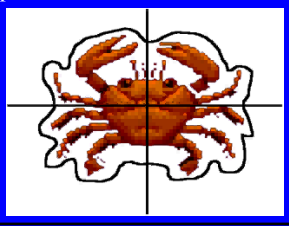
# Target definition (margin selection) for radiotherapy (IMRT)

James Balter, Ph.D.
University of Michigan
Department of Radiation Oncology



## DISCLAIMER

- Member, Scientific Advisory Board, Calypso Medical

## Issues of margin selection

- Key uncertainties exist in:
  - Defining tumor extent
  - Appreciating the range and impact of geometric variation

## Defining the Target

- Proper CTV definition remains one of the most open (target-rich?) research areas in conformal radiotherapy/IMRT
- Lots of tools (PET, MRI/S, CT,US,…), but little truth
- Proper consideration of patient models helps minimize error in GTV definition

## CTV definition references are scarce

**Most definitive summary:**

**Cancer / Radiotherapie Volume 5, Issue 5, Pages 471-719 (October 2001)**

**Volume tumoral macroscopique (GTV) et volume–cible anatomoclinique (CTV) en radiothérapie**
**G. Kantor[1], J. J. Mazeron[1], F. Mornex[1] and P. Maingon[1]**

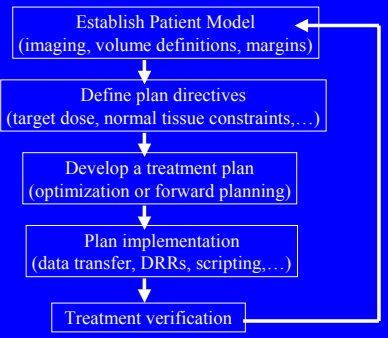
## One minor difficulty:

Ce numéro spécial de *Cancer/Radiothérapie* constitue une première mise au point francophone sur la définition du volume tumoral macroscopique (GTV) et du volume–cible anatomoclinique (CTV) pour les principales localisations tumorales prises en charge en radiothérapie externe et en curiethérapie. Les rapports ICRU 50 et plus récemment 62 individualisent d'une part les volumes qui relèvent de la maladie (GTV et CTV) . . . .

## CTV definition – a dynamic field

- Significant research effort in imaging will impact CTV definition
- To date, however, little is understood about combining information from PET, MRI, MRS,…
- Pathologists are always right!

## The "process" of radiotherapy




## Scope of the problem

- Proper patient setup remains an important element of the radiotherapy QA process
- Unrecognized positioning errors are a clear point of target coverage failure for conformal radiotherapy
- Excessive margins to ensure target coverage increase risk to normal tissues
- IMRT makes these problems more acute

## Patient models for optimization

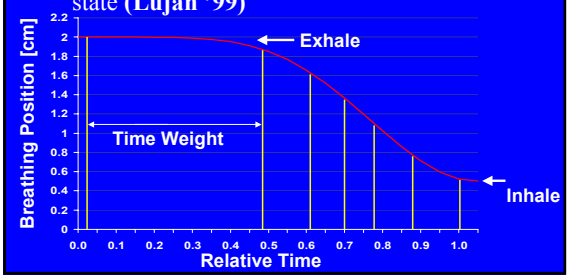
- Patient modeling and/or dose calculation during IMRT planning should consider the range of possible representations of the patient expected to be realized during treatment
- Treatment verification strategies that minimize and characterize residual movement help make this problem tractable

## Modeling the moving patient

- A single, free breathing CT scan may be a poor representation of the patient at any state
- Example model improvements:
  - Single (liver) breath-held CT at exhale, with margin for inhale
  - Inhale and exhale breath held scans with free breathing (20 mA) scan for DRR (lung)
  - ABC-aided CT scans
  - "slow" scanning – rotation times approximating a 4 second breathing cycle
  - "4D" CT

## Bias towards exhale (liver)

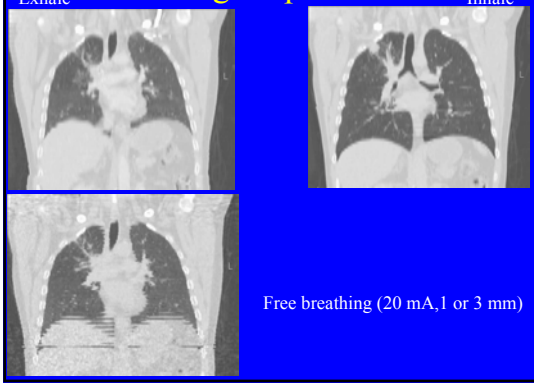
- Population-measured time course of breathing indicates more time spent near the the exhale state **(Lujan '99)**



