SURGERY AND RADIOTHERAPY FOR BRAIN METASTASES

Emilie Le Rhun
Lille University Hospital, France

12 October 2019
DISCLOSURE OF INTEREST

Emilie Le Rhun

- Personal financial interests: Tocagen, Abbvie, Daiichy Sankyo, Mundipharma and Novartis
- Institutional financial interests: Mundipharma and Amgen
- Non-financial interests: Abbvie
Epidemiology

Who are the candidates for a local approach?

Surgery

Radiotherapy

Surgery versus SRT, combination of treatments

Future developments

Supportive care
Epidemiology

Who are the candidates for a local approach?

Surgery

Radiotherapy

Surgery versus SRT, combination of treatments

Future developments

Supportive care
Clinical challenge

cohort of 1,302,166 patients with diagnoses of non-hematologic malignancies originating outside of the CNS between 2010-2013. 26,430 patients with brain metastases at diagnosis of cancer (2%).

Kim et al., 2018
BIOLOGICAL ASPECTS OF METASTASIS TO THE CENTRAL NERVOUS SYSTEM

• Metastasis to brain and spinal cord requires the synergy of cancer cells and the parenchymal tissue of the central nervous system (CNS)

• Different primary tumors are characterized by distinct patterns of CNS metastasis:
  ▶ timing of CNS metastasis
  ▶ incidence of CNS metastasis
  ▶ tropism for the CNS
  ▶ focal versus diffuse metastasis
# CNS METASTASIS FROM SOLID TUMORS

**Historical data predating targeted and immuno therapy**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Incidence Clinical (%)</th>
<th>Incidence Autopsy (%)</th>
<th>Median interval from diagnosis (months)</th>
<th>Range (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>small cell adenocarcinoma</td>
<td>30-45</td>
<td>30-70</td>
<td>2.6</td>
<td>0-15</td>
</tr>
<tr>
<td>squamous cell</td>
<td>24-30</td>
<td>50</td>
<td>2</td>
<td>0-66</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>40</td>
<td>0.2</td>
<td>0-31</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>10-20</td>
<td>20-40</td>
<td>23</td>
<td>0-121</td>
</tr>
<tr>
<td>Melanoma</td>
<td>20-45</td>
<td>40-90</td>
<td>36</td>
<td>3-83</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>20</td>
<td>20</td>
<td>39</td>
<td>19-119</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>4</td>
<td>6-10</td>
<td>22</td>
<td>0-48</td>
</tr>
</tbody>
</table>
Epidemiology

Who are the candidates for a local approach?

Surgery

Radiotherapy

Surgery versus SRT, combination of treatments

Future developments

Supportive care
FACTORS FAVOURING INTENSIFIED LOCAL THERAPY

- Single or solitary metastasis
- Adequate performance status
- No or mild neurological deficits
- No or stable (> 3 months) extracranial tumor manifestations
- Radioresistant tumor
OBJECTIVES OF LOCAL TREATMENTS

« Curative » setting
objective = to treat all brain metastases (in the context of a possible treatment of all other lesions)

Palliative setting
objective = to maintain the quality of life and permit the administration of other treatments;
for lesions with mass effect, fossa posterior lesions, cystic or necrotic lesions
Epidemiology

Who are the candidates for a local approach?

**Surgery**

Radiotherapy

Surgery versus SRT, combination of treatments

Future developments

Supportive care
SURGERY: HOW TO ACHIEVE MAXIMUM-SAFE-RESECTION?

