Surrogate endpoint for overall survival in non-small cell lung cancer using data from the NSCLC Meta-Analysis and the Meta-Analysis of Radiotherapy in Lung Cancer (MAR-LC)

NSCLC Surrogates Collaborative Group

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INTRODUCTION

Worldwide, around one and a half million new cases of lung cancer are diagnosed each year[1]. Approximately 85% of these tumours are of non-small cell histological type[2], including adenocarcinomas, squamous cell and large cell carcinomas. Non-small cell lung cancer (NSCLC) is the main cause of deaths from cancer[3] and five-year survival across all stages of disease is about 14%[4].

Although surgery is generally regarded as optimal treatment, only about 30% of tumours are suitable for potentially curative resection[5]. A further 20% of patients, usually those presenting with locally advanced disease, undergo radical thoracic radiotherapy. The remaining 50% of patients, with late stage or metastatic disease, are usually treated palliatively.

A previous meta-analysis[6] based on individual patient data (IPD) from more than 9 000 patients from over 50 randomised trials, concluded that despite previous scepticism and controversy, modern chemotherapy could have a role in treating all patients with NSCLC. In particular there was some evidence that for resectable disease, cisplatin-based chemotherapy given in addition to surgery could prolong survival. However, it was not clear whether giving chemotherapy after surgery and post-operative radiotherapy was beneficial. Among the seven comparisons of this meta-analysis, five were updated during last years with 87 trials and a total of near 18 900 patients[7-9]. More recently, an IPD- meta-analysis based (MAR-LC: Meta-Analysis of Radiotherapy in Lung Cancer) on 8 trials and 1 594 patients have shown a 3 % improvement in overall survival at 5 years (Hazard ratio = 0.87, p=0.009) with modified fractionation radiotherapy compared to conventional radiotherapy in NSCLC[10]. Based on two trials and 685 patients, similar results (HR = 0.87, p=0.08) were observed in small cell lung cancer with a 3 % improvement in overall survival at 5 years.

The gold standard endpoint to measure the effect of treatment NSCLC is overall survival because it is simple to measure, easy to interpret and its measurement is reliable. 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.

Using a surrogate endpoint at an early time point in clinical trials would permit to decrease the duration before conclusion and the cost of the development of new drug in the non-small cell lung cancer field. In patients with advanced colorectal cancer, progression-free survival was shown to be a reasonable surrogate for overall survival for the evaluation of the effect of chemotherapy[11]. Equally progression-free survival is a appropriate surrogate endpoint for evaluation of treatment effects of chemotherapy and radiotherapy in trials with patients with head and neck cancer[12]. In adjuvant setting, disease-free survival has been shown to be a surrogate for overall survival in colorectal cancer in chemotherapy trials[13]. On

the other hand, in advanced breast cancer, progression-free survival was not a valid surrogated for overall survival[14].

Using the same methods, our objective is to examine disease free-survival, event-free survival or time to loco-regional control as candidate surrogate endpoints for overall survival in trials studying the effect of chemotherapy or radiotherapy in NSCLC.

Objectives

The aim of this project is to assess surrogate endpoints for overall survival when quantifying effect of chemotherapy or radiotherapy in NSCLC using data from five individual patient data meta-analyses of the NSCLC Meta-analyses Collaborative Groups for chemotherapy[7-9] and from one meta-analysis of the MAR-LC Collaborative Group for radiotherapy[10].

The first objective is to evaluate disease-free survival as surrogate endpoints in patient with resectable NSCLC in trials studying the effect of adjuvant chemotherapy.

The second objective is to evaluate if progression-free survival or time to loco-regional failure could be surrogate of overall survival in trials studying chemotherapy in locally advanced NSCLC.

The third objective is to evaluate if progression-free survival or time to loco-regional failure could be surrogate of overall survival in trials studying radiotherapy in locally advanced NSCLC and SCLC.

