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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Mauguen A, Pignon J-P, Burdett S, et al. Surrogate endpoints for overall survival in chemotherapy and radiotherapy trials in operable and locally advanced lung cancer: a re-analysis of meta-analyses of individual patients' data. *Lancet Oncol* 2013; published online May 14. http://dx.doi.org/10.1016/S1470-2045(13)70158-X.

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Contents of appendix:

Appendix A1: Description of trials – operable patients

Data on disease-free survival was available for 64% of the patients in the trials comparing CT vs. no CT and 84 % of the patients in the trials comparing RT + CT vs. RT (CT: chemotherapy, RT: radiotherapy).

Trial	Period of recruitment	Number of patients (in surrogate analysis)	Drugs used and dose per cycle (mg/m^2)	Radiotherapy dose (Gy) / fractions
Operable NSCLC without post-operative RT				
WJSG 3[A1-1]	1988-89	225 (224)	Cisplatin 80 + Vindesine (2–3; once or twice), Mitomycin 8; 2 cycles Tegafur + Uracil (400 total) Daily treatment for 1 year	None
Mineo[A1-2]	1988-94	66 (66)	Cisplatin 100 + Etoposide 120 6 cycles	None
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	None
Park1[A1-4]	1989-98	118 (118)	Cisplatin 100 + Mitomycin C 10 + Vinblastine 6 3-4 cycles	None
Park2[A1-5]	1989-98	108 (107)	Cisplatin 100 + Mitomycin C 10 + Vinblastine 6 3-4 cycles	None
ACTLC4A[A1-6]	1992-95	208 (155)	Cisplatin 80 1 cycles Vindesine 3 (twice) 2 cycles Tegafur + Uracil 400 Daily treatment for 2 years	None
JLCRG[A1-7]	1994-97	999 (999)	Tegafur + Uracil 250 mg/m2 Daily treatment for 2 years	None
ALPI1[A1-8]	1994-99	618 (618)	Cisplatin 100 + Vindesine 3 + Mitomycin C 8 3 cycles	None
JCOG 9304[A1-9]	1994-99	119 (119)	Cisplatin 80 + Vindesine 3 3 cycles	None
ANITA1[A1-10]	1994-00	463 (463)	Cisplatin 100 + Vinorelbine 30 4 cycles	None
JBR10[A1-11]	1994-01	482 (482)	Cisplatin 50 + Vinorelbine 25 4 cycles	None
IALT1[A1-12]	1995-01	1001 (1001)	Cisplatin (80, 100, or 120) + Vindesine (3; weekly then twice weekly); 3-4 cycles	None
IALT2[A1-12]	1995-01	294 (294)	Cisplatin (80, 100, or 120), + Vinorelbine (30; weekly) 3-4 cycles	None
BLT1[A1-13]	1995-01	136 (136)	Cisplatin 50 + Mitomycin 6 + vinblastine 6 or Cisplatin 80 + Vindesine 6 3 cycles	None

BLT2 [A1-13]	1995-01	65 (65)	Cisplatin 50 + Mitomycin 6 + Ifosphamide 3 3 cycles	None
BLT3 [A1-13]	1995-01	118 (118)	Cisplatin 50 + Mitomycin C 6 + Ifosphamide 3 3 cycles	None
CALGB 9633 [A1-14]	1996–2003	344 (344)	Carboplatin (6 mg/mL over 45–60 min) + Paclitaxel 200 4 cycles	None
Operable NSCLC with post-operative RT				
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 Concurrent for 2 cycles
Int 0115 [A1-16]	1991-97	488 (488)	Cisplatin 60 + Etoposide 120*3 4 cycles	50.4 / 28 Concurrent
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

ACTLC: Study Group of Adjuvant Chemotherapy for Lung Cancer. ALPI: Adjuvant Lung Cancer Project Italy. ANITA: Adjuvant Navelbine International Trialist Association. BLT: Big Lung Trial. CALGB: Cancer and Leukemia Group B. EORTC: European Organization for Research and Treatment of Cancer. GETCB : Groupe d'Etude et de Traitement des Cancers Bronchiques. IALT: International Adjuvant Lung Trial. Int = US intergroup trial. JBR10: National Cancer Institute of Canada Clinical Trial Group trial JBR10. JCOG: Japan Clinical Oncology Group. JLCRG: Japan Lung Cancer Research Group. WJSG: West Japan Study Group for Lung Cancer Surgery.

Gy: Grays; NSCLC: non-small cell lung cancer; RT: radiotherapy

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Appendix A2: Description of trials – locally advanced patients, sequential CT

Data on progression-free survival was available for 37% of the patients in the trials comparing RT + Sequential CT vs. RT.

Trial	Period of recruitment	Number of patients (in surrogate analysis)	Drugs used and dose per cycle (mg/m^2)	Radiotherapy dose (Gy) / fractions
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 50 3 cycles (+ 3 cycles if no progression) ; neo-adjuvant + adjuvant	65 Gy, 26 f, 45 D
RTOG 8808 – ECOG 4588 [A2-4]	1989-92	326 (326)	Cisplatin 100 + Vinblastine neo-adjuvant	60 Gy, 2 Gy/f, 6W
BLT adjuvant [A2-5] BLT neoadjuvant [A2-5]	1995-01	119 adjuvant (119) 169 neoadjuvant (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 radiotherapy) decided at baseline by the clinician

BLT: Big Lung Trial. CALGB: Cancer and Leukemia Group B. CEBI: Carcinome épidermoïde bronchique inopérable. ECOG: Eastern Cooperative Oncology Group. EORTC: European Organisation for Research and Treatment of Cancer. GMMA: Gülhane Military Medicine Academy. RTOG: Radiotherapy Oncology Group. Tax: Taxotere. D: days. f: fractions. Gy: Grays. W: weeks.

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Appendix A3: Description of trials – locally advanced patients, concurrent CT

Data on progression-free survival was available for 85% of the patients in the trials comparing RT + Concurrent CT vs. RT.

Trial	Period of recruitment	Number of patients (in surrogate analysis)	Drugs used and dose per cycle (mg/m²)	Radiotherapy dose (Gy) / fractions
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 (208)	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 (159)	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 (30)	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
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 (74)	Cisplatin 30 + Etoposide 100	60 Gy, 40 f bid, 4 W sc
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
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 (51)	Paclitaxel 60	48.5 Gy, 17 f, sc
Brocat Study Group CT/RT 99/97	1997-2002	212 (212)	Paclitaxel 60	60-66 Gy, 30-33 fr
TAX 206 trial	1999-2001	89 (60)	Docetaxel 20	60 Gy, 30 fr

CALGB: Cancer and Leukemia Group B. ECOG: Eastern Cooperative Oncology Group. EORTC: European Organisation for Research and Treatment of Cancer. GMMA: Gülhane Military Medicine Academy. JCOG: Japan Clinical Oncology Group. LAMP ACR: Locally Advanced Multi-Modality Protocol American College of Radiology. NCCTG: North Central Cancer Treatment Group. NKB-CKVO: Nederlandse Kanker Bestrijding – Commissie voor Klinisch Vergelijkend Onderzoek. NPC IIIB: Non Petites Cellules stage IIIB. PMCI: Peter MacCallum Cancer Institute. TAX: Taxotere.
AUC: area under the curve. bid: two fractions per day. ci: continuous infusion. CT: chemotherapy. f: fractions. Gy: Grays. sc: split course. tid: three fractions per day. W: weeks.

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Appendix A4: Description of trials – locally advanced patients, sequential versus concurrent CT

Data on progression-free survival was available for 100% of the patients in the trials comparing RT + Sequential CT vs. RT + Concurrent CT.

Trial	Period of recruitment	Number of patients (in surrogate analysis)	Comments	Randomised chemotherapy	Radiotherapy
WJLCG [A4-1]	1992-94	314 (313)	Unresectable stage III neoadjuvant vs concurrent	Cisplatin 80 + Vindesine 3 + Mitomycin C 8	56 Gy, 28 f
RTOG 9410 [A4-2]	1994-98	407 (407)	neoadjuvant vs concurrent	Cisplatin 100 + Vinblastine 5 5 cycles	60 Gy
GLOT-GFPC NPC 95-01 [A4-3]	1996-2000	205 (202)	IIIA N2, IIIB neoadjuvant vs concurrent+ 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 concurrent	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 concurrent	Cisplatin 100 + Vinblastine 5 4 cycles versus Carboplatin 100 – 6 cycles	60 Gy, 2 Gy/f, 6 W
GMMA Ankara 1995 [A2-6]	1995-96	30 (30)	arm 2 vs 3 neoadjuvant vs concurrent	Cisplatin 40 + Etoposide 200 + Ifosfamide 200 – 2 cycles vs Cisplatin 6 daily	48.5 Gy, 17 f, sc

CALGB: Cancer and Leukemia Group B. EORTC: European Organisation for Research and Treatment of Cancer. GMMA: Gülhane Military Medicine Academy. GLOT-GFPC NPC: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique–Groupe Français Non Petites Cellules. RTOG: Radiotherapy Oncology Group. WJLCG: West Japan Lung Cancer Group.
D: days. f: fractions. Gy: Grays. sc: split course. W: weeks.

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Appendix A5: Description of trials – radiotherapy trials

Data on progression-free survival was available for 100% of the patients the trials in the MAR-LC meta-analysis.

