Secondary malignant neoplasms, progression-free survival and overall survival in patients treated for Hodgkin lymphoma: a systematic review and meta-analysis of randomized clinical trials

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Supplementary Materials

to

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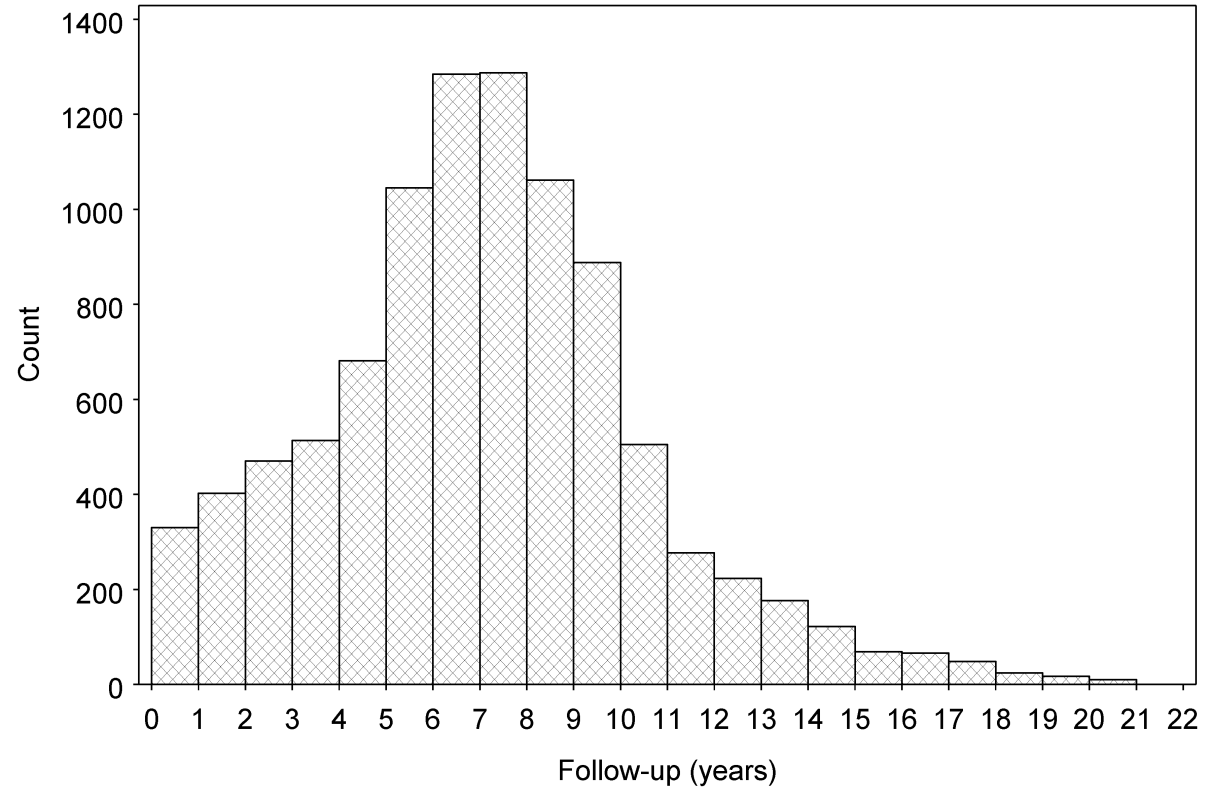
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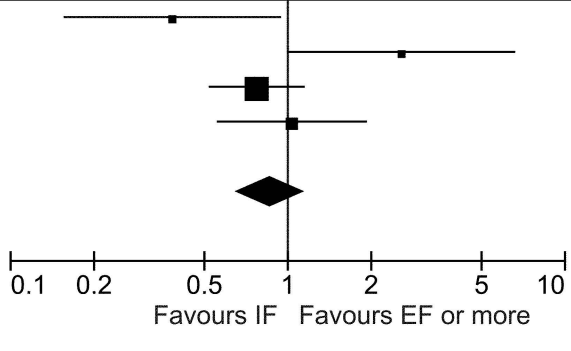
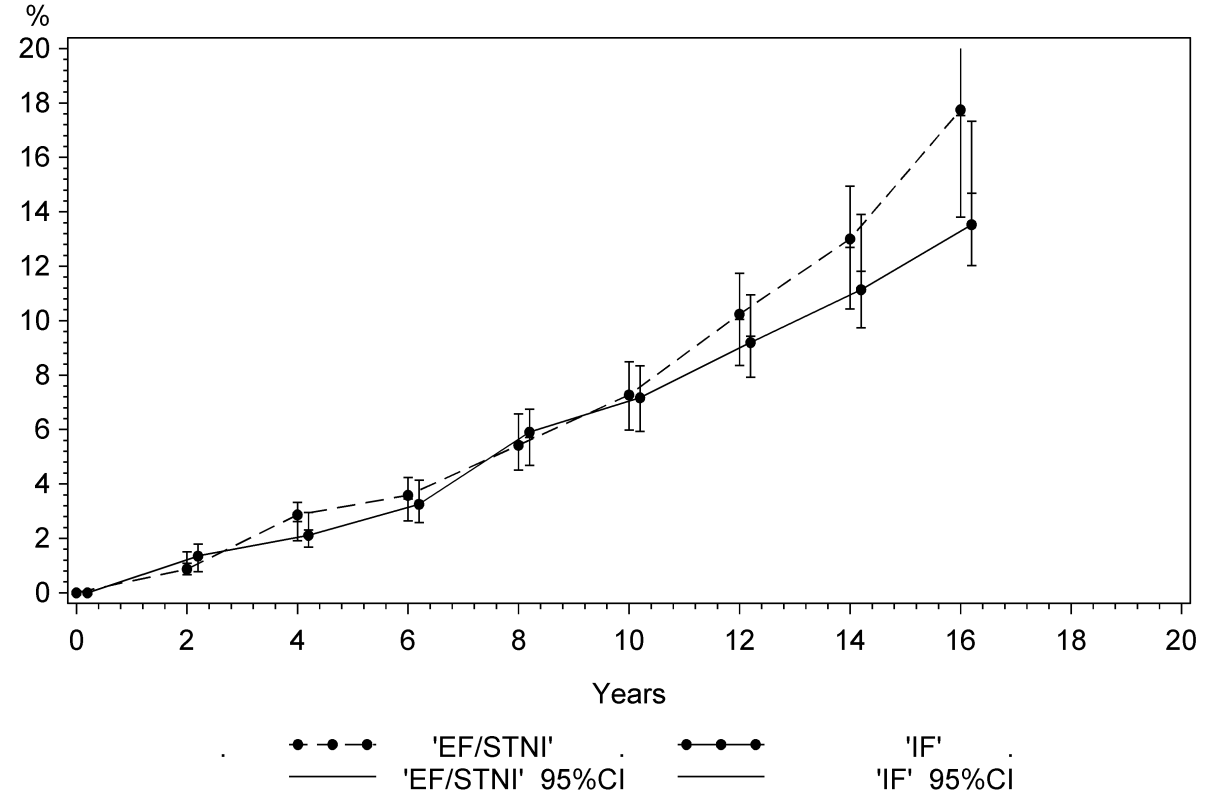
Follow-up (years)

