Beyond the DVH: why we have to include spatial information and some examples of how to do it

Joe Deasy, PhD, and Ziad Saleh, PhD
Memorial Sloan Kettering
Cancer Center

Why the DVH is not enough

- Spatial location may be explanatory in terms of differences in how patients were treated
- Multiple anatomic structures may be involved
- The location within an anatomic structure may be important
- Organs are not biologically homogeneous
- We may not know which tissues are involved

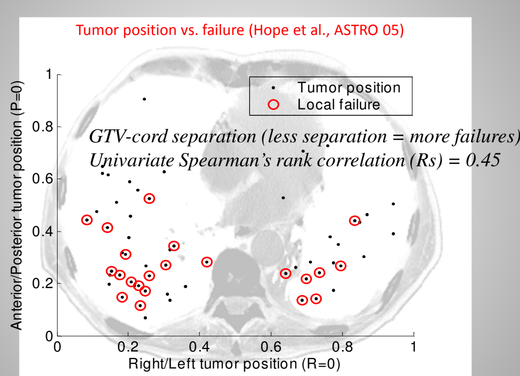
A key theme

- Correlation is not necessarily causation…
- and there are usually many correlates to toxicity in any comprehensive analysis

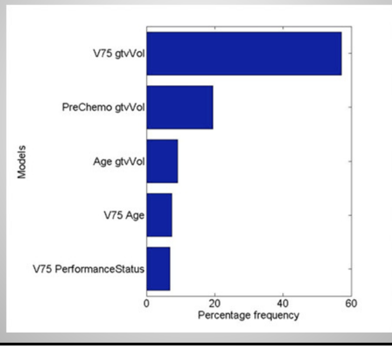
Location with respect to other tissues may itself be an explanatory variable

"Factors affecting local control for non-small-cell lung cancer" (Hope et al., ASTRO 05)

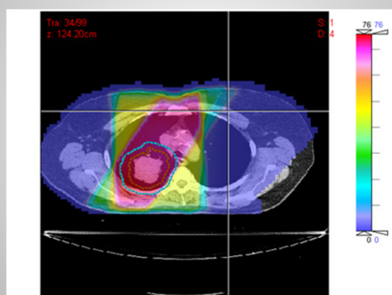
- Purpose: To identify and model clinical, dosimetric, and spatial factors which correlated with local failure in patients with non-small cell lung cancer (NSCLC) treated with definitive 3D-CRT
- Subset: isolated primary tumors (no pos. nodes)
- n = 57
- TCP endpoint: primary tumor failure
- Considered many dose-volume cutpoints for GTV and PTV, as well as min. distance to a 'low' dose, and clinical factors



Best model explains this: GTV and V75 are selected



The clinical issue: less aggressive dosing for tumors near the spinal cord, leading to failures

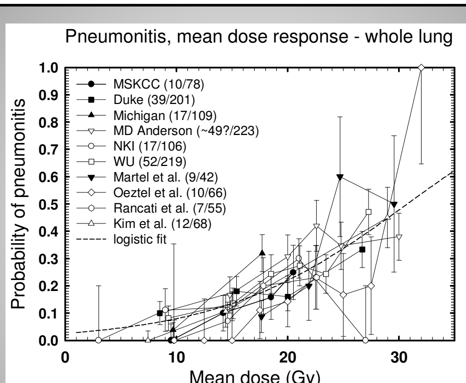


Location within an organ can be important

QUANTEC: ORGAN-SPECIFIC PAPER — Thorax: Lung

RADIATION DOSE–VOLUME EFFECTS IN THE LUNG

Lawrence B. Marks, M.D.,* Soren M. Bentzen, D.Sc.,† Joseph O. Deasy, Ph.D.,‡
Feng-Ming (Spring) Kong, M.D., Ph.D.,§ Jeffrey D. Bradley, M.D.,‡ Ivan S. Vogelius, Ph.D.,†
Issam El Naqa, Ph.D.,‡ Jessica L. Hubbs, M.S.,* Joos V. Lebesque, M.D., Ph.D.,||
Robert D. Timmerman, M.D.,¶ Mary K. Martel, Ph.D.,# and Andrew Jackson, Ph.D.**

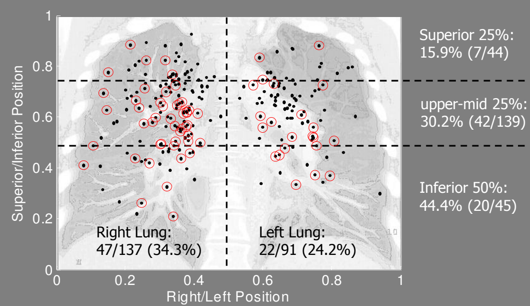


Consistent – but not very predictive.