Trial	Period of recruitment	Number of patients (in surrogate analysis)	Chemotherapy	Randomised radiotherapy
ECOG 3588 [A5-1,*]	1989-1992	417 (417)	Cisplatin 60 mg/m² d1 Etoposide 120 mg/m² d1,2,3 4 cycles (3 w)	Standard: 45 Gy / 25 f / 5 w Experimental: 45 Gy / 30 f / 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 f / 5.5 w Experimental: 48 Gy / 32 f / 5.5 w sc* bid
RTOG 8808- ECOG 4588 [A2-4]	1989-1992	326 (326)	None	Standard: 60 Gy / 30 f / 6 w Experimental: 69.6 Gy / 58 f / 6 w bid
PMCI 88C091 [A3-2]	1989-1995	101 (101)	None	Standard: 60 Gy / 30 f / 6 w Experimental: 60 Gy / 30 f / 3 w bid
PMCI 88C091 CT [A3-2]	1989-1995	107 (107)	Carboplatin 70 mg/m² d1-5 + Carboplatin 70 mg/m² d29-33 in standard arm	Standard: 60 Gy / 30 f / 6 w Experimental: 60 Gy / 30 f / 3 w bid
CHART [A5-3]	1990-1995	563 (563)	None	Standard: 60 Gy / 30 f / 6 w Experimental: 54 Gy / 36 f / 1.5 tid
NCCTG 902451 [A3-9]	1992-1993	74 (74)	None	Standard: 60 Gy / 30 f / 6 w Experimental: 60 Gy / 40 f / 6 w sc bid
NCCTG 942452 [A5-4]	1994-1999	246 (246)	Cisplatin 30 mg/m² d1-3;28-30 Etoposide 100 mg/m² d1-3;28-30	Standard: 60 Gy / 30 f / 6 w Experimental: 60 Gy / 40 f / 6 w sc bid
ECOG 2597 [A5-5]	1998-2001	119 (119)	Carboplatin AUC 6 d1 Paclitaxel 225 mg/m² d1 2 cycles£ (3 w)	Standard: 64 Gy / 32 f / 6.5 w Experimental: 57.6 Gy / 36 f / 2.5 w tid
Gliwice 2001 [A5-6]	2001-2006	58 (58)	None	Standard: 72 Gy / 40 f / 8 w Experimental: 72 Gy / 40 f / 5.5 w
CHARTWEL [A5-7]	1997-2005	300 (300)	None	Standard: 66 Gy / 33 f / 6·5 w Experimental: 60 Gy / 40 f / 2·5 w tid
CHARTWEL CT [A5-7]	1997-2005	106 (106)	Neoadjuvant CT - depends on centres	Standard: 66 Gy / 33 f / 6·5 w Experimental: 60 Gy / 40 f / 2·5 w tid

*: small-cell lung cancer trials.
CHART, Continuous Hyperfractionated Accelerated Radiation Therapy; CHARTWEL, CHART Week-End Less; ECOG, Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer. NCCTG, North Central Cancer Treatment Group; PCMI, Peter MacCallum Institute; RTOG, Radiation Therapy Oncology Group.
AUC: area under the curve. bid: two fractions per day. d: day. f: fractions. Gy: Grays. tid: three fractions per day. w: weeks. sc: split course. NSCLC: non–small-cell lung cancer.

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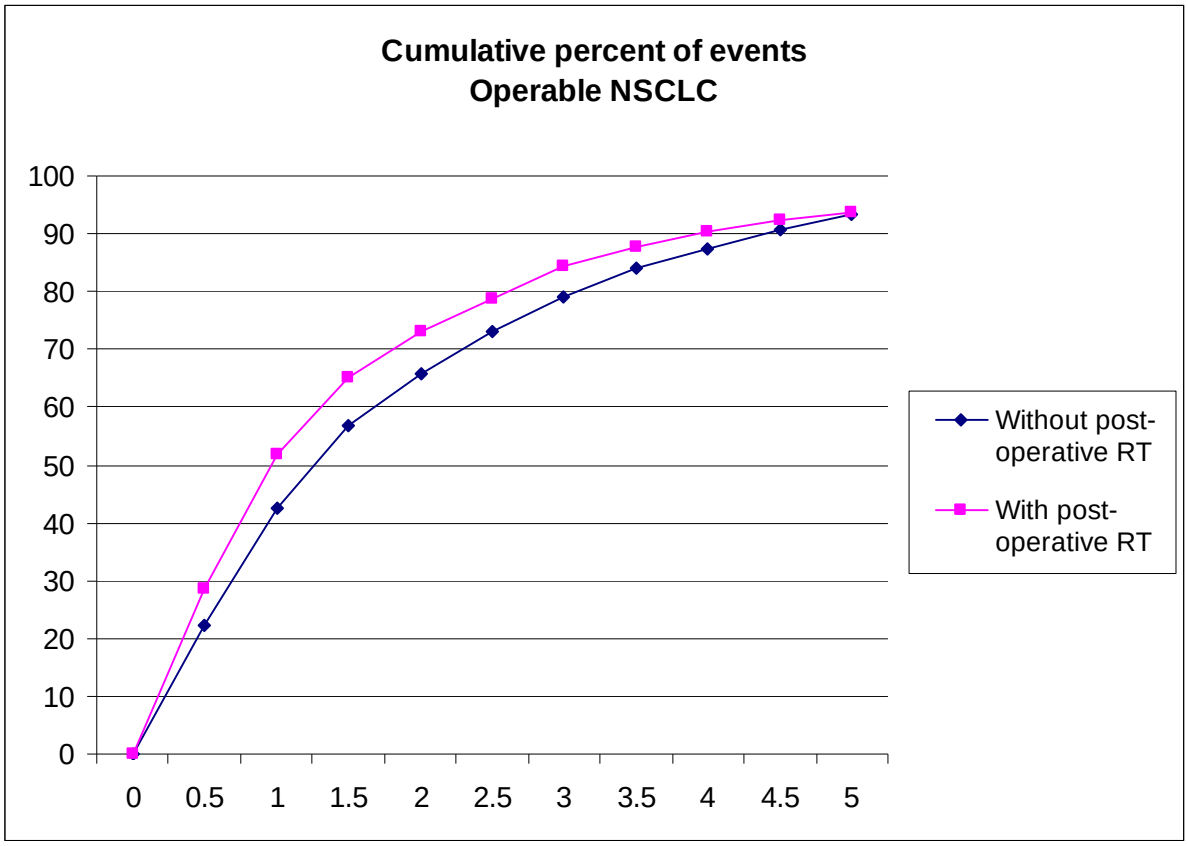
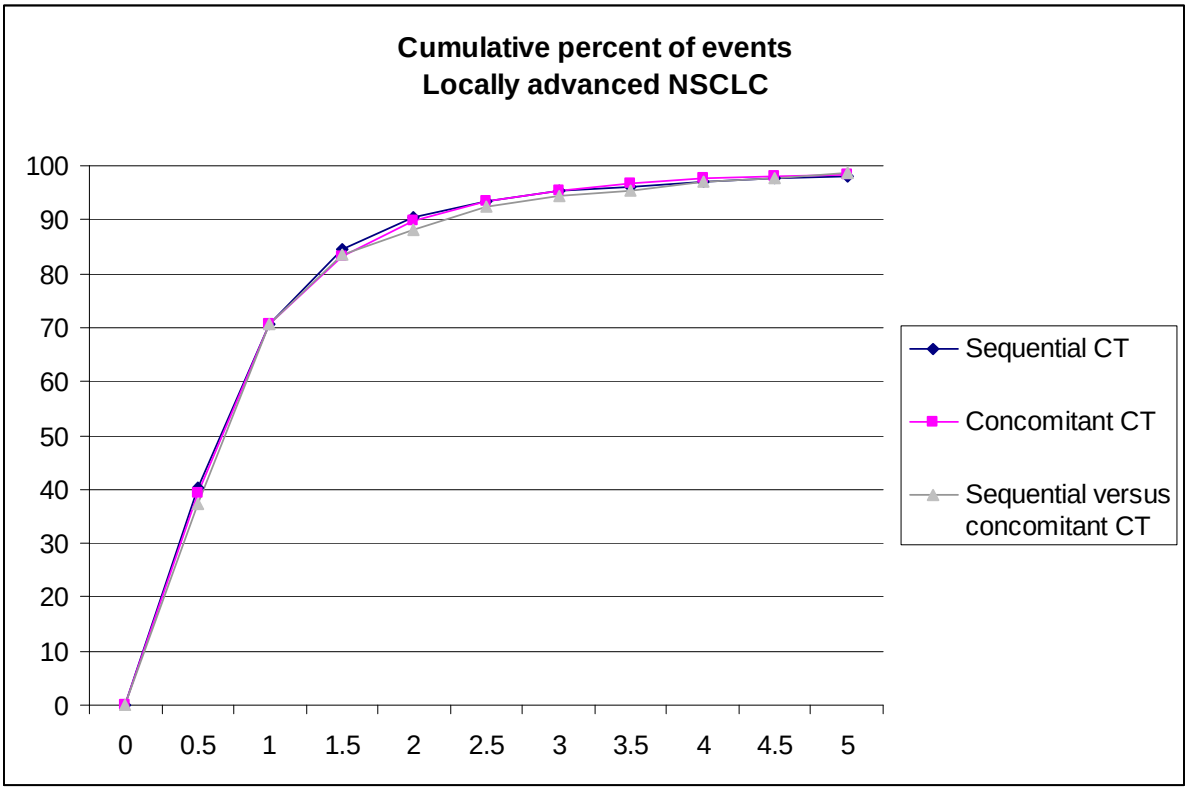
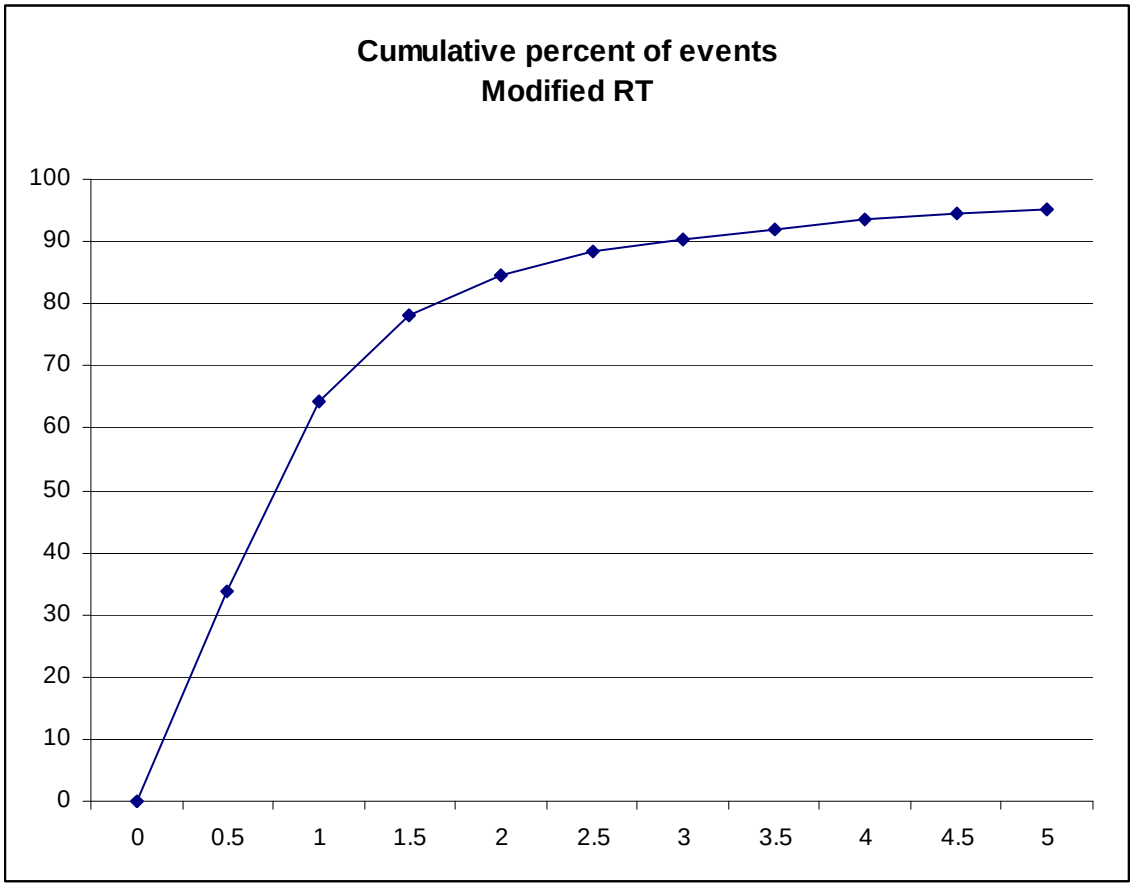
Appendix A6: Cumulative percentage of DFS/PFS events