Study or Subgroup	EF or more Events	EF or more Total	IF Events	IF Total	O-E	Variance	Weight	Peto Odds Ratio Exp[(O-E) / V], Fixed, 95% CI
Milano_STNI_IF	14	68	6	72	-4.6026	4.7982	10.7%	0.38 [0.16, 0.94]
Roma_HD94	5	102	13	107	4.15331	4.3923	9.8%	2.57 [1.01, 6.56]
GHSG HD8	57	532	45	532	-6.52752	25.2736	56.6%	0.77 [0.52, 1.14]
EORTC H8-U	15	324	32	660	0.33881	10.1708	22.8%	1.03 [0.56, 1.91]
Total (95% CI)		**1026**		**1371**			**100.0%**	**0.86 [0.64, 1.16]**
Total events	91		96					

Heterogeneity: Chi² = 9.05, df = 3 (P = 0.03); I² = 67%

Test for overall effect: Z = 0.99 (P = 0.32)

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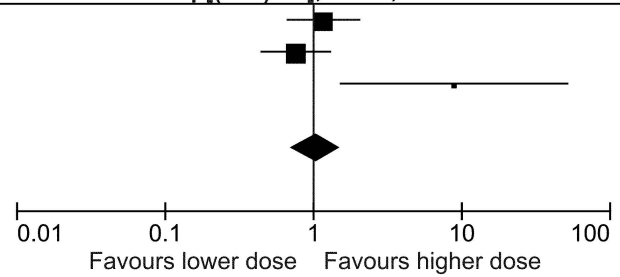
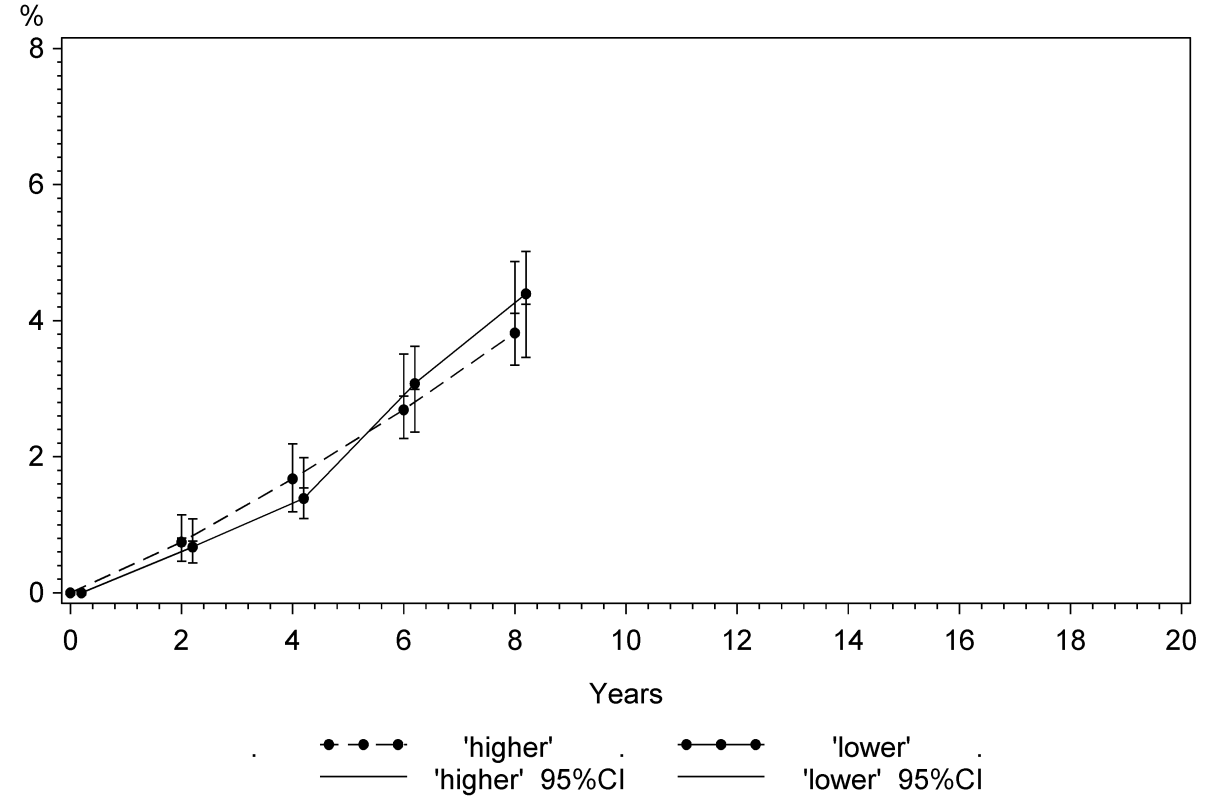
Study or Subgroup	higher dose Events	Total	lower dose Events	Total	O-E	Variance	Weight	Peto Odds Ratio Exp[(O-E) / V], Fixed, 95% CI	Year
GHSG HD11	23	675	27	676	1.89983	12.3808	45.5%	1.17 [0.67, 2.03]	1998
GHSG HD10	31	575	24	588	-3.75147	13.5922	49.9%	0.76 [0.45, 1.29]	1998
EORTC H9-F	0	239	5	209	2.7054	1.2402	4.6%	8.86 [1.52, 51.49]	1998
Total (95% CI)		**1489**		**1473**			**100.0%**	**1.03 [0.71, 1.50]**	
Total events	54		56						

Heterogeneity: Chi² = 7.20, df = 2 (P = 0.03); I² = 72%

Test for overall effect: Z = 0.16 (P = 0.87)

