Overview

Review SRS uncertainties due to:
- image registration
- contouring accuracy
- contouring variability

Assess levels of uncertainty and greatest contributors to overall uncertainty

Discuss appropriate PTV margins to account for uncertainties in SRS
Registration Accuracy

Accuracy depends on registration method:
- Local "box"-based rigid registrations can produce higher accuracy than global rigid registrations
- ROIs should be in close proximity target

Registration Accuracy

- Site-dependent:
  - Registration of spinal sites is less straightforward and has lower accuracy
  - Deformable image registration is tempting for spine registrations but the associated uncertainties are too high for use in SRS

Rigid vs. Deformable Registration

Accuracy depends on registration method:
- Rigid registration is more accurate than deformable registration
  rigid: ~1-2 mm uncertainty*
  deformable: ~5-7 mm uncertainty**

*Benchmark Test of Cranial CT/MR Registration • IJROBP • Kenneth et al. • 2010
**Need for application-based adaptation of DIR • Med. Phys. • Kirby et al. • 2013
***Performance of DIR in low contrast regions • Med. Phys. • Supple et al. • 2013
### Registration Workflow Comparison

<table>
<thead>
<tr>
<th>Simulation and planning images</th>
<th>Gamma Knife</th>
<th>Linac-based SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning</td>
<td>MRI*</td>
<td>CT</td>
</tr>
<tr>
<td>Contouring</td>
<td>MRI*</td>
<td>MRI or PET/CT</td>
</tr>
<tr>
<td>Fusion Type</td>
<td>single-modality rigid registration</td>
<td>multimodal rigid registration</td>
</tr>
</tbody>
</table>

* unless MRI is contraindicated

### Modality

- Modality dependent:
  - Multi-modal registrations are typically less accurate than unimodal registrations, (especially for deformable registration)
  - Registering MRIs of differing sequences is not truly unimodal because of the difference in enhancement for certain regions
  - Different volumes may have different slice thicknesses

### Co-Registration Accuracy

Visual evaluation of registration accuracy can be difficult.
Co-Registration Accuracy

<table>
<thead>
<tr>
<th>Patient number</th>
<th>ΔZ (mm) (mean ± SD)</th>
<th>ΔP (mm) (mean ± SD)</th>
<th>ΔS (mm) (mean ± SD)</th>
<th>ΔS_max (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.37 ± 0.78</td>
<td>1.17 ± 0.89</td>
<td>1.54 ± 1.05</td>
<td>2.50</td>
</tr>
<tr>
<td>2</td>
<td>0.11 ± 0.33</td>
<td>0.88 ± 0.52</td>
<td>0.96 ± 0.58</td>
<td>1.41</td>
</tr>
<tr>
<td>3</td>
<td>0.64 ± 1.27</td>
<td>1.15 ± 1.15</td>
<td>1.92 ± 1.13</td>
<td>3.62</td>
</tr>
<tr>
<td>4</td>
<td>0.36 ± 0.41</td>
<td>1.70 ± 0.86</td>
<td>1.89 ± 0.75</td>
<td>2.72</td>
</tr>
<tr>
<td>5</td>
<td>0.39 ± 1.15</td>
<td>0.81 ± 0.79</td>
<td>1.34 ± 1.26</td>
<td>3.48</td>
</tr>
</tbody>
</table>

Mean (over five anatomical landmarks) distance between correspondent markers: ΔZ, error along crano-caudal direction (mm); ΔP, error in transaxial plane (mm); ΔS, error in 3D space. ΔS_max, maximum 3D error (mm).

Target delineation: Impact of registration • Radio & Onc. • Cattaneo et al. • 2005

Co-Registration Accuracy

45 institutions, 11 methods

Registration accuracy: 1.8 mm +/- 2.2 mm

Manual registration better than automatic registration (p=0.02)

Fig. 5: Distribution of errors indicating the number of submissions falling within 3-mm error bars.

