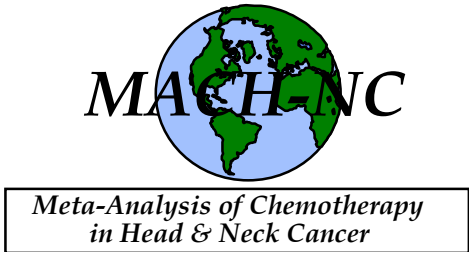

META-ANALYSIS

OF

CHEMOTHERAPY

IN

HEAD AND NECK CANCER

An update with the addition of the trials of the period 1994-2000

Initiated by the Institut Gustave Roussy

Villejuif, France

Protocol **December 2001**

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1. INTRODUCTION AND BACK GROUND

Head and neck squamous cell carcinomas (HNSCC) are frequently occurring tumors with 80 700 new cases (oral cavity, oropharynx, hypopharynx, larynx) in 1996 within the European Community[1] and 40 000 new cases in 2000 within the United States[2]. In 2000, the estimated number of new cases worldwide was 551 000[3]. In oral cavity and pharynx carcinoma, at least 40 % of patients have locally advanced disease at diagnosis[2]. Surgery and/or radiation therapy are standard modalities used to achieve loco-regional control[4]. Despite of this therapeutic approach, the prognosis of HNSCC patients remains poor : the 5-years relative survival rates in USA for the period 1989-1995 was around 45% in white people with 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 [5].

In the past three decades, numerous randomized clinical trials have investigated the efficacy of chemotherapy in HNSCC, as an adjunct to surgery and/or radiotherapy. These trials have mainly included patients with locally advanced disease. Chemotherapy has been used in three ways in the treatment of locally advanced HNSCC[4] : as induction treatment (neoadjuvant chemotherapy) ; concomitantly with radiotherapy ; as adjuvant treatment after radiotherapy and/or surgery. The MACH-NC study[5], a meta-analysis based on individual patients data pooled the results of the randomized trials performed between 1965 and 1993 and compared loco-regional treatment to loco-regional treatment plus chemotherapy. Trials including only naso-pharyngeal carcinoma were not eligible. The overall pooled relative risk was 0.90 corresponding to an absolute benefit of 4% for chemotherapy, from 32% to 36%, at 5 years (5y.). There was a significant interaction ($p<0.01$) between chemotherapy timing and treatment. The treatment according to chemotherapy timing is summarized below:

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

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

The greatest benefit was observed when chemotherapy was given concomitantly with radiotherapy, but heterogeneity of the results within this group prohibited firm conclusions.

Five trials (811 patients), including four concomitant trials and one adjuvant trial explained most of the heterogeneity[6]. These 5 trials which represent about 7% of the data explained 40% of the heterogeneity. Since 4 of these 5 trials contributing to the overall heterogeneity were found within the concomitant group, the interpretation of the effect of chemotherapy in this group has to be considered with **caution**. Indeed, the 5-years absolute survival benefit of concomitant chemotherapy was 8% and decreased to 4% when those 4 trials were excluded. Given this heterogeneity and the fact that a very small number of patients (trials) had a great influence on the overall observed effect, it remains to be shown whether the benefit of chemotherapy concomitant with radiotherapy is as important as suggested (8% absolute survival benefit at 5 years).

Since 1993, more than 20 randomized trials comparing radiotherapy to concomitant radio-chemotherapy have been conducted with more than 7 000 patients accrued in these trials Added to the trials already included in the MACH-NC, data on approximately 11 000 patients will be available. The updated meta-analysis based on this population will allow a more accurate evaluation of the extent of the benefit associated with concomitant chemotherapy and will allow for definitive conclusions on this issue.

Therefore, it was decided to focus the updating of the MACH-NC study on trials with concomitant chemotherapy, to include the trials performed between 1994 and 2000 and to update the follow-up of the most recent trials of MACH-NC. The other comparisons of MACH-NC will be also updated, in particular, the trials with neoadjuvant chemotherapy and those comparing neoadjuvant chemotherapy followed by radiotherapy to concomitant radio-chemotherapy.

Moreover, the marked increase in statistical power due to the increased number of patients will now allow questions which could not be addressed in the previous MACH-NC study to be answered. Indeed, it will be possible to study whether concomitant poly-chemotherapy is superior to concomitant mono-chemotherapy. We will also assess the impact of concomitant chemotherapy separately on distant metastases and local-regional control. The database will also provide the opportunity to evaluate which type of chemotherapy can offer the best effect (5-FU-based or platinum-based etc …). In addition, the effect of chemotherapy will be evaluated when given concomitantly with post operative RT, when given with altered fractionated RT and when given with a lower dose of RT. Finally we will be able to better analyze which population is more likely to benefit from the use of chemotherapy.

The meta-analysis will be based on individual patient data[7] and will used methodology similar to that used in the MACH-NC study[5], the Breast Cancer Overview[8], the Prophylactic Cranial

Irradiation Overview[9], and the Non Small Cell Lung Cancer Overview[10]. A similar collaborative group comprising those involved in trials included in the project will be established and the meta-analysis will be conducted and reported on its behalf.

Both published and unpublished studies will be included in the meta-analysis since there is evidence that both investigators and journal editors are more likely to publish trials with positive results[11]. Basic survival and prognostic information will be collected for all patients randomized in each study because this allows a more reliable and flexible approach, a more sensitive analysis and avoids the potential bias of post-randomization exclusion[7,12]. Updated follow-up information will be sought which will enable us to report on long-term survival.

