

Table S1 Patterns of First and [Cumulative] Recurrences

Metastasized organ	Local CNS	Distant CNS	Any CNS	Primary	Regional node(s)	Loco-regional	Distant Lungs	Non-regional node(s)	Bone	Liver	Adrenal gland	Other	Any extra-cranial	Brain only	Outside brain only	None
Metachronous (n=42)	34.1% [39.0%]	24.4% [39.0%]	51.2% [61.0%]	4.9% [7.3%]	7.3% [17.1%]	9.8% [17.1%]	7.3% [14.6%]	2.4% [12.2%]	9.8% [14.6%]	2.4% [4.9%]	2.4% [7.3%]	4.9% [9.8%]	28.6% [46.3%]	51.2% [34.2%]	29.3% [19.4%]	19.5%
Synchronous (n=82)	15.8% [28.9%]	43.4% [56.6%]	48.7% [64.5%]	25.0% [32.9%]	23.7% [36.8%]	34.2% [46.1%]	26.3% [47.4%]	3.9% [15.8%]	9.2% [27.6%]	11.8% [25.0%]	6.6% [21.1%]	6.6% [21.1%]	52.4% [75.0%]	36.9% [15.8%]	40.8% [26.3%]	9.2%
Solitary (n=77)	13.7% [21.9%]	31.5% [47.9%]	42.5% [57.5%]	19.2% [24.7%]	15.1% [28.8%]	26.0% [37.0%]	24.7% [38.4%]	2.7% [15.1%]	8.2% [23.3%]	5.5% [13.7%]	0% [11.0%]	6.8% [20.5%]	45.5% [67.1%]	37.0% [17.8%]	42.4% [27.4%]	15.1%
Multiple (n=47)	36.4% [50.0%]	45.5% [54.5%]	61.4% [72.7%]	15.9% [22.7%]	22.7% [31.8%]	25.0% [34.1%]	11.4% [31.8%]	4.5% [13.6%]	11.4% [22.7%]	13.6% [25.0%]	11.4% [25.0%]	4.5% [11.4%]	42.6% [61.4%]	50.0% [29.5%]	31.2% [18.2%]	9.1%
+WBRT (n=53)	25.9% [35.2%]	31.5% [39.6%]	49.0% [58.8%]	13.7% [19.6%]	17.6% [25.5%]	25.5% [33.3%]	19.6% [37.3%]	2.0% [7.8%]	17.6% [23.5%]	11.8% [21.6%]	2.0% [7.8%]	7.8% [17.6%]	45.3% [62.7%]	41.2% [23.5%]	37.3% [27.0%]	13.7%
-WBRT (n=71)	18.3% [28.2%]	40.9% [58.0%]	50.0% [66.7%]	21.2% [27.3%]	18.2% [33.3%]	25.8% [37.9%]	19.7% [34.8%]	4.5% [19.7%]	3.0% [22.7%]	6.1% [15.2%]	7.6% [22.7%]	4.5% [16.7%]	43.7% [66.7%]	42.4% [21.2%]	37.9% [21.2%]	12.1%
+UTT (n=51)	21.7% [34.8%]	50.0% [63.0%]	58.7% [71.7%]	6.5% [10.9%]	13.0% [23.9%]	17.4% [28.3%]	23.9% [47.8%]	2.2% [19.6%]	4.3% [26.1%]	6.5% [26.1%]	6.5% [19.6%]	8.7% [26.1%]	39.2% [69.6%]	47.8% [19.6%]	30.4% [10.9%]	10.9%
-UTT (n=31)	6.7% [20.0%]	33.3% [46.7%]	33.3% [53.3%]	53.3% [66.7%]	40.0% [56.7%]	60.0% [73.3%]	30.0% [46.7%]	6.7% [10.0%]	16.7% [30.0%]	20.0% [23.3%]	6.7% [23.3%]	3.3% [13.3%]	74.2% [83.3%]	20.0% [10.0%]	60.0% [40.0%]	6.7%
Combined (n=124)	22.0% [32.5%]	36.4% [50.4%]	49.1% [63.2%]	17.8% [23.9%]	17.8% [29.9%]	25.4% [35.9%]	19.5% [35.9%]	3.4% [14.5%]	9.3% [23.1%]	8.5% [17.9%]	5.1% [16.2%]	5.9% [17.1%]	44.4% [63.7%]	41.5% [22.0%]	37.3% [23.7%]	13.6%

