Surrogate endpoints for overall survival in locally advanced head and neck cancer

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Secretariat

Stefan Michiels
Biostatistics and Epidemiology Unit,
Institut Gustave Roussy,
94805 Villejuif cedex, France
Tel : +33 (0)1 42 11 49 55
michiels@igr.fr

Jean Pierre Pignon
Biostatistics and Epidemiology Unit,
Institut Gustave Roussy,
Villejuif, France
Tel : +33 (0)1 42 11 45 65
pignon@igr.fr

Jean Bourhis
Department of Radiotherapy,
Institut Gustave Roussy,
Villejuif, France

Aurélie Le Maître
Biostatistics and Epidemiology Unit,
Institut Gustave Roussy,
Villejuif, France

Advisory board

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Introduction

Head and neck squamous cell carcinomas (HNSCC) are frequently occurring tumors with 76 800 new cases (oral cavity, pharynx, and larynx) in 1998 within the European Community[1] and 46 000 new cases in 2002 within the United States[2]. In 2002, the estimated number of new cases worldwide was 644 000[2]. In oral cavity and pharynx carcinoma, at least 40 % of patients have locally advanced disease at diagnosis[3]. Surgery and/or radiation therapy are standard modalities used to achieve locoregional control[4]. Despite of this therapeutic approach, the prognosis of HNSCC patients remains poor : the 5-year relative survival rate in USA for the period 1989-1995 was around 45% in white people with locally advanced disease.

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[5,6], a meta-analysis based on individual patients data pooled the results of the randomized trials performed between 1965 and 2000 and compared locoregional treatment to locoregional treatment plus chemotherapy. The overall pooled relative risk was 0.88 corresponding to an absolute benefit of 4% for chemotherapy at 5 years. There was a significant interaction ($p<0.0001$) between chemotherapy timing and treatment.

In recent years, considerable interest has also been raised about non conventional fractionation schedules in radiation therapy for HNSCC. Two types of altered fractionation have been studied:

- 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. By this means, the total dose to the tumor was allowed to increase.
- 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 locoregional control rate, which may ultimately result in a benefit in overall survival. The individual patient data Meta-Analysis of Radiotherapy in Carcinomas of Head and neck, MARCH[7], aimed to evaluate the role of modified fractionation on the survival of patients with HNSCC. This analysis showed that there was a significant (HR = 0.92, p = 0.003) survival benefit with hyperfractionated and/or accelerated radiotherapy, corresponding to an absolute benefit of 3.4% at 5 years. The benefit was significantly (p = 0.02) higher with hyperfractionated radiotherapy (8% at 5 years) than with accelerated radiotherapy.

The gold standard endpoint to measure the effect of treatment of head and neck cancer is overall survival because of the simplicity to measure, the facility to interpret and the reliability of the measurement. The overall survival at 5 years is usually used to permit a global assessment of long term benefits and toxic effects of the treatment. The disadvantage of this endpoint is that it required a lot of patients and an extended follow-up.

Our objective was to study if event-free survival or time-to-locoregional control could be good surrogate endpoints to study the effect of the treatment of locally advanced head and neck cancer. Event-free survival is defined as the time from randomization to the first event (locoregional, distant recurrence or death). The time-to-locoregional control is defined as the time from randomization to the first locoregional event. Using event-free survival or time-to-locoregional control at an early time point as endpoint in clinical trials would permit to decrease the duration and cost of the development of new drug in the head and neck cancer field.

Objectives

The first aim of this project is to evaluate if event-free survival or time-to-locoregional control as surrogate endpoint for overall survival to quantify effects of treatment in head and neck cancer in using data of the two individual patient data meta-analyses MACH-NC and MARCH.

The secondary objective of this analysis is to show that event-free survival is a better surrogate endpoint for overall survival than time-to-locoregional control.

The validation of the surrogate endpoint modeling will be done on recent trials not included in these meta-analyses.