In summary, the constitution of this unique database aims to provide the most comprehensive analysis on the effect of chemotherapy, given concomitantly with radiotherapy. It should contribute to define therapeutic guidelines and to generate new hypotheses to be tested in further randomized trials

2. OBJECTIVES

Assessment of the role of chemotherapy concomitant or alternating with radiotherapy in the treatment of head and neck squamous carcinoma by studying the following comparison :

Radiotherapy

↗

↘

Radiotherapy + concomitant (or alternaning) chemotherapy

3. TRIALS SELECTION CRITERIA

3.1 INCLUSION CRITERIA

All trials must satisfy the following criteria:

Trials must

- compare radiotherapy plus chemotherapy to radiotherapy alone.
- Be randomized in a way which precludes prior knowledge of treatment assignment.
- Be unconfounded, except changes of the radiotherapy in the experimental arm (decreased dose or increased duration).
- Have completed accrual before 31st December 2000.
- Include patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx.
- Not include patients with metastatic disease.

Patients should

- Not receive prior surgery, except for those enrolled in trials of postoperative treatment.
- Not receive prior radiotherapy.
- Not receive prior chemotherapy.
- Undergo a potentially curative locoregional treatment.

4. TRIAL SEARCH

Data from all published and unpublished randomized trials making the above comparisons in HNSCC patients will be sought using electronic database searching for the period 1970-2000 (Medline, Cancerlit, DARE, Embase, CCT meta-register), hand searching (review articles, meeting proceedings) and by contacting experts in the field.

The search strategy used was :
1) for MEDLINE from PubMed

("head and neck neoplasms/drug therapy"[MAJR] OR "head and neck neoplasms/radiotherapy"[MAJR]) AND ("Randomized Controlled Trials"[MESH] OR "Clinical Trials, Phase III"[MESH] OR "clinical trial, phase III"[Publication Type] OR "randomized controlled trial"[Publication Type]) NOT "Neoplasm Metastasis"[MESH]

2) for EMBASE

(Head-and-Neck-Tumor- Drug Therapy MJ. OR Head-and-Neck-Tumor- Radiotherapy MJ.) AND (Phase-3-Clinical-Trial DE OR Randomized-Controlled-Trial DE) NOT Metastasis#.W..DE.

Trials registries (PDQ, ClinProt...) will be also consulted. All trialists who take part in the meta-analysis will be asked to help to identify more trials.

5. DESCRIPTION OF THE TRIALS INCLUDED

Appendix A_1 describes the trials comparing radiotherapy versus concomitant (or alternating) radio-chemotherapy which accrued during the period 1994-2000 and are potentially eligible for the meta-analysis. Twenty-six trials including 7 913 patients were identified. Added to the 26 trials (3 727 patients) included in the period 1965-1993, it is 52 trials and 11 640 that may be available. Two categories of trials have been identified: 1) trials in which radiotherapy is the same in both arms ; 2) trials in which radiotherapy in the chemotherapy arm is characterized by a lower total dose and / or a longer overall time of radiotherapy as compared to the radiotherapy alone arm (radiotherapy confounded trials) **Appendix A_2** describes the trials from the period 1994-2000 identified for the other comparisons of MACH-NC[5]. **Appendix B_1** describes the number of concomitant trials (patients) available by types of chemotherapy and radiotherapy for the period 1965-2000. **Appendix B_2** describes the number of trials (patients) of the other comparisons of MACH-NC for the period 1965-2000 by comparison and main categories (i.e. chemotherapy timing, type of chemotherapy).

6. CRITERIA OF EVALUATION

6.1 ENDPOINTS

The main endpoint will be **survival**, because of its importance and because of the reliability of the measurement. Cause of death will be studied, if possible.

Secondary endpoints such as time to local failure, distant failure, or second primary event-free survival and specific survival will be also considered.

6.2 PROGNOSTIC FACTORS

The prognostic factors (groups) that will be considered are :

- Age (50 or less, 51-60, 61+).
- Sex (male, female).
- Site of the primary tumor (oral cavity, oropharynx, larynx, hypopharynx, other).
- Stage (I-II, III, IV).
- 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
- Site of the primary.
- TNM staging (if not available stage ; in any case, provide information on classification used).
- Allocated treatment.
- Date of randomization.
- Date of last follow-up.
- Survival status.
- Cause of death.
- Date of tumor failure, date of nodal failure
- Date of distant failure
- Date and type of second primary
- Whether excluded from trial analysis.
- Reason for exclusion (if applicable).
- Whether received at least one cycle of chemotherapy.

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 more 8 000 patients it would be possible to detect, with a power exceeding 99%, an absolute improvement in survival from 30 % to 35 % at 5-years. Therefore, the study will have enough power to detect the small but clinically important difference which is likely to occur in clinical oncology.

All randomized patients will be included in the analysis. The analysis will be performed on an intention to treat basis using the stratified (by trial) logrank test. The hazard ratio for individual trials and for each comparison will be reported.

Several comparisons of the results of chemotherapy in **groups of trials** classified according to the type of chemotherapy and radiotherapy are planned as exploratory analyses :

- Single agent chemotherapy versus combination chemotherapy,
- Cisplatin- or carboplatin-based chemotherapy versus nonplatin-based chemotherapy,
- Among platinum-based trials, daily versus 3-weekly treatment,
- 5-FU based chemotherapy versus non 5-FU based chemotherapy,
- Postoperative versus radical radiotherapy,
- Standard versus hyperfractionated radiotherapy,
- Concomitant versus alternating radio-chemotherapy,
- Confounded radiotherapy (lower dose or higher duration in the experimental arm than in the control arm) versus no confounded radiotherapy.

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 endpoints : specific survival, event-free survival, time to local failure, time to distant failure.