Table S2 Univariable and multi-variable analyses for time to progression

Clinical/patient characteristics	UVA	MVA
Male sex (n=65)	HR 1.642, P=0.012	HR 1.692, P=0.010
Age at BM diagnosis	HR 1.014, P=0.159	-
Adenocarcinoma histology (n=86)	HR 0.866, P=0.508	-
Thoracic stage	HR 0.969, P=0.808	-
Upfront systemic therapy (n=80)	HR 1.218, P=0.351	-
Synchronous timing (n=82)	HR 1.455, P=0.077	-
Symptomatic presentation (n=92)	HR 1.355, P=0.184	-
Solitary metastasis (n=77)	HR 0.820, P=0.325	-
Maximal brain metastasis dimension (cm)	HR 1.180, P=0.057	-
CITV (cc)	HR 1.004, P=0.020	HR 1.004, P=0.032
CITV >10 cc (n=43)	HR 1.393, P=0.120	-
SRS dose	HR 1.007, P=0.890	-
Craniotomy at diagnosis (n=36)	HR 0.718, P=0.142	-
WBRT + SRS upfront (n=53)	HR 0.789, P=0.233	-
KPS	HR 0.988, P=0.239	-
DS-GPA	HR 0.668, P=0.022	HR 0.736, P=0.088

Table S3 Univariable and multi-variable analyses for intracranial for time to progression

Clinical/patient characteristics	UVA	MVA
Male sex (n=65)	HR 1.332, P=0.214	-
Age at BM diagnosis	HR 1.017, P=0.135	HR 1.014, P=0.238
Adenocarcinoma histology (n=86)	HR 0.711, P=0.170	HR 0.584, P=0.038
Thoracic stage	HR 0.901, P=0.481	-
Upfront systemic therapy (n=80)	HR 0.880, P=0.595	-
Synchronous timing (n=82)	HR 1.249, P=0.365	-
Symptomatic presentation (n=92)	HR 1.402, P=0.209	-
Solitary metastasis (n=77)	HR 0.683, P=0.105	HR 0.689, P=0.130
Maximal brain metastasis dimension (cm)	HR 1.161, P=0.149	-
CITV (cc)	HR 1.004, P=0.039	HR 1.003, P=0.186
CITV >10 cc (n=43)	HR 1.350, P=0.224	-
SRS dose	HR 1.010, P=0.856	-
Craniotomy at diagnosis (n=36)	HR 0.842, P=0.506	-
WBRT + SRS upfront (n=53)	HR 0.799, P=0.338	-
KPS	HR 0.997, P=0.802	-
DS-GPA	HR 0.612, P=0.018	-

Table S4 Univariable and multi-variable analyses for extracranial time to progression

Clinical/patient characteristics	UVA	MVA
Male sex (n=65)	HR 1.549, P=0.057	HR 1.493, P=0.086
Age at BM diagnosis	HR 1.011, P=0.337	-
Adenocarcinoma histology (n=86)	HR 0.983, P=0.946	-
T stage	HR 1.183, P=0.107	HR 1.123, P=0.296
N stage	HR 0.940, P=0.593	-
Thoracic stage	HR 0.869, P=0.342	-
Upfront systemic therapy (n=80)	HR 1.613, P=0.064	HR 1.211, P=0.515
Synchronous timing (n=82)	HR 1.912, P=0.014	HR 1.637, P=0.103
Solitary metastasis (n=77)	HR 0.857, P=0.519	-
KPS	HR 0.982, P=0.153	-
DS-GPA	HR 0.744, P=0.151	HR 0.707, P=0.089
PET-CT staging (n=88)	HR 1.486, P=0.130	HR 1.131, P=0.652

Table S5 Univariable and multi-variable analyses for extracranial time to progression among 82 patients who developed synchronous brain metastases

