Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Demographic, clinical and radiologic characteristics at baseline

Table 1: Patient characteristics	
Characteristic	**N = 384**
Gender, n (%)	
M	215 (56)
W	169 (44)
Age, Median (IQR)	64 (57 – 72)
anatomical localization, n (%)	
frontal	121 (32)
parietal	75 (20)
temporal	40 (10)
occipital	42 (11)
cerebellar	99 (26)
other	6 (1.6)
Unknown	1
hydrocephalus at baseline, n (%)	47 (12)
Unknown	8
hemorrhage at baseline, n (%)	71 (19)
Unknown	8
LMM at baseline, n (%)	8 (2.1)
Unknown	8

Table 1: Patient characteristics	
Characteristic	**N = 384**
no_of_BrM_Rxs, n (%)	
1	344 (90)
2	34 (8.9)
3	3 (0.8)
4	3 (0.8)
Number of brain metastases at baseline, n (%)	
one	144 (38)
two	127 (33)
more than two	113 (29)
Brain region affected of brain metastasis, n (%)	
supratentorial	234 (61)
infratentorial	60 (16)
both	90 (23)
volume of dominant (resected) brain metastasis (mL), Median (IQR)	8 (4 – 16)
Unknown	12
Extracranial metastasis at baseline, n (%)	
UICC stage IV	318 (86)
UICC stage I-III	52 (14)
Unknown	14
UICC stage, n (%)	52 (14)

Table 1: Patient characteristics	
Characteristic	**N = 384**
Unknown	14
KPS after operation, n (%)	
< 70%	160 (42)
>/= 70%	224 (58)
GPA after operation , n (%)	
>/=2	231 (60)
<2	151 (40)
Unknown	2

eTable 1A: Demographic, clinical and radiologic characteristics at baseline

Baseline characteristics were selected based on previous reports and literature within the field[1-4]. The *gtsummary* package and windows word were used to describe tabular data of our patient cohort, including continuous, categorical or numerical as well as dichotomized variables.

Table 2: Treatment-related patient characteristics	
Characteristic	**N = 384**
Number of brain metastasis resections, n (%)	
1	344 (90)
2	34 (8.9)
3	3 (0.8)
4	3 (0.8)

resection of independent lesions, n (%)	12 (30)
resection due to local recurrence, n (%)	28 (70)
time to local re-resection, Median (IQR)	234 (72 – 503)
primary tumor resection in context of brain metastasis resection, n (%)	
no primary tumor resection	262 (68)
primary tumor resection before brain metastasis resection	87 (23)
primary tumor resection after brain metastasis resection	35 (9.1)
primary tumor resection, n (%)	
no primary tumor resection	262 (68)
primary tumor resection	122 (32)
pre-treatment at baseline, n (%)	
no neoadjuvant treatment	270 (70)
RTx + CTx	94 (24)
RTx + ICI	12 (3.1)
RTx + SMI	8 (2.1)
mode of cranial radiation after first brain metastasis resection, n (%)	
WBRT	120 (36)
local irradation of resection cavity	88 (26)
SRS	0 (0)
not known	129 (38)

|	
fraction of stereotactically irradiated patients, n (%)	
other than SRS	340 (89)
SRS	44 (11)
dose of cranial radiation after first brain metastasis resection, Median (IQR)	31 (30 – 42)
adjuvant treatment groups of interest: RTx + CTx vs. RTx + ICI, n (%)	
RTx + CTx	108 (63)
RTx + ICI	63 (37)
main adjuvant treatment groups, n (%)	
RTx + CTx	108 (57)
RTx + ICI	63 (33)
RTx + SMIs	19 (10)
adjuvant treatment modalities, n (%)	
best supportive care (bsc)	43 (11)
chemotherapy (CTx)	6 (1.6)
not known	34 (8.9)
radiation (RTx)	103 (27)
radiation and chemotherapy(RTx + CTx)	108 (28)
radiation and immune therapy (RTx + ICI)	63 (16)
radiation and targeted therapy (RTx + SMI)	27 (7.0)

eTable 1B: Treatment-related patient characteristics at baseline.