## Lung "triple scan"

Exhale

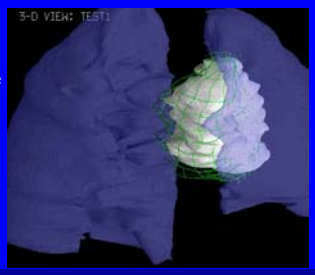
Inhale



Free breathing (20 mA,1 or 3 mm)

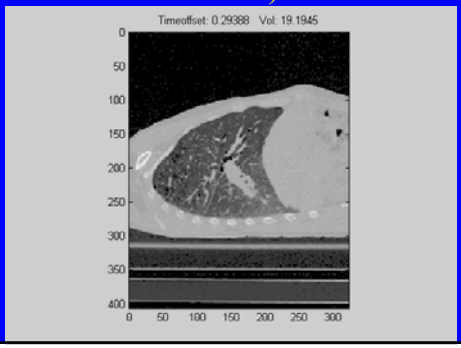
## Tumor definition

- "Moving GTV" constructed by compositing inhale, exhale GTV structures (with connection for space traversed if needed)
- Resulting target different from free-breathing CT and standard margins




Green – PTV from inhale,exhale
White – PTV from free-breathing CT + 1 cm

## 4D CT (movie from Dan Low, Wash. U.)

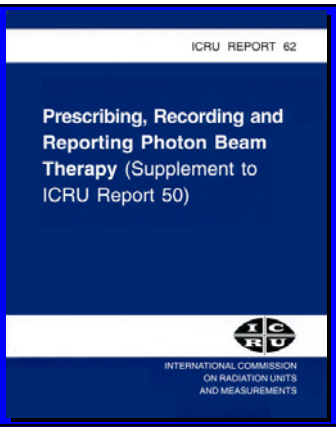



International Commission on Radiation Units and Measurements, Inc.

**ICRU Report 62: Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50)**

*André Wambersie (*) and Torsten Landberg (**)*

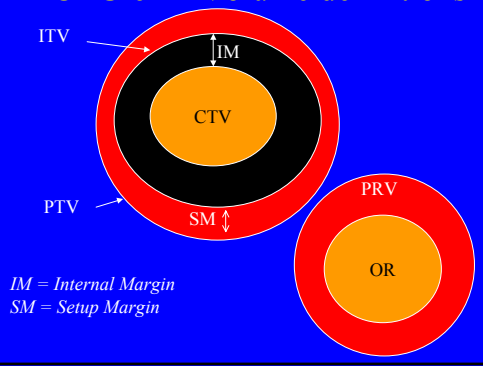
*(*) Université Catholique de Louvain, Cliniques Universitaires St-Luc, 1200 Brussels, Belgium*
*(**) Universitetssjukhuset, 205 02 Malmö, Sweden*




## ICRU 62 definitions

- GTV, CTV, PTV still exist
- New definitions
  - ITV (internal target volume) – expansion of CTV for internal (e.g. breathing) movement
  - OR (organ at risk)
  - PRV (planning organ at risk volume) – expansion of OR for movement (problematic!)

## ICRU 62 – Volume definitions




*IM = Internal Margin*
*SM = Setup Margin*

## How do we determine margins for internal movement?

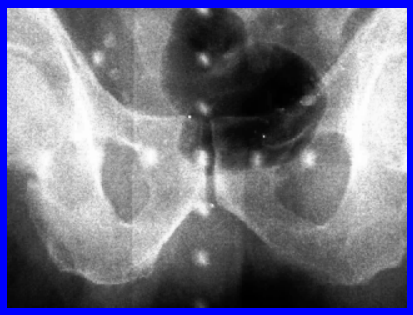
| | medio-lateral movement (mm) | cranio-caudal movement (mm) | dorso-ventral movement (mm) |
|---|---|---|---|
| maximum movement | 5 | 12 | 5 |
| average movement | 2.04 | 3.9 | 2.4 |
| standard deviation | 1.4 | 2.6 | 1.3 |