Cumulative percent of events
Modified RT
100
90
80
70
60
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5

Appendix A7: Summary of data

Table 1: Description of analyzed data in operable NSCLC

	Patients (trials)	Any events			Deaths	
	N	N	% in first 3 years	% deaths in events* (near°)	N	% in first 5 years
Operable non-small cell lung cancer						
Without radiotherapy	5 379 (17)	2 525	79%	25% (26%)	2 163	91%
With radiotherapy	2 247 (7)	1 673	84%	29% (30%)	1 566	92%

*day of event=day of death
°near: day of death-day of event <= 7 days.

Table 2: Description of analyzed data in locally advanced lung cancer

	Patients (trials)	Locoregional events		Any events			Deaths	
	N	N	% in first 2 years	N	% in first 2 years	% deaths in events	N	% in first 5 years
Locally advanced non-small cell lung cancer								
Sequential chemotherapy	1 458 (8)	-	-	1 375	90%	30%* (33%°)	1 333	97%
Concurrent chemotherapy	2 552 (15)	744	90%	2 391	90%	25% (27%)	2 305	98%
Sequential versus concurrent chemotherapy	1 201 (6)	-	-	1 094	88%	23% (26%)	1 065	97%
Locally advanced lung cancer								
Radiotherapy	2 685 (12)	894	86%	2 562	85%	27% (33%)	2 471	94%

*day of event=day of death
°near: day of death - day of event <= 7 days.

Table 3: Follow-up and survival times

Meta-analysis	Median of follow-up (range)	Median of overall survival (range)	Median of disease-free / progression-free survival (range)	Median of duration of loco-regional control (range)
Operable NSCLC				
Without radiotherapy	5.7 y (0-16.7 y)	8.2 y (4 d -16.7 y)	6.4 y (0-16.7 y)	
With radiotherapy	6.4 y (1 d – 22.2 y)	2.5 y (1 d – 22.2 y)	1.6 y (1 d – 22.2 y)	
Locally advanced NSCLC				
Sequential chemotherapy	6.8 y (0-17.8 y)	11.7 m (3 d -17.8 y)	7.9 m (0 -17.8 y)	
Concurrent chemotherapy	5.2 y (0-15.8 y)	14.1 m (0-15.8 y)	8.1 m (0-15.8 y)	21.0 m* (3 d -15.8 y)
Sequential versus concurrent chemotherapy	6.1 y (0-11.2 y)	14.6 m (4 d – 11.2 y)	8.3 m (1 d – 11.2 y)	
Locally advanced lung cancer Radiotherapy	8.6 y (0 – 14.3 y)	15.0 m (0 – 14.3 y)	9.1 m (0 – 14.3 y)	21.3 m* (1 d – 14.3 y)

d=days; m=months; y=years;

* Median durations of loco-regional control were longer than median overall survival because all events other than loco-regional were censored.

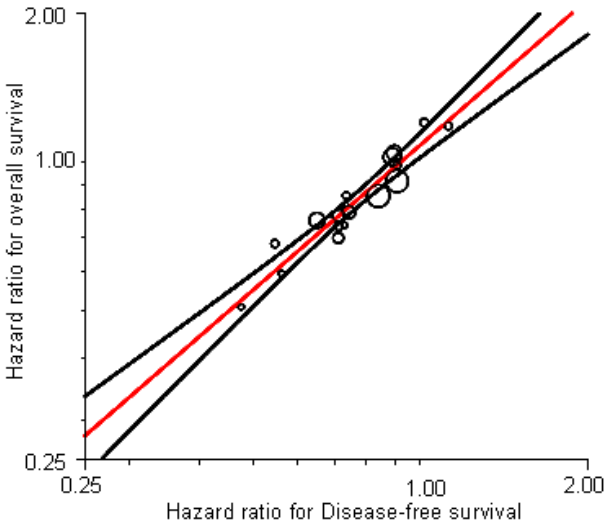
Appendix A8: Surrogacy analyses results

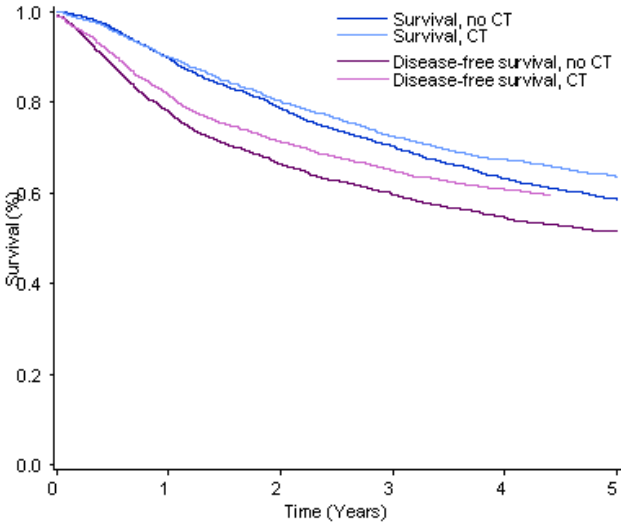
Each time, two models based on Hougaard and on Clayton copulas were fitted, while the optimal model according to the Akaike's criterion was retained and presented.

Abbreviations: CI= confidence interval, DFS=disease-free survival, HR=hazard ratio, LRC=loco-regional control, OS=overall survival, PFS=progression-free survival, STE=surrogate threshold effect

Evaluating effect of adjuvant chemotherapy in operable NSCLC – without post-operative radiotherapy

Hougaard copula	Disease-free survival over the entire time range
Number of trials (number of patients)	17 (5 379)
N events OS	2 163
N events DFS	2 525
Individual level	
ρ^2	0.83 [0.83-0.83]
Trial level, unweighted	
R^2	0.92 [0.88-0.95]
Regression equation, unweighted	log(HR OS)=0.08+0.98.log(HR PFS)
STE	0.88