Table 3: Histopathological and biomarker-related patient characteristics	
Characteristic	**N = 384**
neutrophil-to-lymphocyte ratio, n (%)	
< 5	105 (35)
>/= 5	195 (65)
Unknown	84
tumor subtype, n (%)	
NSCLC	384 (100)
histologic subtype, n (%)	
adenocarcinoma	329 (86)
adenosquamous	4 (1.0)
neuroendocrine differentiation	13 (3.4)
pulmonary sarcomatoid carcinoma	2 (0.5)
squamous cell cancer	36 (9.4)
PDL1 status brain metastasis tissue, n (%)	
< 1	90 (56)
>/= 1	72 (44)
Unknown	222
Ki67 brain metastasis tissue, n (%)	
< 30	123 (38)
>/= 30	205 (62)
Unknown	56
PDL1 extracranial tissue, n (%)	

< 1	30 (32)
>/= 1	63 (68)
Unknown	291
Ki67 extracranial tissue, n (%)	
< 30	36 (40)
>/= 30	53 (60)
Unknown	295
EGFR status of brain metastasis tissue, n (%)	
wildtype	231 (94)
mutated	15 (6.1)
Unknown	138
ALK status of brain metastasis tissue, n (%)	
wildtype	213 (97)
mutated	7 (3.2)
Unknown	164
TTF1 status of brain metastasis tissue, n (%)	
negative	126 (33)
positive	251 (67)
Unknown	7

