MACH-NC

Meta-Analysis of Chemotherapy in Head & Neck Cancer

PROTOCOL

MACH-NC – SURGICAL PATIENTS

Individual patient data meta-analysis of chemotherapy in head and neck cancer: effects of chemotherapy for patients treated with surgery

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INTRODUCTION / BACKGROUND

In latest estimations, head and neck cancer represents 680.000 new cases every year worldwide (1). Mortality is approximately 375.000 cases per year. Squamous cell carcinoma is the most frequent upper airway cancer type around the world. Locally advanced tumors represent 50 % of cases (2). Incidence of head and neck squamous cell carcinoma (HNSCC) is strongly correlated with alcohol and tobacco. As prevalence of these risk factors is globally reducing, tumors associated with human papillomavirus are more and more frequent. Five years survival rate remains low, approximately 50 % for larynx tumors and 30 % in oral cavity and pharynx (3). Locally advanced tumors may benefit from various combinations of loco regional treatments (surgery / radiotherapy) and systemic treatment (chemotherapy / immunotherapy). The evaluation of the benefit of these treatments in HNSCC is crucial as they induce severe toxicity, have a major impact on vital and social functions (speech, swallowing, breathing) and on quality of life (4).

Management of HNSCC is complex and many clinical trials have been designed to explore various combinations of treatments. In previous studies (5) for the MACH-NC group (meta-analysis of chemotherapy in head and neck cancer), we have shown that patient survival, in non-metastatic HNSCC, is globally improved by the use of chemotherapy (6). This meta-analysis on individual patient data compared the result of 63 randomized trials (10741 patients included) performed between 1965 and 1993. Trials included patients treated for non-metastatic HNSCC by chemotherapy in addition to loco regional treatment. Adjuvant, concomitant with radiotherapy, or induction protocols were studied. Global survival benefit was 4% at 5 years in favor of chemotherapy. A significant interaction between chemotherapy timing and treatment effect was found, with an increased benefit when chemotherapy was concomitant with radiotherapy. Results of this first meta-analysis were updated in 2009 (7,8). This update included 93 trials (17 493 patients) and considered indirect comparison of treatments. It showed a 4.5% absolute benefit of chemotherapy added to loco regional treatment at 5 years. The benefit was 6.5% at 5 years for concomitant chemotherapy. In another study, the benefit of chemotherapy was explored in all tumors locations (9). Results were consistent in all tumor locations.

However, we have always studied benefit of chemotherapy added to loco regional treatment, regardless of the nature of this loco regional treatment. Comparisons included patients treated by surgery, radiotherapy, or both. Specific studies were made regarding different type of radiotherapy(10) but overall benefit of chemotherapy for surgical patients was not specifically

studied. Despite the progress of radio-chemotherapy, and the growing interest for immune therapy, surgery still holds a major place in HNSCC treatment strategy (11). In loco regional treatment strategy, many factors may influence the decision (including patient characteristics, tumor characteristics or center preferences). Patients eligible to surgery may have different characteristics and different tumor type. In a preliminary analysis (Appendix 1), based on patients included in the first update of MACH-NC study, patients whose treatment included a surgical option were different from patients treated only with radiotherapy. On 16 275 patients included in this analysis, 5 352 (32.9 %) had surgery as loco regional treatment. These patients had significantly lower stage tumors (48% stage IV versus 65% for radiotherapy patients, $p < 0.0001$) and had more frequently a tumor located in the oral cavity (33% versus 21% for radiotherapy patients, $p < 0.0001$). Age, sex, and performance status were also different. There is strong evidence that in clinical trials included radiotherapy and surgery population differ.

Choosing the surgical option to treat a patient will also affect the global treatment strategy. Timing of chemotherapy can be modified because surgery may cause a delay. The choice between adjuvant or neo adjuvant treatment can be different. Timing is also different as concomitant chemotherapy is not possible with surgery. Finally, if radiotherapy and surgery are combined, indications and effects are different whether surgery or radiotherapy comes first or second. An analysis of the addition of chemotherapy in patients with surgical strategies would be interesting to specify its benefits and disadvantages.

