Radiotherapy in brain tumors: new opportunities and new problems

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Topics of discussion

- General
- Special radiotherapy technique
  - IMRT
  - SRT
- Target and response definition of:
  - Glioma
  - Meningioma
- Conclusion
Brain Neoplasms: General Considerations

- 10% of all tumors
- Most common childhood neoplasms
- Peak incidence at 5th decade
- Different tumors in different ages
- Primary tumors infiltrative, metastatic well-demarcated

Frequent primary brain tumors:
- Astrocytoma/glioblastoma
- Meningioma
- Oligodendroglioma
- Ependymoma
- Medulloblastoma
Radiotherapy for Brain Tumors

- **After Surgery**
  - As adjuvant when a complete resection was obtained. Or on residual tumor with the goal of reducing its size or stopping its progression.

- **When Surgery Is not Appropriate**
  - Radiotherapy may be used instead of surgery for inaccessible tumors or for tumors that have properties that are particularly responsive to radiotherapy.

- **Radio-chemotherapy**
  - Combining chemotherapy with radiotherapy is beneficial in some patients with high-grade tumors.
Development of imaging and radiotherapy technologies


Diagnostic radiology

Radiotherapy
Radiation Therapy

Teletherapy
- 3 DCRT
- IMRT
- IGRT
- DART
- Tomotherapy

Stereotactic radiotherapy
- Gamma Knife
- LINAC based
- Cyberknife

Brachytherapy
- Image Assisted Brachytherapy
Intensity Modulated Radiation Therapy (IMRT)

Automated computed-based technique that attempts to design and deliver very conformal radiation distributions using multiple gantry positions at which multileaf collimators (MLCs) modulate the dose.

Produces highly shaped dose distribution and rapid periphery falloff.
Pts with GBM on right temporal lobe

High dose to optic nerv and chiasma
Treatment of cranio-spinal axis with Tomotherapy HiArt

B.E. 16 y, posterior fossa medulloblastoma
Patient with 3 brain metastases treated with IMRT-SIB: 30 Gy/10fr whole brain and 50 Gy on the lesions
Stereotactic radiotherapy

- SRT is a form of hypofractionated high precision radiation delivery that is characterized mainly by a dose distribution tightly covering the tumor with rapid fall-off

- Large radiation dose for fraction
Management tree for cerebral metastasis

**Solitary**
- 1st preference: Craniotomy & resection for diagnosis & initial treatment of tumour that can be removed with low risk
- 2nd preference: Primary biopsy
- 3rd preference: Brain biopsy for unresectable tumour if primary lesion not easily biopsied or after failed biopsy

**Multiple**
- 1st preference: Primary biopsy
- 2nd preference: Brain biopsy/resection of tumour if primary lesion not easily biopsied or after failed biopsy OR if one brain tumour is life threatening from ICP +/- neurological deficit

Adjuvant treatment: *Radiosurgery*  
*WBRT*  
*Chemotherapy*
SRT to treat HGG relapse

- Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (fSRT) are increasingly used in patients with brain metastasis and recurrent GBM.
- Both SRS and fSRT are powerful noninvasive therapeutic modalities well suited to treat focal neoplastic lesions through the delivery of precise, high-dose radiation.
- Although no randomized clinical trials have been performed, a variety of retrospective studies have been focused on the use of SRS and fSRT for recurrent GBMs.
Standard radiotherapy for High Grade Glioma

3-DCRT: 60 Gy, 2 Gy per fraction

Newly diagnosed HGG: current standard of care

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma
Roger Stupp, M.D et al
NEJM 352:987-996;2005

<table>
<thead>
<tr>
<th>Survival Rate</th>
<th>RT</th>
<th>TMZ/RT</th>
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<tr>
<td>Median OS (mo)</td>
<td>12.1</td>
<td>14.6</td>
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<tr>
<td>2-yr survival</td>
<td>11.2 %</td>
<td>27.3 %</td>
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<tr>
<td>3-yr survival</td>
<td>4.3 %</td>
<td>16.7 %</td>
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<tr>
<td>4-yr survival</td>
<td>3.8 %</td>
<td>12.9 %</td>
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<tr>
<td>5-yr survival</td>
<td>1.9 %</td>
<td>9 %</td>
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Why IMRT for Glioma?

