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Supplementary Online Material

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8

9 Impact of Perioperative Dexamethasone in the Context of Neurosurgical Brain Metastasis
10 Resection

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12 **eTable 1a-d:** Demographic, clinical and radiologic, histopathological and treatment-related
13 characteristics at baseline of COHORT A

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15 characteristics at baseline of COHORT B

16 **eFigure 1:** Kaplan Meier survival estimates and comparison of COHORT A with COHORT
17 B

18 **eFigure 2a-b:** Correlation of total dexamethasone with clinical parameters and daily
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20 **eFigure 3a-b:** Kaplan-Meier analysis for overall survival of different dexamethasone dosage
21 patient groups in COHORT A and B

22 **eFigure 3:** Propensity score matching and resulting mean standardized differences

23 **eFigure 4:** Kaplan-Meier survival curve for matched patients (COHORT C) after propensity
24 score matching

25

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

28

Suppl. table 1a: General patient characteristics

Characteristic	N = 539
Age, Median (IQR)	64 (55 – 72)
Gender, n (%)	
female	279 (52)
male	260 (48)
signs and symptoms at baseline (OP1), n (%)	
headache	67 (12)
sensory-motor symptoms	113 (21)
seizures	52 (9.6)
alterations in behaviour	47 (8.7)
aphasia	41 (7.6)
vertigo/dyscoordination	94 (17)
headache, nausea, vomitus	32 (5.9)
visual impairment	32 (5.9)
during staining	26 (4.8)
incidental or others	35 (6.5)
time of brain metastasis resection, n (%)	
brain metastasis resection after 1st of Januar 2015	329 (61)
brain metastasis resection before 1st of Januar 2015	210 (39)
KPS after operation, n (%)	
high	326 (62)
low	199 (38)
Unknown	14
underlying other diseases, n (%)	
no underlying other diseases	124 (55)
underlying other diseases	102 (45)
Unknown	313

30 **eTable 1a: Demographic, clinical and radiologic characteristics at baseline**
 31 General patient characteristics at baseline (i.e at time of first brain metastasis resection) of
 32 the total cohort of patients of interest (COHORT A) in this study for which further
 33 downstream analysis was performed (N=539). A high postoperative Karnofsky performance
 34 index (KPS) was defined as 70% or higher, whereas a KPS for lower than 70% was
 35 considered low. In 14 patients postoperative KPS and in 313 cases status regarding other
 36 diseases was not available or documented. The *gtsummary* package and windows word
 37 were used to describe tabular data of our patient cohort, including continuous, categorical or
 38 numerical variables.
 39
 40

Suppl. table 1b: Radiological patient characteristics

Characteristic	N = 539
number of brain metastases at baseline, n (%)	
one	149 (33)
two	154 (34)
three or more	150 (33)
Unknown	86
anatomical site at at baseline, n (%)	
frontal	178 (33)
temporal	92 (17)
parietal	67 (13)
occipital	59 (11)
cerebellar	133 (25)
other	6 (1.1)
Unknown	4
presence of extracranial metastasis, n (%)	
no presence of extracranial metastases at baseline	288 (55)
presence of extracranial metastases at baseline	237 (45)
Unknown	14

Suppl. table 1b: Radiological patient characteristics

Characteristic	N = 539
hemorrhage at baseline, n (%)	
no hemorrhage at baseline	389 (76)
hemorrhage at baseline	124 (24)
Unknown	26
hydrocephalus at baseline, n (%)	
no hydrocephalus at baseline	434 (87)
hydrocephalus at baseline	63 (13)
Unknown	42
localization of dominant brain metastasis, n (%)	
supratentorial	332 (63)
infratentorial	90 (17)
both supra-/infratentorial	107 (20)
Unknown	10
tumor volume, n (%)	
< 10	146 (43)
>= 10	197 (57)
Unknown	196
edema volume, n (%)	
< 50	151 (46)
>= 50	176 (54)
Unknown	212

41

42 **eTable 1b:** Baseline radiological characteristics of the total COHORT A (N=539). For
43 patients where no pre-operative MRI was available no exact annotation of anatomical site
44 and no exact number of brain metastases were able to be retrieved. Similarly in 14 cases
45 no CT staging imaging was available in the setting of the brain metastasis resection. In 196
46 and 212 cases there was no information on tumor volume and edema volume, respectively.

Suppl. table 1c: Histopathological and biomarker-related patient characteristics

Characteristic	N = 539
entity, n (%)	
breast cancer	93 (17)
colorectal carcinoma	8 (1.5)
melanoma	91 (17)
NSCLC	286 (53)
oesophageal carcinoma	1 (0.2)
renal cell cancer	26 (4.8)
SCLC	33 (6.1)
unknown primary	1 (0.2)
histological subtype, n (%)	
adenocarcinoma	1 (0.2)
adenocarcinoma (breast)	92 (17)
adenocarcinoma (colorectal)	8 (1.5)
adenocarcinoma (lung)	247 (46)
adenosquamous	3 (0.6)
clear cell renal cell carcinoma	26 (4.8)
melanoma	91 (17)
metaplastic carcinoma	1 (0.2)
neuroendocrine-differentiated tumor	42 (7.8)
pulmonary sarcomatoid carcinoma	1 (0.2)
squamous cell carcinoma (lung)	26 (4.8)
undifferentiated	1 (0.2)
EGFR mutational status, n (%)	14 (7.3)
Unknown	347
ALK status, n (%)	6 (3.4)
Unknown	361