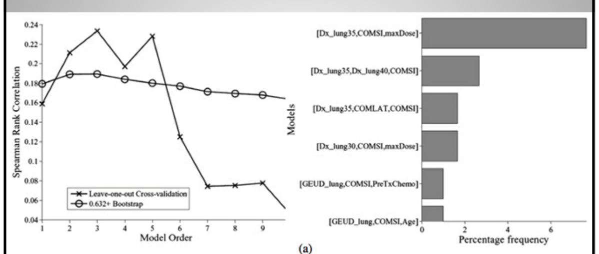
WUSTL RP dataset

- 228 patients with non-small cell lung cancer (NSCLC) treated definitively with radiation +/- chemotherapy between 1991-2001
- 48 cases of RP (steroids or more intensive intervention)
- 3D treatment plan archives available
  - Non-heterogeneity corrected dose distributions
- Minimum six months follow-up post-treatment unless patient developed pneumonitis < 6 mos.

Tumor location is associated with risk of pneumonitis



(Hope et al, IJROBP 2007)

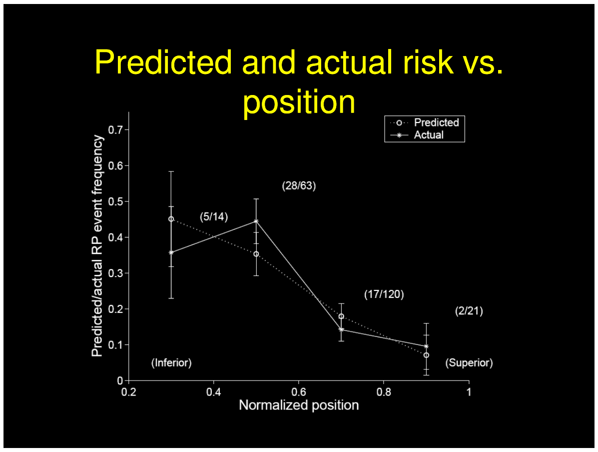


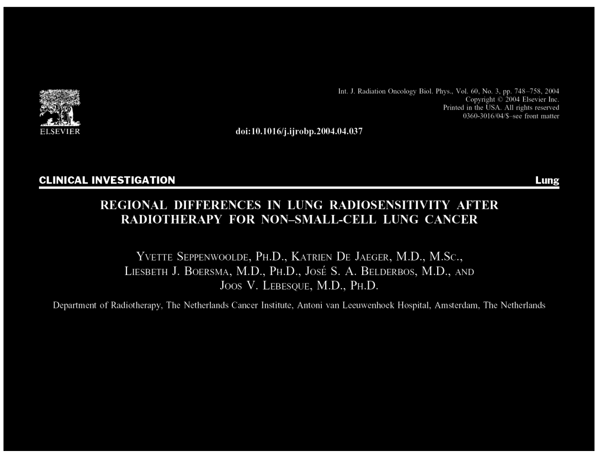
Multi-variate modeling of *combined* WUSTL and RTOG 93-11 datasets (Bradley et al. IJROBP 2007)

- Chosen from many candidate models; logistic function of:

$$-1.5 + 0.11 \times \text{MeanLungDose} - 2.8 \times \text{PosSupInf}$$

- Spearman's rank correlation coefficient 0.3 (on cross validation data)




Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 3, pp. 748–758, 2004
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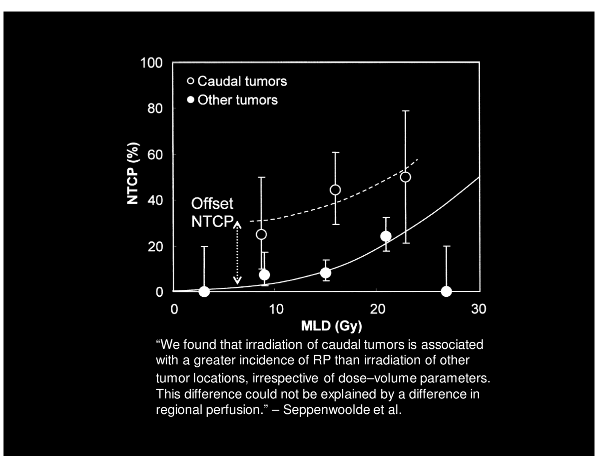
0360-3016/04/$–see front matter
ELSEVIER
doi:10.1016/j.ijrobp.2004.04.037

CLINICAL INVESTIGATION **Lung**

REGIONAL DIFFERENCES IN LUNG RADIOSENSITIVITY AFTER RADIOTHERAPY FOR NON–SMALL-CELL LUNG CANCER

Yvette Seppenwoolde, Ph.D., Katrien De Jaeger, M.D., M.Sc., Liesbeth J. Boersma, M.D., Ph.D., José S. A. Belderbos, M.D., and Joos V. Lebesque, M.D., Ph.D.

