Harvard
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The Role of Protons in the Management of Breast Cancer

PTCOG 54/ San Diego

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May 19th, 2015

Disclosures

- Travel expenses from IBA and Elekta

Overview

- Protons for Locally Advanced Breast Cancer
  - Rationale
  - Patient Selection
  - Dosimetric Comparisons (3D & IMPT)
  - Early Clinical Experience
- Partial Breast Irradiation
- Future
  - PCORI RCT for LABC

RATIONALE FOR PROTON PMRT & PATIENT SELECTION

LABC: Rationale for use

- Protons have been shown to provide substantial normal tissue sparing for several malignancies

- Breast cancer patients are often cured of their disease, but may experience late side effects as a result of radiation therapy and late cardiac toxicity may negate or decrease survival benefit from RT

Cardiac Toxicity

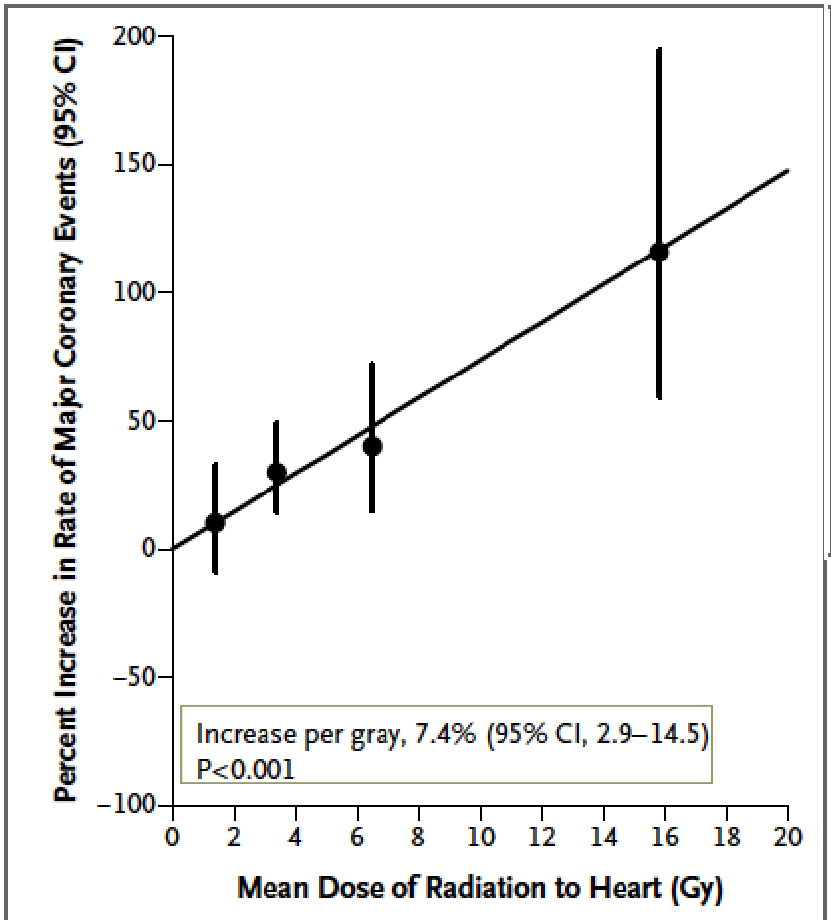


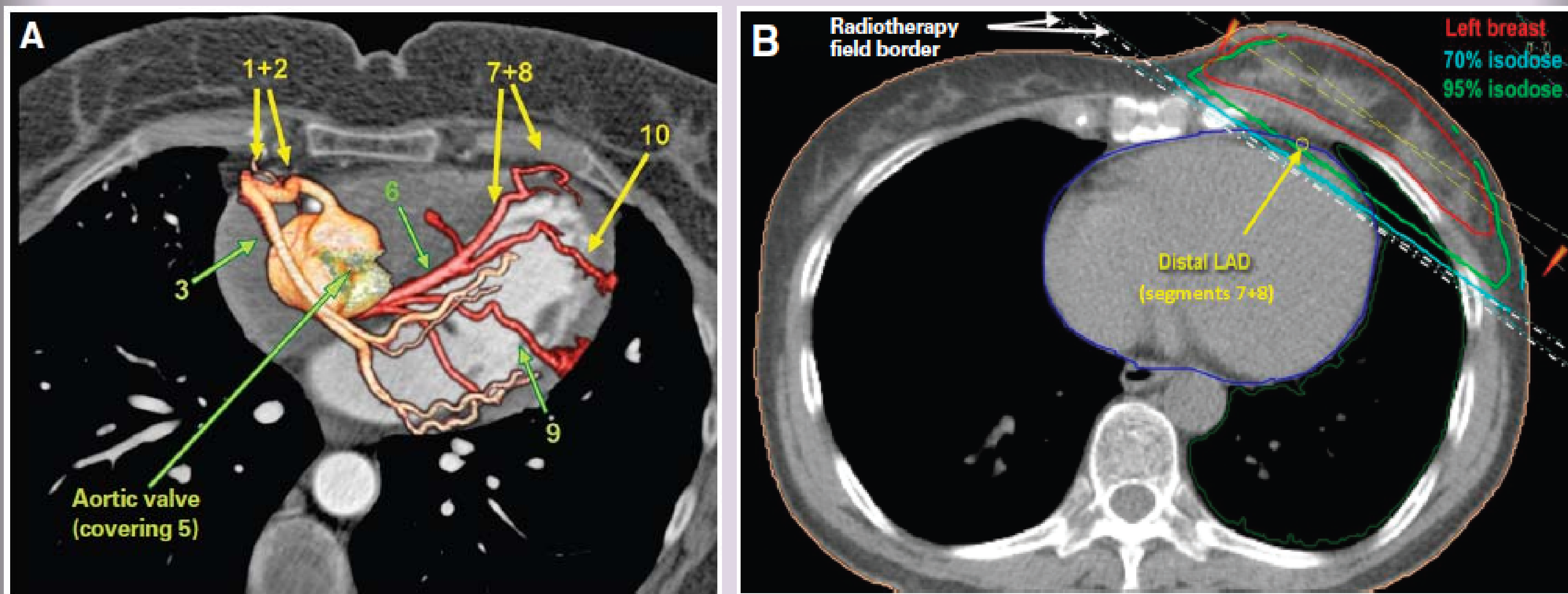
Table 3. Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

Time since Radiotherapy*	No. of Case Patients	No. of Controls	Increase in Rate of Major Coronary Events (95% CI)†
			% increase/Gy
0 to 4 yr	206	328	16.3 (3.0 to 64.3)
5 to 9 yr	216	296	15.5 (2.5 to 63.3)
10 to 19 yr	323	388	1.2 (−2.2 to 8.5)
≥20 yr	218	193	8.2 (0.4 to 26.6)
0 to ≥20 yr	963	1205	7.4 (2.9 to 14.5)

- Myocardial infarction
- Coronary revascularization tx
- Death from ischemic heart disease

Darby et al, NEJM 2013

LAD: Major Vessels



Nilsson et al. *Journal Clinical Oncology* 2011

Protons to Decrease Cardiac Dose

- Mean heart dose with protons for comprehensive coverage (with IMN) < 1 Gy
- Mean heart dose with photons (with IMN) 4-17 Gy
- Extrapolating for Darby, this may translate to a 50% decrease in major cardiac events and an absolute benefit of 1-4%
- EORTC and MA-20 trials complete and indicate a benefit to IMN and regional lymph node RT

MacDonald, Cuaron, Ho, Ares, Jagsi, Darby

Cardiac Surrogate-Strain Echocardiogram

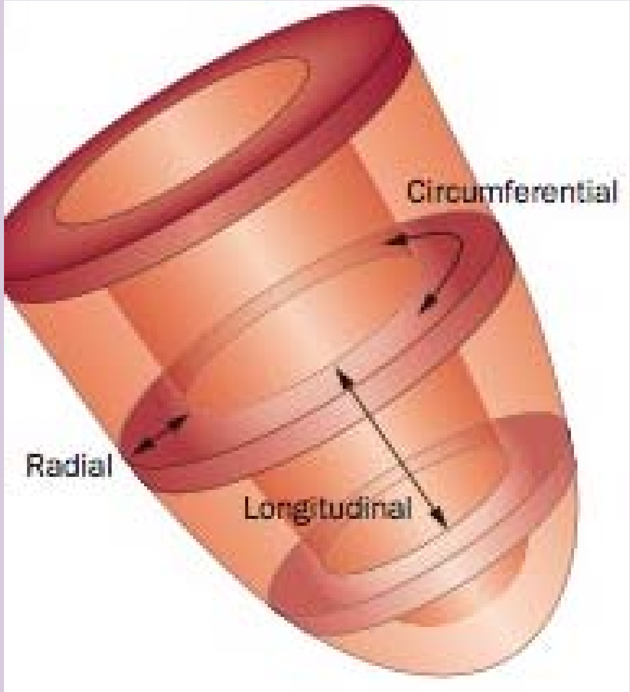
Echo/LVEF

Measures of changes in cavity volume - mainly radial function / mid-myocardium

Strain

Can better delineate layers that may be affected earlier than others and predicts LV dysfunction

- May indicate myocardial damage or indirect myocardial effects by alteration in perfusion
- Predictive of cardiac morbidity for patients treated with cardiotoxic chemotherapy



Courtesy of Marielle Crosbie-Scherrer
Cheung Y, Nat Rev Cardiol 2011
Stevens C, Prog Bioph Mol Biol 2003
Erven K, IJROBP 2013

Strain Photons v Protons

Photon

N=30 (20 L & 10 R) (%)	1st Echo (E1)	2nd Echo (E2)	3rd Echo (E3)	P value ANOVA
LVEF	70.8 ± 6.8	66.2 ± 6.6	67.3 ± 5.9	0.037
Global Systolic LS	-19.5 ± 2.1	-17.4 ± 2.3	-17.4 ± 2.3	<0.001

Proton

N=30 (%)	1st Echo (E1)	2nd Echo (E2)	3rd Echo (E3)	P value ANOVA
LVEF	62 ± 4	62 ± 5	63 ± 3	0.8447
Global Systolic LS	-19.54 ± 2.72	-19.49 ± 2.76	-19.33 ± 3.12	0.9037

Erven K, IJROBP 2011,2013 & personal communication
MacDonald, Tan, Crosbie-Scherrer (manuscript in preparation)