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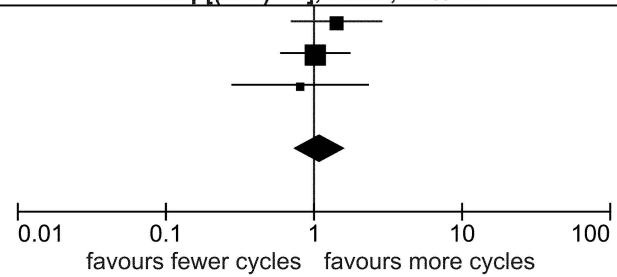
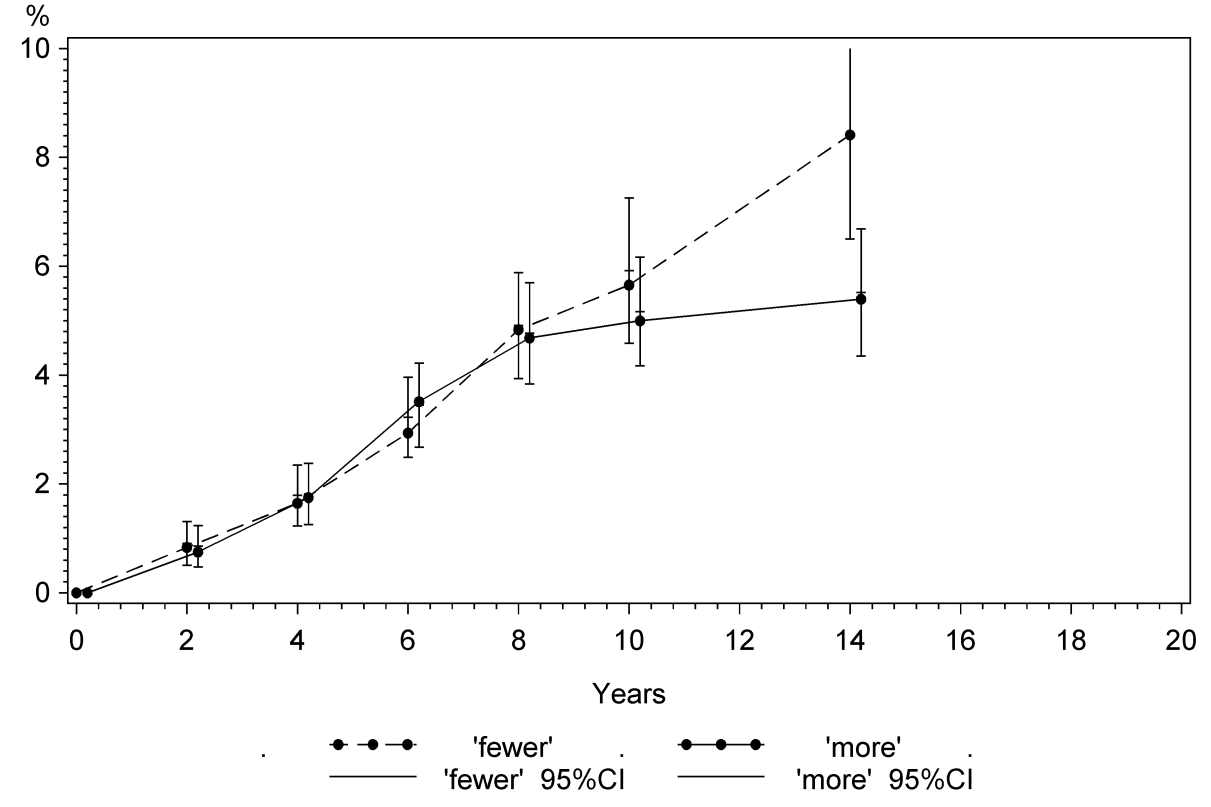
Study or Subgroup	more cycles Events	Total	fewer cycles Events	Total	O-E	Variance	Weight	Peto Odds Ratio Exp[(O-E) / V], Fixed, 95% CI	Year
EORTC H8-U	13	329	19	331	2.76873	7.9031	31.7%	1.42 [0.71, 2.85]	1993
GHSG HD10	27	596	28	594	0.27424	13.5941	54.5%	1.02 [0.60, 1.74]	1998
EORTC H9-U	8	276	6	277	-0.74463	3.4606	13.9%	0.81 [0.28, 2.31]	1998
Total (95% CI)		**1201**		**1202**			**100.0%**	**1.10 [0.74, 1.62]**	
Total events	48		53						