« en bloc » resection

Tools
awake surgery
neuronavigation
per operative US
per operative MRI
5 ALA
....
Aim of the present study was to analyze the oncological impact of 5-ALA fluorescence of cerebral metastases. A retrospective analysis was performed for 84 patients who underwent 5-ALA fluorescence-guided surgery of a cerebral metastasis. Dichotomized fluorescence behavior was correlated to the histopathological subtype and primary site of the metastases, the degree of surgical resection on an early postoperative MRI within 72 hours after surgery, the local in-brain-progression rate and the overall survival. 34/84 metastases (40.5%) showed either strong or faint and 50 metastases (59.5%) no 5-ALA derived fluorescence. Neither the primary site of the cerebral metastases nor their subtype correlated with fluorescence behavior. The dichotomized 5-ALA fluorescence (yes vs. no) had no statistical influence on the degree of surgical resection. Local in-brain progression within or at the border of the resection cavity was observed in 26 patients (30.9%). A significant correlation between 5-ALA fluorescence and local in-brain-progression rate was observed and patients with 5-ALA-negative metastases had a significant higher risk of local recurrence compared to patients with 5-ALA positive metastases. After exclusion of the 20 patients without any form of adjuvant radiation therapy, there was a trend towards a relation of the 5-ALA behavior on the local recurrence rate and the time to local recurrence, although results did not reach significance anymore. Absence of 5-ALA-induced fluorescence may be a risk factor for local in-brain-progression but did not influence the mean overall survival. Therefore, the dichotomized 5-ALA fluorescence pattern might be an indicator for a more aggressive tumor.

Figure 1: Different shades of 5-ALA-induced fluorescence of cerebral metastases. Cerebral metastases may appear as 5-ALA-negative (A, B) or faintly (C, F) or strongly 5-ALA positive (E, F).

Figure 2: 5-ALA-derived fluorescence behavior of cerebral metastases according to their histological subtype and the primary site. Figure 2A shows the 5-ALA-derived fluorescence behavior of cerebral metastases according to their histological subtype (A) and the primary site (B).
HOW DO I KNOW IF MY PATIENT CAN BE OPERATED?

Ask the neurosurgeon!
Epidemiology

Who are the candidates for a local approach?

Surgery

Radiotherapy

Surgery versus SRT, combination of treatments

Future developments

Supportive care
STEREOTACTIC RADIOSURGERY/RADIOThERAPY

Gamma knife

Cyber knife
SINGLE FRACTION VERSUS HYPOFRACTIONATION
Factors favouring hypofractionation

- Large lesion (>30 mm)
- Proximity to an „at risk organ“
- Previous irradiation
- Comorbidities (stroke, vascular dementia....)
SRS of multiple brain metastases

Yamamoto et al, Lancet Oncol 2014

<table>
<thead>
<tr>
<th>Group</th>
<th>Median overall survival, months (95% CI)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 tumour</td>
<td>13.9 (12.0-15.6)</td>
<td>0.76 (0.66-0.88)</td>
<td>0.0004</td>
</tr>
<tr>
<td>2-4 tumours</td>
<td>10.8 (9.4-12.4)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>5-10 tumours</td>
<td>10.8 (9.1-12.7)</td>
<td>0.97 (0.81-1.18)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Figure: Kaplan-Meier curves of overall survival
HR=hazard ratio.
contrast-enhancing necrotic lesions, surrounded by edema, occurring at least 3 months after stereotactic radiotherapy, localized within fields of irradiation.

- **at BM diagnosis**

- **6 months after radiosurgery**

- **9 months after radiosurgery**

- **15 months after radiosurgery**
Epidemiology

Who are the candidates for a local approach?

Surgery

Radiotherapy

**Surgery versus SRT, combination of treatments**

Future developments

Supportive care
Surgery + WBRT versus WBRT alone

Improved local control and overall survival
**Surgery vs. SRT**

*Bindal et al. “Surgery versus radiosurgery in the treatment of brain metastasis.” J Neurosurg 1996 (n=75; retrospective)*

**OS better after surgery:**
- OS surgery 16.4 vs. 7.5 months (SRS) univariate (p = 0.0018) and multivariate (p = 0.0009).
- The difference in survival was due to a higher rate of mortality from brain metastasis in the radiosurgery group than in the surgery group (p < 0.0001) and not due to a difference in the rate of death from systemic disease (p = 0.28)


**No significant difference** in patient survival (p = 0.15);
- the 1-year survival rate was 56% for the RS patients and 62% for the NS patients.

