

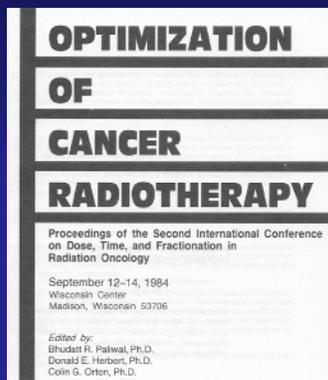
Radiobiological issues in intensity modulated radiation therapy

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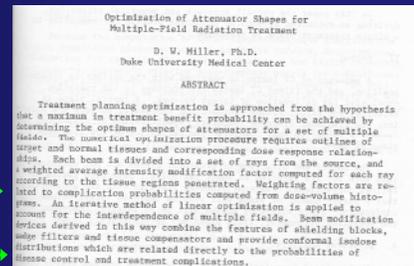
Acknowledgements

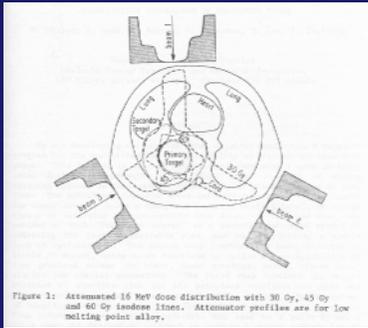
- Jack Fowler
- Avi Eisbruch
- Andy Beavis
- Allan Pollack
- Patricia Lindsay
- Computerized Medical Systems, Inc.
- NCI grants

20 yr. anniversary of first IMRT publication



...by Dan Miller





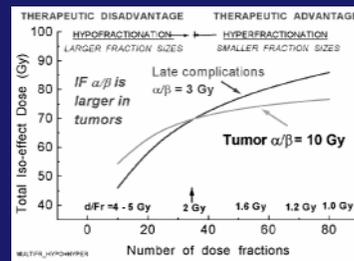
Outline [1/2]

- General issues
 - fractionation effects
 - dose-rate effects
 - dose-response
 - tumors
 - hot/cold spots
 - normal tissues
 - dose response: mean dose, max dose, ...?
 - challenges
 - » data uncertainties
 - » *terra incognita*
 - modeling vs. dose metrics
 - Tradeoffs in IMRT/P

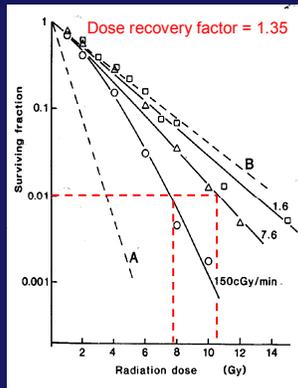
Outline [2/2]

- Site-specific issues
 - Prostate
 - targets
 - CTV vs. GTV
 - target motion
 - complication endpoints
 - rectal bleeding
 - data vs. models, predictions
 - Treatment planning issues
 - H&N
 - post-op vs. gross disease
 - targets
 - gross disease
 - lymphatics
 - complications endpoints
 - parotid glands
 - Treatment planning issues
- Use of biological imaging to guide IMRT?

Slowly proliferating tissues have greater repair capacity, and are more sensitive to fx size than tumors



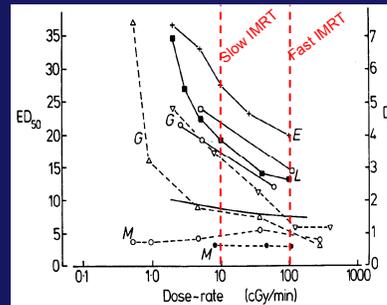
Isoeffect lines (normalized at 2 Gy fractions): more and smaller fractions increases the therapeutic ratio.



Dose-rate effect for a human melanoma cell-line. (From Steel, 1993)

Dose repair effects between 1 Gy/min (fast IMRT) and 0.1 Gy/min (slow IMRT) may be significant.

The dose-rate effect in normal tissues of the mouse



The dose-rate effect may reduce the effectiveness of 2 Gy doses given over 10-15 min, compared to 2 Gy in 1 minute.

Caveat: mouse dose-rate effects are known to be greater than the human dose-rate effect.