Department of Radiotherapy, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands



But maybe we don't know the right DVHs to analyze…

Heart irradiation as a risk factor for radiation pneumonitis

ELLEN X. HUANG[1], ANDREW J. HOPE[2], PATRICIA E. LINDSAY[2], MARCO TROVO[3], ISSAM EL NAQA[1], JOSEPH O. DEASY[1] & JEFFREY D. BRADLEY[1]

[1]*Department of Radiation Oncology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri, USA,* [2]*Princess Margaret Hospital, Toronto, ON, Canada and* [3]*National Cancer Institute, Aviano, Italy*

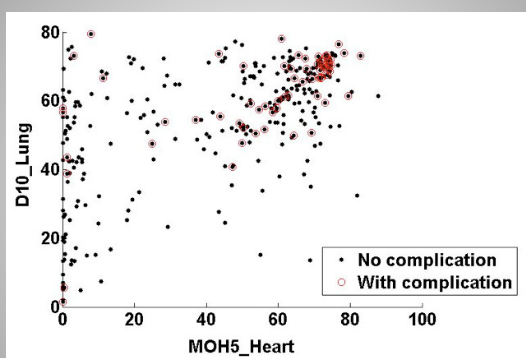
(Acta Oncol, 2010)

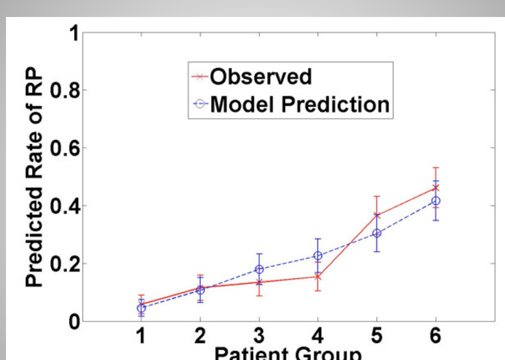
Dataset

- Heart volumes of WUSTL archived plans were re-contoured within CERR by a single physician (n = 209, with 48 RP events).
- Heart and normal lung (lung minus gross tumor volume) dose-volume parameters were extracted for further modeling using CERR.
- Evaluated factors included:
  - clinical (age, gender, race, performance status, weight loss, smoking, histology)
  - dosimetric parameters for heart and normal lungs (D5-D100, V10-V80, mean dose, maximum dose, and minimum dose)
  - treatment factors (chemotherapy, treatment time, fraction size)
  - location parameters (heart center-of-dose, sup-inf within the heart; and center-of-target mass within the normal lungs.)

Highest univariate correlations

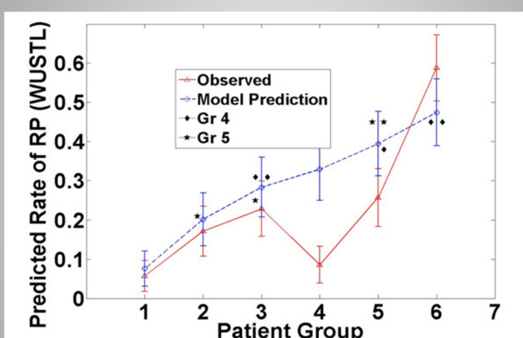
Variable	Spearman Corr.	Significance
D5_Heart	0.256	<0.0002
D10_Heart	0.24	<0.0003
V70_heart	0.239	<0.0003
gEUD_Heart (a=10)	0.249	<0.0001
Maximum Heart Dose	0.227	<0.0006
Superior-Inferior position of GTV	0.219	<0.0008

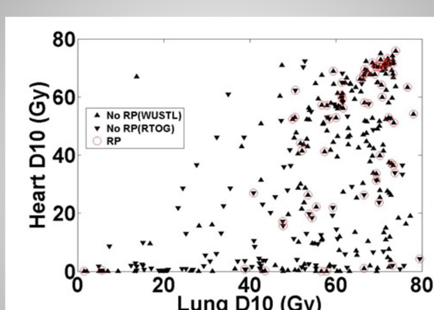




Radiation pneumonitis dose-volume factors: testing the impact of heart irradiation on a multi-institutional dataset

Ellen X Huang[1], J O Deasy[2*], A. J. Hope[3], I El Naqa[4], M. Trovo[5], Walter R. Bosch[1], DSc; John W. Matthews[1], DSc; William T. Sause[6], MD; Mary. V. Graham[7], MD, P. L. Lindsay[3], and J. D. Bradley[1]





Dose-Effect Relationships for Individual Pelvic Floor Muscles and Anorectal Complaints After Prostate Radiotherapy

Robert Jan Smeenk, M.D.,* Aswin L. Hoffmann, M.Sc.,*
Wim P.M. Hopman, M.D., Ph.D.,† Emile N.J. Th. van Lin, M.D., Ph.D.,* and
Johannes H.A.M. Kaanders, M.D., Ph.D.*

*Departments of *Radiation Oncology and †Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands*

Volume 83 • Number 2 • 2012 Pelvic floor muscles and prostate radiotherapy 641

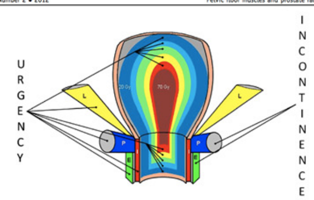


Fig. 2. Schematic image shows rectum, anal canal, and individual pelvic floor muscles. I = internal anal sphincter; E = external anal sphincter; P = puborectalis muscle; L = levator ani muscles. Lines represent associations between complaints and subsites.

