V ZOOM Journal Club 2015

Bologna, 19 Febbraio 2016

NH Hotel De La Gare

Prevenzione della Cardiotossicità

Contornazione e Tecnica

Alessandra Fozza

Azienda U.L.S.S. 12 VENEZIANA

BACKGROUND

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2013 VOL. 368 NO. 11

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

- ✓ RT beginning in the 1950
- ✓ Techniques for measuring cardiac (mean) dose
- ✓ Average anatomy

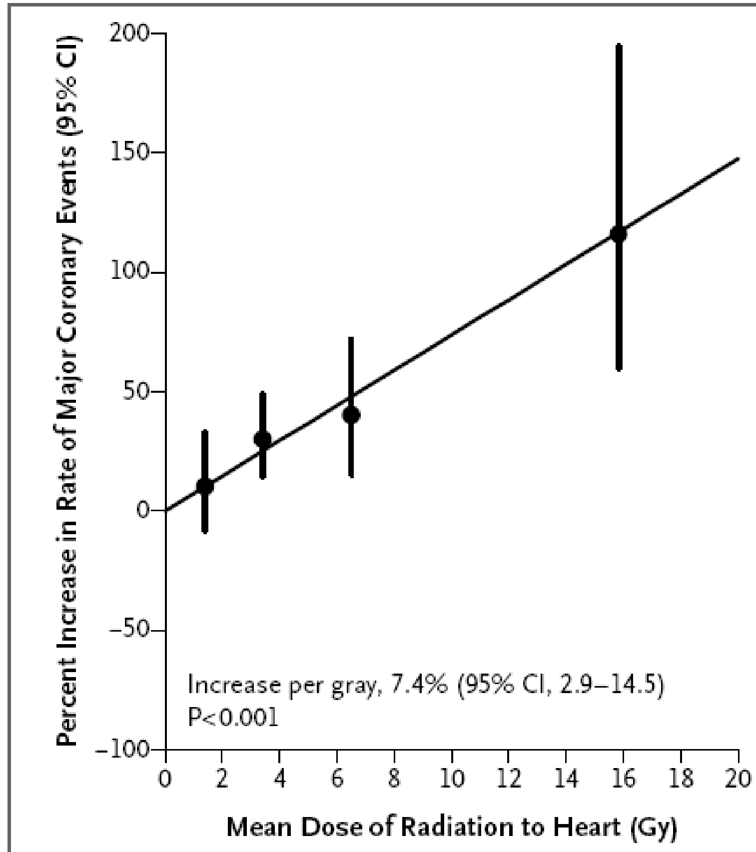


Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

…increased efforts to minimaze cardiac dose in breast cancer radiotherapy may be beneficial to patients!

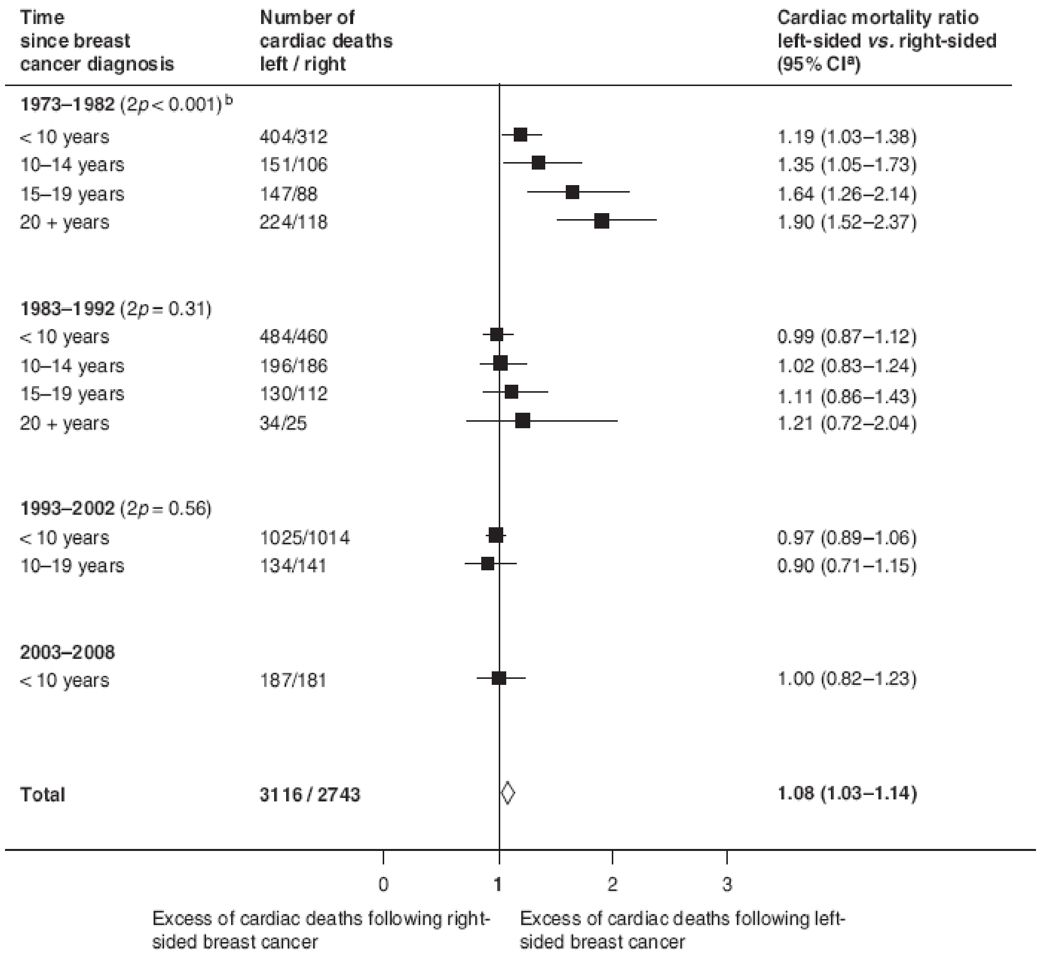
BACKGROUND

Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer

BJC
British Journal of Cancer (2013) 108, 179–182 | doi: 10.1038/bjc.2012.575

K E Henson*[,1], P McGale[1], C Taylor[1] and S C Darby[1]

- 558.871 pts
- 1973-2008
- left vs right

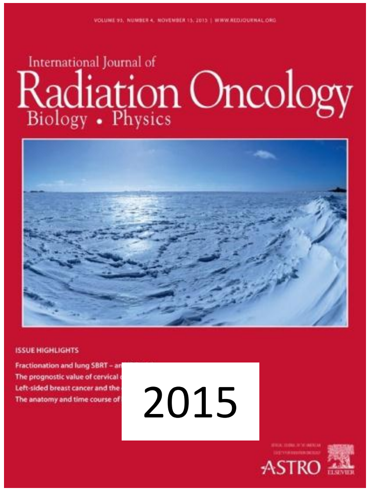


Heart dose from breast cancer RT

Clinical Investigation

Exposure of the Heart in Breast Cancer Radiation Therapy: A Systematic Review of Heart Doses Published During 2003 to 2013

Carolyn W. Taylor, DPhil, FRCR,* Zhe Wang, PhD,*
Elizabeth Macaulay, MSc,† Reshma Jagsi, MD, DPhil,‡
Frances Duane, FFRRCSI,* and Sarah C. Darby, PhD*



Whole-heart dose: the most commonly reported measure

1.1 → 8.5 Gy

Average mean heart dose

Variability affected by:

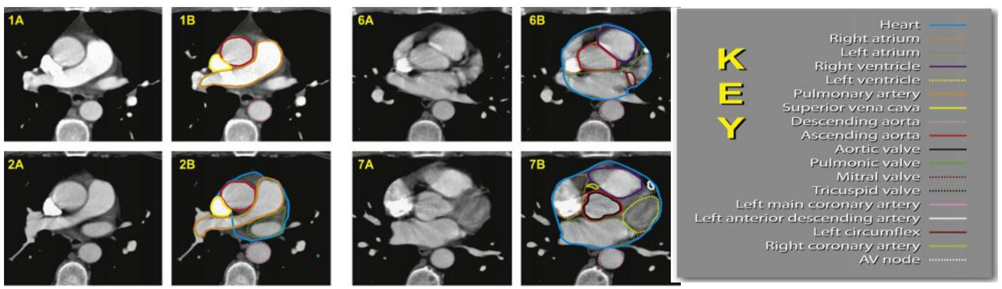
- **Tecnique**
- More extensive **targets**
- Unfavorable **anatomy**
- **Interobserver variation** contouring

Heart Contouring

DEVELOPMENT AND VALIDATION OF A HEART ATLAS TO STUDY CARDIAC EXPOSURE TO RADIATION FOLLOWING TREATMENT FOR BREAST CANCER

Mary Feng, M.D.,* Jean M. Moran, Ph.D.,* Todd Koelling, M.D.,† Aamer Chughtai, M.D.,‡
June L. Chan, M.D.,* Laura Freedman, M.D.,* James A. Hayman, M.D.,*
Reshma Jagsi, M.D., D. Phil.,* Shruti Jolly, M.D.,* Janice Larouere, M.D.,*
Julie Soriano, M.D.,* Robin Marsh, C.M.D.,* and Lori J. Pierce, M.D.*

