Response Assessment in Neuro-Oncology

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Imaging and neuro-oncology

- Today: just some elements
  - Realising pitfalls
  - RANO essentials
  - How to assess a tumor within a clinical trial using RANO criteria
Fluctuating deficits in an anaplastic oligodendrogioma patient

- 50 year old female, treated 13 yrs ago for AOD with RT/PCV
- November 2010: stable MRI scan
- February 2011: admission because of fluctuating paresis right arm, aphasia for days
- MRI: new enhancement, rCBV (perfusion image) increase (ratio 2.24)
Fluctuating deficits 13 years after RT/PCV for Anaplastic Oligodendroglioma

- What treatment would you propose?
  a. Temozolomide
  b. Re-irradiation
  c. Bevacizumab
  d. New anticonvulsant
Fluctuating deficits in an anaplastic oligodendroglioma patient

- Our choice: d
- Clue: fluctuating deficits
- EEG: continuous epileptic discharges
- MRI three months later: normalization
- Diagnosis: peri-ictal enhancement
Peri-ictal enhancement and the SMART syndrome (stroke-like migraine attacks after radiation therapy)

- Multiple case reports on irradiated brain tumor patients
- Presenting with or without seizures, headache and focal deficits
- Or non-convulsive status epilepticus
  - Treat the seizures pro-actively!
- Increasing enhancement, & increased rCBV

Take home message: increase in enhancement does not equal progression!

Rath et al, J Neurol 2012, Kerklaan et al, J Neurol 2011;258:1098-104; Rheims et al, Neuro Oncol 2011;13:775-82
Endpoints

- Endpoint
  - Overall Survival
- Imaging Related Endpoints
  - PFS according to RANO criteria and assessed by central review and local investigators
  - Objective response rate (ORR)
- Quality of Life/Survival endpoints
  - HRQoL
  - Cognition
  - etc
Temozolomide in recurrent anaplastic astrocytoma
male, 44 yrs of age, first surgery and RT in 1996, recurrence in 8/01 & start temozolomide, TTP 8 mo
T1 contrast enhanced MR in brain tumors: limitations

- Basically: uses area of enhancement as the primary target
  - Enhancement implies leaky vessels = endothelial proliferation?

  blood brain barrier disruption

  - *Enhancement does not equal tumor but reflects high grade tumor activity*

- Enhancement is *aspecific*
  - Other causes: infarction, inflammation, necrosis

- Brain tumors are frequently difficult to measure
RANO criteria: no magic

Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group


- Current standard for assessing treatment response for high-grade gliomas
Surgery for low grade 1p/19q co-deleted OD

- Sept 2014 1st seizure
- November 2014 resection, wait and see
- March 2015: new enhancement: PD?
49 year old male, treated for glioblastoma
• Recurrence in July 2012
• Gross total re-resection August 2, 2012
• Start chemotherapy 4 weeks after surgery,
• New baseline MRI scan 4 weeks later: increase

Without a new baseline scan: SD would have been diagnosed as PD
Pseudoprogression

- Treatment effects may mimic progression within 12 weeks of RT
- True progression can be called within the 12 weeks if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line)
- If there is no new enhancement outside of the radiation field, progression must be confirmed by imaging >12 weeks from radiation therapy
- If disease burden is no longer increasing, true progression is not confirmed and the timepoint with the largest SPPD within the 12 weeks from radiation therapy should be considered the ‘new baseline’ for % change purposes
Non-1p/19q co-deleted oligodendroglioma

- Female, 30 years
- Asymptomatic right frontal lesion
- Complete resection, oligodendroglioma
- No 1p/19q loss
- RT 59.4 Gy
- 4 mo post RT: new enhancement
- 2 years later: disappearance of all enhancement
Incidence of pseudoprogression in low-grade gliomas treated with radiotherapy

- 63 cases of low grade glioma treated with RT, median f-up 5 yrs (range 1-10 yrs): PsPD observed in 13 patients (20.6%),
- Occurred after median of 12 months (range 3-78 months); median duration 6 months (range 2-26 months)
- Always occurred within the RT high dose fields (> 45 Gy).
- Area of the enhancement of psPD smaller compared to "true" PD
  - median size 54mm² [range 12-340mm²] vs 270mm² [range 30-3420mm²], p = .009

van West et al, NeuroOncol 2017;19:719-25
Imaging protocol: standardization

- EORTC/International standardized MR protocol
  - Basic
  - Advanced Imaging
- 2014: international wish to develop a standardized imaging protocol
  - NBTS
    - Jumpstarting Brain Tumor Drug Development Coalition
- All current MR imaging within consortia, big pharma needs to be performed according to the imaging recommendations by the NBTS
- You can do this at home…