The important number of patients included in the MACH-NC database allows us to perform this analysis with adequate statistical power to detect a small benefit of chemotherapy in the subgroup of operated patients.
The analysis will be based on the first update of MACH-NC database, regrouping 93 randomized clinical trials for which patient individual data are available. Both published and unpublished trials will be included to avoid the publication bias (positive results are more likely to be published). Individual data includes patient baseline characteristics, treatment allocation and description, survival information and adverse effects. Follow up is updated if possible.

The aim of the study is to re-evaluate previous results regarding the benefit of chemotherapy in HNSCC in operated patients to improve their treatment strategy.

OBJECTIVES

The main objective is to assess the role of chemotherapy, adjuvant or neo-adjuvant, with surgery in the treatment of head and neck squamous cell carcinoma by studying the difference in overall survival for the following comparison:

Loco regional treatment including surgery

Loco regional treatment including surgery + Chemotherapy (induction, concomitant with radiotherapy or adjuvant)

Secondary objectives

- Comparison between the two arms on secondary endpoints :
    - Event-free survival
    - Early deaths (death for any cause within 6 months after surgery)
    - Time to loco-regional (without distant failure) and distant failure (with or without locoregional failure)
- Description of chemotherapy compliance.
- Investigate interaction between trial characteristics and treatment effect. The trial characteristics studied will be :
    - Chemotherapy timing (preoperative/neo-adjuvant, postoperative/adjuvant or concomitant to post-operative radiotherapy)
    - Post-operative-radiotherapy or not, if not confounded with chemotherapy timing
    - Type of chemotherapy drugs.
    - Extension of surgery.
- Interaction between patient's characteristics (e.g. age) and treatment effect.

TRIALS SELECTION CRITERIA

All trials satisfy the MACH-NC2 inclusion criteria and other specific criteria for this study identified by (*):

Trials must:

- Compare surgery plus chemotherapy to surgery without chemotherapy. (locoregional treatment for MACH-NC2)
- Be randomized in a way that precludes prior knowledge of treatment assignment.
- Have completed accrual before 31/12/2000.
- Include patients with squamous cell carcinoma of the larynx, oropharynx, hypo pharynx, or oral cavity.
- Not include patients with metastatic disease.
- Have included more than 60 patients. (*)
- Not propose pre-operative radiotherapy, but trials with postoperative radiotherapy are eligible. (*)
- Not propose organ preservation for larynx tumors.
- Allow individual identification of the loco regional treatment. (*)

Patients should:

- Not have undergone prior surgery.
- Not have received prior chemotherapy except in trials with induction CT in both arms that randomized after induction phase the addition or not of another timing of chemotherapy.
- Have undergone curative surgical treatment. (*)

TRIAL SEARCH

Data collection protocol is the same used in the MACH-NC update published in 2009 (8). Data from all published and unpublished randomized trials making the comparisons described in the study, in HNSCC patients were 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 took part in the meta-analysis were asked to help identify more trials.

From this general database only trials including a surgical treatment will be included for analysis (see trials flow chart, appendix 2). All articles included in MACH-NC 2, were reviewed. First round of selection selected all trials comparing a control group (patients with loco regional treatment that includes surgery) with at least one arm of the same loco-regional treatment with chemotherapy before or after surgery. Second round of selection excluded trials according to selection criteria presented above. Regarding trials where surgical patients were mixed with radiotherapy alone patients, we only included trials where more than 50% of patients had surgery.

DESCRIPTION OF THE TRIALS INCLUDED

Appendix 3 describes all trials evaluating the addition of chemotherapy before or after loco-regional treatment with surgery. Inclusion period trials range from 1965 to 2000.

We identified 24 trials (25 comparisons), representing 5 000 patients that potentially may be included in the meta-analysis. Trials can be classified according to two main criteria:

- Adjunction of adjuvant radiotherapy to the loco regional treatment (with or without concomitant chemotherapy)
- Timing of the chemotherapy (adjuvant or neo-adjuvant)

CRITERIA OF EVALUATION

ENDPOINTS

Main endpoint will be overall survival because of its reliability and importance in oncology. If possible the cause of death will be studied.
Secondary endpoints will be event-free survival, early mortality, local and distant control, and chemotherapy compliance. Individual data for chemotherapy compliance are limited: chemotherapy yes/no or number of cycles of chemotherapy.
Event-free survival (EFS) was defined as the time from randomization to the first event (locoregional, distant recurrence or progression, or death from any cause).

