing treatments. P-Score would be 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst (Rücker G, Schwarzer G, 2015).

This work will be performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions (Hutton et al., 2015). P-values <0.05 will be considered significant. All analyses will be performed using the R software version 3.2.1.

3.3. SENSITIVITY ANALYSES AND VALIDATION OF THE MODEL HYPOTHESIS

Clinical sensitivity analyses will be performed in coherence with the standard meta-analysis, either by excluding a certain category of patients or a certain category of trials.

Network meta-analysis will be repeated after:

- exclusion of trials that are considered outliers on the overall survival analysis in the standard MA
- secondary sensitivity analyses will be performed according to the standard MA protocol, i.e. exclusion of:
    - possible low quality trials: including less than 100 patients, with a median follow-up shorter than five years, for which date of randomization wasn't available,
    - trials with distinctive loco-regional treatment: including surgery for local treatment, with alterning radiotherapy and split course radiotherapy, where radiotherapy is confounded (i.e. where radiotherapy modalities are different in the 2 treatment arms, excepted for MARCH)
    - trials with non-conventional chemotherapy: without platin-based chemotherapy, *with polychemotherapy ≥3drugs other than TaxPF or with only one drug as induction chemotherapy,* with adjuvant chemotherapy.

Subgroup analyzes may be performed to take into account: age, performance status and tumor site.

4. PRESENTATION AND PUBLICATION

This analysis will be presented at an international meeting and published as a full paper. Authorship rules will be the same as those used in the standard meta-analysis and published on behalf of the MACH-NC and MARCH collaborative group.

5. REFERENCES

Blanchard, P., Hill, C., Pignon, J.P., and MACH-NC and MARCH Collaborative Groups (2011). Mixed treatment comparison meta-analysis of altered fractionated radiotherapy and chemotherapy in head and neck cancer. J. Clin. Epidemiol. 64, 985–992.

Blanchard, P et al. Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the meta-analysis of chemotherapy in head and neck cancer group. J Clin Oncol 2013;31:2854−60.

Blanchard P, on behalf of the MARCH collaborative Group. Meta-analysis of radiotherapy in head and neck carcinomas: an update. 17th ECCO meeting, September 2013, Amsterdam. Eur J Cancer 2013;49 (Suppl 3): S12.

Higgins JPT, Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558, 2002.

Hutton. B: The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015; 162:777-784.

Krahn, U., Binder, H., and König, J. (2013). A graphical tool for locating inconsistency in network meta-analyses. BMC Med. Res. Methodol. 13, 35.

Pignon JP, on behalf of the MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head & neck cancer (MACH-NC): an update on 93 randomized trials and 17 346 patients. Radiother Oncol 2009;92:4-14.

Pignon JP, 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. Lancet 2000; 355: 949–55.

Rücker, G: Network meta-analysis, electrical networks and graph theory. Res Synth Methods 3:312–324, 2012.

Rücker, G., Schwarzer, G., Krahn, U., and König, J. (2015). netmeta: Network meta-analysis with R.

Rücker G, Schwarzer G: Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol 15:58, 2015.

Salanti G, Ades AE, Ioannidis JPA: Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 64:163–171, 2011.