THE EMERGING ROLE OF IMAGE-GUIDANCE FOR BREAST RADIOTHERAPY

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*****No disclosures*****

Learning Objectives

- Review the clinical targets for breast RT as a function of cancer stage
- Learn about innovative uses of advanced radiotherapy techniques for breast treatment
- Highlight the emerging role of IGRT to guide planning and treatment

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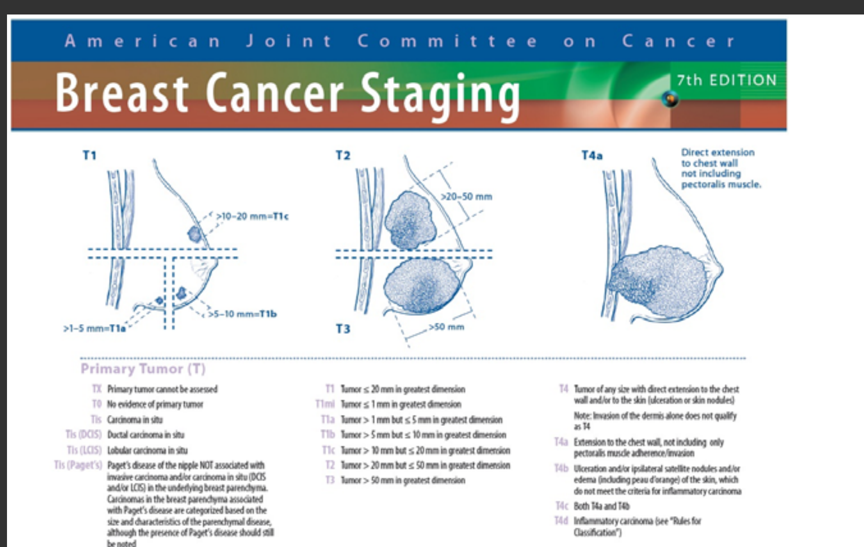
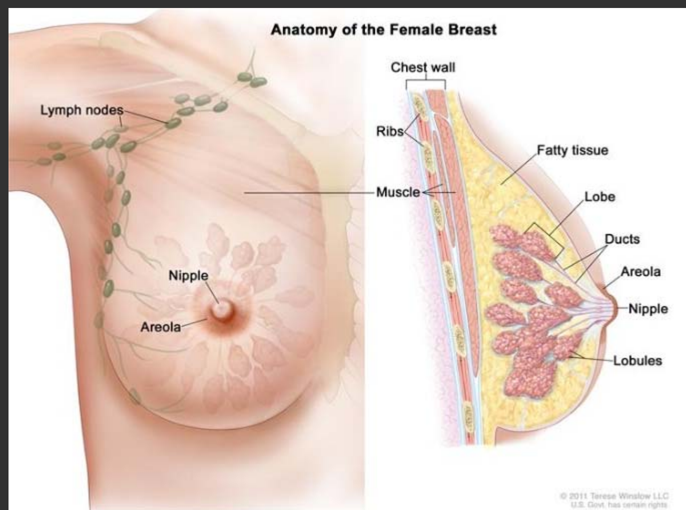
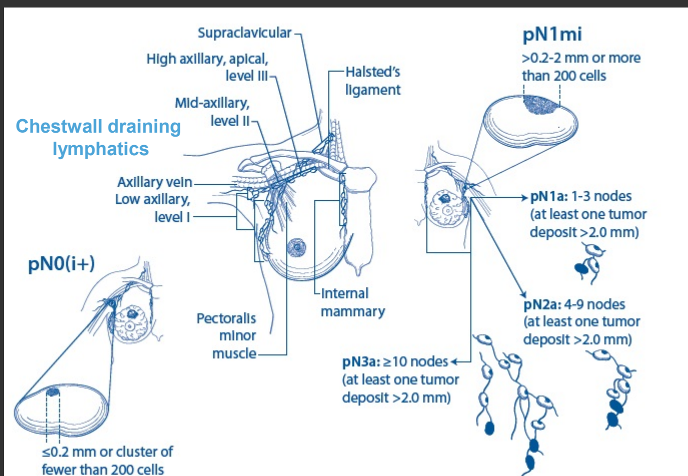


Breast Anatomy





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Breast Cancer Staging

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

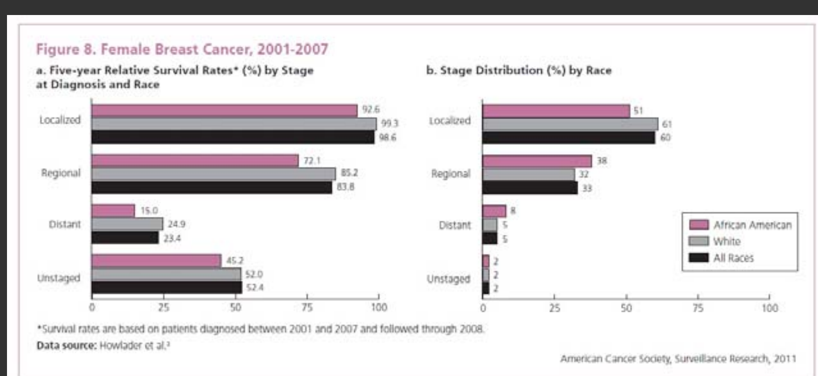
Early stage *non-invasive* cancer:
DCIS

Early stage *invasive* cancer:
Small tumor and/or 0-3 positive nodes

Locally advanced/inflammatory cancer:
Large tumor and/or ≥ 4 positive nodes

Metastatic cancer

Breast Cancer Survival



Survival rates for all women diagnosed with breast cancer are:
- 89% at 5 years
- 82% at 10 years
- 77% at 15 years

Radiotherapy for Breast Cancer

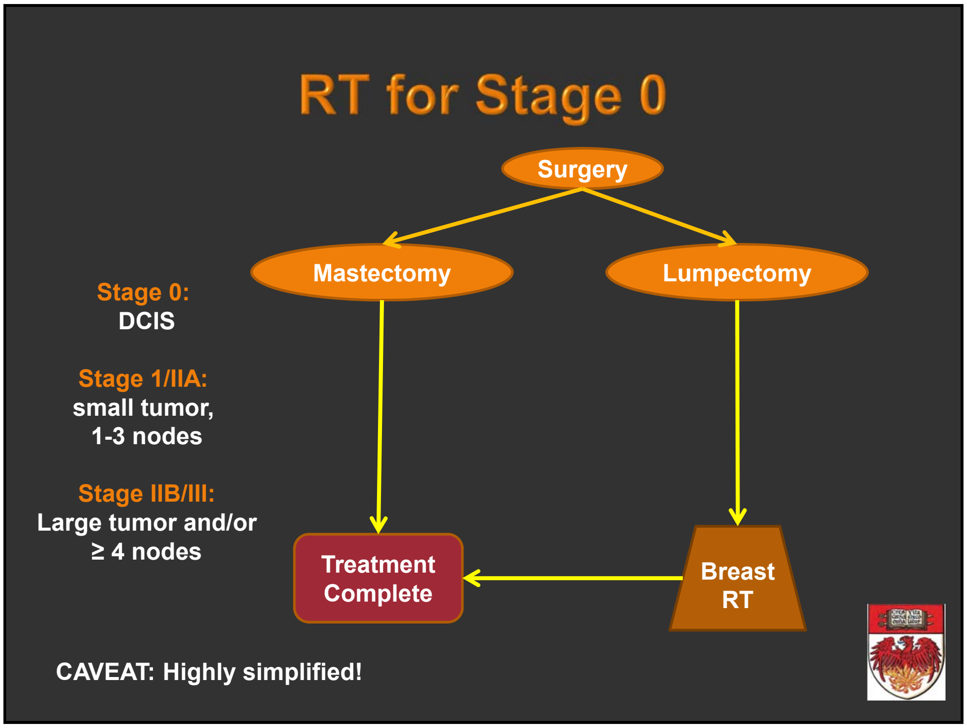
- Radiotherapy is a locoregional treatment that is *always* combined with surgery & often with chemotherapy
- Goals of treating with RT:
  - To reduce local-regional recurrence
  - To improve disease-free survival
  - *To improve overall survival?*
  - To palliate

