Risk factors for the development of brain tumor-related epilepsy in patients with brain metastasis

SEPTEMBER 22, 2018, MARSEILLE

Fabian Wolpert M.D.
Department of Neurology and Brain Tumor Center
University Hospital and University of Zurich

Brain tumor related epilepsy (BTRE) in patients with brain metastasis (BM)

- 20-35% of BM patients develop BTRE *(Oberndorfer et al., 2002; Wu et al., 2017)*

- Primary prophylaxis provides no benefit in general *(Sirven et al., 2004; Ansari et al., 2014; Lee et al., 2013)*, but possibly for selected subgroups, e.g. melanoma patients or perioperative prophylaxsis *(Goldblum et al. 2012)*

- EANO guidelines: BTRE unequivocal indication for antiepileptic drugs, primary prophylaxis not recommended *(Soffietti et al. 2017)*

The dilemma of neurooncologists

„To start or not to start, that is the question"

Potential risk factors from the literature

- Pre-operative:

    - young age

    - high tumor volume

    - frontal location

    - headache, cognitive deficits

    - multipe BM
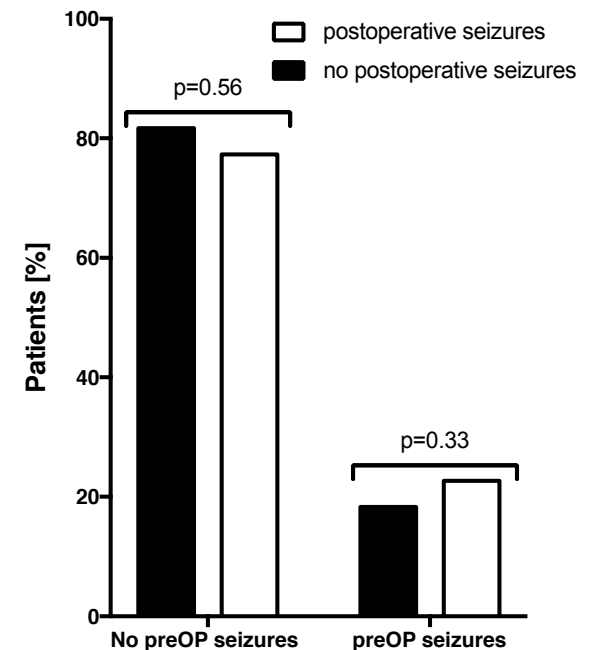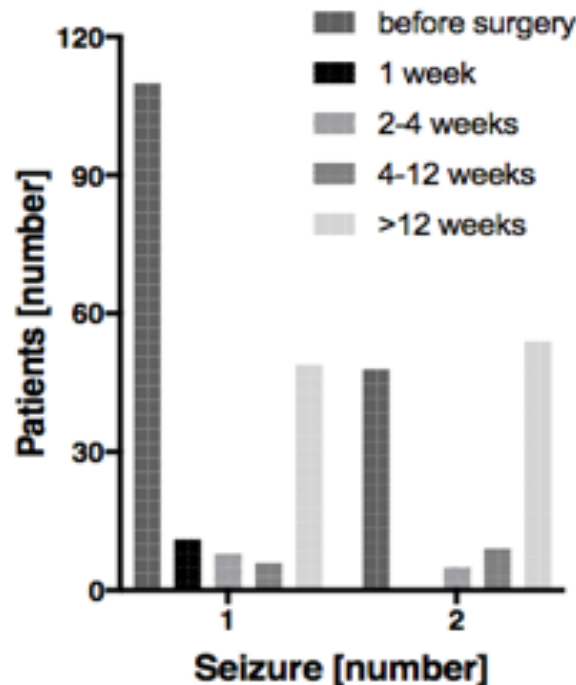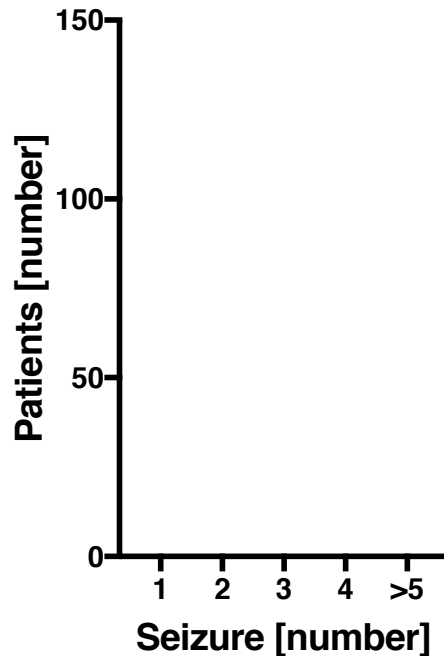
    - temporal or occipital lobe