Range of movements (mm) of the CTV in relation to an internal fix-point (vertebral body) in 20 patients with lung cancer, studied fluoroscopically during normal respiration. (From Ekberg *et al.,* 1998.) (ICRU 62)

## Internal margins

- Movement of internal structures is most directly appreciated by serial (interfractional movement) or dynamic (intrafractional movement) imaging
- Techniques include MRI, fluoroscopy, "4D" CT
- Limited tools exist to date to aid in margin definition for internal movement

## Daily Images of a Prostate Patient Taken After Setup Via Skin Marks



## Influence of technology on setup verification

- Portal films – high dose and time-consuming, but provide increased information over skin marks
- EPIDs – improved image quality and reduced dose; availability of digital enhancement and alignment tools
- In-room diagnostic X-Ray and CT- improved target visualization

## The Hunting of the Snark (an agony in eight fits)

Lewis Carroll

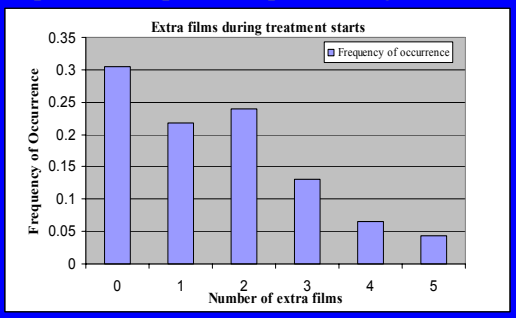
## The hunting of the ~~snark~~ skin mark
## (an agony in eight films)

(apologies to Mr. Carroll)

## Current standard of practice

- It is generally accepted that a weekly portal film/image serves to document proper setup
- What happens when a weekly image reflects a setup error?
  - Correct and re-image
    - Same fraction or next fraction?
    - Throw away the "bad" image?
    - How much does the patient benefit?

## Repeat films (patient repositioning - 1997)

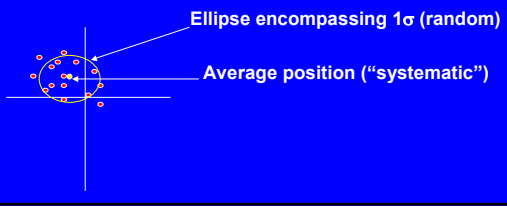



## The nature of position

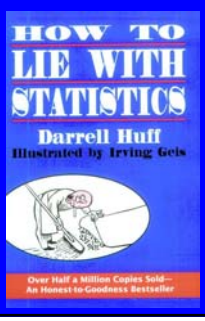
- Patient position about a single axis can be classified as a random variable
- There is generally an average "systematic" value and a random variation about this average

## Components of setup error

- "systematic" - the average offset of the target from the planned position
- random - the variation per setup about the average observed position




## Dutch reports: population systematic and random errors = 2-3 mm



## Sources of Systematic Error

- Systematic errors have been attributed to differences in table sag, laser calibration, and mechanical calibration between different rooms (CT, simulator, accelerator)
- Could the random variation of the patient also be a source of systematic error?

## Sampling Random Error As a Systematic Offset

- Position = average position + random component
- Each positioning (CT, sim,Vsim, treatment start, treatment) samples the random component
- The average error in observing the mean via a single sample is ~0.8 σ (using a simplistic model)
- Thus, systematic error includes the combination of random offset at CT and that at treatment start (average error of ~1.1 σ --> up to 7 mm for the body)

## Does systematic error persist?

Repeat filming after first treatment day:
1.4 sessions per patient
Repeat filming after two weeks of treatment:
0.98 sessions per patient
Patients that needed multiple films after first two weeks: 57%

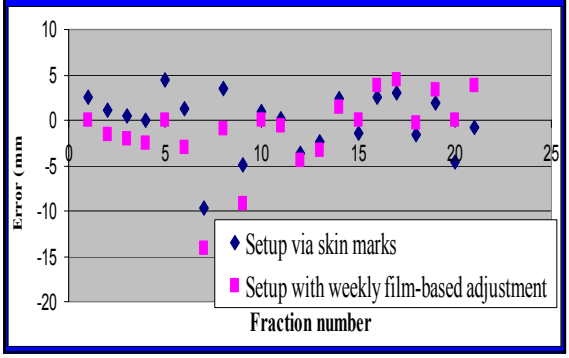
## Do we resolve systematic errors?