- More accurately define/administer dose distributions (conform to complex 3D shape of target and deliver uniform dose to that complex shape)
  - Maximize the dose to the target
  - Minimize the dose to normal tissues
    - Optics, brainstem, cord, temporal lobe, hippocampus, etc.

- Hypofractionation
- Concomitant boost (SIB)
- Dose escalation
Hypofractionation

Shorter overall treatment time

“..greatest morbidity that most patients suffer as a result of cranial irradiation is the extra 5-6 weeks during which they must return each day” Weiss 1995

“However, six weeks of daily radiotherapy does seem inappropriate in relation to the short expected survival time in this subset and there is an increasing emphasis on reducing the overall treatment time and the number of hospital visits by such patients” (Tejpal 2005)

Cost advantages

“..Hypofractionated Radiotherapy result in cost savings in terms of patient time, machine time and health care expenditures” Chang 2003
SIB with IMRT in HGG

<table>
<thead>
<tr>
<th>Study</th>
<th>Volume</th>
<th>Total Dose (Gy)</th>
<th>Fract Dose (Gy)</th>
<th>N Fr</th>
<th>OS</th>
<th>PFS</th>
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<tr>
<td><strong>Sultanem</strong></td>
<td>GTV</td>
<td>60</td>
<td>3</td>
<td>20</td>
<td>mOS 9.5m</td>
<td>mPFS 5.2 m</td>
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<td><em>IJROBP 04</em></td>
<td>GTV+1.5 cm</td>
<td>40</td>
<td>2</td>
<td></td>
<td>OS@1y 40%</td>
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<td><strong>Floyd</strong></td>
<td>GTV</td>
<td>50</td>
<td>5</td>
<td>10</td>
<td>mOS 7m</td>
<td>mPFS 6 m</td>
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<td><em>IJROBP 04</em></td>
<td>Peritumoral edema</td>
<td>30</td>
<td>3</td>
<td></td>
<td>OS@ 1 y 77%</td>
<td>PFS@1y 31%</td>
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<td><strong>Nakamatsu</strong></td>
<td>GTV+0.5 cm</td>
<td>70</td>
<td>2.5</td>
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<td>OS@1y 77%</td>
<td>PFS@1y 31%</td>
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<td>GTV+2.5 cm</td>
<td>56</td>
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<tr>
<td><strong>Iuchi</strong></td>
<td>GTV+0.5</td>
<td>48-68</td>
<td>6-8.5</td>
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<td>OS@1y 71.4%</td>
<td>PFS@1y 71.4%</td>
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<td><em>IJROBP 06</em></td>
<td>GTV+2 cm</td>
<td>40</td>
<td>5</td>
<td></td>
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<td>Peritumoral edema</td>
<td>32</td>
<td>4</td>
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Standard radiation therapy planning in gliomas

Based on morphological imaging:

- CT to plan dose distribution
- MR is higher to contours definition (T1 gad T2 FLAIR)
- CT - MR fusion: integrates information of the two techniques
Target volume definition in HHG

GTV: postoperative MRI T1 including the contrast-enhancing lesion and surgical cavity

CTV: MR T2/FLAIR imaging abnormality plus an uniform margin (2 cm) expansion within the brain, which includes the microscopic extension

Definition of the target with the morphological imaging: limits and uncertainties

- The enhancement after Gd T1 MRI may not be indicative of tumor activity
- Volumes defined on probabilistic criteria of infiltration
- The hyperintensity on T2 or Flair may under/overestimate the infiltration
- Unable to distinguish different grading in an inhomogeneous mass
- Uncorrect definition of the true extension
- Unable to distinguish critical functional areas
Needs of multimodality imaging

18F-Choline  FLAIR_long TR  PET-MR fusion
Multimodal imaging is useful for:

- Define true tumoral volume
- Characterize biological features
- Reduction of the dose to functional areas and/or healthy tissues
- Predictive value on the response
- Discriminate between necrosis and progression
Define true tumoral volume

Edema or tumor?
The key finding of this study is the ability to differentiate two types of peritumoral edema (i.e., purely vasogenic vs tumor infiltrated).
A, Transverse contrast-enhanced T1-weighted MR shows enhancing mass (outlined) in the left frontal lobe.

