Web-appendix 1: searching strategy

Base	Search strategy	Limites	References	Date
PubMed MEDLINE	(("Lung Neoplasms/radiotherapy"[MeSH] AND Randomized Controlled Trial[ptyp]) OR ("Lung Neoplasms/radiotherapy"[MAJR] AND "Randomized Controlled Trials"[MeSH Terms]) OR ("Lung Neoplasms"[MAJR] AND (radiother*[Title] OR radiat*[Title]) AND random*[Title]) OR (lung[Title] AND (radiother*[Title] OR radiat*[Title]) AND random*[Title])) AND ("1980"[PDAT] : "3000"[PDAT])	2007-1980	575 Fichier joint pubmed-resultcancer poumon radither random 11 01 07.txt	11-janv.-07
EMBASE via Datastar Dialog	(LUNG-CANCER-RT.MJ. OR LUNG.TI. AND CANCER.TI. AND radiother$.TI.) AND (random$.TI. OR RANDOMIZED-CONTROLLED-TRIAL.DE.) AND CLINICAL-TRIAL#	2007-1980	125 Fichier joint	11-janv.-07
Cochrane Central Register of Controlled Trials	There are 5 results out of 479462 records for: "lung cancer radiotherapy and randomized in Publication Type not PubMed, from 1980 to 2007 in The Cochrane Central Register of Controlled Trials"	2007-1980	1 Fichier joint	11-janv.-07
ASTRO Annual Meeting	http://www.redjournal.org/content/astro_abstracts	2006-2005	8	12-Jan-07
ASCO's comprehensive database of abstracts http://www.asco.org/	search for lung in Title and randomized in Title and radiotherapy in Title within selected meetings returned 14 items.	2006-1995	14	12-Jan-07

- Web-appendix 2: excluded trials
- *Absence of arm with conventional radiotherapy*
  - Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Pajak TF. A Randomized Phase I/II Trial of Hyperfractionated Radiation Therapy With Total Doses of 60.0 Gy to 79.2 Gy: Possible Survival Benefit With 69.6 Gy in Favorable Patients With Radiation Therapy Oncology Group Stage III Non-Small-Cell Lung Carcinoma: Report of Radiation Therapy Oncology Group 83-11. J Clin Oncol 1990; 8:1543-1555.
  - Kagami Y, Nishio M, Narimatsu N, Ogawa H, Sakurai T. Prospective randomized trials comparing hyperfractionated radiotherapy with conventional radiotherapy in stage III non-small cell lung cancer. Nippon Igaku Hoshasen Gakkai Zasshi 1992; 52:1452-1455.
  - Coy P, Hodson I, Payne DG, Evans WK, Feld R, MacDonald AS, Osoba D, Pater JL. The effect of dose of thoracic irradiation on recurrence in patients with limited stage small cell lung cancer. Initial results of a Canadian Multicenter Randomized Trial. Int J Radiat Oncol Biol Phys 1988; 14:219-226.
- *Counfounded by different chemotherapy in the two arms*
  - Nalca Andrieu M, Eraslan A, Hicsonmez A, Guney Y. Concomitant boost technique versus conventional radiotherapy in locally advanced non-small cell lung cancer. Radiother Oncol 2006; 81(Suppl 1):S385. [Poster]
  - Wang G, Song M, Xu H, Fang Y. prospective trial of combined hyperfractionated radiotherapy and bronchial arterial infusion of chemotherapy for locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys1996;34:309-313.
- *Trials comparing different doses and durations of conventional or hypofractionated (3 or 4 Gy) radiotherapy*
  - Perez CA, Stanley K, Rubin P et a/. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat cell carcinoma of the lung: Preliminary report by the Radiation Therapy Oncology Group. Cancer 1980 45: 2744-27 5 3,
  - Perez CA, Stanley K, Grundy G et al. Impact of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat cell carcinoma of the lung: Report by the Radiation Therapy Oncology Group. Cancer 1982; 50: 1091-1099.
  - Perez CA, Pajak TF, Rubin P, Simpson JR, Mohiuddin M, Brady LW, Perez-Tamayo R, Rotman M.Long-Term Observations of the Patterns of Failure in Patients With Unresectable Non-Oat Cell Carcinoma of the Lung Treated With Definitive Radiotherapy. Report by the Radiation Therapy Oncology Group. Cancer 1987 ;59 :1874-1881.
- *Randomized phase I*
  - Tsuchiya S, Ohe Y, Sugiura T, Fuwa N, Kitamoto Y, Mori K, Kobayashi H, Nakata K, Sawa T, Hirai K, Etoh T, Saka H, Saito A, Fukuda H, Ishizuka N, Saijo N. Randomized phase I study of standard-fractionated or accelerated-hyperfractionated radiotherapy with concurrent cisplatin and vindesine for unresectable non-small cell lung cancer: A report of Japan Clinical Oncology Group Study (JCOG 9601). Jpn J Clin Oncol 2001; 31:488-494.