Description of included trials

Individual patient data used for this analysis are extracted from data of the updated NSCLC Meta-Analysis published in 2010 in the Lancet or in the Journal of Clinical Oncology or reported in 2008 at the WCLC meeting or in 2010 at ELCC meeting. The trials accrued patients between 1980 and 2003 (NSCLC Meta-Analysis) or between 1989 and 2006 (MAR-LC).

Appendix A-1 describes trials testing the adjunction of adjuvant chemotherapy to surgery with or without radiotherapy included in the comparisons 1 and 3 of the NSCLC Meta-analysis. These meta-analyses concern 34 and 13 trials respectively. Among them information about disease-free survival is available for 18 (5 432 patients) and 8 trials (2 247 patients) respectively.

Appendix A-2 describes trials of the comparison 4 of the NSCLC Meta-analysis, comparing radiotherapy plus chemotherapy (sequential or alternated radio-chemotherapy) versus radiotherapy alone. It includes 23 trials, 8 of them have information about progression-free survival (1 458 patients).

Appendix A-3 describes trials comparing radiotherapy plus concomitant chemotherapy versus radiotherapy alone (comparison 5 of the NSCLC Meta-analysis). Among the 17 trials concerned, 13 have information on progression-free survival (2 255 patients). The same trials have also information on time to loco-regional failure.

Appendix A-4 describes trials comparing, in addition of radiotherapy treatment, sequential chemotherapy versus concomitant chemotherapy (comparison 6 of the NSCLC Meta-analysis). Information about progression-free survival was available for all of these 6 trials (1 201 patients).

Appendix A-5 describes trials comparing conventional radiotherapy to hyperfractionated or accelerated radiotherapy. Among the 10 trials included in the meta-analysis, all have information on progression-free survival (2 279 patients). Eight of them have information about time to loco-regional failure (1 673 patients).

Statistical methods

Separate analyses will be performed for the adjuvant trials and for the trials including patients with locally advanced disease trials. A distinct analysis will be performed for the trials of radiotherapy. Although they all assessed efficiency of adjunction of chemotherapy in NSCLC, prognosis of these patients are different, better for patient who can benefit of surgery (comparisons 1 and 3). All randomised patients will be analysed in their allocated arm according to the intention-to-treat principle.

Five analyses will be performed (1) trials assessing the impact of adjuvant chemotherapy after surgery followed or not by radiotherapy (first objective), (2) trials assessing the impact of sequential chemotherapy adding to radiotherapy, (3) trials assessing the impact of concomitant radiotherapy adding to radiotherapy, (4) trials assessing the impact of sequential chemotherapy adding to radiotherapy versus concomitant radio-chemotherapy (second objective), (5) trials assessing the impact of modified fractionation radiotherapy versus conventional radiotherapy (third objective).

A correlation approach will be used to assess the validity of candidate surrogates as a surrogate for overall survival[15]. This approach has already been used by Buyse et al.[11] to assess the relationship between event-free survival and overall survival in advanced colorectal patients, by Sargent et al.[13] to investigate the relationship between disease-free survival and overall survival in the adjuvant setting of colon cancer, by Burzowksi et al. [14] in breast and by Michiels et al. [12] in locally advanced head and neck cancer. This approach investigates correlation at a trial level and at an individual level. Exploratory analyses will investigate if the correlation values are stronger according to age (<65 vs. ≥65), tumour stage (I and II vs. III) and histology (adenocarcinoma vs. squamous) in adjuvant trials and chemotherapy generation (second vs. third) in locally advanced trials.

In locally advanced disease, the comparison between progression-free survival and time to loco-regional control will be done on all trials and then separately for sequential and concomitant chemotherapies. A separate analysis will be performed for the trials on radiotherapy.

Endpoints definition

Overall survival (OS) is defined as time from randomisation to death whatever the cause. Patients still alive at the last visit were censored at the date of last follow-up Disease-free survival (DFS) is defined, for patients who benefited of surgery, as the time from randomisation to the first event (loco-regional or distant recurrence, death). Patients without documented evidence of an event are censored at the date of last follow-up. Progression-free survival (PFS) is defined for patients who did not benefit of surgery, as the time from

randomisation to the first event (loco-regional or distant progression or death). Patients without documented evidence of an event were censored at the date of last follow-up.