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

9. WORKING PARTIES IN THE META-ANALYSIS

In order to complete the meta-analysis successfully, three groups with specific functions have been created : 1) the Secretariat 2) the Steering Committee 3) the MACH-NC Trialists' Collaborative Group (MACH-NCTCG).

The Secretariat is in charge of the coordination of the meta-analysis. It is responsible for completing the trial register and for inviting investigators to provide data available on patients. The Secretariat is also in charge of checking, processing and analyzing the data. Finally, the Secretariat is responsible for preparing reports, publications and works in very close collaboration with the Steering Committee.

The Steering Committee will include international experts in the field of oncology, radiotherapy, and surgery involved in head and neck cancer, and experts in meta-analysis. The list of its members is given on the following page. The Steering Committee will support the Secretariat with medical and methodological expertise, help determine trials relevant to the overview, and promote contact between investigators and all the collaborators.

The MACH-NCTCG will include the investigators responsible for trials included in the meta-analysis. The members of the Secretariat and the Steering Committee will also be included in this group. It will be responsible for providing the Secretariat with data on patients and for discussing the reports prepared by the Steering Committee and the Secretariat.

10. PRACTICAL CONSIDERATIONS

The Secretariat, located in the Biostatistics Department at Institut Gustave Roussy, will be responsible for liaising with trialists. The main database will be run by the Secretariat. All data, updating and correction should be sent there. All supplied data will remain confidential and used exclusively for the meta-analysis. A meeting of all group members will be organized by the Secretariat to discuss the preliminary results.

11. PUBLICATION POLICY

Any publication arising from this project will be made in the name of the MACH-NC Group and include a list of all collaborators.

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Appendix A1: Description of the trials comparing radiotherapy to radio-chemotherapy

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

TABLE A-1: RANDOMIZED TRIALS OF RADIOCHEMOTHERAPY VERSUS RADIOTHERAPY IN HNSCC

Sites	Number of patients randomized	Inclusion period	Stage	Radiotherapy dose (Gray)/ duration (weeks)	Chemotherapy drug/dose (mg/m²)	reference
OP, OP, HP, L operable	100	1990-95	III/IV	68-72 Gy/ 7-8 wks	C: 20 mg/m^2 x 4, wks$_{1,3}$ F: 1000 mg/m^2 x 4, wks$_{1,3}$	Adelstein (2000)
OP, OP, HP, L NP, S, O operable & inoperable	122	1990-95	II/III/IV	75 Gy/ 6 wks, bid 70 Gy/ 7 wks, sc, bid$^{\%}$	C: 12 mg/m^2 x 4, wks$_{1,6}$ $^{\&}$ F: 600 mg/m^2 x 4, wks$_{1,6}$	Brizel (1998)
HNSCC inoperable	86	1992-94	?	70 Gy/ 7 wks	Cb: 45 mg/m^2 x 5, wks$_{1,3,5,7}$	Gabriele (1994)
HNSCC inoperable	68	1992-95	III/IV	69.2 Gy/ 6.5 wks, bid 80 Gy/ 9 wks, bid, alt$^{@}$	C: 20 mg/m^{2}x 7, wks$_{1,4,7,10}$ F: 300 mg/m^2 x 4, wks$_{1,4,7,10}$ FA: 20 mg/m^2 x 4, wks$_{1,4,7,10}$	Giglio (1998)

sc= split course, **po** = post-operative **alt** = alternating.

$^{\&}$ Two other cycles after completion of all local therapy: same dose of F, 80 mg/m²/wks of C for the third cycle, and 100/m²/wks for the fourth.

$^{\%}$ Seven day interruption in the RT-CT arm after 40 Gy and lower total dose to the primary tumor.

$^{@}$ RT alternating with CT: 80 Gy, 2 Gy/d wks 2-3, 1.5 Gy x 2/d wks 5-6 & 8-9

TABLE A-1: RANDOMIZED TRIALS OF RADIOCHEMOTHERAPY VERSUS RADIOTHERAPY IN HNSCC (followed)

Sites	Number of patients randomized	Inclusion period	Stage	Radiotherapy dose (Gray)/ duration (weeks)	Chemotherapy drug/dose (mg/m²)	reference
OP	127[#]	1993-98	III/IV	66-70 Gy/ 7 wks	Cb : 75 mg/m^{2}x 4, wks$_{1,5,9}$ F : 1000 mg/m^{2}x 4, wks$_{1,5,9}$	Olmi (1996) ORO-01
OP	226	1994-97	III/IV	70 Gy/ 7 wks	Cb: 70 mg/m^{2}x 4, wks$_{1,4,7}$ F: 600 mg/m^{2}x 4, wks$_{1,4,7}$	Calais (1998) GORTEC 94.01
OC, OP, HP, L Most inoperable	158*	1990-96	II/III/IV	55 Gy/ 2.5 wks, bid	Mi: 20 mg/m² d$_5$	Dobrowsky (2000)
L, HP operable	59[∀]	1996-99	II/III/IV	70 Gy/ 7 wks 70 Gy/ 7 wks, bid	C: 100 mg/m², wks $_{1,4,7}$	EORTC 22954[%]
OC, OP, HP, L,	57[∀]	1996-99	II/III/IV	80.5 Gy/ 7 wks, bid 70 Gy/ 7 wks	C: 100 mg/m², wks $_{1,4,7}$	EORTC-22962[£]

sc= split course, **po** = post-operative **alt** = alternating.

[#] patients of the third arm with hyperfractionated radiotherapy excluded

***** patients of third arm with conventional radiotherapy excluded

[∀] Early closure because of low accrual.

[%] Centers choose between conventional or bid RT, and between evaluation at 2 months after completion of RT with salvage surgery if non CR (option 1) or evaluation after 40-50 Gy (4-5 wks). In this second case (option 2), the RT is complete up to 70 Gy if PR or CR, if not surgery is performed. As in option 1, an evaluation is planned 2 months after completion of RT with salvage surgery if no CR.