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 1, pp. 10–18, 2011



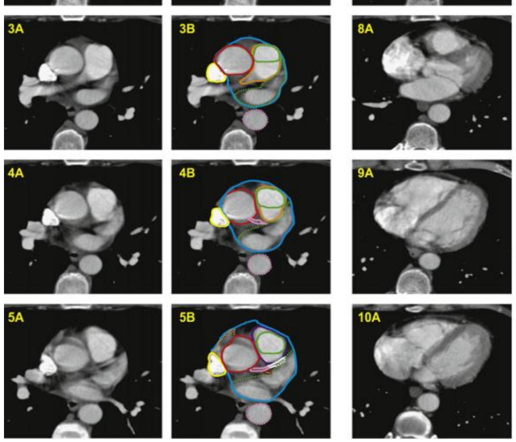


Table 4. Spectrum of radiation damage to the heart*

Structure	Abnormality	Natural history	Pathology
Pericardium	Pericarditis	Chronic asymptomatic effusion and/or pericarditis with symptoms: hemodynamic compromise with either constriction or tamponade	Fibrous thickening and fluid production
Myocardium	Myocarditis	Progressive diastolic dysfunction and restrictive hemodynamics with symptoms: CHF	Diffuse interstitial fibrosis/ microcirculatory damage leading to capillary obstruction/ extensive fibrosis
Endocardium	Valvular damage	Over time, progressive stenosis and regurgitation	Cusp and/or leaflet fibrosis
Vascular System	Arteritis	Premature CAD/accelerated atherosclerosis Pulmonary hypertension	Ostial and proximal stenosis; LAD, RCA, and left main more than left circumflex Pathology similar to atherosclerosis
Conduction System		All forms of heart block and conduction delay	Fibrosis of conduction system
Autonomic Dysfunction		Supraventricular tachycardia; heart rate variability	

Heart Contouring

- ✓ Data are conflicting regarding the association of RT with **valvular dysfunction**

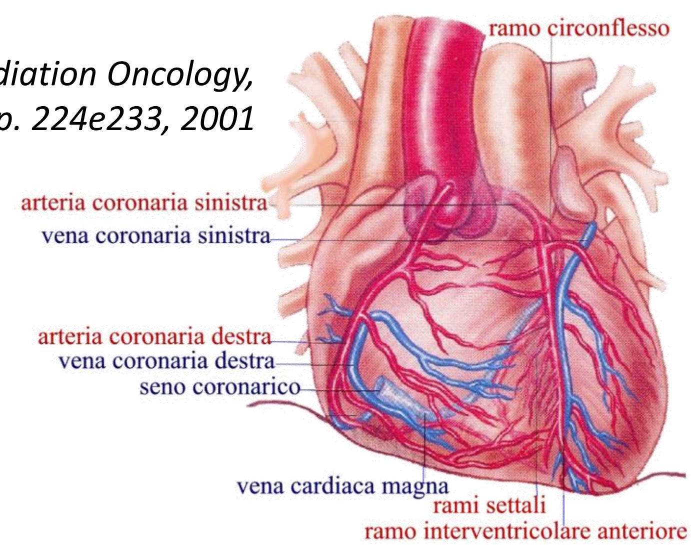
  - *Larris EE et al. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast conservation treatment . JCO 2006, Vol. 1, No. 24, pp. 4100-6, 2006*
  - *Borger JH et al. Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: the role of irradiated heart volume. Int J Radiat Oncol Biol Phys. 2007 Nov 15;69(4):1131-8. Epub 2007 Jul 2*

- ✓ In breast cancer patients, the **most commonly affected vessel is the left anterior descendent coronary artery**, usually encompassed by the highest dose volume, both in post-mastectomy and breast-conserving treatment setting

  - *Gagliardi D et al. Partial irradiation of the heart. Seminars in Radiation Oncology, Vol. 11, No. 3, pp. 224e233, 2001*

Table 3. Mean absolute value*

Structure	Pre-atlas (mean ± SD) dose difference (Gy)	Post-atlas (mean ± SD) dose difference (Gy)	*p* value
Heart	0.88 ± 0.15	0.14 ± 0.14	<0.001
Left main coronary artery	1.68 ± 1.53	0.88 ± 1.56	0.005
LAD artery	3.90 ± 2.80	2.56 ± 3.31	<0.001
Right coronary artery	1.15 ± 1.07	0.61 ± 0.39	0.001
Left ventricle	0.25 ± 0.20	0.15 ± 0.14	0.13
Right ventricle	1.06 ± 0.73	0.46 ± 0.37	0.008



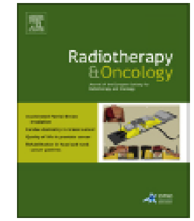
Heart Contouring

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

Radiotherapy and Oncology 108 (2013) 254–258

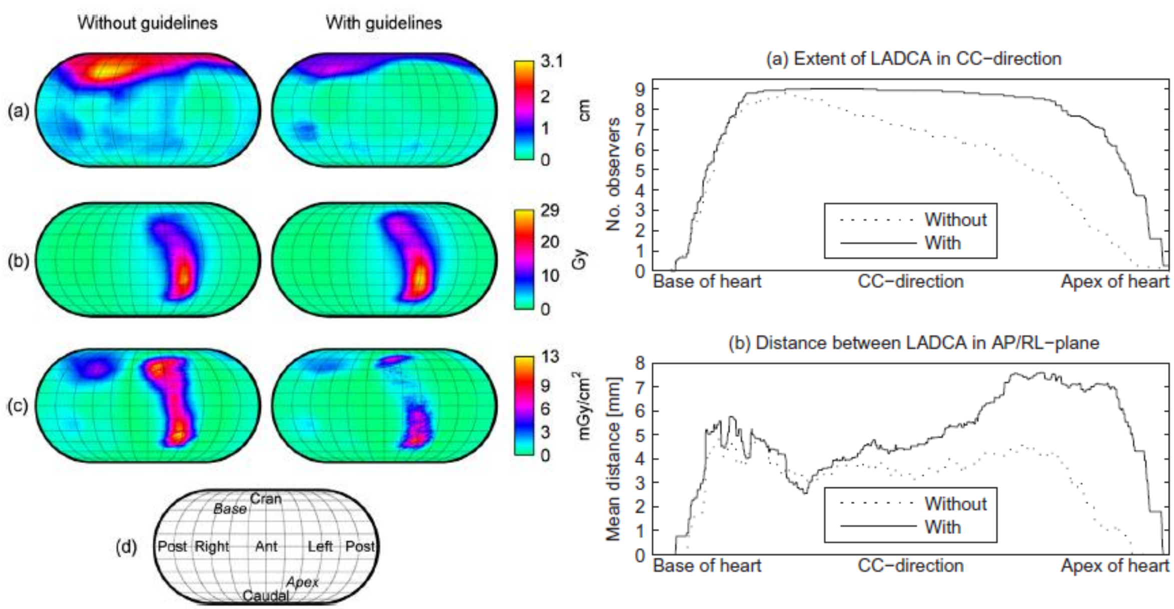
journal homepage: www.thegreenjournal.com



Cardiac dosimetry in breast cancer

Inter-observer variation in delineation of the heart and left anterior descending coronary artery in radiotherapy for breast cancer: A multi-centre study from Denmark and the UK

CrossMark



CV in the estimated doses to the **heart**:

- ✓ *mean dose* **7.5%** without and **3.6%** with guidelines
- ✓ *maximum dose* **8.7%** without and **4.0%** with guidelines.

CV in the estimated doses to the **LADCA** :

- ✓ *mean dose* **27%** without and **29%** with guidelines
- ✓ *maximum dose* **39%** without and **31%** with guidelines

For the **heart** → **little** inter-observer **variation** in the estimated dose especially when guidelines is used

For **LADCA** → **substantial variation** in the estimated dose, which **is not reduced with guidelines**

OUTLINE
2015

- **Cardiac radiation dose** and **Heart atlas**
- **Reduction in cardiac exposure**:

  Which technique?
  - Deep-inspiratory **Breath-hold**
  - **IMRT** and Arc Therapy
  - **Prone** breast radiotherapy
  - **Proton** Beam Therapy

Cardiac Radiation Dose

- ✓ Conventional CT is a fundamentally static imaging modality without the capability to capture and depict the cardiac motion. Instead, **heart is usually blurred in CT images** due to the **motion artifacts**

- ✓ Without special contrast dye, CT provides limited contrast between blood in heart chambers and the surrounding myocardium. The heart region in TPS is actually a mixture of myocardium and blood, although **only the radiation dose to the myocardium is accountable for heart risks**

Chen Ting et al. Tagged MRI based cardiac motion modeling and toxicity evaluation in breast cancer radiotherapy. Frontiers in Oncology; 5:1-4.2015

Cardiac Radiation Dose

- ✓ There is **significant intra- and inter-fractional heart motion**. As heart beats involuntarily during and between radiation treatments, myocardium deforms and moves non-rigidly against the fixed radiation beam so that **the static dose distribution calculated in CT based TPS does not reflect the accurate radiation dose distribution in heart**

- ✓ Based on radiation beam geometry, **only part of the heart will receive clinically significant level of radiation** during breast cancer treatment. It is possible that the **global heart function remains stable temporarily** while cells in the irradiated part of the myocardium lose part or all of their functions. **Regional heart function**, which can be derived from regional heart wall motion and strain analysis, is a **better indication of heart damage** corresponding to radiation dose

Chen Ting et al. Tagged MRI based cardiac motion modeling and toxicity evaluation in breast cancer radiotherapy. Frontiers in Oncology; 5:1-4.2015