11 H/N patients
imaged daily
setup evaluated weekly using conventional means

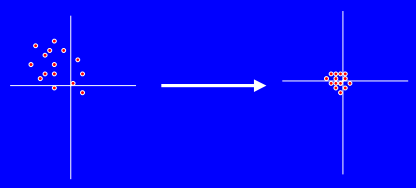
Setup errors in mm as population mean(σ):

| Type | AP | Lat | IS |
|---|---|---|---|
| Week1 syst | 2.2 (2.6) | 2.9 (3.4) | 2.6 (4.5) |
| Course syst | 2.1 (2.9) | 2.9 (3.4) | 2.2 (3.3) |
| Week1 rand | 1.5 (0.9) | 1.9 (1.0) | 1.8 (1.2) |
| Course rand | 2.1 (0.8) | 2.2 (0.6) | 2.6 (2.2) |

## Does weekly filming help?



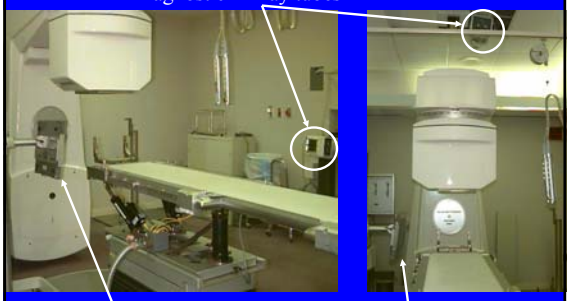

## Daily on-line repositioning



**Maximum effort required - all errors (above threshold) are corrected**
**High precision - setup limited by accuracy of measurement and repositioning systems**

## On-line Diagnostic Imaging and Computer-controlled Setup Adjustment

Diagnostic X-Ray tubes

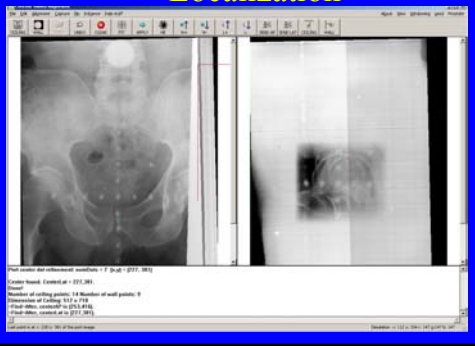


30x40 cm 127 μ pixel AMFPI (DPIX)

## On-line Diagnostic X-ray Setup Protocols

- 3D setup measurement and automated adjustment (prostate) via CCRS
- 2+D setup measurement and adjustment (liver) via active Breathing control (ABC) (manual setup adjustment)
- Both protocols accomplish setup, treatment, and post-setup evaluation with about 10 added minutes per fraction

## Automated Graticule Localization



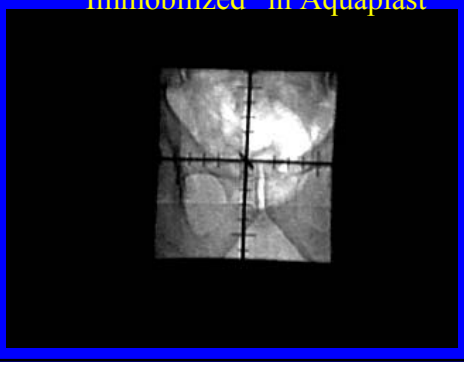
## Automated Prostate Localization

## Prone vs. Supine Positioning

| | Left – Right | | Anterior - Posterior | | Inferior Superior | |
|---|---|---|---|---|---|---|
| | ave | sd | ave | sd | ave | sd |
| Prone Initial | 0.42 | 4.5 | -0.68 | 6.6 | 0.67 | 6.1 |
| Prone Final | 0.39 | 2.2 | 0.69 | 3.0 | 0.61 | 2.7 |
| Supine Initial | 0.26 | 3.9 | -5.41 | 2.4 | 3.28 | 3.9 |
| Supine Final | -0.40 | 1.5 | -2.31 | 1.6 | 0.59 | 1.2 |