[£] 4 arms trials, two arms with concomitant cisplatin and radiotherapy similar to the arms without chemotherapy (2x2 factorial design).

TABLE A-1: RANDOMIZED TRIALS OF RADIOCHEMOTHERAPY VERSUS RADIOTHERAPY IN HNSCC (followed)

Sites	Number of patients randomized	Inclusion period	Stage	Radiotherapy dose (Gray)/ duration (weeks)	Chemotherapy drug/dose (mg/m²)	reference
OC,OP,HP, L, NP	130	1991-93	III/IV	77 Gy/ 7 wks, bid	C: 6 mg/m² x 5, wks $_{1\ to\ 7}$	Jeremic (1999)
OC, OP, HP, L inoperable	295$^{\forall}$	1992-99	III,IV	70 Gy / 7 wks 60-70 Gy/ 11-12wks, sc$^{\$}$	C: 100 mg/m², wks $_{1,4,7}$ C: 75 mg/m², wks $_{1,4,9}$ F: 1000 mg/m² x 4, wks $_{1,4,9}$	Adelstein (2000) Int 0126
OC, OP, HP	263	1995-99	III,IV	69.9 Gy / 5.5 wks, b	Cb: 70 mg/m² x 5, wks $_{1,4,}$ F: 600 mg/m² x 5, wks $_{1,4,}$	Staar (2001)**
OC, OP, HP, L inoperable	136	1992-??	II, III,IV	60 Gy / 8 wks, alt 75 Gy / 6 wks, cb	C: 20 mg/m² x 5, wks $_{1,4,7,10}$ F: 200 mg/m² x 5, wks $_{1,4,7,10}$	Benasso (2000)$^{£}$
OC,OP,HP	384	1996-99	III/IV	77.6 Gy/ 6 wks, bid 70.6 Gy/ 6 wks, bid$^{\$\$}$	Mi: 10 mg/m², wks $_{1,6}$ F: 600 mg/m² x 5, wks $_{1}$	Budach (2001)
OC, OP, HP, L inoperable	558$^{\forall}$	1996-99	III/IV	66 Gy /6.5 wks	Mi: 15 mg/m² d_5	Grau (2001) IAEA-CRP-MMC

sc= split course, **po =** post-operative **alt** = alternating, cb = concomitant boost.

$^{\forall}$ early closure because of low accrual. $^{\$}$ three-arms : conventional RT (20 Gy x 3), conventional RT + C (100 mg/m²), split course RT (5 wks rest) with C (75 mg/m²)+ F.

$^{£}$ in the CT-RT arm, 3 series of RT (20 Gy x 3) on weeks 2,3,5,6,8,9, ; in the RT only arm (75 Gy), concomitant boost in the last two weeks.

$^{\$\$}$ RT-CT arm. ** second randomization, prophylactic G-CSF or not; wks 1-3, 1.8 Gy daily, wks 4-6, bid, 1._/1.5 Gy daily.

TABLE A-1: RANDOMIZED TRIALS OF RADIOCHEMOTHERAPY VERSUS RADIOTHERAPY IN HNSCC (followed)

Sites	Number of patients randomized	Inclusion period	Stage	Radiotherapy dose (Gray)/ duration (weeks)	Chemotherapy drug/dose (mg/m²)	reference
HNSCC operated or RT only	970	1991-2000	II, III, IV	60 Gy/6 wks, alt or 50-55/3 wks	Mx: 100 mg/m², wks $_{1,3}$ or VBMF	Tobias (2001) UKHAN-1[§]
L operable	547	1992-2000	III, IV	70 Gy/ 7 wks	C: 100 mg/m², wks $_{1,4,7}$ F: 1000 mg/m² x 5, wks$_{1,4,7}$	RTOG 9111[§§] (2000)
OC, OP, HP, L operable & inoperable	224	1994-2000	II, III, IV	74.4 Gy/6.5 wks, bid	C: 20 mg/m^2 x 5, wks$_{1,5}$	SAKK 10-94 (2000)

sc= split course, **po =** post-operative **alt** = alternating.

[§] 4 arms-trial for patients without previous surgery (n=715): RT alone, RT + simultaneous CT, RT followed by CT, both. If prior surgery (n=255 patients), randomized to RT vs RT + simultaneous CT. Two options according to center: RT 50-55 Gy/ 3 wks ± Mx or RT 60 Gy/ 6 wks alternating with VBMF. Mx dose is 100 mg/m² with FA rescue at wks 1 and 3 for the simultaneous arm. For the simultaneous part, 4 cycles of VBMF are given at wks 1, 4, 7 et 10. The VBMF regimen includes Vc (1.4 mg/m²), B (30 mg im), F (500 mg/m²), Mx (100 mg/m²) with FA rescue.

***** 3 one-week series separated by a rest week in the CT arm. In PR or CR, 2 other cycles of chemotherapy, 3 weeks a part are planned.

[§§] three-arms trial: conventional radiotherapy, RT + concomitant C, larynx preservation arm with first 2-3 cycles of C + F and then according to the tumor response RT or RT + surgery.