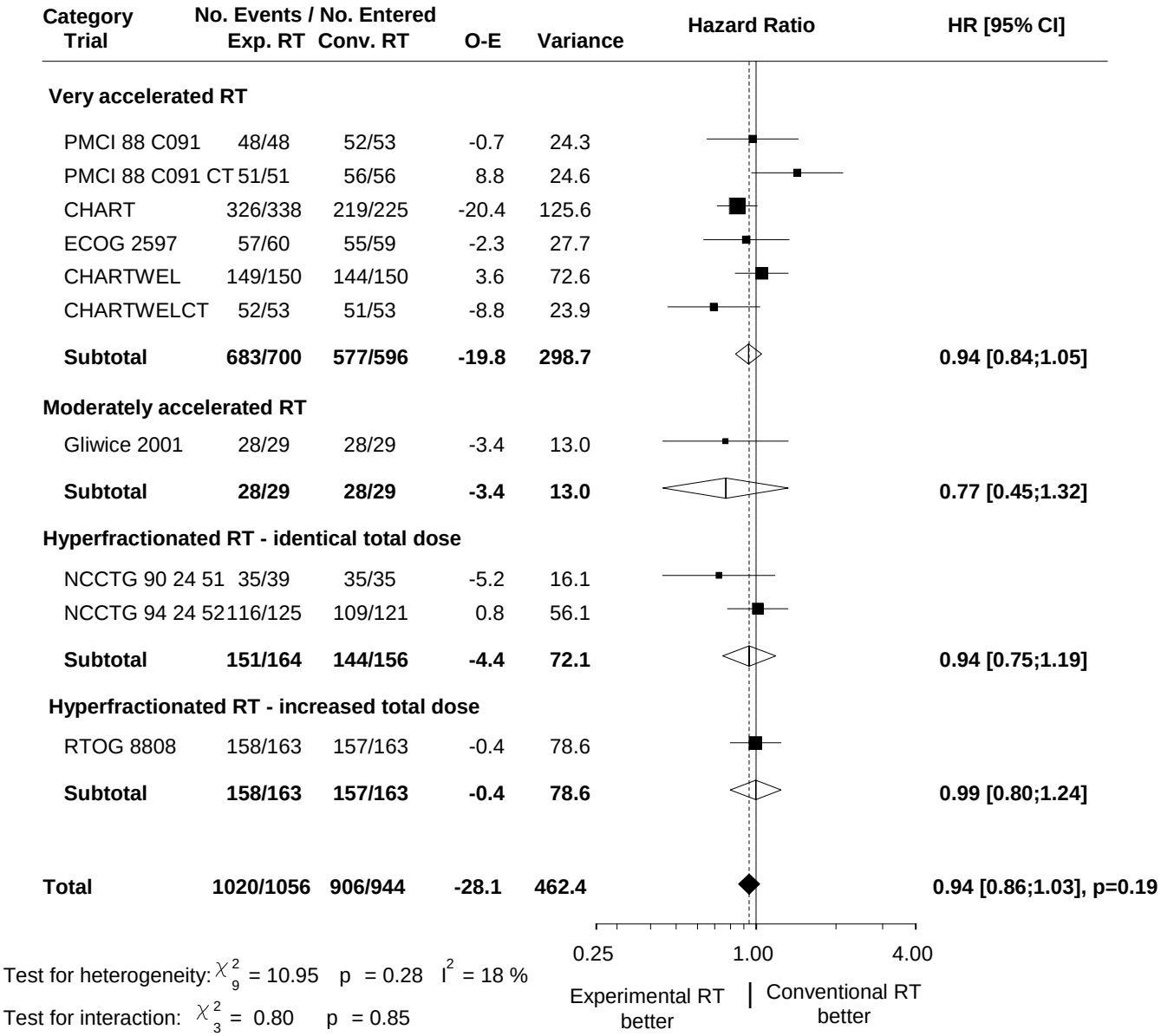
Web-appendix 3: definition of radiotherapy group

ACCELERATION	LOWER	IDENTICAL (+/- 5%)	HIGHER
0-13%		Schild 1990 SCLC NCCTG 90 NCCTG 94	RTOG 88-08
14-49%		ECOG 3588 SCLC Gliwice 2001	
≥ 50%	CHART ECOG 2597 CHARTWEL CHARTWEL CT	PMCI PMCI CT	
	Hyperfractionated < 1.25 Gy / Normal 1.25-1.75 Gy / 1.8-2 Gy	Hyperfractionated < 1.25 Gy / Normal 1.25-1.75 Gy / 1.8-2 Gy	Hyperfractionated < 1.25 Gy / Normal 1.25-1.75 Gy / 1.8-2 Gy

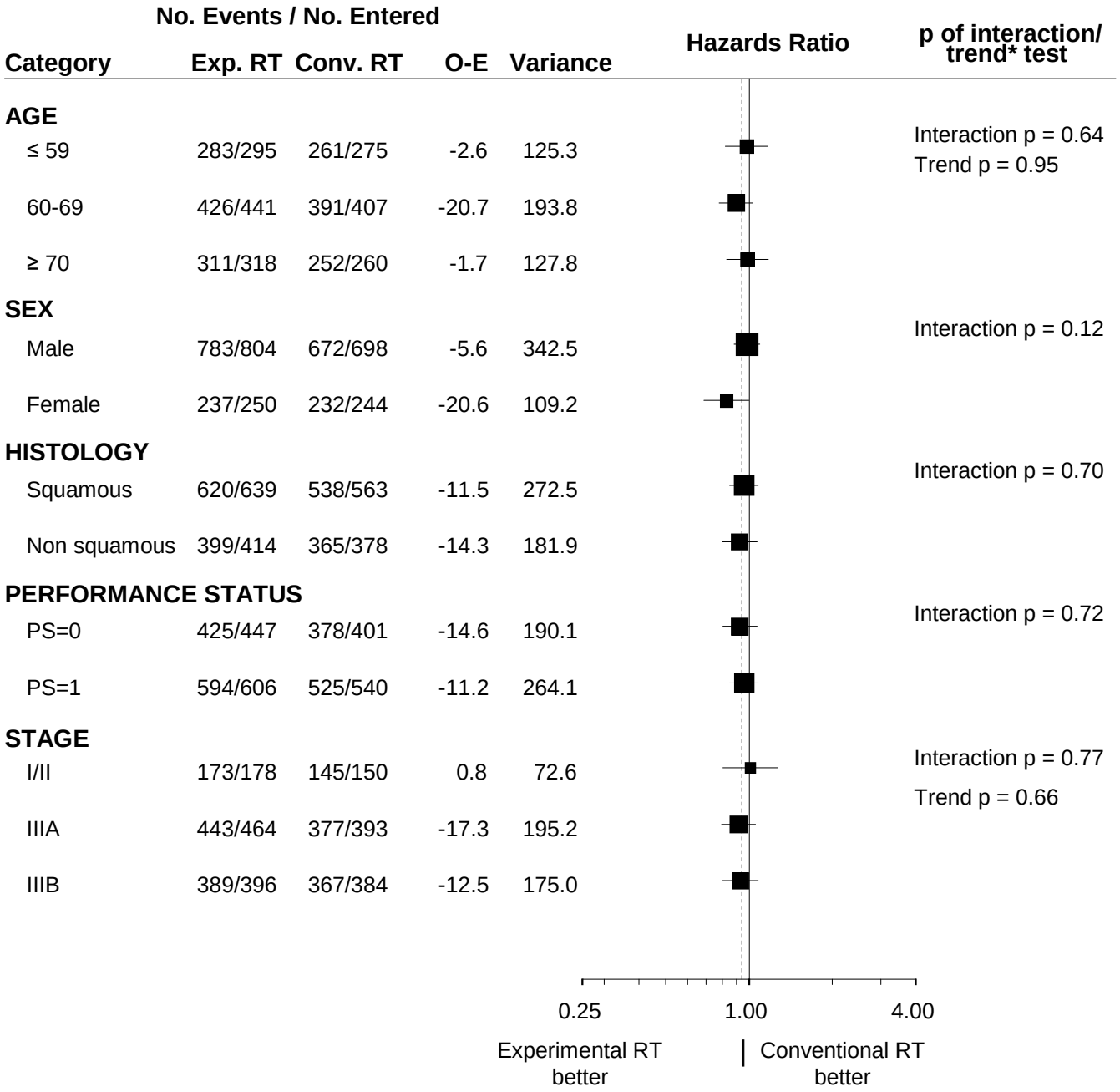
In black: small cell lung cancer trials (n=2)
In blue: very accelerated RT trials (n=6)
In purple: moderately accelerated RT (n=1)
In red: hyperfractionated RT - identical total dose (n=2)
In orange: hyperfractionated RT - increased total dose (n=1)