The time-to-loco-regional failure (LRF) is defined as the time from randomisation to the first loco-regional event. Patients with distant event or death were censored at the dates of distant event or death respectively; patients without documented evidence of distant event or death are censored at the date of last follow-up.

Trial level surrogacy

First the correlation at the trial level will be assessed. Correlation between treatment effect on candidate surrogate and treatment effect on OS will be quantified through a linear regression model. Treatment effects will be estimated by log hazard ratios. The linear regression model will be weighted by the trial size. If the coefficient of correlation R estimated by this model is close to 1, the risk reduction for OS will be considered strongly correlated with the risk reduction for the candidate surrogate.

In order to enhance interpretation for the clinician's point of view, the correlation between effect of treatment on 3-year disease-free survival and 5-year overall survival will also be regarded in the adjuvant chemotherapy trials, using the cut-off points of the adjuvant colon cancer studies[13], and in the locally advanced disease trials, using the cut-off points from the head and neck cancer studies[12] that is 2-year progression-free survival and 5-year overall survival will be explored. The event rates over time will be evaluated in order to explore whether other cut-off points are more appropriate.

Individual level surrogacy

Then correlation will be assessed at the individual level. The association between distributions of OS and the candidate surrogate endpoint will be evaluated by a bivariate survival model[16-17]. Both models based on Hougaard and on Clayton copulas will be fitted. The best model according to the Akaike's criterion will be chosen. An estimated correlation coefficient ρ close to 1 will indicate a strong correlation between OS and the candidate surrogate.

Effective surrogacy

The candidate surrogate endpoint will be acceptable only if its correlation coefficients ρ and R are close to 1[17].

Surrogate threshold effect

One objective of a surrogate endpoint is to predict the treatment effect on OS observing treatment effect on the surrogate endpoint. In this way, the Surrogate Threshold

Effect (STE) will be calculated[18]. STE is defined as the minimum treatment effect that is necessary on the surrogate to be able to predict a non-zero effect on overall survival. Its calculation is based on the linear regression used for the determination of trial level surrogacy. Graphically this value is situated at the vertical of the intersection of the line hazard ratio of OS=1 and the confidence interval of the regression line.

Validation strategy

A leave-one-out cross-validation will be used to validate the results obtained. It consists in re-estimating the linear model on all trials except one. The fitted model will be used in the left trial to predict the treatment effect on OS based on the observed treatment effect on EFS. Predicted hazard ratio and actual hazard ratio will be compared for each trial.

Limits of surrogate endpoint studies

Some important limits in the interpretation of surrogate need to be precised. Firstly, a surrogate endpoint can only be validated for the drugs evaluated in the corresponding meta-analyses. That is, surrogates studied on adjuvant chemotherapies may in principle only be used to study similar adjuvant chemotherapies. In order to use surrogate endpoints for new treatments, such as targeted therapy, specific surrogate endpoint evaluation studies have to be performed in trials using these drugs.

Secondly, the use of second line treatment can be an important confounding factor. Surrogate endpoints results obtained in trials in which patients received no or infrequent second line treatment may not be valid in a population that would receive second line treatment in a larger proportion.

Finally, the use of surrogate endpoints in future clinical trials of the drugs evaluated in the meta-analyses should not be used as an excuse for not performing a long term follow-up of the patients. This follow-up is necessary to control on unexpected adverse reactions, but also to get sufficient power to analyse the overall survival endpoint. The use of the surrogate endpoint would allow to conclude more rapidly on the treatment effect, but not lead to prematurely stop following-up of the patients.

Working parties in this study

Two groups with specific functions have been created:

1) the Secretariat
2) the Advisory Board

The Secretariat is in charge of the coordination of the study. It is responsible for is 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.