(Units of millimeters)

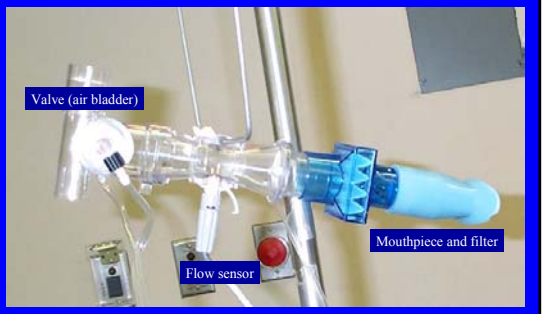
## Example Movie - Prone Patient "Immobilized" in Aquaplast



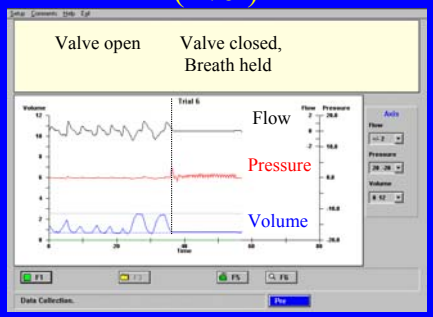
## Results - Cranial-caudal Marker Movement

| | Normal Breathing | Deep Breathing |
|---|---|---|
| supine - flat pad | < 1 mm | 2.0 - 7.3 mm |
| supine - false top | < 1 mm | 0.5 - 2.1 mm |
| prone - alpha cradle | 0.9 - 3.6 mm | 3.8 - 10.3 mm |
| prone aquaplast | 2.3 - 5.1 mm | 6.4 - 10.5 mm |

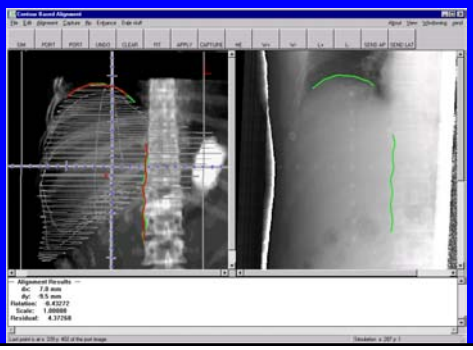
## ABC Device - Vmax




## Breath Hold at Normal Exhale (liver)




## ABC - In-room Image Alignment



## ABC Liver Trial - Results

| Patient | Initial $\sigma_{LR}$ | $\sigma_{IS}$ | $\sigma_{AP}$ | Final $\sigma_{LR}$ | $\sigma_{IS}$ | $\sigma_{AP}$ |
|---|---|---|---|---|---|---|
| 1 | 3.69 | 10.75 | 4.15 | 2.64 | 4.44 | 3.71 |
| 2 | 3.46 | 4.09 | 2.57 | 2.56 | 3.54 | 2.48 |
| 3 | 3.65 | 7.20 | 2.50 | 1.95 | 2.40 | 1.70 |
| 4 | 5.92 | 9.01 | 3.90 | 1.44 | 3.36 | 2.90 |
| 5 | 2.83 | 5.08 | 8.30 | 1.85 | 3.03 | 2.30 |
| 6 | 2.53 | 5.79 | 2.80 | 2.89 | 3.73 | 1.70 |
| 7 | 4.59 | 5.27 | 3.70 | 1.59 | 2.48 | 2.10 |
| 8 | 5.66 | 6.34 | 2.10 | 1.68 | 4.66 | 1.70 |
| $\sigma_{avg}$ (mm) | **4.04** | **6.69** | **3.75** | **2.07** | **3.45** | **2.32** |

## *Diaphragm-Radiograph Analysis*

Reproducibility of liver position relative to skeleton in cranial-caudal direction.

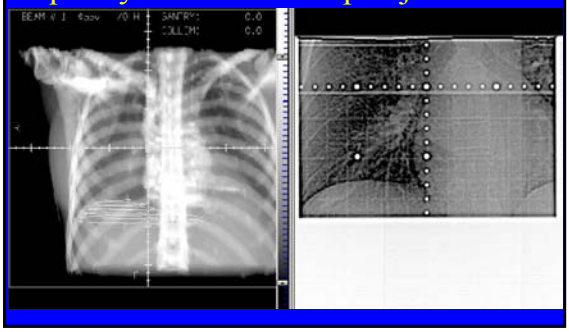
| | Ave. σ | Range of σ |
|---|---|---|
| Intra-fraction | 2.5 mm | 1.8 - 3.7 mm |
| Inter-fraction | 4.4 mm | 3.0 - 6.1 mm |

ABC IMMOBILIZES, but does not POSITION!