Characteristics	NSCLC trials n=2000		SCLC trials n=685	
	Conventional RT n=944 (%)	**Modified RT** n=1056 (%)	**Conventional RT** n=342 (%)	**Modified RT** n=343 (%)
Sex				
Male	698 (74)	804 (76)	201 (59)	198 (58)
Female	244 (26)	250 (24)	141 (41)	145 (42)
Unknown	2 (<1)	2 (<1)		
Age				
≤ 59	275 (29)	295 (28)	118 (35)	135 (39)
60 -69	407 (43)	441 (42)	165 (48)	148 (43)
≥ 70	260 (28)	318 (30)	59 (17)	60 (18)
Unknown	2 (<1)	2 (<1)		
Performance status				
PS=0	401 (43)	447 (42)	163 (48)	136 (40)
PS=1	538 (57)	601 (57)	159 (46)	187 (54)
PS=2	2 (<1)	5 (1)	19 (6)	20 (6)
Unknown	3 (<1)	3 (<1)	1 (<1)	
Histology				
Adenocarcinoma	125 (13)	140 (13)	small-cell	small-cell
Squamous	563 (60)	639 (61)	100%	100%
Large cell	49 (5)	61 (6)		
Other	60 (6)	60 (6)		
Non squamous unspecified	107 (11)	116 (11)		
NSCLC unspecified	37 (4)	37 (3)		
Unknown	3 (<1)	3 (<1)		
Stage				
I/II	150 (16)	178 (17)	limited stage	limited stage
III unspecified	3 (<1)	3 (<1)	100%	100%
IIIA	393 (42)	464 (44)		
IIIB	384 (41)	396 (37)		
IV	2 (<1)	3 (<1)		
Unknown	12 (1)	12 (1)		

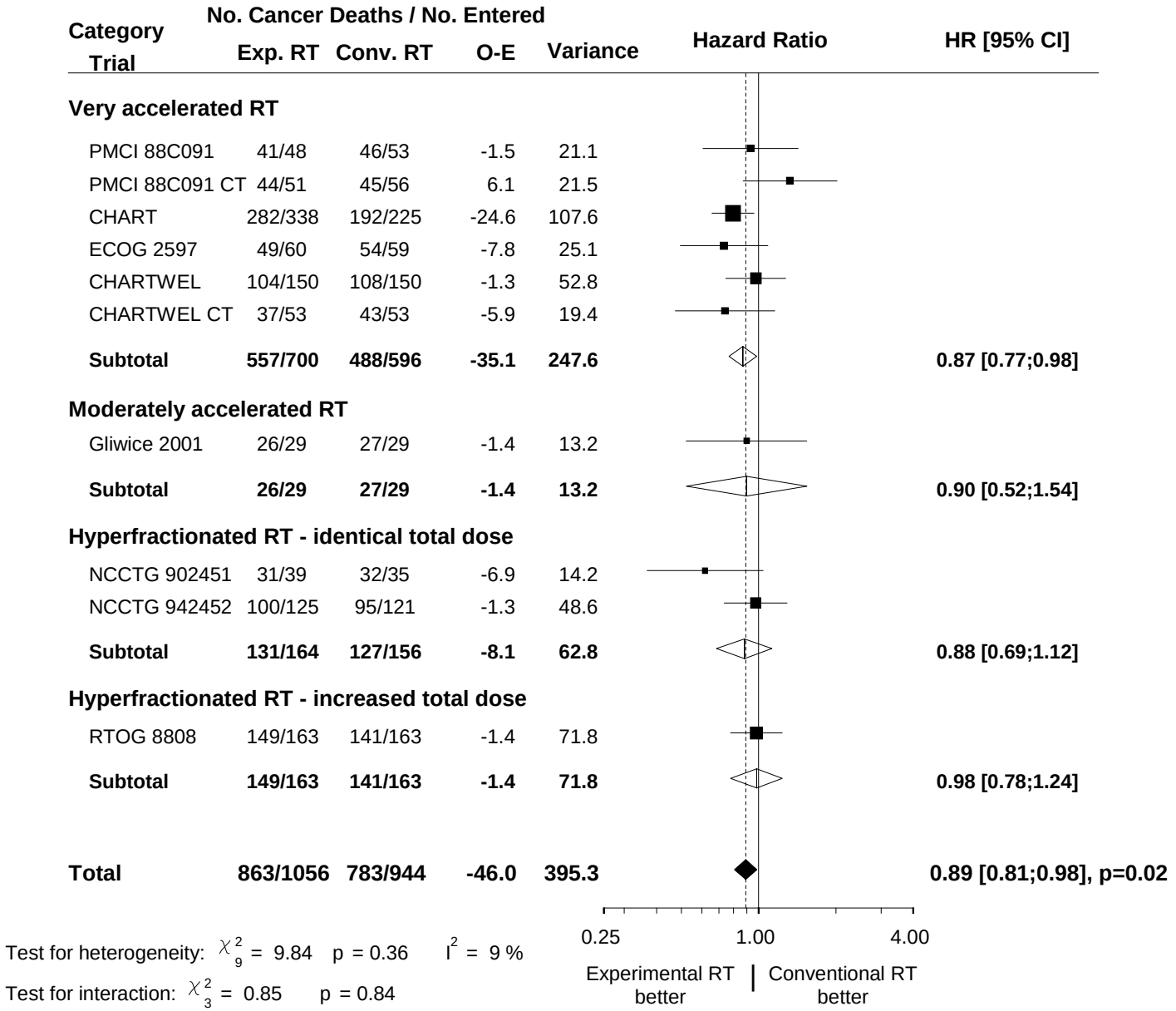
Web-Table 1: Description of randomized patients