PROGNOSTIC FACTORS

The following individual prognostic factors will be considered:

- Sex (male or female)
- Age in class (<50, [50-60[, [60 and more)
- Performance status (WHO or equivalent: 0,1,2 and more)
- Primary tumor site (larynx, oropharynx, hypo pharynx, oral cavity)
- Stage (I-II, III, IV)

The following trial factors will be also considered:

- Type of chemotherapy drugs
- Timing of chemotherapy
- Post-operative-radiotherapy or not, if not confounded with chemotherapy timing
- Neck dissection strategy
- Surgical margins strategy for induction trials (i.e. the tumor size before or after chemotherapy induction)
- Planned number of chemotherapy cycles and possibility of early loco-regional treatment for non-responding patients in induction trials.

DATA COLLECTION AND QUALITY CONTROL

For each eligible trial, the main investigator provides the individual data of patient included. The following characteristics are routinely collected for all randomized patients:

- Age
- Sex
- Primary tumor location
- Performance status
- TNM staging
- Date of randomization
- Allocated treatment
- Extension of tumor and neck surgery
- Type of chemotherapy drugs
- Timing of chemotherapy
- Chemotherapy received (yes/no) and if possible number of cycles received
- Type of radiotherapy (trial level)
- Radiotherapy dosage and fractions (trial level)
- Date of last follow up
- Survival status
- Cause of death
- Date of loco-regional failure
- Date of distant failure
- Whether patient was excluded from the trial and reason of exclusion

STATISTICAL ANALYSIS PLAN

Method used will be similar to the one used in the previous meta-analyses (8,12) . Median follow up will be analyzed using the inversed Kaplan Meier (Schemper's method).
All randomized patients will be included in an intent-to-treat analysis. Survival distribution will be compared using a stratified (by trial) log rank test based on a fixed effects model. Pooled hazard ratio of deaths will be calculated using Peto's estimation and reported in a forest plot. Survival curves will be obtained by Peto's method, taking in account stratification and variation over time. Absolute benefit of chemotherapy will be estimated using Peto's method and as secondary method restricted mean survival difference at 5-years.

Survival analyses will be performed for the primary endpoint (overall survival) and for secondary endpoints (event-free survival, time to early death, time to loco-regional failure, and time to distant failure).
Statistical heterogeneity will be tested using the Cochran test for heterogeneity and Higgins I^2 test will be used to evaluate trials consistency (13,14). In case of significant heterogeneity ($p<0.10$), sensitivity analyses will be performed to search for its source. Other sensitivity analyses excluding small trials, old trials and trials with short follow up will be performed. Interaction between treatment effect and individual covariates will be studied using multivariate stratified (by trial) Cox model. Interaction test will be considered as significant if $p <0.10$. Proportional hazard assumption will be assessed par Grambsch and Therneau's test.

If heterogeneity may not be explained, a random effect model may be used (15). Patient's characteristics and secondary outcome distributions will be compared using Chi^2 test.
All tests (other than heterogeneity and interaction tests) will be two sided with a 5% type one error probability level.

PUBLICATIONS 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 1: Population analysis in MACH-NC 2