Dashed lines refer to r.h. scale -----

← Solid lines refer to l.h. scale

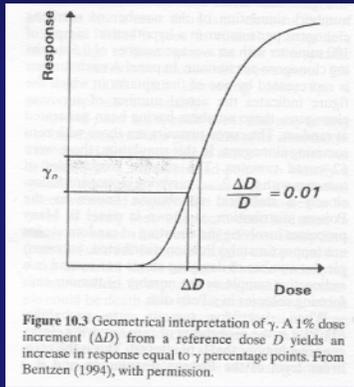
(From Steel (1993))

Radiation biology principles: what is a tumor?

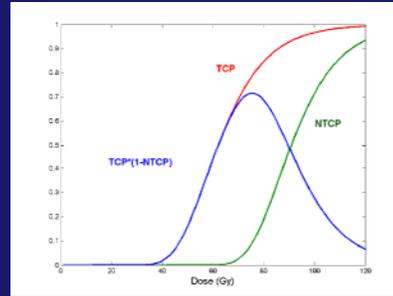
- Tumors are masses of malignant (and 20-50% normal) cells; typically 10^8 cells or more.
- All 'clonogenic' tumor cells must be killed, either directly or indirectly (e.g., nutrient starvation) in order to local control to be achieved. Local control is the usual goal of radiation therapy.
- Local control does not necessarily translate to survival (e.g., there may already be distant metastatic cells which are viable).

Radiation biology principles: cell kill

- 2 Gy will kill about half the cells, for any given fraction. That is, a surviving cell is thought to be about as viable as an unirradiated cell.
- Normal tissue cells recover better from fractionated radiation than tumor cells, for reasons which are still incompletely known.
- Hence: Probability of cell survival = $\exp(-\alpha d)$.



Goal: high TCP at low NTCP



The mathematics of curing a tumor: a simplified TCP model

$$\begin{aligned} \text{TCP} &= (1 - \text{prob. of survival})^{\text{no. clonogens}} \\ &= (1 - \exp(-\alpha \text{ dose}))^N \\ &\approx (1 - N \exp(-\alpha \text{ dose})) \\ &\approx \exp(-N \exp(-\alpha \text{ dose})) \end{aligned}$$

α is the radiosensitivity parameter and is cell-line dependent.

A TCP model for nonuniform dose distributions

$$\begin{aligned} \text{TCP} &= \prod_{i=1}^{M \text{ Voxels}} \text{VCP}, \quad (\text{VCP} = \text{voxel control prob.}) \\ &= \prod_{i=1}^{M \text{ Voxels}} \exp(-N/M \exp(-\alpha \text{ voxel_dose})) \end{aligned}$$

So a low control probability for any voxel means a low overall probability of control.

(Goitein, Webb and Nahum)

TCP model caveats

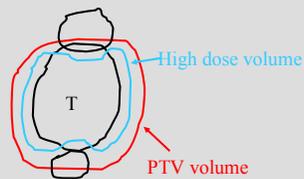
- Tumor regression during therapy is common, except for slow growing disease (e.g., breast or prostate cancer). This makes direct application of mechanistic models problematic (until better intra-treatment imaging!).
- Inter-patient heterogeneity in tumor cell radiosensitivity, hypoxia, numbers of clonogens, and rate of clonogen reproduction makes models less predictive for a particular patient than they otherwise could be.

Tumor dose-distributions: what dose distributions maximize local control?

- All clonogens must be sterilized, including those right out to the periphery of the Gross tumor volume (GTV)!
- Even small cold spots can be catastrophic, as the density of clonogens may be as high as 10^8 clonogens/cm³!
- But normal tissues constrain the tumor dose.
- The advantage of IMRT with respect to tumor dose distributions: *the target volume which must be constrained to a reduced dose can be minimized*. Dose is sculpted near the constraining normal structure.

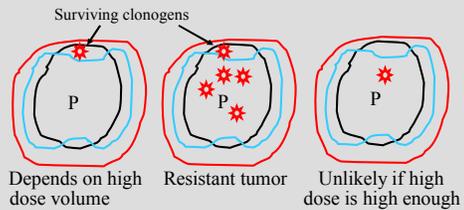
Dose heterogeneity: a commonplace with IMRT (1/2)

Small under-dosage regions, if required to reduce normal tissue toxicity, do not destroy the benefit of conformal high tumor doses (Deasy, 1996, Goitein *et al.*, 1997).