eTable 1C: Histopathological and biomarker-related characteristics of brain metastasis tissue at baseline. *Information on molecular characteristics (i.e. driver mutations) of primary tumor tissue was not included into tabular data - only results from brain metastasis tissue were listed.
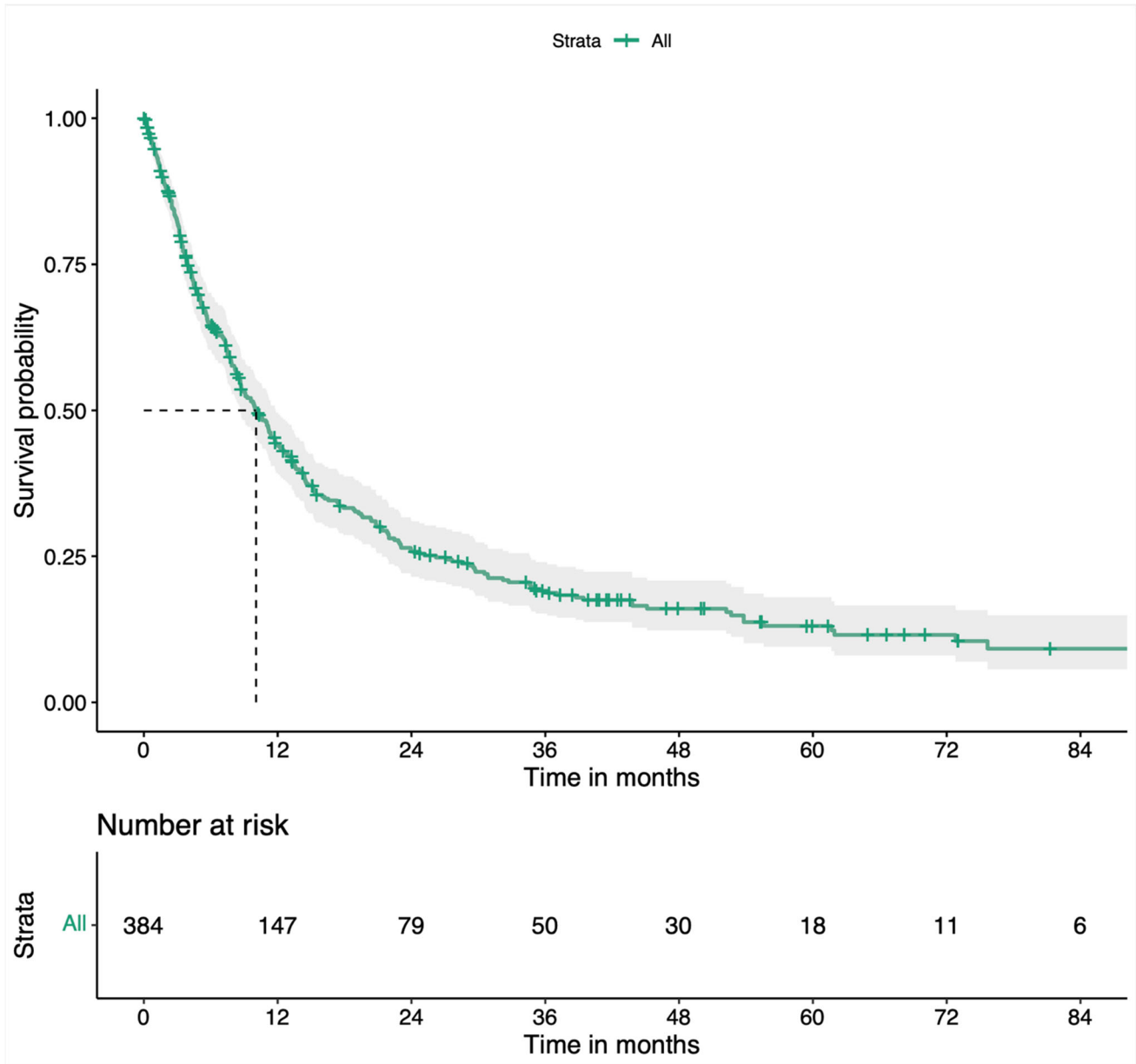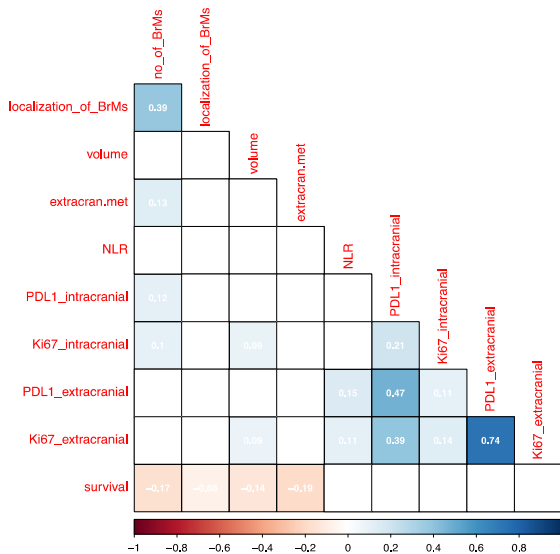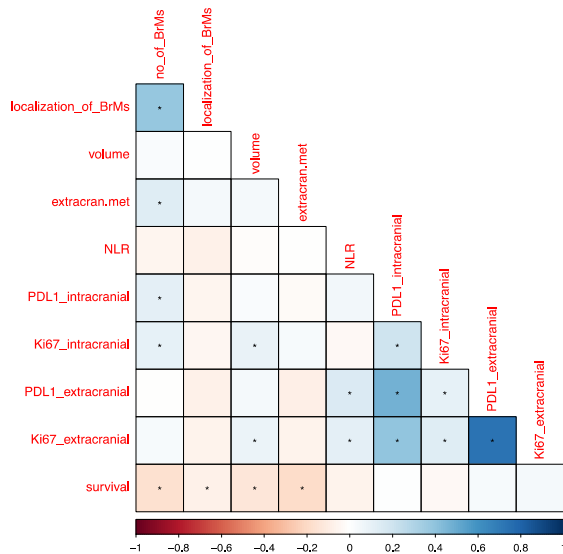
eFigure 1: Kaplan Meier survival estimates of the whole patient cohort

Kaplan Meier survival analysis for OS in the entire patient cohort of NSCLC patients subjected to craniotomy and brain metastasis removal (N=384).