Suppl. table 1c: Histopathological and biomarker-related patient characteristics

Characteristic	N = 539
ROS1 status, n (%)	0 (0)
Unknown	375
TTF1 status, n (%)	
negative	104 (33)
positive	214 (67)
Unknown	221
progesterone receptor expression (Remmele score), n (%)	
< 4	85 (97)
>/= 4	3 (3.4)
Unknown	451
estrogen receptor expression (Remmele score), n (%)	
< 4	60 (68)
>/= 4	28 (32)
Unknown	451
Her2/NEU expression (DAKO score), n (%)	
0+	22 (25)
1+	14 (16)
2+	9 (10)
3+	42 (48)
Unknown	452
Ki67 index (%), n (%)	
< 30	267 (58)
>/= 30	195 (42)
Unknown	77
intracranial PD-L1 TPS (%), n (%)	
< 1	102 (64)

Suppl. table 1c: Histopathological and biomarker-related patient characteristics

Characteristic	N = 539
>= 1	57 (36)
Unknown	380

48

49 **eTable 1c:** Histopathological characteristics of COHORT A (N=539). Histology is listed
50 separately from entity to show distinct histopathological subtypes. Oncogenic drivers such
51 as EGFR, ALK, ROS1 and BRAF were available only in corresponding entity, e.g. BRAF for
52 melanoma or EGFR for lung cancer; the NA values were classified as not available or not
53 applicable where needed to simplify the structure of the table. Similarly immune scores
54 (Remmele score) for progesterone receptor (PR) and estrogen receptor (ER) as well as
55 Her2/NEU2 score (DAKO score) were only evaluated and available in tissues from breast
56 cancer patients. Ki67 index was dichotomized with a cut-off of 30%, whereas intracranial
57 PD-L1 status (tumor proportion score, TPS) was dichotomized into samples with < 1% PD-
58 L1 surface expression on tumor cell membranes, and those with \geq 1% PD-L1 expression.
59 Information on molecular characteristics (i.e. oncogenic driver mutations) or PD-L1 TPS of
60 primary tumor tissue was not included into tabular data - only results from brain metastasis
61 tissue are listed.

62

Suppl. table 1d: Treatment-related patient characteristics

Characteristic	N = 539
primary tumor resection, n (%)	
no primary tumor resection	234 (45)
primary tumor resection	281 (55)
Unknown	24
naive, n (%)	
naive	289 (55)
pre-treated	238 (45)
Unknown	12

Suppl. table 1d: Treatment-related patient characteristics

Characteristic	N = 539
adjuvant RTx, n (%)	
no SRS	206 (74)
SRS	72 (26)
Unknown	261
adjuvant systemic treatment, n (%)	
BSC	34 (8.8)
RTx only	72 (19)
RTx + CTx	142 (37)
RTx + targeted therapy	38 (9.8)
RTx + CPI	100 (26)
Unknown	153

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64 **eTable 1d:** Treatment-related characteristics of COHORT A. In 153 cases subsequent
65 therapy after brain metastasis resection was not documented or incompletely documented,
66 whereas 142 patients received radiation therapy (RTx) and chemotherapy (CTx) mainly
67 including carboplatin- or cisplatin-based regimens, 100 patients checkpoint inhibition (CPI)
68 mainly receiving combined chemoimmunotherapy (N=14), Nivolumab or
69 Nivolumab/Ipilimumab combinations (N=29), or Pembrolizumab (N=35) or other
70 combinations of different checkpoint inhibitors (N=22) (data not shown). 34 patients (8,8%)
71 received best supportive care (BSC).

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Table 2a: General patient characteristics

Characteristic	N = 483
Age, Median (IQR)	64 (54 – 71)
Gender, n (%)	
female	256 (53)

Table 2a: General patient characteristics

Characteristic	N = 483
male	227 (47)
signs and symptoms at baseline (OP1), n (%)	
headache	65 (13)
sensory-motor symptoms	97 (20)
seizures	43 (8.9)
alterations in behaviour	41 (8.5)
aphasia	39 (8.1)
vertigo/dyscoordination	84 (17)
headache, nausea, vomitus	31 (6.4)
visual impairment	31 (6.4)
during staining	25 (5.2)
incidental or others	27 (5.6)
time of brain metastasis resection, n (%)	
brain metastasis resection after 1st of Januar 2015	298 (62)
brain metastasis resection before 1st of Januar 2015	185 (38)
KPS after operation, n (%)	
high	306 (65)
low	164 (35)
Unknown	13
underlying other diseases, n (%)	
no underyling other diseases	106 (52)
underyling other diseases	96 (48)
Unknown	281

74

75 **eTable 2a: Demographic, clinical and radiologic characteristics at baseline**76 General patient characteristics at baseline (i.e at time of first brain metastasis resection) of
77 COHORT B for which further downstream analysis was performed (N=483), see consorts

78 diagram **Figure 1**. A high postoperative Karnofsky performance index (KPS) was defined as
 79 70% or higher, whereas a KPS for lower than 70% was considered low. In 13 patients
 80 postoperative KPS was not available. The *gtsummary* package and windows word were
 81 used to describe tabular data of our patient cohort, including continuous, categorical or
 82 numerical variables.