Cardiac Radiation Dose

frontiers in ONCOLOGY

OPINION ARTICLE
published: 03 February 2015
doi: 10.3389/fonc.2015.00009

Tagged MRI based cardiac motion modeling and toxicity evaluation in breast cancer radiotherapy

Ting Chen[1], Meral Reyhan[1], Ning Yue[1], Dimitris N. Metaxas[2], Bruce G. Haffty[1] and Sharad Goyal[1]*

- ✓ Intra-fr motion 1.3±0.3cm (kV-fluoroscopy)
- ✓ Inter-fr location 1.5cm (CBCT)

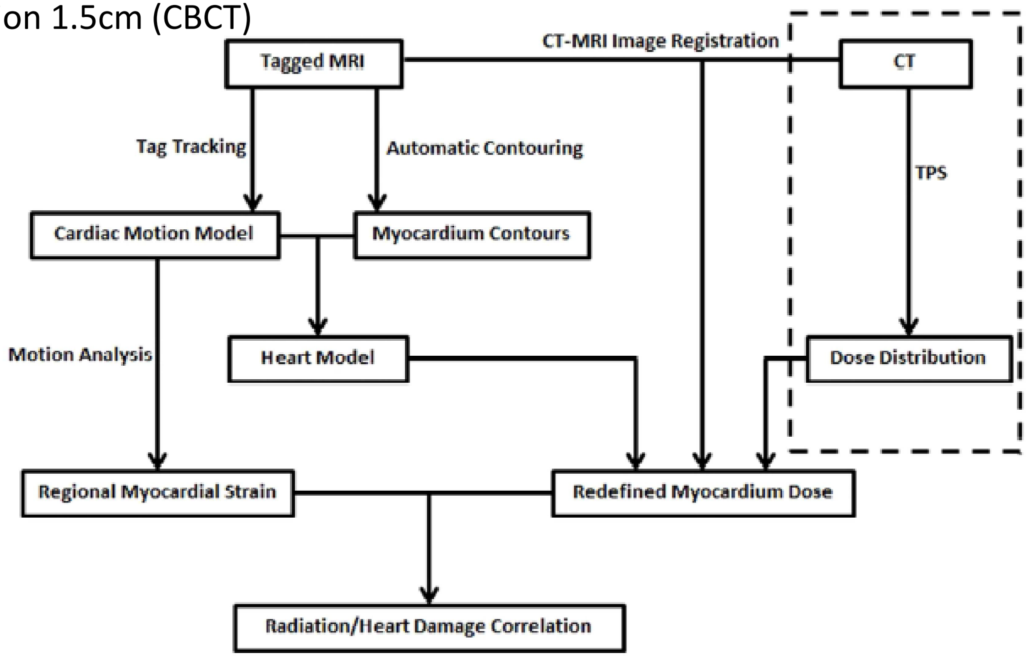


FIGURE 1 | The work flow of the cardiac motion tracking and myocardium dose evaluation method. The part encircled by the dashed line is the current CT based heart dose calculation and evaluation in the treatment planning system.

- ✓ Establishing a **correlation between myocardium dam-age and radiation dose** for breast cancer pts using MRI
- ✓ Using MRI, regional heart function loss could be detected and the **radiation dose can be adjusted by generating the accumulative dose during cardiac cycle**

Heart Contouring

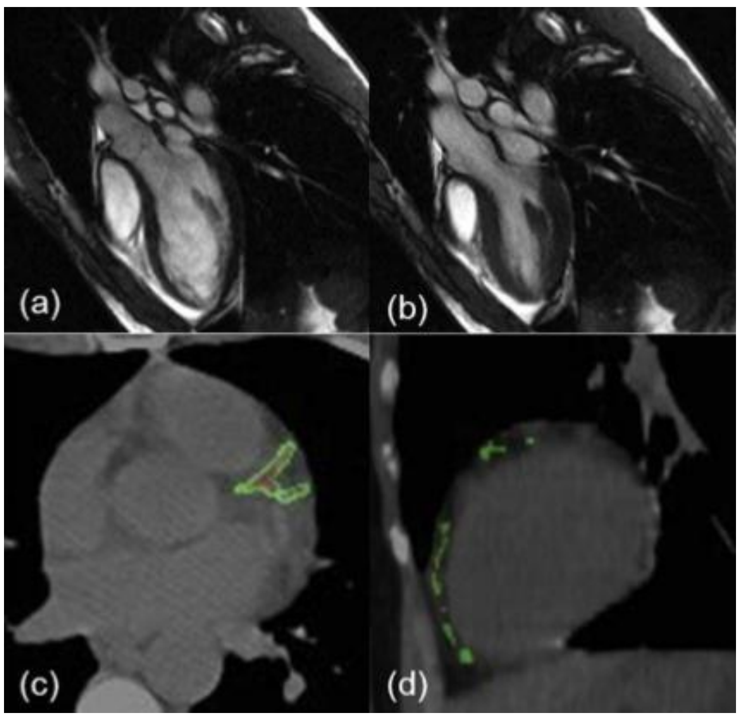
Accuracy of Routine Treatment Planning 4-Dimensional and Deep-Inspiration Breath-Hold Computed Tomography Delineation of the Left Anterior Descending Artery in Radiation Therapy

Physics Contribution

International Journal of Radiation Oncology biology • physics

Int J Radiation Oncol Biol Phys, Vol. 91, No. 4, pp. 825–831, 2015

Benjamin M. White, PhD,* Sabina Vennarini, MD,† Lilie Lin, MD,* Gary Freedman, MD,* Anand Santhanam, PhD,‡ Daniel A. Low, PhD,‡ and Stefan Both, PhD*



1) Serie planari risemplificate di immagini **RMN** x creare un volume 3D
2) Algoritmo di **registrazione deformabile** di immagini per determinare il **dislocamento** del tessuto durante il ciclo cardiaco
3) I **movimenti misurati** poi usati come **limite spaziale** per caratterizzare le “sbavature” nella delineazione della LAD da parte dei clinici (radiologi)
4) Gli artefatti di movimento coronale sono stati quantificati applicando un **filtro x accentuare la struttura della LAD** rispetto alle sbavature di movimento
5) **Co-registrato sulla 4D-CT** la massima insp ed esp per quantificare il movimento della LAD

Heart Contouring

Physics Contribution

International Journal of Radiation Oncology biology • physics

Accuracy of Routine Treatment Planning 4-Dimensional and Deep-Inspiration Breath-Hold Computed Tomography Delineation of the Left Anterior Descending Artery in Radiation Therapy

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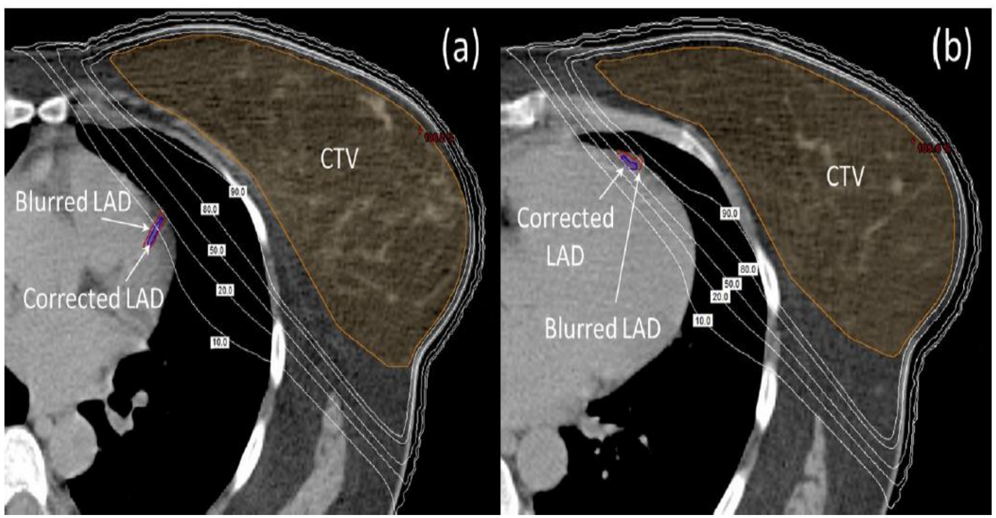

- ✓ The **LAD** volume **overestimation** had the dosimetric impact of **decreasing the reported mean LAD dose** contour by **23% +/- 9%** on average in the DIBH.
- ✓ An **anisotropic margin** of **2.7 mm (LR)**, **4.1 mm (SI)**, **and 2.4 mm (AP)** was quantitatively determined to account for motion blurring and patient setup error

OUTLINE
2015

Reduction in cardiac exposure: Which technique?