Ellingson et al. Neuro Oncol. 2015 Sep;17(9):1188-98. doi: 10.1093/neuonc/nov095
## The EORTC Imaging Protocol

<table>
<thead>
<tr>
<th>3D T1w pre-contrast MPRAGE, 3D IR FSPGR T1w</th>
<th>DWI</th>
<th>2D FLAIR Transverse</th>
<th>3D FLAIR (optional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• minimum TE</td>
<td>• minimum TE</td>
<td>TE: 90-140ms</td>
<td>• TE: 90-140ms</td>
</tr>
<tr>
<td>• TI, TR and flip angle according to manufacturer specific / field strength specific recommendations for optimum image quality</td>
<td>• TR &gt; 3000 ms</td>
<td>TR: 6000-10000 ms</td>
<td>• TR: 6000-10000 ms</td>
</tr>
<tr>
<td>• Spectral fat suppression</td>
<td>• Spectral fat suppression</td>
<td>TI: 2000-2500 ms (use TI according to optimized protocol for specific inversion pulses and field strength)</td>
<td>• TI: 2000-2500 ms (use TI according to optimized protocol for specific inversion pulses and field strength)</td>
</tr>
<tr>
<td>• b: 0 and 1000 s/mm² (3 directions)</td>
<td>• SENSE / SMASH / GRAPPA / ASSET: optional for 1.5 T, obligatory for 3 T.</td>
<td>SENSE / SMASH / GRAPPA / ASSET allowed</td>
<td>• SENSE / SMASH / GRAPPA / ASSET: optional for 1.5 T, obligatory for 3 T.</td>
</tr>
<tr>
<td>• SENSE / SMASH / GRAPPA / ASSET allowed</td>
<td>• Slice orientation: transverse</td>
<td>Slice orientation: transverse</td>
<td>Slice orientation: sagittal or transverse</td>
</tr>
<tr>
<td>• Slice orientation: sagittal or transverse</td>
<td>• Slice thickness: 5mm</td>
<td>Slice thickness: 5mm</td>
<td>Slice thickness: 1.5 mm</td>
</tr>
<tr>
<td>• Slice thickness: ≤ 1.5 mm</td>
<td>• Slice gap: 0</td>
<td>Slice gap: 0</td>
<td>Slice thickness: 1.5 mm</td>
</tr>
<tr>
<td>• Full brain coverage</td>
<td>• Number of slices: Full brain coverage</td>
<td>Number of slices: Full brain coverage</td>
<td>Number of slices: Full brain coverage</td>
</tr>
<tr>
<td></td>
<td>• FOV: 240 mm x 240 mm</td>
<td>FOV: 240 mm x 240 mm</td>
<td>FOV: 250 mm x 250 mm</td>
</tr>
<tr>
<td></td>
<td>• Matrix: 128 x 128 or higher</td>
<td>Matrix: 256 x 256 or higher</td>
<td>Matrix: 224 x 224 or higher</td>
</tr>
<tr>
<td></td>
<td>Postprocessing: Calculation of ADC maps (diffusion trace maps)</td>
<td>Slice positioning as in sequence 2</td>
<td>Slice positioning as in sequence 1</td>
</tr>
</tbody>
</table>

**0.1 mmol/kg BW of a Gd-based contrast agent**
The essentials

- **Complete Response (CR)**
  - 100% decrease in SPPD* from Baseline

- **Partial Response (PR)**
  - ≥ 50% decrease in SPPD from Baseline

- **Stable Disease (SD)**
  - < 50% decrease in SPPD from Baseline and <25% increase from nadir

- **Progressive disease**
  - > 25% increase from nadir

*SPPD: Sum of Perpendicular Diameters
The essentials cont-ed

- Steroids
  - No response possible in case of increase
  - In case of taper: tumor area may increase
  - Steroids increase alone does not equal progression