Proton Strain and Biomarkers

Parameter N=30	1st Echo (E1)	2nd Echo (E2)	3rd Echo (E3)	P value ANOVA
LVEF (%)	62 ± 4	62 ± 5	63 ± 3	0.84
Global Systolic LS (%)	-19.5 ± 2.7	-19.5 ± 2.8	-19.3 ± 3.1	0.90
Septal wall LS (%)	-19.1 ± 3.1	-18.8 ± 3.0	-20.0 ± 3.0	0.23
Lateral wall LS (%)	-20.0 ± 4.6	-20.5 ± 4.4	-20.2 ± 6.3	0.66
Inferior wall LS (%)	-18.6 ± 4.0	-19.5 ± 4.4	-19.7 ± 6.1	0.66
Anterior wall LS (%)	-19.6 ± 4.0	-21.1 ± 4.2	-20.9 ± 5.5	0.28
Posterolateral wall LS (%)	-20.3 ± 5.8	-19.9 ± 5.7	-17.7 ± 5.6	0.09
Anteroseptal wall LS (%)	-19.6 ± 4.5	-18.8 ± 5.7	-19.1 ± 4.1	0.77
Novel Serum Biomarkers				
TNIH (pg/ml)	13.7 ± 18.7	8.7 ± 6.4	6.9 ± 6.9	0.0002
NT-proBNP (pg/ml)	81.9 ± 60.3	102.7 ± 68.9	90.7 ± 63.8	0.067
Myeloperoxidase (MPO) (pmol/L)	444.3 ± 185.8	615.2 ± 487.5	656.1 ± 642.9	0.067

Tan, T & MacDonald S, unpublished

Protons to Improve Coverage of Lymph Nodes

For a prescription of 50 Gy Photons, LN-MRI identified lymph nodes

- 82% of malignant and 79% of benign LN-MRI LN covered by 45 Gy
- Only 60% covered by 50 Gy line (64% of malignant and 59% of benign)
- 8% of LN received less than 50% of prescription dose

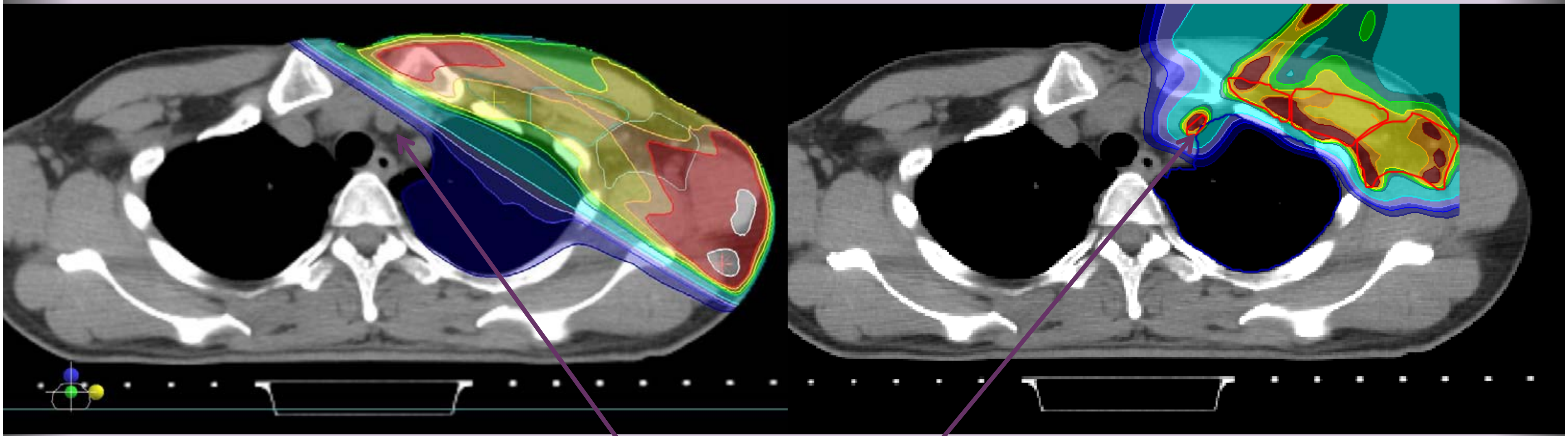
MacDonald SM, et al Int J Radiat Oncol Biol Phys. 2010

Protons to Improve Target Coverage

- With use of standard fields for Photons
  - *For prescription of 50 Gy RTOG Volume Coverage*
    - 45 Gy covered
      - <u>74</u>% of chest wall
      - 84% of Level 1 LN
      - 88% of Level 2 LN
      - 93% of Level 3 LN
      - 84% of SCV LN
      - <u>80</u>% of IMN

Fontanilla, et al Practical Radiation Oncology 2012

Protons to Improve Coverage while decreasing Pneumonitis & Lymphedema?