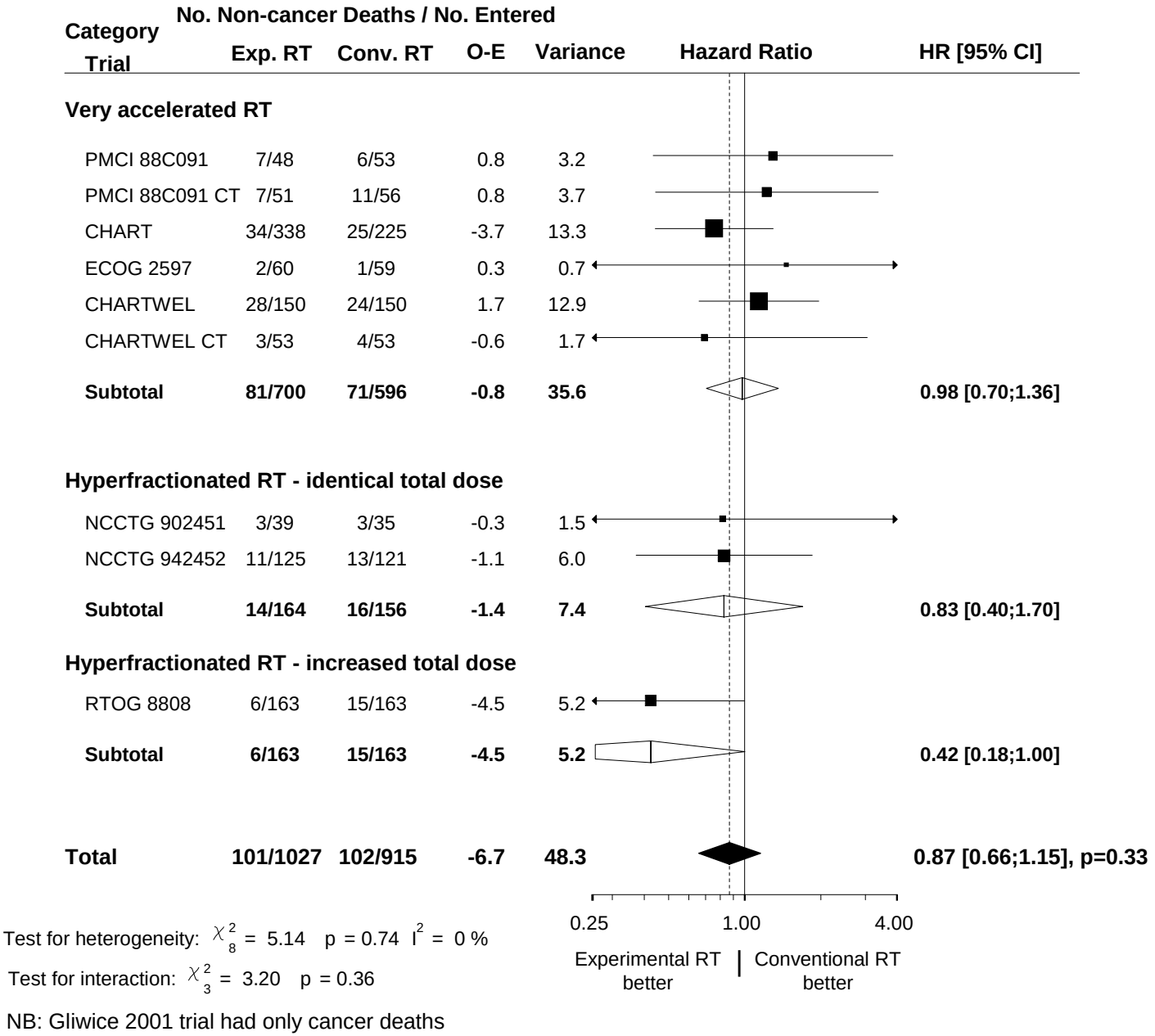
Web-Figure 1: Effect of modified radiotherapy versus conventional radiotherapy on progression-free survival, by radiotherapy types in non-small cell lung cancer trials
Each trial is represented by a square, the center of which denotes the hazard ratio for that trial comparison with the horizontal lines showing the 95% confidence intervals (CIs). The size of the square is directly proportional to the amount of information contributed by the trial. The clear diamonds represent pooled hazard ratios for the trial groups and the black diamond the overall hazard ratios, with the center denoting the hazard ratio and the extremities the 95% CI. The fixed effect model was used.
Conv.: Conventional; **Exp.**: Experimental; **HR**: Hazard ratio; **RT**: Radiotherapy



Web-Figure 2: Effect of modified radiotherapy versus conventional radiotherapy on progression-free survival, by patients characteristics in non-small cell lung cancer trials. See web-Figure 1 for legend details.