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Table 2b: Radiological patient characteristics

Characteristic	N = 483
number of brain metastases at baseline, n (%)	
one	133 (33)
two	138 (34)
three or more	131 (33)
Unknown	81
anatomical site at at baseline, n (%)	
frontal	153 (32)
temporal	84 (18)
parietal	63 (13)
occipital	55 (11)
cerebellar	120 (25)
other	4 (0.8)
Unknown	4
presence of extracranial metastasis, n (%)	
no presence of extracranial metastases at baseline	270 (57)
presence of extracranial metastases at baseline	200 (43)
Unknown	13
hemorrhage at baseline, n (%)	

Table 2b: Radiological patient characteristics

Characteristic	N = 483
no hemorrhage at baseline	354 (77)
hemorrhage at baseline	104 (23)
Unknown	25
hydrocephalus at baseline, n (%)	
no hydrocephalus at baseline	388 (87)
hydrocephalus at baseline	59 (13)
Unknown	36
localization of dominant brain metastasis, n (%)	
supratentorial	298 (63)
infratentorial	76 (16)
both supra-/infratentorial	100 (21)
Unknown	9
tumor volume, n (%)	
< 10	130 (42)
>= 10	182 (58)
Unknown	171
edema volume, n (%)	
< 50	138 (46)
>= 50	160 (54)
Unknown	185

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88 **eTable 2b:** Baseline radiological characteristics of patients after excluding short-term
89 survivors (< 2 months) and patients with very low KPS values (i.e. < 50%) (COHORT B)
90 (N=483). For patients where no pre-operative MRI was available no exact annotation of
91 anatomical site and no exact number of brain metastases were able to be retrieved.
92 Similarly in 13 cases no CT staging imaging was available in the setting of the brain
93 metastasis resection (**see also eTable1b in the supplementary section**).

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Table 2c: Histopathological and biomarker-related patient characteristics

Characteristic	N = 483
entity, n (%)	
breast cancer	88 (18)
colorectal carcinoma	7 (1.4)
melanoma	75 (16)
NSCLC	261 (54)
oesophageal carcinoma	1 (0.2)
renal cell cancer	24 (5.0)
SCLC	26 (5.4)
unknown primary	1 (0.2)
histological subtype, n (%)	
adenocarcinoma	1 (0.2)
adenocarcinoma (breast)	87 (18)
adenocarcinoma (colorectal)	7 (1.4)
adenocarcinoma (lung)	227 (47)
adenosquamous	3 (0.6)
clear cell renal cell carcinoma	24 (5.0)
melanoma	75 (16)
metaplastic carcinoma	1 (0.2)
neuroendocrine-differentiated tumor	36 (7.5)
pulmonary sarcomatoid carcinoma	1 (0.2)
squamous cell carcinoma (lung)	21 (4.3)
EGFR mutational status, n (%)	14 (7.8)
Unknown	304
ALK status, n (%)	6 (3.6)

Table 2c: Histopathological and biomarker-related patient characteristics

Characteristic	N = 483
Unknown	316
ROS1 status, n (%)	0 (0)
Unknown	330
TTF1 status, n (%)	
negative	90 (31)
positive	196 (69)
Unknown	197
progesterone receptor expression (Remmele score), n (%)	
< 4	80 (96)
>= 4	3 (3.6)
Unknown	400
estrogen receptor expression (Remmele score), n (%)	
< 4	55 (66)
>= 4	28 (34)
Unknown	400
Her2/NEU expression (DAKO score), n (%)	
0+	20 (24)
1+	14 (17)
2+	9 (11)
3+	40 (48)
Unknown	400
Ki67 index (%), n (%)	
< 30	239 (58)
>= 30	175 (42)
Unknown	69
intracranial PD-L1 TPS (%), n (%)	

Table 2c: Histopathological and biomarker-related patient characteristics

Characteristic	N = 483
< 1	96 (68)
>/= 1	45 (32)
Unknown	342

98

99 **eTable 2c:** Histopathological characteristics of COHORT B (N=483). Histology is listed
100 separately from entity to show distinct histopathological subtypes. Oncogenic drivers such
101 as EGFR, ALK, ROS1 and BRAF were available only in corresponding entity, e.g. BRAF for
102 melanoma or EGFR for lung cancer; the NA values were classified as not available or not
103 applicable where needed to simplify the structure of the table. Similarly immune scores
104 (Remmele score) for progesterone receptor (PR) and estrogen receptor (ER) as well as
105 Her2/NEU2 score (DAKO score) were only evaluated and available in tissues from breast
106 cancer patients. Ki67 index was dichotomized with a cut-off of 30% with 69 patients without
107 documented Ki67 index. Information on molecular characteristics (i.e. driver mutations) of
108 primary tumor tissue was not included into tabular data - only results from brain metastasis
109 tissue were listed.