- Deep-inspiratory **Breath-hold**
- **IMRT** and Arc Therapy
- **Prone** breast radiotherapy
- **Proton** Beam Therapy

✓ Dosimetric studies

✓ Small n° of pts

✓ Many retrospective

✓ No clinical impact data

Deep-inspiratory Breath-hold

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

2014

Review

Cardiac dose sparing and avoidance techniques in breast cancer radiotherapy

CrossMark

Chirag Shah [a], Shahed Badiyan [b], Sameer Berry [a], Atif J. Khan [c], Sharad Goyal [c], Kevin Schulte [a], Anish Nanavati [d], Melanie Lynch [a], Frank A. Vicini [e,*]

Technique	Key findings	Cardiac dose reductions
Breath hold	(1) Imaging studies confirm deep inspiration optimal point for cardiac protection (2) Feasibility demonstrated in clinical setting with treatment times less than 20 min (3) Dosimetric studies demonstrate reduction in low dose and high dose cardiac dosimetries (4) Studied with breast conserving therapy with or without regional therapy and in the post-mastectomy setting (5) Can be combined with Intensity Modulated Radiation Therapy	(1) Decreased cardiac volume in field [9–11,18,20–23,30] (2) Reduced mean, maximum, $V_{5\,Gy}$, $V_{10\,Gy}$, $V_{15\,Gy}$, $V_{20\,Gy}$, $V_{25\,Gy}$, $V_{30\,Gy}$, $V_{40\,Gy}$, $V_{50\,Gy}$ [12,16,17,21,22,24–30] (3) Reduced left anterior descending dose [17,25,27,29–30] (4) Reduced cardiac mortality probability (4.8% vs. 0.1%) [14] Median Cardiac Mortality NTCP 0.1% *(Korreman SS- Int J Radist Oncol Biol Phys 2006)*

- ✓ V- Breath Hold
- ✓ Breathing cycle management:
  - ABC
  - Respiratory gating

Deep-inspiratory Breath-hold

Journal of Medical Radiation Sciences

Open Access

REVIEW ARTICLE

The cardiac dose-sparing benefits of deep inspiration breath-hold in left breast irradiation: a systematic review

Lloyd M. Smyth, MMedRad (RT), BBiomed,[1,2] Kellie A. Knight, HScD, MHlthSc (RT), BAppSc (RT),[2] Yolanda K. Aarons, BAppSc (MedRad),[1] & Jason Wasiak, MPH[1]

Table 1. Summary of the studies included for dosimetric analysis.

Study	Size	Treatment site	Modality	Prescribed dose (Gy)
Lee et al.[12]	n = 25	Left breast	3DCRT	50.4 Gy
Mast et al.[13]	n = 20	Left breast	3DCRT	42.45 Gy
			IMRT	
Swanson et al.[14]	n = 87	Left breast and LCW ± SCF	IMRT	45 Gy
Hayden et al.[15]	n = 30	Left breast	IMRT (SIB)	50 Gy (60 Gy)
Hjelstuen et al.[16]	n = 17	Left Breast + SCF + AX + IMC	3DCRT	50 Gy
Wang et al.[17]	n = 20	Left breast	IMRT	42.4 Gy
				50 Gy
Vikström et al.[18]	n = 17	Left breast	3DCRT	50 Gy
Borst et al.[19]	n = 19	Left breast	IMRT	50 Gy
			IMRT (SIB)	50.7 Gy (64.4 Gy)
Stranzl et al.[20]	n = 11	Left breast + IMC	3DCRT	Not reported
Stranzl et al.[21]	n = 22	Left breast	3DCRT	50 Gy

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Table 2. Studies reporting mean heart dose and mean LADCA dose for free breathing versus DIBH plans for left breast irradiation.

	Mean heart dose (Gy)			Mean LADCA dose (Gy)		
Study	FB	DIBH	Reduction Gy (%)	FB	DIBH	Reduction Gy (%)
Lee et al.[12†]	4.5	2.5	2.0 (44%)***	26.3	16.0	10.3 (39%)***
Mast et al.[13]	3.3†	1.8†	1.5 (45%)**	18.6†	9.6†	9.0 (48%)**
	2.7‡	1.5‡	1.2 (44%)**	14.9‡	6.7‡	8.2 (55%)**
Swanson et al.[14‡]	4.2	2.5	1.7 (40%)****	–	–	–
Hayden et al.[15‡]	6.9	3.9	3.0 (43%)****	31.7	21.9	9.8 (31%)****
Hjelstuen et al.[16†]	6.3	3.1	3.2 (51%)***	23.0	10.9	12.1 (53%)***
Wang et al.[17‡]	3.2	1.3	1.9 (59%)***	20.0	5.9	14.1 (71%)***
Vikström et al.[18†]	3.7	1.7	2.0 (54%)*	18.1	6.4	11.7 (65%)*
Borst et al.[19‡]	5.1	1.7	3.4 (67%)***	11.4	5.5	5.9 (52%)***
Stranzl et al.[20†]	4.0	2.5	1.5 (38%)**	–	–	–
Stranzl et al.[21†]	2.3	1.3	1.0 (43%)***	–	–	–

3D-CRT 1.9 Gy
IMRT 2.2 Gy

3D-CRT 8.8 Gy
IMRT 9.5 Gy

Deep-inspiratory Breath-hold

Journal of Medical Radiation Sciences

Open Access

REVIEW ARTICLE

The cardiac dose-sparing benefits of deep inspiration breath-hold in left breast irradiation: a systematic review

Lloyd M. Smyth, MMedRad (RT), BBiomed,[1,2] Kellie A. Knight, HScD, MHlthSc (RT), BAppSc (RT),[2] Yolanda K. Aarons, BAppSc (MedRad),[1] & Jason Wasiak, MPH[1]

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Table 3. The stability and reproducibility of performing DIBH.

				Riproducibilità						Instabilità					
				Inter-fraction variation						Intra-fraction variation					
				Magnitude of translation (mm)			Magnitude of rotation (°)			Magnitude of translation (mm)			Magnitude of rotation (°)		
Author	Size	Imaging modality	Anatomy assessed	AP	SI	LR	AP	SI	LR	AP	SI	LR	AP	SI	LR
Betgen et al.[22†]	n = 19	3DSI CBCT	Breast Surface	1.2	3.1	1.0	1.42	0.48	0.09	0	0.5	0.2	0.07	0.03	0.03
Gierga et al.[23†]	n = 20	3DSI	Breast Surface	2.0	1.2	0.3	–	–	–	–	–	–	–	–	–
McIntosh et al.[24†]	n = 10	kV	Heart Position	2.0	1.0	1.0	–	–	–	–	–	–	–	–	–
Cerviño et al.[25]	n = 20	3DSI	Breast surface	Variation in chest wall excursion (mm)						Variation in chest wall excursion (mm)					
				2.1[†], 0.5[‡]						1.5[†], 0.7[‡]					

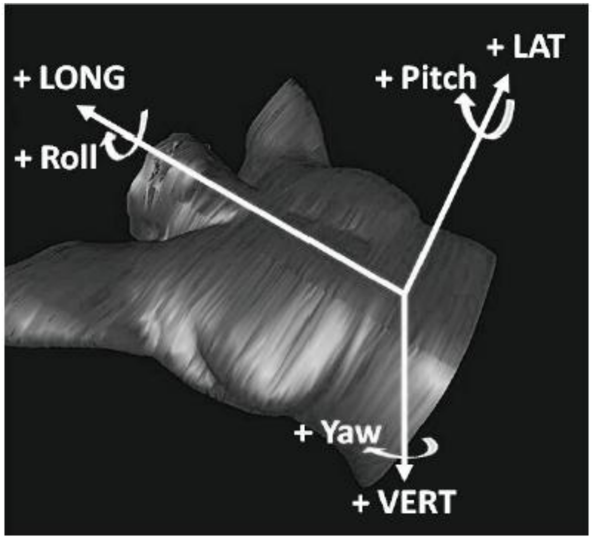
Deep-inspiratory Breath-hold

JOURNAL OF APPLIED CLINICAL MEDICAL PHYSICS, VOLUME 16, NUMBER 4, 2015

Dosimetric effect due to the motion during deep inspiration breath hold for left-sided breast cancer radiotherapy

Xiaoli Tang,[1a] Tim Cullip,[2] John Dooley,[2] Timothy Zagar,[2] Ellen Jones,[2]
Sha Chang,[2] Xiaofeng Zhu,[2] Jun Lian,[2] Lawrence Marks[2]
Medical Physics Department,[1] Memorial Sloan Kettering Cancer Center, West Harrison,

-AlignRT: 30 pts, ≠ fx, breast ± IMN (10 pts), tangential fields
- To quantify the **degree of breath-hold motion** and its **dosimetric consequences**



Real Time Deltas-RTD: tolerance level ±3mm, ±3°

TABLE 1. Beam-on portions of RTD statistics over all 30 patients.

	Average ± SD (over all patients)					
RTDs	*VERT (mm)*	*LONG (mm)*	*LAT (mm)*	*Yaw°*	*Roll°*	*Pitch°*
Mean	0.49±0.93	-0.17±0.82	-0.01±0.97	0.30±1.15	0.04±1.17	0.39±1.26
SD	0.90±0.36	0.91±0.76	0.82±0.49	0.42±0.43	0.38±0.37	0.49±0.25
Max.	2.71±0.42	2.41±0.99	2.07±0.90	1.40±1.17	0.85±1.10	1.21±1.02
Min.	-1.99±1.00	-2.49±0.67	-2.02±1.02	-0.89±1.11	-0.79±1.22	-0.95±1.36
Mean of |RTDs|	0.81±0.61	0.68±0.51	0.76±0.57	0.96±0.70	0.93±0.74	1.03±0.78
SD of |RTDs|	1.29±0.96	0.85±0.57	0.85±0.46	0.49±0.33	0.43±0.29	0.50±0.23

Deep-inspiratory Breath-hold

Table 2. The planned and delivered heart, lungs, and IMN dose coverages.