Web-Figure 3: Effect of modified radiotherapy versus conventional radiotherapy on cancer deaths, by radiotherapy types in non-small cell lung cancer trials. See web-Figure 1 for legend details.

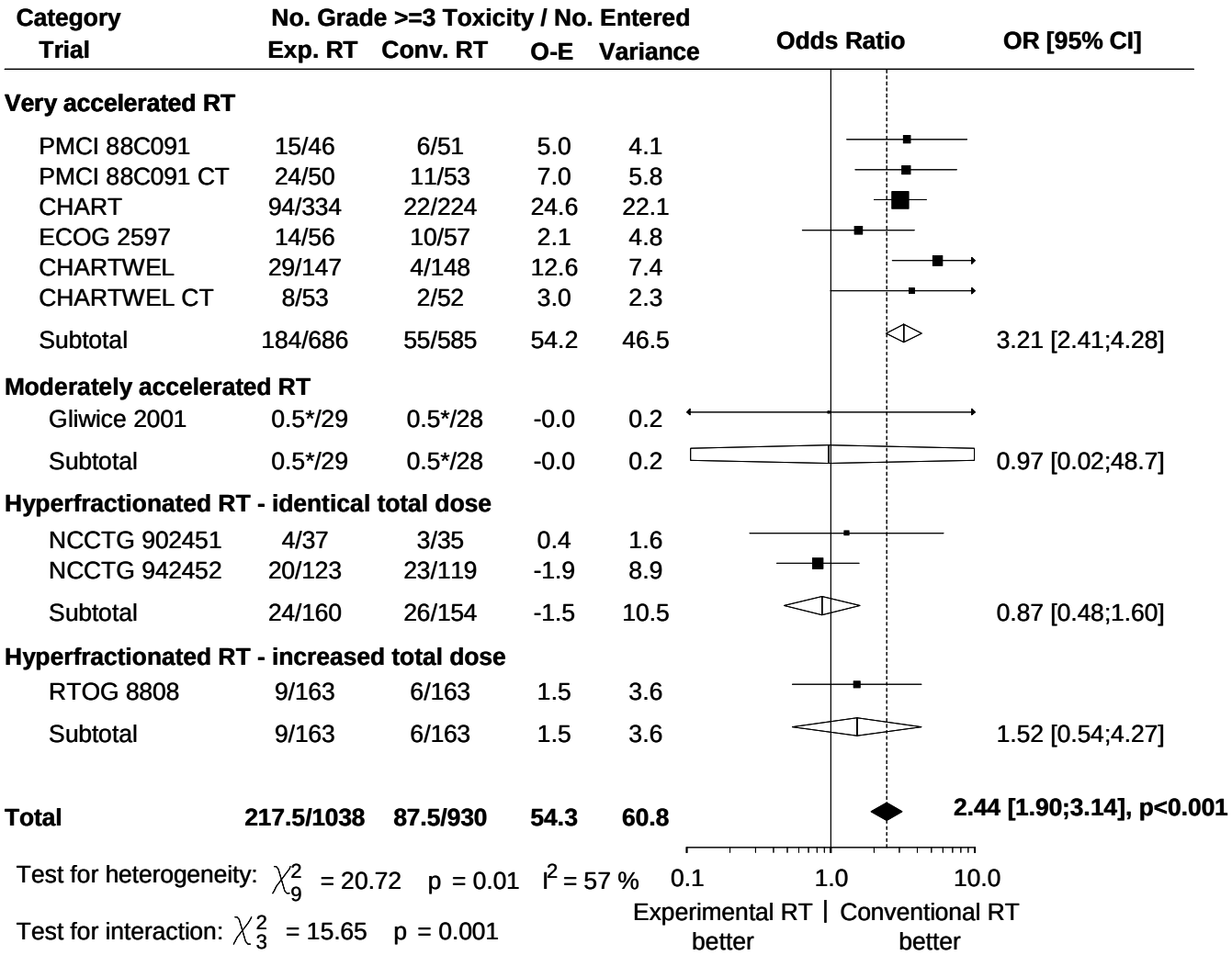


Web-Figure 4: Effect of modified radiotherapy versus conventional radiotherapy on non-cancer deaths, by radiotherapy types in non-small cell lung cancer trials. See web-Figure 1 for legend details.