B, Transverse T2-weighted MR shows another ROI encompassing both the tumor and the surrounding signal intensity abnormality; the area between the two ROIs represents the peritumoral edema.

C, Data from this MD overlay map indicate a mean MD of 0.759 ± 0.135 10^{-3} \text{mm}^2/\text{sec} in the tumor and of 0.496 ± 0.117 10^{-3} \text{mm}^2/\text{sec} in the peritumoral edema at histogram analysis.

D, Data from this FA overlay map indicate a mean FA of 0.200 ± 0.077 in the tumor and of 0.285 ± 0.116 in the peritumoral edema at histogram analysis. The measured TII of this glioblastoma multiforme is 88.

“In the current study, we attempted to quantify the distinct contribution of tumor infiltration to FA changes by using a more robust method of data analysis. On the basis of a higher TII, presumed tumor-infiltrated edema, such as that adjacent to gliomas, can now be distinguished from vasogenic edema composed purely of extracellular water, such as the edema adjacent to meningiomas and metastases. In the future, the TII may be useful for clinical applications such as determining tumor resectability and the surgical approach, determining postoperative treatment options and assessing treatment responses, and determining likelihoods and/or rates of recurrence.”
Define true tumoral volume

T2 or FLAIR, or…?
Planning T2 MRI fused with FLAIR images from same date and T1 MRI obtained at time of failure. The failure volume (rGTV) is contoured in light green. The T2 and FLAIR CTVs are outlined in red and cyan respectively. The T2 and FLAIR PTVs are outlined in orange and dark blue respectively. The FLAIR PTV encompasses a greater portion of the failure volume than T2 PTV. Overlay of the 95% dose color wash shows that the failure is central.

Although both T2 and FLAIR MRI sequences are used to define high grade glial neoplasm and surrounding edema, our results show that the volumes generated using these techniques are different and not interchangeable. These differences have bearing on the use of intensity modulated radiation therapy (IMRT) and highly conformal treatment as well as on future clinical trials where the bias of using one technique over the other may influence the study outcome.
Multimodal imaging is useful for:

- Define true tumoral volume
- Characterize biological features
- Reduction of the dose to functional areas and/or healthy tissues
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- Discriminate between necrosis and progression
Metabolic imaging

Provides information on the molecular and biological characteristics

- PET
- Magnetic Resonance Spectroscopy
- Diffusion or perfusion MRI
- Functional MRI
Magnetic Resonance Spectroscopy (MRS)

- Provide information on tumor pathology based on the spatial distribution of cellular metabolites (Cho, NAA, Cr, lactates, lipids).
- By the change of concentration it is possible to differentiate normal tissue from pathological.
- In malignant gliomas, an increase in choline, an index of cell proliferation, and a reduction of NAA and Cr.
Use of MR spectroscopy and functional imaging in the treatment planning of gliomas

1A NARAYANA, MD, 2J CHANG, PhD, 2S THAKUR, PhD, 2,3W HUANG, PhD, 3S KARIMI, MD, 2,3B HOU, PhD, 2A KOWALSKI, MS, 2G PERERA, MS, 3A HOLODNY, MD and 4,5P H GUTIN, MD
Spectrometric volumes were different from those defined on MRI conventional.

“Comparison of target volumes with (a,b) MR spectroscopic imaging (MRSI) information and fluid attenuated inversion recovery (FLAIR) defined CTV, and (c,d) MRSI defined CTV showing both overestimation (upper arrow) and underestimation (lower arrow) with MRI defined volumes” A NARAYANA, et al
MRS showed areas of malignant infiltration beyond the area of enhancement.

Laprie A  IJROBP 2005
Multimodal imaging is useful for:

- Define true tumoral volume
- Characterize biological features
- Reduction of the dose to functional areas and/or healthy tissues
- Predictive value on the response
- Discriminate between necrosis and progression
Functional MRI (fMRI)

- Explore the functional anatomy of the brain and provides a map of brain function, by defining the location of eloquent areas near the tumor.
- There are no data about dose constraints on eloquent area.

Activation at of programmed movement fingers of right hand.