Anorectal dysfunction after prostate radiotherapy ● R. J. Smeenk *et al.*

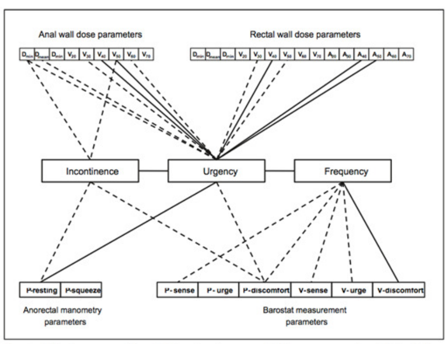


Fig. Associations between complaints and the investigated parameters. Solid lines represent p values <0.01; dashed lines represent p values 0.01–0.05. This figure summarizes the associations listed in Tables 2 and 3 with $p < 0.05$. In addition, anal D_{mean}, V_{20}, and V_{30} were associated with V-sense and V-urge (p values ranging from 0.02 to 0.05).

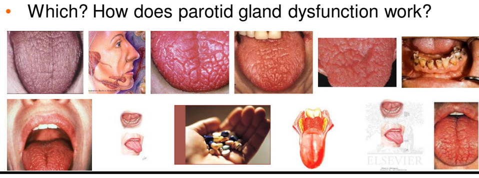
Organs are not homogeneous

Stem cell sparing radiotherapy for head and neck cancer to preserve salivary gland function

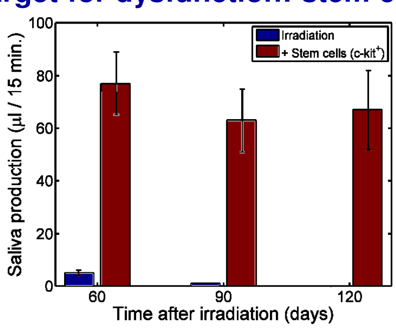
Peter van Luijk
Department of Radiation Oncology
University Medical Center Groningen / University of Groningen
Groningen
The Netherlands

Xerostomia (Dry mouth)

- World-wide, yearly 200,000 Head & Neck cancer patients treated with radiotherapy develop xerostomia
  - Reduced quality of life
  - High medical / societal cost
- Current approach: Minimize mean dose to parotid glands
- New, high-precision technology could spare substructures!
- Which? How does parotid gland dysfunction work?

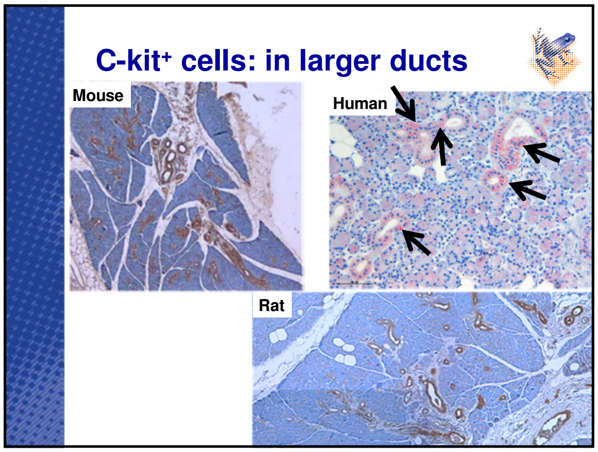


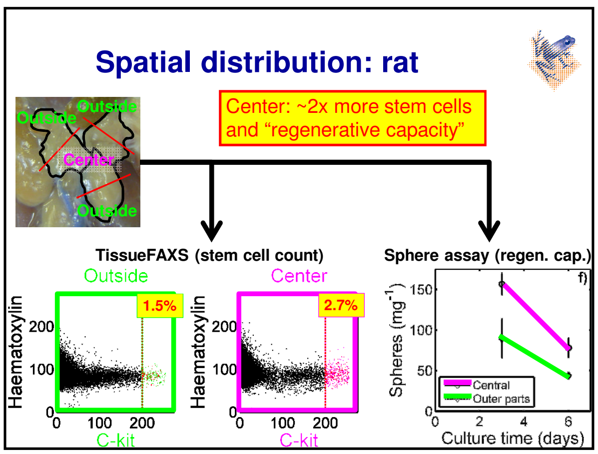
Target for dysfunction: stem cell

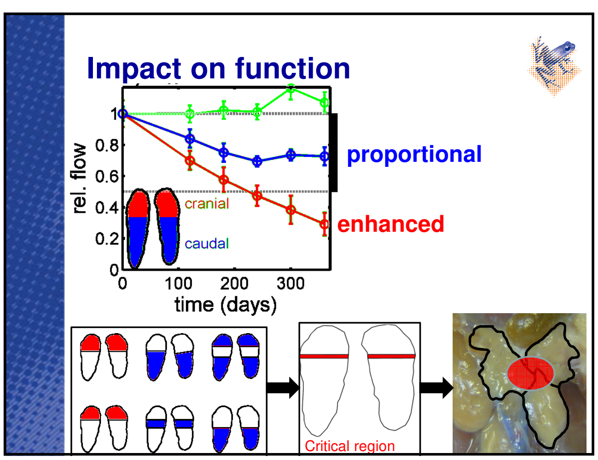


Stem cell transplantation rescues the gland function

Lombaert IM et al. PLoS One. 2008 Apr 30;3(4):e2063.