A   **B**

**eFigure 2: Correlation matrices of radiological and biomarker-related characteristics on survival**

Correlation plots using non-parametric Spearman's correlation test to measure the degree of associatation between different clinically linked covariates, with correlation coefficients depicted in case a significant correlation was present (A). The right correlation plot shows the respective significance levels (B).

eTable 2: Univariable and multivariable Cox proportional regression in the whole patient cohort

Dependent: Surv(survival, censoring)				all	HR (CPH univar. analysis)	HR (CPH multivar.analysis)	
localization_of_BrMs	supratentorial			234 (60.9)	-	-	
	infratentorial			60 (15.6)	1.10 (0.80-1.51, p=0.550)		
	both			90 (23.4)	1.48 (1.12-1.95, p=0.005)	1.62 (0.95-2.77, p=0.077)	
GPA2 (lung mol GPA score)	GPA below 2,5			246 (64.4)	-	-	
	GPA at least 2,5			136 (35.6)	0.45 (0.35-0.57, p<0.001)	0.98 (0.60-1.58, p=0.924)	

|				
no_of_BrMs (number of brain metastases)	one	144 (37.5)	-	-
	two	127 (33.1)	1.39 (1.05-1.84, p=0.021)	0.89 (0.56-1.41, p=0.610)
	more than two	113 (29.4)	1.96 (1.47-2.60, p<0.001)	1.16 (0.66-2.06, p=0.604)
extracran.met (extracranial metastasis)	No	257 (66.9)	-	-
	Yes	127 (33.1)	1.81 (1.42-2.31, p<0.001)	**2.17 (1.34-3.51, p=0.002)**
primary_tumor.Rx2 (primary tumor resection)	no primary tumor resection	262 (68.2)	-	-
	primary tumor resection	122 (31.8)	0.47 (0.36-0.61, p<0.001)	**0.51 (0.32-0.82, p=0.006)**
adj.RTx3 (modality of adjuvant RTx)	other than SRS	340 (88.5)	-	-
	SRS	44 (11.5)	0.56 (0.39-0.82, p=0.002)	
adj.tx2 (adjuvant theray after neurosurgery)	RTx + CTx	108 (63.2)	-|	-|
	RTx + ICI	63 (36.8)	0.45 (0.30-0.68, p<0.001)	**0.32 (0.20-0.51, p<0.001)**