TABLE A-1: RANDOMIZED TRIALS OF RADIOCHEMOTHERAPY VERSUS RADIOTHERAPY IN HNSCC (followed)

Sites	Number of patients randomized	Inclusion period	Stage	Radiotherapy dose (Gray)/ duration (weeks)	Chemotherapy drug/dose (mg/m²)	reference
OC, OP, HP, L operated	334	1993-2000	III/IV	66 Gy/6.5 wks, po	C: 100 mg/m² wks $_{1,4,7}$	Bernier (2001) EORTC 22931
OC, OP, HP, L operated	459	1995-2000	$2N^+$,R^+ or M^+	60 Gy/ 6 wks, po	C: 100 mg/m², wks $_{1,4,7}$	RTOG 9501 (2000)
OC,OP,HP,L inoperable	109	1996-2000	IV	62 Gy/ 3 wks, bid 62 Gy/ 5 wks, bid, sc*	C: 100 mg/m², wks $_{1,3,5}$ F: 1000 mg/m² x 5, wks $_{1,3,5}$	Etessami A (2001) GORTEC 9601
OC, OP, HP, L, no prior surgery	412	19??-2000	III/IV	70 Gy / 7 wks	Pm : 40 mg/m², wks$_{1,7}$	NCI-V98-1416 (2000)
OC, OP, HP, L Inoperable	1644	1992- 1998	III/IV	60-65 Gy/ 6-6.5 wks	C: 50 mg/m², wks $_{1,4}$ C: 70 mg/m², wks $_{1,4}$ C: 50 mg/m², wks $_{1,2,3,4,5,6}$	Bhowmik (2001)*
OC, OP, HP, L Inoperable	528	1992- 1998	III/IV	60-65 Gy/ 6-6.5 wks	C: 70 mg/m², wks $_{1,4}$ F: 1000 mg/m², wks $_{1,4}$ C: 70 mg/m², wks $_{1,4}$ F: 1000 mg/m² x 3, wks $_{1,4}$	Bhowmik (2001)**

sc= split course, **po =** post-operative **alt** = alternating, **cb** = concomitant boot.
* 4-arm trial : RT alone, 3 arms with RT + C ; * 3-arm trial: RT alone, 2 arm with RT + CF

TABLE A-2: RANDOMIZED TRIALS OF RADIOCHEMOTHERAPY VERSUS RADIOTHERAPY IN HNSCC: **Ongoing trials**

Sites	Nb of patients randomized /planned	Inclusion period	Stage	Radiotherapy dose (Gray)/ duration (weeks)	Chemotherapy drug/dose (mg/m²)	reference
OP, HP, L operated	141/186	1994-	N+	45-72 Gy/6-8 wks, po	Cb : 50 mg/m² x2, weekly x 6-8	Baillet (2001)
OP, HP inoperable	140/160	1997-	IV	75.6-80.4/ 6.3-6.6 wks bid	C : 100 mg/m² x 1, $wks_{1,4,7}$ F : 750 mg/m² x 5, $wks_{1,4,7}$ [£]	FNLCC 96003 Bensadoun (2000)

sc= split course, **po =** post-operative **alt** = alternating.

[£] dose decreased to 750 mg/ day for second and third cycles instead of 750/mg².

List of abbreviations

CT	Chemotherapy
RT	Radiotherapy
Nb	Number
wks	weeks
OC	Oral cavity
OP	Oropharynx
HP	Hypopharynx
NP	Nasopharynx
L	Larynx
S	Sinus
O	Other
HNSCC	Head and Neck Squamous Cell Carcinoma
N+	Positive node
M+	Surgical margin positive
R+	Extra nodal capsular spread
sc	split course,
po	post-operative,
alt	alternating
EORTC	European Organisation for Research and Treatment of Cancer
FNLCC	Fédération Nationale des Centres de Lutte contre le Cancer
GORTEC	Groupe d'Oncologie Radiothérapie Tête et Cou
IAEA-CRP-MMC	International Atomic Energy Agency - Clinical Research Program – Mitomycine

INT	US INTergroup trial
NCI	National Cancer Institute
RTOG	Radiation Therapy Oncology Group
SAKK	Swiss Group for Clinical Cancer Research
UKHAN	United Kingdom Head And Neck (UKCCR head and Neck Collaborative Group)
A	Doxorubicin
B	Bleomycin
C	Cisplatin
Cb	Carboplatin
Cy	Cyclophosphamide
F	5-Fluorouracil
FA	Folinic Acid
HC	Hydrocortisone
Hu	Hydroxyurea
LA	Leucovorin Acid
Mi	Mitomycin
Mp	6-Mercaptopurine
Mx	Methotrexate
Pm	Porfiromycin
Px	Paclitaxel
Tg	Tegafur
U	UFT (Tegafur + uracil)
Vc	Vincristine
Vd	Vindesine
Vb	Vinblastine

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Appendix A2: Other trials eligible for MACH-NC update

See abbreviations on pages 18-19 and references on pages 27.

TABLE A-3: RANDOMIZED TRIALS OF SEQUENTIAL RADIOCHEMOTHERAPY VERSUS CONCOMITANT OR ALTERNATING RADIOTHERAPY IN HNSCC

Sites	Nb of patients randomized	Inclusion period	Stage	Radiotherapy dose (Gray)/ duration (weeks)	Chemotherapy drug/dose (mg/m²)	reference
HNSCC	322	1991-2000	II, III, IV	60 Gy/6 wks, alt	Vc: 1.4 mg/m², wks 1,4 B: 30 mg im, wks 1,4 Mx: 100 mg/m², wks 1,4 F: 500 mg/m², wks 1,4	UKHAN-1[§] (2000)
				60 Gy/6 wks,	Vc: 1.4 mg/m², wks 11,13 B: 30 mg im, wks 11,13 Mx: 100 mg/m², wks 11,13 F: 500 mg/m², wks 11,13	
HP inoperable	96	199?-9?	IV	70 Gy/ ? wks 70 Gy/ ? wks,	C: 25 mg/m² x 5, wks 1,3 F: 750 mg/m² x 5, wks1,3 C: 25 mg/m² x 5, wks 1,4, F: 750 mg/m² x 5, wks1,4,	Iro (1997)

sc= split course, **po =** post-operative **alt** = alternating.

