Treatment planning for radiation mediated gene therapy
C.A. Pelizzari

Abstract:

Planning for gene therapy, alone and in combination with radiation, poses problems similar in some respects to those encountered in planning for external beam radiotherapy, brachytherapy and radioimmunotherapy. Modeling of the modulation of radiosensitivity, radioprotection and direct cell killing by gene therapy agents can aid in optimization of gene and radiation fractionation regimes. This combines aspects of biological modeling of radiation response in tumors and normal tissue, and of biodistribution calculations for radioimmunotherapy. Image-based evaluation of therapy effects may facilitate adaptive treatment strategies analogous to those previously developed for external beam therapy. Integration of information from anatomic and functional imaging modalities will be essential to the success of such an approach. Simultaneous optimization of distributions of radiation dose and gene therapy agent, similar to inverse planning of IMRT dose distributions, may also prove useful. Incorporation of biological modeling directly into this planning process will be a key challenge.

Features in common with more familiar planning problems

- Radioimmunotherapy – modeling of uptake kinetics; biodistribution
- Brachytherapy - localization of interstitial implants / injections; “dose spread kernel”
- 3D CRT – external beam irradiation of sensitized or transfected volume, sparing nearby normal tissues
- All – modeling probability of treatment success as with TCP

Similarities and differences to planning for existing treatment types

- Interstitial adenoviral therapy for prostate (Hopkins)
- Image guided injection at grid of sites: similar to US-guided prostate seed implant
- Goal: uniform coverage of target volume as with PTV
- Requires: estimate of extent of treated region around each injection site
- Superposition calculation - similar to summation of seed dose kernels
- Can model biological effect, e.g. “biochemical response probability”
- May need to take into account viral replication, vector transport through circulation (S. Li, 2002)

Dosimetric model and its verification: Shidong Li et al., JHMI

- Plan with modified MMS RTP system
- Model spread around each injection site as sphere: 0.1mL -> 10mm sphere
- Experimentally verified with excised prostate
  - Ultrasound, fluorescence microscopy
- Biochemical response probability model vs “viral dose” fitted to clinical data
- Define effective volume, “local viral dose”

Similarities and differences to planning for existing treatment types

- Combined RT / gene Tx ("radiation mediated" or "radiation induced" gene therapy)
- Irradiation to promote gene expression: requires conformal RT planning
- Goal: irradiate PTV with prescription dose as for 3DCRT, following intratumoral delivery of vector
- Requires: accurate delivery of gene vector prior to irradiation
- Image guided injection useful
- Robotics for precise control of injection?

Robotically assisted percutaneous injection of gene vector (Gabor Fichtinger, JHU CISST; Clif Burdette, Burdette Medical)

- Original goal: ultrasound guided robotic ^{125}I seed implantation
- Injection and seed implantation highly analogous
- Verify accuracy with MRI, pathology
- Measure extent of injection transport via dye in images of pathology slices
- Demonstrated in-MRI, in-CT, TRUS guided robotic operation

Potential for adaptive image guidance (U Chicago)

- Visualize extent of tissue damage due to therapy
  - Potentially use as kernel for superposition to model damage distribution from plan?
- MRI, MRS, EPR imaging
- Adapt subsequent injection fractions to preferentially treat “cold spots”
- Testing in prostate tumor xenografts

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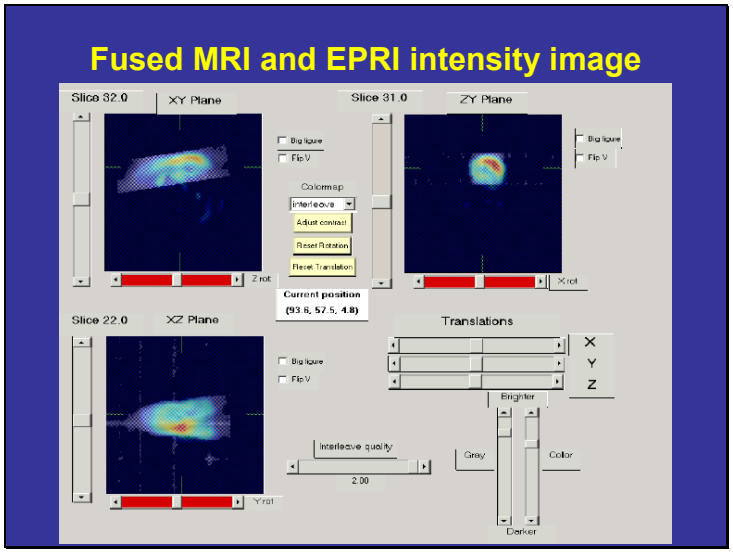

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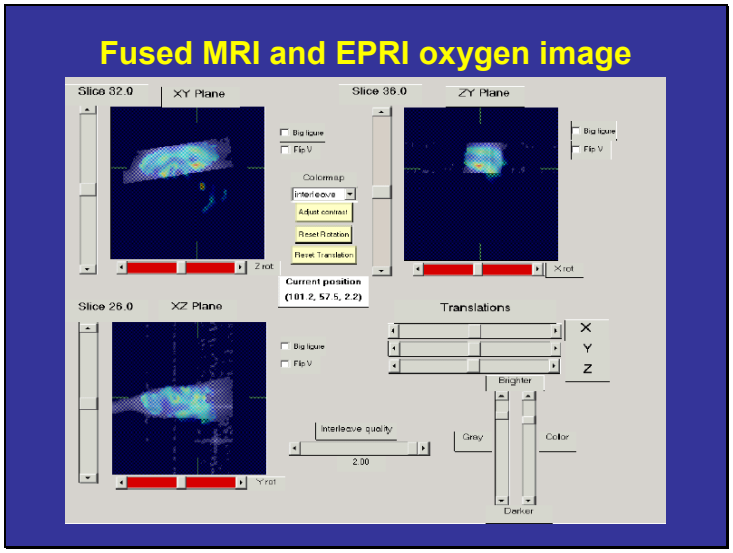

Modeling of gene therapy mediated radiosensitization (T. Wheldon et al, 1998)

- **Transfection kinetics**
  - **3 classes: transfected, untransfected but susceptible, impervious**
- **Define therapeutic advantage of gene vs non-gene sensitized RT**
- **Account for fractionation**
- **Impervious cell fraction may limit enhancement**