Neuroimaging assessment of brain metastases in the targeted therapy era

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Overview

• RANO for HGG
• Proposed RANO for BM
• Remaining problems
  – Radiation Necrosis
  – New imaging techniques
• MR-Imaging: What is on the horizon?
RANO for HGG

- Introduced in 2010
- Work in progress
# Macdonald Criteria

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response (CR)</strong></td>
<td>Requires all of the following:</td>
</tr>
<tr>
<td></td>
<td>• Complete disappearance of all enhancing measurable and nonmeasurable disease</td>
</tr>
<tr>
<td></td>
<td>• No new lesions</td>
</tr>
<tr>
<td></td>
<td>• No corticosteroids</td>
</tr>
<tr>
<td></td>
<td>• Stable or improved clinically</td>
</tr>
<tr>
<td><strong>Partial response (PR)</strong></td>
<td>Requires all of the following:</td>
</tr>
<tr>
<td></td>
<td>• ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions</td>
</tr>
<tr>
<td></td>
<td>• No new lesions</td>
</tr>
<tr>
<td></td>
<td>• Stable or reduced corticosteroid dose</td>
</tr>
<tr>
<td></td>
<td>• Stable or improved clinically</td>
</tr>
<tr>
<td><strong>Stable disease (SD)</strong></td>
<td>Requires all of the following:</td>
</tr>
<tr>
<td></td>
<td>• Does not qualify for CR, PR or PD</td>
</tr>
<tr>
<td></td>
<td>• Stable clinically</td>
</tr>
<tr>
<td><strong>Progressive disease (PD)</strong></td>
<td>Defined by any of the following:</td>
</tr>
<tr>
<td></td>
<td>• ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions</td>
</tr>
<tr>
<td></td>
<td>• Any new lesion</td>
</tr>
<tr>
<td></td>
<td>• Clinical deterioration</td>
</tr>
</tbody>
</table>
Major Changes in RANO HGG Criteria

- Definition of Measurable lesions
- Inclusion of T2 progress
- Inclusion of Pseudoprogression/Pseudoregression
Measurable lesions:

- bidimensionally contrast enhancing lesions with clearly defined margins by CT or MRI scan,
- two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are 5 mm apart with 0-mm skip.
- As with RECIST version 1.1, if MRI is performed with thicker slices, size of a measurable lesion at baseline should be two times the slice thickness.
Non-measurable lesions

- Unidirectional lesions
- Lesions without sharp delineation
- Lesions with a size less than 2x of the slice thickness
No measurable lesion

Pseudoprogression (PsP)

- Up to 50% of patients undergoing their first postradiation MRI show increased contrast enhancement that eventually subsides without any change in therapy.

Wen P, Kesari S, Malignant glioma in adults, NEJM 2008
Pseudoprogression in patients with glioblastoma: clinical relevance despite low incidence, Radbruch, Neuro-oncology 2014
Pseudoprogression in RANO HGG

• Within the first 12 weeks of completion of radiotherapy, when pseudoprogression is supposed to be most prevalent, progression can only be determined
  – if the majority of the new enhancement is outside of the radiation field
  – if there is pathologic confirmation of progressive disease

• Otherwise: confirmatory scan in 4 weeks
Inclusion of T2 Progress/ Pseudoregression

• PD is considered:
  – Increase of enhancement on T1-weighted images of at least 25 %
  – **Significant T2-signal increase**, even if there is stable or decreasing enhancement on T1-weighted images
## Summary: RANO Criteria for HGG

<table>
<thead>
<tr>
<th>Criterion</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 gadolinium enhancing disease</td>
<td>none</td>
<td>≥ 50% ↓</td>
<td>&lt;50% ↓ but &lt; 25% ↑</td>
<td>≥ 25% ↑*, **</td>
</tr>
<tr>
<td>T2/FLAIR</td>
<td>stable or ↓</td>
<td>stable or ↓</td>
<td>stable or ↓</td>
<td>↑*</td>
</tr>
<tr>
<td>New lesions</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>present*</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>none</td>
<td>stable or ↓</td>
<td>stable or ↓</td>
<td>NA †</td>
</tr>
<tr>
<td>Clinical status</td>
<td>stable or ↑</td>
<td>stable or ↑</td>
<td>stable or ↑</td>
<td>↓*</td>
</tr>
<tr>
<td>Requirement for response</td>
<td>all</td>
<td>all</td>
<td>all</td>
<td>any*</td>
</tr>
</tbody>
</table>

* Progression occurs when this criterion is present.
† Increase in corticosteroids alone will not be taken into account in determining progression in absence of persistent clinical deterioration.