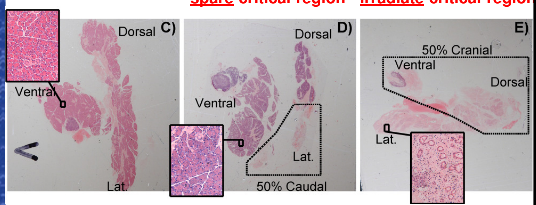

C-kit⁺ cells: in larger ducts
Mouse
Human
Rat


Spatial distribution: rat
Outside
Outside
Center
Outside
Center: ~2x more stem cells and "regenerative capacity"
TissueFAXS (stem cell count)
Outside
Center
1.5%
2.7%
Haematoxylin
C-kit
Sphere assay (regen. cap.)
Spheres (mg⁻¹)
Central
Outer parts
Culture time (days)


Impact on function
rel. flow
time (days)
cranial
caudal
proportional
enhanced
Critical region

Rat morphology

Control	50% Caudal **spare critical region**	50% Cranial **irradiate critical region**



Local damage irradiated tissue

Global degeneration entire gland

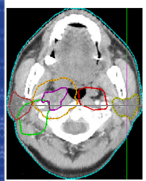
Interim conclusion

The parotid glands response to partial irradiation depends critically on dose to its stem cells, located in its major ducts.

Human gland

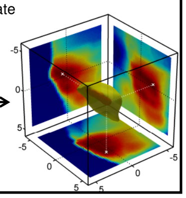
- Data: British Columbia Cancer Agency
  - 36 patients
  - Stimulated total saliva before / 1 yr post-treatment
  - 2 parotid glands
  - Pre-treatment flow >5 and <12 ml/min
- Critical region in the parotid gland, dose to which is most predictive of saliva production

Human gland



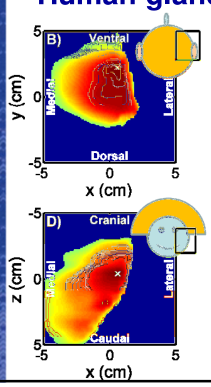
	Dose left	Dose right	Total flow
Pat 1			
Pat 2			
Etc…			

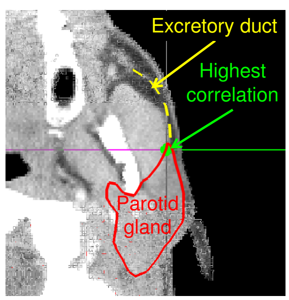
correlate



- Align glands by
  - Mirroring left → right
  - Match center of gravity
- Correlate point dose to outcome

Human gland





But is this correlation reflective of biological causation?

Drumroll, please…

CLINICAL INVESTIGATION — Prostate

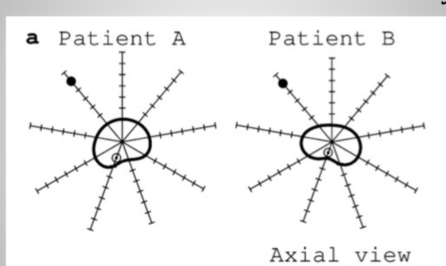
RELATING DOSE OUTSIDE THE PROSTATE WITH FREEDOM FROM FAILURE IN THE DUTCH TRIAL 68 GY VS. 78 GY

Marnix G. Witte, Ph.D.,* Wilma D. Heemsbergen, Ph.D.,* Román Bohoslavsky, M.Sc.,* Floris J. Pos, M.D., Ph.D.,* Abrahim Al-Mamgani, M.D.,† Joos V. Lebesque, M.D., Ph.D.,* and Marcel van Herk, Ph.D.*

*Department of Radiation Oncology, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; and †Department of Radiation Oncology, Erasmus Medical Center–Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

(IJROBP, 2010)

Prostate-specific grid used to overlay dose distributions on same anatomy



Dose outside the prostate ● M. G. Witte *et al.*

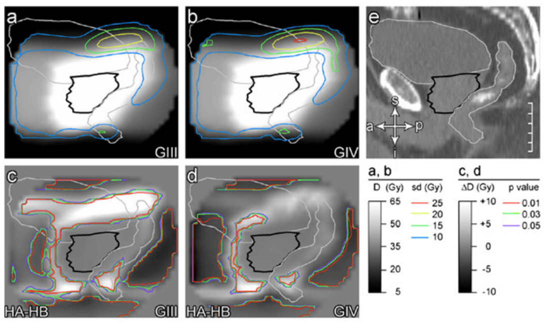


Fig. 1. (a, b) The average planned dose over the patients of both hospitals in group III (a) and group IV (b), mapped onto the anatomy of a representative patient in sagittal view (e). Colored contours indicate the standard deviation of the dose. The mapping was based on delineated prostate contours (black line). (c, d) The difference in average dose between hospitals A and B for treatment groups III and IV. Colored contours indicate the *p* values acquired by performing a *t*-test in every point.