Courtesy of dr. Spagnolli
Multimodal imaging is useful to:

- Define true tumoral volume
- Characterize biological features
- Reduction of the dose to functional areas and/or healthy tissues
- **Predictive value on the response**
- Discriminate between necrosis and progression
Sixty pts with HGG undergoing chemo-RT were enrolled in a study of intratreatment MRI 1, 3, and 10 weeks after the initiation of the treatment.

Diffusion MRI evaluated using the fDM-VI at 3 weeks also correlated with patient survival at 1 year (PPV 82.1% and NPV 60.0%), and might allow for response-based therapy alteration.

The use of 3-week fDM-VI as an early biomarker for survival was at least as prognostic as the Macdonald criteria at 10 weeks, with similar PPV and NPV, but was obtained 7 to 8 weeks earlier.
Multimodal imaging is useful for:

- Define true tumoral volume
- Characterize biological features
- Reduction of the dose to functional areas and/or healthy tissues
- Predictive value on the response
- Discriminate between necrosis and progression
Treatment induced necrosis is often undesirable but unavoidable effect, and to differentiate this from recurrent or progressing tumors on morphologic imaging has always been a challenge.
Morphologic MRI imaging characteristics of recurrent disease include contrast enhancement, mass effect, and vasogenic edema. However, similar features are also seen with radiation necrosis and/or ‘pseudo-progression’.

Perfusion imaging MRI or CT have been used to obtain measures of tumor vascular physiology and hemodynamics. High grade tumor with rapidly growing tumor vasculature can have same vascular problem of necrosis.

MRs can provide valuable information but low spatial resolution and other factor make this method difficult to use.

Diffusion weighted imaging (DWI) or Diffusion tensor imaging (DTI)

PET based techiques
Necrosis or progression? What can we help?

Even though many of these non-invasive imaging techniques can help to evaluate response after treatment, there is:

-a lack of standardization as far as image acquisition and post-processing.

-limited resolution.

“Despite these limitations, there is a greater need to develop and use some of these functional imaging biomarkers as with the advent of newer chemotherapeutic agents and use of combination therapies, recurrence patterns and adverse treatment effects seen on conventional imaging have become too complex. Functional imaging modalities can also be used for treatment guidance once RPT and TIN could be differentiated in vivo in a mixture of heterogeneous appearance seen on morphologic imaging.”

Rajan Jain, J Neurooncol, 2009
Human meningioma cells strongly express somatostatin receptor (SSTR 2).

With increasing conformity using IMRT or SRT the need for accurate target volume delineation is of outmost importance. Of special importance is the fact that target volume definition after single or repeated surgical intervention is frequently hampered by artifacts. In general the use of highly conformal treatment techniques mandates improved pretherapeutic imaging.

In 26 consecutive patients with preferentially skull base meningioma, (MRI) and planning-computed tomography (CT) was complemented with data from (DOTATOC)-PET/CT.

Results: The integration of the DOTATOC data led to additional information concerning tumor extension in 17 of 26 patients (65%).
[\textsuperscript{68}Ga]-DOTATOC-PET/CT for meningioma IMRT treatment planning

Barbara Gehler\textsuperscript{1}, Frank Paulsen\textsuperscript{1}, Mehmet Ö Öksüz\textsuperscript{3,8}, Till-Karsten Hauser\textsuperscript{4}, Susanne M Eschmann\textsuperscript{6}, Roland Bares\textsuperscript{3}, Christina Pfannenberg\textsuperscript{5}, Michael Bamberg\textsuperscript{1}, Peter Bartenstein\textsuperscript{7}, Claus Belka\textsuperscript{2} and Ute Canswindt\textsuperscript{*2}

Large skull base meningioma with orbital invasion and close relation to the sella turcica region, [\textsuperscript{68}Ga]-DOTATOC-PET (top left)/CT image fusion (top right). Physiological tracer uptake of the pituitary gland. CTV/GTV contours (below left): red = GTV-PET; green = GTV-MR/CT; yellow = CTV, CTV enlargement by GTV-PET. Dose distribution with enclosing 90\% PTV isoline.
“actually seeing is certainly a good thing, but it is useless if you have not seen well”

Augusto Murri (1841-1932), Director of Clinical Medicine, University of Bologna, one of the greatest innovators of medicine of his time
thanks for your attention