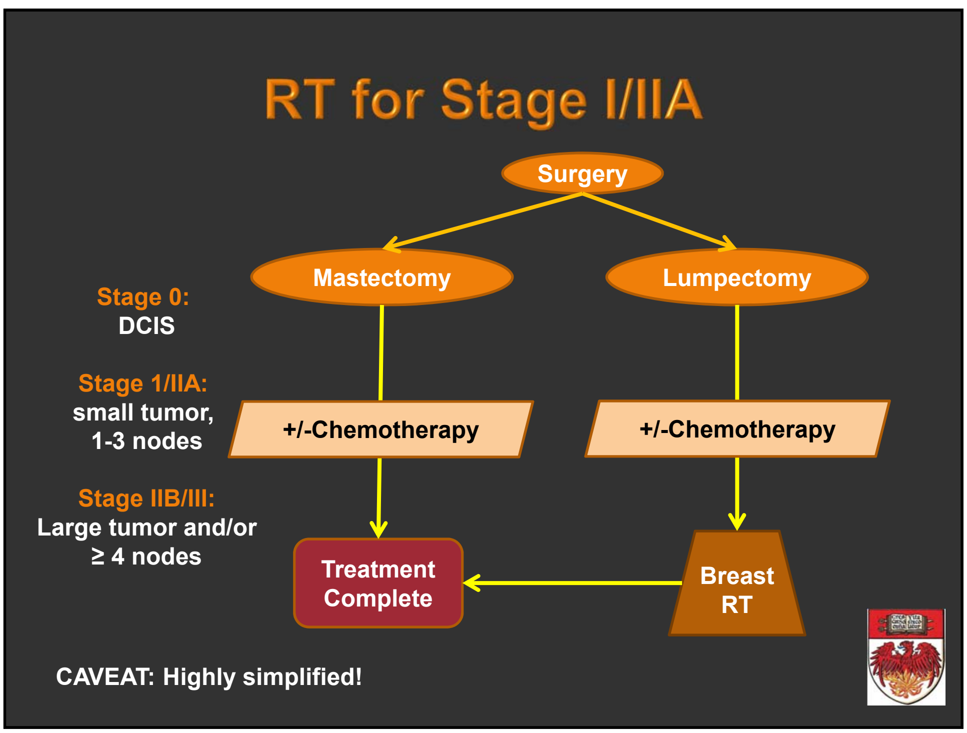
Breast-Conserving Surgery and Radiotherapy in Early-Stage Breast Cancer: The Importance of Local Control

Abram Recht, MD, FASTRO,* and Lawrence J. Solin, MD, FACR, FASTRO†

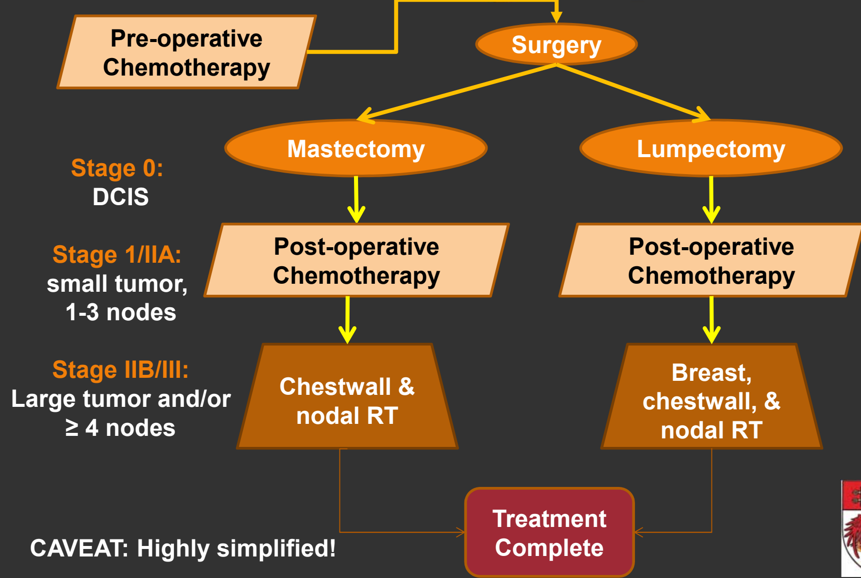
Semin Radiat Oncol 21:3-9 © 2011 Elsevier Inc. All rights reserved.

- "Modeling of the data showed that the avoidance of 4 local recurrences by year 5 was associated with the avoidance of 1 breast cancer death by year 15…
- '4-to-1' relationship was also seen for trials randomizing patients with positive nodes to receive postmastectomy radiation therapy or not…
- Benefits of adding RT occur earlier for local control than for breast cancer mortality…
- Radiation was associated with a very small risk in complications….largely caused by excess cardiac disease."


RT for Stage 0
Surgery
Mastectomy
Lumpectomy
Stage 0:
DCIS
Stage 1/IIA:
small tumor,
1-3 nodes
Stage IIB/III:
Large tumor and/or
≥ 4 nodes
Treatment Complete
Breast RT
CAVEAT: Highly simplified!


RT for Stage I/IIA
Surgery
Mastectomy
Lumpectomy
Stage 0:
DCIS
Stage 1/IIA:
small tumor,
1-3 nodes
Stage IIB/III:
Large tumor and/or
≥ 4 nodes
+/-Chemotherapy
+/-Chemotherapy
Treatment Complete
Breast RT
CAVEAT: Highly simplified!

RT for Stage IIB/III



RT for ~80%* of Breast Cancer Patients

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
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Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

In situ cancer:
RT to breast

Early stage invasive cancer:
RT to breast

MA20 investigating:
RT to breast/chestwall + nodes!

Early stage invasive cancer:
RT to breast and chestwall

Locally advanced/inflammatory cancer:
RT to breast and chestwall
RT to regional mammary nodes

*Poortmans et al., *Semin Radiat Oncol*, 22: **29-39**, 2012.