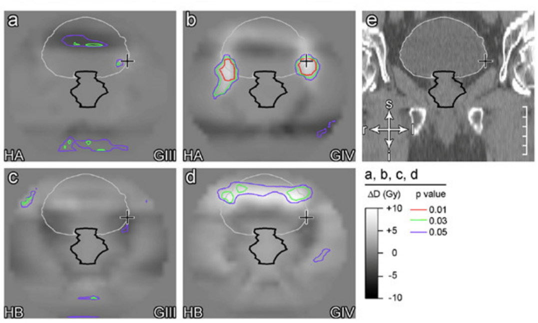


Fig. 2. Dose difference maps for failure around the prostate, per hospital (a, b: hospital A; c, d: hospital B) and per treatment group (a, c: group III; b, d: group IV) in coronal view.

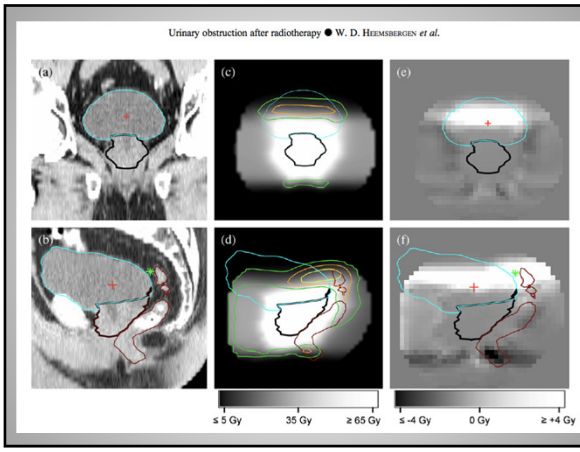
CLINICAL INVESTIGATION **Prostate**

URINARY OBSTRUCTION IN PROSTATE CANCER PATIENTS FROM THE DUTCH TRIAL (68 GY VS. 78 GY): RELATIONSHIPS WITH LOCAL DOSE, ACUTE EFFECTS, AND BASELINE CHARACTERISTICS

Wilma D. Heemsbergen, Ph.D.,* Abrahim Al-Mamgani, M.D.,† Marnix G. Witte, Ph.D.,* Marcel van Herk, Ph.D.,* Floris J. Pos, M.D., Ph.D.,* and Joos V. Lebesque, M.D., Ph.D.*

*Department of Radiation Oncology, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; and †Department of Radiation Oncology, Erasmus Medical Center–Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

(IJROBP, 2010)



What if you don't know the important tissues?

Exploring the Spatial Correlation Between 3D Dose Distribution and Toxicity in Normal Tissue

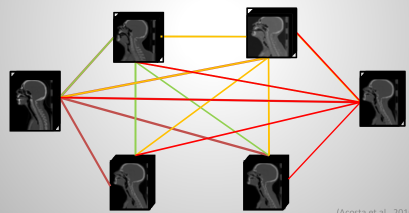
Ziad Saleh[1], Aditya Apte[1], Gregory Sharp[2], Shyam Rao[1], Nancy Lee[1], and Joseph Deasy[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY
[2]Massachusetts General Hospital, Boston, MA

AAPM 2012, Charlotte, NC

Methodology using full 3D dose

- Deform CT scans, dose distribution, and structures onto "reference patient"
- Perform dose-to-complication correlation, voxel-by-voxel, over entire anatomy

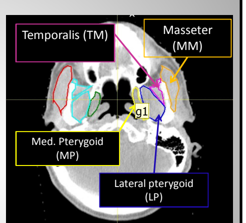


(Acosta et al., 2010; Witte et al., 2010)

Materials

- 37 patients with head and neck cancer with **right**-sided tumor
- Patients were treated with definitive IMRT and prescription dose of 70 Gy
- Complication endpoint: **Trismus**
  - 12 patients (Grade >= 1)

"The lack of ability to open the mouth fully due to a decrease in the range of motion of the **muscles of mastication**," as defined by NCI (CTCAE 4.0).