Heterogeneity: Chi² = 0.92, df = 2 (P = 0.63); I² = 0%

Test for overall effect: Z = 0.46 (P = 0.65)

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Supplementary Table S1: Subgroup analyses age

SMN				
Comparison (standard vs experimental)	**Age subgroup**	**Peto Odds Ratio**	**p-values**	
			Treatment group	**Interaction**
CMT vs chemotherapy alone	<=50	0.39	**0.04**	0.59
	>50	0.55	0.21	
Extended vs involved-field RT (after CT)	<=50	0.85	0.36	0.93
	>50	0.82	0.46	
Higher dose vs 20 Gy RT (after CT)	<=50	0.97	0.93	0.82
	>50	1.06	0.82	
More vs fewer CT cycles	<=50	0.88	0.64	0.22
	>50	1.44	0.20	
Standard-dose vs intensified CT (regimen +/- RT)	<=50	2.11	**0.01**	**0.02**
	>50	0.78	0.44	
Overall Survival				
Comparison (standard vs experimental)	**Age subgroup**	**Cox Hazard Ratio**	**p-values**	
			Treatment group	**Interaction**
CMT vs chemotherapy alone	<=50	0.82	0.48	0.57
	>50	0.62	0.25	
Extended vs involved-field RT (after CT)	<=50	1.03	0.85	0.11
	>50	0.69	0.06	
Higher dose vs 20 Gy RT (after CT)	<=50	0.90	0.66	0.95
	>50	0.88	0.60	
More vs fewer CT cycles	<=50	0.94	0.79	0.69
	>50	1.07	0.76	
Standard-dose vs intensified CT (regimen +/- RT)	<=50	0.74	**0.02**	0.08
	>50	1.08	0.62	
Progression Free Survival				
Comparison (standard vs experimental)	**Age subgroup**	**Cox Hazard Ratio**	**p-values**	
			Treatment group	**Interaction**
CMT vs chemotherapy alone	<=50	1.55	**0.004**	**0.02**
	>50	0.56	0.15	
Extended vs involved-field RT (after CT)	<=50	1.13	0.34	**0.03**
	>50	0.69	0.05	
Higher dose vs 20 Gy RT (after CT)	<=50	1.26	0.06	0.31
	>50	0.99	0.96	
More vs fewer CT cycles	<=50	1.19	0.23	0.73
	>50	1.10	0.65	
Standard-dose vs intensified CT (regimen +/- RT)	<=50	0.72	**0.0003**	**0.008**
	>50	1.15	0.35	

SMN = secondary malignant neoplasms, CMT = combined-modality treatment, RT = radiotherapy, CT = chemotherapy.

Supplementary Table S2: Subgroup analyses gender

SMN				
Comparison (standard vs experimental)	**Gender subgroup**	**Peto Odds Ratio**	**p-values**	
			Treatment group	**Interaction**
CMT vs chemotherapy alone	female	0.25	**0.01**	0.20
	male	0.60	0.22	
Extended vs involved-field RT (after CT)	female	1.03	0.90	0.28
	male	0.74	0.14	
Higher dose vs 20 Gy RT (after CT)	female	0.84	0.55	0.35
	male	1.21	0.47	
More vs fewer CT cycles	female	1.09	0.76	1.0
	male	1.09	0.74	
Standard-dose vs intensified CT (regimen +/- RT)	female	1.86	0.06	0.20
	male	1.06	0.85	
Overall Survival				
Comparison (standard vs experimental)	**Gender subgroup**	**Cox Hazard Ratio**	**p-values**	
			Treatment group	**Interaction**
CMT vs chemotherapy alone	female	0.48	0.11	0.26
	male	0.88	0.63	
Extended vs involved-field RT (after CT)	female	0.81	0.30	0.44
	male	0.98	0.90	
Higher dose vs 20 Gy RT (after CT)	female	0.97	0.90	0.84
	male	0.90	0.63	
More vs fewer CT cycles	female	0.86	0.55	0.50
	male	1.07	0.74	
Standard-dose vs intensified CT (regimen +/- RT)	female	0.78	0.13	0.54
	male	0.88	0.34	
Progression Free Survival				
Comparison (standard vs experimental)	**Gender subgroup**	**Cox Hazard Ratio**	**p-values**	
			Treatment group	**Interaction**
CMT vs chemotherapy alone	female	1.76	**<0.00001**	**0.001**
	male	1.18	0.36	
Extended vs involved-field RT (after CT)	female	0.87	0.37	0.50
	male	1.09	0.50	
Higher dose vs 20 Gy RT (after CT)	female	1.37	0.06	0.34
	male	1.11	0.46	
More vs fewer CT cycles	female	1.12	0.55	0.84
	male	1.17	0.30	
Standard-dose vs intensified CT (regimen +/- RT)	female	0.75	**0.02**	0.47
	male	0.85	0.09	

SMN = secondary malignant neoplasms, CMT = combined-modality treatment, RT = radiotherapy, CT = chemotherapy.