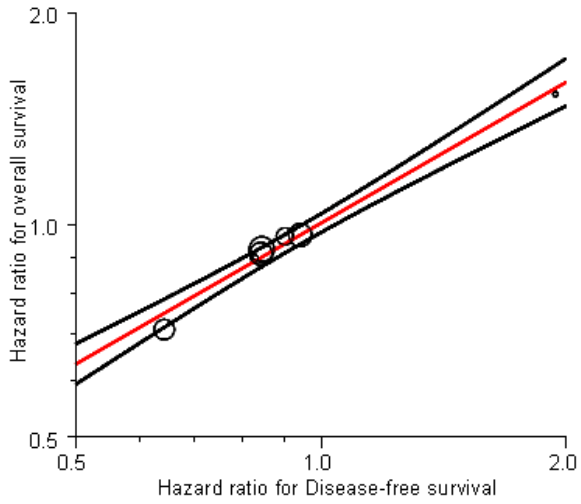


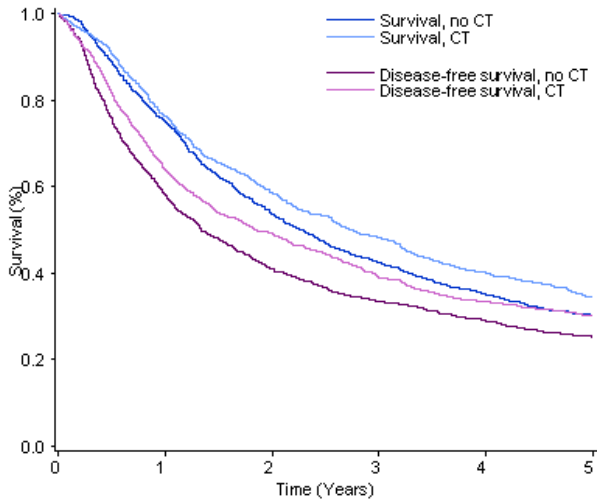


R^2 – weighted regression	Intercept [95% CI] – weighted regression	Slope [95% CI] – weighted regression
0.83	0.05 [-0.01 – 0.11]	0.91 [0.68 – 1.14]

Evaluating effect of adjuvant chemotherapy in operable NSCLC – with post-operative radiotherapy

Hougaard copula	Disease-free survival over the entire time range
Number of trials (number of patients)	7 (2 247)
N events OS	1 566
N events DFS	1 673
Individual level	
ρ^2	0.87 [0.87-0.87]
Trial level, unweighted	
R^2	0.99 [0.98-1.00]
Regression equation, unweighted	log(HR OS)=0.01+0.66.log(HR PFS)
STE	0.95

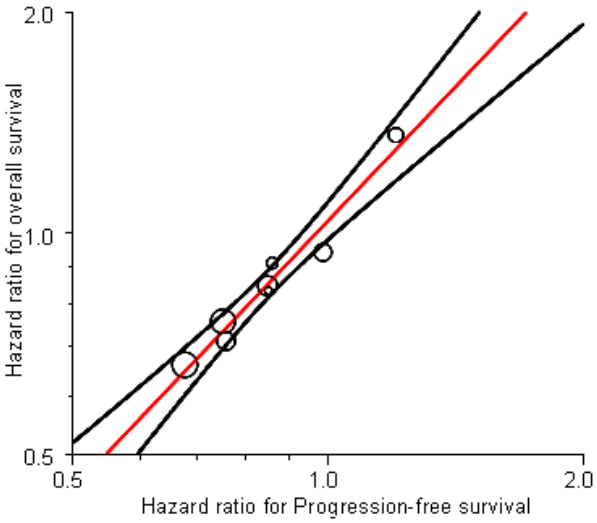


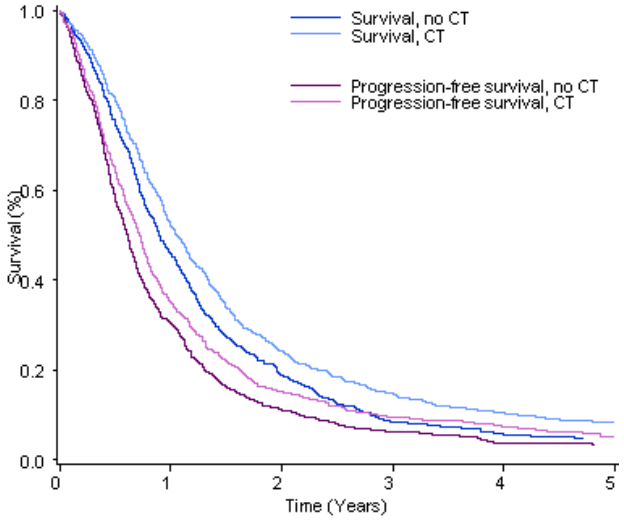


R^2 – weighted regression	Intercept [95% CI] – weighted regression	Slope [95% CI] – weighted regression
0.96	0.03 [-0.01 – 0.07]	0.77 [0.61 – 0.94]

Evaluating effect of sequential chemotherapy in locally advanced NSCLC

Clayton copula	Progression-free survival over the entire time range
Number of trials (number of patients)	8 (1 458)
N events OS	1 333
N events PFS	1 375
Individual level	
ρ^2	0.77 [0.77-0.77]
Trial level, unweighted	
R^2	0.96 [0.93-0.99]
Regression equation, unweighted	log(HR OS)=0.04+1.22.log(HR PFS)
STE	0.93



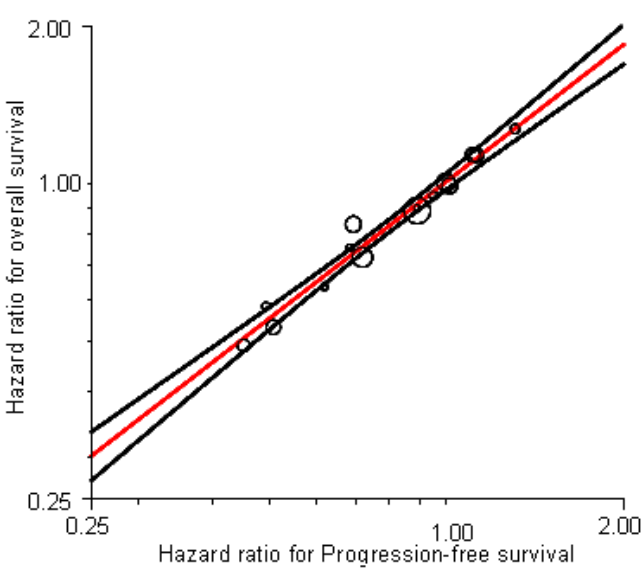


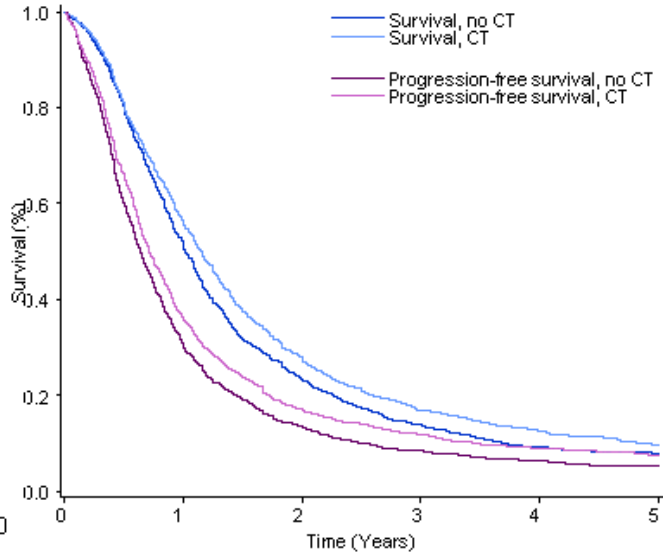
R^2 – weighted regression	Intercept [95% CI] – weighted regression	Slope [95% CI] – weighted regression
0.96	0.03 [-0.03 – 0.10]	1.16 [0.93 – 1.40]

Evaluating effect of concurrent chemotherapy in locally advanced NSCLC

Progression-free survival

Hougaard copula	Progression-free survival over the entire time range
Number of trials (number of patients)	15 (2 552)
N events OS	2 305
N events PFS	2 391
Individual level	
ρ^2	0.85 [0.85-0.85]
Trial level, unweighted	
R^2	0.97 [0.96-0.99]
Regression equation, unweighted	log(HR OS)=0.01+0.87.log(HR PFS)
STE	0.95

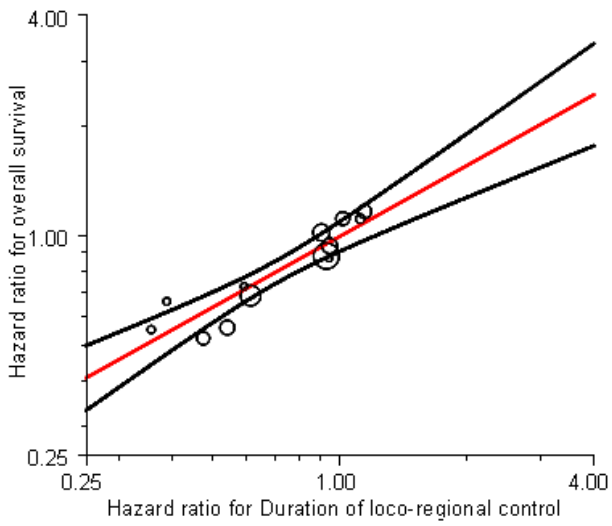


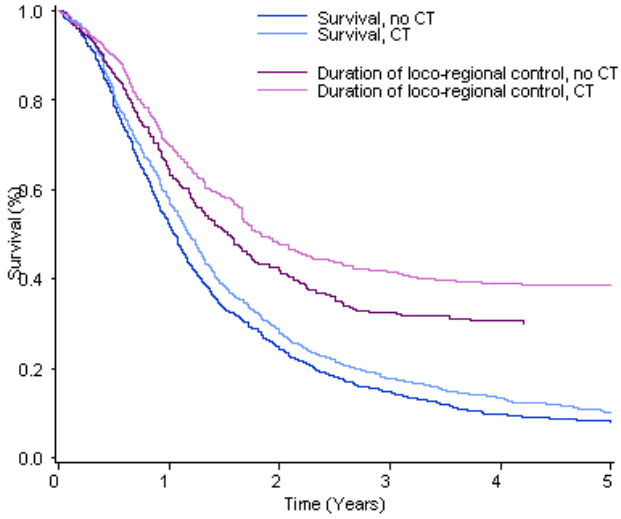


R^2 – weighted regression	Intercept [95% CI] – weighted regression	Slope [95% CI] – weighted regression
0.96	0.01 [-0.03 – 0.04]	0.88 [0.78 – 0.99]