Description of "historical trials" included

Appendix A-1 describes the trials comparing **concomitant** chemotherapy added to a locoregional treatment to a locoregional treatment alone, included in the **MACH-NC** meta-analysis. Fifty trials including 9 471 patients were identified.

Trials have been separated in two categories:

- *trials including patients during the period 1965-1993*
- *trials including patients during the period 1994-2000*

Appendix A-2 describes the trials comparing **neoadjuvant** chemotherapy added to a locoregional treatment to a locoregional treatment alone, included in the **MACH-NC** meta-analysis. Thirty one trials including 5 269 patients during the period 1965-1993 were identified.

Appendix A-3 describes the trials comparing **adjuvant** chemotherapy added to a locoregional treatment to a locoregional treatment alone, included in the **MACH-NC** meta-analysis. Nine trials including 2 567 patients were identified.

Trials have been separated in two categories:

- *trials including patients during the period 1965-1993*
- *trials including patients during the period 1994-2000*

Appendix A-4 describes the trials altered fractionated radiotherapy to standard radiotherapy included in the **MARCH** meta-analysis. Fifteen trials including 6 515 patients during the period 1979-1999 were identified.

Trials have been separated in three categories :

- *trials with hyperfractionated radiotherapy*: this group tested the effect of increasing the total dose with hyperfractionation, allowing the delivery of a higher total dose in the same overall time, as compared to the reference arm;
- *trials with accelerated radiotherapy without total dose reduction*: this group represented a pure test of the effect of accelerating RT, while keeping the total dose the same ;
- *trials with accelerated radiotherapy with total dose reduction*: this group tested the effect of markedly reducing the overall time, while the total dose was also reduced.

Note that we exclude trials which had no recorded recurrences: one trial in the neoadjuvant chemotherapy meta-analysis (680 patients), and one trial in the adjuvant

chemotherapy one (499 patients). We also exclude two small trials (58 and 27 patients) from the same center in the concomitant chemotherapy meta-analysis, in which all patients have dead within 2 years after randomization.

Eligibility criteria of "validation trials"

In the framework of updating the MACH-NC and MARCH meta-analyses we will collect individual patient data of recent trials.

Analysis on chemotherapy effect on head and neck cancer
Trials used for validation will be recent trials analyzing the effect of adding a chemotherapy to a loco-regional treatment in locally advanced head and neck cancer.

Analysis on altered fractionated radiotherapy effect on head and neck cancer
Trials used for validation will be recent trials comparing conventional radiotherapy with accelerated or hyperfractionated radiotherapy or both in locally advanced head and neck cancer.

Statistical methods

Event-free survival is defined as the time from randomization to the first event (locoregional, distant recurrence or death). Patients without documented evidence of an event are censored at the date of last follow-up.

The time-to-locoregional control is defined as the time from randomization to the first locoregional event. Patients with distant recurrence or death are censored at the dates of distant recurrence or death respectively, patients without documented evidence of distant recurrence or death are censored at the date of last follow-up.

Separate analyses will be performed for (a) the trials assessing the treatment effect of adding a concomitant chemotherapy to radiotherapy alone (the concomitant MACH-NC trials), for (b) the trials assessing the treatment effect of adding a neoadjuvant chemotherapy to radiotherapy alone (the neoadjuvant MACH-NC trials), for (c) the trials

assessing the treatment effect of adding a adjuvant chemotherapy to radiotherapy alone (the adjuvant MACH-NC trials), and for (d) the trials assessing the effect of non-conventional fractionation schedules as compared to a standard schedule (the MARCH trials).

We will use a correlation approach to assess the validity of event-free survival or time-to-locoregional control as a surrogate for survival[8]. This approach has already been used by Buyse et al[9] to assess the relationship between progression-free survival and overall survival in advanced colorectal patients, and by Sargent et al[10] to investigate the relationship between disease-free survival and overall survival in the adjuvant setting of colon cancer. We will investigate in exploratory analyses if the correlation values are stronger according to age (<65 vs. ≥65), tumour stage (I, II vs. III, IV) and tumour site (larynx vs. non-larynx).