Supplementary Table S3: Subgroup analyses stage and CT treatment

Secondary Malignant Neoplasms				
Comparison (experimental)	**Subgroup**	**Peto Odds Ratio**	**p-values**	
			Treatment group	**Interaction**
CMT vs chemotherapy alone	early stage	0.67	0.68	0.63
	advanced stage	0.41	**0.01**	
Standard-dose vs intensified CT (regimen +/- RT)	BEACOPP	1.06	0.83	0.06
	Stanford	0.90	0.86	
	EBVCAD	6.03	**0.005**	
	CHlVPP	2.14	0.10	
Overall Survival				
Comparison (experimental)	**Subgroup**	**Cox Hazard Ratio**	**p-values**	
			Treatment group	**Interaction**
CMT vs chemotherapy alone	early stage	1.97	0.35	0.14
	advanced stage	0.64	0.06	
Standard-dose vs intensified CT (regimen +/- RT)	BEACOPP	0.58	**0.0005**	**0.006****
	Stanford	1.11	0.64	
	EBVCAD	1.10	0.74	
	CHlVPP	1.23	0.23	
Progression Free Survival				
Comparison (experimental)	**Subgroup**	**Cox Hazard Ratio**	**p-values**	
			Treatment group	**Interaction**
CMT vs chemotherapy alone	early stage	2.56	**<0.00001**	**<0.0001**
	advanced stage	0.74	0.12	
Standard-dose vs intensified CT (regimen +/- RT)	BEACOPP	0.47	**<0.00001**	**<0.00001****
	Stanford	1.46	**0.01**	
	EBVCAD	0.96	0.85	
	CHlVPP	1.03	0.82	

CMT = combined-modality treatment, RT = radiotherapy, CT = chemotherapy.
Odds/hazard ratios (OR, HR) assess the risk of SMN for the experimental treatment compared with the standard treatment: values < 1 favor the experimental treatment.
Subgroup effects and Interactions were tested in RevMan ('test for subgroup differences').
** Significant difference in treatment effect between BEACOPP and each other regimen
NB: analyses of subgroups are *not* censored at HL progression

Supplementary Table S4: Sensitivity analyses for SMN, censoring at date where study follow-up becomes <75% complete

Comparison (Std vs Exp)	**Censored SMN (Std : Exp)**	**Odds Ratio**	**p-value**
CMT vs chemotherapy alone	4 : 3	0.348	0.0031
Extended vs involved-field RT (after CT)	37 : 39	0.842	0.38
Higher dose vs 20 Gy RT (after CT)	4 : 4	1.033	0.87
More vs fewer CT cycles	8 : 10	0.849	0.46
Standard-dose vs intensified CT (regimen +/- RT)	10 : 19	1.365	0.24

SMN = secondary malignant neoplasms, CMT = combined-modality treatment, RT = radiotherapy, CT = chemotherapy, Std = standard treatment, Exp = experimental treatment

Supplementary Table S5: Sensitivity analyses for SMN, not counting non-melanoma skin cancers (Peto, all SMN, uncensored)

Comparison (Std vs. Exp)	**Excluded SMN (Std : Exp)**	**Odds Ratio**	**p-value**
CMT vs chemotherapy alone	0 : 1	0.398	0.0054
Extended vs involved-field RT (after CT)	5 : 8	0.824	0.21
Higher dose vs 20 Gy RT (after CT)	1 : 4	0.976	0.90
More vs fewer CT cycles	3 : 0	0.967	0.87
Standard-dose vs intensified CT (regimen +/- RT)	0 : 0	no change	

SMN = secondary malignant neoplasms, CMT = combined-modality treatment, RT = radiotherapy, CT = chemotherapy, Std = standard treatment, Exp = experimental treatment