- Data on surgery vs. SRS is very limited. No RTCs!
SURGERY VERSUS SRT

Factors favouring surgery over SRT

• Unknown primary tumor
• Neuroradiologically uncertain lesion
• Presentation of the tumor: large cystic or necrotic lesion, mass effect
• Molecular profiling needed

Factors favouring SRT over surgery

• Lesion non surgically accessible
• High surgical risk
Surgery + WBRT versus SRS + WBRT

Heavily debated, but no difference.

Table 3: Surgery + WBRT versus SRS + WBRT

<table>
<thead>
<tr>
<th>First author (Year)</th>
<th>Interventions</th>
<th>Median survival</th>
<th># pts with recurrence/progression*</th>
<th>Median time to recurrence/progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>At original site:</td>
<td></td>
</tr>
<tr>
<td>Bindal [16] (1996)</td>
<td>G1: Surgery ± WBRT(^b) (n = 62) (matched to G2) G2: SRS ± WBRT(^b) (n = 31)</td>
<td>G1: 16.4 months G2: 7.5 months (Log-rank; (P = 0.0018))</td>
<td>1 yr freedom from LR rate: G2 poorer than G1 [Data: NR] 1 yr freedom from DR rate: G1: 75% G2: 69%</td>
<td>At original site: G1: Median not reached G2: 6 months (Log-rank; (P = 0.001)) At distant brain site: G1: Median not reached G2: Median not reached (Log-rank; (P = NS))</td>
</tr>
<tr>
<td>Garell [17] (1999)</td>
<td>G1: Surgery + WBRT (n = 37) G2: SRS + WBRT (n = 38)</td>
<td>G1: 8 months G2: 125 months (Log-rank (P = NS))</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Schogg [18] (2000)</td>
<td>G1: Surgery + WBRT (n = 60) G2: SRS + WBRT (n = 67)</td>
<td>G1: 9 months G2: 12 months (Test unclear (P = NS))</td>
<td>At original site: G1: 11/66 (17%) G2: 3/67 (5%) (P = NR) At distant brain sites: G1: 10/66 (15%) G2: 7/67 (10%) (P = NR)</td>
<td>At original site: G1: 3.9 months G2: 4.9 months (Test unclear; (P &lt; 0.05)) At distant brain sites: G1: 3.7 months G2: 4.4 months (Test unclear; (P = NS))</td>
</tr>
<tr>
<td>O’Neill [19] (2003)</td>
<td>G1: Surgery ± WBRT (n = 74) G2: SRS ± WBRT(^b) (n = 23)</td>
<td>Median survival: NR 1 yr survival rate: G1: 62% G2: 56% (Log-rank; (P = NS))</td>
<td>At original site: G1: 11/64 (17%) G2: 0/21 (0%) (P = NR) Overall in brain: G1: 19/64 (30%) G2: 6/21 (29%) (P = NR)</td>
<td>NR</td>
</tr>
</tbody>
</table>

* Number of pts with recurrence/progression of brain metastases, unless otherwise specified.

\(^b\) WBRT use similar at baseline in both groups.
Surgery + WBRT versus surgery alone

Improved local control, but no effect on overall survival
Adjuvant WBRT after surgery/radiosurgery

Purpose
This European Organisation for Research and Treatment of Cancer phase III trial assesses whether adjuvant whole-brain radiotherapy (WBRT) increases the duration of functional independence after surgery or radiosurgery of brain metastases.

Patients and Methods
Patients with one to three brain metastases of solid tumors (small-cell lung cancer excluded) with stable systemic disease or asymptomatic primary tumors and WHO performance status (PS) of 0 to 2 were treated with complete surgery or radiosurgery and randomly assigned to adjuvant WBRT (30 Gy in 10 fractions) or observation (OBS). The primary end point was time to WHO PS deterioration to more than 2.