**No PD in case of enhancement increase ≥ 25% in the radiation field within 12 weeks after completion of RCT.
Starting Point Proposed RANO BM

• welcome trend away from automatic exclusion of patients with BM from clinical trials

• irregular response criteria for assessment of CNS metastases has made interpretation of trial results challenging
Proposed RANO BM Criteria

• RANO Metastatic Working Group convened 2011: medical oncologists, neuro-oncologists, radiation oncologists, neurosurgeons, neuroradiologists, neuropsychologists, biostatistics

• RANO BM Criteria cover only evaluation of parenchymal brain metastases NOT leptomeningeal metastases, dural metastases or bone metastases invading the brain
Proposed RANO BM Criteria

- RECIST 1.1 and the RANO response assessment criteria for high-grade gliomas (HGG)
- Gaps were identified; areas of controversy were resolved: evidence-based approach or expert opinion and consensus
- RANO BM: Work in Progress
Measurable disease according to RANO BM

- contrast enhancing lesion with a minimum size of 10 mm in one dimension, visible on two or more axial slices that are at most 5 mm apart with 0-mm skip
- if MRI is performed with thicker slices, size of a measurable lesion at baseline should be two times the slice thickness
- Cavities or cysts are considered non-measurable unless there is a nodular component measuring ≥ 10 mm in longest diameter and ≥ 5 mm in the perpendicular plane
Non-Measurable disease according to RANO BM

- All other lesions, including lesions with longest dimension < 10 mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, and leptomeningeal disease.
Tumor Response Evaluation according to RANO BM

• Only patients with measurable CNS disease at baseline should be included in protocols where objective CNS tumor response is the primary endpoint.

• Baseline documentation: When more than one measurable lesion is present at baseline, all lesions up to a maximum of five will be identified as target lesions.

• A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters (sum LD).
Evaluation of Target Lesions

- Complete response (CR): Disappearance of all CNS target lesions sustained for at least 4 weeks; no new lesions; no corticosteroids; stable or improved clinically
Evaluation of Target Lesions

- **Partial response (PR):** At least a 30% decrease in the sum LD of CNS target lesions, taking as reference the baseline sum LD sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
Progressive disease (PD): At least a 20% increase in the sum LD of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).
Evaluation of Target Lesions

• **Stable disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the small sum LD while on study.
## Summary of RANO BM

<table>
<thead>
<tr>
<th>Criterion</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target lesions</strong></td>
<td>None</td>
<td>≥ 30% decrease in sum LD relative to baseline</td>
<td>&lt; 30% decrease relative to baseline but &lt; 20% increase in sum LD relative to nadir</td>
<td>≥ 20% increase in sum LD relative to nadir</td>
</tr>
<tr>
<td><strong>Non-target lesions</strong></td>
<td>None</td>
<td>Stable or improved</td>
<td>Stable or improved</td>
<td>Unequivocal PD</td>
</tr>
<tr>
<td><strong>New lesion(s)</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>None</td>
<td>Stable or decreased</td>
<td>Stable or decreased</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Clinical status</strong></td>
<td>Stable or improved</td>
<td>Stable or improved</td>
<td>Stable or improved</td>
<td>Worse</td>
</tr>
<tr>
<td><strong>Requirement for response</strong></td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>Any</td>
</tr>
</tbody>
</table>
Corticosteroid Use and Clinical Deterioration

• An increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor does not qualify for PD.
Preclinical and clinical data demonstrate a differential response in intracranial versus extracranial metastases.

Many systemic agents are not expected to have CNS activity, e.g. due to drug penetration.