Loco-regional control

Hougaard copula	Loco-regional control over the entire time range
Number of trials (number of patients)	13 (2 123)
N events OS	1 929
N events LRC	744
Individual level	
ρ^2	0.71 [0.71-0.71]
Trial level, unweighted	
R^2	0.85 [0.77-0.92]
Regression equation, unweighted	log(HR OS)= 0.00+0.64.log(HR LRC)
STE	0.89

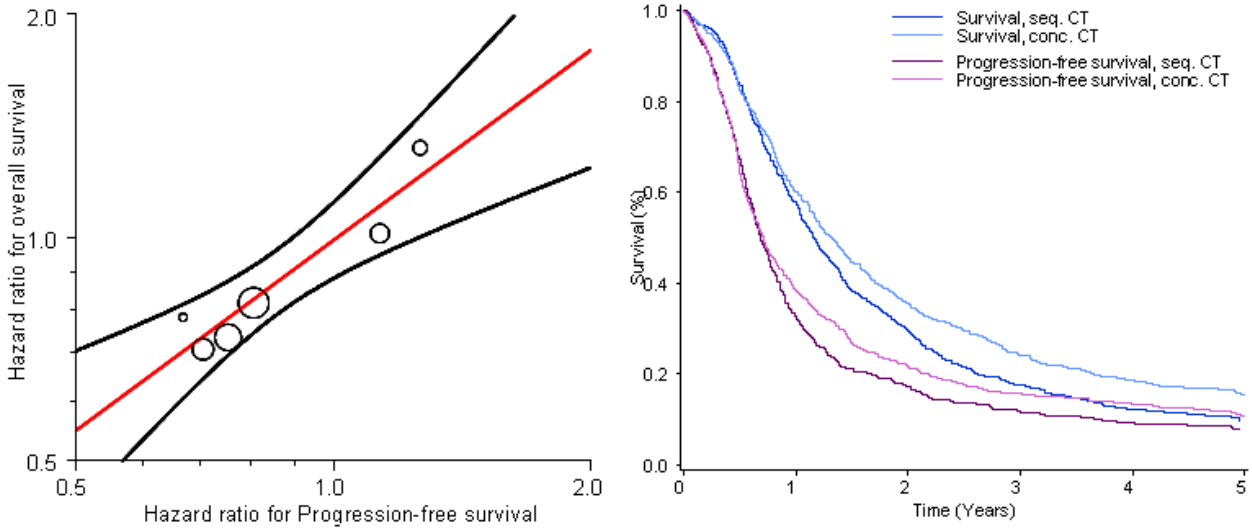




R^2 – weighted regression	Intercept [95% CI] – weighted regression	Slope [95% CI] – weighted regression
0.87	-0.01 [-0.08 – 0.07]	0.75 [0.56 – 0.94]

Evaluating effect of sequential versus concurrent chemotherapy in locally advanced NSCLC

Hougaard copula	Progression-free survival over the entire time range
Number of trials (number of patients)	6 (1 201)
N events OS	1 065
N events PFS	1 094
Individual level	
ρ^2	0.83 [0.83-0.83]
Trial level, unweighted	
R^2	0.89 [0.81-0.97]
Regression equation, unweighted	log(HR OS)=-0.01+0.85.log(HR PFS)
STE	0.90

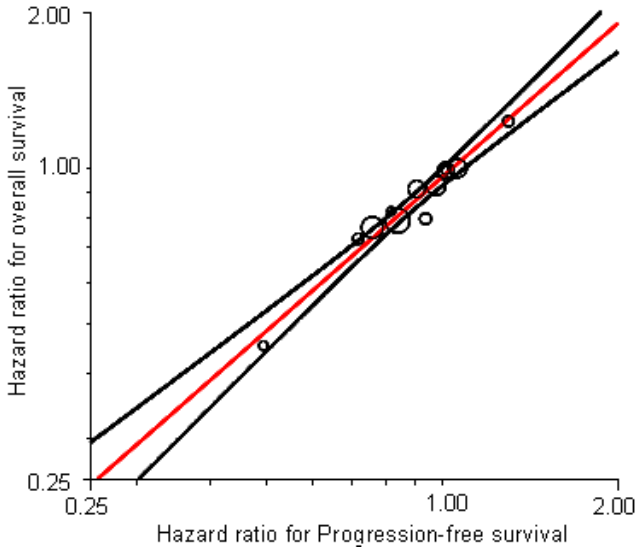


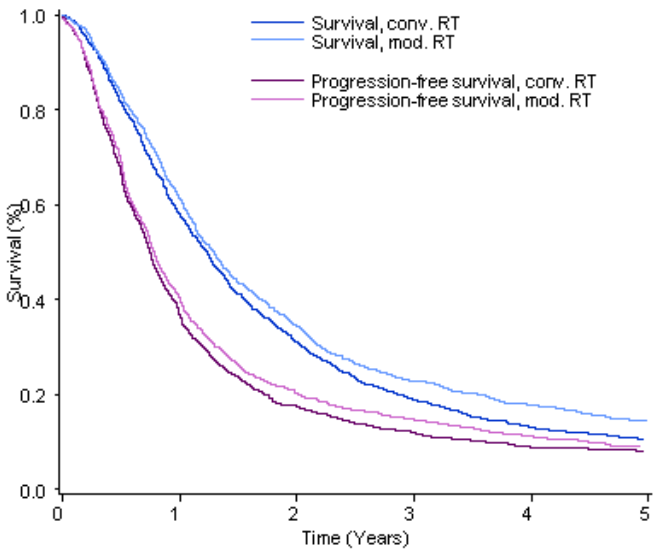
R^2 – weighted regression	Intercept [95% CI] – weighted regression	Slope [95% CI] – weighted regression
0.92	-0.03 [-0.12 – 0.06]	0.90 [0.55 – 1.25]

Evaluating effect of modified radiotherapy versus conventional radiotherapy in lung cancer

Progression-free survival

Hougaard copula	Progression-free survival over the entire time range
Number of trials (number of patients)	12 (2 685)
N events OS	2 471
N events PFS	2 562
Individual level	
ρ^2	0.81 [0.81-0.81]
Trial level, unweighted	
R^2	0.96 [0.93-0.98]
Regression equation, unweighted	log(HR OS)=-0.04+0.99.log(HR PFS)
STE	1.00

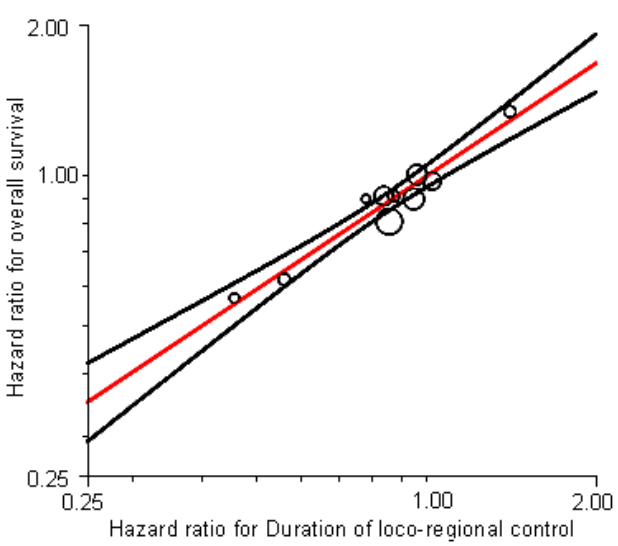


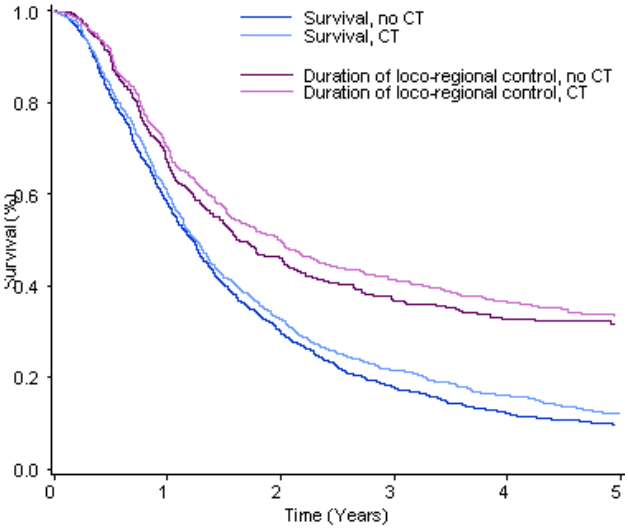


R^2 – weighted regression	Intercept [95% CI] – weighted regression	Slope [95% CI] – weighted regression
0.94	-0.04 [-0.08 – -0.01]	0.94 [0.78 – 1.11]

Loco-regional control

Hougaard copula	Loco-regional control over the entire time range
Number of trials (number of patients)	10 (2 079)
N events OS N events LRC	1 915 894
Individual level	
ρ^2	0.61 [0.61-0.61]
Trial level, unweighted	
R^2	0.95[0.91-0.98]
Regression equation, unweighted	log(HR OS)= 0.00 +0.75.log(HR LRC)
STE	0.95





R^2 – weighted regression	Intercept [95% CI] – weighted regression	Slope [95% CI] – weighted regression
0.88	-0.03 [-0.08 – 0.03]	0.76 [0.53 – 0.99]