- Clinical status
  - In case of deterioration: equals progression

- New Lesion
  - Equals progression

- T2/FLAIR to be assessed
T2 and FLAIR in RANO

• Introduction of T2/FLAIR in RANO criteria was driven by anti-VEGF treatment associated pseudo-responses

• T2/FLAIR abnormalities considered not measurable

• **Significant** increase is considered PD

• Limited relevance in evaluation of other non-anti-VEGF treatments

**BELOB case 144:** Well defined local recurrence: after one cycle decrease in enhancement, but increase in T2 abnormalities and mass effect
Measuring

- Measure the sum of products of perpendicular diameters of all measurable enhancing lesions
- Measure at least two if more than 1 lesion is present
  - Up to a maximum of 5 lesions
  - Additional lesions are non-target
- Measure on the plane & slice where the lesion is largest
  - adjust the perpendicular measurement to the longest short axis
Measurable disease

Too small lesions cannot be measured reliably

Measurable (RANO):
• Enhancing disease

• Minimal bidirectional diameter of ≥ 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip

• Rationale: too small lesions cannot be measured reliably

• For progression: ideally, the change should be significant (5mm increase in maximal diameter or 25% increase in sum of the products of perpendicular diameters of enhancing lesions)
Special Considerations for classification of lesions: Lesions with cysts or surgical cavities

- Lesions around a cyst or surgical cavity are to be considered non-measurable unless there is an enhancing component meeting the measurable disease criteria
  - The cystic or surgical cavity should not be measured in determining response
- Lesions with a necrotic component
  - Lesions with a necrotic component can be selected as target if they are the only lesion(s) present, otherwise they should be selected as non-target.

The necrotic/cystic part is unlikely to shrink even in responding tumors.
Defining Lesions at Baseline

Lesions

Measurable

Non-measurable

Target

Non-target

Measurable lesions not selected as target
MR measurements for study evaluation

- Preferably: done by the same person
- Document the used MRI series and slice(s)
- Review previous measurements at the time of new measurements (for consistency)
- A different plane may be used compared to the baseline scan
- Do also document measurements in the patient file (source document)
% Change of Sum of PerPendicular Diameter (SPPD)

- The % change in SPPD is determines response or progression of the target lesions.

From Baseline (for response):

\[
\text{Current SPPD-Baseline SPPD)} \times 100 = \% \text{ change from Baseline} \\
\text{Baseline SPPD}
\]

From Nadir (for progression):

\[
\text{Current SPPD-Nadir SPPD)} \times 100 = \% \text{ change from Nadir} \\
\text{Nadir SPPD}
\]
Sum of the Product of the Perpendicular Diameters (SPPD)

- SPPD is calculated at every evaluation for all target lesions.
- The change in SPPD determines response or progression of the target lesions.
- In case of multiple lesions: select at least two.
- Emphasis to be placed on lesions that are likely to allow reproducible repeated measurements.

\[
\begin{align*}
15 \times 10 &= 150 \\
20 \times 10 &= 300 \\
\end{align*}
\]

\[= 450 \text{mm}^2\]
Overall Assessment

- Complete Response – all the following must be true
  - Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks
  - No new lesions
  - Stable or improved non-enhancing non-measurable (T2/FLAIR) lesions
  - Patients must be off corticosteroids (or on physiologic replacement doses only)
  - Stable or improved clinically.

Note: Patients with non-measurable disease only cannot have a CR; the best response possible is SD.
Overall Assessment

- Partial Response – all the following must be true
  - ≥50% decrease compared with baseline in SPPD of all measurable enhancing lesions sustained for at least 4 weeks
  - Enhancing non-measurable disappeared or is stable
  - No new lesions
  - Stable or improved non-enhancing non-measurable (T2/FLAIR) lesions
  - Corticosteroids dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan
  - Stable or improved clinically

Note: Patients with non-measurable disease only cannot have a PR; the best response possible is SD.
Overall Assessment

- Stable Disease – all the following must be true
  - Does not qualify for CR, PR, or PD
  - Stable non-enhancing non-measurable (T2/FLAIR) lesions
  - Corticosteroids dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan

Note: If the corticosteroid dose was increased for new symptoms and signs (no radiographic confirmation of PD) and follow-up imaging shows PD, the last scan considered SD will be the scan that coincides with corticosteroid dose equivalent to the baseline
Dexamethasone: key factor in response evaluation