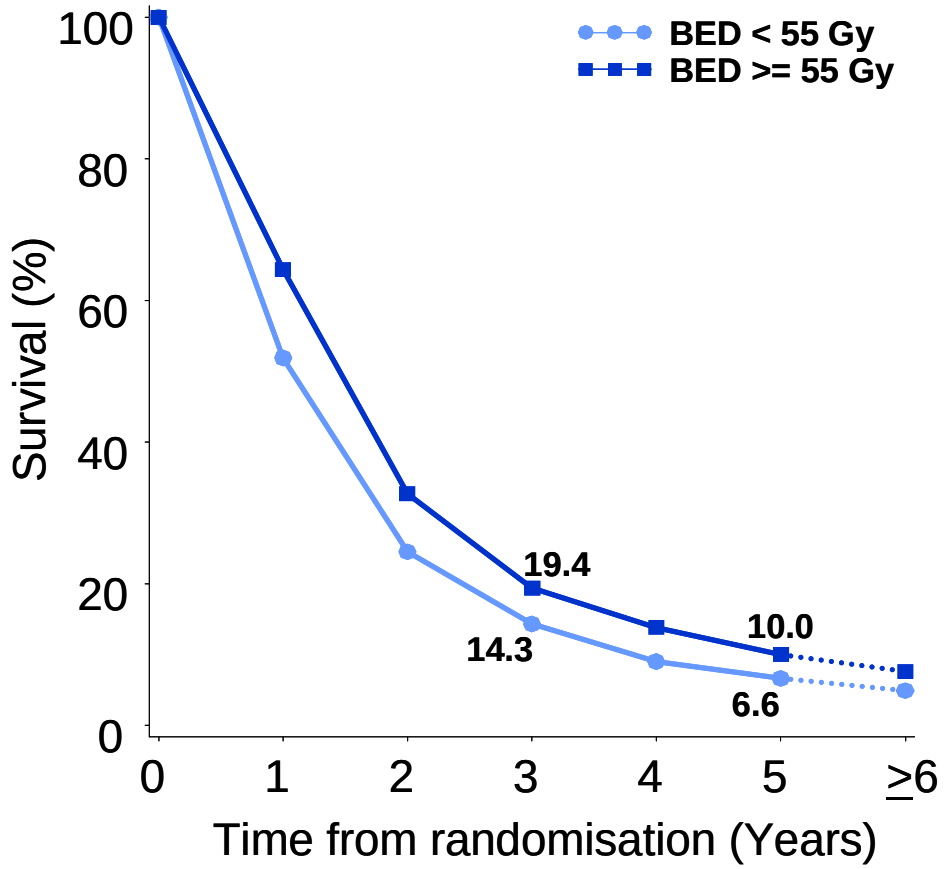
Trial	Total dose (Gy)*		Total no of fractions*		Total duration (days)**	
	Conventional RT	Modified RT	Conventional RT	Modified RT	Conventional RT	Modified RT
RTOG 8808/ ECOG 4588	60 Gy / 90%	69.6 Gy / 85%	30 fr / 89%	58 fr / 84%	40 d / 59%	39 d / 64%
	60.0 [0-69.6]	*69.6 [0-73.9]*	*30 [0-58]*	*58 [0-59]*	*44 [9-66]*	*42 [4-67]*
					8 MD	9 MD
PMCI 88C091	60 Gy / 92%	60 Gy / 100%	30 fr / 92%	30 fr / 100%	40 d / 87%	19 d / 83%
	60.0 [0-60]	*60.0 [60-60]*	*30 [0-30]*	*30 [30-30]*	*42 [5-48]*	*19 [18-24]*
		2 MD		2 MD	1 MD	2 MD
PMCI 88C091CT	60 Gy / 96%	60 Gy / 98%	30 fr / 96%	30 fr / 98%	40 d / 87%	19 d / 94%
	60 [0-60]	*60 [0-60]*	*30 [0-30]*	*30 [0-30]*	*40 [34-53]*	*19 [18-39]*
	2 MD		2 MD		3 MD	1 MD
CHART MRC	60 Gy / 94%	54 Gy / 98%	30 fr / 94%	36 fr / 97%	40 d / 72%	12 d / 95%
	60 [0-66]	*54 [8.5-60.5]*	*30 [0-33]*	*36 [1-36]*	*43 [17-57]*	*12 [1-44]*
		1 MD		1 MD	2 MD	2 MD
CHARTWEL	66 Gy / 95%	60 Gy / 95%	33 fr / 95%	40 fr / 94%	45 d / 83%	18 d / 95%
	66 [0-72]	*60 [0-66]*	*33 [0-58]*	*40 [0-66]*	*45 [10-59]*	*18 [3-47]*
					1 MD	2 MD
CHARTWEL CT	66 Gy / 92%	60 Gy / 98%	33 fr / 92%	40 fr / 96%	45 d / 90%	18 d / 91%
	66 [0-66]	*60 [50-66]*	*33 [0-33]*	*40 [20-40]*	*45 [26-56]*	*18 [5-48]*
					1 MD	
ECOG 2597	64 Gy / 91%	57.6 Gy / 98%	-	-	-	-
	64 [0.6-68.4]	*57.6 [5.8-57.7]*	-	-	-	-
	2 MD	4 MD				

MD: Missing Data
*Results: theoretical / % pts with >90% of theoretical
observed median [range]
**Results: theoretical / % pts with 90% to 110% of theoretical
observed median [range]

Web-Table 2: Observed compliance to treatment (total dose received, number of fractions and duration)