Practical considerations

The first part of this study, analysis of surrogate endpoints in comparisons of the NSCLC meta-analysis, will be done in the near future as data bases are available.

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

Appendix A-1: **Description of trials comparing surgery ± radiotherapy + adjuvant chemotherapy vs. surgery ± radiotherapy (comparisons 1 and 3)**
34 trials (5432 patients) and 8 trials (2247 patients)

Trial	Period of recruitment	Number of patients	Drugs used and dose per cycle (mg/m^2)	Radiotherapy dose (Gy) / fractions
Comparison 1 (Platinum + vinca alkaloid / etoposide)				
WJSG 3[A1-1]	1988-89	225 (225)	Cisplatin 80 + Vindesine (2–3; once or twice), mitomycin 8; 2 cycles Tegafur + Uracil (400 total) Daily treatment for 1 year	N/A
Mineo [A1-2]	1988-94	66 (66)	Cisplatin 100 + Etoposide 120 6 cycles	N/A
Xu [A1-3]	1989-92	70 (70)	Cisplatin 100 + Cyclophosphamide 300 + Vincristine 1·4 + Doxorubicin 50 + lomustine 50 4 cycles oral tegafur (600–900 total) Daily treatment for 1 year	N/A
Park1 [A1-4]	1989-98	118 (118)	Cisplatin 100 + Mitomycin C 10 + Vinblastine 6 3-4 cycles	N/A
Park2 [A1-5]	1989-98	108 (107)	Cisplatin 100 + Mitomycin C 10 + Vinblastine 6 3-4 cycles	N/A
ACTLC4A [A1-6]	1992-95	104 (104)	Cisplatin 80 1 cycles Vindesine 3 (twice) 2 cycles Tegafur + Uracil 400 Daily treatment for 2 years	N/A
ACTLC4B [A1-6]	1992-95	104 (103)	Tegafur + Uracil 400 (total) Daily treatment for 2 years	N/A
JLCRG [A1-7]	1994-97	999 (999)	Tegafur + Uracil 250 mg/m2 Daily treatment for 2 years	N/A
ALPI1 [A1-8]	1994-99	618 (618)	Cisplatin 100 + Vindesine 3 + Mitomycin C 8 3 cycles	N/A
JCOG 9304 [A1-9]	1994-99	119 (119)	Cisplatin 80 + Vindesine 3 3 cycles	N/A
ANITA1[A1-10]	1994-00	463 (463)	Cisplatin 100 + Vinorelbine 30 4 cycles	N/A
JBR10 [A1-11]	1994-01	482 (482)	Cisplatin 50 + Vinorelbine 25 4 cycles	N/A
IALT1 [A1-12]	1995-01	1001 (1001)	Cisplatin (80, 100, or 120) + vindesine (3; weekly then twice weekly); 3-4 cycles	N/A
IALT2 [A1-12]	1995-01	294 (294)	Cisplatin (80, 100, or 120), + vinorelbine (30; weekly) 3-4 cycles	N/A