Results
Of 359 patients, 199 underwent radiosurgery, and 160 underwent surgery. In the radiosurgery group, 100 patients were allocated to OBS, and 99 were allocated to WBRT. After surgery, 79 patients were allocated to OBS, and 81 were allocated to adjuvant WBRT. The median time to WHO PS more than 2 was 10.0 months (95% CI, 8.1 to 11.7 months) after OBS and 9.5 months (95% CI, 7.8 to 11.9 months) after WBRT (P = .71). Overall survival was similar in the WBRT and OBS arms (median, 10.9 v 10.7 months, respectively; P = .89). WBRT reduced the 2-year relapse rate both at initial sites (surgery: 59% to 27%, P < .001; radiosurgery: 31% to 19%, P = .040) and at new sites (surgery: 42% to 23%, P = .008; radiosurgery: 48% to 33%, P = .023). Salvage therapies were used more frequently after OBS than after WBRT. Intracranial progression caused death in 78 (44%) of 179 patients in the OBS arm and in 50 (28%) of 180 patients in the WBRT arm.

Conclusion
After radiosurgery or surgery of a limited number of brain metastases, adjuvant WBRT reduces intracranial relapses and neurologic deaths but fails to improve the duration of functional independence and overall survival.

SRS: local control of approximately 70% at 1 year
Adjuvant SRS vs WBRT after surgery

Findings: Between Nov 10, 2011, and Nov 16, 2015, 194 patients were enrolled and randomly assigned to SRS (98 patients) or WBRT (96 patients). Median follow-up was 11.1 months (IQR 5.1–18.0). Cognitive-deterioration-free survival was longer in patients assigned to SRS (median 3.7 months [95% CI 3.45–5.06]; 93 events) than in patients assigned to WBRT (median 3.0 months [2.56–3.25]; 93 events; hazard ratio [HR] 0.47 [95% CI 0.35–0.63]; p=0.0001), and cognitive deterioration at 6 months was less frequent in patients who received SRS than those who received WBRT (28 [52%] of 54 evaluable patients assigned to SRS vs 41 [85%] of 48 evaluable patients assigned to WBRT; difference −33.6% [95% CI −45.3 to −21.8]; p=0.00031). Median overall survival was 12.2 months (95% CI 9.7–16.0; 69 deaths) for SRS and 11.6 months (9.9–15.0; 67 deaths) for WBRT (HR 1.07 [95% CI 0.76–1.50]; p=0.70). The most common grade 3 or 4 adverse events reported with a relative frequency greater than 4% were hearing impairment (three [3%] of 93 patients in the SRS group vs eight [9%] of 92 patients in the WBRT group) and cognitive disturbance (three [3%] vs five [5%]). There were no treatment-related deaths.
At 6 months, for patients having cognitive evaluations, cognitive deterioration was less frequent in the SRS arm (52% vs. 85% \( p=0.00031 \)) reaching statistical significance for immediate memory (\( p=0.00062 \)), delayed memory (\( p=0.00054 \)), processing speed (\( p=0.023 \)), and executive function (\( p=0.015 \)).

no significant difference was observed in survival (primary endpoint) or cause of death.
Fig. 2. A 57-year-old woman with brain metastases from lung adenocarcinoma underwent whole-brain radiation therapy (WBRT). (A, B) T2-weighted magnetic resonance imaging (MRI) before WBRT. (C, D) Follow-up T2-weighted MRI scan 5 months after WBRT revealed near-total white matter T2 hyperintensities and severe ventriculomegaly, diagnosed as leukoencephalopathy grade 3.
Memantine

Adult brain metastasis patients treated with WBRT

- 508 eligible patients
- primary endpoint: preservation of HVLT-R compared with placebo at 24 weeks
  - trend to less decline in delayed recall (HVLT-R) at 24 weeks \((p=0.059)\)
  - longer time to cognitive decline under memantine, and the probability of cognitive function failure at 24 weeks was 53.8% in the memantine arm vs. 64.9% in the placebo arm \((p=0.01)\)
  - better results on memantine for executive functions, processing speed and delayed recognition

memantine 20 mg/d within initiation of WBRT, for 24 weeks
placebo
NRG Oncology CC001: A Phase III Trial of Hippocampal Avoidance in Addition to Whole Brain Radiotherapy Plus Memantine to Preserve Neurocognitive Function in Patients with Brain Metastases


Figure 1.
Time to Cognitive Function Failure
Separation of curves starting at 3 mos
Median f/u for alive patients: 7.90 months

Figure 2.
Intracranial Progression-Free Survival

Figure 3.
Overall Survival
non-inferiority, phase 3, randomised trial

- small difference in QALYs
- absence of a difference in survival and quality of life between the two groups

WBRT provides little additional clinically significant benefit for this patient group.
FAREWELL TO WHOLE BRAIN RADIOTHERAPY?