	Heart Mean Dose (cGy)		*Lungs V20 (%)*		*IMN 40 Gy Coverage (%)*		*IMN Mean Dose (cGy)*	
	Planned	*Delivered*	*Planned*	*Delivered*	*Planned*	*Delivered*	*Planned*	*Delivered*
Average	99	101	6.59	6.74	83	77	4642	4518
SD	66	66	1.19	1.79	33	36	658	781
Max.	412	381	8.92	10.08	100	100	5203	5186
Min.	35	32	4.70	3.53	1	1	2915	2503
Average Difference	2		0.15		-6		-123	
Average Absolute Difference	20		0.98		6		123	
Range of the Difference	[-41, 76]		[-2.12, 4.12]		[-26, 0.1]		[-411 -11]	
SD of the Difference	28		1.45		9			

- **Averaged mean motion** during DIBH was smaller than or nearly 1mm and 1° → relative **reproducibility**
- **Mean heart dose** and **lungs V20** reasonable **close to what planned**

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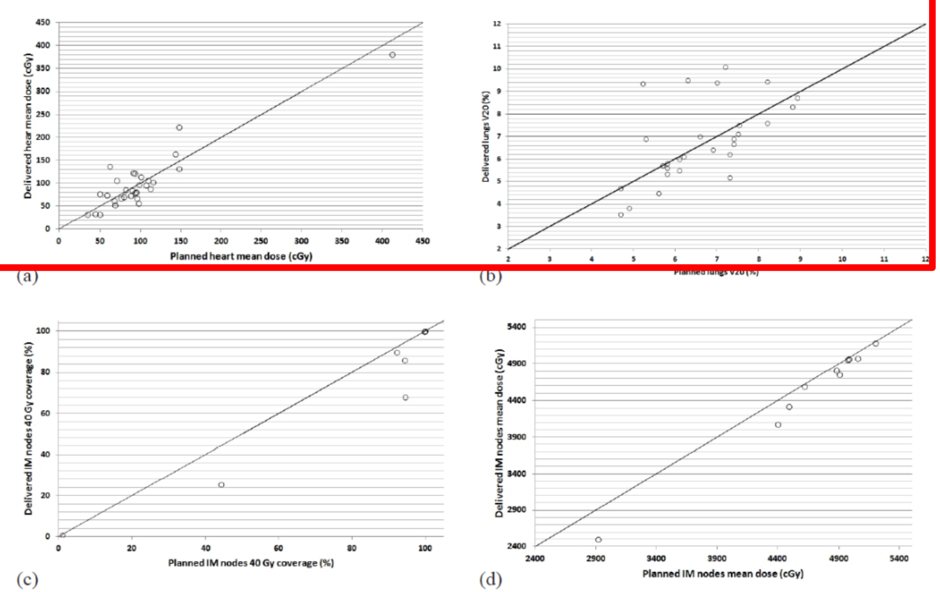
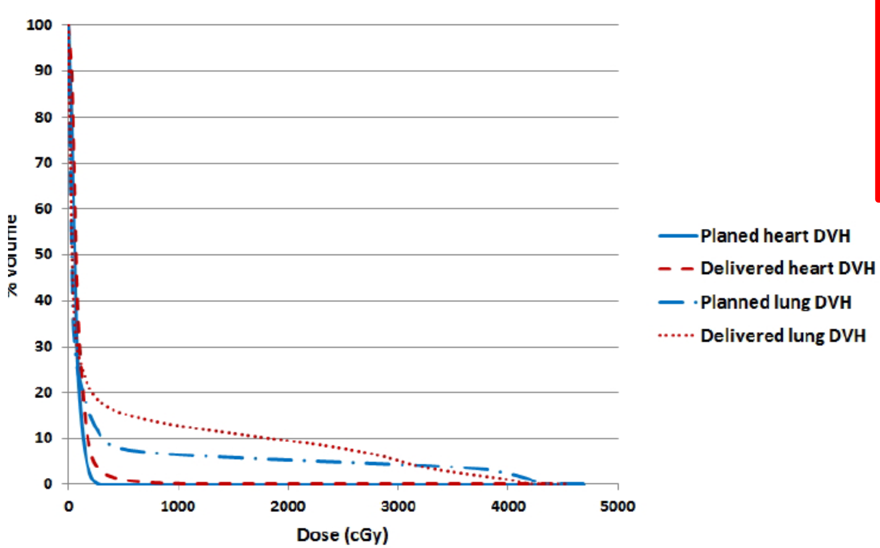




Deep-inspiratory Breath-hold

1) Rigid body model →

RESPIRATORY MOTION OF THE HEART AND POSITIONAL REPRODUCIBILITY UNDER ACTIVE BREATHING CONTROL

RESHMA JAGSI, M.D., D.PHIL., JEAN M. MORAN, PH.D., MARC L. KESSLER, PH.D., ROBIN B. MARSH, C.M.D., JAMES M. BALTER, PH.D., AND LORI J. PIERCE, M.D.

Department of Radiation Oncology, University of Michigan, Ann Arbor, MI

Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 1, pp. 253–258, 2007

- ✓ **Inter-fraction DIBH motion** of the heart had reproducibility of **3 mm** in the **A-P**, **7 mm** in the **S-I**, and **3 mm** in the **L-R directions**

2) No **PTV** DVH comparison

Deep-inspiratory Breath-hold

Cardiac dose reduction with deep ins... ca... wi...

RADIATION ...LOGY (2015) 10:200

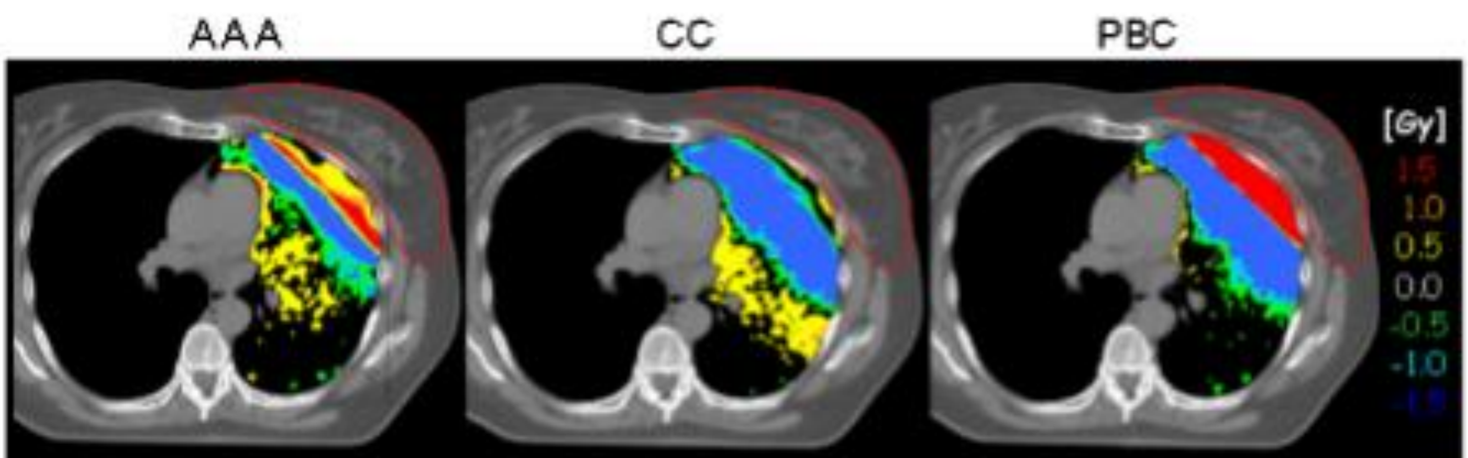
IOP PUBLISHING PHYSICS IN MEDICINE AND BIOLOGY

Phys. Med. Biol. 53 (2008) 2375–2390 doi:10.1088/0031-9155/53/9/011

The impact of photon dose calculation algorithms on expected dose distributions in lungs under different respiratory phases

Antonella Fogliata[1], Giorgia Nicolini[1], Eugenio Vanetti[1], Alessandro Clivio[1,3], Peter Winkler[4] and Luca Cozzi[1,2,4,5]

Characteristics	...hort	FB vs. DIBH *p*-value*
Median age (y...	2	0.349
AJCC Stage	0	
DCIS		
I		
II		0.013
III		
ER/PR positive		
HER 2+ (for im...		N/A
Surgery		
Breast cons...		
Mastectomy		<0.001**
RT boost to seroma		
RT to internal mamm...		0.002**
Breast/Chest wall RT (Gy/# fraction)		
40/16		<0.001**
42.5/16		
45/25		0.029
50/25		
Supraclavicular noda... (Gy/# fraction)		
37.5/16		0.134
45/25		



…during DIBH lung density is decreased, reducing the relative lung volume irradiated!

OUTLINE

Reduction in cardiac exposure: Which technique?