Trial level surrogacy

A linear regression model will be used to quantify the correlation between the effect of the treatment on overall survival and the effect of the treatment on event-free survival and time-to-locoregional control. Treatment effects are estimated by log hazard ratios. The linear regression model will be weighted by the trial size or adjusted for measurement error if more appropriate. If the coefficient of correlation R estimated by this model is closed to 1, we will consider that risk reduction for overall survival is strongly correlated with risk reduction for event-free survival or time-to-locoregional control. We will also test the correlation between effect of treatment on overall survival at 5 years and effect of the treatment on event-free survival or time-to-locoregional control at 2 or 3 years (the choice between the optimal cut-off at 2, or 3 years will be based on the observed event rates in the first years for each of the two endpoints).

Individual surrogacy

The association between distribution of the reference endpoint (overall survival) and the surrogate endpoint (event-free survival or time-to-locoregional control) will be evaluated by a bivariate survival model[11-12]. If the correlation coefficient ρ estimated by this method is close to 1, we will consider that there is a strong correlation between overall survival and the surrogate endpoint. The same analysis will be done with overall survival at 5 years and event-free survival and time-to-locoregional control at 2 or 3 years.

Correlation coefficient

The surrogate endpoints event-free survival and time-to-locoregional control will be acceptable only if their respective correlation coefficients ρ and R are close to 1[12]. We will compare if event-free survival is a "better" surrogate for overall survival than time-to-locoregional control by using a confidence interval approach for the correlation values.

Surrogate threshold

Based on our linear model we will calculate the surrogate threshold effect (STE)[13], defined as the minimum treatment effect on the surrogate (event-free survival or time-to-locoregional control) necessary to predict a non-zero effect on overall survival.

Validation strategy 1: Internal validation

We will apply a leave-one-out-crossvalidation strategy on the n historical trials as follows: each trial will be left out once and at each leave-one-out step the linear model will be completely rebuilt from scratch on the n-1 other trials, the model will be applied to the left-out-trial so that we can compare the predicted and observed treatment effect (log(HR)) on overall survival of the left-out-trial.

Validation strategy 2: External validation

Coefficients of the models estimated on historical trials will be used to obtain prediction limits for the treatment effects on overall survival in the validation trials, based on the treatment effects on event-free survival or time-to-locoregional control observed in the validation trials. The observed treatment effects on overall survival will be checked for agreement with the prediction limits.

Working parties in this study

Three groups with specific functions have been created :

1) the Secretariat
2) the Advisory Board
3) Investigators Group

The Secretariat is in charge of the coordination of the study. 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 Investigators Group consists of investigators of the trials who have provided individual patient data.

Practical considerations

The first part of this study, the analysis of surrogate endpoints in MARCH and MACH-NC meta-analyses will be done in the near future (when the databases are available). The validation of the model, which takes more time because of the collection of data, will be realized in a longer term when the meta-analyses will be updated.

All trial data will be held securely and will not be used, circulated or distributed in any way that allows access to individual trial data, without first seeking permission from trial investigators.

Publication policy

The Secretariat will prepare the manuscript and will submit it for revision to the Advisory Board. Any publication arising from this project will be made in the name of the group (Secretariat and Advisory Board) and include a list of all investigators responsible for trials included in this study.

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Appendix A – Description of historical trials

Table A-1 : **Description of trials comparing locoregional treatment versus locoregional treatment plus concomitant chemotherapy**