ASCO American Society of Clinical Oncology
www.asco.org

NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. **(5-year followup reported at 2011 meeting)**

- Patients with node-positive or high-risk node-negative disease treated with BCT and adjuvant chemotherapy and/or endocrine therapy were randomized to WBI or WBI plus regional nodal irradiation (RNI) to the *internal mammary, supraclavicular, and high axillary lymph nodes*
- Adding RNI significantly improved:
  - Local-regional disease-free survival (96.8% vs 94.5%)
  - Distant disease-free survival (92.4% vs 87.0%).
- There was a trend towards improvement in overall survival (92.3% vs 90.7%, p=0.07)
- RNI lowered the absolute risk of a distant metastatic event within 5 years of diagnosis, from 13% down to 7.7%.

Personalized Radiotherapy

- Prognostic factors:
  - Tumor size & location
  - Nodal status
  - Histologic subtype & grade
  - Multifocality/multicentricity
  - Patient age/menopausal status
  - Receptor status (ER, PR, HER2-neu)
  - Resection margin distance
  - Lymphovascular invasion
  - Extracapsular extension
  - Genetic marker status (BRCA1, BRACA2)
- Adjuvant hormone therapy:
  - Tamoxifen
  - Aromatase inhibitor
  - Herceptin

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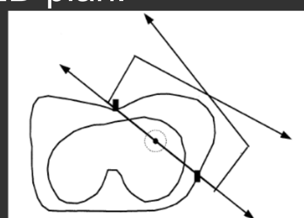
Radiotherapy Techniques

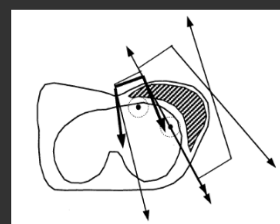
- 2D planning
- 3D CT-based planning
- Field-in-field (FIF) segments to modulate intensity of tangent beams
- Inverse-planned IMRT:
  - Multiple static gantry angles (coplanar or not)
  - Intensity-modulated arc therapy (VMAT, RapidArc)
- Partial breast irradiation (PBI)
  - Usually delivered in hypofractionated regimen

2D vs 3D Radiotherapy Planning

- Accepted 2D planning criteria:
  - Central lung distance (CLD) ≤ 3cm
  - Mean heart distance (MHD) ≤ 1.5cm
- "The 3D tangential plan failed to reduce the volumetric dose of lung and heart from that of a 2D plan."



Plan A



Plan C

Kong et al., *Int J Radiat Oncol Biol Phys*, **54(3):** 963–971, 2002.

3D Radiotherapy Planning

- For opposed beams, dose to critical organs is a function of beam angles.
- 3D CT data but no target volumes contoured?
- 3D CT data used to:
  - Determine tangent angles
  - Match beams for IMN, supraclavicular nodes
  - Shield critical organs from radiation (design blocks)
  - Delineate surgical cavity
  - Optimize dose homogeneity within tangents

FIF Radiotherapy Planning

- "Beaumont technique" used aperture-based optimization constrained to traditional tangent fields
- Compared to planning with wedges, IMRT:
  - Significantly reduced moist desquamation
  - Significantly reduced palpable induration
  - Significantly reduced rates of grade 2 or greater dermatitis, edema, and hyperpigmentation
- Hypofractionated IMRT provides comparable toxicity…except:
  - Excludes acute dermatitis
  - No boost was given

Shah et al., *Practical Radiation Oncology*, in press, 2012.

3D Radiotherapy Planning

- "As the radiotherapy community moves to more comprehensively treat the regional lymphatics for potential improvements in survival in breast cancer patients, it seems that the current techniques may not be capable of meeting this challenge without potentially increasing the probability of late-onset treatment-related morbidities.
- The (Beaumont) techniques we have embraced are the necessary 'stepping-stones' to these more complex applications."

Vicini et al., *Int J Radiat Oncol Biol Phys*, **58**(5):1642–1644, 2004.

Inverse-Planned IMRT

- Increased degrees of freedom, due to increased number of beam angles and radiation intensity levels, enables precise placement of steep dose gradients within the patient
- The use of many different beam angles results in low doses being delivered to the entire heart and contralateral lung, organs not irradiated conventionally

IS MULTIBEAM IMRT BETTER THAN STANDARD TREATMENT FOR PATIENTS WITH LEFT-SIDED BREAST CANCER?

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- Conclusions: "IMRT significantly improved conformity and homogeneity for plans when the breast + IMNs were in the CTV. Heart and lung volume receiving high doses were decreased, but more healthy tissue received low doses."
- Discussion: "Current practice is to use conformal IMRT if the plan results in an absolute reduction in heart V_{30} of 10% or greater compared to MWT or DIM technique."

Beckham *et al*, *Int J Radiat Oncol Biol Phys*, **69**(3):918-924, 2007.

Role of IMRT for breast?

- "Requires complete development of MWT (≤3.5cm lung) or DIM plans to make the decision to use IMRT..
- Balancing the short- to medium-term benefits of reducing the volume of heart and left lung receiving a high dose of RT against the risk of later malignancy requires an individual assessment of the treatment volume goals and the patient's longevity prospects with and without RT."

Beckham *et al*, *Int J Radiat Oncol Biol Phys*, **69**(3):918-924, 2007.

CTV Contouring for IMRT 7mm expansion to PTV

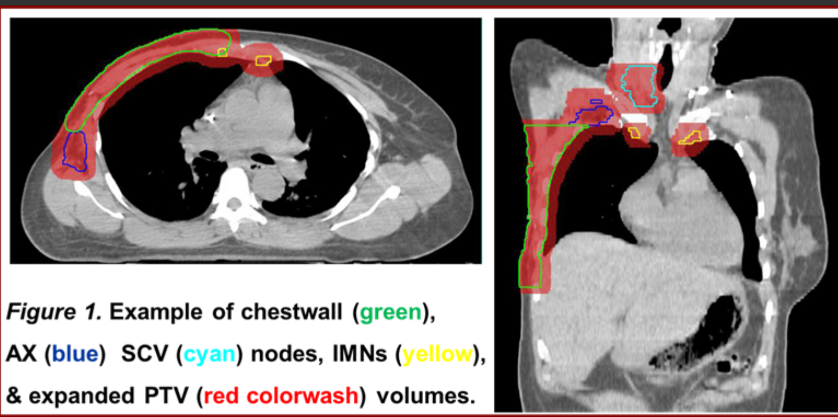
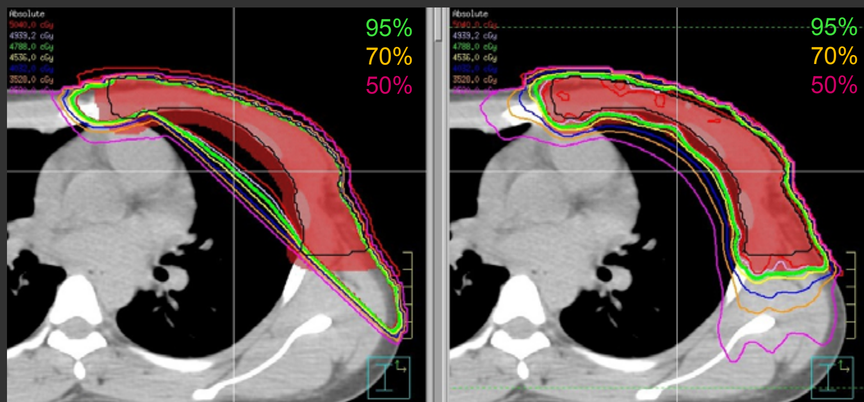