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111

Table 2d: Treatment-related patient characteristics

Characteristic	N = 483
primary tumor resection, n (%)	
no primary tumor resection	208 (45)
primary tumor resection	253 (55)
Unknown	22
naive, n (%)	
naive	260 (55)
pre-treated	213 (45)
Unknown	10

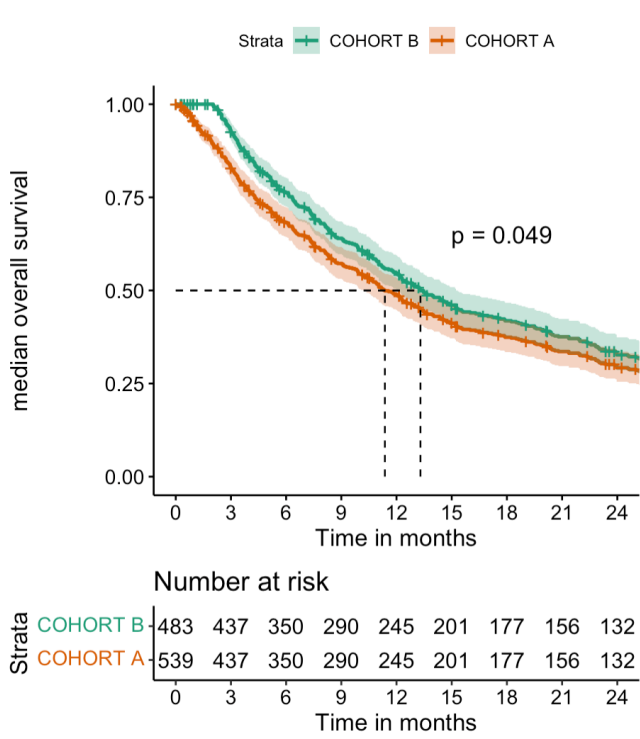
Table 2d: Treatment-related patient characteristics

Characteristic	N = 483
adjuvant RTx, n (%)	
no SRS	192 (73)
SRS	72 (27)
Unknown	219
adjuvant systemic treatment, n (%)	
BSC	15 (4.4)
RTx only	63 (18)
RTx + CTx	135 (39)
RTx + targeted therapy	38 (11)
RTx + CPI	93 (27)
Unknown	139

112

113 **eTable 2d:** Treatment-related characteristics of COHORT B; in 139 cases subsequent
114 therapy after brain metastasis resection was not documented or incompletely documented,
115 whereas 135 patients received radiation therapy (RTx) and chemotherapy (CTx) mainly
116 including carboplatin- or cisplatin-based regimens, 93 patients checkpoint inhibition (CPI)
117 mainly receiving combined chemoimmunotherapy (N=14), Nivolumab or
118 Nivolumab/Ipilimumab combinations (N=29), or Pembrolizumab (N=35) or other
119 combinations of different checkpoint inhibitors (N=22) (data not shown) (see also
120 supplementary table 1d).

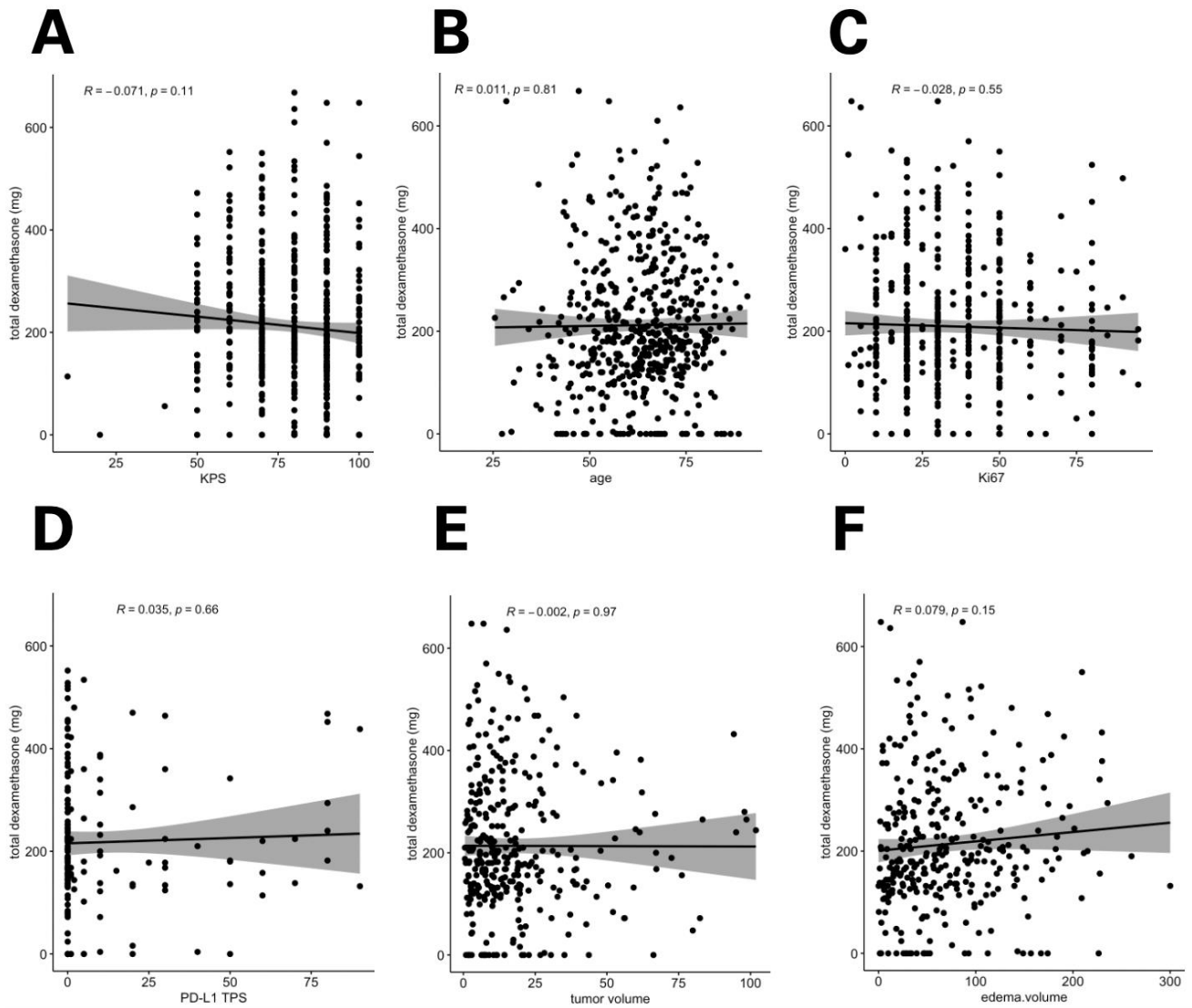
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eFigure 1: Kaplan Meier survival estimates and comparison of COHORT A with COHORT B