PRO
- improved control in CNS
- reduced neurotoxicity with memantine?
- hippocampal sparing?
- hair-sparing WBRT?

CONTRA
- preservation of neurocognitive function
- preservation of QOL
- no impact on OS
Prophylactic Cranial Irradiation Versus Observation in Radically Treated Stage III Non–Small-Cell Lung Cancer: A Randomized Phase III NSCLC 11/DCRG 02 Study

Fig. 1. CONSORT diagram. NSCLC = non-small-cell lung cancer; PCI = prophylactic cranial irradiation.

Fig. 2. Kaplan-Meier estimates of progression-free survival. PTSD = posttraumatic stress disorder; PCI = prophylactic cranial irradiation.

Fig. 3. Number of neurologic adverse events (AEs) over time. (A) Prophylactic cranial irradiation (PCI) arm only. (B) Observation arm only. Trt. before initiation.
COMBINATION RT – SYSTEMIC PHARMACOTHERAPY

what means concomitant?

only few data available

need for clinical trials!

Table 1. Drugs half-lives (approximate values, from transparency commissions)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Median half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemuranelib</td>
<td>51.6 (29.8–119.5)</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>8 (when orally administered)</td>
</tr>
<tr>
<td>Trametinib</td>
<td>127</td>
</tr>
<tr>
<td>Erdafitinb</td>
<td>362</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>41</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>98</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>456</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>24</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>370</td>
</tr>
<tr>
<td>Trastuzumab-entansine</td>
<td>600</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>578</td>
</tr>
</tbody>
</table>

Table 5. Immune checkpoint inhibitors and RT

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary</th>
<th>n</th>
<th>RT</th>
<th>Drug</th>
<th>Brain control</th>
<th>Median survival</th>
<th>Toxicity</th>
<th>Median follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al. [9]</td>
<td>Melanoma</td>
<td>20</td>
<td>SRS</td>
<td>Ipilimumab</td>
<td>Not improved versus SRS alone</td>
<td>Not improved versus SRS alone (median 8.6 vs 6.5 months)</td>
<td>No increased toxicity</td>
<td>7.3</td>
</tr>
<tr>
<td>Knutley et al. [1]</td>
<td>Melanoma</td>
<td>77</td>
<td>SRS</td>
<td>Ipilimumab</td>
<td>Brain local</td>
<td>31%</td>
<td>31%</td>
<td>No a-before RT</td>
</tr>
<tr>
<td>Sil et al. [10]</td>
<td>Melanoma</td>
<td>70</td>
<td>NKIIT (16)</td>
<td>Ipilimumab</td>
<td>Not significantly improved in ip group</td>
<td>18.7 months (versus 6.3 without ip)</td>
<td>No increased toxicity</td>
<td>10</td>
</tr>
<tr>
<td>Matthew et al. [11]</td>
<td>Melanoma</td>
<td>38</td>
<td>SRS</td>
<td>Ipilimumab</td>
<td>67%</td>
<td>18.4 months</td>
<td>No increased toxicity</td>
<td>6</td>
</tr>
<tr>
<td>Kies et al. [12]</td>
<td>Melanoma</td>
<td>46</td>
<td>SRS</td>
<td>Ipilimumab</td>
<td>Brain local</td>
<td>61%</td>
<td>48% (95% CI)</td>
<td>No increased toxicity</td>
</tr>
<tr>
<td>Tu et al. [13]</td>
<td>Melanoma</td>
<td>10</td>
<td>SRS</td>
<td>Ipilimumab</td>
<td>During or after SRS</td>
<td>16.5 months</td>
<td>No increased toxicity</td>
<td>NR</td>
</tr>
<tr>
<td>Geisbrecht et al. [14]</td>
<td>Melanoma</td>
<td>13</td>
<td>NKIIT</td>
<td>Ipilimumab</td>
<td>59%</td>
<td>3, 6-35, 50%</td>
<td>No increased toxicity</td>
<td>4</td>
</tr>
<tr>
<td>Cohen-Addar et al. [15]</td>
<td>Melanoma</td>
<td>46</td>
<td>SRS</td>
<td>Ipilimumab</td>
<td>35% before SRS</td>
<td>6.5%</td>
<td>3%</td>
<td>No increased toxicity</td>
</tr>
<tr>
<td>Alamr et al. [16]</td>
<td>Melanoma</td>
<td>2</td>
<td>SRS</td>
<td>Nivolumab</td>
<td>During or after SRS</td>
<td>6.4%</td>
<td>11%</td>
<td>No increased toxicity</td>
</tr>
<tr>
<td>Ahmed et al. [17]</td>
<td>Melanoma</td>
<td>26</td>
<td>SRS</td>
<td>Nivolumab</td>
<td>During or after SRS</td>
<td>3%</td>
<td>12%</td>
<td>No increased toxicity</td>
</tr>
</tbody>
</table>