Cox regression analysis of potential prognostic covariates and overall survival for the whole patient cohort (N=384).
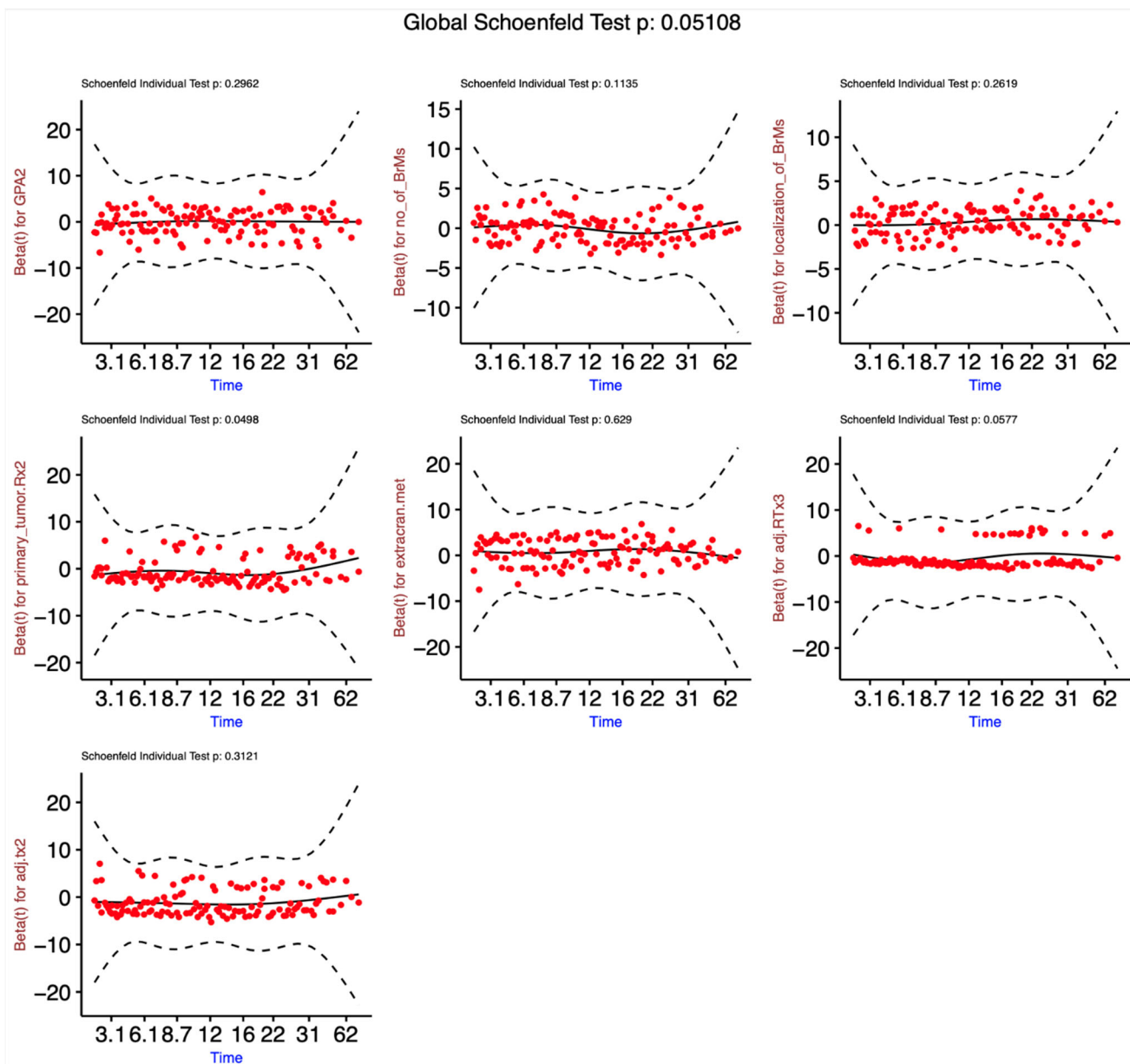
eFigure 3: Testing for the proportional hazards (PH) assumption with Schoenfeld residuals