Trials	Inclusion period	Sites	Stage	Median follow up	Patients analysed / randomised
Inclusion between 1965 and 1993					
UW-77	1977-78	OC,OP,HP,NP,L	III,IV	*	58/58
MDA-70	1970-72	OC,OP,HP,NP,L,O	III,IV	*	36/42
WIA-OC5a [$]	1971-72	OC	III,IV	23.9	50/50
UW-79	1979-80	OC,OP,HP,NP,L	III,IV	*	27/27
NRH-78	1978-81	OC,OP,HP,NP,L,O	II to IV	14.5	222/222
Turku	1975-79	OC, HP,L,O	I to IV	18.1	46/46
Manchester	1979-84	OC,OP,HP,NP,L	I to IV	13.9	313/313
EORTC73-OC	1973-75	OP	II to IV	7.0	199/226
Barcelona [a]	1978-88	OC,HP, NP, L,O	III,IV	12.8	573/600
ECOG2382	1982-87	OC,OP,HP,NP,L,O	I to IV	9.1	371/371
Ontario	1987-91	OC,OP,HP,L	III,IV	5.7	175/175
RT-BLM-73 [$]	1973-76	OC	II,III	10.7	46/46
PMHCGS [$]	1982-86	HP,L	I to IV	10.0	212/212
INRCHN-8 [$]	1987-90	OC,OP,HP,NP,L	II to IV	5.1	157/157
Bergen	1973-75	OC,OP,NP,L,O	I to IV	21.1	32/32
Toulouse	1984-88	OC,OP,HP,L,O	I to IV	8.9	90/90
CH-7401	1985-90	OC,OP,HP,L,O	II to IV	5.9	62/62
Bavaria89	1989-93	OC,OP,HP,L	III,IV	1.6	298/298
LOHNG91	1991-93	OC,OP,HP,O	III,IV	10.9	64/64
WIA-OC5b [$]	1972-73	OC	III,IV	21.4	79/79
Kragujevac [b]	1988-91	OC,OP,HP,NP,L	III,IV	4.8	159/159
WIA-OC5c [$]	1974-75	OC	III,IV	19.3	40/40
AC Camargo [c]	1984-86	OC,OP,HP	IV	9.6	60/60
Yale80	1980-86	OC,OP,HP,NP,L	II,III,IV	12.9	120/120
Yale86	1986-92	OC,OP,NP,HP,L,O	I to IV	6.1	83/83
SecogII [$,d]	1984-89	OC,OP,HP,NP,L,O	III,IV	13.2	155/155

*****: all patients dead
a: third arm with bifractionnated RT not eligible
b: three-arm trial with 2 chemotherapy arms
c: three-arm trial with a neoadjuvant arm
d: 3-arm trial with a neoadjuvant arm ; patients allocated to the chemotherapy arms were randomised to receive B/Mx/Vb or the same chemotherapy + F.
$ Confounded trial = trial using either a lower dose of radiotherapy or the same dose delivered in a longer time in the chemotherapy arm than in the control arm.

Table A-1 : **Description of trials comparing locoregional treatment versus locoregional treatment plus concomitant chemotherapy** (followed)

Trials	Inclusion period	Sites	Stage	Median follow up	Patients analysed / randomised
Inclusion between 1994 and 2000					
RPC 3250	1990-1995	OC, OP, L HP,	III, IV	8.8	100/100
Duke 90040	1990-1996	OC, OP, L, HP, NP, O	II to IV	7.5	116/120
IAR 92	1992-1995	OC, OP, L HP, O	III, IV	8.3	55/68
GORTEC 9401	1994-1997	OP	III, IV	5.3	222/226
Kragujevac2	1991-1993	OC, OP, L, HP, NP	III, IV	6.5	130/130
ORO-9301 [e]	1993-1998	OP	II to IV	6.7	121/127
Vienna [f]	1990-1997	OC, OP, L, HP	II to IV	5.9	158/158
Cologne 95	1995-1999	OP, HP	II to IV	4.7	240/263
INRC-HN-9	1992-1998	OC, OP, L, HP, NP	II to IV	4.3	136/143
ARO 95-6	1994-1999	OC, OP, HP	III, IV	5.0	373/384
IAEA-MMC [$]	1996-1999	OC, OP, L, HP	III, IV	2.8	478/478
SAKK 10-94	1994-2000	OC, OP, L HP	II to IV	4.0	224/224
EORTC 22931	1994-2000	OC, OP, L HP	I to IV	5.0	334/334
RTOG 9501	1995-2000	OC, OP, L HP, O	I to IV	4.0	416/459
GORTEC 9601	1996-2000	OC, OP, L HP, O	IV	3.3	109/109
NCI-V98-1416	1997-2000	OC, OP, L HP + P	II to IV	0.9	393/393
Lucknow	1990-1991	OC, OP, L HP	III, IV	4.8	38/38
HECOG 9405	1995-1999	OC, OP, L HP	II to IV	6.5	124/128
LOHNG97	1997-2001	OC, OP, L HP, O	III, IV	2.3	95/114
UKHAN [g]	1990-2000	OC, OP, L, HP, NP, O	I to IV	5.2	970/970
RTOG 9111 [h]	1992-2000	OP, L, O	II to IV	4.0	518/547
Int0126 [i $]	1992-1999	OC, OP, L, HP	III, IV	5.8	268/295
EORTC 22954 [$]	1996-1999	L, HP	II to IV	4.5	59/59
EORTC 22962 [j $]	1996-1999	OC, OP, L, HP	II to IV	4.1	57/57