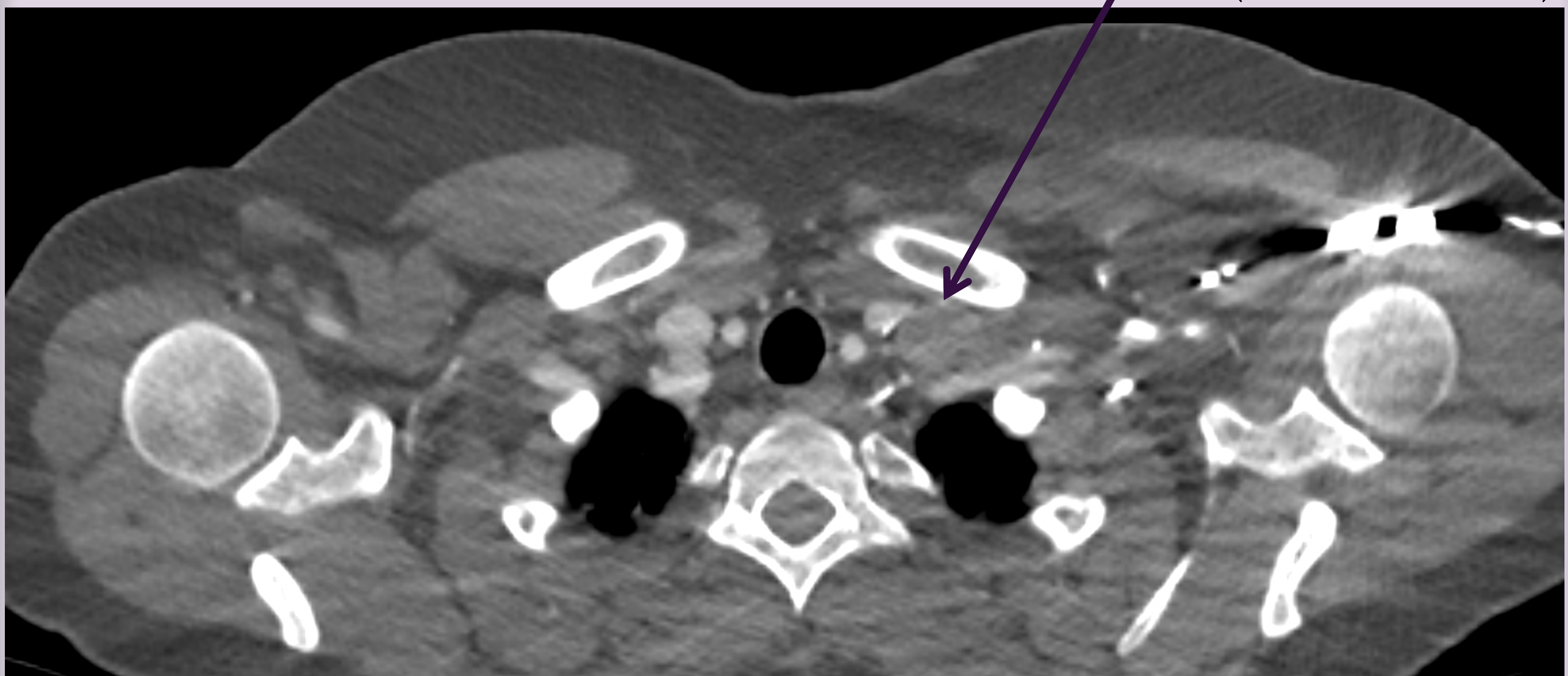


Photons

Protons

I think we rarely cover this area with photons

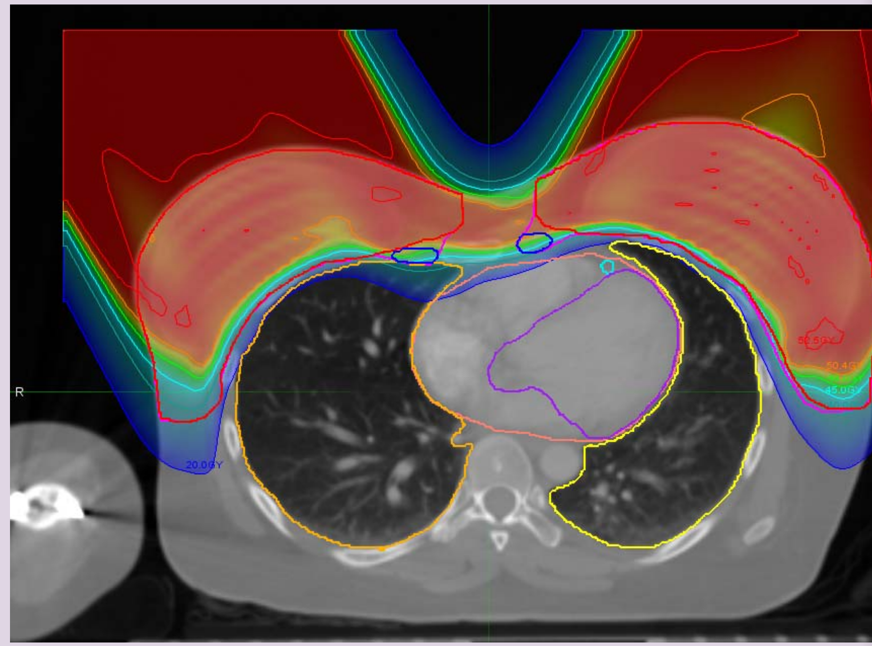
We do see disease here



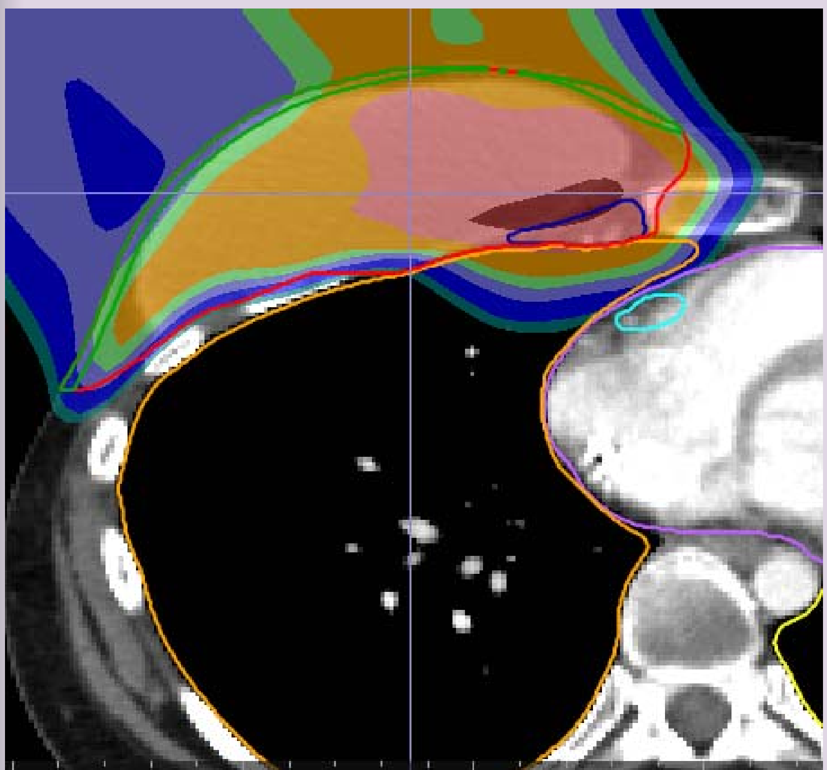
Pre-chemotherapy Chest CT

Patient Selection

- Advanced disease
- IMN involvement
- Cardiotoxic chemo
- Young age
- Permanent implants
- Poor cardiac anatomy
- Left LIQ tumors
- Pre-existing cardiac disease
- Decreased arm mobility



R sided PMRT with IMPT



- Generally, we assume a greater benefit for patients with L sided breast cancer
- R sided patients with IMN involvement can have very high mean heart doses and RCA coronary disease

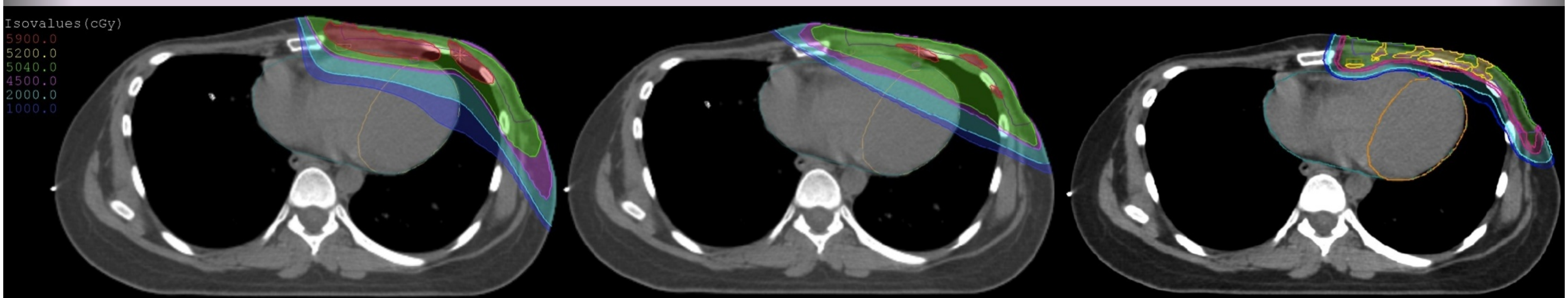
Technical Considerations

- Intact breast more prone to set up uncertainties and swelling/changes in tissue during radiation
- Skin dose is higher with 3D protons
  - Skin dose is intentionally increased to the chest wall when using photons (use of bolus) but skin dose for intact breast is less

For these reasons we started with PMRT, but the use of scanning techniques to minimize skin dose and imaging to ensure set-up accuracy should allow for this treatment

COMPARATIVE DOSIMETRY STUDIES

3D conformal Protons



Photons/Electrons | Photons | Protons

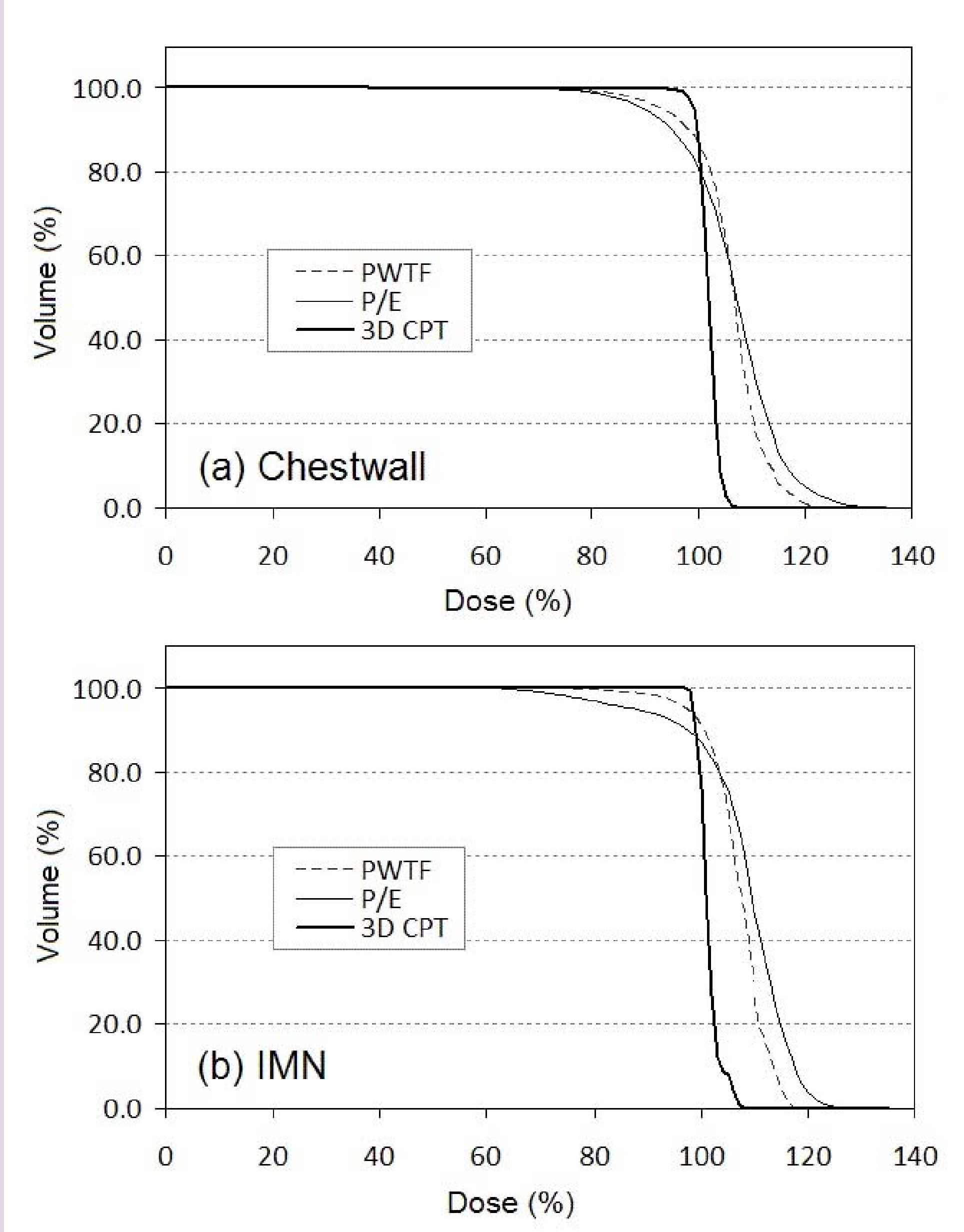
*MacDonald SM, et al, Radiat Oncol,*2013