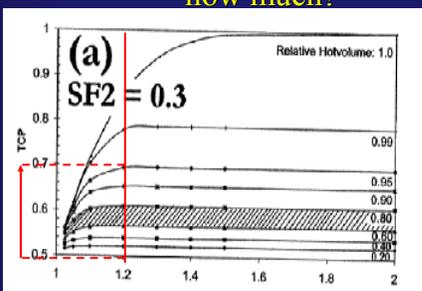


Dose heterogeneity: not always a bad thing (2/2)

How can treatment fail?



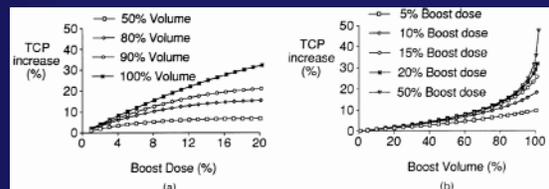
Boosting tumor sub-volumes: how much?



SF2 = surviving fraction after 2 Gy

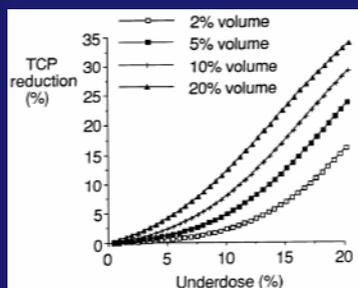
From Tome and Fowler (2000) IJROBP.

A boost of 20% achieves most of the benefit unless the cold volume is very small (<1%) (Deasy, 1997)

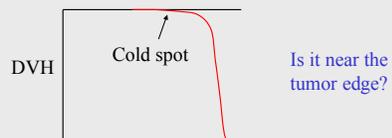


From Goitein et al. (1986)

The effect of cold regions: idealized uniform tumor



The effect of PTV cold-spots: ?



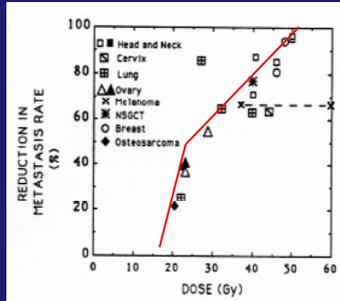
The effect on local control is uncertain due to:

- tumor regression
- positional uncertainties
- margin (GTV to PTV)
- D95 often used, but without critical justification

Middle of the GTV is worse than PTV edge!

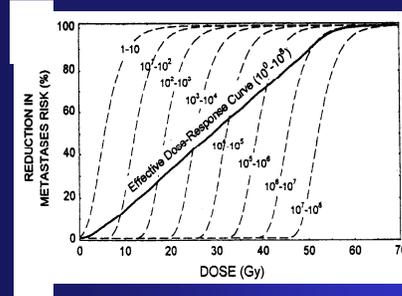
Dose-response curve for sub-clinical disease (rationale for CTV!)

My curve



From Withers, Peters, and Taylor (1995) IJROBP.

Dose-response curve for sub-clinical disease



Even low doses can be effective in eradicating subclinical disease, in proportion to the dose delivered.

(From Withers and Suwinski (1998))

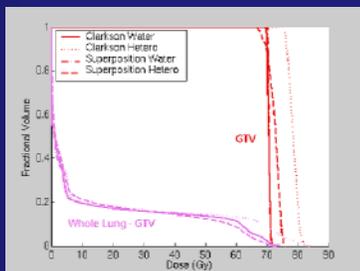
Sub-clinical disease

- Doses which must be reduced due to normal tissue tolerance are expected to still reduce metastatic disease, in proportion to the local dose value, with complete sterilization at about 55-60 Gy (2 Gy fx).
- IMRT can be used, if needed, to conform regional irradiation to avoid normal tissue structures (Mundt@U-Chicago, Pollack@FCCC).
- Overall delivery time of the regional field: should be delivered as fast as possible consistent with normal tissue toxicity. Micrometastases grow exponentially during therapy (Withers and Suwinski, 1998) and therefore should be treated *as soon as possible*. Sometimes integrated with single dose pattern for all Fx's.

Obstacles to acquiring normal tissue dose-response data

1. Positional uncertainties
2. Dose accuracy
3. Not enough data
4. Data not varied enough
5. Old dose distributions not like new IMRT dose distributions
6. Don't know how to (best) model the response

Dose accuracy example: a bad lung heterogeneity correction is worse than none at all



(Patricia Lindsay, Deasy et al.)

