Normal Tissue Dose-Response Relationship in Lung High Dose SBRT Patients

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ofractionated Conformal High-Dose Radiation Therapy (HCHDRT)

- 9–20 fractions at multiple angles given 2–3 weeks to a total dose of 50-56 Gy
- Uses BrainLAB Novalis multimicro leaves to conform the beam tightly to the tumor profile
- Developed initially for stationary targets in the head and neck & extended by our group and others to treat lung and liver lesions
- 15-20 second repeated end-expiration breath-holding used to minimize target motion

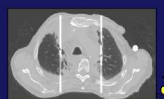
e mean by conformal high-dose radiation therapy is the same as that known in the treatment of head and neck tumors, namely, fractionated treatment of 10-80 daily fractions spread out over 2-8 week intervals to a total dose of 50-e intent is to ablate any tissue within the high-dose region.

Lung Radiation Damage Late Effects

Effect	Time Scale	Key Tissue Response
Immediate	1hr–7 days	Cellular injury, DNA damage and apoptosis Surfactant loss & resultant alveolar collapse
Acute	1–3 months	Inflammatory response, infiltration with macrophages, vascular damage
Late Effects	3–6 months +	Progressive tissue fibrosis and pneumonitis

Traditional protocol
AP-PA fields to 45 Gy
+ oblique tangents at 20 Gy

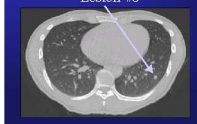
Late effects damage:
large homogeneous region:

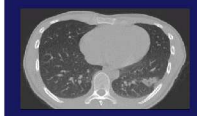


4. Damage to the lung is an unavoidable complication of thoracic irradiation. Acute radiation effects give way to chronic late-effects of progressive tissue fibrosis and pneumonitis that take precedence 3-6 months post-radiation therapy. Standard radiation delivers near-uniform dose to a large volume, as exemplified in the typical opposing AP–PA fields plan shown.

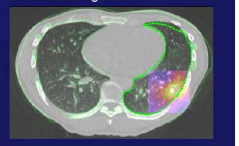
Extracting the dose-response data

Lesion #3





1. Non-rigid registration in 3D
2. Register computed dose field
3. Extract lung volume



4.Tabulate dose and DCT# for each pixel

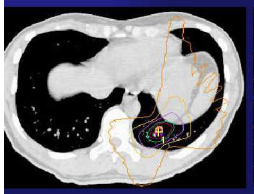
7. Image analysis: The current (6,12,18?month) lung CT dataset (~70 slices of 1x1x3mm voxels) is first registered in 3D to the treatment planning CT image set. The 3D dose matrix is then exported from the treatment planning station and registered to the CT images. The elements of the dose matrix are prescribed precisely to match the size and location of the CT voxels. A mask of the lung volume is then computed automatically and used to isolate the lung voxels from surrounding structures. The change in CT intensity and the dose value at each voxel are then tabulated.

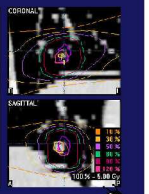
Conclusions

- **We have measured the full radiation dose response relationship of normal lung tissue in patients treated with HCHDRT using follow-up CT image acquisitions**
- **Applications: We propose to use these approach to answer a variety of questions, including ?What is the role of *in vivo* circulating cytokine levels present during radiation treatment and the development of pulmonary late effects?**
- **Limitations:**
  - **reliable quantitative results will require 3D image registration with near pixel-dimension accuracy, requiring a non-deformable registration approach.**
  - **The relationship between changes in CT Hounsfield units and the underlying tissue pathology will need to be better understood.**

HCHDRT Treatment Plans

- 12 mm diameter lung lesion (1 of 5 lesions)
- 50 Gy total dose given in 10 fractions over 10 days
- Dose delivered in two 110° arcs

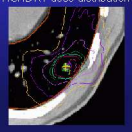




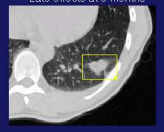
J. Flavin Novalis Stereotactic Radiosurgery Center has been functioning for ears, and over 200 patients have been treated, with approximately 5 patients on HCHRT protocols. Patients often present with multiple metastatic lesions.