BLT1 [A1-13]	1995-01	136 (136)	Cisplatin 50 + Mitomycin 6 + vinblastine 6 or Cisplatin 80 + vindesine 6 3 cycles	N/A
BLT2 [A1-13]	1995-01	118 (118)	Cisplatin 50 + Mitomycin C 6 + Ifosphamide 3 3 cycles	N/A
BLT3 [A1-13]	1995-01	65 (65)	Cisplatin 50 + Mitomycin 6 + Ifosphamide 3 3 cycles	N/A
CALGB 9633 [A1-14]	1996–2003	344 (344)	Carboplatin (6 mg/mL over 45–60 min) + Paclitaxel 200 4 cycles	N/A
Comparison 3 (Platinum + vinca alkaloid / etoposide)				
GETCB 01CB82 [A1-15]	1982-86	267 (267)	Cisplatin 75 + Doxorubicin 40 + Vincristine 1.2 + Lomustine 80* alternating with Cyclophosphamide 600 3 cycles	60-65 / 30-33 After chemotherapy
EORTC 08861 [unpublished]	1986-90	24 (24)	Cisplatin 100 + Vindesine 6 4 cycles	56 / 28 After 2 cycles Concomitant for 2 cycles
Int 0115 [A1-16]	1991-97	488 (488)	Cisplatin 60 + Etoposide 120*3 4 cycles	50.4 / 28 Concomitant
ALPI3 [A1-8]	1994-99	470 (470)	Cisplatin 100 + Vindesine 3*2 + Mitomycin 8 3 cycles	50-54 / 25-27 After chemotherapy
ANITA3 [A1-10]	1994-00	377 (377)	Cisplatin 100 + Vinorelbine 30*4 4 cycles	45-60 / 23-30 After chemotherapy
BLT4 [A1-13]	1995-01	49 (49)	**MIC**: Cisplatin 50, Mitomycin 6, Ifosfamide 3 **MVP**: Cisplatin 50, Mitomycin 6, Vinblastine 6 **CV**: Cisplatin 80, Vindesine 3*2 **NP**: Cisplatin 80, Vinorelbine 30*2 3 cycles	40-60 / 15-30 After chemotherapy
IALT3-4 [A1-12]	1995-01	572 (572)	Cisplatin 80, 100 or 120 + Vindesine 3*2 N=16 or Vinblastine 4*2 N=119 or Vinorelbine 30 weekly N=206 or Etoposid 30*3 N=231 3 or 4 cycles	$\leq$ 60 After chemotherapy

* Total dose

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Appendix A-2: **Description of trials comparing radiotherapy vs. radiotherapy + sequential chemotherapy or alternated radio-chemotherapy (comparison 4)**
8 trials; 1458 patients

Trial	Period of recruitment	Number of patients (in surrogate analysis)	Drugs used and dose per cycle (mg/m^2)	Radiotherapy dose (Gy) / fractions
Platinum + vinca alkaloid / etoposide				
CALGB 8433 [A2-1]	1984-87	180 (180)	Cisplatin 100 + Vinblastine 5 2 cycles ; neo-adjuvant	60 Gy, 2 Gy/f, 6-7 W
EORTC 08842 [A2-2]	1984-89	75 (73)	Cisplatin 100 + Vindesine 3 2 cycles ; neo-adjuvant + alternated	55 Gy, 20 f
CEBI 138 [A2-3]	1983-89	353 (353)	Cisplatin 100 + Cyclophosphamide 200 + Vindesine 1.5 + Lomustine / CCNU 50 3 cycles (+ 3 cycles if no progression) ; neo-adjuvant + adjuvant	65 Gy, 26 f, 45 days
RTOG 8808 – ECOG 4588 [A2-4]	1989-92	326 (326)	Cisplatin 100 + Vinblastine neo-adjuvant	60 Gy, 2 Gy/f, 6W
BLT [A2-5]: BLT adjuvant BLT neoadjuvant	1995-01	288 119 adjuvant, 169 neoadj. (119 + 169)	Cisplatin 50 + Mitomycin C 6 + Ifosfamide 3 or Cisplatin 50 + Mitomycin C 6 + Vinblastine 6 or Cisplatin 80 + Vindesine 3 or Cisplatin 80 + Vinorelbine 30 3 cycles ; adjuvant or neo-adjuvant	not standardized, followed local practice
GMMA Ankara 1995 [A2-6]	1995-96	30 (30)	Cisplatin 40 + Etoposide 200 + Ifosfamide 200 2 cycles ; neo-adjuvant	36 Gy 12 f, split course 7 D free, 12.5 Gy 5 f
Taxane Only				
Tax SI009 [A2-7]	1995-99	208 (208)	Docetaxel 100 maximum of 3 cycles ; neo-adjuvant	Local treatment (surgery or RT) decided at baseline by the clinician

D: day; W: Week; f: fraction; ci: continuous infusion

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Appendix A-3: **Description of trials comparing radiotherapy vs radiotherapy + concomitant chemotherapy (comparison 5)**
13 trials; 2255 patients