Chest Wall and IMN

More homogeneous coverage with protons

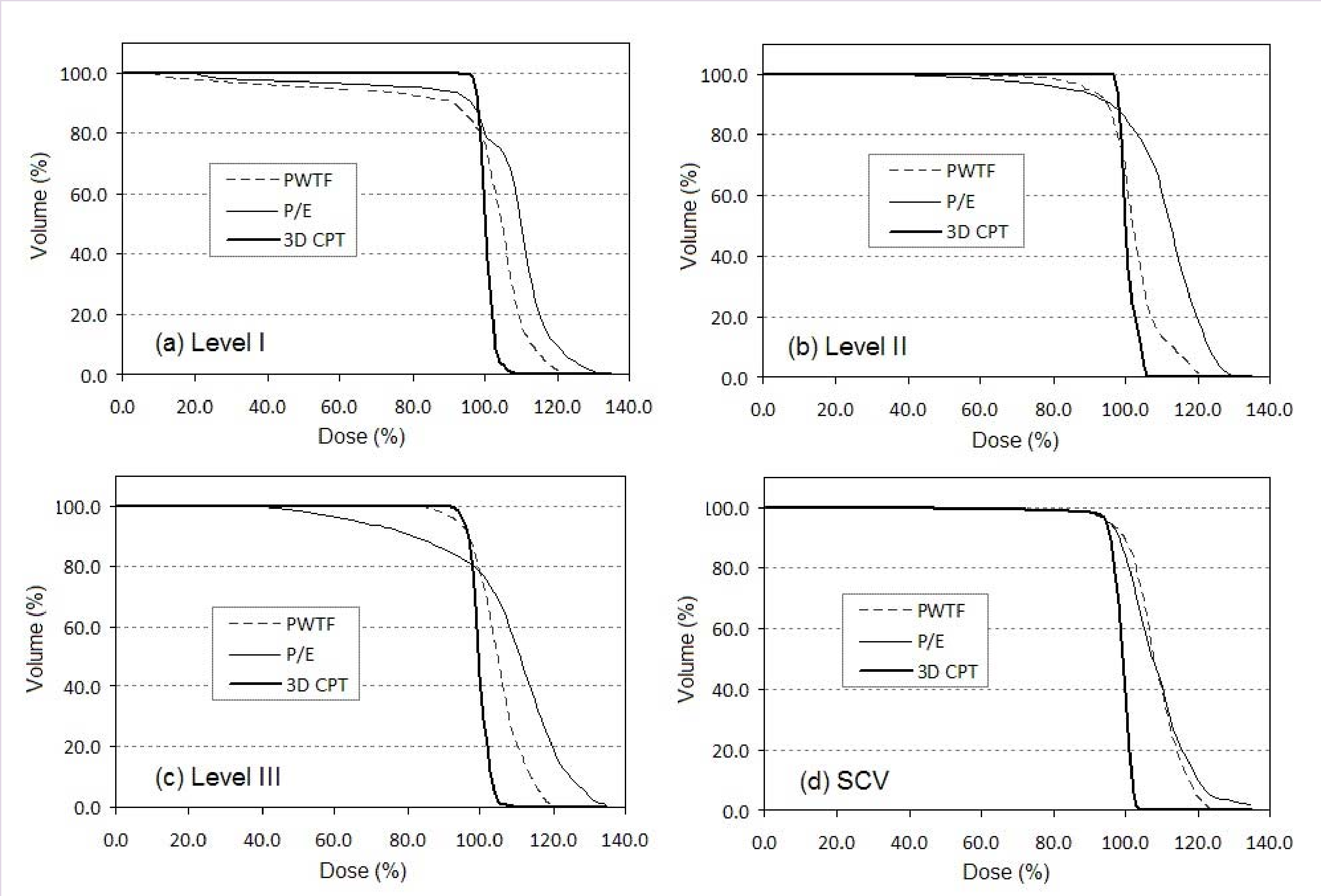
Less “Hot” and “Cold” spots

Improved coverage of target volumes with protons



MacDonald SM, et al, Radiat Oncol,2013

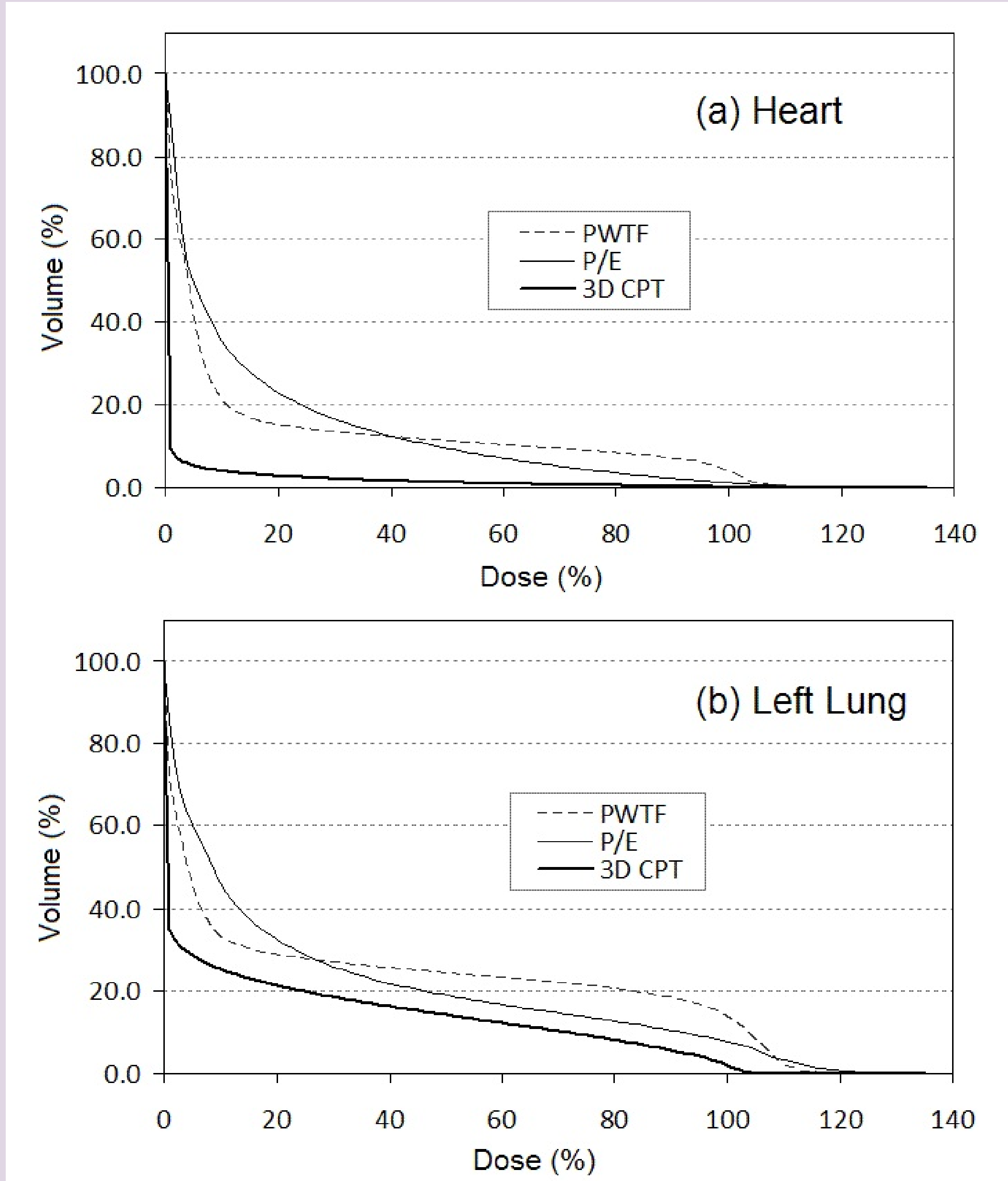
SCV and Axilla



*MacDonald SM, et al, Radiat Oncol,*2013

Heart and Lung

Decreased dose to
Heart and lung



MacDonald SM, et al, Radiat Oncol,2013

Conclusions

- Improved target volume coverage with better avoidance of the heart and lung can be achieved for patients with breast cancer requiring PMRT

- Similar results for implants published

Jimenez RB et al, *Radiother Oncol* , 2013

EARLY CLINICAL EXPERIENCE

PMRT Proton MGH Trial Early Results

- Phase I/II pilot trial to assess feasibility of proton delivery following mastectomy
- Endpoints
  - Acute toxicity; skin toxicity and pneumonitis
  - Secondary: EFS, long-term cosmesis and other toxicity
- Eligibility
  - Requirement of PMRT to chest wall +/- LN
  - No metastatic disease
  - Unfavorable cardiac anatomy (estimated heart V20 >5%)and/or optimal plan would require manipulation or removal of permanent implant (s)

MacDonald et al Int J Radiat Oncol Biol Phys, 2013

Methods

- All patients underwent CT simulation with IVC
- Contours according to RTOG guidelines with exception of exclusion of the ribs from the chest wall, left ventricle and LAD contoured
- Dose to chest wall 50.4 Gy(RBE) and LN 45-50.4 Gy(RBE)

MacDonald et al Int J Radiat Oncol Biol Phys, 2013

Methods

- Patients evaluated weekly and at 4 and 8 weeks following RT
- Skin graded by CTCAE version 4 and photographs obtained if patient signed optional consent for photography
- Strain echocardiograms and ultra-sensitive troponin obtained prior to RT and at 4 and 8 weeks following RT

MacDonald et al Int J Radiat Oncol Biol Phys, 2013

Table 1 Patient Characteristics

	n = 12
Age, median (range) years	42 (31 - 68)
Left-sided cancer	11
T1	2
T2	7
T3	3
N+	11
Lymphovascular Invasion	5
Luminal A/B	6
Triple Negative	3
HER2/neu +	3
Immediate Reconstruction	5
Bilateral	4
Unilateral	1
Delayed Reconstruction	1
Neoadjuvant chemotherapy	5
Adjuvant chemotherapy	7
Hormonal therapy	10
IMN Involvement	3
Duration of RT, median (range) days	42 (37 - 45)

Acute Toxicity

Table 2 Acute toxicities

	Maximum during RT	4 weeks post-RT	8 weeks post-RT
Skin			
Hyperpigmentation	0	2	6
Grade 1	3	8	3
Grade 2	9	0	0
Grade 3	0	0	0

- No cases of Radiation Pneumonitis with median follow up of 6 months (range, 3.5-11.2 mo)

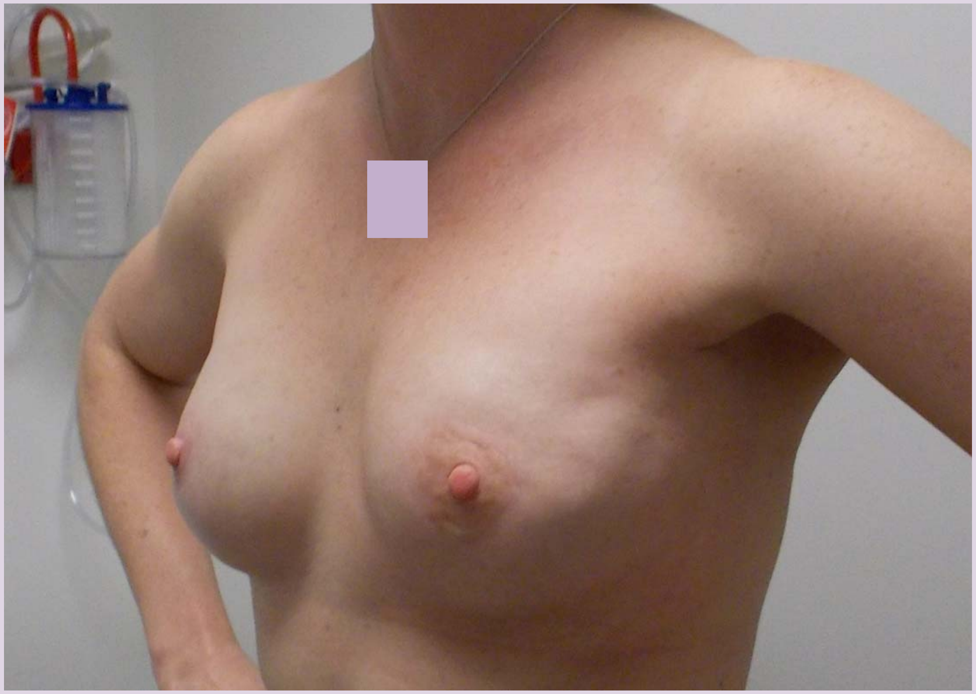
To Date

- 50 patients enrolled on trial
- No grade 4 toxicity/ Skin grade 2
- 1 pneumonitis
- 1 implant loss
- 2 rib fractures (1 spontaneous and 1 after fall and with diagnosis of osteopenia)
- We have seen implant contracture
- We have seen esophagitis
- 3 patients with telangectasia
- 30 pts strain data & us troponin no abnormality