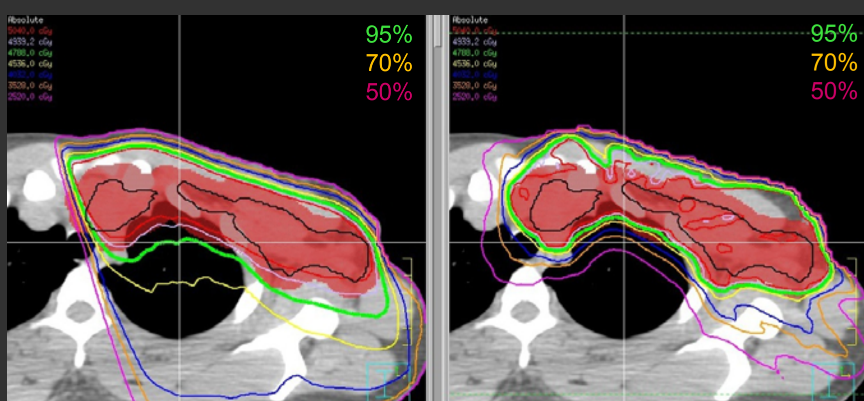
Figure 1. **Example of chestwall (green), AX (blue) SCV (cyan) nodes, IMNs (yellow), & expanded PTV (red colorwash) volumes.**

Are we treating more or less lung with PTV?



3D Plan IMRT Plan

Are we treating more or less lung with PTV?



3D Plan IMRT Plan

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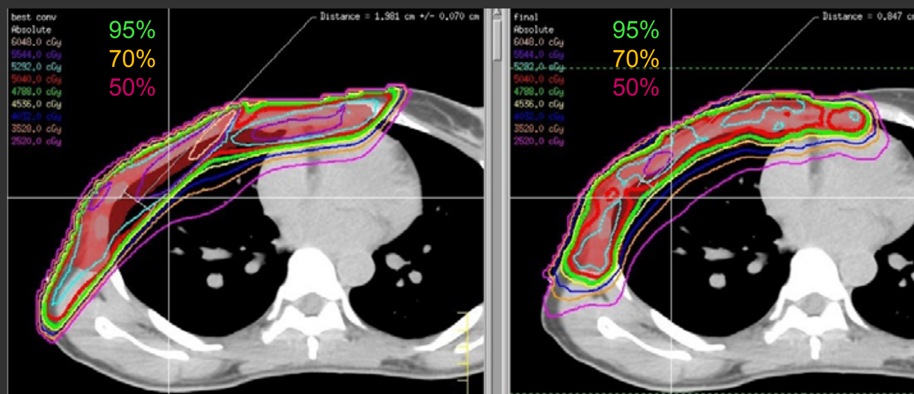
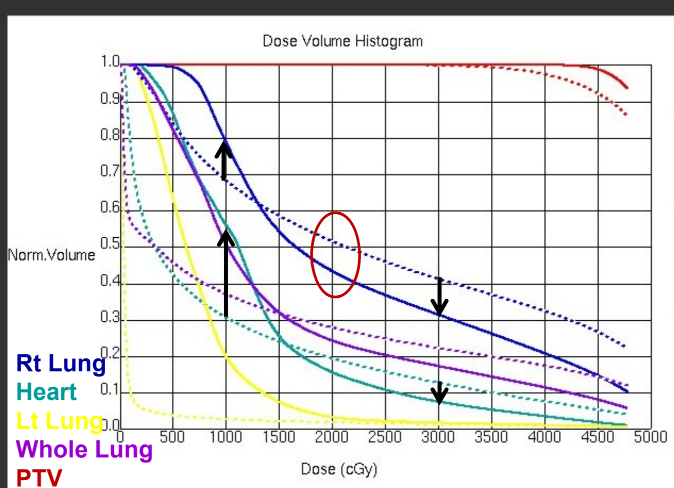


3D Plan   IMRT Plan

Are we treating more or less lung with PTV?



Heart & Lung V_{10} ↑

Lung V_{30} ↓ 10%

Heart V_{30} ↓ 5%

Solid Line = IMRT Plan, Dashed Line = 3D Plan

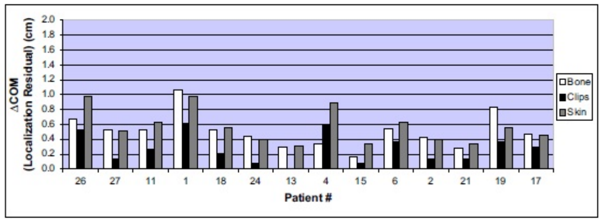
IMRT vs. 3D to *Right* Breast/Cw, Nodes + Bilateral IMNs in 5 patients to 50.4Gy

		3D				IMRT				
		MEAN	STDEV	MIN	MAX	**MEAN**	STDEV	MIN	MAX	**Significant at p < 0.05**
Contralateral Breast	Mean Dose (cGy)	**454**	265	153	651	**765**	354	513	1170	
Heart	V30Gy (%)	**16.8**	1.3	15.5	18.2	**4.9**	1.8	4.0	7.6	*
	V20Gy (%)	**25.6**	3.4	22.7	30.3	**12.8**	3.1	9.8	16.5	*
	V5Gy (%)	**50.9**	29.9	14.0	97.5	**84.8**	11.7	69.1	96.1	
	Mean Dose (cGy)	**1408**	222	1268	1738	**1209**	104	1085	1340	
Ipsilateral Lung	V30Gy (%)	**50.6**	4.9	44.4	56.3	**32.7**	7.0	23.3	39.7	*
	V20Gy (%)	**65.8**	10.8	58.4	81.9	**45.1**	12.1	30.7	59.8	
	V5Gy (%)	**93.2**	7.9	83.0	99.7	**95.5**	3.5	90.9	99.5	
	Mean Dose (cGy)	**3211**	269	2918	3495	**2318**	364	1876	2723	*
Whole Lung	V30Gy (%)	**30.0**	4.5	24.8	35.0	**19.6**	5.1	13.1	24.5	*
	V20Gy (%)	**39.1**	4.7	34.0	45.3	**27.6**	8.4	17.6	36.8	
	V5Gy (%)	**62.9**	10.9	55.5	82.0	**73.2**	8.0	64.7	82.6	
	Mean Dose (cGy)	**2029**	249	1680	2255	**1594**	294	1245	1851	*
Liver	V20Gy (%)	**18.2**	6.4	10.1	24.4	**14.7**	3.9	12.0	20.5	
Cord	Max Dose (cGy)	**1093**	821	358	2258	**1732**	778	1061	2519	
PTV	HI	**0.44**	0.24	0.13	0.81	**0.70**	0.12	0.57	0.88	*
	CI	**1.99**	0.45	1.59	2.58	**1.14**	0.02	1.11	1.16	*

Partial Breast Irradiation

- Rationale:
  - Ipsilateral recurrences primarily occur near tumor bed
  - "Elsewhere" tumor rate comparable to that in contralateral breast (<15% at 13 years)
- Target volumes (per NSABP B-39/RTOG 0413):
  - GTV = Surgical cavity (delineated by clips)
  - CTV = GTV + 1.5cm *Quadrentectomy*
  - PTV = CTV + 1cm
- Delivered in hypofractionated regimen

Surrogate for Surgical Cavity?