- Deep-inspiratory **Breath-hold**
- **Prone** breast radiotherapy
- **IMRT** and Arc Therapy
- **Proton** Beam Therapy

Prone breast radiotherapy

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review

Cardiac dose sparing and avoidance techniques in breast cancer radiotherapy

Chirag Shah [a], Shahed Badiyan [b], Sameer Berry [a], Atif J. Khan [c], Sharad Goyal [c], Kevin Schulte [a], Anish Nanavati [d], Melanie Lynch [a], Frank A. Vicini [e,*]

Prone	(1) Dosimetric studies demonstrate a reduction in cardiac dose in >50% cases but in some cases worse cardiac dose (2) Large breast volumes were associated with reduction in cardiac dose with technique, less consistent in small breast volume (3) Prospective data demonstrate acceptable toxicity and clinical outcomes (4) Studied with breast conserving therapy with or without regional therapy (5) Can be combined with intensity modulated radiation therapy or	(1) 75–85% of left sided cases reduced cardiac volume in field [33–35] (2) Non-significant decrease in mean heart, $V_{40\,Gy}$, $V_{5\,Gy}$ [36,39]; decreased cardiac $V_{35\,Gy}$ [38] (3) Decreased mean cardiac dose (4.6 Gy vs. 3.0 Gy) [40]

OUTLINE

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2015

Prone breast radiotherapy

International Journal of
Radiation Oncology
biology • physics

Prone Hypofractionated Whole-Breast Radiotherapy Without a Boost to the Tumor Bed: Comparable Toxicity of IMRT Versus a 3D Conformal Technique

Table 2 Dosimetric analysis by treatment planning group

Variable	3D-CRT (n = 40) [median (range)]	IMRT (n = 57) [median (range)]	p Value
% Dmax	109.96 (106.10–113.90)	107.28 (104.63–114.89)	<0.0001*
Breast dose			
Dmax (cGy)	4,680.55 (4,514.30–4,885.40)	4,562.90 (4,165.00–4,889.80)	<0.0001*
Mean dose (cGy)	4,066.60 (3,633.80–4,191.60)	4,368.00 (3,698.50–4,426.00)	<0.0001*
Homogeneity index	1.15 (1.11–1.30)	1.05 (1.02–1.21)	<0.0001*
In-field OAR*			
In-field heart volume (cm^3)	0 (0–3.86)	0 (0–4.90)	0.59*
In-field lung volume (cm^3)	0.04 (0–47.23)	0 (0–64.74)	0.61*
Heart dose			
V5 (cm^3)	0 (0–3.12)	0 (0–2.54)	0.47*
Dmax (cGy)	283.55 (140.40–4,182.70)	362.00 (0–4,246.00)	0.28*
Lung dose			
V5 (cm^3)	0.06 (0–5.42)	0.43 (0–5.97)	0.06*
Dmax (cGy)	1,264.25 (111.80–4,461.00)	2,469.10 (110.00–4,403.20)	0.08*

Pract Radiat Oncol. 2015 Nov 9. pii: S1879-8500(15)00398-7. doi: 10.1016/j.prro.2015.10.022. [Epub ahead of print]

Breast, chest wall, and nodal irradiation with prone set-up: Results of a hypofractionated trial with a median follow-up of 35 months.

Shin SM[1], No HS[1], Vega RM[1], Fenton-Kerimian M[1], Maisonet O[1], Hitchen C[1], Keith DeWyngaert J[1], Formenti SC[2].

2015

Prone breast radiotherapy

ELSEVIER

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

2015

Phase III randomised trial

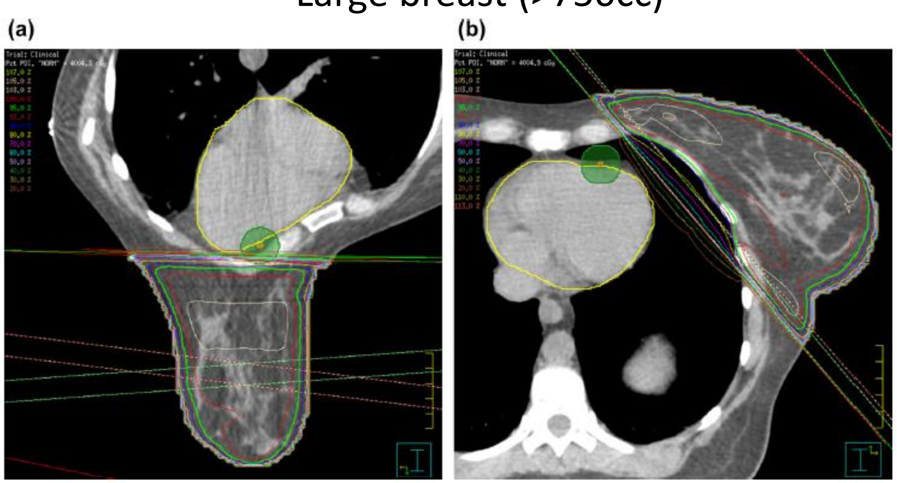
The UK HeartSpare Study (Stage IB): Randomised comparison of a voluntary breath-hold technique and prone radiotherapy after breast conserving surgery

CrossMark

Frederick R. Bartlett [a,*], Ruth M. Colgan [b], Ellen M. Donovan [b], Helen A. McNair [a], Karen Carr [a], Philip M. Evans [b,c], Clare Griffin [d], Imogen Locke [a], Joanne S. Haviland [d], John R. Yarnold [e], Anna M. Kirby [a]

34 pts → 28 pts data available

Large breast (>750cc)



Results (sVBH vs. pFB)

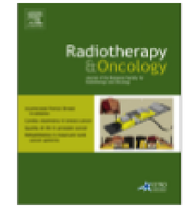
- Heart NTDmean 0.44 vs. 0.66 ($p < 0.001$)
- LAD NTDmean 2.9 vs. 7.8 ($p < 0.001$)
- LAD max 21.0 vs. 36.8 ($p < 0.001$)

DIBH

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

Radiotherapy and Oncology 108 (2013) 242–247



Phase III randomised trial

The UK HeartSpare Study: Randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy

CrossMark

Frederick R. Bartlett [a,*], Ruth M. Colgan [b], Karen Carr [a], Ellen M. Donovan [b], Helen A. McNair [a], Imogen Locke [a], Philip M. Evans [b,c], Joanne S. Haviland [d], John R. Yarnold [a,e], Anna M. Kirby [a]

- ✓ V-DIBH vs ABC
- ✓ 23 pz
- ✓ Studio di fattibilità, riproducibilità, risparmio OAR…comfort pz, delivery time!

Conclusions: v_DIBH and ABC_DIBH are comparable in terms of positional reproducibility and normal tissue sparing. v_DIBH is preferred by patients and radiographers, takes less time to deliver, and is cheaper than ABC_DIBH.

Right–left (R–L)	MD	0.3	0.3	0.78	0.4	0.4	0.93
	Σ	4.4	2.5		3.2	2.4	
	σ	3.8	2.4	0.07	2.3	2.3	0.99
Superior–inferior (S–I)	MD	2.3	3.4	0.32	−0.1	1.7	0.10
	Σ	4.9	3.9		2.9	3.6	
	σ	3.3	4.1	0.62	3.4	2.7	0.42
Anterior–posterior (A–P)	MD	−1.7	0.3	0.03	−1.8	0.6	0.01
	Σ	3.3	2.8		2.7	3.0	
	σ	2.6	2.7	0.76	3.5	2.7	0.53

OUTLINE

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IMRT and Arc Therapy

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Radiotherapy & Oncology

2014

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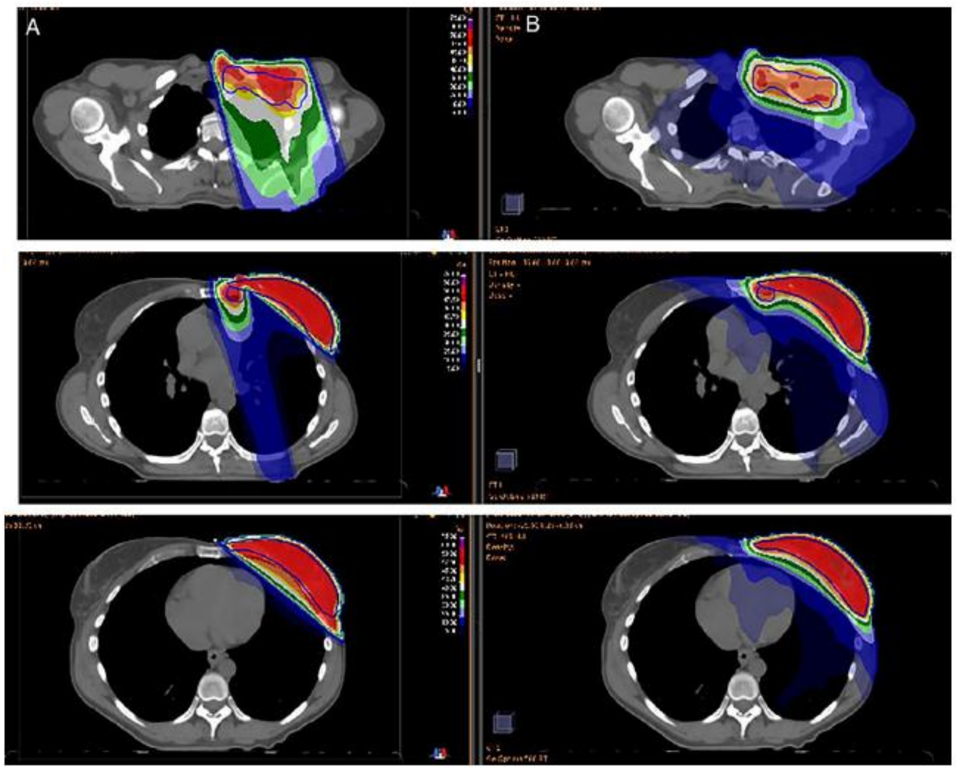
	accelerated partial breast irradiation	
Intensity modulated radiation therapy	(1) Dosimetric studies demonstrate reduction in low dose and high dose cardiac dose parameters as well as dose to the left ventricle and coronary arteries (2) Feasibility demonstrated in clinical setting (3) Multiple techniques available with cardiac sparing preserved (4) Studied with breast conserving therapy with or without regional therapy and in the post-mastectomy setting (5) Can be combined with breath hold, prone technique, or accelerated partial breast irradiation	(1) Reduction in cardiac NTCP compared with 3D-CRT [57,71,72] (2) Decreased mean dose, $V_{5\,Gy}$, $V_{15\,Gy}$, $V_{20\,Gy}$, $V_{30\,Gy}$ (10–50%), maximum dose [54,58–61,64–66,68,71,73,74,76] (3) Reduced dose to left anterior descending, left ventricle [62,63,80]