e: patients of the third arm with hyperfractionated radiotherapy excluded
f: patients of third arm with conventional radiotherapy excluded
g : 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.
h : 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.
i : 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.
j : 4 arms trials, two arms with concomitant cisplatin and radiotherapy similar to the arms without chemotherapy (2x2 factorial design).
$ early closure because of low accrual.

List of abbreviations
OC = oral cavity, OP = oropharynx, HP = Hypopharynx, L = Larynx, P = Pharynx, O = Other;

Trial group abbreviations : AC Camargo = Hospital AC Camargo (Brazil), Aro = Academic Radiation Oncologists, CH = Chapel Hill (USA), ECOG = Eastern Cooperative Oncology Group (USA), EORTC = European Organisation for Research and Treatment of Cancer, GORTEC = Groupe d'Oncologie Radiothérapie Tête et Cou, HECOG = Hellenic Cooperative Oncology Group, IAEA = International Atomic Energy Agency, INRC-HN= Instituto Nazionale per la Ricerca sul Cancro-Head and Neck (Italy), INT= US INTer group trial, LOHNG = Ljubljana Oncology Head and Neck Group (Slovenia), MDA= MD Anderson (USA), NCI = National Cancer Institute, NRH = Norwegian Radium Hospital (Norway), Ontario = McMaster University and Cancer Care Ontario - Hamilton and Ottawa regional Cancer Centres (Canada), PMHCG = Princess Margaret Hospital Cooperative Group Study (Canada), RPC= Radiological Physics Center, RTOG = Radiation Therapy Oncology Group (USA), SAKK = Swiss Group for Clinical Cancer Research, SECOG = South-East Co-operative Oncology Group (England), Turku = Turku University (Finland), UKHAN = United Kingdom Head And Neck, UW =University of Washington Radiation Oncology ; WIA-OC = Cancer Institute (WIA) Oral Cavity (India).

Table A-2 : **Description of trials comparing locoregional treatment versus locoregional treatment plus neoadjuvant chemotherapy**