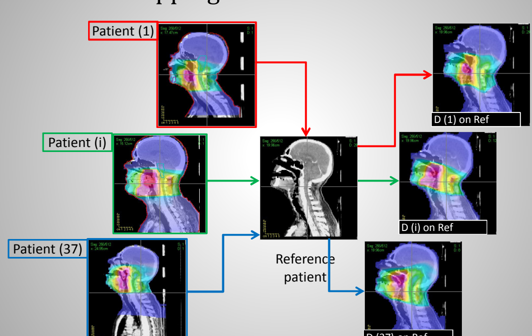


Mastication muscles

1. Masseter
2. Temporalis
3. Lateral pterygoid
4. Medial pterygoid

Bensadoun et al. "A systematic review of trismus induced by cancer therapies in head and neck cancer patients", 2010)

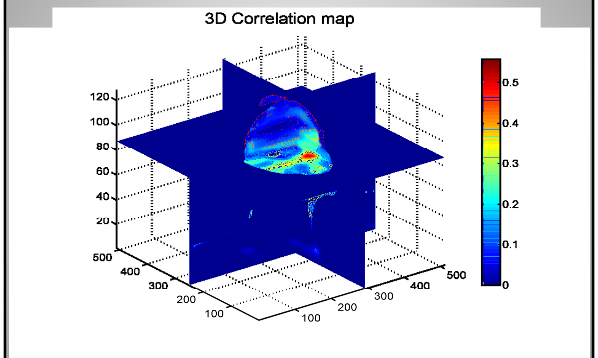
Dose mapping onto "Reference Patient"



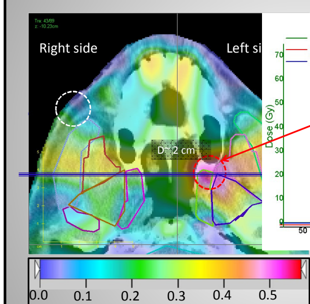
Slide 53

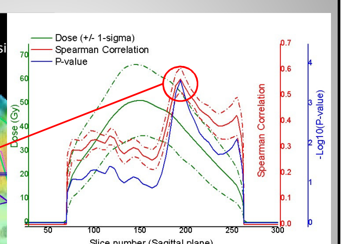
g1 Use lowercase "p" in "Med. pterygoid" to match the other labels.
georges, 7/23/2012

Dose-to-complication 3D correlation map



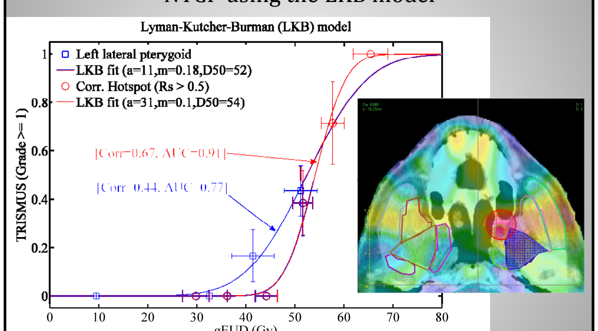
Dose-to-complication correlation "hot spot"





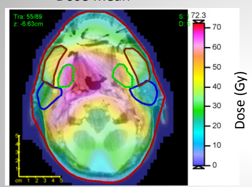
and needs to be validated.

NTCP using the LKB model

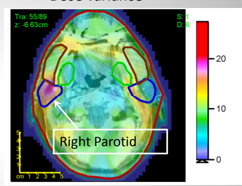


Patient cohort dose characteristics {37 Pts}

Dose mean



Dose variance



Higher dose is received on the right side as expected, since all patients had tumors on the right side.

The square root of the dose variance shows the effect of sparing of the right parotid gland.

Interim conclusions

- Applying this method to a patient cohort of 37 H&N patients, we identified a region of high correlation with trismus. However, the clinical implication of this region needs to be validated.
- Does this point have biological vs. physical significance? We are testing that with more patients.
- Even if it is not of fundamental biological signficance (i.e., 'the critical structure'), the analysis indicates aspects of treatment likely to affect trismus. -> might lead to rules that can lead to reduced toxicity.

But is the crucial deformable image registration algorithm step accurate?

Slide 58

---

g2 Insert comma: "expected, since"
georges, 7/23/2012

g3 Insert "s" after "tumor"
georges, 7/23/2012

Memorial Sloan-Kettering Cancer Center

A New Automatically Generated Metric for Evaluating the Spatial Precision of Deformable Image Registration: Distance Discordance

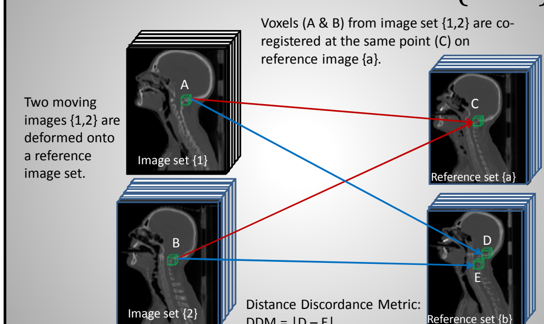
Ziad H. Saleh[1], Aditya P. Apte[1], Gregory C. Sharp[2], and Joseph O. Deasy[1]
[1]Memorial Sloan Kettering Cancer Center, New York, NY
[2]Massachusetts General Hospital, Boston, MA