Prostate setup variations



PTV prescribed with 1st day CT

Organ motion detected on first 5 days (Beaumont Hospital)

Dose response

- Data is improving, but currently not 'authoritative'
- Tissues may be roughly divided into those whose response correlates to:
 - volume above a dose threshold (spinal cord, esophagus, small bowel, rectum)
 - mean dose (brain, lung, parotid glands, PTV)
 - min dose (tumor itself)

Correlation is not prediction!

- Typically, many parts of the DVH are correlated with each other, due to
 - Construction of the DVH
 - Similarity of single-institution patient treatments
- Therefore it is difficult to determine authoritatively which parts of the DVH are important, and with what relative weight

Prediction is not correlation!

- If the state of previous plans was mathematically ‘under-described’ (say by a single point on a DVH curve), then the resulting DVH may not look like the original dataset.
- A potential problem with all simple dose descriptors: max, mean, min, V20, etc....
- Less of a problem with NTCP and TCP models...if they work!

The concept of equivalent uniform dose (EUD)

- Generalized EUD Formulated by Niemierko (Niemierko 1999), denoted EUD_a
- The concept of EUD, and of Brahme’s earlier *Deff* definition (Brahme 1984), is to find that dose which, if given uniformly, would give the same tumor control probability (TCP) or normal tissue control probability (NTCP).
- A revised definition of *Deff* aims to include tumor or normal tissue radiosensitivity heterogeneity (Mavroidis, Lind and Brahme 2001).

EUD_a is a power-law average over the dose distribution:

$$EUD_a(d) = \left(\frac{1}{n} \sum_{i=1}^n d_i^a \right)^{1/a}$$

EUD_a is equivalent to the dose-volume histogram reduction scheme in the Lyman-Kutcher-Burman NTCP model: n in that model has the role of $1/a$ in EUD_a .

EUD_a behavior as a function of a

Abramowitz & Stegun (1964) call this the “generalized mean”

Several results relevant to understanding the behavior of EUD_a are given by Abramowitz (Abramowitz 1964):

1. As $a \rightarrow \infty$, $EUD_a(d)$ approaches the maximum of d .
2. As $a \rightarrow -\infty$, $EUD_a(d)$ approaches the minimum of d .
3. When $a = 1$, $EUD_a(d)$ equals the mean dose.
4. As $a \rightarrow 0$, $EUD_a(d)$ approaches the geometric mean of d_i :

$EUD_a \rightarrow \left(\prod_{i=1}^n d_i \right)^{1/n}$. Hence, when $a = 0$ and any voxel dose is zero, EUD is zero.

5. If any dose values are zero, and $a < 0$, then $EUD_a(d) = 0$.

How does GEUD behave as a is varied?

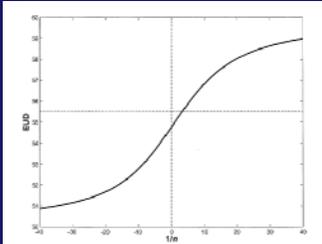


Fig. 1. The effect of variations in a on the equivalent uniform dose (EUD). EUD is plotted for a two-component dose distribution containing equivolume voxels at 50 Gy and 60 Gy. The entire region $1 < a < \infty$ is mapped into $0 < 1/a < 1$.

Two-bin dose distribution of doses 50 Gy and 60 Gy.
From Deasy (2000) IJROBP.

The IMRT treatment planning paradox

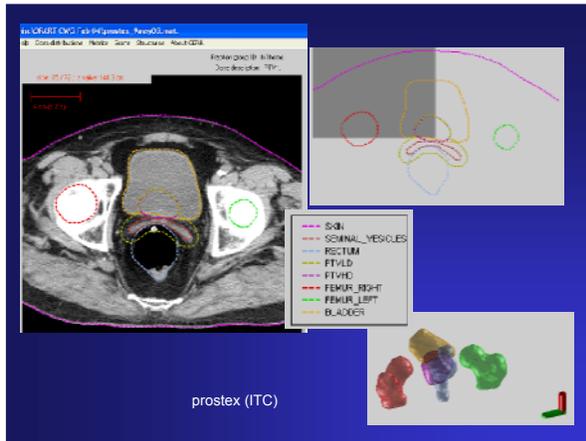
- Paradox: IMRT plans must be different from previous plans to show an improvement!
- But we can only use previous plans to guess what the effect is. So CRT data analysis may not be accurate for IMRT!
- The way out:
 - Population differences in previous treatments
 - General trends: modeling
 - Gathering and modeling a tremendous amount of IMRT data...