## GATING – a word of caution

- The relationship between external markers and the tumor is inferred
- Investigators (Ford, Mageras, Vedam, Murphy) have demonstrated phase shifts between external signals and internal movement
- Some form of image-based verification is essential for gated radiotherapy

## Modern EPIDS have sufficient quality for online setup adjustment



## What is the true benefit of daily online adjustment?

- Van Herk determined population based margins:

  margin required $\cong$ **2.5 Σ + 0.7 σ**

  Σ – population modeled systematic error

  σ – population modeled random error

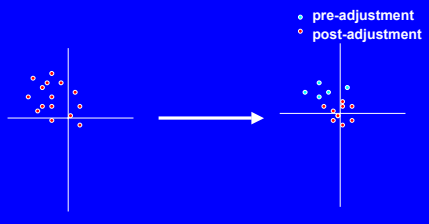
Systematic error influences margin far more than random variations

Studies by other investigators support this general finding

## What is the benefit of online daily repositioning?

- Except in cases of individuals with very large random variations or close proximity to critical structures, the majority of benefit in margin reduction comes not from reduction of random error, but in fact from minimization of the systematic component of setup offset
- This may be more efficiently achieved via offline or adaptive techniques of assessing setup

## Off-line Observation and Systematic Error Correction




**Minimum treatment delay -off-line evaluation**
**Variable precision - limited by the random component of setup**

## Example of Offline correction

- ~2/3 of all patients now treated at UM use offline measurement for setup correction
- Setup corrected on fraction 1, followed by offline measurement through day 4 and adjustment on day 5
- Results show residual systematic errors that are removed/reduced on day 5:

| | Σ (Maximum) "systematic" error observed | | |
|---|---|---|---|
| Site: | lateral | Anterior-Posterior | Cranial-Caudal |
| Pelvis | 3.1 (10.1) mm | 2.5 (5.7) mm | 2.6 (8.0) mm |
| Chest | 3.3 (10.2) mm | 3.8 (10.3) mm | 3.7 (9.1) mm |
| Abdomen | 2.9 (6.9) mm | 2.6 (5.8) mm | 3.9 (19.1) mm |
| H/N | 2.5 (7.4) mm | 2.5 (6.5) mm | 3.0 (9.4) mm |

These numbers are the actual positions that would have been treated without observation, and unlikely to be reduced significantly by weekly films

## Random variations

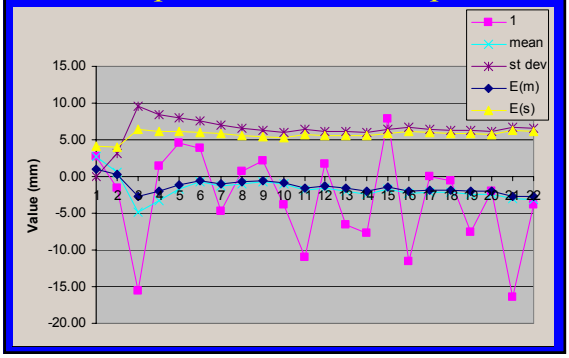
| Site: | $\overline{\sigma}$ (Max) (mm) (observed "random" variations) lateral | Anterior-Posterior | Cranial-Caudal |
|---|---|---|---|
| Pelvis | 2.6 (6.2) | 2.4 (6.3) | 2.7 (7.0) |
| Chest | 3.0 (7.9) | 2.6 (7.0) | 3.4 (11.8) |
| Abdomen | 2.5 (9.1) | 3.1 (9.1) | 3.1 (12.4) |
| H/N | 2.1 (8.4) | 2.2 (8.6) | 2.7 (5.8) |