Kaplan Meier survival analysis for OS in the entire patient cohort of brain metastasis patients subjected to craniotomy and brain metastasis removal (N=539) (“all” or COHORT A) with an OS of 11.4 months (95%CI: 10.2 – 13.2) in comparison to the collective of patients after applying exclusion criteria (i.e. excluding patients with less than 2 months OS and patients with KPS less than 50%, “2 months and KPS<50excl” or COHORT B) showing a OS of 13.3 months (95%CI: 12.1 – 15.2) (p=0.049).



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eFigure 2a: Correlation of total dexamethasone with clinical parameters

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Pearson correlation (95% CI in gray; Pearson correlation coefficient R and cognate p value

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in the upper left section of each graphic) of total dexamethasone (i.e. pre-operative and

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post-operative dexamethasone) in resected brain metastases with a) age, b) KPS, c) Ki67

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and d) PD-L1 TPS, e) tumor volume and f) edema volume. Only data for COHORT A are

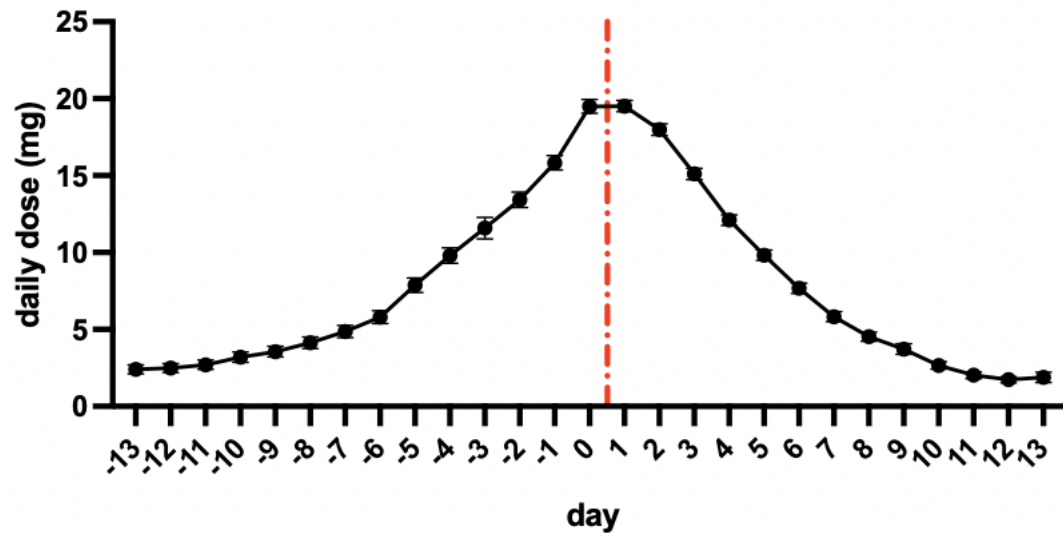
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shown.

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147 **eFigure 2b: Daily perioperative dexamethasone doses**