The radiobiology of prostate IMRT

- Prostate
 - targets
 - CTV vs. GTV
 - target motion
 - complication endpoints
 - rectal bleeding
 - data vs. models, predictions
 - Treatment planning issues

Radiobiological issues in prostate IMRT

- Target endpoints
 - local control (usually biochemical surrogate)
 - targeting
 - dose-response/dose-correlates
 - role of hypoxia
 - regional control (lymph node irradiation)
 - more difficult treatment planning!



What is the PTV?

- Usually the entire prostate plus a margin for geometrical variation between fxs.
- The margin may be reduced in the anterior-rectal region (MSKCC).
- Therefore much of the PTV does not contain cancer cells.

Prostate PTV determined by repeat CTs

PTV prescribed with 1st day CT

Organ motion detected on first 5 days
(Beaumont Hospital)

The High Risk Patient: lymph node irradiation

(courtesy Allan Pollack, FCCC) 4/23/04

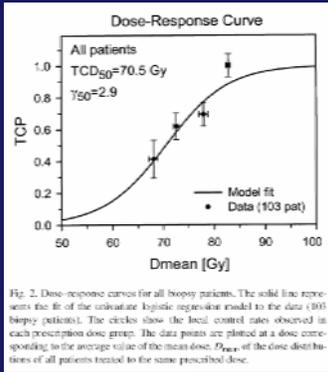
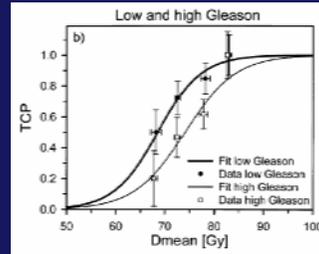


Fig. 2. Dose-response curves for all biopsy patients. The solid line represents the fit of the univariate logistic regression model to the data (103 biopsy patients). The circles show the local control rates observed in each prescription dose group. The data points are plotted at a dose corresponding to the average value of the mean dose, D_{mean} , of the dose distributions of all patients treated to the same prescribed dose.

(Levegrun et al., Rad Onc, 63 (2002))

Dmean = mean of PTV dose

1 std. dev. error bars

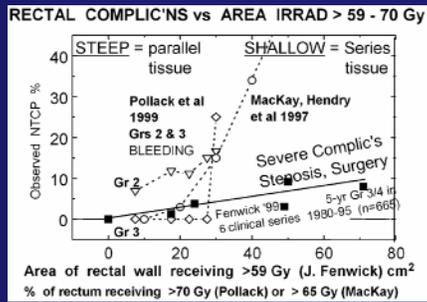


Mean dose does as well as or better than any dose metric tested. (Levegrun et al., IJROBP 47 (2000))

Gleason score ≤ 6 vs. > 6

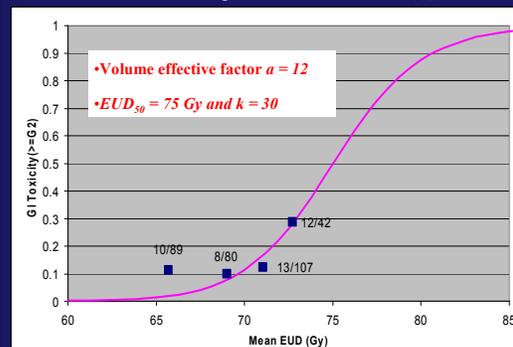
(Levegrun et al., Rad Onc, 63 (2002))

The endpoint can change based on dose distribution characteristics: Rectal stenosis common in pre-RT era, uncommon post CRT and RT (rectal bleeding).