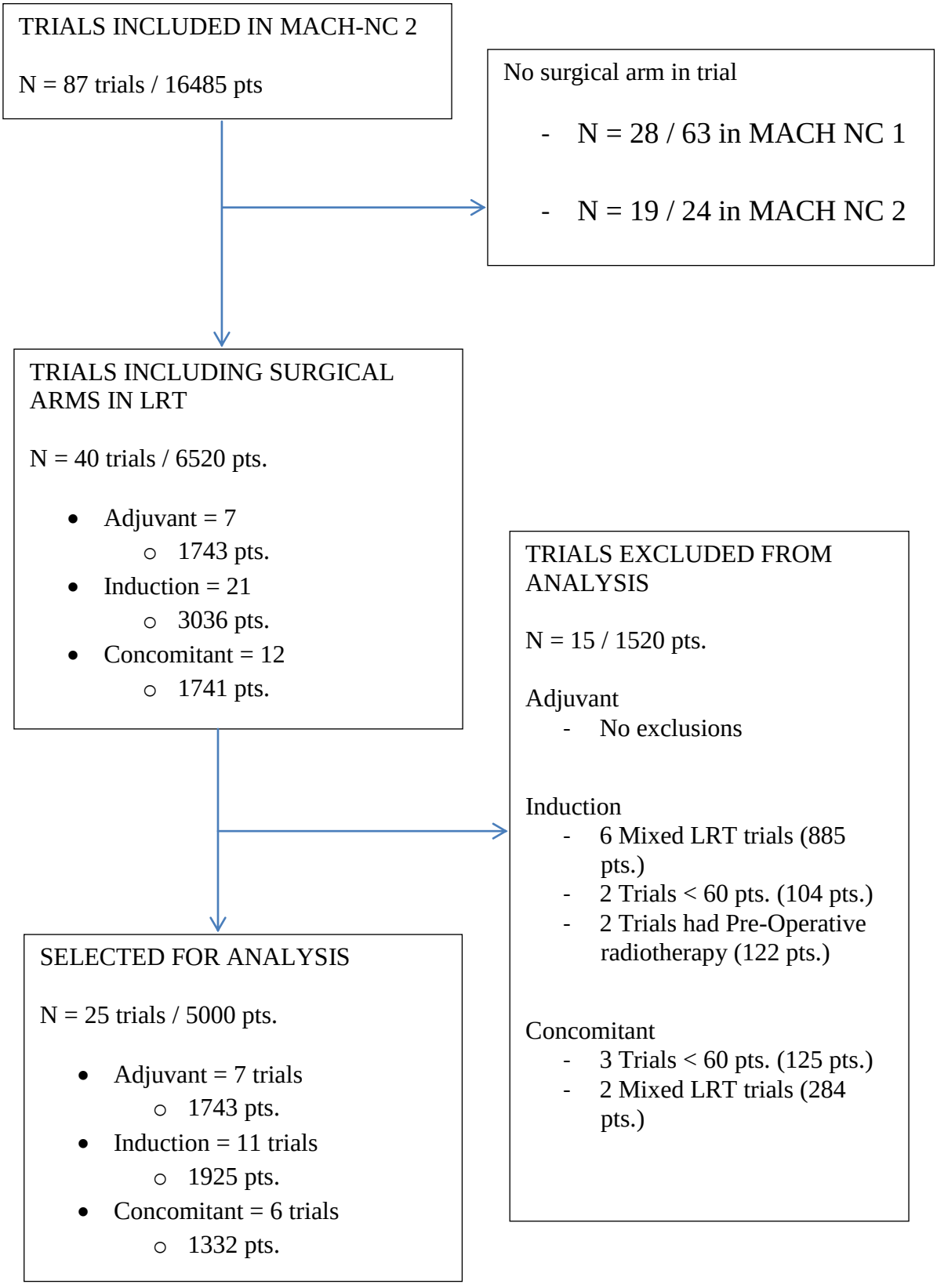
Comparison of patients' characteristics between trials with and without surgery

		SURGERY[a] N=5352	NO SURGERY N=10 923	p - value
Sex	**Male**	4539 (84.8)	8713 (80)	< 0.0001
	Female	793 (14.8)	1869 (17)	
	Missing	20 (0.4)	341 (3)	
Age	**< 50**	1218 (23)	2378 (22)	< 0.0001
	[50-60[	1978 (37)	3672 (34)	
	[60-70[	924 (17)	1909 (17)	
	≥70	1060 (20)	2593 (24)	
	Missing	172 (3)	371 (3)	
PS	**0**	1960 (37)	3557 (33)	< 0.0001
	1	1110 (21)	4113 (38)	
	2 and more	111 (2)	903 (8)	
	Missing	2171 (40)	2350 (21)	
Site	**Oral cavity**	1749 (33)	2303 (21)	< 0.0001
	Oropharynx	1376 (26)	4205 (39)	
	Hypopharynx	1024 (19)	1607 (15)	
	Larynx	928 (17)	2111 (19)	
	Others	245 (4)	596 (5)	
	Missing	30 (1)	101 (1)	
Stage	**I-II**	550 (10)	763 (7)	< 0.0001
	III	1904 (36)	2760 (25)	
	IV	2550 (48)	7053 (65)	
	Missing	348 (6)	347 (3)	
T-stage	**0-2**	1601 (30)	2228 (20)	< 0.0001
	3	2185 (41)	3917 (36)	
	4	1207 (23)	4391 (40)	
	Missing	359 (7)	387 (4)	
N-stage	**0**	1989 (37)	3402 (31)	< 0.0001
	1	1264 (24)	2128 (19.5)	
	2	1296 (24)	3143 (29)	
	3	470 (9)	1908 (17.5)	
	Missing	333 (6)	333 (3)	
Timing	**Adjuvant**	1743 (33)	824 (7)	< 0.0001
	Induction	2152 (40)	2261 (21)	
	Concomitant	1457 (27)	7838 (72)	