Summary of unweighted regression lines

Table 4: Summary of surrogacy results

	Non weighted Regression intercept	[	95%	CI	]	Non weighted Regression slope	[	95%	CI	]	STE
Progression/Disease-free survival											
Operable NSCLC											
Without post-operative radiotherapy	0.08	[	0.02	0.14	]	0.98	[	0.82	1.14	]	0.88
With post-operative radiotherapy	0.01	[	-0.02	0.04	]	0.66	[	0.57	0.76	]	0.95
Locally advanced NSCLC											
Sequential chemotherapy	0.04	[	-0.02	0.10	]	1.22	[	0.96	1.48	]	0.93
Concurrent chemotherapy	0.01	[	-0.03	0.05	]	0.87	[	0.78	0.96	]	0.95
Sequential versus concurrent chemotherapy	-0.01	[	-0.13	0.11	]	0.85	[	0.44	1.27	]	0.90
Locally advanced lung cancer											
Radiotherapy	-0.04	[	-0.08	0.00	]	0.99	[	0.84	1.14	]	1.00
Loco-regional control											
Locally advanced NSCLC											
Concurrent chemotherapy	0.00	[	-0.10	0.09	]	0.64	[	0.46	0.83	]	0.89
Locally advanced lung cancer											
Radiotherapy	0.00	[	-0.05	0.05	]	0.75	[	0.61	0.90	]	0.95

Appendix A9: Sensitivity analysis: different cut-off points

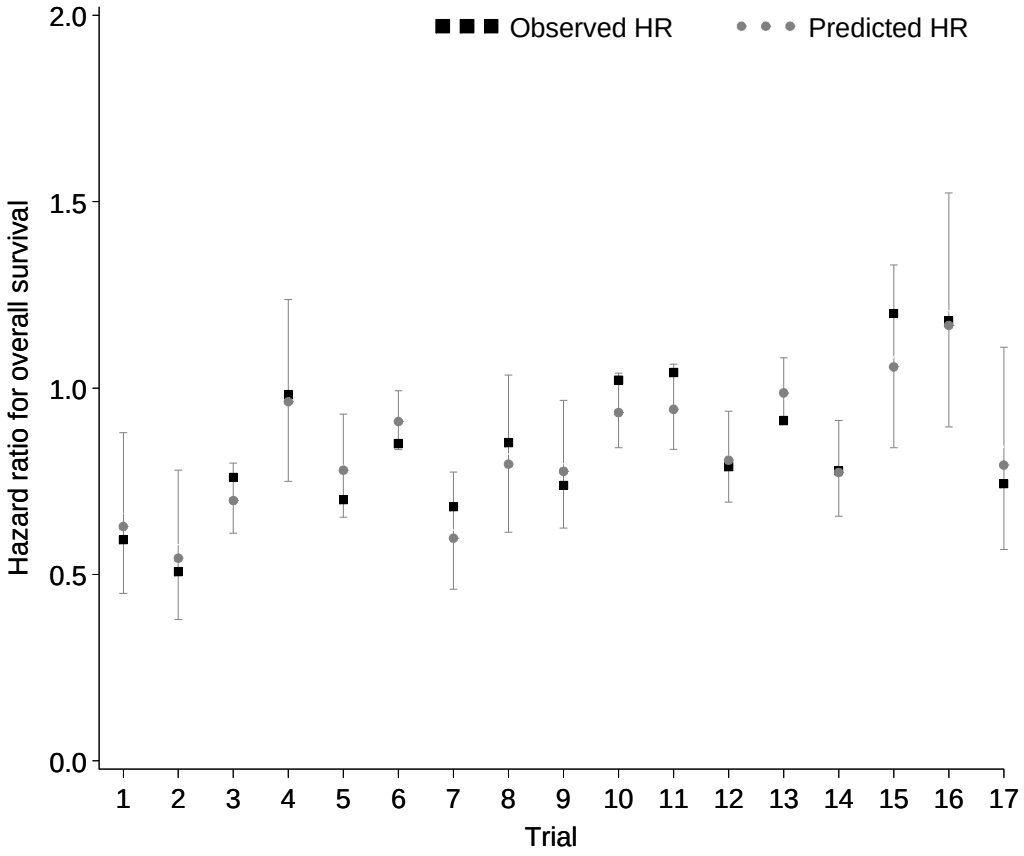
Different cut-off time points are explored for DFS/PFS. OS is censored at 5 years.

	Number of events (% of total events)	Individual level	Trial level, unweighted			STE
		ρ^2	R^2	Intercept	Slope	
Adjuvant, CT vs no CT						
Cut-off at 1 yr	1077 (43%)	0.66 [0.66-0.66]	0.62 [0.47-0.76]	0.02 [-0.10;0.15]	0.67 [0.38-0.96]	0.84
Cut-off at 1.5 yr	1436 (57%)	0.71 [0.71-0.71]	0.75 [0.65-0.86]	0.05 [-0.04;0.16]	0.78 [0.54-1.03]	0.85
Cut-off at 2 yr	1658 (66%)	0.74 [0.74-0.74]	0.86 [0.80-0.92]	0.07 [-0.01;0.14]	0.82 [0.64-1.00]	0.86
Cut-off at 2.5 yr	1845 (73%)	0.76 [0.76-0.76]	0.87 [0.80-0.93]	0.06 [-0.01;0.13]	0.80 [0.62-0.97]	0.86
Cut-off at 3 yr	1994 (79%)	0.77 [0.77-0.77]	0.88 [0.83-0.93]	0.06 [-0.01;0.13]	0.81 [0.65-0.97]	0.87
Adjuvant, RT+ CT vs RT						
Cut-off at 1 yr	869 (52%)	0.72 [0.72-0.72]	0.95 [0.92-0.99]	0.02 [-0.04;0.07]	0.61 [0.46-0.77]	0.90
Cut-off at 1.5 yr	1091 (65%)	0.76 [0.76-0.76]	0.95 [0.92-0.99]	0.01 [-0.05;0.07]	0.60 [0.45-0.76]	0.90
Cut-off at 2 yr	1221 (73%)	0.77 [0.77-0.77]	0.94 [0.90-0.98]	0.01 [-0.05;0.08]	0.59 [0.42-0.77]	0.89
Cut-off at 2.5 yr	1320 (79%)	0.79 [0.79-0.79]	0.96 [0.92-0.99]	0.02 [-0.04;0.07]	0.67 [0.50-0.84]	0.90
Cut-off at 3 yr	1411 (84%)	0.81 [0.81-0.81]	0.96 [0.93-0.99]	0.01 [-0.05;0.06]	0.66 [0.51-0.82]	0.92
Locally advanced, RT + Seq. CT vs RT						
Cut-off at 1 yr	969 (70%)	0.76 [0.76-0.76]	0.79 [0.67-0.92]	-0.04 [-0.14;0.07]	1.13 [0.56-1.71]	0.95
Cut-off at 1.5 yr	1160 (84%)	0.74 [0.74-0.74]	0.86 [0.77-0.95]	-0.03 [-0.10;0.05]	0.98 [0.58-1.38]	0.96
Cut-off at 2 yr	1244 (90%)	0.74 [0.74-0.74]	0.77 [0.63-0.91]	-0.02 [-0.12;0.08]	0.98 [0.44-1.52]	0.94
Locally advanced, RT + Conc. CT vs RT						
Cut-off at 1 yr	1689 (71%)	0.76 [0.76-0.76]	0.93 [0.90-0.97]	0.00 [-0.05;0.05]	0.75 [0.63-0.87]	0.94
Cut-off at 1.5 yr	1990 (83%)	0.77 [0.77-0.77]	0.94 [0.90-0.97]	0.00 [-0.05;0.05]	0.77 [0.65-0.89]	0.94
Cut-off at 2 yr	2149 (90%)	0.79 [0.79-0.79]	0.95 [0.92-0.97]	0.00 [-0.04;0.05]	0.80 [0.68-0.91]	0.94
Locally advanced, RT+ Seq. CT vs RT						
Cut-off at 1 yr	773 (71%)	0.72 [0.72-0.72]	0.64 [0.41-0.87]	-0.07 [-0.22;0.08]	0.60 [-0.02;1.22]	0.92
Cut-off at 1.5 yr	912 (83%)	0.76 [0.76-0.76]	0.70 [0.49-0.87]	-0.06 [-0.21;0.08]	0.61 [0.05-1.17]	0.91
Cut-off at 2 yr	964 (88%)	0.77 [0.77-0.77]	0.75 [0.58-0.92]	-0.05 [-0.19;0.08]	0.64 [0.13-1.16]	0.91
MAR-LC						
Cut-off at 1 yr	1644 (64%)	0.72 [0.72-0.72]	0.77 [0.66-0.88]	-0.09 [-0.16;-0.02]	0.86 [0.53-1.19]	1.02
Cut-off at 1.5 yr	2004 (78%)	0.74 [0.74-0.74]	0.83 [0.74-0.91]	-0.06 [-0.13;0.01]	1.05 [0.71-1.38]	1.00
Cut-off at 2 yr	2165 (85%)	0.76 [0.76-0.76]	0.85 [0.78-0.93]	-0.05 [-0.11;0.02]	1.02 [0.72-1.32]	0.99