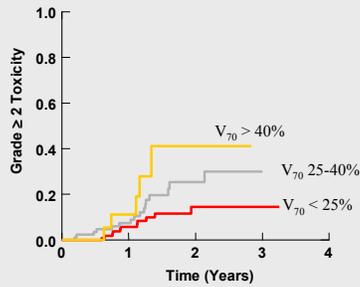
(courtesy Jack Fowler)

Rectum Dose Response (Chronic Toxicity $\geq G2$)

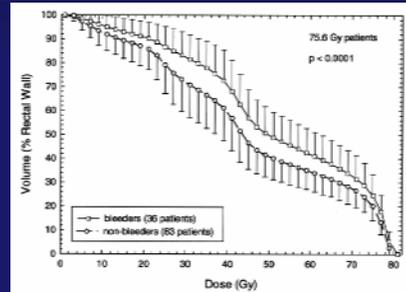


(courtesy Beaumont Hospital)

Chronic Rectal Toxicity Rectal Wall V70

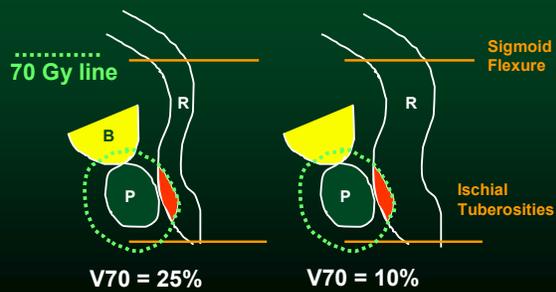


(courtesy Beaumont Hospital)



Late rectal bleeding from external beam radiotherapy treatment to 75.6 Gy, as reported by Jackson et al (2001). Average DVHs for patients with late rectal bleeding (squares) and without late rectal bleeding (circles) are shown. Bars show the standard deviation of the corresponding DVHs at each dose point. The p-value is with respect to the null hypothesis that bleeders and non-bleeders have the same distribution of DVH shapes. This curve illustrates the difficulty of choosing a dose threshold below which volume irradiated does not matter.

Filling Effects on Rectal DVH Parameters: Sim With Rectum Empty



(FCCC) 4/23/04

Planning Constraints

- PTV Constraints
 - » Absolute: DVH, PTV Min PTV Max
 - » Effective: Prescription isodose coverage
- Normal Tissue DVH Constraints
- Normal Tissue Dose Gradient Constraints
 - » Examine transverse cuts
 - » 100%, 90%, and 50% lines

(FCCC) 4/23/04

DVH Planning

- Prostate
 - » Based on PTV
 - ❖ Considers uncertainties
- Rectum and Bladder
 - » Based on planning CT outline
 - ❖ Does not consider uncertainties

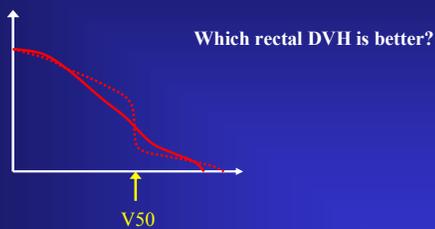
(FCCC) 4/23/04

Normal Tissue DVH Criteria

- Rectum
 - » $\leq 17\%$ to ≥ 65 Gy
 - » $\leq 35\%$ to ≥ 40 Gy
- Bladder
 - » $\leq 25\%$ to ≥ 65 Gy
 - » $\leq 50\%$ to ≥ 40 Gy

(FCCC) 4/23/04

The problem with a single DVH point



Big problem when single DVH pts used for optimization: pinned DVH

Penile Bulb/Cavernosal Bodies Constraints?

- Possible reduction in impotence
 - » Pickett: D95 > 14 Gy
- Reduces margin on prostate apex
 - » Possible increase in failure rates
- Now routinely outlined at FCCC
 - » Best viewed on MRI
 - » No routine constraints off protocol
 - » Randomized trial in progress

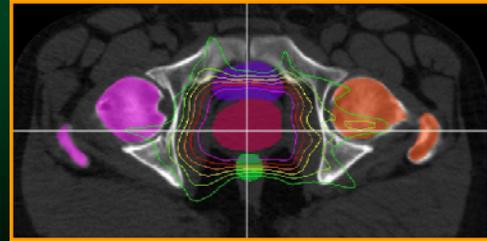
(FCCC) 4/23/04

Normal Tissue Dose Gradient Constraints

- Sharp dose fall-off desired
 - » Check slice by slice
- 90% line < half rectal width
- 50% line < full rectal width