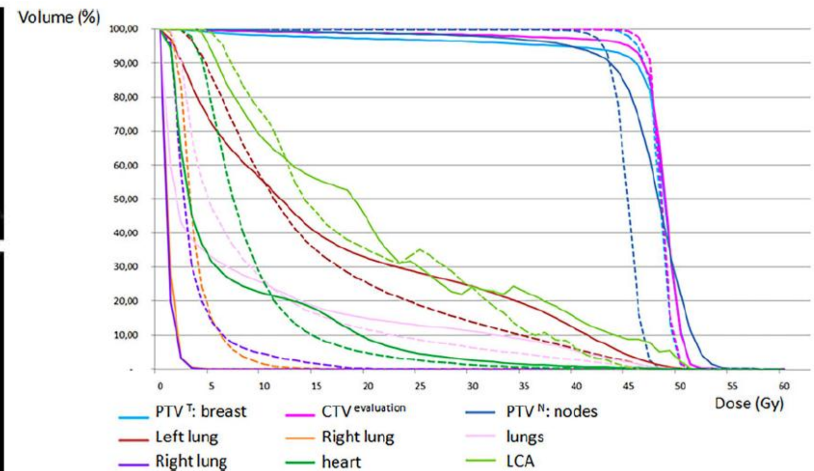
- ✓ Field in field (con modulazione…o anche senza)
- ✓ Step and Shoot
- ✓ VMAT
- ✓ TomoTherapy (Direct-Helical)

IMRT and Arc Therapy

Volumetric-modulated arc therapy for left-sided breast cancer and all regional nodes improves target volumes coverage and reduces treatment time and doses to the heart and left coronary artery, compared with a field-in-field technique

Journal of Radiation Research, Vol. 56, No. 6, 2015, pp. 927–937





- ✓ VMAT improved PTV coverage and HI
- ✓ Decreased dose exposure of the LCA
- ✓ VMAT could be used for complex treatments
- ✓ Patient age should be considered

MONOISO ——— VMAT - - - - - - -

IMRT and Arc Therapy

	MONOISO Mean	min	max	VMAT Mean	min	max	Wilcoxon's signed rank test
Right lung							
Dmean (Gy)	**0.8**	0.6	1	**4.0**	3	8.5	0.002
D2% (Gy)	**2.2**	1.7	2.7	**9.3**	7.9	10.4	0.002
V10 (%)	**0.1**	0	0.3	**7.4**	0.6	59.6	0.002
V5Gy (%)	**0.2**	0	0.6	**14.5**	11.6	18.2	0.002
Lungs							
Dmean (Gy)	**8.1**	6.5	9.8	**8.8**	7.7	9.6	0.016
V5Gy (%)	**33.0**	26	37.8	**47.3**	39.9	54.1	0.002
Right breast							
Dmean (Gy)	**0.4**	0.3	0.6	**3.2**	2.5	3.7	0.002
D2% (Gy)	**6.7**	1	52.9	**12.3**	6.3	17.8	0.084*
V5Gy (cm^3)	**0.0**	0	0	**90.0**	27.7	147	0.002
V5Gy (%)	**0.0**	0	0	**13.8**	8	17.5	0.002

Lung cancer IMRT:

- **controlateral lung V5 < 17%**
- **lungs V5 < 50%**

IMRT and Arc Therapy

RESEARCH Open Access

CrossMark

A comparative dosimetric study of left sided breast cancer after breast-conserving surg

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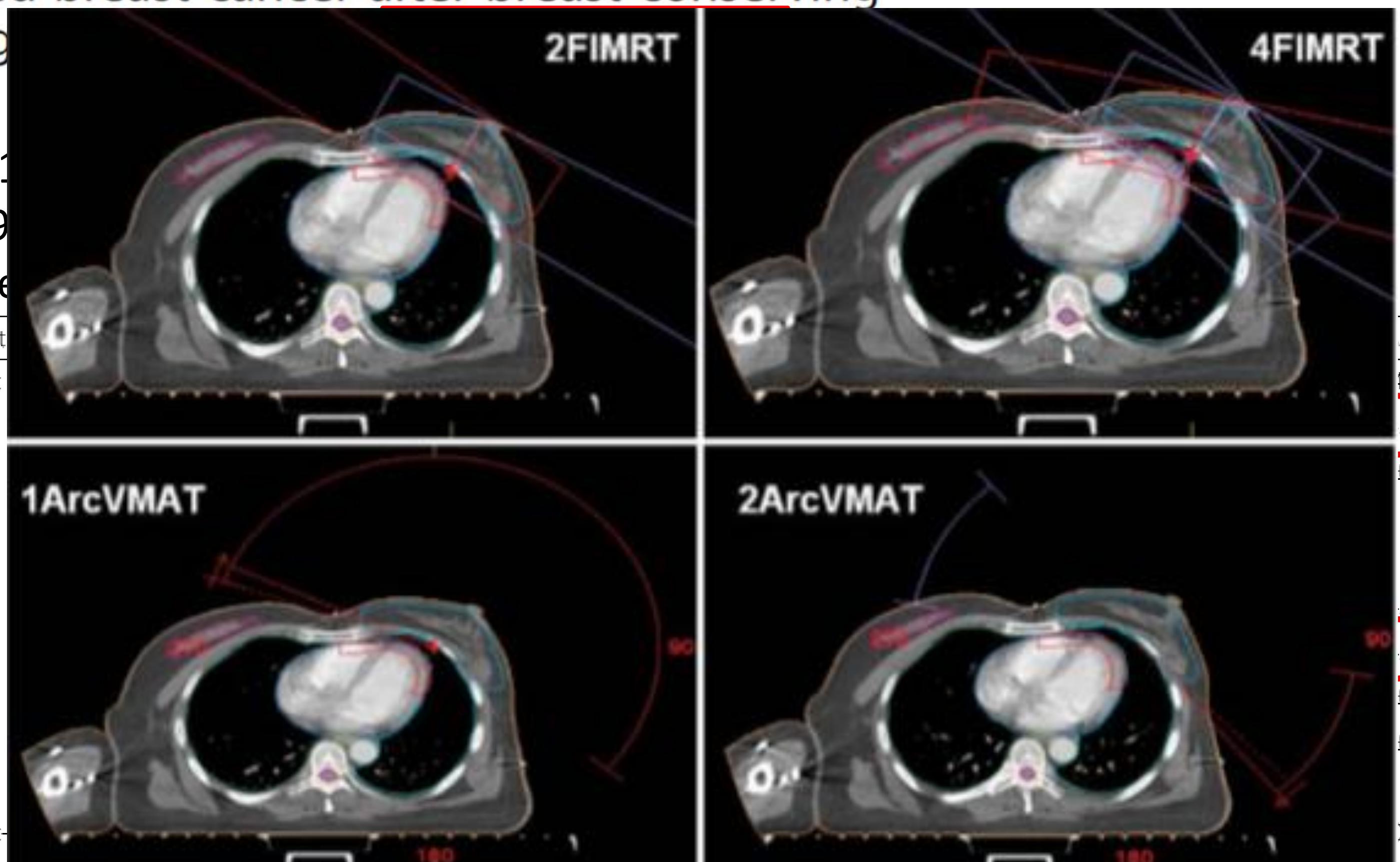

Struct					AT
Heart					4 B,b
					.2 B,b
					± 9.2 % B,b
					2.6 % A
					0.5 % B,b
CA					.3
					.9 B
					± 15.2 % B
					± 13.3 % B
					3.5 % B
Heart-					) B,b
	V5	2.4 % ± 2.0 %	5.6 % ± 5.3 %	7.3 % ± 6.1 %	10.5 % ± 8.5 % B,b
	V20	0.3 % ± 0.6 %	0.6 % ± 1.2 %	0.6 % ± 1.2 %	0.6 % ± 1.1 %
	V40	0.1 % ± 0.2 %	0.1 % ± 0.2 %	0.1 % ± 0.2 %	0.0 % ± 0.1 %

OUTLINE

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Proton Beam Therapy

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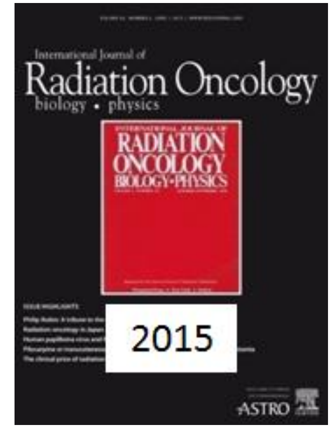
Proton beam irradiation	(1) Dosimetric studies demonstrate reduction in low dose and maximum cardiac dose (2) Feasibility demonstrated in small prospective studies (3) Studied with breast conserving therapy with or without regional therapy and in the post-mastectomy setting (4) Can be combined with accelerated partial breast irradiation	(1) Reduction in cardiac $V_{22.5\,Gy}$, $V_{20\,Gy}$, $V_{5\,Gy}$ [89,90,93] (2) Reduction in maximum cardiac dose compared with 3D-CRT/IMRT (19 Gy vs. 23–25 Gy) [86] (3) Mean dose – one study with no difference [78], two studies with reduction [88,90] (4) Reduction in cardiac NTCP (2.1% vs. 0.5%) [87]