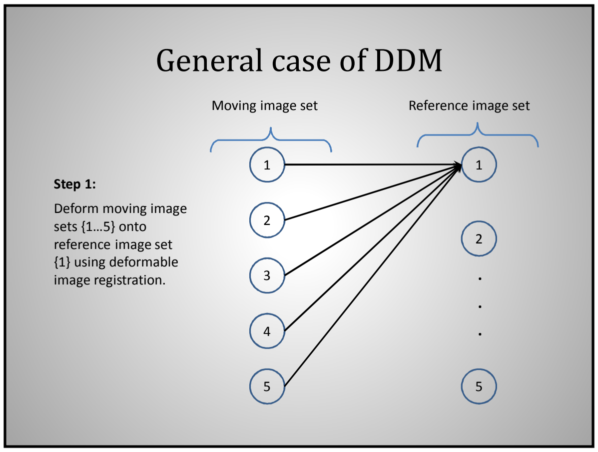
AAPM 2012, Charlotte, NC

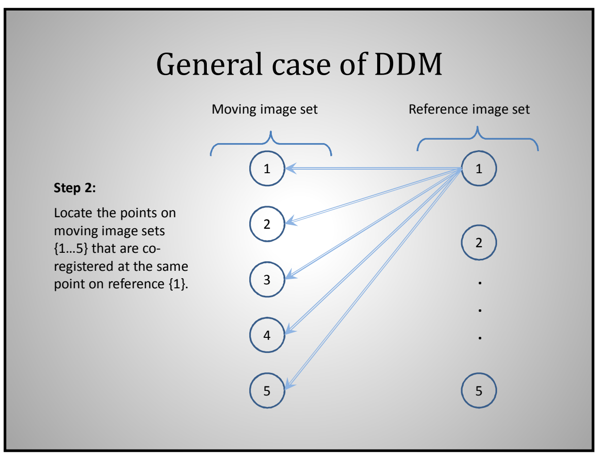
Motivation and goals

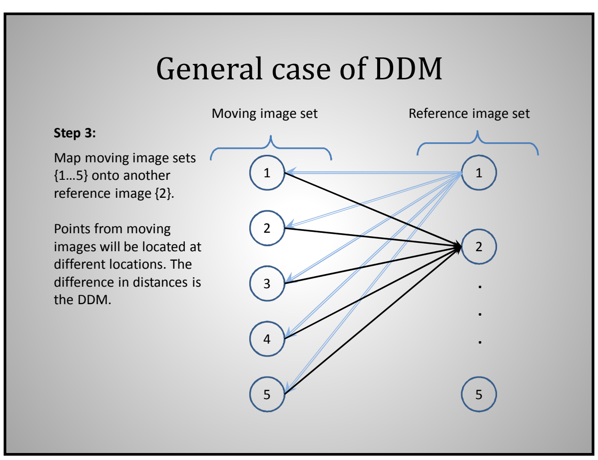
- Uncertainties in deformable image registration can be attributed to the lack of features in homogenous medium or misaligned edges in heterogeneous regions.
- Under some circumstances, these uncertainties become a significant source of error in dose mapping, especially in regions of high-dose gradient.
- We propose a resampling method to quantify uncertainties in deformable image registration based on reproducibility, rather than absolute error.

Distance Discordance Metric (DDM)



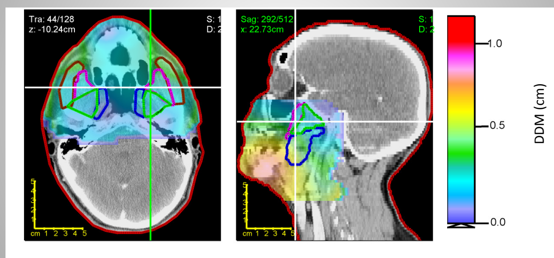

General case of DDM
Moving image set
Reference image set
Step 1:
Deform moving image sets {1…5} onto reference image set {1} using deformable image registration.
1
2
3
4
5
1
2
5


General case of DDM
Moving image set
Reference image set
Step 2:
Locate the points on moving image sets {1…5} that are co-registered at the same point on reference {1}.
1
2
3
4
5
1
2
5


General case of DDM
Moving image set
Reference image set
Step 3:
Map moving image sets {1…5} onto another reference image {2}.
Points from moving images will be located at different locations. The difference in distances is the DDM.
1
2
3
4
5
1
2
5

Distance discordance map: head and neck patients

Ref. Pt {1} → Mov. Pt {2…7} → Ref. Pt {2…7}



Interim conclusions

- We proposed a new metric called "Distance Discordance," which is based on a resampling technique to quantify the uncertainties in deformable image registration.
- This metric provides a tool to evaluate the performance of different deformation algorithms on multiple image sets.
- Utilizing the distance discordance histogram parameters, certain images or sub-volumes can be excluded from an image set.
- This method requires the generation of inverse transformations, which can be computationally expensive and time consuming.

Beyond the DVH: where are we going?

- Full dose-deformed analyses to reference anatomies
  - Always informative
  - Not always definitive
- Methods to spatially quantify deformable image registration accuracy will be crucial
- Potential applications:
  - Intra-organ sensitivity
  - Identifying critical organ sub-elements (heart, bronchii, arteries, lung)
  - Identifying unsuspected treatment aspects/unsuspected tissues, etc.