Bilateral Nipple Sparing Mastectomy with Implants

End of RT | 4 weeks after RT | 8 weeks after RT

1 year post protons



Still with excellent cosmesis 3 years post-protons

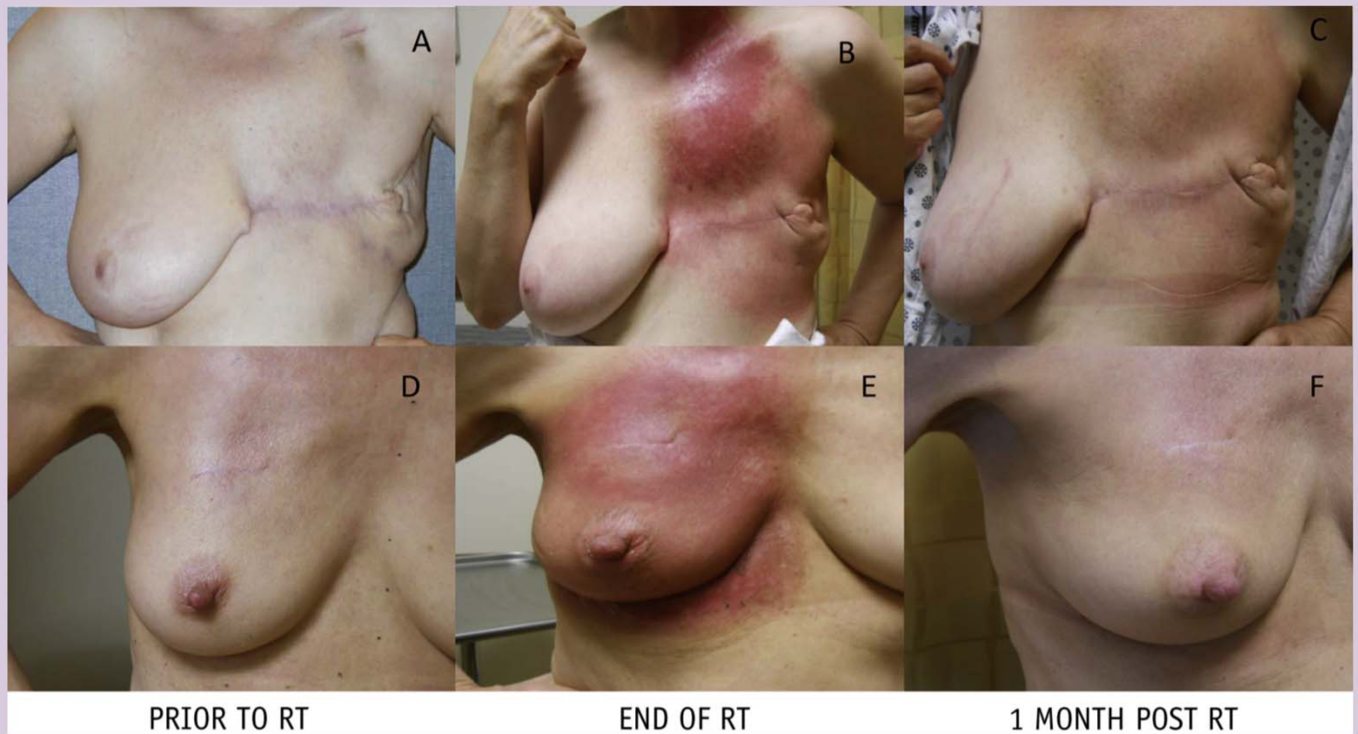
Telangectasia 2 ½ years post

Procure Experience

- 30 patients (PMRT and BCT)
- 71.4% grade 2 skin
- 28.6% grade 2 esophagitis
- Grade 3
- 1 implant loss

Cuaron, et el IJROBP June 2015

Procure Experience



Cuaron, et el IJROBP June 2015

Conclusions

- Proton radiation is feasible with acceptable acute toxicity for select patients when conventional techniques are not optimal
- Additional follow up is necessary to evaluate long-term outcomes

MacDonald et al Int J Radiat Oncol Biol Phys, 2013

CLINICAL EXPERIENCE FOR APBI

Proton Therapy for PBI; MGH

- In the setting of a Phase I/II clinical trial, 19 patients were treated with proton 3D-PBI & 79 with photon/electron APBI
- Dose was 32 Gy(RBE) at 4 Gy(RBE) per fraction delivered BID over 4 days
- One to three fields were used to provide PTV coverage & one field was treated per fraction

**Trials of APBI & protons combine 2 research questions (modality and fractionation)*

Kozak et al, IJROBP 2006
Galland-Girodet, IJROBP 2014

Clinical Outcomes

- Median f/u 82.5 months
- No significant difference in LRC
- 7 Year physician rated outcomes
  - Good-excellent cosmesis
    - 62% for protons v 94% for photons
  - Telangiectasia
    - 69% for protons v 16% for photons
  - Pigmentation changes
    - 54% for protons v 22% for photons

Galland-Girodet, et al IJROBP 2014

Clinical Outcomes

- No difference in breast pain, breast edema, fat necrosis, skin desquamation, rib pain or rib fracture
- No difference in patient- reported cosmetic outcome or patient satisfaction

Galland-Girodet, et al IJROBP 2014

Conclusions

- Local control is similar
- Cosmesis as reported by physicians inferior
  - Recommend use of more than one field per treatment plan and all fields delivered per treatment
  - IMPT/scanning will likely improve skin sparing

Non-Target Tissues

- The non-target breast tissue volume receiving 50% of the prescribed dose was reduced by 36% with proton therapy as compared to mixed beam therapy.
- Small but significant reductions in dose to heart and lung

Kozak et al, IJROBP 2006
Galland-Girodet, IJROBP 2014

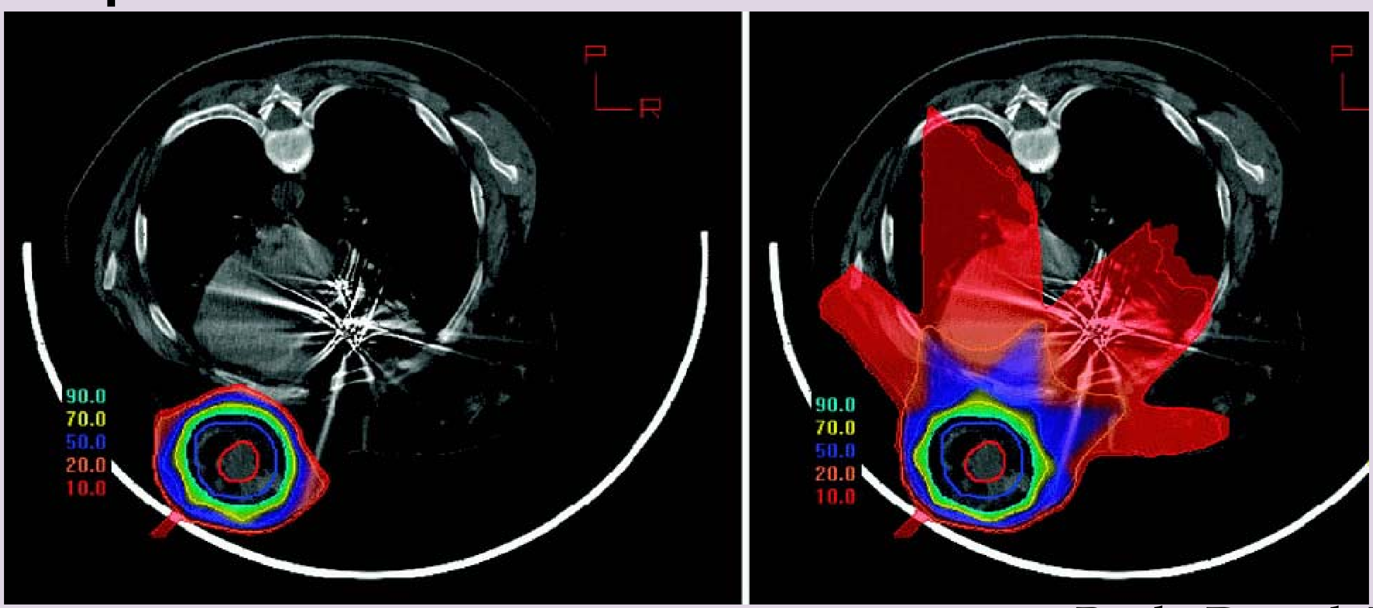
Conclusions

- Clinically feasible
- Small but significant sparing of heart and lung with the use of protons
- Substantial sparing of non-target breast tissue
  - External beam option for PBI that increases sparing of non-target breast tissue

Kozak et al, IJROBP 2006

Protons PBI; Loma Linda

- Phase I/II clinical trial 100 patients, all protons
- Dose 40 Gy(RBE) at 4 Gy(RBE)/fx over 10 treatment days, 2 to 4 fields treated daily, composite skin dose < 90%



Bush, D et al, IJROBP, 2014

Results Proton PBI Loma Linda

- Median f/u 60 months
- 5 year LRC 97%
- Patients and physician reported cosmesis good to excellent in 90% patients
- Only 7 patients with telangiectasia (grade I)

Bush, D et al, IJROBP, 2014

Cost Comparison

- MGH reported cost analysis for proton PBI
  - 3D-CPBI proton $13, 200
  - 3D-CPBI photon $ 5, 300
  - Whole breast RT $ 10, 900
- Although protons more expensive WB & photon PBI, less expensive than PBI brachytherapy
  - Whole breast RT $10, 600
  - Mammosite $ 18, 300
  - Interstitial $ 17, 300