Note: Measurements are from a limited number of observations per patient

## Adaptive Radiation therapy (ART)

- Described by Yan (Beaumont)
- Typical ART implementation:
  - Initiate treatment with large fields and frequent observation
  - Predict average offset and mean
  - Adjust after a few observations and reduce margin, frequency of observation
  - increase margin and frequency of observation if surprised by an outlier
  - NOTE: Given sufficiently large daily variation, Adaptive modeling selects a subset of patients for on-line localization

## Adaptive Model - Example




## Advantages of ART

- Potential to customize treatment to the individual patient
- Reduces the number of wasted observations
- Rapidly resolves systematic offsets

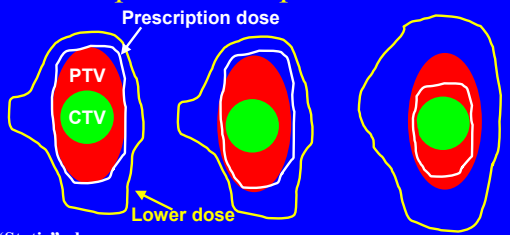
## Tradeoffs

- Advantage - far higher confidence in daily positioning
- "disadvantage" - Portal images will be a more honest representation of daily setup, and thus fewer "perfect" images will be recorded

## Further Obstacles to ART

- Cost – The change in paradigm requires considerations of billing / reimbursement
- Education – The concepts related to adaptive radiotherapy significantly differ from traditional training
- Infrastructure – The effort for evaluation of setup shifts away from the linac and physician workroom

## Impact of Setup Variation

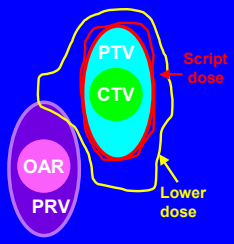



"Static" plan: Prescription dose Covers PTV

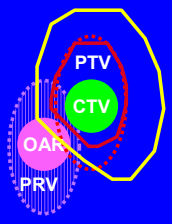
Systematic error: Shifts dose distribution (CTV still covered)

Random error: Blurs doses (high dose volumes reduce, lower dose volumes increase)

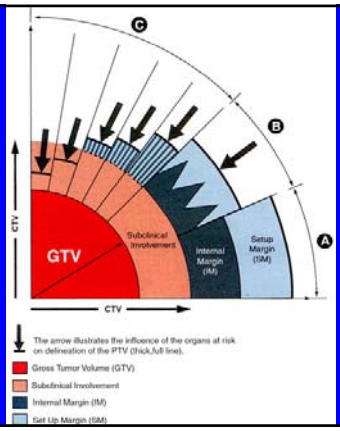
## PTV, PRV, and Setup Variations




Margins are not problematic

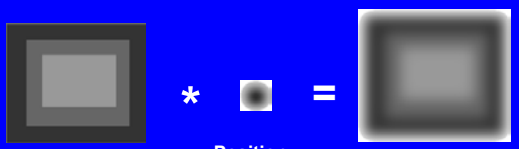



Overlapping margins force complicated tradeoffs in Optimization!




## Accounting for Random Errors in Dose Calculations

- Convolve with a (Gaussian) kernel (Mageras, Lujan, Keall,…)
- Robust plan optimization (e.g. MIGA – Vineberg)

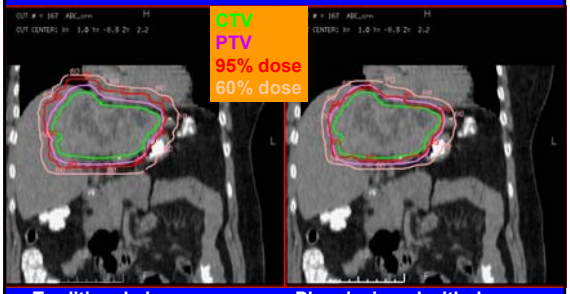



Original dose distribution

Position Distribution kernel

Convolved dose distribution

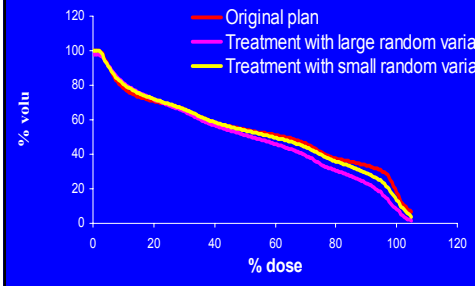
## Planning With Inclusion of Variations