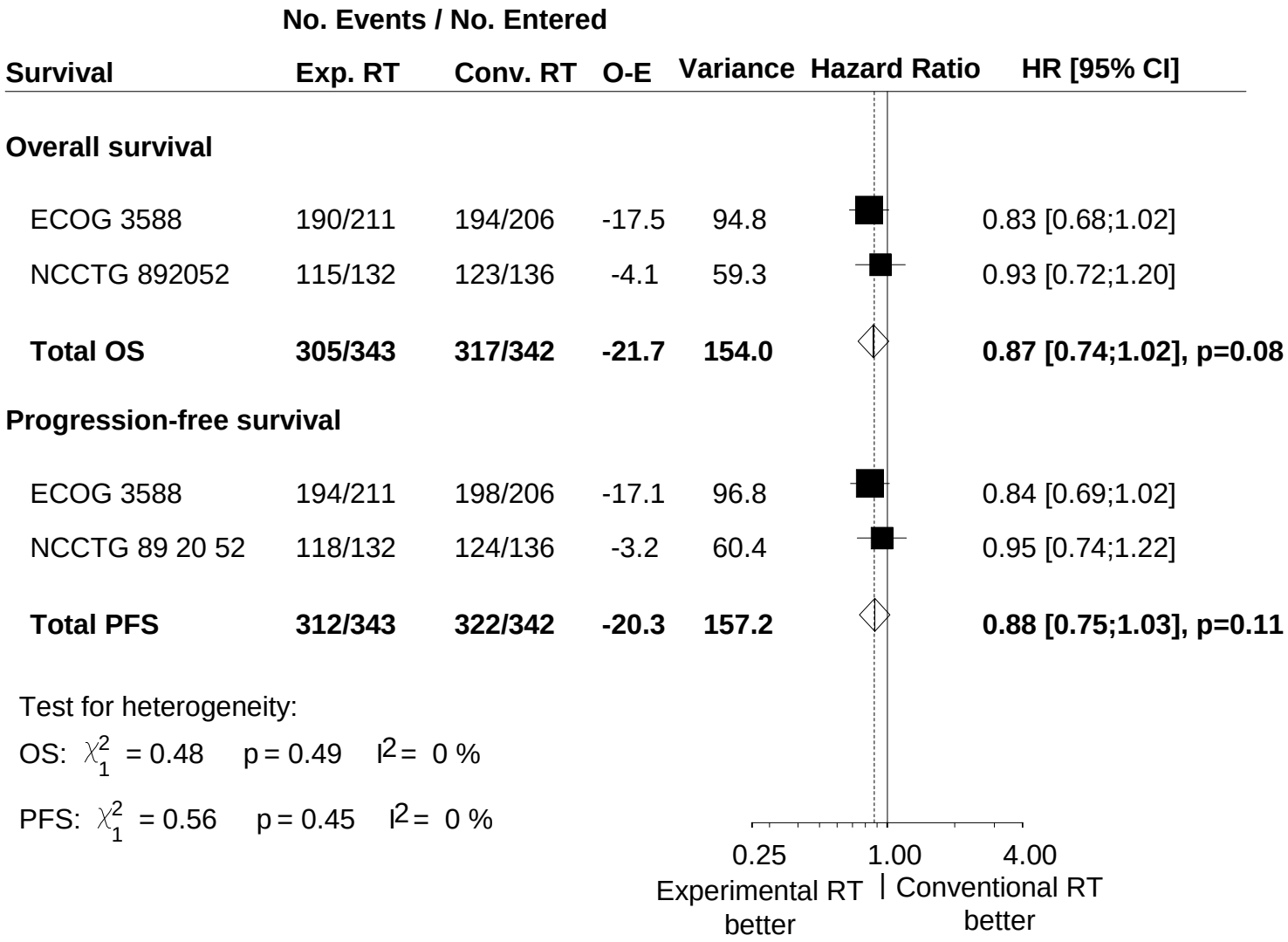


Web-Figure 5: Effect of modified radiotherapy versus conventional radiotherapy on acute esophageal toxicity, by radiotherapy subsets in non-small cell lung cancer trials. See Web-Figure 1 for legend details.