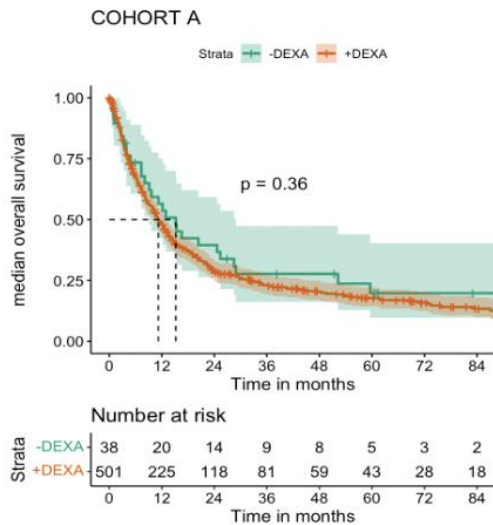
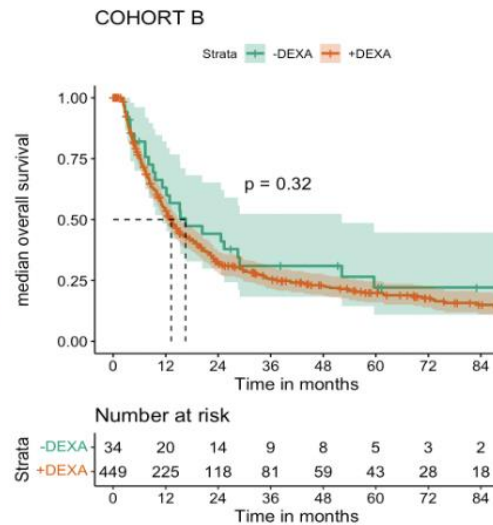
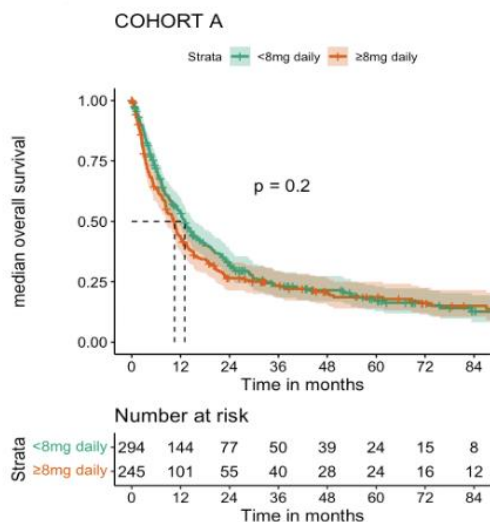
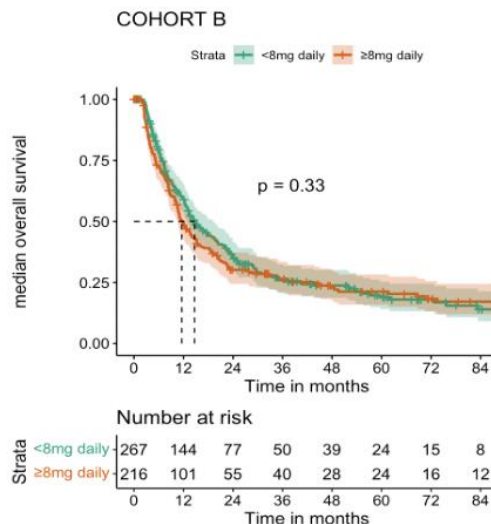
148 Mean values (mean with standard error of the means (SEM)) of daily dexamethasone for
 149 the total cohort of patients on the y-axis and days in relation to day 0 (day of surgical brain
 150 metastasis resection) are displayed for the total cohort of patients (N=539). Graph was
 151 produced with GraphPad Prism. Data for cohort A are shown.

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A**B****C****D**

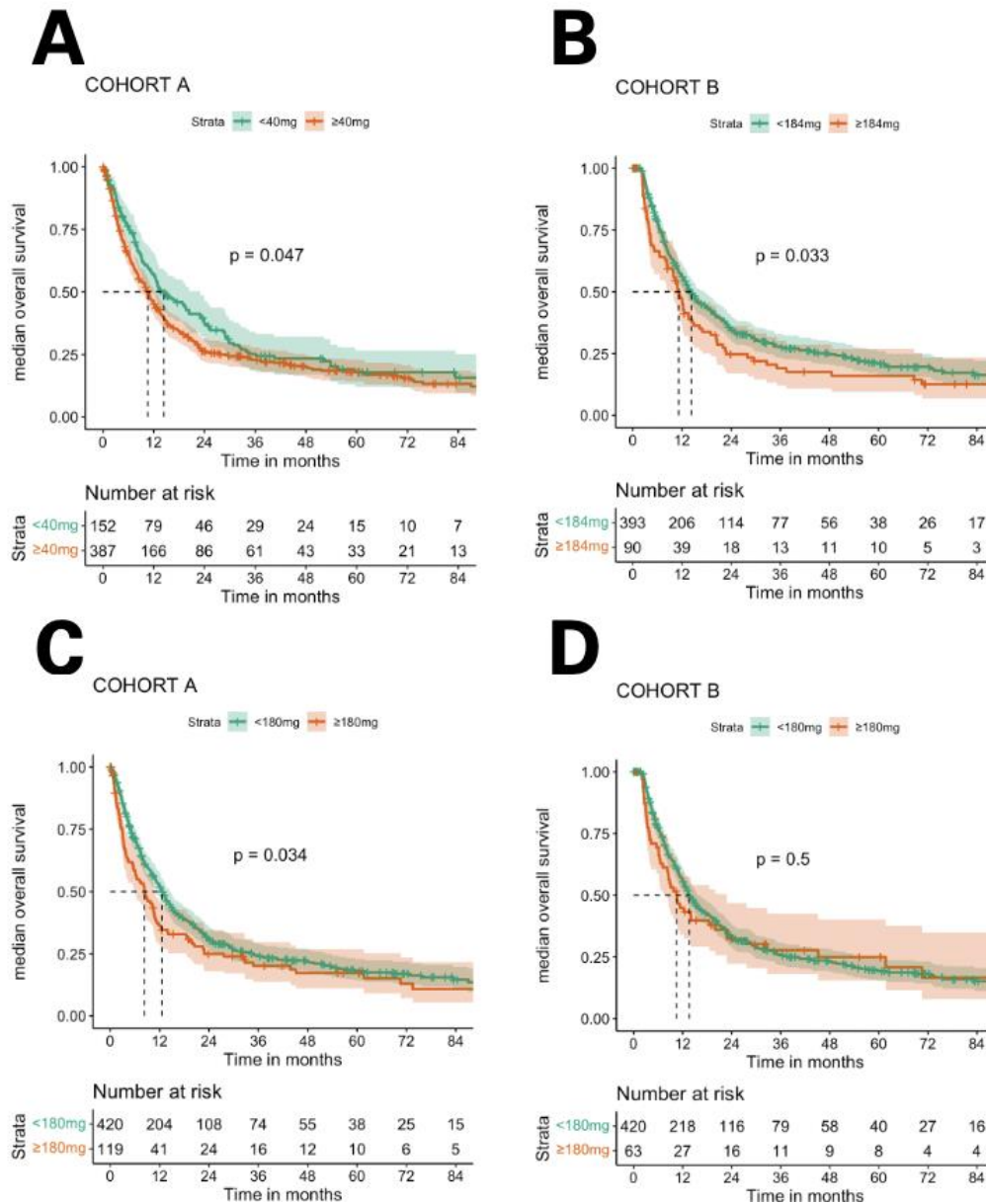
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157 **eFigure 3a: Kaplan-Meier analysis for overall survival of different dexamethasone**
 158 **dosage patient groups in COHORT A and B**