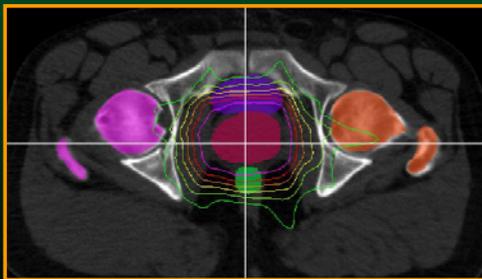
(FCCC) 4/23/04

Normal Tissue Dose Gradient: Acceptable



(FCCC) 4/23/04

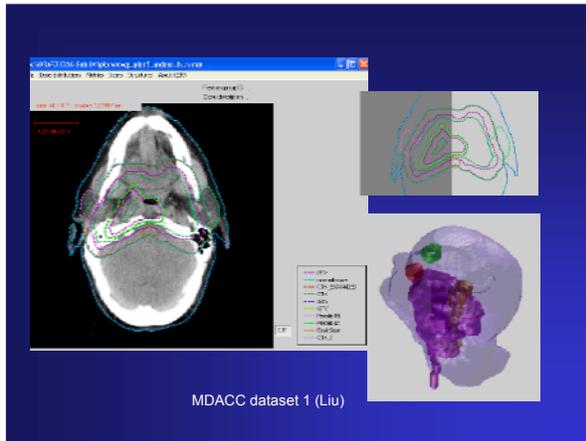
Normal Tissue Dose Gradient: Unacceptable



(FCCC) 4/23/04

Radiobiological issues: H&N

- Complex dose distribution (hard-to-avoid tradeoffs between target, normal tissues)
- Avoiding xerostomia (parotid salivary gland damage)



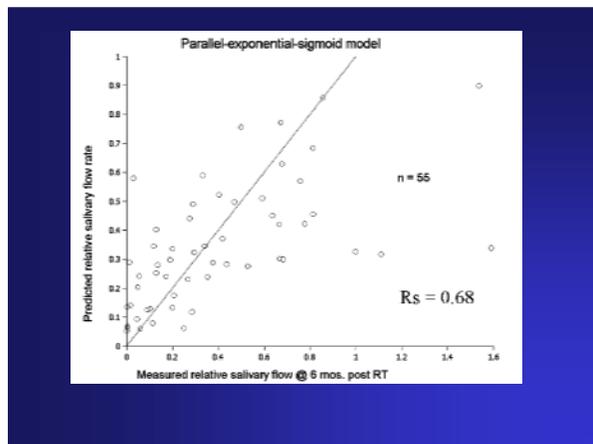
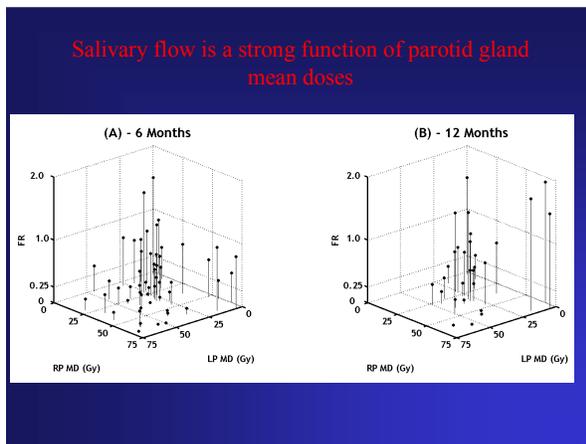
CLINICAL INVESTIGATION **Head and Neck**

A PROSPECTIVE STUDY OF SALIVARY FUNCTION SPARING IN PATIENTS WITH HEAD-AND-NECK CANCERS RECEIVING INTENSITY-MODULATED OR THREE-DIMENSIONAL RADIATION THERAPY: INITIAL RESULTS

K. S. CLIFFORD CHAO, M.D., JOSEPH O. DEASY, Ph.D., JERRY MAREKMAN, D.Sc., JOYCE HAYNIE, R.N., CARLOS A. PEREZ, M.D., JAMES A. PURDY, Ph.D., AND DANIEL A. LOW, Ph.D.