    - bone involvement

    (Skardelly et al 2015 and Wu et al. 2017)

- Postoperative

Seizure frequency and influence of surgery in the Zurich cohort:

- 237 of 811 (29.2%) of patients with BTRE

- Two onset peaks: early before surgery or late after >12 weeks

- No improvement of seizure control or increase of new seizures after surgery

Risk profile factors for BTRE in non-operated patients

	All patients (n=241)	No seizures (n=191, 79.3%)	One or more epileptic seizures (n=50, 20.7%)	**p=
Number of BM, median (range)	4 (1-64)	4 (1-64)	2 (1-19)	0.013

- No association of seizure risk and localization, primary tumor, depth (subcortical or cortical), KPS, radiotherapy, hemorrhagic transformation

Risk profile for pre-operative seizures

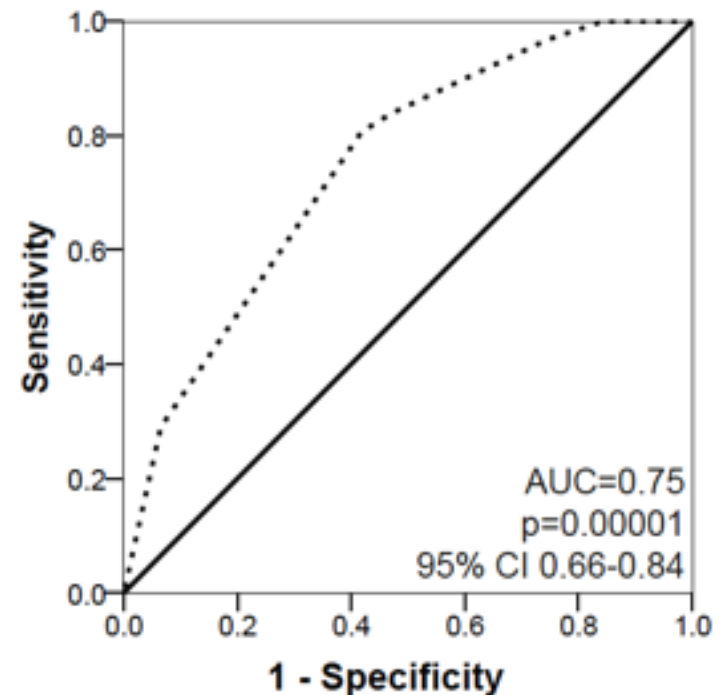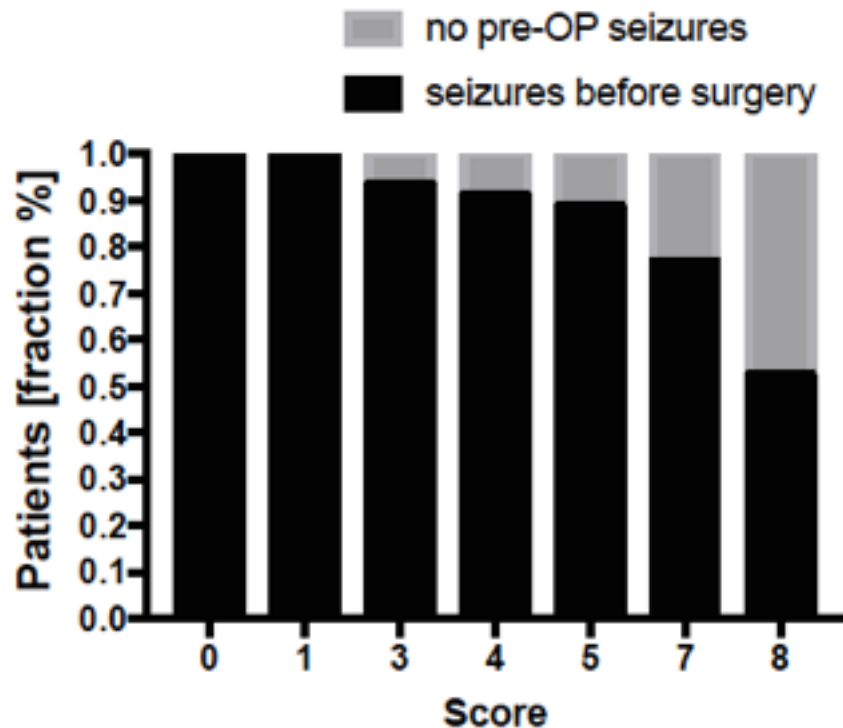|	All operated patients (n=568)	No pre-operative seizures (n=471, 80.8%)	One or more pre-operative seizures (n=112, 19.2%)	p*=
Primary tumor, n (%)				
unknown (%)	38 (2.7)	31 (81.6)	7 (18.4)	0.895
lung cancer (%)	224 (43.8)	166 (74.1)	58 (25.9)	0.006
melanoma (%)	92 (21.3)	78 (84.8)	14 (15.2)	0.159
breast cancer (%)	71 (11.6)	67 (94.4)	4 (5.6)	0.002
renal cell cancer (%)	24 (2.3)	19 (79.2)	5 (20.8)	0.892
gastrointestinal (%)	56 (4.3)	44 (78.6)	12 (21.4)	0.740
other (%)	67 (14.0)	55 (82.1)	12 (17.9)	0.733
Location of BM (supra- versus infratentorial)				
supratentorial BM	199	150 (75.4)	49 (24.6)	<0.001
Location of singular supratentorial BM				0.020
frontal	95	63 (66.3)	32 (33.7)	0.005
parietal	45	34 (75.6)	11 (24.4)	0.847
occipital	25	21 (84.0)	4 (16.0)	0.267
temporal	33	31 (93.9)	2 (6.1)	0.110