Taghian et al, IJROBP 2006; Suh, et al, IJROBP2005

Overall Conclusions APBI

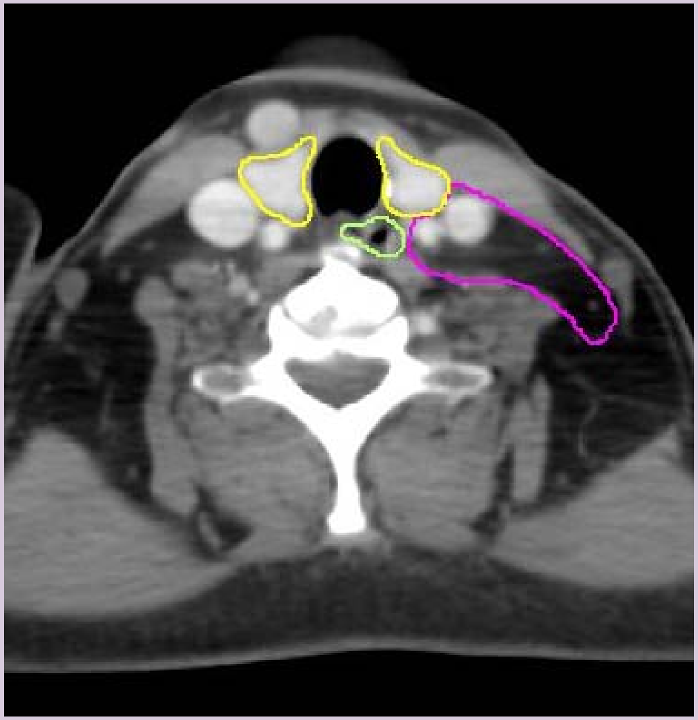
- Still awaiting results of RTC (NSABP B-39/RTOG 0413) to establish APBI as standard
- Delivery with protons requires careful attention to skin dose
  - Perhaps 90% established by Loma Linda is a good constraint
- Immobilization for intact breast and set up verification of paramount importance

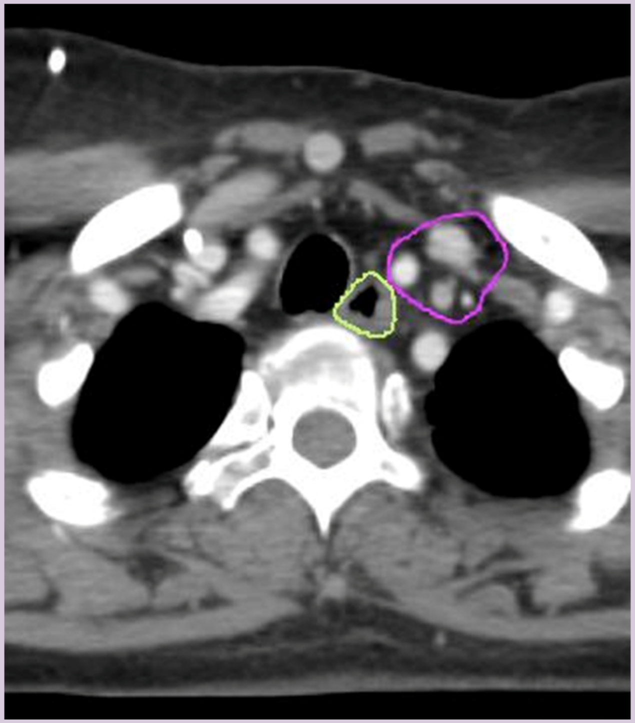
Overall Conclusions APBI

- Proton APBI is more expensive than photon APBI but less expensive than brachytherapy
- Benefit is uninvolved breast tissue sparing & small but significant reduction cardiac and pulmonary tissues

Things we have learned

Esophagus & Thyroid Gland

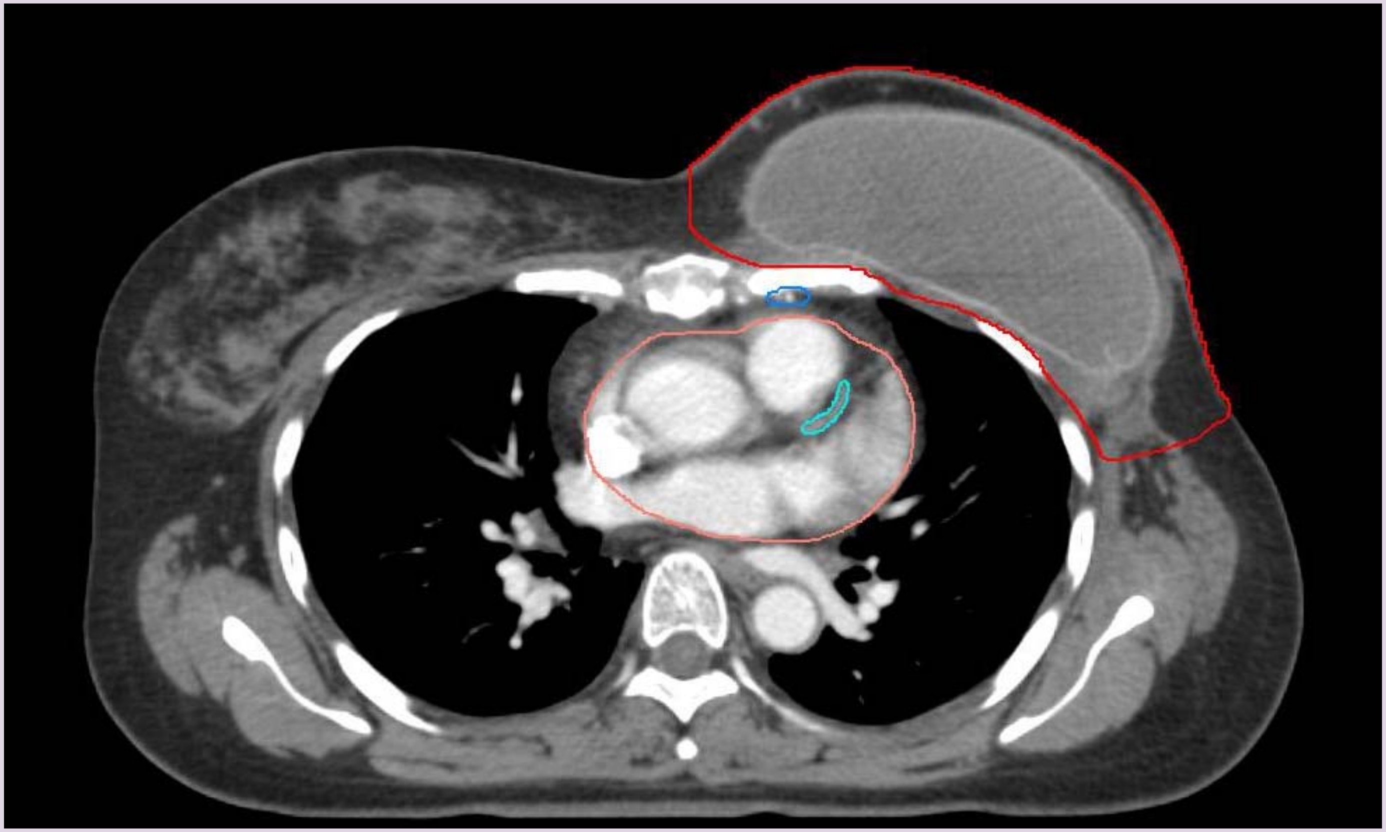




SCV volume is in very close proximity to the esophagus and thyroid

Limit maximum esophageal dose to 40 Gy(RBE); No limit thyroid, but obtain pre-treatment TSH

IV Contrast helpful for Vessels/Left Ventricle



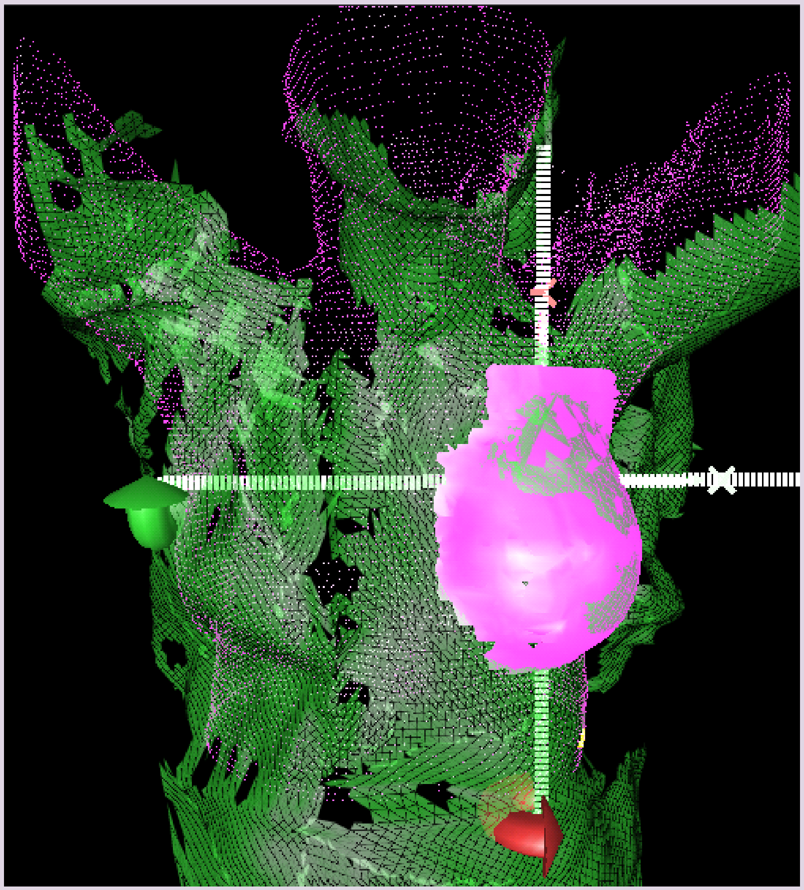
Limit maximum LAD dose to 3 Gy(RBE); Left Ventricle to 5 Gy(RBE)
Mean heart dose < 0.5-1 Gy(RBE)