159 Kaplan Meier analysis stratified according to the following characteristics: **A)** intake of
 160 dexamethasone within the total cohort or COHORT A (n=539) of patients dichotomized into
 161 2 groups: patients that did not receive perioperative dexamethasone (-DEXA in green;
 162 median OS was 15.2 months; 95% CI: 9.10-28.9) or those which received dexamethasone
 163 during the pre- or postoperative period (+DEXA in red; median OS was 11.2 months; 95%
 164 CI: 9.97-13.0) (p=0.36); **B)** intake of dexamethasone within the subcohort COHORT B or
 165 “3months and KPS<50excl” (n=483) dichotomized into 2 groups: patients that did not
 166 receive perioperative dexamethasone (-DEXA in green; median OS was 16.5 months (95%

167 CI: 11.2-52.2) or those which received dexamethasone during the pre- or postoperative
168 period (+DEXA in red; median OS was 13.3 months (95% CI: 11.8-15.2) (p=0.32); **C**) intake
169 of dexamethasone within the total cohort (n=539) of patients dichotomized into 2 groups:
170 patients that did receive perioperative dexamethasone below 8 mg daily (< 8mg daily, in
171 green; median OS was 13.0 months (95% CI: 11.17-15.3), or those which received
172 dexamethasone \geq 8 mg daily (during the pre- or postoperative period (+DEXA in red;
173 median OS was 10.5 months (95% CI: 8.43-12.0) (p=0.2); **D**) intake of dexamethasone
174 within the subcohort COHORT B or “3months and KPS<50excl” (n=483) of patients
175 dichotomized into 2 groups: patients that did receive perioperative dexamethasone below 8
176 mg daily (< 8mg daily, in green; median OS was 14.7 months, 95% CI: 12.9-19.1) or those
177 which received \geq 8 mg dexamethasone daily during the pre- or postoperative period
178 (+DEXA in red; 11.6 months, 95% CI: 10.5-14.9) (p=0.33).

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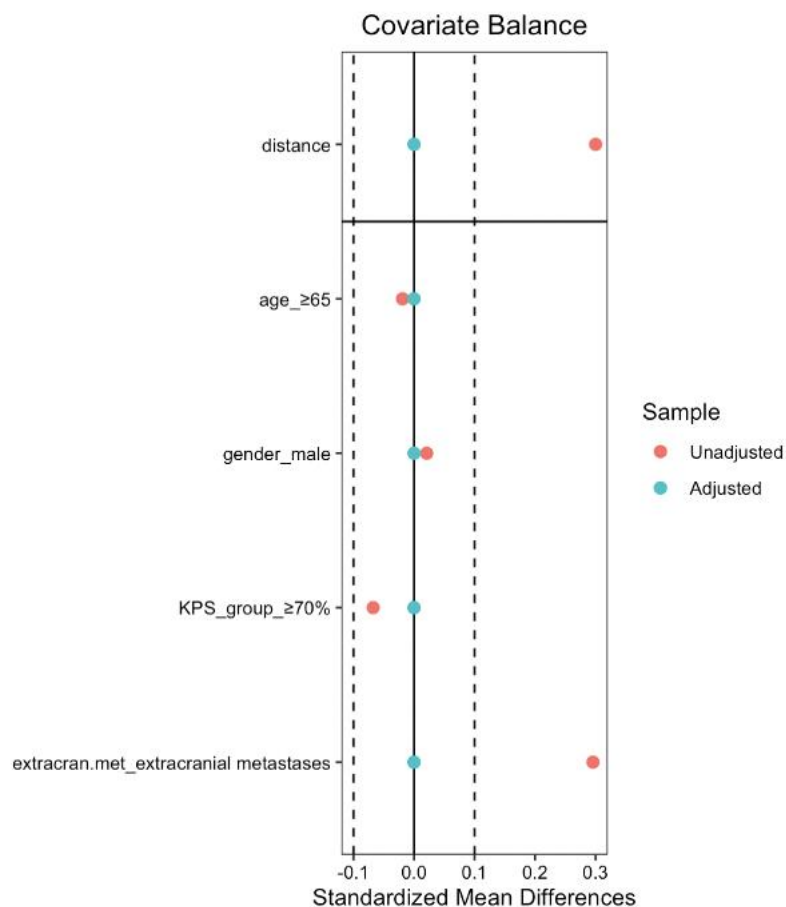