Vice versa, local CNS therapies (e.g. radiosurgery) do not affect extracranial sites.
Approach of RANO GBM

- CNS is a separated compartment, scored irrespective of extracranial response
# CNS and non-CNS Response Assessment

<table>
<thead>
<tr>
<th>CNS (by RANO-BM)</th>
<th>Non-CNS (by RECIST 1.1)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, PR, or SD</td>
<td>CR, PR, or SD</td>
<td>Log as CNS CR, PR, or SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Log as non-CNS CR, PR, or SD</td>
</tr>
<tr>
<td>CR, PR, or SD</td>
<td>PD</td>
<td>Log as CNS CR, PR, or SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Log as non-CNS PD</td>
</tr>
<tr>
<td>PD</td>
<td>CR, PR, or SD</td>
<td>Log as CNS PD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Log as non-CNS CR, PR, or SD</td>
</tr>
<tr>
<td>PD</td>
<td>PD</td>
<td>Log as both CNS and non-CNS PD</td>
</tr>
</tbody>
</table>
Recommendations for Minimum Requirements for Brain Imaging

MR Scanners: 1.5T and 3T MR scanners only

Localizer/Scout

3D T1w pre-contrast (MPRAGE, 3D IR FSPGR T1w)
- minimum TE
- T1, TR and flip angle according to manufacturer specific / field strength specific recommendations for optimum image quality
- Slice/3D slab orientation: sagittal or transverse
- FOV: 256 mm x 256 mm
- Matrix: 256x256
- Slice thickness: ≤ 1.5 mm
- Full brain coverage

DWI
- single shot EPI sequence
- b: 0 and 1000 s/mm² (3 directions)
- Slice orientation: transverse
- Slice thickness: 5mm
- Slice gap: 0
- Number of slices: Full brain coverage
- FOV: 240 mm x 240 mm
- Matrix: 128 x 128 or higher
- Postprocessing: Calculation of ADC maps

2D FLAIR, transverse
- Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence
- Slice orientation: transverse
- Slice thickness: 5mm
- Slice gap: 0
- Number of slices: same as sequence 2
- FOV: 240 mm x 240 mm
- Matrix: 256 x 256 or higher
- Slice positioning as in sequence 2

3D FLAIR (OPTIONAL)
- Contrast agent injection
  - 0.1 mmol/kg BW of a Gd-based contrast agent

T2w-TSE
- Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence
- Slice thickness: 5mm
- Slice gap: 0
- Number of slices: same as sequence 2
- FOV: 240 mm x 240 mm
- Matrix: 256 x 256 or higher
- Slice positioning as in sequence 2

3D T1w post-contrast (MPRAGE, 3D IR FSPGR T1w)
- Sequence parameters and slice positioning as in sequence 1
Guidance in the case of uncertain attribution of radiographic findings and/or equivocal cases

Methods used to distinguish between radiation necrosis and true progression should be specified prospectively in the clinical protocol

1. Repeat the scan at the next protocol scheduled evaluation
2. Histopathological evaluation
3. Advanced MR/PET Imaging techniques
Pseudoprogression of a Melanoma BM
True Progression of a Melanoma BM
<table>
<thead>
<tr>
<th>RANO HGG</th>
<th>RANO BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bidimensionally measured</td>
<td>• Unidimensionally measured</td>
</tr>
<tr>
<td>• Exclusively CNS assessment</td>
<td>• CNS and Non-CNS assessment independent</td>
</tr>
<tr>
<td>• T2-progress qualifies for PD</td>
<td>• T2-signal not considered</td>
</tr>
<tr>
<td>• Enhancement within 12 weeks after RCT in radiation field does not qualify for PD</td>
<td>• No clear recommendation for treatment related effects such as radiation necrosis</td>
</tr>
</tbody>
</table>

New Imaging Methods are needed!!
Advanced MR Imaging

- ce-T1
- SWI
- DCE-Perfusion
- DSC-Perfusion
- Diffusion
- Advanced Postprocessing
- FMRI
- Ultra High Field: 7 Tesla
- CEST (pH Imaging?)
- X-Nuclei Imaging (O17)
Diffusion MR Imaging for DD True Progression and Pseudoproggression (PsP)

- ADC – possible parameter – Hypothesis:
  - low ADC values – high cellularity – True Progression
  - high ADC values – low cellularity – PsP

- Postprocessing of ADC maps:
  - Region of Interest Analysis does not reflect the heterogeneity of GBM
  - Parametric Response Maps*: Voxelwise analysis of changes in ADC values

Workflow: 1. step

1. Segmentation of contrast enhancement on ce-T1

2. Coregistration and transfer of ROI to ADC baseline and ADC f/u

3. Calculation of rADC values by division of ROI with contralateral reference-ROI

new enhancement at 3 months

baseline ADC

3 months ADC
Workflow: 2. step

Voxelwise Subtraction of rADC values at baseline and follow up, presentation with scatter plot.