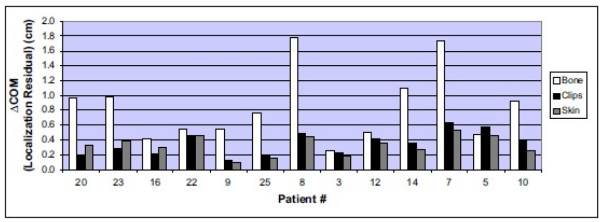


Fig. 1. Patient data comparing distances between the centers of masses (ΔCOMs) of the initial planning computed tomography (CT) scan and second CT scan with each type of registration: bony anatomy (white), clips (black), and skin surface (grey). Smaller bars show smaller distances between COMs and therefore better registration. Patients are ordered from left to right, with better to worse performance of clip registration relative to skin.

Hasan et al., *Int J Radiat Oncol Biol Phys*,**70(4)**:1239–1246, 2008.

Surrogate for Surgical Cavity?

Table 2. Target registration error comparison

Technique	Images (*n*)	TRE (mm) Median	Lower quartile	Upper quartile
Laser	94	7.1	5.2	9.7
Chest wall	81	5.4	4.1	7.5
Surface imaging (SurfRef-CT)	56	4.9	3.4	6.7
Surface imaging (SurfRef-fx1, nongated)	25	6.2	3.2	1.1
Surface imaging (SurfRef-fx1, gated)	49	3.2	2.3	4.1
kV X-ray/clips	93	2.4	2.0	3.2

Abbreviations: TRE = target registration error; SurfRef-CT = computed tomography-based reference surface; SurfRef-fx1 = reference surface generated from first fraction; kV = kilovoltage.

Note, values for laser, chest wall, and kilovoltage clips include both gated and nongated data; with data for surface imaging (SurfRef-CT) given as gated only.

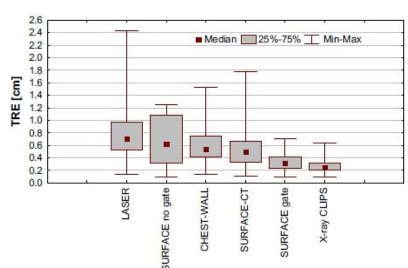


Fig. 6. Target registration error results in box-plot format. SURFACE = results with use of first fraction reference surface (SurfRef-fx1); SURFACE-CT = results with computed tomography (CT)-based reference surface. Results shown for each imaging modality, except for surface imaging, include both gated and nongated data.

Gierga et al., *Int J Radiat Oncol Biol Phys*, **70(4)**:1239–1246, 2008.

Recent Radiotherapy Trends

- More frequent regional nodal irradiation
- More frequent tumor bed or chestwall boost
- Partial breast irradiation for select patients
- Hypofractionated regimens (WBI & PBI)
- Contouring targets (per RTOG breast atlas)

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- Review the clinical targets for breast RT as a function of cancer stage
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IGRT Goals

- To deliver higher tumor dose while sparing nearby critical organs
- To improve setup accuracy by accounting for:
  - Geometric uncertainties
  - Organ motion
- Serve as a QA and safety tool to verify treatment accuracy
- "IGRT provides the means to measure geometrical offsets and develop more accurate PTV margins." (Bujold et al., *Semin Radiat Oncol* **22**:50-61,2012)
- Instead of relying on surrogates for positioning (i.e., bony landmarks), use tumor itself if visible or has implanted fiducials

IGRT to Optimize PTV Margins

- 14 patients receiving inverse-planned, multi-beam IMRT to cw + regional nodes (+ IMNs)
- Daily kV positioning for 450 treatment fractions
- Only translational shifts following correction for patient rotation were included
- Systematic and random components of error were computed following the methodology of van Herk (*Int J Radiat Oncol Biol Phys*, **47(4)**:1121-1135,2000):

$$PTV margin = 2.5 \cdot \Sigma + 0.7 \cdot \sigma$$

Results to be presented at ASTRO 2012.

Daily kV Setup to Bony Landmarks & Surgical Clips

AP kV Treatment Position

LAT kV Treatment Position

IGRT to Optimize PTV Margins

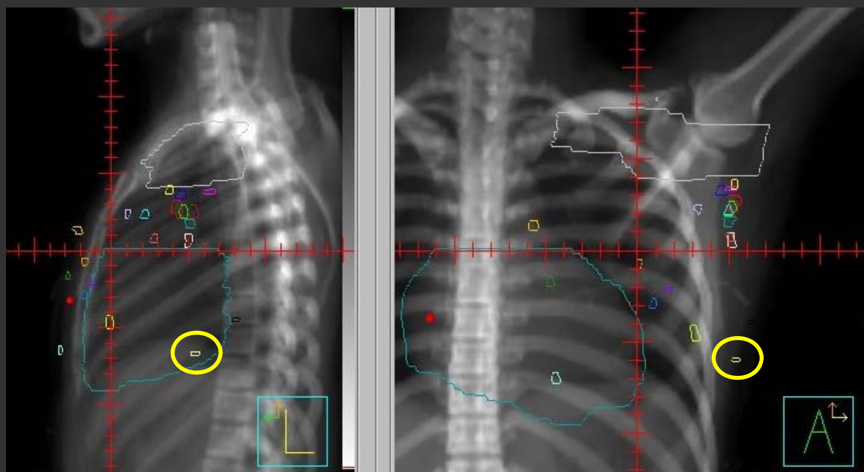
	AP (cm)	SI (cm)	LR (cm)
Mean Absolute shifts (± SD)	0.18 (±0.24)	0.25 (±0.25)	0.23 (±0.24)
% shifts within 5 mm	90.89	79.78	84.44
% shifts within 7 mm	97.33	92.89	94.22
% shifts within 10 mm	99.11	98.44	98.44
Total setup error (M) cm	-0.006	-0.012	-0.060
SD of systematic error (Σ)	0.058	0.16	0.17
SD of random error (σ)	0.30	0.34	0.30
PTV expansion (cm)	0.35	0.63	0.63

Table 1: Setup errors and PTV expansions for 14 patients with clips.

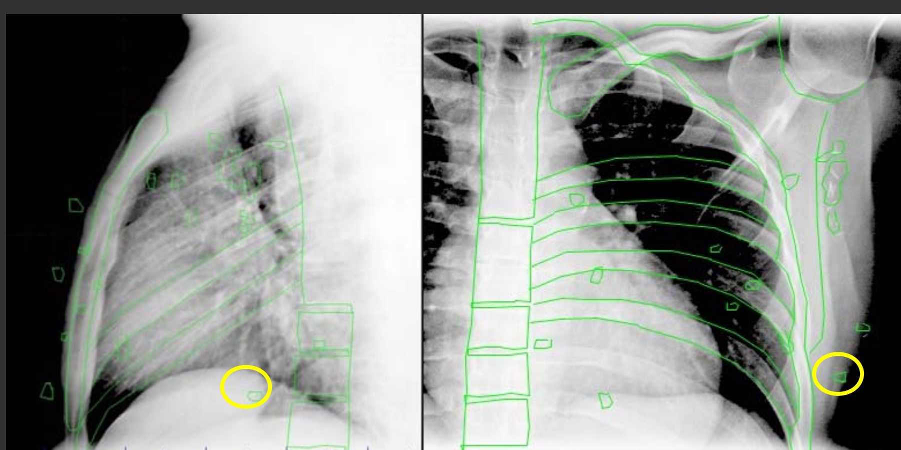
- While a uniform 7mm PTV margin would account for setup errors in more than 90% of treatment sessions, approximately 1/3 of the treatment sessions would be implemented without correction for rotations by forgoing daily image-guidance.

