

## Heterogeneity Corrections in Clinical Trials

Niko Papanikolaou  
Departments of Radiology and Radiation Oncology  
U of TX Health Science Center, San Antonio, TX  
Eric Klein  
Department of Radiation Oncology  
Washington University, St Louis, MS



### To Do or NOT to Do That is (or was) the question

- Should heterogeneity corrections be included in clinical trials ?
- How do the dose algorithms include the effect of inhomogeneities in the dose calculation?

### Why have accurate dose algorithms

- Effectiveness of radiation therapy depends on maximum TCP and minimum NTCP. Both of these quantities are very sensitive to absorbed dose (5% change in dose corresponds to 20% change in NTCP)
- We learn how to prescribe from clinical trials and controlled studies. Their outcome depends on the accuracy of reporting data

### Inhomogeneity Corrections Clinical Examples - Lung

- Mah & Van Dyk (1991)
  - reviewed 100 thoracic patients
- Conclusions
  - Within lung, corrections are significant (0.95-1.24)
  - Target dose corrections are significant (0.95-1.21)
  - Substantial variation over patients (-5% to +21%)
  - Dose uniformity reduced in corrected distributions
  - In ~80% patients, probability of lung damage underestimated by >5% (up to 19%) if corrections not applied

## Inhomogeneity Corrections Clinical Examples

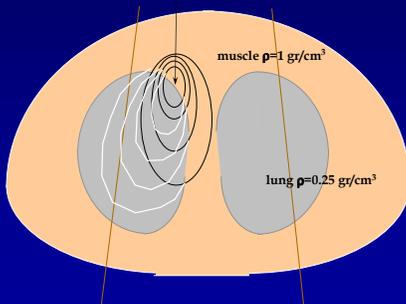
- Orton *et al* (1998)
  - Developed benchmark test case
  - Reviewed 322 patients enrolled in **RTOG 88-08**
- Results
  - Benchmark lung corrections
    - Measured: 1.14 (Co-60)-1.05 (24 MV)
    - Calculated: 1.17 (Co-60)-1.05 (24 MV)
  - Patients: 0.95-1.28, mean=1.05, SD=0.05
    - For lateral fields: mean=1.11, SD=0.08
- Conclusion
  - Lung corrections lead to significant variations
  - Density corrections will help reduce these variations

## RADIATION THERAPY ONCOLOGY GROUP RTOG 0412/SWOG S0332

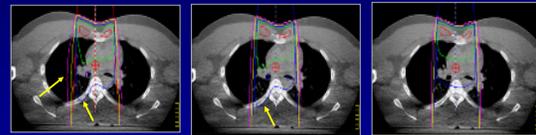
### PHASE III RANDOMIZED TRIAL: STAGE IIIA (N2) NON-SMALL CELL LUNG CANCER

**6.4.1 Dose Calculation:** Doses are to be calculated *with heterogeneity correction*, i.e., correction is to be made for density differences between air spaces, lung, water-density or bony tissue. Treatment planning should be performed in accordance with the prescribing doses to each target, together with restrictions in dose to normal tissues.....

## Convolution/Superposition: Heterogeneities



## Dose calculation examples

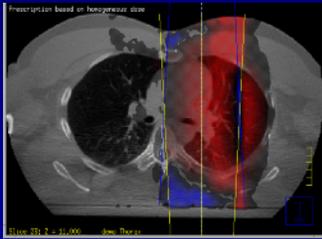


Convolution/Superposition  
(kernel scaled by density)  
3D

Homogeneous Scatter  
(water kernel)  
2.5D

Homogeneous Primary  
and Scatter  
2.5D

## 3D Dose Calculation - 10MV beams 90 cGy per beam to iso



Homo at iso 5034 cGy  
Hetero (2.5D) at iso 4869 cGy  
Dose at isocenter is 3.3% lower  
for the 2.5D calc

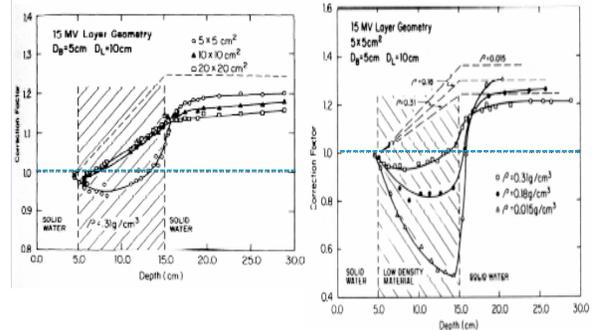
Homo at iso 5034 cGy  
Hetero (3D) at iso 5401 cGy  
Dose at isocenter is 7.3% higher  
for the 3D calc