Analysis on compared patients in the MACH NC 2 analysis (17 493)
Patients included in trials were radiotherapy or surgery could be used as loco regional treatment were excluded (1218)
(a) the 5352 patients in the surgery group includes the 5000 patients included in the meta analysis and the 352 patients included in small trials or in pre-operative radiotherapy trials (excluded in this meta-analysis)

APPENDIX 2: TRIAL FLOW CHART

Figure 1: Trial selection flow chart.
See appendix 4 for the list of abbreviations. The initial 16 485 patients are the patients included in the different trials. After duplication of control arms in multiarm trials, there are 17 493 patients included in the MACH-NC 2 analysis. However there is no duplication in trials included for this meta-analysis.



APPENDIX 3: TRIAL DESCRIPTION

Name (ref)	Accrual period	Sites ††	Nb Pts	Stage	Drug ††	Dose of CT	LRT	Radiotherapy	Tumor surgery ††	Neck Surgery ††	Timing of CT	Median follow up (years)
GETTEC adj (1) ¶	1983 – 1985	OC OP HP L O	286	I to IV	B C Mx	3 cycles /21d 15 mg d3, 4, 5 150 mg d1 100 mg d2 + 5 cycles Mx 100 mg /mth B 15 mg x 2 /mth	S+RT	50 Gy/5 wks ± 15 Gy Boost /2wks if R+	RS Accept R+	RND EC+ only	ADJ	8.9
HNU-87b** (2) †	1987 – 1990	OC OP HP L, O	424	II to IV	U (po)	300 mg/d x365	S	None	RS	NS	ADJ	4.2
Int0034 (3) ¶	1985-1990	OC OP HP L , O	499	II to IV	C F	3 cycles 100 mg/m^2 d1 1 g/m^2 /24h d1-5	S+RT	50 Gy 1.8-2Gy/frac +/- boost 10 Gy if High risk	RS R0 only	RND if N+ MND if N0 * +/- bilateral	ADJ	8.2
JHCFUS (4) †	1985 – 1989	OC OP HP L, O NP CUP	191	I to IV	Hc (po)	300-600 mg /d x 84	S	None	NS	NS	ADJ	2.9
KKD-86 (5) †	1986 – 1989	OC NP	112	I to IV	U (po)	400 mg/d x365	S	None	NS	NS	ADJ	6.9
TMHR-4 (6)	1987-1989	OC	135	III IV	Mx	50 mg/m^2 d3-d10-d17	S	None	RS R0 only	MND if N0 RND if N+	ADJ	1.3
Pitie-74 (7)	1974 – 1978	OC	96	II to IV	B Mx LA	30 mg/wks. x 15 400 mg/mth x24 100 mg/wks. x24	S[1] S+RT	NS	NS	NS	ADJ	5.6
AHNTG (8)	1986 – 1993	OC OP HP L, O	149	II to IV	C F	Every 3wks x3 100mg/m^2 d1 1g/m^2 d1-4	S[2] S+RT	NS	Undefined margins	NS	IND	6.9
GETTEC neo2 (9)	1986 – 1992	OP	143	II to IV	C F	Every 3 wks x3 100 mg/m^2 d1 1 g/m^2 d1-5	S+RT	10 wks. post op 50 Gy/7wks +/- 15 Gy Boost 2 Gy/frac	RS Initial Margins	MND if N0 and < 3 cm Else RND	IND	12.0