- 32 year old male glioblastoma patient
- March 20 2014 progressive disease: 52 x 34 mm
- April 3 admission: headache, right sided weakness; start dexamethasone 16 mg daily, with taper to 12 mg daily
- April 11 new baseline MRI scan at start new treatment: decrease in size, 50 x 27 mm (76%)

Works in both directions:
- Decrease SPPD after start or increase steroids
- Increase SPPD at decrease or discontinuation of steroids

Always: register steroid dosage at time MR evaluation
Overall Assessment

- Progressive Disease – if any of the following are true
  - $\geq 25\%$ increase in SPPD of enhancing lesions compared with the nadir, on stable or increasing doses of corticosteroids
  - Clear progression of non-measurable disease
  - Significant increase in non-enhancing non-measurable (T2/FLAIR) lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy
    - Increase should not be caused by comorbid events
  - Any new lesion
  - Clear clinical deterioration not attributable to other causes apart from the tumor or changes in corticosteroid dose

*Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.
PD is diagnosed when tumor increases 25% from nadir, not necessarily baseline

Nadir = the lowest SPPD value from any timepoint
# Summary of the RANO Response Criteria

<table>
<thead>
<tr>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1 gadolinium enhancing disease</strong></td>
<td>none</td>
<td>≥50% ↓</td>
<td>&lt;50% ↓ but &lt;25% ↑</td>
</tr>
<tr>
<td><strong>T2/FLAIR</strong></td>
<td>stable or ↓</td>
<td>stable or ↓</td>
<td>stable or ↓</td>
</tr>
<tr>
<td>New lesions</td>
<td>none</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>none</td>
<td>stable or ↓</td>
<td>stable or ↓</td>
</tr>
<tr>
<td>Clinical status</td>
<td>stable or ↑</td>
<td>stable or ↑</td>
<td>stable or ↑</td>
</tr>
<tr>
<td>Requirement for response</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
</tbody>
</table>

<sup>a</sup>Progression occurs when this criterion is present.

<sup>b</sup>Increase in corticosteroids alone will not be taken into account in determining progression in absence of persistent clinical deterioration.

*Wen et al, J Clin Oncol 2010;28:1963-72*
## Overall Assessment Post-Baseline

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td>PD</td>
<td>PD</td>
</tr>
<tr>
<td>MRI assessment</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>Steroid dose</td>
<td>PD</td>
<td>PD</td>
<td>PD</td>
<td>PD</td>
<td>PD</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Only in conjunction with clear neurological signs and symptoms deterioration*
## Overall Assessment Post-Baseline

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment</td>
<td>--</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td>PD</td>
</tr>
<tr>
<td>MRI assessment</td>
<td>--</td>
<td>SD</td>
<td>SD</td>
<td>PD</td>
<td>PD</td>
</tr>
</tbody>
</table>

Steroid dose: 
- Baseline: --
- Cycle 1: SD

Imaging: 
- Baseline: --
- Cycle 1: SD
- Cycle 2: SD
- Cycle 3: PD
- Cycle 4: PD

PD: Progressive Disease
SD: Stable Disease
BL: Baseline
TP: Timepoint
Some details

- Failure to return for evaluation as a result of death or deteriorating condition is to be considered progression.
  - For progression: ideally, the change should be significant (5mm increase in maximal diameter or 25% increase in sum of the products of perpendicular diameters of enhancing lesions)
- If in doubt about PD (‘equivocal PD’), RANO allows continuation of treatment
  - If the next scan confirms PD then the date of PD is backdated to the date of the scan with equivocal PD
Re-operated patients in studies with OS, PFS endpoints

- Patient may have been operated for recurrence.
- If operated protocol may stipulate that:
  - Residual and measurable disease after surgery is not required but surgery must have confirmed the recurrence
- If so: required:
  - a post-surgery MRI must be available within 48 hours following surgery: defines target (if present)
  - an MRI scan has to be done within 2 weeks prior to randomization
  - surgery completed at least 2 weeks before randomization and patients should have fully recovered as assessed by investigators.
RANO is about communication

- Objective of outcome scoring is to understand and communicate the imaging findings....

Brueghel, the elder. Babel’s Tower