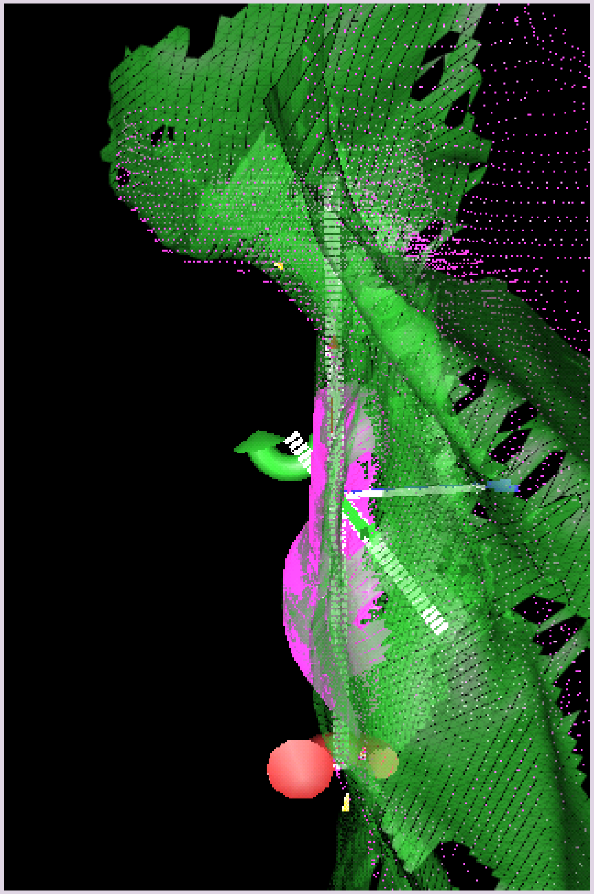
Feng, et al Int J Radiat Oncol Biol Phys. 2011

What you contour is what you treat

To treat skin in this area, you must connect SCV to IMN

Patient Set up/ Vision RT



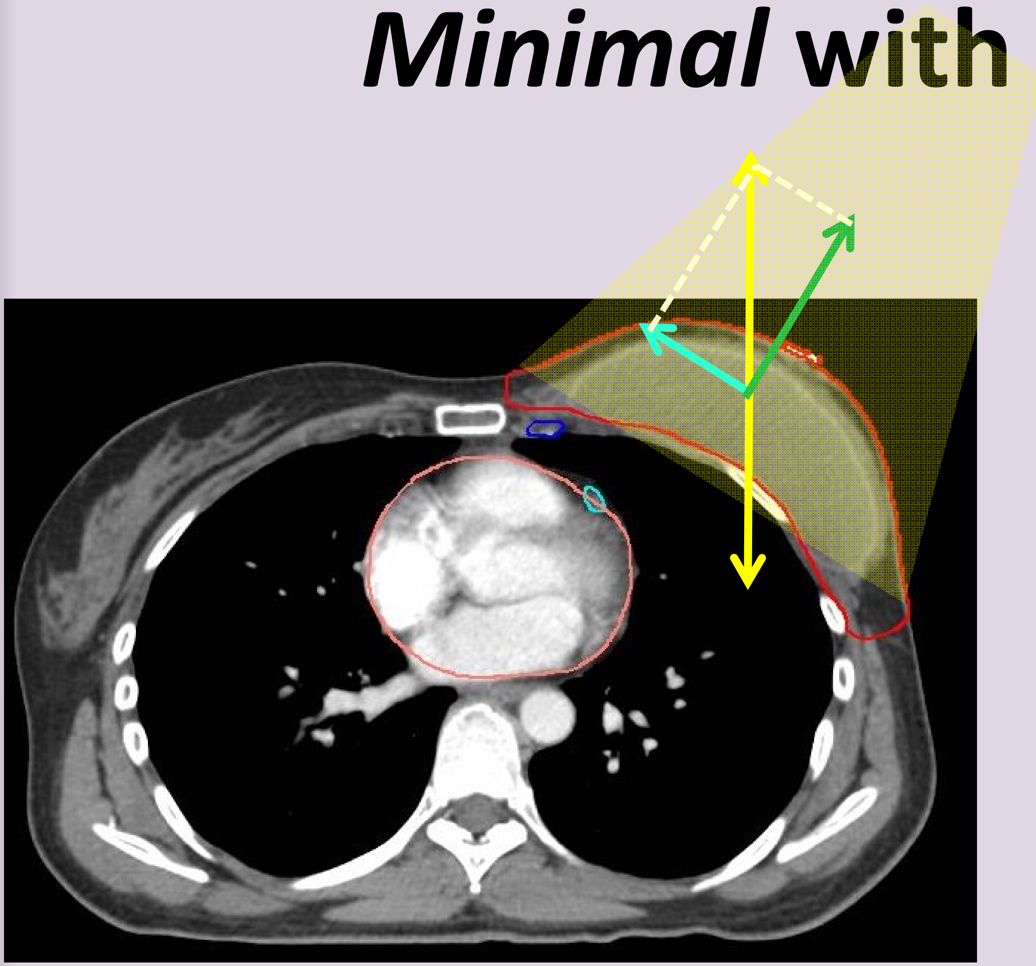


Courtesy of Estelle Batin

Arm posts / Chin strap

Courtesy of Estelle Batin

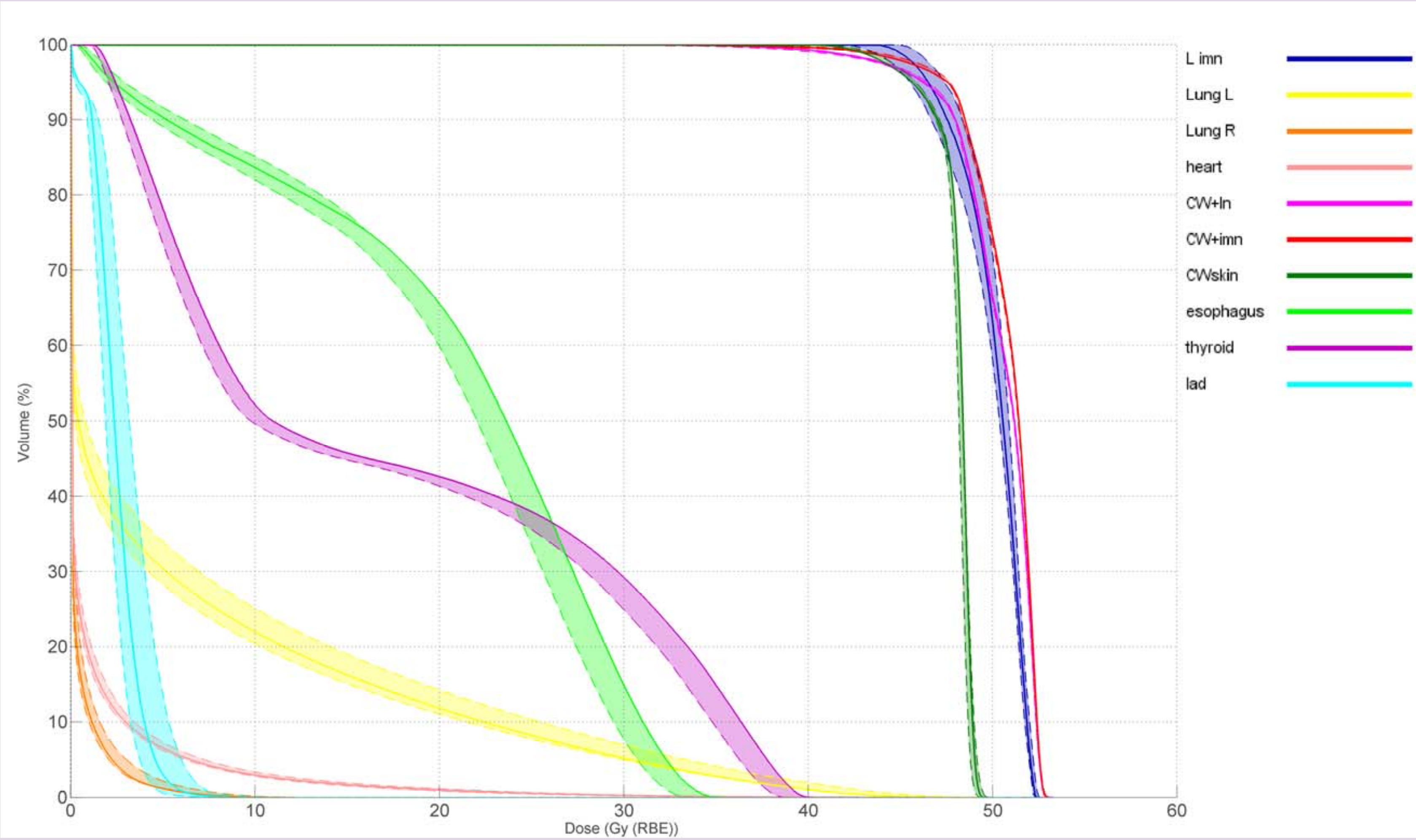
Target Motion Due to Respiration *Minimal* with Protons



- AP motion ~ 3 mm
- Beam at 30 degree from vertical
- Motion along beam has no effect on dose distribution
- Targeting error (motion perpendicular to beam) ~ 1.5 mm