Results to be presented at ASTRO 2012.

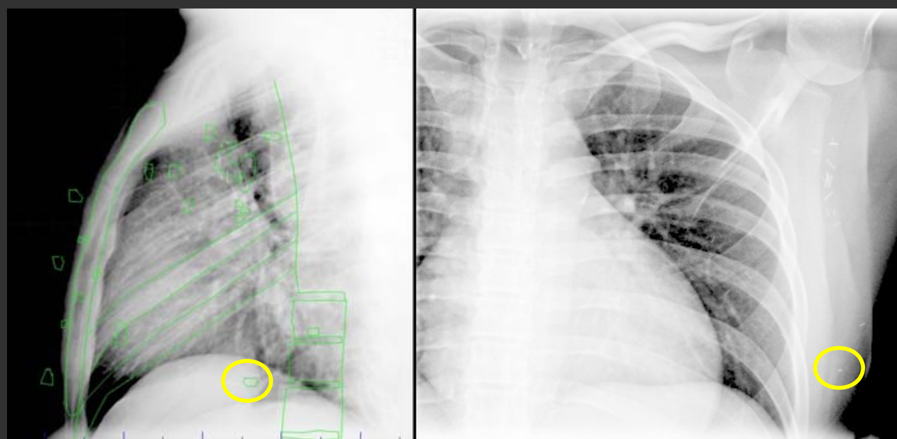
Surgical Clip Locations



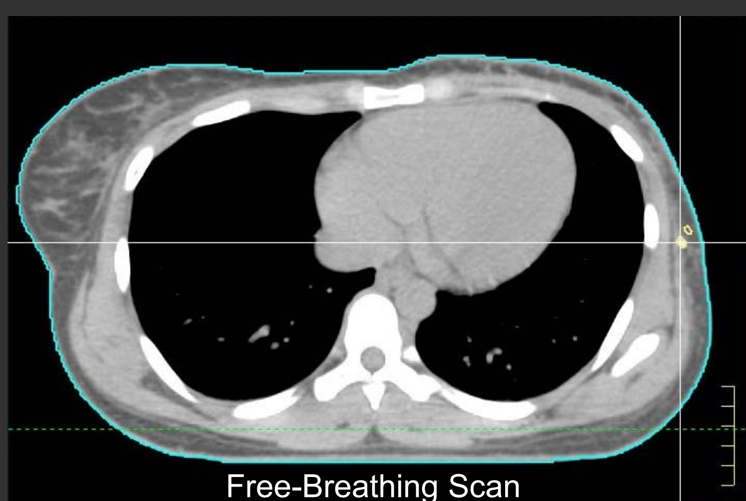
Surgical Clip Locations



Surgical Clip Locations

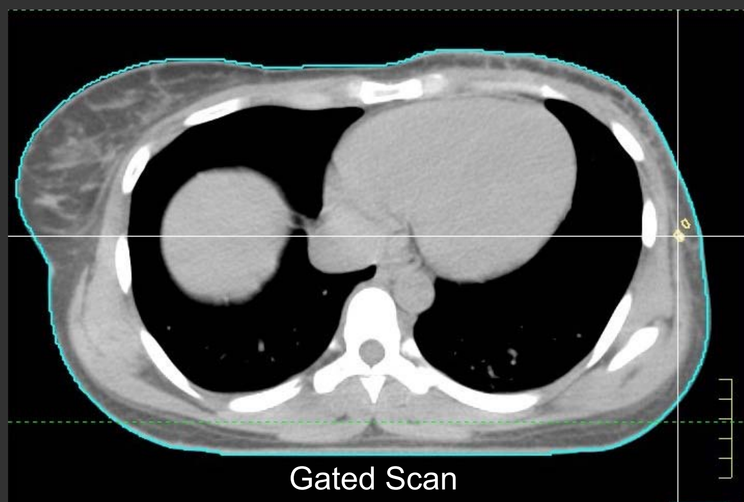


Clip Location Comparison



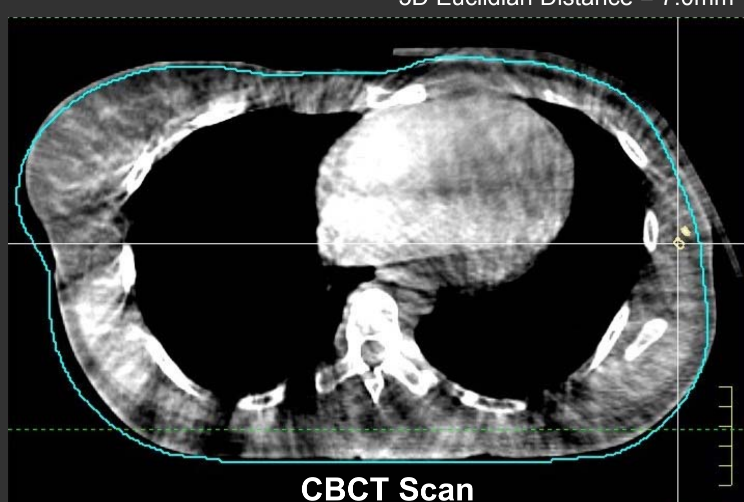
Clip Location Comparison

3D Euclidian Distance = 1.6mm



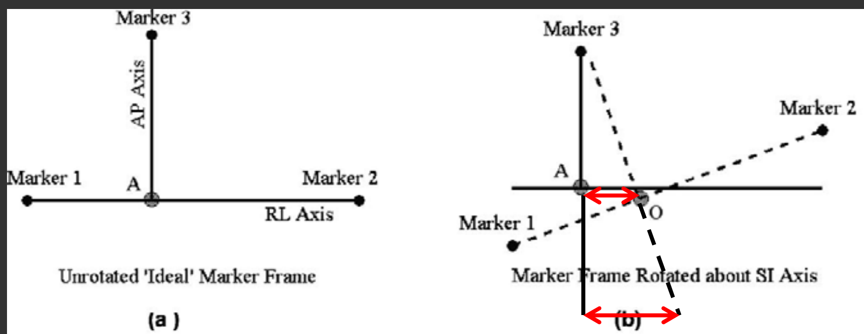
Clip Location Comparison

3D Euclidian Distance = 7.0mm



Rotational/Translational Error Misinterpretation

"Error can be introduced by a rotational shift….Point A, the measured isocenter, is offset by the translational error from Point O, the true origin. An increase in the degree of rotation results in a corresponding increase in the calculation error."