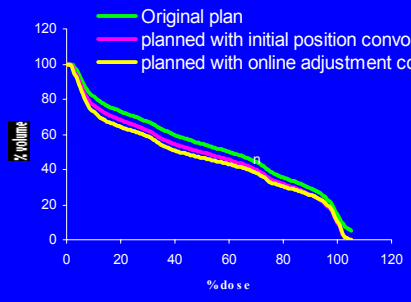

Traditional plan: PTV based on 0.7-1.5 σ

Plan designed with dose convolved for setup errors

## Delivered Liver Dose - Result



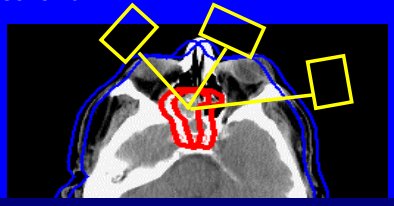
## Planning With Convolution - Results




## Multiple Instances of Geometry Approximation (MIGA):

**MIGA accounts for setup uncertainty/motion by simultaneous optimization of the plan to multiple instances of the patient anatomy.**

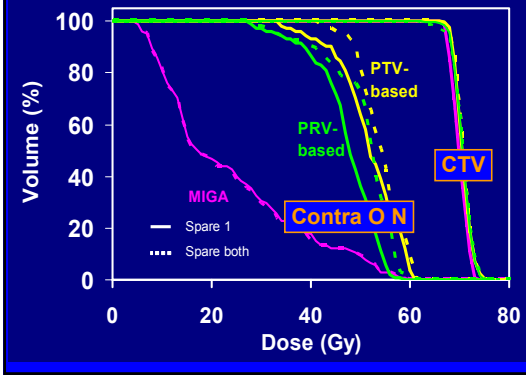
## MIGA schema



- **Use single set of beams and multiple instances of patient anatomy**
- **Do dose calculations to each anatomy instance**
- **Perform optimization to all instances concurrently, based on a weighted sum of the different instances**

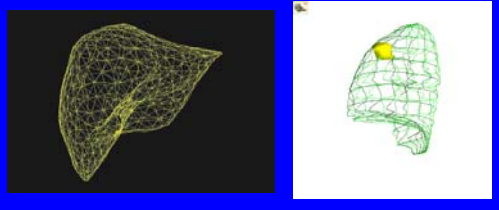
McShan et al, ESTRO 2001

## Example – parotid sparing with optic nerve consideration



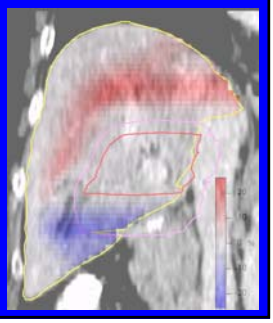

## Dynamic models

- The generation of "4D" patient models will impact dose calculation, and potentially increase coherence between planned and delivered doses



## Impact of motion and deformation

- summed dose from static model minus that including deformation
- Red: dose overestimated by static model
- Blue: dose underestimated by static model



## ICRU – dose reporting

- Level 1 – ICRU "reference point", PTV minimum and maximum doses
- Level 2 – full 3D calculations with heterogeneity, report PTV, PRV, … volumes and dose distributions (e.g. RTOG)
- Level 3 – Currently undefined methods for dose reporting (e.g., BNCT, IMRT)

## Dose prescription and reporting

- ICRU 62 requires a reference point that is in the PTV and furthermore in a region of low dose gradient
- While potentially achievable in conformable radiotherapy, IMRT via fluence optimization presents significant difficulty
- Even if the 3D dose distribution provides a homogeneous dose region, it is likely that the individual beams project steep dose gradients through the reference location

## Dose reporting for organs at risk

- As shown, the delivered dose to normal tissue adjacent to the tumor may vary significantly from that planned
- Neither PRV nor OR dose volume histograms are clearly representative of expected risk (especially for parallel organs)

## Summary

- Margins are a difficult problem for IMRT
- Given that the CTV is properly defined, treatment planning to ensure CTV coverage can be facilitated by:
  - Patient modeling to reduce artifacts or unrealistic patient models
  - Treatment verification strategies that understand the patient-specific nature of setup variation
- Modern developments will provide a framework to better understand the impact of movement and setup variation to facilitate robust treatment planning