Lung Tissue Late Effects in HCHDRT

HCHDRT dose distribution



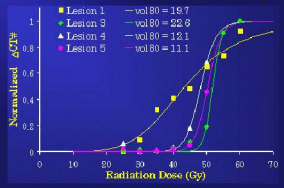
Late effects at 6 months



- Exhibits full spectrum of response versus dose
- Dose fields known precisely
- Reaction sites unobscured by background tissues
- Follow-ups at 6-mo intervals for analysis of response versus time
- Results across the patient population enables the study of the effects of different sensitizing agent and circulating cytokines
- Multiple sites per patient enables controlled study of the effects of treatment volume, fraction size, etc.

5. In contrast to standard large field technicues, HCHDRT delivers a localized region of high dose to the lung target, a well defined dose field gradient and ~zero dose to distal sites, making HDRT suitable for study of the tissue dose-response relationship. Other desirous features include: availability of accurate 3D dose fields; Image sets at 6-month intervals (timescales associated with long-term effects); availability of multiple analysis sites within the each subject; and availability of multiple subject datasets.

Volume effect on the dose response



i. sort the data in 5 Gy-wide bins
ii. fit to an S-shaped curve: $\Delta CT\# = 1/(1+(d/d_{50})^{k})$
iii. larger local PTV's to exhibit left-ward shift of curve

8. The 6-month post-therapy data was sorted into 5 Gy-wide bins and the d_{50} and k parameters fit to the sorted data. There is a general trend for larger targets to exhibit a left-ward shifted (B_{50}). A 5th treatment site, the smallest, did not present with a measurable CT number change. Presumably, its curve is located far off to the right, at yet higher doses than prescribed for treatment. A lower slope (K) indicates a broader range of sensitivities (i.e. greater tissue heterogeneity) associated with larger PTVs.

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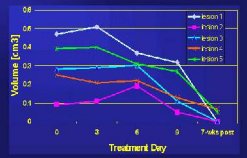
Typical Clinical Results

Patient #1: 5 lung lesions ? treated Jan 2001

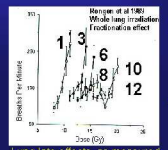


Follow-ups: 18-months post-therapy: no evidence of disease (NED)
24 mo: 4 new lung nodules at different sites found and treated with HCHDRT
30 mo: NED

we have treated over 70 such lung lesions and have achieved greater than ld control rate (only one instance of disease progression at a site previously The incidence of long term survival of these patients provides new insights into effects of radiation treatment.

Modeling Normal Lung tissue Response to Radiation

Normal Tissue Complication Probability Curves



Lung late effects, as measured by breathing rates in mice, versus dose and for the number of fractions ranging from 1–12

Linear-quadric model: NTCP ~ $e^{(-\alpha d-\beta d^2)}$
—championed by Kellerer (1972)
—leads to α/β ratio analysis

Sigmoidal d_{50} model: $= 1/(1-(d/d_{50})^{k})$
—d_{50} : dose where 50% of the cells die
—k : defines steepness of response

6. Radiobiologically, the sensitivity of lung to fractional dose and to dose rate is modeled mathematically using cell survival analysis techniques. The common linear-quadratic model predicts cell survival that declines exponentially with both a linear and a quadratic dependence on dose. A low α/β (<5Gy) indicates a high sensitivity to dose per fraction and to dose rate. We employ a sigmoidal dose-response model to capture the saturation of damage at very high doses. The S-shaped profile displays an inflection point at the d_{50} value (=50% survival) and a slope of k around the d_{50} point.

Volume and time effects on the dose-response

Right-ward shift from 6 to 12 months: increasing d_{50}
—suggests 'slow repair?
Shape is preserved: K is constant
—tissue heterogeneity remains

9. The analysis was repeated for the 2 largest treatment sites at 12-months post therapy. We observe that the d_{50} value increases over time, resulting in a right-ward shift of the curve. The observation that the damage is diminishing over time challenges the conventional theory that radiation damage progresses throughout the patient's lifetime. The apparent decrease in lung CT opacity may be due to 'slow repair?in which tissues from outside of the irradiated volume grow into the affected region and replace lost tissue function and architecture.

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