Risk profile for post-operative seizures

	All operated patients (n=572)	No post-operative seizures (n=481, 84.1%)	One or more post-operative seizures (n=91, 15.9%)	P=
Localization of BM				
singular supratentorial BM	199 (74.3)	160 (80.4)	39 (19.6)	0.007
singular infratentorial BM	69 (25.7)	65 (94.2)	4 (5.8)	Ref.
Localization of singular supratentorial BM				
frontal	95	81 (85.3)	14 (14.7)	0.099[a]
parietal	45	35 (75.6)	11 (24.4)	0.352[a]
occipital	25	16 (64.0)	9(36.0)	0.027[a]
temporal	33	29 (87.9)	4 (12.1)	0.236[a]
Number of surgeries				
one surgery	463 (81.9)	407 (87.9)	56 (12.1)	Ref.
two or more surgeries	102 (18.1)	70 (68.6)	32 (31.4)	>0.001
Cerebral venous thrombosis (CVT)				
no CVT	523 (98.3)	443 (84.7))	80 (15.3)	Ref.
confirmed CVT	9 (1.7)	5 (55.6)	4 (44.4)	0.017
Extent of resection of supratentorial singular BM (n=236)				0.011
Biopsy or Incomplete resection, n (%)	92 (62.2)	67 (72.8)	25 (27.2)	0.003
gross total resection, n (%)	56 (37.8)	52 (92.9)	4 (7.1)	

- No association with age, gender, primary tumor, infiltration depth

Risk profile for post-operative seizures: multivariate analysis and score model

Factor	Odds Ratio (95% CI)	P=	Score
Incomplete resection (y/n)	4.6 (1.6-13.1)	0.005	3 points
Supratentorial localization (y/n)	5.8 (1.4-24.3)	0.017	4 points
Multiple surgeries (y/n)	1.9 (0.9-4.0)	0.095	1 point

Strenghts and limitations

- Pro:
  - Large, well defined cohort
  - Sample size allows to perform subgroup analyses

- Contra
  - Retrospective data from single institution
  - High fraction of operated patients, possible bias to underreporting of patients with extensive disease

Outlook

- External validation of risk model

- Further analysis of cohort: tumor volumetry and EEG data

- Prospective validation of risk models model in controlled trials

- New data might be helpful for:

  - Identification of subgroups that might benefit from primary prophylaxis
  - Improved prediction of seizure risk (e.g. driving ban)
  - risk stratification for clinical trials

Acknowledgements

Brain Tumor Center Zurich of the University Hospital and University Zurich

Center for Hematology and Oncology

Department of Neuroradiology

Department of Neurosurgery

Department of Neurology

Department of Nuclear Medicine

Department of Radiation Oncology

Institute of Neuropathology