[§] 4 arms-trial for patients without previous surgery (n=715): RT alone, RT + simultaneous CT, RT **followed by** CT, both. If prior surgery (n=255 patients), randomized to RT vs RT + simultaneous CT. Two options according to center: RT 50-55 Gy/ 3 wks ± Mx or RT 60 Gy/ 6 wks alternating with VBMF. Mx dose is 100 mg/m² with FA rescue at wks 1 and 3 for the simultaneous arm. For the simultaneous part, 4 cycles of VBMF are given at wks 1, 4, 7 et 10. The VBMF regimen includes Vc (1.4 mg/m²), B (30 mg im), F (500 mg/m²), Mx (100 mg/m²) with FA rescue.

TABLE A-4: RANDOMIZED TRIALS OF SEQUENTIAL RADIOCHEMOTHERAPY VERSUS CONCOMITANT OR ALTERNATING RADIOTHERAPY IN HNSCC: **Ongoing trials**

Sites	Nb of patients randomized /planned	Inclusion period	Stage	Radiotherapy dose (Gray)/ duration (weeks)	Chemotherapy drug/dose (mg/m²)	reference
L, HP operable	276/564	1996-	II, III, IV	70 Gy/ 7 wks 60 Gy/ 9 wks, alt	C : 100 mg/m², wks $_{1,4,7}$ F : 1000 mg/m² x 5, wks$_{1,4,7}$ C : 20 mg/m² x 5, wks $_{1,4,7,10}$ F : 200 mg/m² x 5, wks$_{1,4,7,10}$	EORTC 24954** (2000)

** In the sequential arm (CT followed by RT), the third cycle (option 1) or a third and a fourth (wks 10, option 2) is given only if PR or CR. In the alternating arm, 4 cycles with lowers daily dose (option 1) or 2 cycles followed by two other if CR or PR (option 2) are given. The third course of radiotherapy is given only if CR or PR in option 2. Salvage surgery if performed when no response is observed. Each center choose one option.

TABLE A-5: RANDOMIZED TRIALS OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY RADIOTHERAPY IN RESPONDERS OR SURGERY PLUS RADIOTHERAPY IN NON RESPONDERS VERSUS SURGERY FOLLOWED BY RADIOTHERAPY IN HNSCC:

Sites	Nb of patients randomized /planned	Inclusion period	Stage	Radiotherapy dose (Gray)/ duration (weeks)	Chemotherapy drug/dose (mg/m²)	reference
L	44	19??-??	II/III/IV[&]	69.9 Gy/ ? wks[&&] 56-70 Gy/ ? wks	C: 100 mg/m^2, wks$_{1,3}$ Px: 200 mg/m^2, wks$_{1,3}$	Hoppe (1996) [&&&]

[&] supraglottic (T2-T4, N0-N3) and glottic (T3-T4, N0-N3) laryngeal carcinoma (tumor volume < 80 ml) [&&] in the chemotherapy arm, 69.9 Gy if complete or partial response, surgery and post operative radiotherapy if stable or progression ; in the control arm, the treatment was surgery plus postoperative radiotherapy (56 Gy in R0 and 70 Gy in R1 resection). [&&&] the study was a 2:1 randomized trial with 32 patients in the chemotherapy arm and 12 in the control arm.

TABLE A-6: NEOADJUVANT CHEMOTHERAPY FOLLOWED BY RADIOCHEMOTHERAPY VERSUS RADIOTHERAPY IN HNSCC:

Sites	Nb of patients randomized /planned	Inclusion period	Stage	Radiotherapy dose (Gray)/ duration (weeks)	Chemotherapy drug/dose (mg/m^2)	reference
OC, OP, HP, L	38	1990-91	III/IV	70 Gy/ -7 wks	Cy: 600 mg/m^2, $wks_{1,2}$ Mx: 60 mg/m^2, $wks_{1,2}$ F: 600 mg/m^2, $wks_{4,5,6,7}$	Kumar (1997) &&

&& 2 cycles of induction chemotherapy by Cy and Mx followed by radiotherapy on weeks 4 with concomitant F.

TABLE A-7: RANDOMIZED TRIALS OF ADJUVANT CHEMOTHERAPY + LOCO-REGIONAL TREATMENT VERSUS LOCO-REGIONAL:

Sites	Nb of patients randomized /planned	Inclusion period	Stage	Radiotherapy dose (Gray)/ duration (weeks)	Chemotherapy drug/dose (mg/m²)	reference
HNSCC	388	1991-2000	II, III, IV	60 Gy/6 wks	Vc: 100 mg/m², wks $_{11,13}$ B: 30 mg im, wks $_{11,13}$ Mx: 100 mg/m², wks $_{11,13}$ F: 500 mg/m², wks $_{11,13}$	UKHAN-1[§] (2000)

[§] 4 arms-trial for patients without previous surgery (n=715): RT alone, RT + simultaneous CT, RT followed by CT, both. If prior surgery (n=255 patients), randomized to RT vs RT + simultaneous CT. Two options according to center: RT 50-55 Gy/ 3 wks ± Mx or RT 60 Gy/ 6 wks alternating with VBMF. Mx dose is 100 mg/m² with FA rescue at wks 1 and 3 for the simultaneous arm. For the simultaneous part, 4 cycles of VBMF are given at wks 1, 4, 7 et 10. The VBMF regimen includes Vc (1.4 mg/m²), B (30 mg im), F (500 mg/m²), Mx (100 mg/m²) with FA rescue.