Benchmark Test of Cranial CT/MR Registration • IJROBP • Kenneth et al. • 2010

Frame-Based Registration

• When not using a single MR scan for GK contouring and planning, GammaPlan's auto registration can produce errors of up to 2 mm
  - Fiducial based registration compared to anatomical local box registration

MR to CT Registration Errors • Med. Phys. • Sudhyadhom et al. • 2014
Contouring Accuracy

Contouring accuracy is affected by:
- Modality
- Spatial resolution
- Signal to noise ratio (SNR)
- MR field strength
- Planning image timing
- Contrast injection timing
- Additional factors: slice thickness, image artifacts, motion blur, spatial distortion

Contouring Accuracy

Modality affects GTV & CTV contouring:
- Tumor volumes across sites are typically larger on CT+MRI

<table>
<thead>
<tr>
<th>Modality</th>
<th>Mean Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT only</td>
<td>29.6 cm³</td>
</tr>
<tr>
<td>MRI only</td>
<td>51.4 cm³</td>
</tr>
<tr>
<td>CT+MRI</td>
<td>56.5 cm³</td>
</tr>
</tbody>
</table>

MR GTVs were 74% larger than CT only
CT+MRI GTVs were 10% larger than MR only

Influence of MRI on GTV delineation • JROBP • Emami et al. • 2003
Modality

Modality affects GTV & CTV contouring:
- Tumor volumes across sites are typically larger on CT+MRI

<table>
<thead>
<tr>
<th>Modality</th>
<th>Mean Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT only</td>
<td>59.5 cm³</td>
</tr>
<tr>
<td>CT + MRI</td>
<td>69.6 cm³</td>
</tr>
</tbody>
</table>

A difference of 10 cm³!

Interobserver variations GTV delineation • Radio & Onc • Weltens et al. • 2001

Spatial Resolution & SNR

- Spatial resolution and SNR also affect imaging accuracy
  - Slice thickness contributes substantially to contouring and image fusion accuracy
  - SNR is greater concern for MRI

- In most cases, visual inspection is employed to determine appropriate resolution and SNR levels

Slice Thickness

- Slice thickness affects image registration accuracy:
  - Thinner slices improve accuracy (improves interpolated image accuracy)
  - Typical planning CT and MRI slice thicknesses range from 1 mm to 3mm
**MR Field Strength**

MRI field strength affects spatial resolution and SNR, but 1.5 T is sufficient (small effects on contours).

**Planning Image Timing**

Greater than 2 week wait times between MR acquisition and treatment significantly reduce survival.

**Timing of Contrast Injection**

Contrast injection timing significantly impacts GTV.

Contrast injection delay (median of 65 minutes):

- GTV increase in 82% of cases.

Evaluation of target localization using 3T MRI • *IJROBP* • MacFadden et al. • 2010

Imaging to Treatment in RS: Too Long? • *IJROBP* • Seymour et al. • 2013

Delineation brain mets on CT for RS: accuracy • *Br J Radiol* • Sidhu et al. • 2004
Additional Factors

• Slice thickness
• Image artifacts (e.g. metal artifacts)
• Motion blur
• Spatial distortion (especially MRI)

Contour Variation

5 patients, 9 observers

<table>
<thead>
<tr>
<th>Modality</th>
<th>Volume Ratio (largest: smallest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT only</td>
<td>(2.8, 1.8, 1.8, 1.9, 1.7)</td>
</tr>
<tr>
<td>CT + MRI</td>
<td>(2.4, 1.7, 1.9, 2.7, 1.5)</td>
</tr>
</tbody>
</table>

Volumes vary up to 30% of the mean volume
GTV range: as large as 174% and as small as 65.8% of mean volume

Interobserver variations GTV Delineation • Radio & Onc. • Weltens et al. • 2001
Contour Variation
7 patients, 5 observers