Proton Beam Therapy



Clinical Investigation

Early Toxicity in Patients Treated With Postoperative Proton Therapy for Locally Advanced Breast Cancer

John J. Cuaron, MD,* Brian Chon, MD,† Henry Tsai,

… "These patients were not part of a clinical trial. Patients were generally referred because of **unfavorable cardiopulmonary anatomy.** Postlumpectomy patients were not offered treatment if **large breast size** (defined as having breast anatomy that was prone to significant interfraction mobility) **would preclude accurate setup**"

Table 2 Dosimetry values

PTV	
V100 (%)	89.20 (68.56-96.30)
V95 (%)	96.43 (79.39-99.60)
V110 (%)	13.30 (3.02-34.98)
Max point dose, Gy (RBE)	58.84 (50.8-70.5)
Heart (left-sided tumors, n=27)	
Mean dose, Gy (RBE)	1.0 (0.09-3.20)
V20 (%)	1.16 (0-6.0)
V5 (%)	5.00 (0.17-14.40)
Max point dose, Gy (RBE)	22.80 (2.48-43.70)
Lungs	
Total V20 (%)	7.31 (0.14-13.2)
Ipsilateral V20 (%)	16.50 (6.1-30.3)
Ipsilateral V5 (%)	34.35 (22.5-53.8)
Contralateral V5 (%)	0.34 (0-5.30)
Contralateral breast	
Mean dose, Gy (RBE)	0.29 (0.03-3.50)
V5 (%)	1.46 (0-9.90)
Spinal cord	
Max point dose, Gy (RBE)	1.24 (0-28.1)
Esophagus	
Mean dose, Gy (RBE)	7.50 (0-19.59)
V30 (%)	10.80 (0-37.0)
V40 (%)	3.40 (0-28.9)
Max point dose, Gy (RBE)	45.65 (0-65.4)

Proton Beam Therapy

CURRENT OPINION

New frontiers in proton therapy: applications in breast cancer

Curr Opin Oncol 2015, 27:427–432

REVIEW

Roberto Orecchia[a,b,c], Piero Fossati[a,b,c], Stefano Zurrida[a], and Marco Krengli[b,d]

- ✓ **In-silico** studies show a clear **advantage in terms of dose homogeneity** to the target and dose **reduction to the non-target structures** including heart, lungs, and healthy breast tissues

- ✓ **Clinical studies** have shown the **feasibility of proton therapy** in breast cancer and allowed optimizing the technique by using **multiple beams and intensity modulation**

Conclusion: Few phase I/II clinical studies on proton therapy have been published with relatively short follow-up. Thus **it is too early to draw definitive conclusions on the utility of proton therapy in breast cancer**

OUTLINE

Reduction in cardiac exposure: Which technique?

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- **APBI**

APBI

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Accelerated partial breast irradiation	(1) Dosimetric studies demonstrate reduction in low dose and high dose cardiac dosimetries with each technique (2) Limited to early stage patients meeting certain criteria (3) Can be combined with prone technique or intensity modulated	(1) Reduced mean dose to 1.2 Gy [112] (2) Reduction in V_{5Gy}, V_{10Gy}, V_{20Gy}, $V_{50\%}$, $V_{90\%}$, $V_{100\%}$; decreased volume receiving low and high dose compared with whole breast [104,106,107,109,113]

- ✓ **Interstitial brachytherapy** has the longest follow up of any APBI technique to date. Dosimetric studies have demonstrated **low cardiac doses** with modern, image-guided techniques

- ✓ In light of higher rates of local recurrence noted with **IORT**, this technique **is not recommended** to be used **off-protocol** despite the potential for improved cardiac sparing

APBI

Contents lists available at ScienceDirect

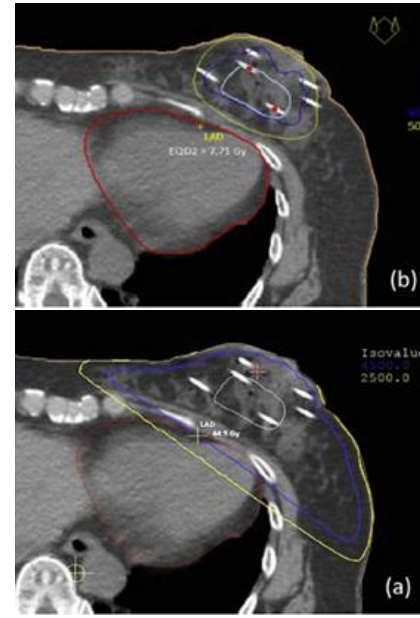
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Coronary artery dosimetry

Assessing radiation exposure of the left anterior descending artery, heart and lung in patients with left breast cancer: A dosimetric comparison between multicatheter accelerated partial breast irradiation and whole breast external beam radiotherapy

Radiotherapy and Oncology 117 (2015) 459–466



Heart	D_{50cc}	D_{25cc}	D_{10cc}	D_{5cc}	D_{2cc}	D_{1cc}	$D_{0.5cc}$	$D_{0.1cc}$	MHD	
Mean WBEBRT	22.4 ± 12.3 (44.8)	36.2 ± 11.7 (72.9)	44.5 ± 7.8 (89.1)	46.9 ± 6.0 (93.7)	48.5 ± 4.1 (96.9)	48.6 ± 3.8 (97.2)	49.8 ± 2.5 (99.6)	50.6 ± 1.7 (101.1)	6.0 ± 2.1 (12.0)	Gy ± SD (% of 50 Gy)
Mean MCAPBI	5.4 ± 2.1 (10.7)	7.0 ± 2.8 (14.0)	9.2 ± 3.8 (18.2)	10.6 ± 4.4 (21.1)	12.2 ± 5.1 (24.6)	13.2 ± 5.5 (26.5)	14.2 ± 5.8 (28.4)	16.3 ± 6.3 (32.5)	2.3 ± 0.9 (4.6)	Gy ± SD (% of 50 Gy)
p-Value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	
	V_{25Gy}	V_{20Gy}	V_{10Gy}							
Mean WBEBRT	8.8 ± 4.9	10.2 ± 5.1	14.4 ± 5.5	% volume ± SD						
Mean MCAPBI	0.0 ± 0.0	0.3 ± 0.4	5.3 ± 4.6	% volume ± SD						
p-Value	<0.01	<0.01	<0.05							

15 pts

Ipsilateral Lung	D_{50cc}	D_{25cc}	D_{10cc}	D_{5cc}	D_{2cc}	D_{1cc}	$D_{0.5cc}$	$D_{0.1cc}$	MLD	
Mean WBEBRT	43.8 ± 6.6 (87.5)	47.7 ± 3.3 (95.4)	49.6 ± 2.0 (99.2)	50.3 ± 1.7 (100.7)	51.0 ± 1.5 (102.0)	51.4 ± 1.4 (102.7)	51.6 ± 1.3 (103.2)	52.0 ± 1.3 (104.1)	10.7 ± 2.6 (21.4)	Gy ± SD (% of 50 Gy)
Mean MCAPBI	6.6 ± 2.6 (13.3)	9.1 ± 3.5 (14.8)	12.4 ± 4.5 (18.6)	14.6 ± 5.0 (20.9)	16.9 ± 5.5 (22.9)	18.4 ± 5.7 (24.5)	19.7 ± 5.8 (26.3)	22.2 ± 6.1 (29.4)	2.3 ± 0.7 (4.6)	Gy ± SD (% of 50 Gy)
p-Value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	
	V_{20Gy}	V_{10Gy}	V_{5Gy}							
Mean WBEBRT	21.8 ± 5.7	28.5 ± 6.4	35.9 ± 7.0	% volume ± SD						
Mean MCAPBI	1.0 ± 0.9	6.9 ± 3.8	23.9 ± 10.8	% volume ± SD						
p-Value	<0.01	<0.01	<0.05							

CONCLUSIONS

CONTOURING:
- ✓ Nuove co-registrazioni di immagini per pz selezionate
- ✓ MdC
- ✓ Applicabilità clinica e costi

BH:
- ✓ Fattibilità (tutti i centri e maggior % delle pz)
- ✓ Riproducibilità
- ✓ Costi (DIBH vs ABC/Gating)
- ✓ Associabile altre tecniche
- ✓ Nota negativa: discomfort e delivery time ?!

PRONE:
- ✓ Mammelle voluminose
- ✓ Associabile a v-DIBH

IMRT:
- ✓ Anatomia "complicata"
- ✓ Linfonodi (CMI)
- ✓ NO giovani

Open issues

- ✓ **Other cardiac constraints** (LAD, Mean dose or Dmax?)
- ✓ **Patients selection for heart-sparing radiotherapy tecniques** (unfavorable anatomy, individual cardiac risk factors)
- ✓ **Risk adapted breast radiotherapy** (NO radiotherapy or PBI in Low risk patients)
- ✓ **Blood tests** (i.e. BPN) for cardiac monitoring of patients (risk factors for CAD, high dose RT despite modern technique, regional nodal irradiation including IMC)

The Breast 25 (2016) 45–50

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Original article

Brain natriuretic peptide as a cardiac marker of transient radiotherapy-related damage in left-sided breast cancer patients: A prospective study

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…GRAZIE!