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Appendix B1: Trials comparing radiotherapy to concomitant or alternating radio-chemotherapy

The trials performed in 1993, or before, (accrual period) corresponds to those included in MACH-NC[5]. Those after 1993 correspond to the new trials to be included. Because the Int 126 three-arm trial has arms that belong to different studied categories, the control arm (99 patients) was counted twice. In the UKHAN trial, centers may choose between concomitant with methotrexate (not confounded comparison) or alternating, with VBMF radio-chemotherapy (confounded comparison).Then, overall, for the period posterior to 1993, 26 comparisons (7 913 patients) from 24 trials.

Number of patients (comparisons) according to trial characteristic and period

Characteristics	Number of patients (comparisons)		
	≤1993 (MACH-NC)	>1993 (updating)	Total
Type of chemotherapy			
Cisplatin or carboplatin + 5-FU[µ]	517 (3)	2 576 (12)	3 093 (15)
PolyCT with platin	87 (2)	0 (0)	87 (2)
PolyCT without platin	489 (4)	622 (2)	1 111 (6)
Monochemotherapy	2 634 (17)	4 715 (12)	7 349 (29)
Cisplatin or carboplatin (2)[µµ]	*620 (3)*	*2 856 (8)*	*3 476 (11)*
Mitomycin or porfiromycin (1)[$]	*203 (2)*	*1 128 (3)*	*1 331 (5)*
Other	*1 811 (12)*	*731 (1)*	*2 542 (13)*
TOTAL	3 727 (26)	7 913 (26)	11 640 (52)
Postoperative RT			
Yes	90 (1)	1 048 (3)	1 138 (4)
No	3 637 (25)	6 865 (22)	10 502 (47)
TOTAL	3 727 (26)	7 913 (27)*	11 640 (53)*
Treatment timing			
Alternating	397 (4)	443 (3)	840 (7)
Concomitant	3 330 (22)	7 470 (23)	10 800 (45)
TOTAL	3 727 (26)	7 913 (26)	11 640 (52)
Type of RT		**	
Hyper-fractionated	None	1 574 (10)	1 574 (10)
Conventional	3 727 (26)	6 203 (15)	9 930 (41)
TOTAL	3 727 (26)	7 777 (25)	11 504 (51)
Confounded RT[§]			
Yes	739 (7)	1 255 (7)	1 994 (14)
No	2 988 (19)	6 658 (19)	9 646 (38)
TOTAL	3 727 (26)	7 913 (26)	11 640 (52)

[µ] carboplatin = 3 trials after 1993 (616 patients). [µµ] carboplatin = two trials with one after 1993 (86 patients), the oldest trial was a 3-arm trial (control, cisplatin, carboplatin ; 159 patients). [$] porfiromycin = 412 patients, one trial. * In the UKHAN trial, 255 operated patients were randomized between postoperative RT and postoperative RT + concomitant methotrexate. ** one trial used conventional RT in the RT-CT arm and HF RT in the control arm (136 patients) and is not included in this comparison between conventional and hyper-fractionated radiotherapy. [§] Trial with moderate change of the radiotherapy in the chemotherapy arm as compared to control arm (decreased dose or increased duration).

Among the 20 trials after 1993 using platin compounds, 8 use daily treatment (1 158 patients) and 12 (4 274 patients) injection each three weeks.

Appendix B2: Other trials eligible for MACH-NC

The trials performed in 1993, or before, (accrual period) corresponds to those included in MACH-NC[5]. Those after 1993 correspond to the new trials to be included.

Type of trials	Number of patients (trials)		
	<1993 (MAC-NC)	>1993 (updating)	Total
Neoadjuvant	5 269 (31)	38 (1)	5 307 (32)
Adjuvant	1 854 (8)	388 (1)	2 242 (9)
Organ preservation	602 (3)	42 (1)	646 (4)
Sequential versus concomitant radio-chemotherapy	861 (6)	418 (2)	1 375 (8)

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Meta-Analysis of Chemotherapy in Head & Neck Cancer

Appendix C : How to send data to the Secretariat.

FORMAT FOR THE DATA

The preferred format for the information is described on the following pages. However, if a different format is more convenient for you, this should cause no great difficulty as long as it is clearly specified.

WAYS OF SENDING THE DATA

EITHER: 1. As long as it will not cause delay, **the easiest way for us to receive the data is by e-mail**[1]. We should be able to read any standard floppy disk[2] or magnetic tape[3] if you let us know its specification. Please accompany any tape or disk with a printout of its contents.

OR: 2. Send a lineprinter listing from your computer, (preferably with blank lines between each line of data to help us avoid punching errors), giving as much as possible of the information requested on the form.

OR: 3. If you would prefer to enter the individual patient data onto forms, please contact the secretariat (tel: 33 1 42 11 45 65 ; fax: 33 1 42 11 52 58) and a pad of them will be sent to you immediately.

It is important when trying to achieve a synthesis of the results of many different trials to include all patients ever randomized, whether eligible or not, whether or not they received their allocated treatment, whether properly followed up or not. Please try to get as near as possible to that ideal (or, at least please indicate where post randomization exclusions or losses have occurred), as long as to do so will not delay you sending us data. If it will cause a delay, then send us what you can now, and send the extra information later.

Please, fill out and mail (or fax) the enclosed form to the secretariat to facilitate data processing.

---

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

[2] The preferred specification would be IBM compatible, 3.5" disk, ASCII Format.

[3] Convenient specifications for us are 9-track, 1600bpi, phase-encoded (PE) or 6250bpi group-encoded (GCR), Vax copy or unlabelled ASCII/EBCDCI.