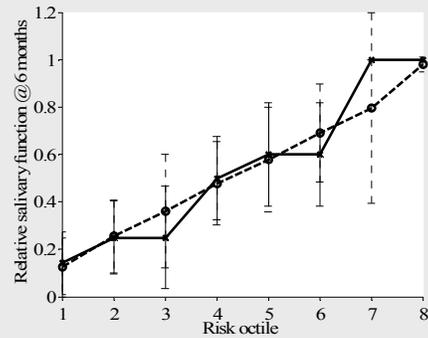
(IJROBP, 2002)

- Xerostomia ('dry mouth') primarily due to parotid gland irradiation
- Xerostomia often defined as relative salivary flow capacity less than 25% pretreatment
- We collected pre- and post-RT stimulated salivary flow measurements



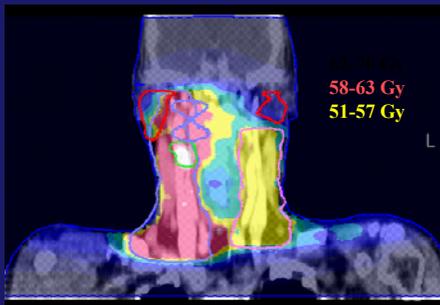
Avoiding xerostomia

- Reducing mean dose to either parotid below 20-25 Gy greatly reduces the risk of xerostomia.
- Further mean dose reductions increase gland functionality.



Logistic factors: dose-volume model, gender, and age.

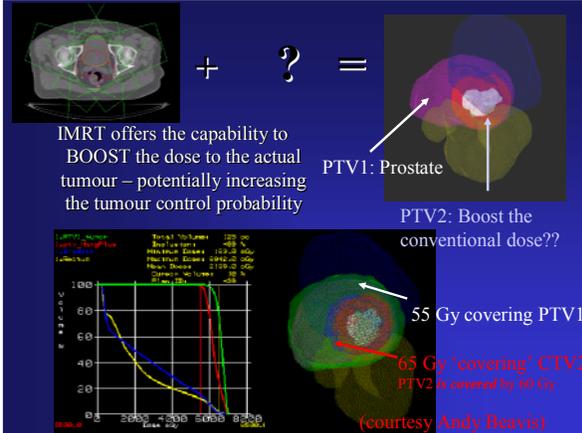
Implications for parotid gland sparing



(courtesy Eisbruch et al.)

Biological targeting

- Meaning of PET or MRSI image volumes unclear, except...as another means of determining what should receive a 'high' dose
- FDG: increased glycolysis correlates both with proliferation and hypoxia (Pugachev et al., this meeting). Overall radiobiological meaning unclear.
- Hypoxia vs. proliferation
 - Both are bad
 - Which is worse?



IMRT offers the capability to BOOST the dose to the actual tumour – potentially increasing the tumour control probability

PTV1: Prostate

PTV2: Boost the conventional dose??

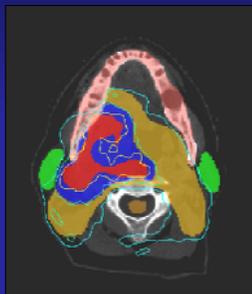
55 Gy covering PTV1

65 Gy covering GTV2 PTV2 is covered by IMRT

(courtesy Andy Dawson)

⁶⁰Cu-ATSM (Hypoxia) - Guided IMRT

- 80 Gy in 35 fractions to the hypoxic tumor sub-volume as judged by Cu-ATSM PET (red)
- GTV (blue) simultaneously receives 70 Gy in 35 fractions
- Clinical target volume (yellow) receives 60 Gy
- More than half of the parotid glands (green) are spared to less than 30 Gy.



Chao *et al.* IJROBP 4: 1171-82, 2001

Gains From IMRT

- Dose escalation
- Normal tissue conformal avoidance
- Improved target coverage

(courtesy Allan Pollack)

Open radiobiological issues

- Evaluating PTV dose distributions
 - Interplay between cold-spot location/margin/setup accuracy should be explored.
- Value of partial-PTV boosting
- Ranking treatment plans
 - Using single DVH point has pitfalls, especially is optimization on single DVH point.
 - How many are needed?
 - Will more complicated models do better?
 - When is it that the difference between plans doesn't matter?

Summary

- Significant data available to estimate dose response for prostate disease
- Significant data available for ranking rectal treatment plans, if DVH is of 'conventional shape,' i.e., not *pinned* by DVH constraint point.
- Significant data and modeling available for estimating xerostomia risk