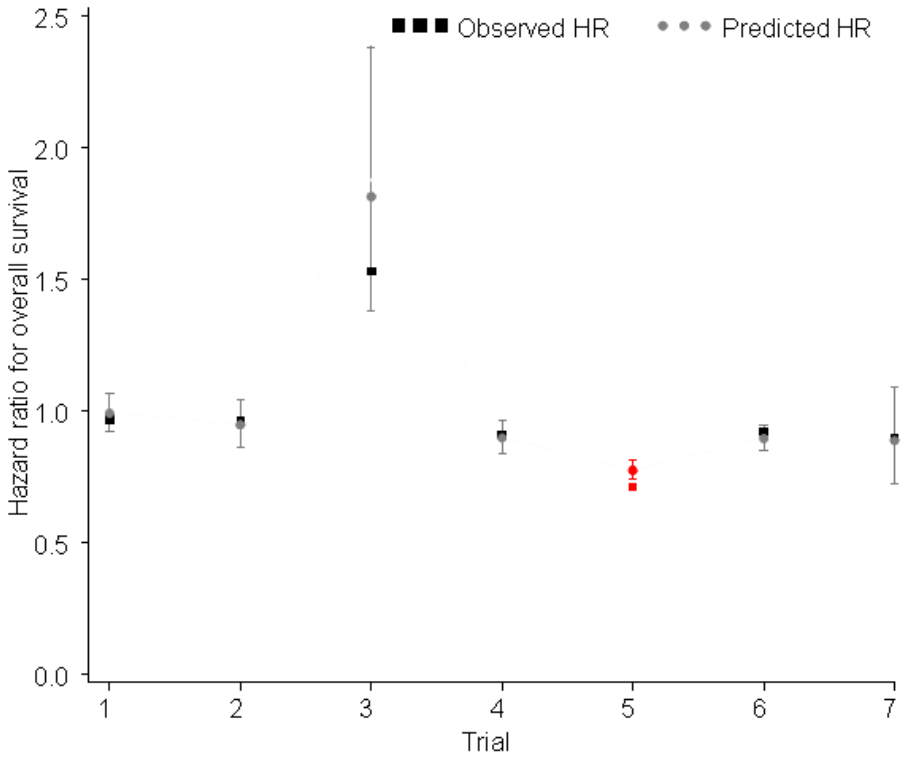
CT=chemotherapy; conc=concurrent;RT=radiotherapy, sequ=sequential See appendix 8 for other abbreviations

Appendix A10: Leave-one out crossvalidation results

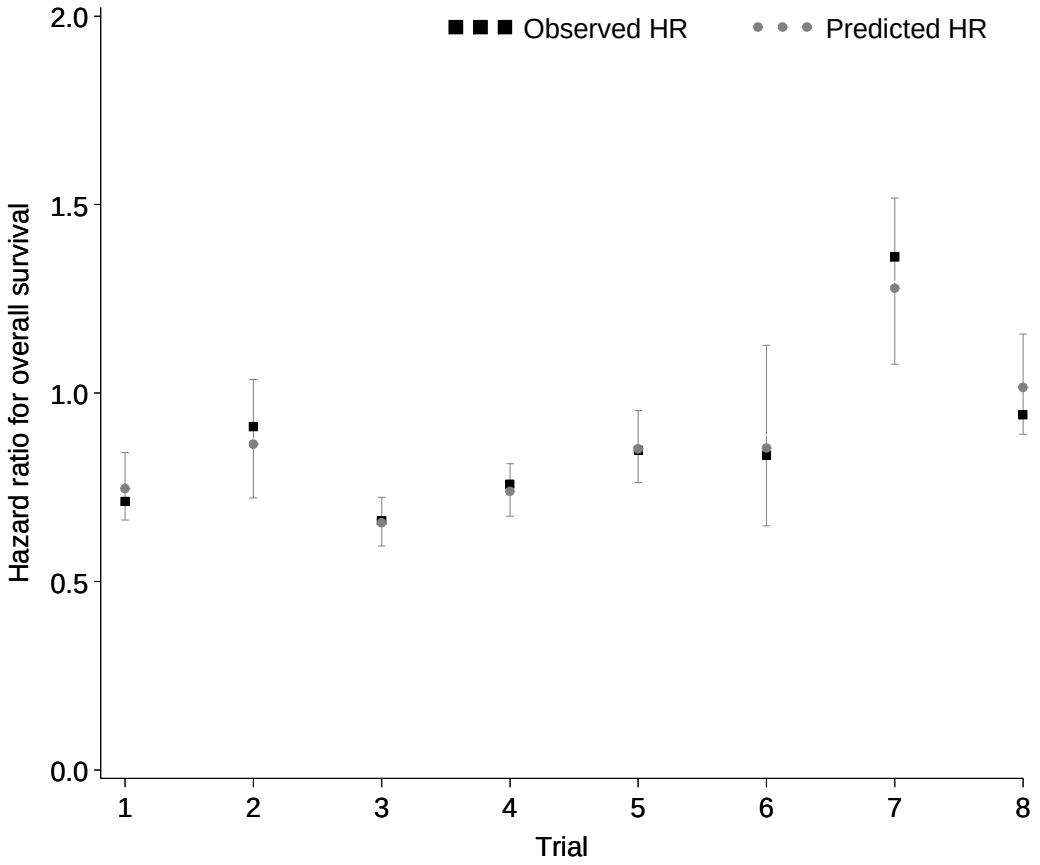
Operable NSCLC without post-operative radiotherapy – DFS



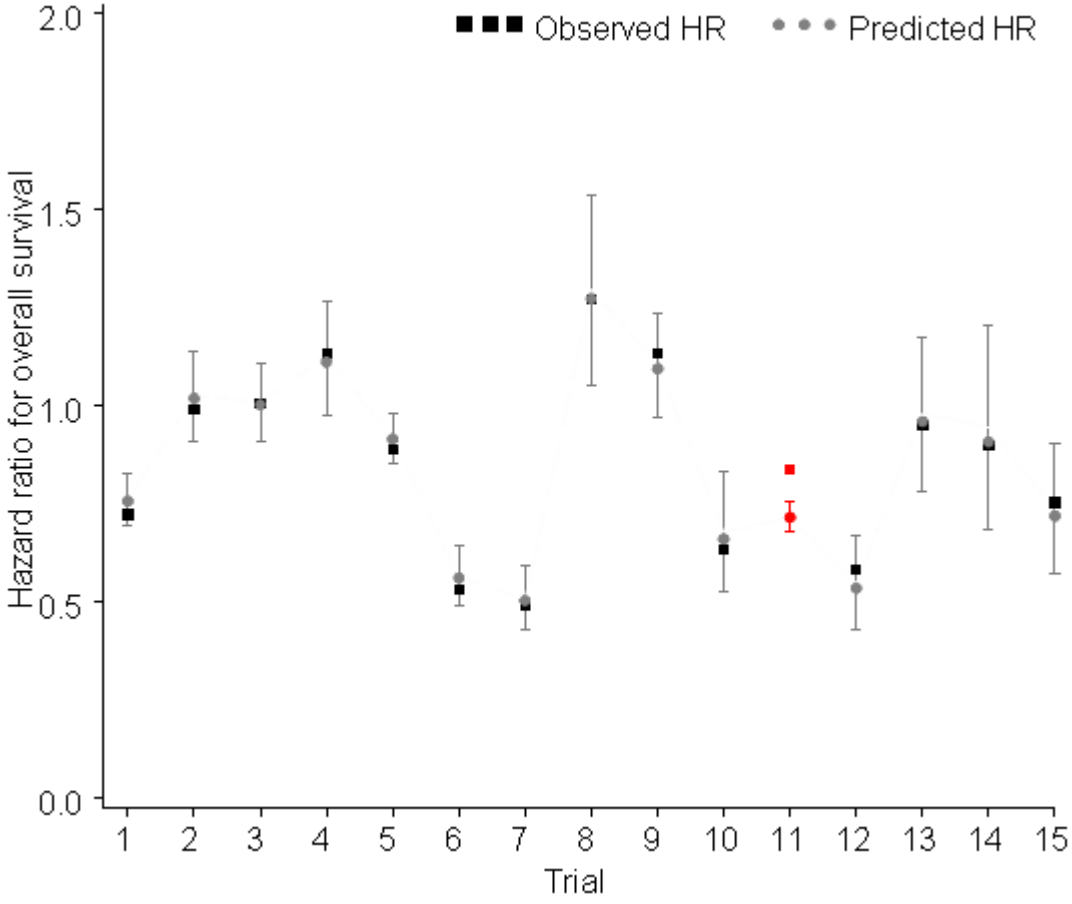
Operable NSCLC with post-operative radiotherapy - DFS



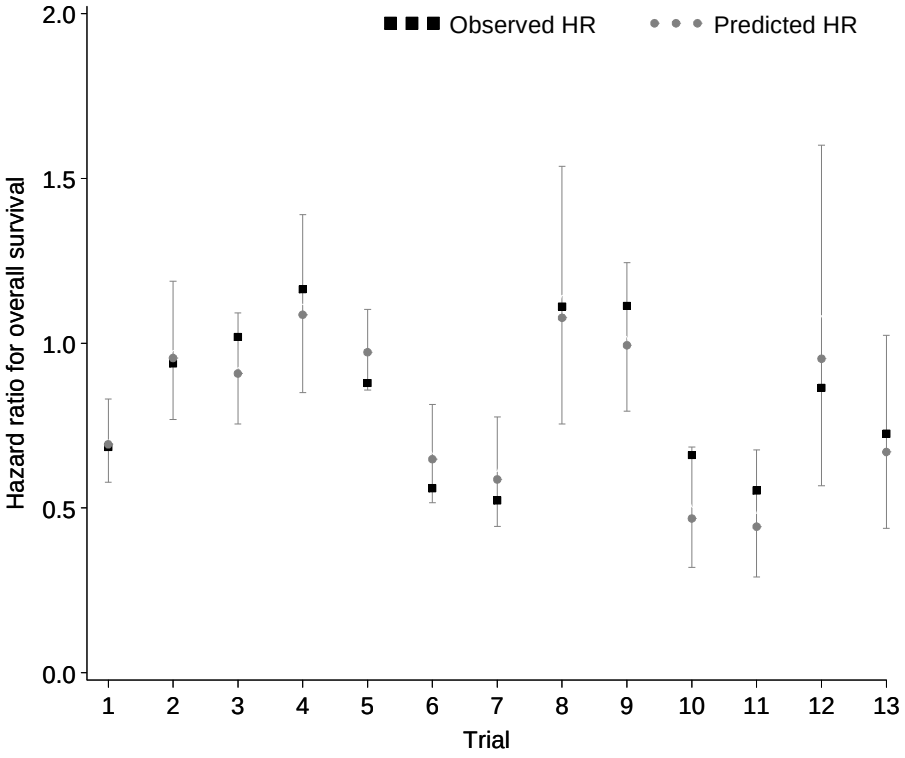
Locally advanced NSCLC, sequential chemotherapy – PFS