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

Column	Variable	Format/Coding
2-11	Patient identifier	10 characters
13-20	Date of birth	dd/mm/yyyy, 99999999=Unknown
	or age	6 blanks (columns 13-18), 2 digits (columns 19-20), 99=Unknown
22	Sex	1=Male, 2=Female, 9=Unknown
24-26	Performance Status	For Karnofsky index use 3 digits, for WHO or ECOG index use 2 blanks (column 24-25) and one digit (column 26)
28	Site of primary	1=Oral cavity, 2=Oropharynx, 3=Larynx, 4=Hypopharynx, 5=Nasopharynx, 6=Cervical node(s) without primary, 7=Others, 9=Unknown
30	T	0=T_0, 1=T_1, 2=T_2, 3=T_3, 4=T_4, 5=T_X, 6=T_{is}, 9=Unknown
32	N	0=N_0, 1=N_1, 2=N_2, 3=N_3, 4=N_X, 9=Unknown
34	M	0=M_0, 1=M_1, 9=Unknown
	or Stage	1 digit (column 34) with blanks in columns 30 & 32, 9=Unknown
36	Squamous cell	0=No, 1=Yes
38	Treatment allocated	1=No Chemotherapy, 2=Chemotherapy
40-47	Date of randomization	dd/mm/yyyy, 99999999=Unknown
49-56	Date of last follow-up or death	dd/mm/yyyy, 99999999=Unknown
58	Survival status	0=Alive, 1=Dead

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

Column	Variable	Format/Coding
60	Cause of death	0=Alive, Cancer=1, Toxicity of chemotherapy=2, Toxicity of radiotherapy=3 Complication of surgery=4, Other=5 (including death related to second line treatment), 9=Unknown
62	Tumor failure*,	0=No, 1=Yes
64-71	Date of tumor failure	dd/mm/yyyy, 99999999=Unknown
73	Nodal failure*,	0=No, 1=Yes
75-82	Date of nodal failure	dd/mm/yyyy, 99999999=Unknown
84	Distant failure (metastasis)	0=No, 1=Yes
86-93	Date of distant failure (metastasis)	dd/mm/yyyy, 99999999=Unknown
95	Second primary	0=No, 1=Yes
97	Date of second primary	dd/mm/yyyy, 99999999=Unknown
99-106	Type of second primary	Lung=1, Esophagus=2, Stomac=3, Colorectal=4, Liver=5, Head& neck=6, Other=7 (specify) 9=Unknown
108	Excluded from your analysis	0=No, 1=Yes
110-121	Reasons for exclusion	12 characters
123	Received at least one cycle of chemotherapy	0=No, 1=Yes

** A loco-regional failure corresponds either to a patient who never achieved a complete remission or to a patient who relapsed after an initial complete remission. In the first case, the date of first event should be the date of randomization and in the second case the date of occurrence of the relapse. If T and N failures are not available separately, please provide loco-regional failures and specify it when sending the data.*

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Meta-Analysis of Chemotherapy in Head & Neck Cancer

Data Collection Form

Name of contact clinician : ..... Name of trial : .....

Date trial opened for patient entry : .....(dd/mm/yy) Date trial closed to patient entry .....

Please list the treatments used in each arm of the trial :

Arm 1..... ***Arm 3*** .....

Arm 2..... ***Arm 4*** .....

I am able to use suggested coding : Yes ☐ / No ☐

Please indicate :
. The TNM or staging classification used :

.....

.....

. The Performance status coding used : WHO ☐ ECOG ☐ Karnofsky ☐ Other ☐

If other, specify : .....

Guarantee of Confidentiality of Individual Trial Results

Any data supplied will remain the property of the trialist(s) who supplied it.
This data will remain confidential and will not be used, circulated or distributed in any way that allows access to individual trial data.

I wish my data to remain confidential : Yes ☐ / No ☐

I enclose a copy of the trial protocol : Yes ☐ / No ☐ ***Signature*** .....

Please return this form completed to Dr Pignon, MACH-NC Secretariat, Dpt of Biostatistics,Institut Gustave-Roussy, Rue Camille Desmoulins, 94805 - VILLEJUIF Cedex - France - Telephone : 33 1.42.11.45.65 - Facsimile : 33 1.42.11 52.58

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

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

Name :		
Did we get your tiltle, affiliation and address correct ? If not, please give correct details :		
Telephone : (arear code & number) Fax : e-mail :		
Please give your own reference or protocol number for this study.		
Are the details concerning your study correct ?	YES	NO
Is the most recent publication cited in the reference list ?	YES	NO
If no, please give details :		

Are you willing to take part in this meta-analysis ? **YES** **NO**

If yes, please indicate wich of the following survival and pronostic factor Information you would be able to supply for each patient randomised

Treatment allocated	YES	NO	Stage TNM	YES	NO
Date of randomisation	YES	NO	Cause of death	YES	NO
Survival status	YES	NO	Date of tumor failure	YES	NO
Date of death/last follow-up	YES	NO	Date of nodal failure	YES	NO
Date of birth or age	YES	NO	Date of distant failure	YES	NO
Sex	YES	NO	Date and type of second 2nd primary	YES	NO
Performance status	YES	NO	Wether excluded from the analysis	YES	NO
Site of the primary	YES	NO	Reason for exclusion	YES	NO
			Receiced at list 1 cycle of chemotherapy	YES	NO

Please give the method of randomistion used in this study

Central telephone call Sealed envelope Other (please specify)

Please state stratification factors used (if any) :

What proportions was this study designed to have in each arm ? (eg 1 : 1)

Please give the name and address of the appropriate contact for the collection data :

Please give details of any relevant publications or trials you many know that are Not listed in the references or Appendix A of the protocol :

Please note that any information supplied will be treated in strict confidence and used only for the purpose of the meta-analysis

Please complete and return this form to :

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