About 10% difference from 2.5D

## Convolution predicted CF

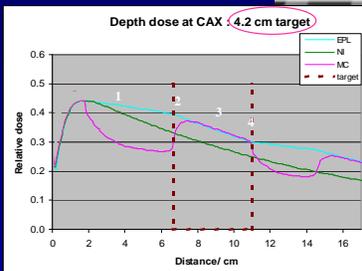
vs field size

vs density



## MC vs PB vs Homogeneous (NI)

6MV beam  
Corvus implementation



P. Rassiah (2006)

The effect of inhomogeneity is included  
in the conv/superposition algorithm by:

- 20% 1. Scaling the TERMA by tissue density
- 20% 2. Scaling the kernel by tissue density
- 20% 3. Applying O'Connor theorem to both the TERMA and the kernel
- 20% 4. Calculating the TERMA in radiological space and scale the water kernel by the tissue density
- 20% 5. Applying tissue specific convolution kernels

## TG-65: Published in August of 2004

TISSUE INHOMOGENEITY CORRECTIONS  
FOR MEGAVOLTAGE PHOTON BEAMS  
Report of Task Group 65 of the Radiation Therapy Committee  
of the American Association of Physicists in Medicine

Nikos Papanikolaou	University of Arkansas, Little Rock, Arkansas, USA
Jerry J. Battista	London Regional Cancer Centre, London, Ont., Canada
Arthur L. Boyer	Stanford University, Stanford, California, USA
Constantin Kappas	University of Thessaly, Medical School, Larissa, Hellas
Eric Klein	Mallinckrodt Institute of Radiology, St Louis, MO, USA
T. Rock Mackie	University of Wisconsin, Madison, Wisconsin, USA
Jeff V. Siebers	Virginia Commonwealth University, Richmond, Virginia
Michael Sharpe	Princess Margaret Hospital, Toronto, Canada
Jake Van Dyk	London Regional Cancer Centre, London, Ont., Canada

## TG-65 Recommendations

- The physicist should understand the effect of the dose calculation resolution grid, and its effect in computed dose.
- The physicist should maintain an open dialogue with clinicians and be clear on limitations of the TPS. For each clinical site (eg. left breast, right lung, larynx etc), there should be 5-10 treatment plans generated, with & without inhomogeneity corrections. The dose prescription should be the same for both cases.

*TG-65 recommends energies of 12 MV or less for lung radiotherapy.*

## Current Practice: Prescription

- Heterogeneous plan used for *up-front* MU
- Select the calculation point to be in the appropriate place (not necessarily the isocenter)
- Dose prescribed to the appropriate isodose line (such as 95%)
  - i.e., 7095cGy @ 95%, which is 7468cGy @ Isocenter
- Limited to 6 MV
- Dose grid, use 3mm Resolution

## RPC: Credentialing for Lung Protocols

- RPC evaluates dose to TLDS
  - Criteria:  $\pm 0.05$
- Evaluate DTA from film data
  - $\pm 5$  mm at all sides of target
- Analysis does not currently include variation across the target but RPC has proposed to include such evaluation



## Summary of Systems Passing Existing Criteria

System/Algorithm	Percent of Points Within:		
	5%	7%	10%
Pencil Beam-Clarkson	69 $\pm$ 28%	82 $\pm$ 14%	91 $\pm$ 8%
Convolution-Superposition	88 $\pm$ 23%	96 $\pm$ 13%	98 $\pm$ 7%

## Should heterogeneity corrections be included in clinical trials ?

- 20% 1. Yes; the treatment outcomes will improve
- 20% 2. Yes; The accuracy of the reported dose will allow for further dose escalation
- 20% 3. Yes; will enable us to perform radiobiological evaluations of plans
- 20% 4. Yes; Accurate reporting of planned dose between participating institutions will allow for a meaningful evaluation of the trial outcomes
- 20% 5. No; we have historically prescribed based on homogeneous dose planning and we do not know what do deal with inhomogeneities

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## Conclusions

- The motivation for high dose accuracy stems from:
  - Steep dose response of tissue
  - Narrow therapeutic windows
- Early calculation models are based on broad beam data and assume CPE conditions that introduce calculation errors
- Inhomogeneity based computations alter both the relative dose distribution and the absolute dose to the patient
- Credentialing with RPC. New Protocols are now requiring inhomogeneity corrected doses to be reported

## Conclusions

- State of the art algorithms for photon dose computation should be used for both conventional and IMRT planning (convolution/superposition or better)
  - What you calculate is what you get ...
  - Better outcome analysis and studies
- Pencil beam algorithms can introduce significant systematic and convergence errors in IMRT and should be avoided when possible.
- Monte Carlo algorithms are now fast enough to become contenders in the RTP arena, but they don't demonstrate a clear improvement over the convolution/superposition implementation.

Thank you



The University of Texas Medical School at San Antonio



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