Name (ref)	Accrual period	Sites ††	Nb Pts	Stage	Drug ††	Dose of CT	LRT	Radiotherapy	Tumor surgery ††	Neck Surgery ††	Timing of CT	Median follow up (years)
BNH003 (10)	1990 – 1992	OC OP	124	III IV	C F	3 cycles every? 100 mg/m^2 d1 1 g/m^2 d1-4	S +RT	45/60 Gy 2Gy/frac	Undefined margins	NS	IND	3.7
Cologne (11)	1988 – 1993	OC OP HP	97	II to IV	Cb F	Every 4wks x 1-3 360 mg/m^2 d1 1g/m^2 d1-5	S +RT	60-66Gy/6-7 wks 48 Gy on N- 2 Gy/frac	Accept R+ Initial margins	MND if N0 RND if N+ +/- bilateral	IND	2.0
Creteil-82 (12)	1982 - 1987	OC OP	122	II to IV	B C F Mx LA	3 c / every 4wks 10 mg/m^2 d1-5 120 mg/m^2 d4 600 mg/m^2 120 mg/m^2 10 mg/6h	S+RT [4]	55 Gy/70 Gy /6 wks RTAlone : 45 Gy on N 70 Gy on T 1.8 Gy/frac	RS Undefined margins	NS	IND	5.0
EORTC 24844 (13) ¶	1985 – 1991	OP	139	II to IV	C F	3c every 3wks 100 mg/m^2 d1 1g/m^2 d1-5	S +RT	50 Gy/5 wks 2g/frac 14 Gy Boost if R+/ EC+/3 N+	RS Initial Margins	RND if N+ MND if N0	IND	2.8
GSTTC86po ** (14)	1983-1990	OC OP HP	66	III IV	C F	4c every 3 wks 100 mg/m^2 d1 1 g/m^2 d1-5	S +RT	45-50 Gy 2 Gy/frac	RS Initial margins	NS	IND	11.3
SWOG8006 (15)	1980 – 1985	OC OP HP L	167	II to IV	B C Mx Vc	3 c every 3 wks 15u/m^2 d1 d8 50 mg/m^2 d1 40 mg/m^2 d1 2 mg d1	S+RT	NS	Initial margins	NS	IND	13.7
EORTC 24771 ¶ (16)	1977-1982	HP L	231	II to IV	B Mx Vc	1c 15 mg 20 mg/m^2 d2-3 1.5 mg/m^2 d1	S +RT	50 Gy 15 Gy boost if R+/EC+	RS Undefined margins	RND only	IND	5.9
EORTC78-OCP (17)	1978 – 1984	OC OP	225	I to IV	B (ia) Vc (ia)	1c 15 mg d1-12 1 mg d1/5/9	S [3] S+RT	Optional RT Mean dose 55 Gy on T and N	Undefined margins	NS	IND	4.9
HNCP‡ (18) ¶	1978 – 1982	OC HP L	462	II to IV	B C	1c 15 mg/m^2 d3-7 100 mg/m^2 d1 Maintenance : 80 mg/m^2/mth x6	S +RT	50 Gy/5wks 10 Gy boost if R1/EC+ 20 Gy boost if R2	Initial margins	RND if N+ MND* if N0	IND	5.3

Name (ref)	Accrual period	Sites ††	Nb Pts	Stage	Drug ††	Dose of CT	LRT	Radiotherapy	Tumor surgery ††	Neck Surgery ††	Timing of CT	Median follow up (years)
Toulouse (19)	1984-1988	OC OP HP L O	90	III IV	C	7-9 c (every wks) 50 mg/d	S+RT	54 Gy /5-6 wks 65-70 Gy if R1/EC+ 1.7 – 2 Gy/frac	NS Accept R+	NS Accept EC +	CONC	8.9
Yale80po** (20)	1980 – 1986	OC OP HP L	78	II to IV	Mi	1 or 2c 15mg/m^2 d5	S+RT	50 Gy 6 Gy boost if R+ 1.8-2 Gy/frac	NS	NS	CONC	13.3
EORTC 22931 (21) ¶	1994 – 2000	OP OC HP L, O	334	I to IV	C	D1-22-43 100 mg/m^2	S+RT	54Gy / 5.5 wks 12 Gy boost 2Gy/frac	RS Accept R+	RND if N3 MND if N0-N2 Include EC- and EC+	CONC	5.0
LOHNG97 (22)	1997 – 2001	OC OP HP L, O	114	III IV	B Mi	5mg x 2/wks 15 mg/m^2 x 1	S+RT	54-56 Gy 64-70 Gy boost if R+ 2 Gy/frac	RS Accept R+	RND if N3 MND if N0/+	CONC	2.3
RTOG 9501 (23) ¶	1995 – 2000	OC OP HP L, O	459	I to IV	C	D1-22-43 100 mg/m^2	S+RT	60/66 Gy /6wks 2Gy/frac	RS Accept R+	MND Include EC- and EC+	CONC	4.0
UKHAN1po 1** (24) ¶	1990-2000	OP OC HP, L NP, O	195	I to IV	Mx	D1-14 100mg/m^2	S+RT	Center based 50-60 Gy 1.8 – 2.75/frac	RS Accept R+	ND	CONC	4.8
UKHAN1po 2** (24) ¶	1990 – 2000	OC OP HP, L NP, O	62	II to IV	Vc B Mx F	1.4mg/m^2 30 mg 100mg/m^2 500mg	S+RT	Center based 50-60 Gy 1.8 – 2.75/frac	RS Accept R+	ND	CONC	4.5