Statistical testing including graphical diagnostics based on scaled Schoenfeld residuals for each covariate of interest (prognostic covariates): GPA score, number of brain metastases, localization of brain metastases, primary tumor resection, extracranial metastases, modality of adjuvant radiation therapy, adjuvant therapy; only adj.TTx3 (juvant radiation therapy) reached a nearly significance, hence global Schoenfeld test was not significant, therefore proportional hazards assumption was assumed.
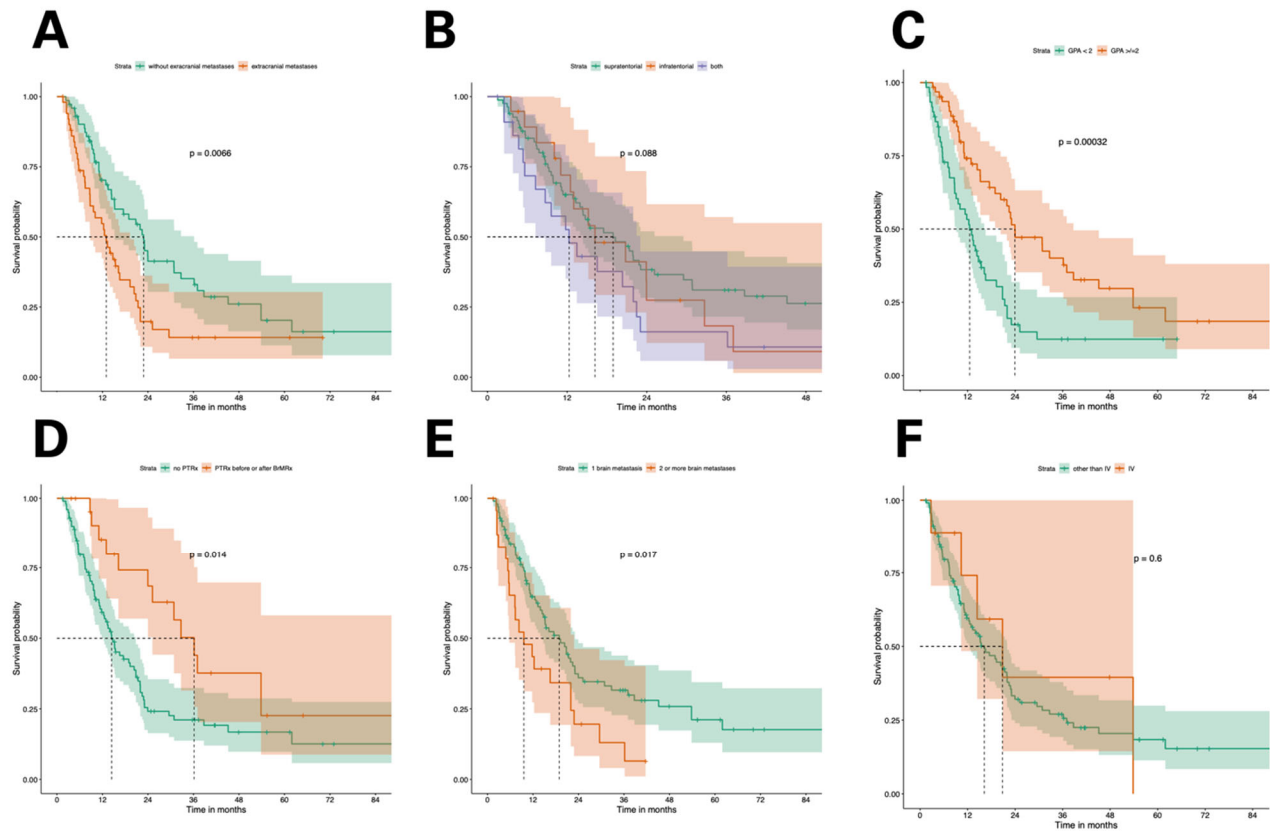
eFigure 4: Stratified Kaplan-Meier curves in matched patients for overall survival

Kaplan Meier analysis stratified according to the following characteristics: **A)** presence of extracranial metastases; **B)** localization of brain metastatic lesions at baseline (i.e. before first brain metastasis resection); **C)** graded prognostics assessment (GPA) score; **D)** status of primary tumor resection; **E)** number of brain metastasis resections; **F) UICC stage.**