Trials	Inclusion period	Sites	Stage	Median follow up	Patients analysed / randomised
GETTECneo1	1986-91	OP	II to IV	12.3	174/174
IGR-65	1965-67	OC,OP	IV	23.9	36/39
RTOG 6801	1968-73	OC,OP,HP,L	III,IV	4.3	680/712
Pitié-81	1981-85	OC,OP,O	I to IV	11.3	112/116
HNCGIC02	1983-86	OC,OP,HP,L	II to IV	10.2	100/100
HNCGIC03	1986-89	OC,OP,HP,L	II to IV	7.2	108/108
Las Palmas	1987-89	OC,OP,HP,NP,L	III,IV	3.2	36/42
GETTECneo2	1986-92	OP	II to IV	12.0	144/144
Denver-77	1977-83	OC,OP,HP,O	III,IV	*	59/59
HNCP [a]	1978-82	OC,HP,L	II to IV	5.3	462/462
MCW-2	1983-86	OC,OP,HP,NP,L,O	III,IV	8.3	63/63
SWOG 8006	1980-85	OC,OP,HP,L	II to IV	13.6	167/167
Buenos Aires [b]	1981-86	OC,OP,HP,NP,L	III,IV	7.0	120/120
EORTC 24771	1977-82	HP	II to IV	5.9	231/231
EORTC 78-OCP	1978-84	OC,OP	I to IV	4.9	225/225
Créteil-86	1986-89	OC,OP,HP,L	II to IV	6.0	156/156
Créteil-82	1982-87	OC,OP	II to IV	5.0	122/131
HNAP-02	1989-92	OC,OP,HP,L	III,IV	5.2	50/50
Parma	1987-91	OC,OP,HP,L	II to IV	6.2	69/69
Rennes-87	1987-90	OP,HP	I to IV	6.4	133/133
EORTC 24844	1985-91	OP	II to IV	2.8	139/139
MCW-1	1979-82	OC,OP,HP,NP,L,O	III,IV	5.9	83/83
CFHNS [c]	1988-91	OC,OR,L,HP	II to IV	5.7	324/324
SHNG 85	1985-92	OC,OP,HP,L	II to IV	7.2	461/461
BNH 003	1990-92	OC,OP,HP,O	III,IV	3.7	124/124
AHNTG	1986-93	OC,OP,HP,NP,L,O	II to IV	7.1	280/280
Songkhla	1988-92	OC,OP,HP,O	III,IV	4.1	54/54
Cologne	1988-93	OC,OP,HP	II to IV	2.0	97/97
SECOGII [d]	1984-89	OC,OP,HP,NP,L,O	III,IV	12.5	163/163
AC Camargo [e]	1984-86	OC,OP,HP	III,IV	6.5	60/60
GSTTC-86	1986-90	OC,OP,HP,O	III,IV	11.3	237/237

***** 57 deaths / 59 patients
a : Three-arm trial with one neoadjuvant and one neoadjuvant. + adjuvant
b : Three-arm trial with 3 chemotherapy arms (A1, A2)
c : No surgery if complete response
d : Three-arm trial with a concomitant arm ; patients allocated to the chemotherapy arms were randomised to receive B/Mx/Vb or the same chemotherapy + F.
e : Three-arm trial with a concomitant arm

List of abbreviations
OC = oral cavity, OP = oropharynx, HP = Hypopharynx, L = Larynx, P = Pharynx, O = Other;

Trial group abbreviations : AC Camargo = Hospital AC Camargo (Brazil), AHNTG = Australian Head and neck Trial Group, BNH = B. Nanavati Hospital (India), CFHNS = Carboplatin French Head and Neck Study), EORTC = European Organisation for Research and Treatment of Cancer, GETTEC = Groupe d'Etude des Tumeurs de la Tête Et du Cou (France), GSTTC = Gruppo di Studio sui Tumori della Testa et del Collo (Italy), HNAP = Head and Neck Adjuvant Project (Japan), HNCGIC = Head and Neck Cancer Group of Institut Curie (France), HNCP = Head and Neck Contract Program (USA), IGR= Institut Gustave-Roussy (France), MCW = Medical College of Wisconsin (USA), RTOG = Radiation Therapy Oncology Group (USA), SECOG = South-East Co-operative Oncology Group (England), SHNG= Scandinavian Head and Neck Group, SWOG = Southwest Oncology Group (USA)

Table A-3 : **Description of trials comparing locoregional treatment versus locoregional treatment plus adjuvant chemotherapy**

Trials	Inclusion period	Sites	Stage	Median follow up	Patients analysed / randomised
Inclusion between 1965 and 1993					
HNU-87a	1987-90	OC,OP,HP,L,O	I,II	4.1	111/111
Pitié-74 [a]	1974-77	OC	II to IV	5.6	96/96
GETTECadj [b]	1982-85	OC,OP,HP,L,O	I to IV	8.9	286/286
Int 0034	1984-89	OC,OP,HP,L	II to IV	8.2	499/499
HNU-87b	1987-90	OC,OP,HP,L,O	I to IV	4.2	424/424
TMH R-4	1986-89	OC	III,IV	1.3	135/135
JHCFUS	1985-89	OC,OP,HP,L,NP,O	I to IV	2.9	191/191
KKD-86	1986-89	OC	I to IV	6.9	112/112
Inclusion between 1994 and 2000					
UKHAN [c]	1990-2000	OC, OP, L, HP, NP, O	I to IV	5.8	713/713

a : Third arm with immunotherapy ineligible
b : All patients had positive nodes and capsular rupture
c : 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.