*No neck dissection for T3N0 glottic or supraglottic or floor of the mouth and T4N0 median supraglottic; ** Part of a larger trial; †Article in Japanese; ‡ HNCP is a 3 arm trial : LRT alone, Induction + LRT, Induction + LRT + Maintenance therapy; ¶ Protocol available; (1) S= 75% S+RT = 25%; (2) S= 24% S+Rt = 76% ; (3) S=30% S+RT=70%; (4) S+RT = 59% RT = 41%;

†† Abbreviations : RS = Radical Surgery; RND = Radical Neck Surgery; MND = Modified Neck Surgery; NS = Not Specified; S = Surgery; RT = radiotherapy; OC = Oral Cavity,; OP = Oropharynx; L = Larynx; HP = Hypopharynx; NP = Nasopharynx; O = Others; C = Cisplatin; Mx = Methotrexate; B = Bleomycin; Vc = Vincristine; Mi = Mitomycin; F = 5 fluoro-uracil; Cb = Carboplatin; U =UFT (tegafur + uracil); HC = hecycarbonyl 5 fluorouracil, wks = weeks, pts = patients, EC extra capsular extension; R+ : margin of resection with invasive cancer, frac : fraction

APPENDIX 4: LIST OF ABREVIATIONS

List of abbreviations

HNSCC	Head and Neck Squamous Cell Carcinoma
S	Surgery
CT	Chemotherapy
RT	Radiotherapy
Nb	Number
C	Cycle
Gy	Gray
wks	weeks
mth	month
d	day
pts	patients
po	post-operative
Frac	fraction

Site

OC	Oral cavity
OP	Oropharynx
HP	Hypopharynx
NP	Nasopharynx
L	Larynx
S	Sinus
O	Other
U	Unknown

Surgery

N+	Positive node
M+	Surgical margin positive
R+	Invaded surgical margins
R0	Tumor free surgical margins
EC+	Extra nodal capsular spread
RND	Radical neck dissection

MND	Modified neck dissection
RS	Radical surgery
ND	Neck dissection

Study or Group names

MACH-NC	Meta-Analysis of Chemotherapy in Head and Neck Cancer
MACH-NC2	first update of MACH-NC
MACH-NC3	second update of MACH-NC
EORTC	European Organisation for Research and Treatment of Cancer
INT	US INTergroup trial
RTOG	Radiation Therapy Oncology Group
SWOG	Southwest Oncological Group
HNCP	Head and Neck Cancer Program
GETTEC	Groupe d'Etude des Tumeurs de la Tête Et du Cou
HNU	Head and Neck UFT Study Group
KKD	The Oral Surgery Malignant Tumor Research Association in Kanto Kohshinetsu District
UKHAN	United Kingdom Head and Neck (UKCCR head and Neck Collaborative Group)

Chemotherapy

B	Bleomycin
C	Cisplatin
Cb	Carboplatin
F	5-Fluorouracil
FA	Folinic Acid
LA	Leucovorin Acid
Mi	Mitomycin
Mx	Methotrexate
U	UFT (Tegafur + uracil)
Hc	HCFU (carmofur)
Vc	Vincristine

APPENDIX 5: References of the included trials

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