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182 **eFigure 3b: Kaplan-Meier analysis for overall survival of different dexamethasone**
183 **dosage patient groups in COHORT A and B**

184 Kaplan Meier analysis stratified according to the following characteristics: **A)** cumulative
185 intake of pre-operative dexamethasone within the total cohort or COHORT A (n=539) or
186 COHORT A dichotomized into 2 groups according to optimal cutpoint of 40 mg: patients
187 with < 40 mg cumulative dexamethasone in the pre-operative period showed a median OS
188 of 14.4 months (95% CI: 11.73-23.0) compared to patients with ≥ 40 mg cumulative
189 dexamethasone in the pre-operative period with an OS of 10.6 months (95% CI: 8.63-12.2)
190 (p=0.047); **B)** In COHORT B patients with < 184 mg cumulative dexamethasone in the pre-

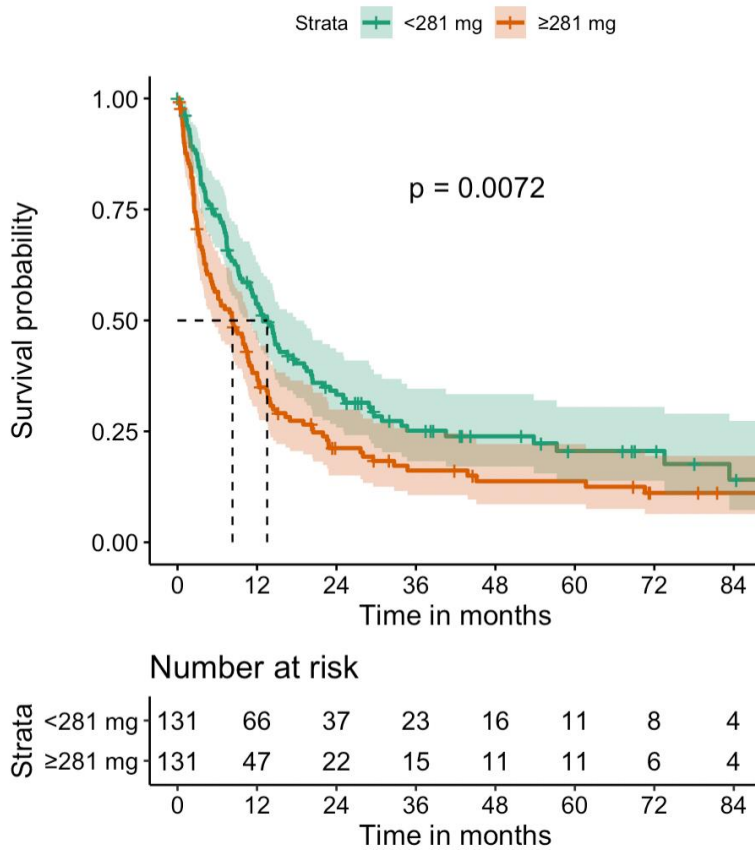
191 operative period showed a median OS of 14.3 months (95% CI: 12.50-17.4) as compared to
 192 those patients with ≥ 184 mg cumulative dexamethasone in the pre-operative period with
 193 an OS of 11.2 months (95% CI: 8.43-14.4) ($p=0.033$); **C**) the cutpoint for postoperative
 194 dexamethasone dosage was 180 mg which in turn resulted in two subgroups: the patient
 195 group with < 180 mg cumulative dexamethasone showed a median OS of 12.6 months
 196 (95% CI: 11.03-14.6) vs. those patients with ≥ 180 mg cumulative dexamethasone in the
 197 pre-operative period with an OS of 8.33 months (95% CI: 5.77-10.9) ($p=0.034$); **D**) for the
 198 COHORT B optimal cutpoint with 180 mg of post-operative dexamethasone: patients with $<$
 199 180 mg cumulative dexamethasone ($n=420$) showed a median OS of 13.6 months (95% CI:
 200 12.30-16.0) vs. patients with ≥ 180 mg cumulative dexamethasone in the post-operative
 201 period ($n=63$) with an OS of 10.5 months (95% CI: 8.23-22.8) ($p=0.5$).
 202



203 **eFigure 4: Propensity score matching and resulting mean standardized differences**
 204 Distribution of standardized mean differences before (unadjusted) and after (adjusted)
 205 propensity score matching (PSM) in COHORT A for covariates considered in the PSM
 206 including age, gender, KPS and presence of extracranial metastases.
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211 **eFigure 5: Kaplan-Meier survival curve for matched patients after propensity score**
 212 **matching**

213 Kaplan-Meier curve and associated risk table displaying overall survival of the two cohorts
 214 of patients receiving <281 mg perioperative dexamethasone with a median OS of 13.5
 215 months (95% CI: 10.9-17.9) vs. ≥ 281 mg perioperative dexamethasone with a median OS
 216 of 8.3 months (95% CI: 5.37-10.9) (p=0.0072).

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