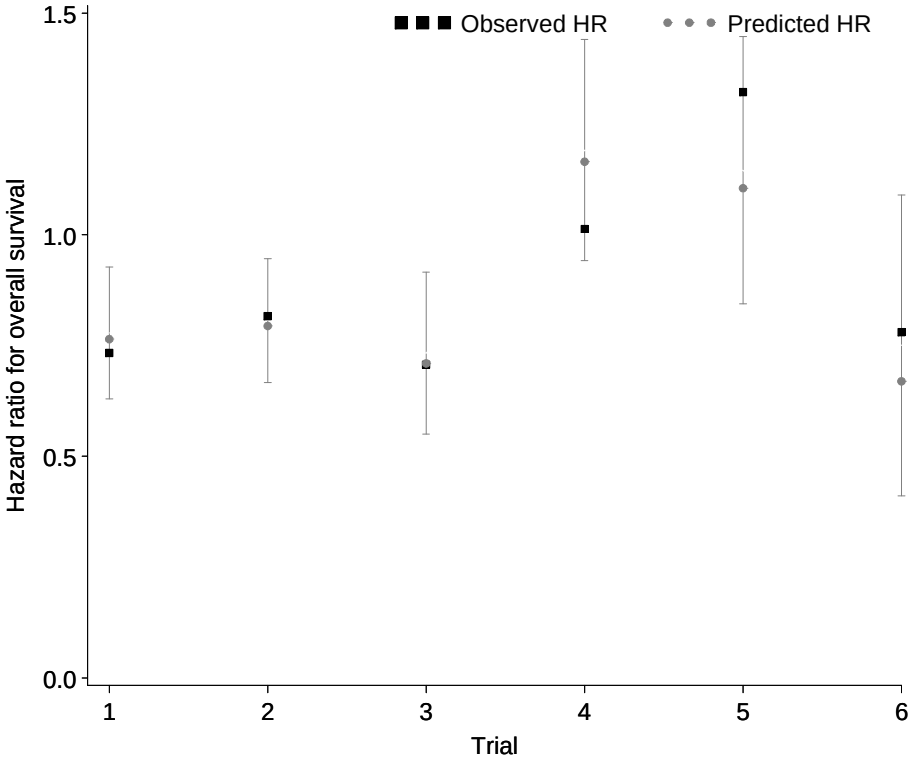
Locally advanced NSCLC, concurrent chemotherapy – PFS



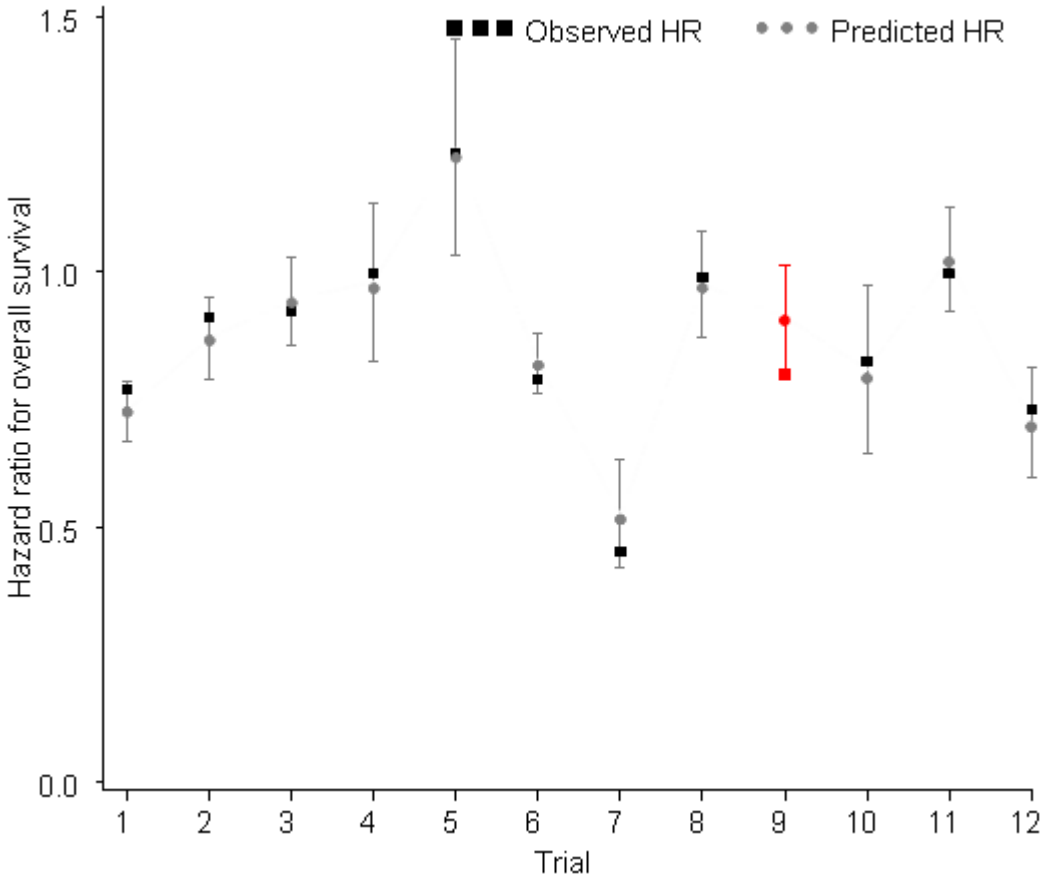
Locally advanced NSCLC, concurrent chemotherapy – LRC



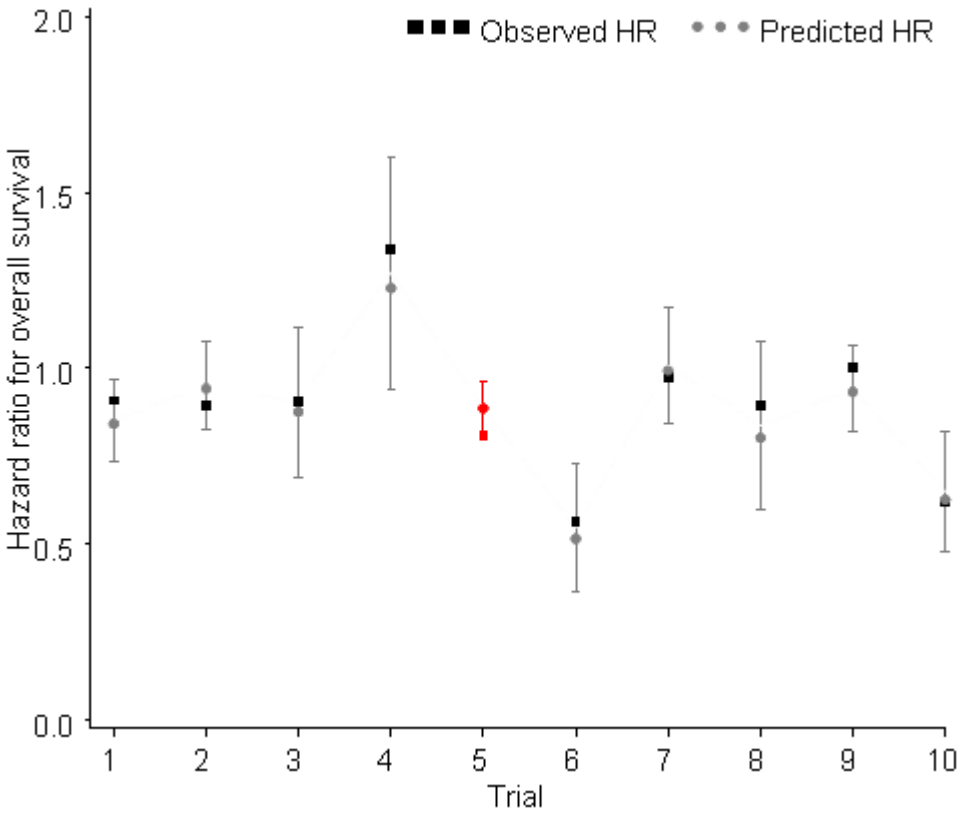
Locally advanced NSCLC, sequential versus concurrent chemotherapy – PFS



Modified radiotherapy – PFS



Modified radiotherapy - LRC



Results are for validation of DFS/PFS if no otherwise specified.

Table 5: Summary of cross-validation results

Meta-analysis	Number of trials with predicted effect on OS included in the 95% prediction interval / Total number of trials
Operable NSCLC	
Without radiotherapy	17 / 17
With radiotherapy	6 / 7
Locally advanced NSCLC	
Sequential chemotherapy	8 / 8
Concurrent chemotherapy	14 / 15 (13 / 13 for LRC)
Sequential versus concurrent chemotherapy	6 / 6
Locally advanced lung cancer	
Radiotherapy	11 / 12 (9/10 for LRC)

DFS=disease-free survival, LRC=loco-regional control, OS=overall survival, PFS=progression-free survival