*Followed-up: SRS, stereotactic radiosurgery; OS, overall survival; NKIIT, whole-brain radiation therapy; NSCLC, non-small-cell lung cancer; NR, not reported; NS, non-significant; NA, not applicable. RT, radiotherapy; ip, intravenous; SRS, stereotactic radiosurgery; OS, overall survival; NKIIT, whole-brain radiation therapy; NSCLC, non-small-cell lung cancer; NR, not reported; NS, non-significant; NA, not applicable. RT, radiotherapy.
Epidemiology

Who are the candidates for a local approach?

Surgery

Radiotherapy

Surgery versus SRT, combination of treatments

**Future developments**

Supportive care
LASER-induced thermal ablation (LITT) in brain metastases

How to combine neurosurgery with SRS?

Surgery followed by SRS for one large and some smaller lesions

SRS followed by surgery to improve local control, reduce the incidence of radionecrosis, and decrease the risk of leptomeningeal spread
Perspectives in radiotherapy: Artificial Intelligence

Autosegmentation for contouring
Knowledge based atlases
Deep learning based methods

Model-based automated target delineation
Deep learning derived tumor infiltration maps
Peakam et al. 2019

CTV\textsubscript{EORTC} 276.8 cc
CTV\textsubscript{RTOG} 240.9 cc
CTV\textsubscript{deep learning} 207.2 cc

Based on DTI imaging = surrogate for infiltrative tumor
EORTC and RTOG based on 2cm margin!

Automatic generation of treatment plans:

- Fast plan generation
- Reduced interobserver variation
- Equally acceptable dose distribution

Oomics driven Radiotherapy
- Incorporating -omics information for treatment refinement
- Incorporating -omics information for response assessment and outcome prediction

New developments in radiation oncology: Promise and limitations
Nicolaus Andratschke
Epidemiology

Who are the candidates for a local approach?

Surgery

Radiotherapy

Surgery versus SRT, combination of treatments

Future developments

Supportive care
Management of edema

- Steroids are the mainstay for anti-edema treatment.

- The need for anti-edema treatment is typically not simply defined by its size on imaging but primarily based on the patient's clinical condition:

  - High doses are justified in acute severe edema.

  - A randomized trial comparing 4 and 8 mg of dexamethasone as well as 4 and 16 mg per day in patients with metastastic brain tumors, did not show a superior effect of the higher doses on the patients' condition as defined by the Karnofsky performance index. However, patients receiving higher dexamethasone doses were more likely to suffer from side effects (Vecht 1994).

  - Clinically asymptomatic patients mostly do not require anti-edema treatment with steroids.