List of abbreviations
OC = oral cavity, OP = oropharynx, HP = Hypopharynx, L = Larynx, P = Pharynx, O = Other;

Trial group abbreviations : GETTEC = Groupe d'Etude des Tumeurs de la Tête Et du Cou (France), HNU = Head and Neck UFT (Japan), INT= US INTer group trial, JHCFUS = Japanese H C F U Study, KKD = Kanto Koshinetsu District (Japan), TMH = Tata Memorial Hospital (India), UKHAN = United Kingdom Head And Neck.

Table A-4 : **Description of trials comparing altered fractionated radiotherapy to conventional radiotherapy**

Trials	Inclusion period	Sites	Stage	Median follow up (years)	Patients analysed / randomised
Hyperfractionated RT					
EORTC 22791	1980-1987	**OP**	II to IV	10.3	356 / 356
RIO	1986-1989	OP, L	III, IV	6.7	103 / 112
PMH-Toronto	1988-1995	OP, L, HP	II to IV	7.4	336 / 336
RTOG 9003 [a]	1991-1997	OC,OP, L, HP	II to IV	6.0	1113 /1113
Accelerated RT without total dose reduction					
EORTC 22851	1985-1995	OC, OP, L, O	II to IV	4.8	512 / 512
RTOG 9003 [a]	1991-1997	OC,OP, L, HP	II to IV	6.0	1113 /1113
BCCA 9113	1991-1995	OC, OP, L, HP	III, IV	7.8	82 / 82
DAHANCA	1991-1999	OC, OP, L, HP, O	I to IV	6.8	1485 / 1485
Oro 9301 [b]	1993-1998	OP	III, IV	6.6	128 / 128
CAIR	1994-1996	OC, OP, L, HP	II to IV	5.7	100 / 100
KBN P0 79	1995-1998	L	I to III	4.1	395 / 395
Accelerated RT without total dose reduction					
RTOG 7913	1979-1983	OC, OP, L, HP,O	II to IV	9.2	210 / 210
CHART	1990-1995	OC, OP, L, HP, O	I to IV	7.0	918 / 918
Vienna [c]	1990-1997	OC, OP, L, HP	II to IV	5.6	159 / 159
TROG 9101	1991-1998	OC, OP, L, HP	III, IV	3.9	350 / 350
GORTEC 9402	1994-1998	OC, OP, L, HP	III, IV	4.8	268 / 268

a : 4 arms trials, each experimental arm was compared with the control arm, the three corresponding comparison were called RTOG 9003 HF, for hyper-fractionated, RTOG 9003 S for Split Course, and RTOG 9003 B, for boost
b : Third arm with radio-chemotherapy;
c : Third arm with accelerated radiotherapy + mitomycin C.

List of abbreviations :
OC = oral cavity, OP = oropharynx, HP = Hypopharynx, L = Larynx, O = Other;

Trial group abbreviations :
BCCA = British Columbia Cancer Agency, CAIR = Continuous Accelerated Irradiation, CHART = Continuous Hyperfractionated Accelerated Radiation Therapy, DAHANCA = Danish Head and Neck Cancer Study Group, EORTC = European Organisation for Research and Treatment of Cancer, GORTEC = Groupe d'Oncologie Radiothérapie Tête et Cou, KBN = Komiet Badan Naukowych (Committee for Scientific Research), PMH-Toronto = Princess Margaret Hospital, Toronto; RTOG = Radiation Therapy Oncology Group, TROG = Trans-Tansman Radiation Oncology Group.