Ezzell et al, *Med Phys,* **34(8)**:3233-3242, 2007

Rotational/Translational Error Misinterpretation

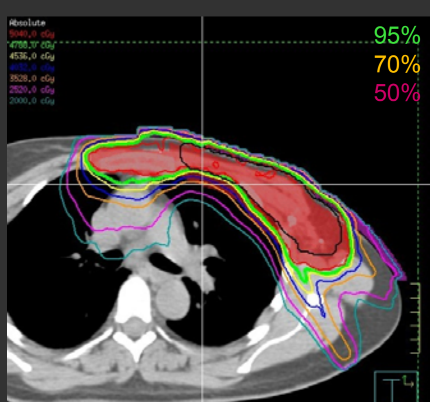
- Error misinterpretation is exacerbated for large targets:
  - Chestwall + RN PTV average volume: 1404 ± 479 cc
  - Right lung average volume: 1442 ± 379 cc
  - Left lung average volume: 1228 ± 335 cc
- Average 3D displacement of 20 clips in CBCT (3.2mm) compared to gated scan (1.6mm)
- Deformation (e.g., shoulder joint) can affect translational misinterpretation

Can PTV Margin Be Reduced?

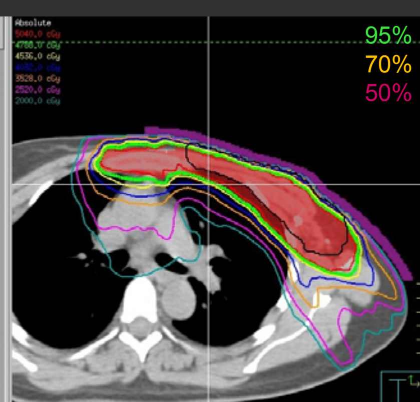
	AP (cm)	SI (cm)	LR (cm)
Mean Absolute shifts (± SD)	0.18 (±0.24)	0.25 (±0.25)	0.23 (±0.24)
% shifts within 5 mm	90.89	79.78	84.44
% shifts within 7 mm	97.33	92.89	94.22
% shifts within 10 mm	99.11	98.44	98.44
Total setup error (M) cm	-0.006	-0.012	-0.060
SD of systematic error (Σ)	0.058	0.16	0.17
SD of random error (σ)	0.30	0.34	0.30
PTV expansion (cm)	0.35	0.63	0.63

Table 1: Setup errors and PTV expansions for 14 patients with clips.

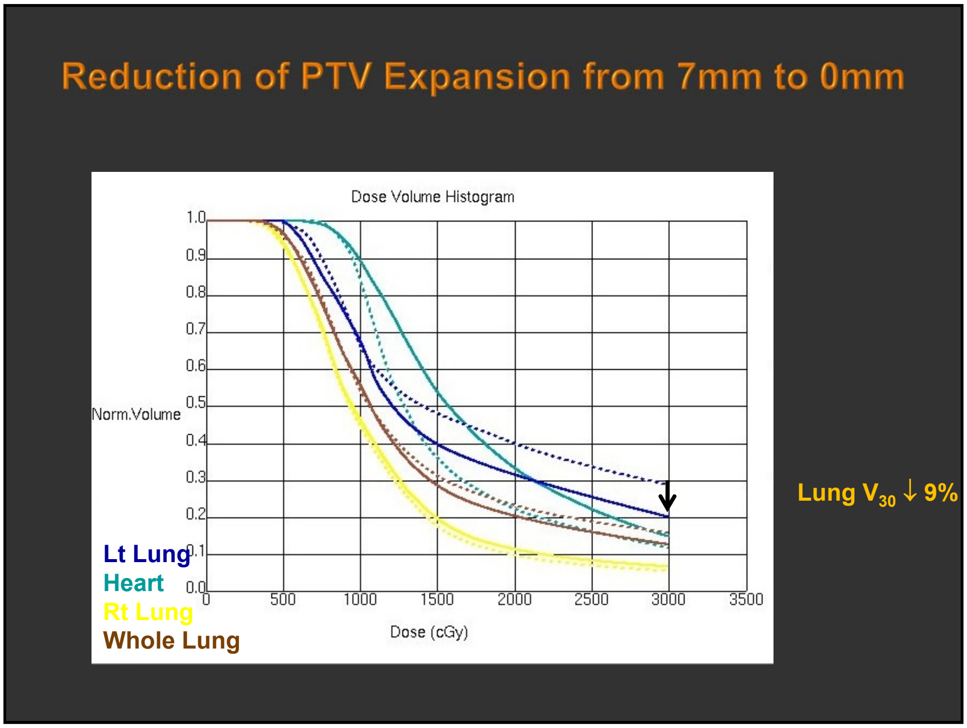
Reduction of PTV Expansion from 7mm to 0mm

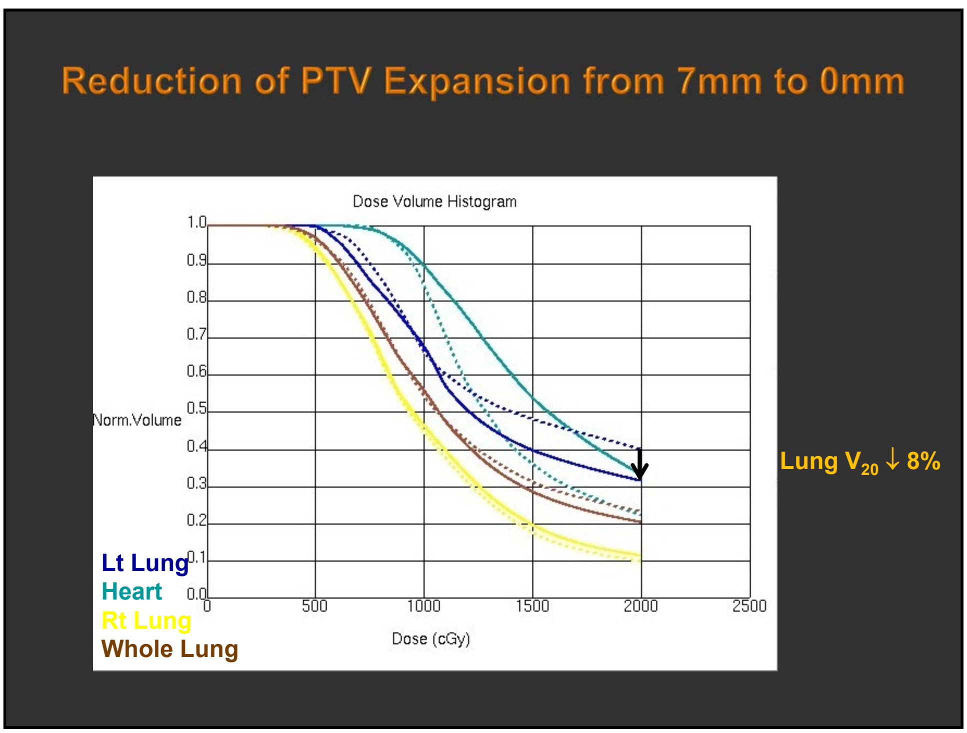


0 mm margin



7 mm margin

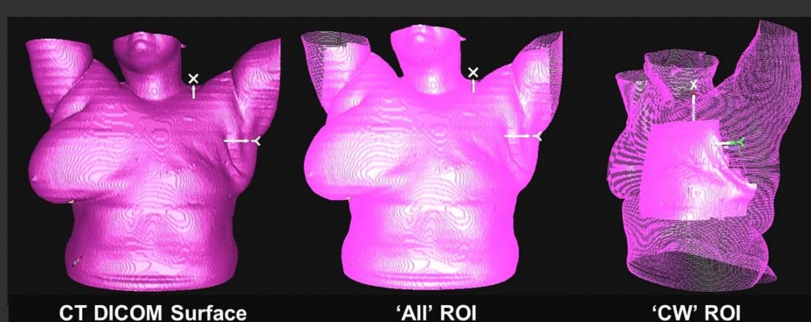

Reduction of PTV Expansion from 7mm to 0mm
Dose Volume Histogram
Norm.Volume
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
500
1000
1500
2000
2500
3000
3500
Dose (cGy)
Lt Lung
Heart
Rt Lung
Whole Lung
Lung V30 ↓ 9%