- The prophylactic use of steroids, e.g. perioperatively or during radiotherapy or immunotherapy of patients with primary or secondary brain tumors, is discouraged.
2 retrospective cohorts of PD-L1 naïve advanced NSCLC treated with single agent PD-L1 blockade steroids at anti-PD-L1 therapy initiation
Main steroid related toxicity

- Diabetes
- Effects on mood (cognitive disorders, hypomania, depression)
- Steroid-induced proximal myopathy
- Muscular-skeletal complications (particularly osteoporosis)
- Digestive complications (especially risk of gastro-intestinal complications)
- Cutaneous complications
- Ophthalmologic disorders
- Immune suppression with the risk of infection
- Risk of venous thromboembolic disease
- Electrolyte disturbances
## EDEMA

<table>
<thead>
<tr>
<th>Diagnosis of brain edema should be performed using T2-weighted or FLAIR MR sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-edema treatment should only be considered in brain tumor patients requiring relief from neurological deficits</td>
</tr>
<tr>
<td>Dexamethasone is the drug of choice for the treatment of symptomatic tumor-associated brain edema</td>
</tr>
<tr>
<td>The initial dexamethasone dose is typically in the range of 4-16 mg/day given as a single daily intravenous or oral administration. The steroid dose should be tapered to the lowest dose needed to control clinical symptoms</td>
</tr>
<tr>
<td>Treatment with steroids imposes an increased risk for the development of pneumocystis jirovecii pneumonia (PJP). Appropriate PJP prophylaxis, e.g., with trimethoprim-sulfamethoxazole, should be considered in patients requiring steroid treatment for more than 4 weeks or undergoing radio- or chemotherapy in parallel</td>
</tr>
</tbody>
</table>
Corticosteroids + Bevacizumab vs. Corticosteroids + Placebo (BEST) for Radionecrosis After Radiosurgery for Brain Metastases - ALLIANCE - NCT02490878

- Phase II trial (bev 10 mg/kg or placebo at d1, d15 of a 28 day cycle, for 4 cycles)
- Brain metastases

- **Primary Outcome Measures:**
  Patient-reported outcome (symptoms) of radionecrosis

- **Secondary Outcome Measures:**
  - Toxicities associated with bevacizumab and corticosteroids using CTCAE Version 4.0 and DSQ-C.
  - Quality of life measure using the Single Item Linear Analogue Scale (LASA)
  - Quality of life measure using the Dexamethasone Symptoms Questionnaire - Chronic (DSQ-C) and the MDASI-BT score
  - Progression free survival
  - Corticosteroid dose over time
  - Maximum radiographic response
  - Time to stopping corticosteroids
Only **20% of patients with newly diagnosed brain metastases** present with seizures and tumor control probably is again the most important predictor of seizure control, as in patients with primary tumors.

**Alternative etiologies** than brain metastases include neurotoxicity from cancer therapy, paraneoplastic syndromes, metabolic disturbances such as hypoglycemia or electrolyte alterations, and cerebrovascular disease.

**Electroencephalography (EEG)** may help in the initial assessment of patients with suspected seizures and can be used to estimate future seizure risk or for the differential diagnosis of altered neurocognitive function or vigilance. An EEG is of particular importance if a non-convulsive status epilepticus needs to be ruled out in case of worsening of neurological symptoms or vigilance problems that are otherwise not well explained. Finally, EEG will help to distinguish epileptic seizures from psychogenic seizures.
**SEIZURES**

New onset seizures in cancer patients without a history of brain tumor should trigger neurological work-up including cerebral MRI.

Since worsening of a preexisting seizure disorder in brain tumor patients often heralds tumor progression, repeat MRI and other potentially necessary workup such as blood and cerebrospinal fluid examination should be considered.

**Primary anticonvulsant prophylaxis is not indicated in brain tumor patients**

Agents available as intravenous preparations such as levetiracetam, valproic acid, phenytoin or benzodiazepines should be considered for the acute perioperative phase if perioperative prophylaxis is thought to be necessary.