Trial	Period of recruitment	Number of patients (in surrogate analysis)	Drugs used and dose per cycle (mg/m²)	Radiotherapy dose (Gy) / fractions
Platinum alone				
EORTC 08844 [A3-1]	1984-89	331 (331)	Arm 2 : Cisplatin 30 – 4 cycles Arm 3: Cisplatin 6 daily x 20	55 Gy, 20 f, 7 W
PMCI 88 C091 [A3-2]	1989-95	208 (197)	Arm 3: Carboplatin 70 Arm 4: Carboplatin 70	60 Gy, 30 f, 3 (tid) or 6 W
CALGB-ECOG [A3-3]	1991-94	282 (282)	Carboplatin 100 – 6 cycles	60 Gy, 30 f, 6 W
NKB-CKVO 9411 [A3-4]	1994-98	160 (153)	Carboplatin 840 ci during 6 weeks	60 Gy, 30 f, 6 W
NPC IIIB 96-01 [A3-5]	1996-2003	584 (580)	Carboplatin 15 daily x 33 Induction CT in both arms	66 Gy, 33 f, 6 W
GMMA Ankara 1995 [A2-6]	1995-96	30 (28)	Cisplatin 6 daily	48.5 Gy 17 f, sc
JCOG 9812 [A3-6]	1999-01	46 (46)	Carboplatin 30 daily x 20	60 Gy, 30 f, 6 W
Platinum + Etoposide				
Kragujevac 88 [A3-7]	1988-89	169 (169)	Carboplatin 100 + Etoposide 100 Arm II : Weekly Arm III : 3 cycles	64.8 Gy, 54 f bid, 5.4 W
Kragujevac 90 [A3-8]	1990-91	131 (131)	Carboplatin 50 + Etoposide 50	69.6 Gy, 58 f bid, 5.8 W
NCCTG 90 24 51 [A3-9]	1992-93	74 (71)	Cisplatin 30 + Etoposide 100	60Gy : 40 f bid, 4 W sc
Platinium + Taxane				
LAMP ACR 427 [A3-10]	1998-2001	177 (174)	Carboplatin AUC2 + Paclitaxel 45 mg/m² weekly Induction CT in both arms	63 Gy, 34 f, 7 W
Taxane only				
Uludag [A3-11]	1996-2001	45 (45)	Paclitaxel 30-60	RT: 59.4 Gy, 1.8 Gy/f RT-CT: 63 Gy, 1.8 Gy/f
GMMA Ankara 97 [A3-12]	1995-96	51 (48)	Paclitaxel 60	48.5 Gy 17 f, sc

D: day, W: Week, f: fraction, ci: continuous infusion, sc: split course

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Appendix A-4: **Description of trials comparing Radiotherapy + sequential chemotherapy vs. radiotherapy + concomitant chemotherapy (comparison 6)**
6 trials; 1201 patients

Trial	Period of recruitment	Number of patients (in surrogate analysis)	Comments	Randomised chemotherapy	Radiotherapy
Platinum based regimens					
WJLCG [A4-1]	1992-94	314 (313)	Unresectable stage III neoadjuvant vs concomitant	Cisplatin 80 + Vindesine 3 + Mitomycin C 8	56 Gy, 28 f
RTOG 9410 [A4-2]	1994-98	407 (407)	neoadjuvant vs concomitant	Cisplatin 100 + Vinblastine 5 5 cycles	60 Gy
GLOT-GFPC NPC 95-01 [A4-3]	1996-2000	205 (202)	IIIA N2, IIIB neoadjuvant vs concomitant+ adjuvant	Cisplatin 120 + Vinorelbine 30 versus Cisplatin 20 + Etoposide 50 then Cisplatin 80+ Vinorelbine 30	66 Gy, 33 f, 6.5 W
EORTC 08972 [A4-4]	1999-2003	158 (158)	Inoperable stage I, II, III neoadjuvant vs concomitant	2 cycles : Cisplatin 75 + Gemcitabine 1250 – 2 cycles versus Cisplatin 6 daily	66 Gy, 24 f, 32 D
CALGB 8831 [A4-5]	1988-1989	91 (91)	Adjuvant vs concomitant	Cisplatin 100 + Vinblastine 5 4 cycles versus Carboplatin 100 – 6 cycles	60 Gy, 2 Gy/f, 6W
GMMA Ankara 1995 [A2-6]	1995-96	30 (30)	arm 2 vs 3 neoadjuvant vs concomitant	Cisplatin 40 + Etoposide 200 + Ifosfamide 200 – 2 cycles vs Cisplatin 6 daily	48.5 Gy 17 f, sc