Reduction of PTV Expansion from 7mm to 0mm
Dose Volume Histogram
Norm.Volume
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
500
1000
1500
2000
2500
Dose (cGy)
Lt Lung
Heart
Rt Lung
Whole Lung
Lung V20 ↓ 8%

Surface Imaging as a Surrogate for kV?

- Post-mastectomy chestwall targets expected to be less affected by deformation than breast
- We investigated the accuracy of 3D surface matching using AlignRT (v4.5) compared to positioning with daily orthogonal kV imaging
- 130 surfaces from 10 patients:
  - Immobilized with upper/lower custom alphacradles
  - Treated *without* respiratory management
  - Treated with inverse-planned IMRT to cw + nodes
  - Setup with skin marks/kV imaging only

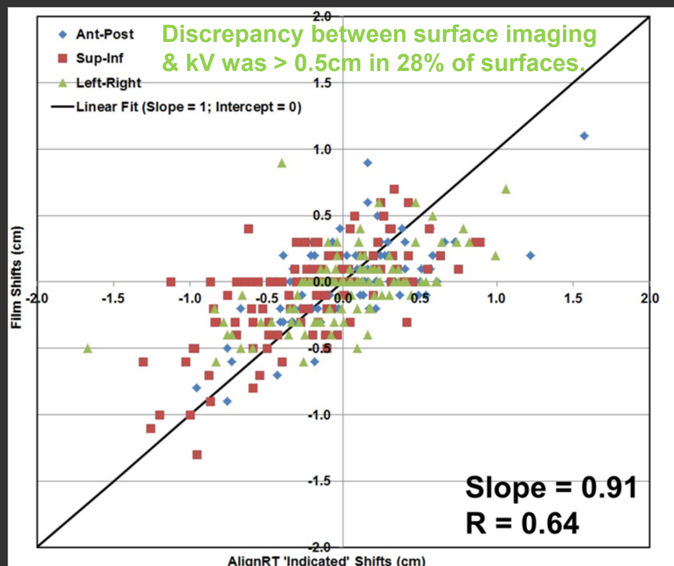
Surface Imaging



3D surface image and ROIs selected for registration.

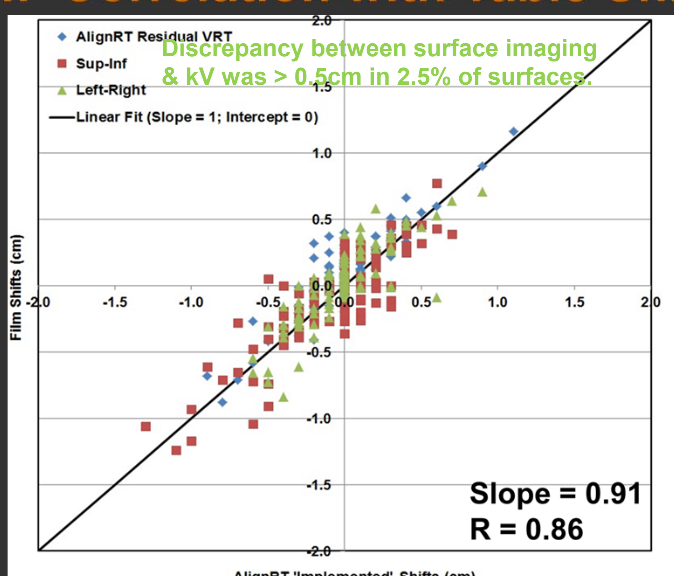
Results presented in Poster SU-E-J-70

'Cw' Correlation with kV



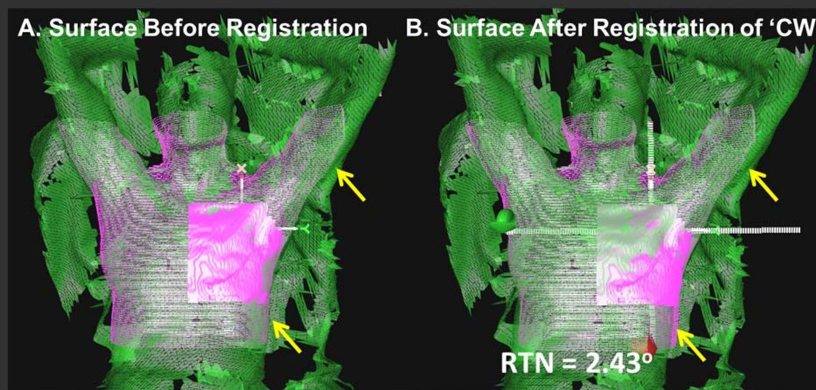
Results presented in Poster SU-E-J-70

'Cw' Correlation with Table Shifts



Results presented in Poster SU-E-J-70

Registration of ‘cw’ ROI



Registration of ‘All’ yielded rotation of 0.47°.

‘All’: $0.27^{o} \pm 0.18^{o}$
‘Cw’: $0.62^{o} \pm 0.58^{o}$

Surface Imaging: Conclusions

- Surface registration depends upon the ROI
- A smaller ROI (‘cw’) showed:
  - Higher correlation with kV shifts
  - Less stability when calculating table rotations
- Before clinical implementation:
  - Investigate the sources of error that prevent a direct one-to-one correlation between AlignRT and kV 3D shifts (e.g., respiratory motion, misinterpretation errors due to kV imaging)
  - Reconcile frequent mismatch (> 25%) between kV & AlignRT shifts > 0.5cm

IGRT Limitations

- "Variability in repositioning is dominated by the ability of therapists to make small, controlled changes in the position of the patient." (Milliken *et al.*, *Int J Rad Onc Biol Phys*, 38(4):855-866, 1997)
- IGRT does not preclude need for:
  - Good immobilization
  - Adequate PTV margins
  - Common sense!

Conclusions

- Breast RT undergoing significant clinical changes with advent of new technology:
  - Larger target including nodes (MA.20 trial)
  - Smaller target (PBI trials)
- To make impact on survival, planning techniques need to harness the power of IGRT:
  - Improve dosimetric conformality
  - Reduce PTV margins in order to spare critical organs
  - Improve positioning accuracy for large target by detecting/correcting deformations

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