*Levetiracetam and lamotrigine* are preferred options of first choice because of their efficacy and overall good tolerability.

Brain tumor patients who have suffered epileptic seizures and are not candidates for surgery, e.g., patients with multiple brain metastases from a known cancer, should receive secondary prophylaxis until local control has been achieved.

**Enzyme-inducing anticonvulsants should be avoided** in patients with brain tumors, notably in patients who are candidates for systemic anti-cancer pharmacotherapy.

Judgements on the competency to drive need to adhere to national guidelines and law and should consider not only epilepsy, but also other aspects of neurological and neurocognitive function.
A higher risk of venous thromboembolic events (VTE) is observed in patients with brain tumors compared to other cancer sites (standard morbidity rate 46.31) (Petterson et al., 2015).

Symptoms and signs can be subtle.

VTE has been less investigated in patients with brain metastases, however, a retrospective study reported an incidence of 20% (Donato et al., 2015; Liebman et al., 2016)
## VTE

Routine primary thromboprophylaxis in the ambulatory setting is not recommended for all brain tumor patients

**Primary thromboprophylaxis should be considered for brain cancer patients with acute medical illness or immobilization**

*Low molecular weight heparin (LMWH)* should be considered as the first line of primary thromboprophylaxis of VTE for patients with brain tumors after brain tumor surgery

Primary thromboprophylaxis should be initiated within 24 hours after brain tumor surgery for brain tumor patients

Duration of thromboprophylaxis should be limited to the post-operative period (7-28 days) after brain cancer surgery

**Therapeutic doses of low molecular weight heparin (LMWH) should be used for treatment of VTE in brain tumor patients**

DOAC should not be routinely considered as an alternative for brain tumor patients with VTE

The duration of therapeutic anticoagulation for treatment of VTE should be 6 months for brain tumor patients who are in complete remission and should be prolonged in patients with active cancer or those receiving ongoing anti-cancer treatment

**Antiplatelet drugs** should be considered for *secondary prophylaxis* of stroke in patients with brain tumors unless there is an underlying cause such as atrial fibrillation that requires therapeutic anticoagulation according to standard stroke guidelines.

Diagnosis of suspected ICH should be done with MRI (including contrast-enhanced and blood-sensitive sequences); if an underlying brain tumor is not known but possible, repeat MRI is recommended after 2-3 months

Basic rules of conservative ICH management should also apply to brain tumor patients, with surgical interventions indicated when removal of the bleeding source is considered useful for symptom control.
Other symptomatic approaches

- Neurocognitive impairment
- Rehabilitation
- Supportive and End-of-Life Care: delirium, behavioural disorders, depressive symptoms, nutrition, hydration, respiration, fatigue, pain
Conclusions

- Surgery allows a tissue-based diagnosis, avoids misdiagnosis and facilitates targeted therapy.

- Surgery may allow for more rapid neurological improvement than any other anti-cancer treatment and remains the only effective treatment for large brain (oligo)metastasis.

- SRS has become the dominant modality of radiotherapy where the use of whole brain radiotherapy is increasingly questioned.

- The optimal integration of surgery and SRS into multimodality treatment concepts requires randomized clinical trials.

- Repeat surgery or biopsy competes with CSF liquid biopsy as an emerging management strategy to reflect branched tumor evolution.
Neurological and vascular complications of primary and secondary brain tumors: EANO-ESMO Clinical Practice Guidelines for prophylaxis, diagnosis, treatment and follow-up

Patrick Roth¹, Andrea Pace², Emilie Le Rhun³, Michael Weller¹, Cihan Ay⁴, Elizabeth Cohen-Jonathan Moyal⁵, Marijke Coomans⁶, Raffaele Giusti⁷, Karin Jordan⁸, Ryo Nishikawa⁹, Frank Winkler¹⁰, Roberta Ruda¹¹, Salvador Villà¹², Martin J.B. Taphoorn⁶,¹³, Wolfgang Wick¹⁰, Matthias Preusser¹⁴, on behalf of the EANO Executive Board and ESMO Guidelines Committee*