Slide Courtesy of Hsaio-Ming Lu

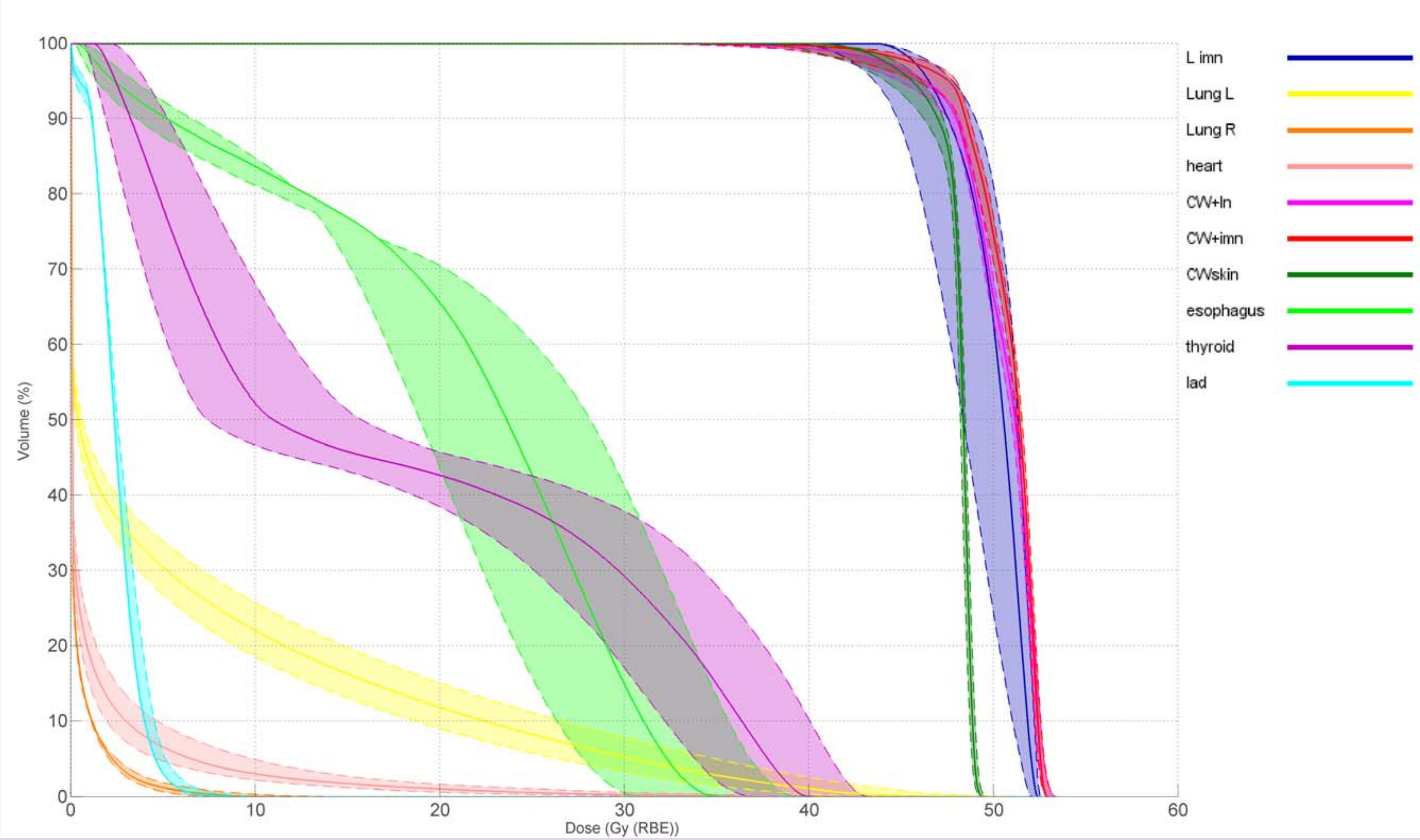
Respiratory Motion



10 phases from 4D CT; solid line planned treatment

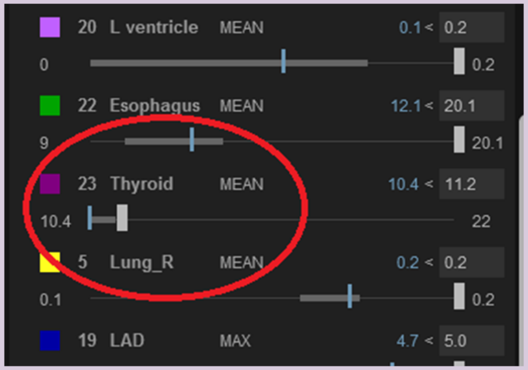
Courtesy of Nick Depauw

Robustness



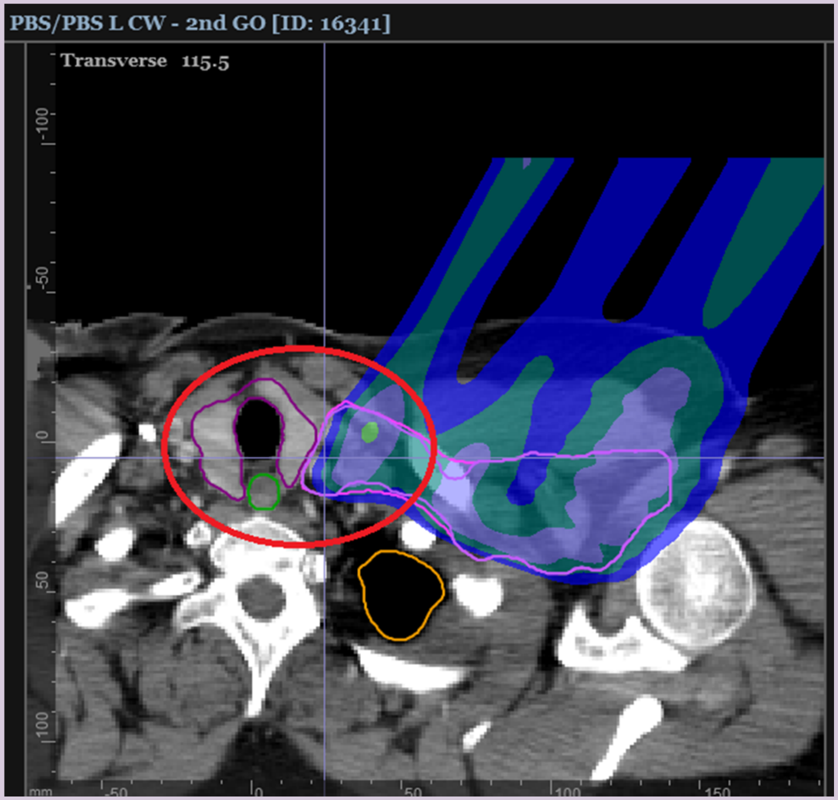
+/- 3 mm & +/- 2° ; solid line planned treatment

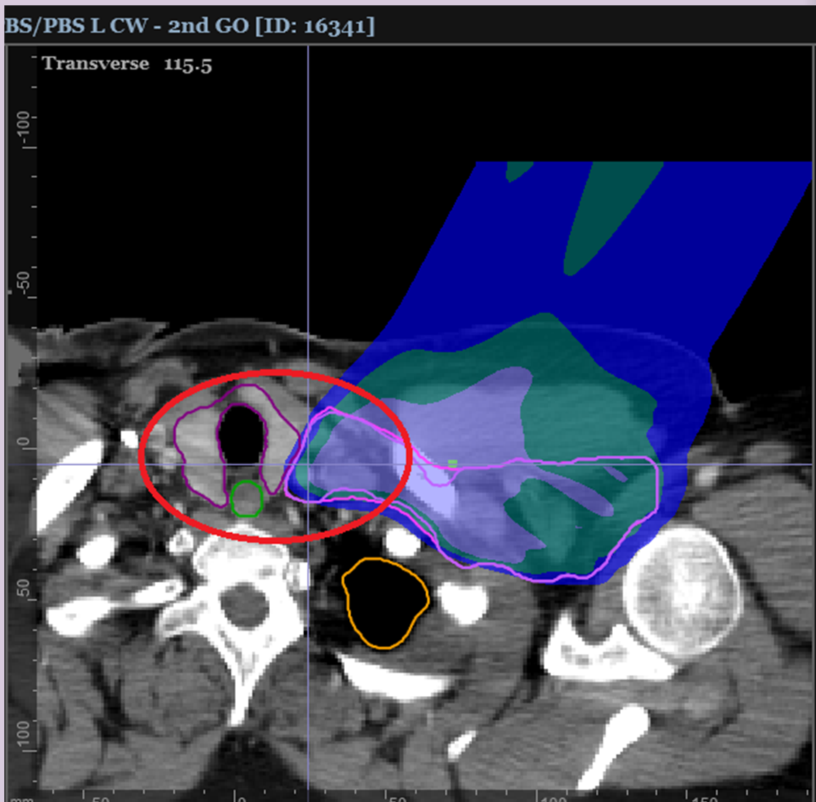
Courtesy of Nick Depauw



Favor Scanning

More Efficient, No Match, Skin Dose & Ability for Adjustments





FUTURE

PCORI Breast RTC

Justin Bekelman PI; Shannon MacDonald and Oren Cahlon Co-PI

Locally Advanced Breast Cancer (Stage IIA-IIIC) Requiring breast/chest wall and regional nodal RT

STRATIFICATION

(by cardiac risk factors; Age)

RANDOMIZATION

Arm 1

Photon RT

Arm 2

Proton RT

Target accrual 1716

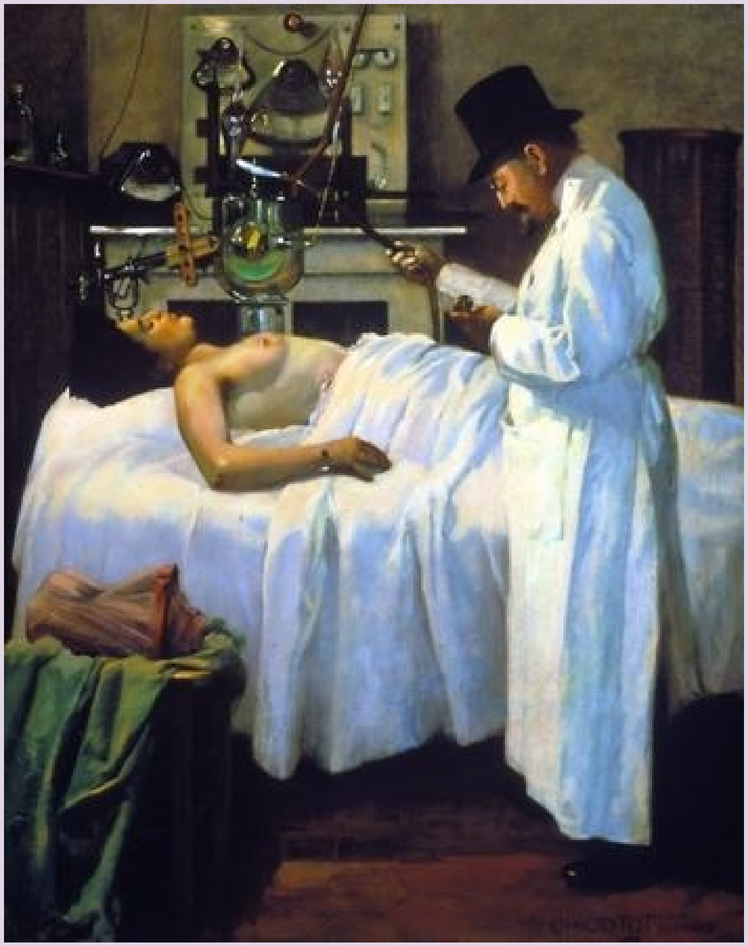
Specific Aims

- Assess effectiveness protons v photons in reducing major cardiovascular events
- Assess non-inferiority of protons v photons LRR
- Assess effectiveness in improving HRQOL
- Develop predictive models to examine association of RT dose and MCE

Conclusions

- Protons may be of benefit for patients with LABC & early breast cancer
- Dosimetric comparisons suggest superior plans with protons, further improved with PBS with ability to spare skin
- Delivery is feasible, acute toxicity acceptable, but long-term follow up is needed

Thank you



- Hsiao-Ming Lu, PhD
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- Jay Flanz, PhD