Clinical/patient characteristics	Synchronous patients in POR cohort (n=82)	
	Cox UVA for extracranial TTP	Cox MVA for extracranial TTP
Male sex (n=44)	HR 1.182, P=0.525	-
Age at BM diagnosis	HR 1.011, P=0.433	-
Adenocarcinoma histology (n=55)	HR 0.719, P=0.248	HR 0.583, P=0.080
T stage	HR 1.130, P=0.281	-
N stage	HR 1.061, P=0.687	-
Thoracic stage	HR 0.806, P=0.198	HR 0.754, P=0.113
Upfront systemic therapy (n=63)	HR 1.083, P=0.814	-
Upfront thoracic therapy (n=51)	HR 0.447, P=0.003	HR 0.366, P=0.001
Solitary metastasis (n=50)	HR 0.865, P=0.593	-
KPS	HR 0.975, P=0.071	HR 0.973, P=0.066
DS-GPA	HR 0.729, P=0.157	-
PET-CT staging (n=65)	HR 1.165, P=0.640	-

Table S6 Univariable and multi-variable analyses for overall survival

Clinical/patient characteristics	UVA	MVA
Male sex (n=73)	HR 1.275, P=0.208	-
Age at BM diagnosis	HR 1.022, P=0.029	HR 1.019, P=0.081
Adenocarcinoma histology (n=92)	HR 0.676, P=0.054	HR 0.648, P=0.039
Thoracic stage	HR 0.842, P=0.163	-
Upfront systemic therapy (n=85)	HR 0.941, P=0.763	-
Synchronous timing (n=89)	HR 0.899, P=0.587	-
Symptomatic presentation (n=103)	HR 1.798, P=0.011	HR 1.532, P=0.079
Solitary metastasis (n=85)	HR 0.738, P=0.126	-
Maximal brain metastasis dimension (cm)	HR 1.185, P=0.032	-
CITV (cc)	HR 1.002, P=0.078	-
CITV >10 cc (n=49)	HR 1.543, P=0.028	HR 1.298, P=0.211
SRS dose	HR 0.936, P=0.195	-
Craniotomy at diagnosis (n=39)	HR 0.780, P=0.262	-
WBRT + SRS upfront (n=64)	HR 1.269, P=0.215	-
KPS	HR 0.960, P<0.001	HR 0.968, P=0.002
DS-GPA	HR 0.483, P<0.0001	-

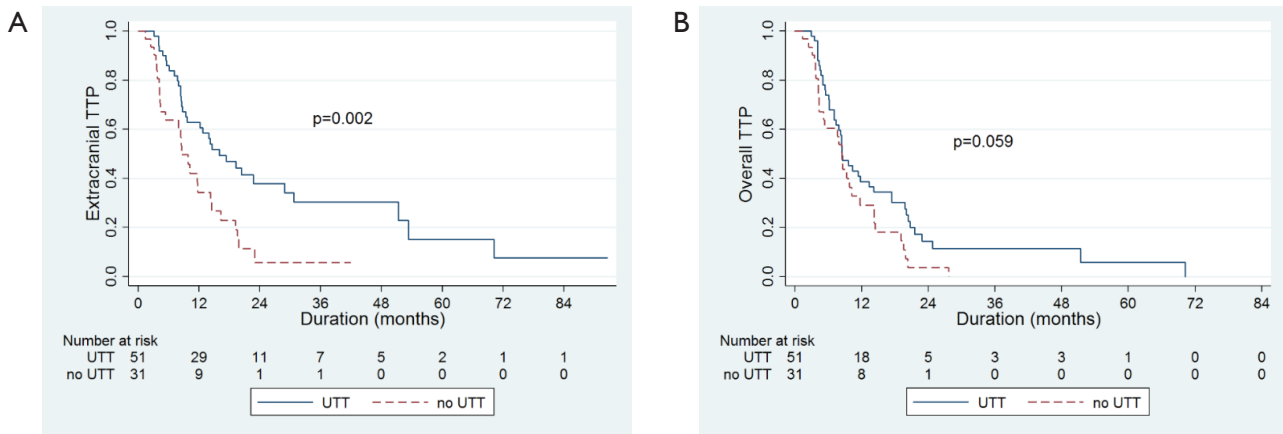


Figure S1 Extracranial (A) and overall TTP (B) among patients with synchronous brain metastases treated with vs. without upfront thoracic therapy.