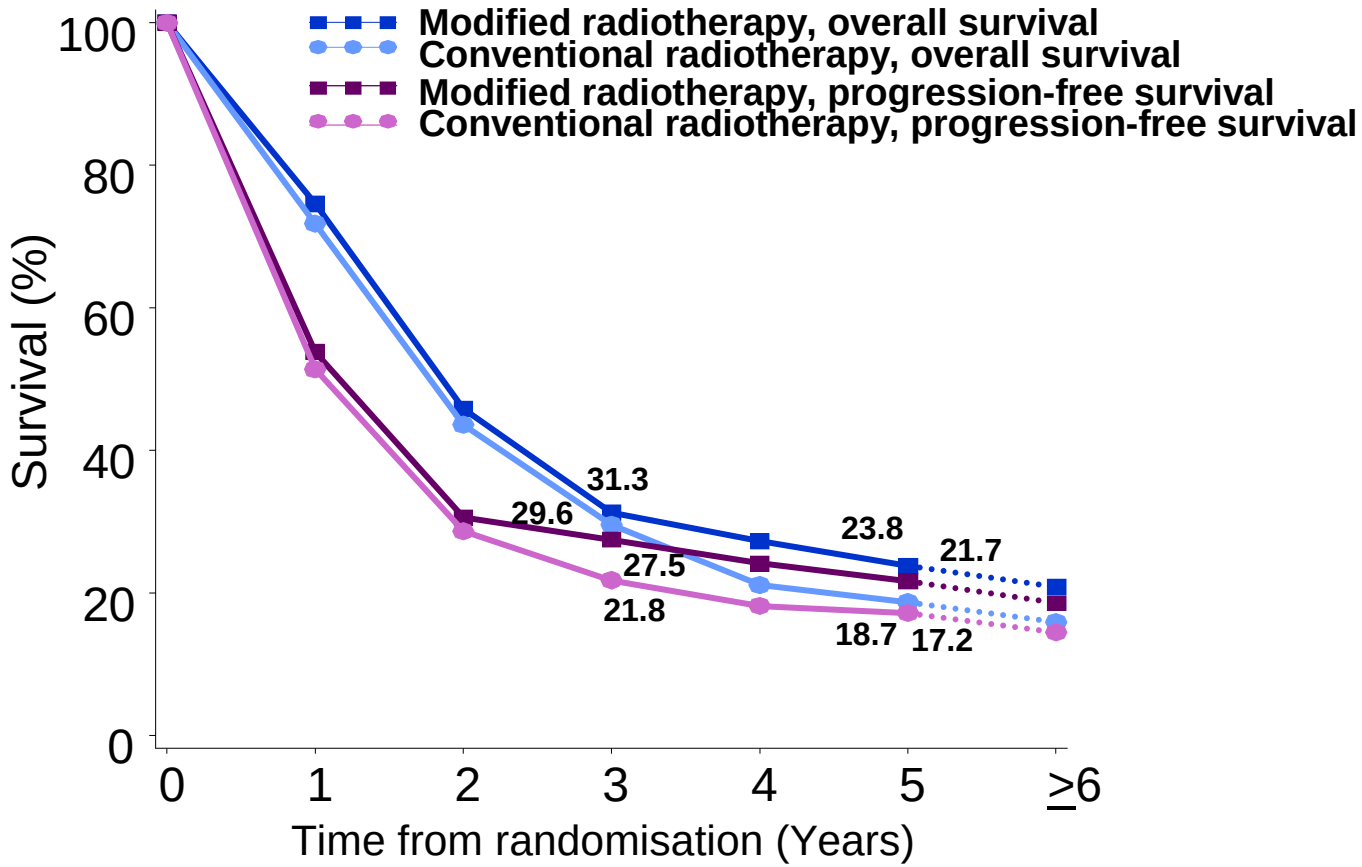


Deaths/ person-years by period	Year 0-2	Year 3-5	≥6
BED < 55 Gy	314 / 408	58 / 114	11 / 41
BED ≥ 55 Gy	738 / 1349	211 / 484	40 / 135

Web-Figure 6: Survival curves according to biological equivalent dose (BED) value. A BED of 55.5 Gy corresponds to 60 Gy in 30 fractions over 40 days.

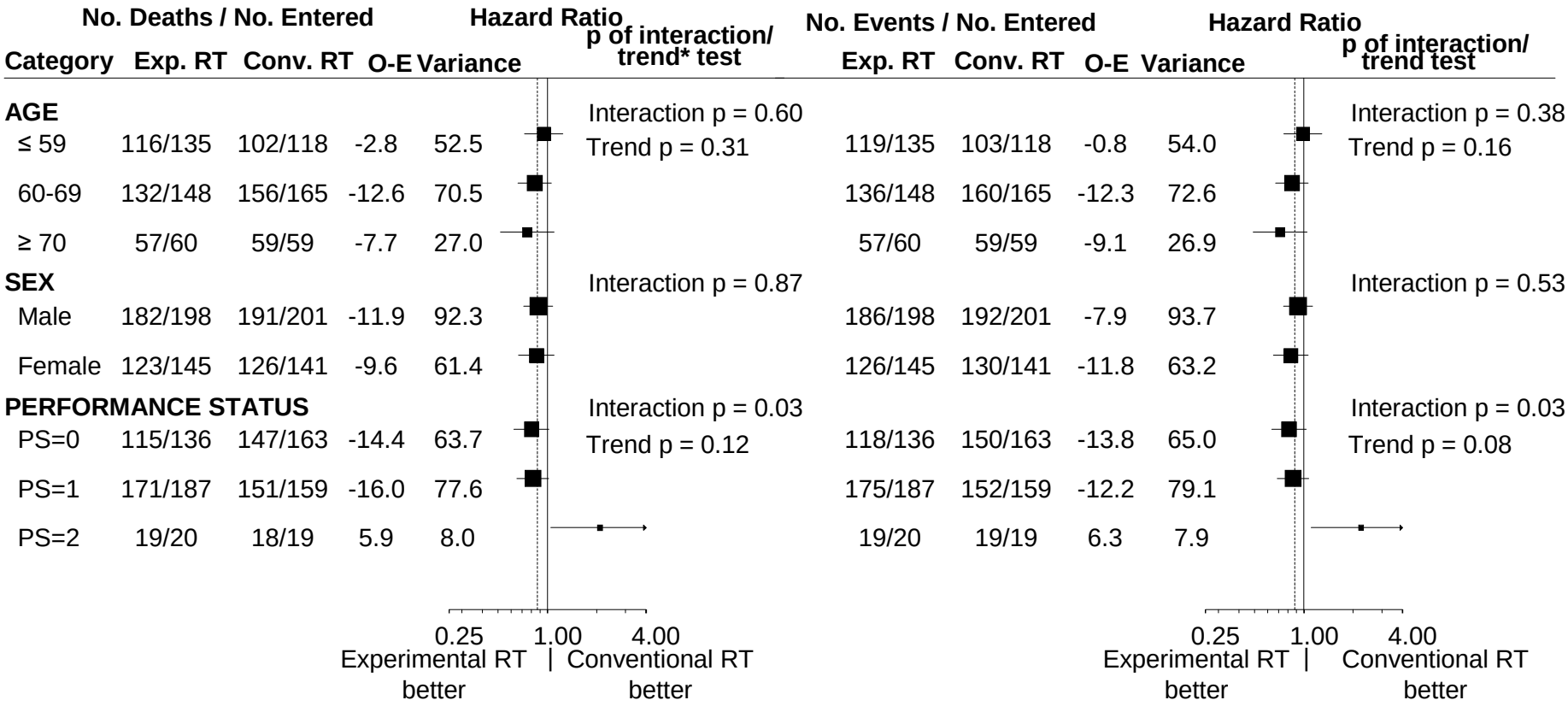


Web-Figure 7: Effect of modified radiotherapy versus conventional radiotherapy on overall and progression-free survivals, by radiotherapy types in small cell lung cancer trials. See web-Figure 1 for legend details.



Number of deaths/ person-years by period	Years 0-2	Years 3-5	Years ≥6
Modified RT	185 / 504	73 / 317	47 / 346
Conventional RT	196 / 495	84 / 267	37 / 229
Number of events/ person-years by period	**Years 0-2**	**Years 3-5**	**Years ≥6**
Modified RT	240 / 402	29 / 259	43 / 285
Conventional RT	249 / 387	38 / 200	35 / 200

Web-Figure 8: Survival curves for the small cell lung cancer trials



Web-Figure 9: Effect of modified radiotherapy versus conventional radiotherapy on overall and progression-free survival, by patients characteristics in small cell lung cancer trials