<table>
<thead>
<tr>
<th>Modality</th>
<th>Concordance Index</th>
<th>Agreement Ratio (AR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>unregistered</td>
<td>14.1 +/- 12.7%</td>
<td>.24 +/- .18</td>
</tr>
<tr>
<td>registered</td>
<td>47.4 +/- 12.4%</td>
<td>.67 +/- .15</td>
</tr>
</tbody>
</table>

CT+ registered MR reduces interobserver GTV variability

Target delineation interobserver variability • Radio & Onc • Cattaneo et al. • 2005

Contour Variation
31 patients, 6 observers

Mean AR = 0.19 +/- 0.14
AR < 0.6 for all patients

Fig. 1. Contouring variations in a patient with a branum arteriovenous malformation. (a) Target volume presented as different color. All contours were automatically projected on computed tomography images used for further analysis (b).

Digital subtraction angiogram

Agreement ratio (AR) = \( \frac{\text{common overlapping volume}}{\text{encompassing volume}} \)

SRS for brain AVMs: Interobserver variability • IROBP • Buis et al. • 2005

Margins
What margin for SRS?

- Margins should be sufficient to account for treatment uncertainties and guarantee target coverage
- They must be balanced to minimize potential negative side effects resulting from increased normal tissue dose (more important for SRS)
- Some clinics choose not to include margin expansions (CTV = PTV)

What is an appropriate margin?

- **Internal margin (IM):**
  - Residual motion, deformation
- **Setup margin (SM):**
  - Ensures adequate clinical coverage
  - Includes all uncertainties
  - Appropriate for hypofractionation

Margins – not your simple PTV

Margin recipes based on standard fractionation (van Herk 1999) are not appropriate for few fractions:

\[ M = 2.5 \sum_{tot} + 0.7 \sigma_{tot} \]

Several groups have adapted the van Herk recipe for hypofraction:

- Stroom and Heijmen (2003)
- Gordon and Siebers (2007)
Herschtal Margin for SBRT

• Adjusted van Herk formula as lower limit
• Developed method for estimating upper limit
• Model interpolates between limits
• Verified using MC simulation
• Specific to each clinic

Calculating margins for hypofractionated RT • PMB • Herschtal et al. • 2013

Summary

• Contours can vary substantially from physician to physician
  – Minimize by appropriate imaging choices (modality, MR field strength, etc.)
  – Generally not accounted for in PTV
• Contouring accuracy: small contribution to overall uncertainty (~1-2mm)
  – Minimized by imaging choices (slice thickness, reduction of image artifacts, etc.)
• Image registration: small contribution (~1-2mm)
  – Rigid registration, manual vs. automatic
Which of the following SRS workflow choices is likely to contribute MOST to overall uncertainty?

- 10% 1. extend frame immobilization
- 19% 2. CTV contouring variability
- 33% 3. rigid image registration
- 24% 4. 3 mm MRI slice thickness
- 14% 5. 3 mm plan CT slice thickness

Which of the following SRS workflow choices is likely to contribute MOST to overall uncertainty?

1. Answer: CTV contouring variability


Which of the following is currently LEAST appropriate for SRS?

- 11% 1. mask immobilization
- 4% 2. CBCT image guidance
- 21% 3. contouring using PET-CT
- 14% 4. deformable registration
- 18% 5. planning on MRI
Which of the following is currently LEAST appropriate for SRS?

1. Answer: deformable registration.
2. Rigid registration is sufficient for the majority of SRS cases. Moreover, the uncertainty associated with deformable registration (as high as 7 mm) is too high to warrant use in SRS.


Acknowledgements

UCSF:
Dilini Pinnadiwadge, Ph.D.
Martina Descovich, Ph.D.
Atchar Sudhyadhom, Ph.D.
Jean Pouliot, Ph.D.
Alexander Gottschalk, M.D.
Zachary Seymour, M.D.
Sonja Dieterich, Ph.D. [UC Davis]

Thank you!