A — Distribution of Propensity Scores

B — Covariate Balance
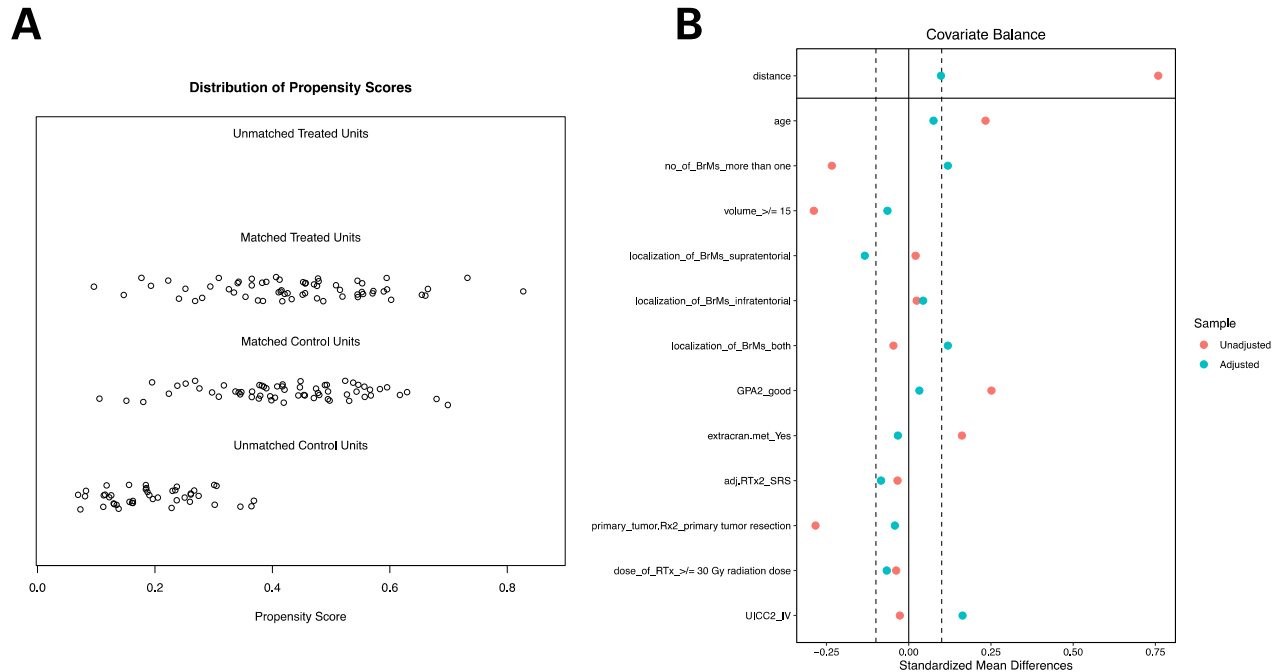
eFigure 5: Distribution of propensity scores and standardized mean differences

Distribution map after propensity score matching (PSM) (**A**). Plot displaying the standardized mean difference (SMD) of each covariate considered for PSM between treatment groups standardized (**B**). R code can be accessed upon request via Github: https://github.com/dasilew/clinicalNSCLC_1.

eTable 3: Univariable and multivariable Cox proportional regression in the matched cohort

explanatory		HR (CPH univar. analysis)	HR (CPH multivar. analysis)
gender	Male Female	1.00 (0.65-1.54, p=0.996)	
age		1.02 (1.00-1.05, p=0.077)	
GPA2 (GPA score)	Bad GPA (2 or less) Good GPA (>/= 2)	0.48 (0.31-0.74, p=0.001)	**0.46 (0.22-0.99, p=0.047)**
extracranial metastases	No Yes	1.88 (1.22-2.91, p=0.004)	1.02 (0.49-2.12, p=0.961)
volume	< 15 >/= 15	0.98 (0.64-1.51, p=0.932)	
Number of_brain metastases	One >/= 1	1.84 (1.11-3.06, p=0.019)	1.30 (0.64-2.65, p=0.471)

Localization of brain metastasis	infratentorial	1.35 (0.75-2.44, p=0.322)	
Localization of brain metastasis	Both (supra-/infratentorial)	1.71 (1.00-2.93, p=0.052)	
UICC stage	Stage IV	0.79 (0.32-1.95, p=0.610)	
Primary tumor resection	No Yes	0.40 (0.20-0.78, p=0.007)	**0.26 (0.12-0.53, p<0.001)**
Adjuvant RTx (SRS vs. other modalities)	SRS	0.64 (0.36-1.11, p=0.113)	
Adjuvant RTx + ICIs vs. RTx + CTx		0.44 (0.28-0.69, p<0.001)	**0.27 (0.16-0.45, p<0.001)**

Univariable and multivariable Cox proportional regression analysis for matched data

(N=124).