D: day, W: Week, f: fraction, sc: split course

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Appendix A-5: **Description of trials comparing conventional radiotherapy vs hyperfractionnated or accelerated radiotherapy (MAR-LC)**
10 trials and 2279 patients in EFS analysis; 8 trials and 1673 patients in LRF analysis

Trial	Period of recruitment	Number of patients (in surrogate analysis)	Chemotherapy	Randomised radiotherapy
ECOG 3588 [A5-1]	1989-1992	417 (417 EFS only)	Cisplatin 60 mg/m² d1 Etoposide 120 mg/m² d1,2,3 4 cycles (3 w)	Standard: 45 Gy / 25 fr / 5 w Experimental: 45 Gy / 30 fr / 3 w bid
NCCTG 892052 [A5-2]	1990-1996	268 (268)	Cisplatin 30 mg/m² d1,2,3 Etoposide 130 mg/m² d1,2,3 6 cycles‡ (4 w)	Standard: 50.4 Gy / 28 fr / 5.5 w Experimental: 48 Gy / 32 fr / 5.5 w sc* bid
RTOG 8808-ECOG 4588 [A5-3]	1989-1992	326 (326 EFS 325 LRF)	None	Standard: 60 Gy / 30 fr / 6 w Experimental: 69.6 Gy / 58 fr / 6 w bid
PMCI 88C091 [A5-4]	1989-1995	101 (101 EFS 97 LRF)	None	Standard: 60 Gy / 30 fr / 6 w Experimental: 60 Gy / 30 fr / 3 w bid
PMCI 88C091 CT [A5-4]	1989-1995	107 (107 EFS 100 LRF)	Carboplatin 70 mg/m² d1-5 + Carboplatin 70 mg/m² d29-33 in standard arm	Standard: 60 Gy / 30 fr / 6 w Experimental: 60 Gy / 30 fr / 3 w bid
CHART [A5-5]	1990-1995	563 (563 EFS 517 LRF)	None	Standard: 60 Gy / 30 fr / 6 w Experimental: 54 Gy / 36 fr / 1.5 tid
NCCTG 902451 [A5-6]	1992-1993	74 (74 EFS 71 LRF)	None	Standard: 60 Gy / 30 fr / 6 w Experimental: 60 Gy / 40 fr / 6 w sc† bid
NCCTG 942452 [A5-7]	1994-1999	246 (246 EFS 237 LRF)	Cisplatin 30 mg/m² d1-3;28-30 Etoposide 100 mg/m² d1-3;28-30	Standard: 60 Gy / 30 fr / 6 w Experimental: 60 Gy / 40 fr / 6 w sc† bid
ECOG 2597 [A5-8]	1998-2001	119 (119 EFS only)	Carboplatin AUC 6 d1 Paclitaxel 225 mg/m² d1 2 cycles£ (3 w)	Standard: 64 Gy / 32 fr / 6.5 w Experimental: 57.6 Gy / 36 fr / 2.5 w tid
Gliwice 2001 [A5-9]	2001-2006	58 (58)	None	Standard: 72 Gy / 40 fr / 8 w Experimental: 72 Gy / 40 fr / 5.5 w

D: day, W: Week, fr: fraction, sc: split course, bid: RT given twice a day, tid: radiotherapy given three times a day.

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