Visualization on follow up ce-T1

Quantification of voxels
1) $rADC\ (\text{baseline}) - rADC\ (\text{follow up}) > 0.25$ (Decrease of rADC)
2) $rADC\ (\text{baseline}) - rADC\ (\text{follow up}) < -0.25$ (Increase of rADC)
Patients and Methods

Patients

- 36 Patients with histologically proven GBM
- Postoperative baseline MRI with 72 hours including DWI
- Standard therapy with temozolomide and RCT
- New Enhancement in 1st follow up after completion of RCT
- 7 Pseudopropgression, 29 true progression

MRI

- 3 Tesla Siemens Trio or Verio
- ce-T1 (0.1 mmol / kg body weight DOTAREM); DWI: TE = 90 ms, TR = 5300 ms, flip angle = 90°, slice thickness = 5 mm, $b$-values of 0 and 1200 s/mm$^2$
Results

Example: Pseudo-progression

Example: True Progression
Results

Percentage of voxels with rADC decrease

PsP

p<0.01

True Progression

PsP

Percentage of voxels with rADC increase

ROC analysis (threshold of 30 % rADC decrease)

AUC=0.84

ROC analysis (threshold of 30 % rADC increase)

AUC=0.79

ROC analysis

(threshold of 30 % rADC decrease)

AUC=0.84
What is on the horizon?
Ultra-High-Field: 7 Tesla
Quantification of Tumor Vessels at 7 Tesla
Quantification of Tumor Vessels at 7 Tesla

A. Tumor Total Vessel Length vs. Control

B. Tumor Total Vessel Surface Area vs. Control

C. Tumor Total Vessel Volume vs. Control

D. Tumor Mean Vessel Diameter vs. Control

E. Tumor # Vessel Branches vs. Control

F. Tumor Mean Vessel Branch Length vs. Control
Chemical Exchange Saturation Transfer (CEST)

- Amide proton transfer imaging
- Exchangeable solute protons that resonate at a frequency different from the bulk water protons are selectively saturated using RF irradiation
- Transfer of saturation to bulk water – water signal becomes attenuated

a) off-resonant: full water signal
b) on-resonant water: no water signal
c) CEST-resonant: decreased w. signal

Asymmetry analysis

$$\text{CEST}_{\text{asym}} = S(a) - S(c) \approx \text{PTR}$$

pH-Imaging??
Identification of PsP with CEST

Advanced CEST

Tumor Enhancement

Contralateral White Matter
"Dangers" of Advanced MR Imaging

Do not lose sight of the clinical relevance in MR Imaging
## Incidence of Pseudoprogression

<table>
<thead>
<tr>
<th>Scan</th>
<th>True Progression</th>
<th>Pseudoprogression</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stable</td>
<td>Decrease &lt; 50 % of enhancement</td>
<td>Decrease &gt; 50 % of enhancement</td>
</tr>
<tr>
<td>1st Post-Radiation Scan</td>
<td>39=86.67%</td>
<td>3=6.67%</td>
<td>1=2.22%</td>
</tr>
<tr>
<td>Average scan date after initial diagnosis 34.0±18.0 d, median 28 d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Post-Radiation Scan</td>
<td>15=88.24%</td>
<td></td>
<td>1=5.88%</td>
</tr>
<tr>
<td>Average scan date after initial diagnosis 113.3±15.2 d, median 111.5 d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd Post-Radiation Scan</td>
<td>8=88.89%</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Average scan date after initial diagnosis 187.8±23.5 d, median 193 d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th Post-Radiation Scan</td>
<td>8=100%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Average scan date after initial diagnosis 305.0±53.6 d, median 302.5 d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>70=88.61%</td>
<td>2=2.53%</td>
<td>4=5.06%</td>
</tr>
</tbody>
</table>

Incidence of PsP was heavily overestimated!!!
Pseudoprogression in patients with glioblastoma: clinical relevance despite low incidence, Radbruch, Neuro-oncology 2014
Conclusion

• RANO BM first step to a harmonization for therapy assessment within clinical trials
• Still a long way to go to include advanced imaging methods
• Urgently needed: large multi-center clinical trials with harmonized imaging parameters and postprocessing techniques
Thank you for your attention!