Cardiac effects of Radiotherapy for Breast Cancer

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Radiotherapy in Ca Breast

EBRT

Brachytherapy

- Post BCS
- Post mastectomy
- Palliative– following local recurrence

Aim:

- Maximise local control
- Improve survival
- ***Minimal complications***

Cardiac effects of Radiotherapy for Breast Cancer

- Basics
- Pathophysiology
- Evidence of RIHD
- Dose volume data
- Ways to improve
- Clinical data
- Future perspective

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Radiation Response In Normal Tissues

- Response of tissue or organ to radiation depends on 3 factors viz.
  1. Inherent radiosensitivity of individual cells
  2. Population kinetics of the cells in the tissue
  3. Structural arrangements of the functional subunits (FSUs) in the tissue

     -- serial / parallel

These factors combine to account for the substantial variation in radio-responsiveness of various organs and tissues

RIHD – Radiation Induced Heart Disease

Defn: Clinical and pathological conditions of injuries to the heart and large vessels resulting from therapeutic irradiation of malignancies

Heart Development

- 8th week of gestation – embryonic morphogenesis
- 6 months – full adult number of myocytes
- After this heart growth - myocyte enlargement
- Fajardo & Stewart showed that heart and vasculature are radiosensitive organs

Fajardo, L.F., J.R. Stewart, *Morphology of radiationinduced heart disease. Arch Pathol, 1968. 86(5): p. 512-9.*

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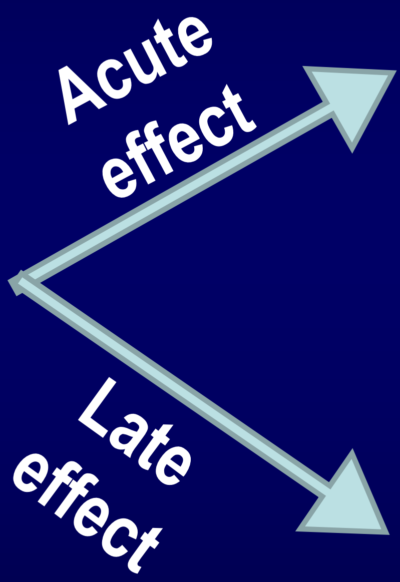
Pathophisiology

- Microangiopathy
- Macroangiopathy
- Atherosclerosis



<u>Fibrosis</u>

Made of a network of collagens fibers that separates the myocytes

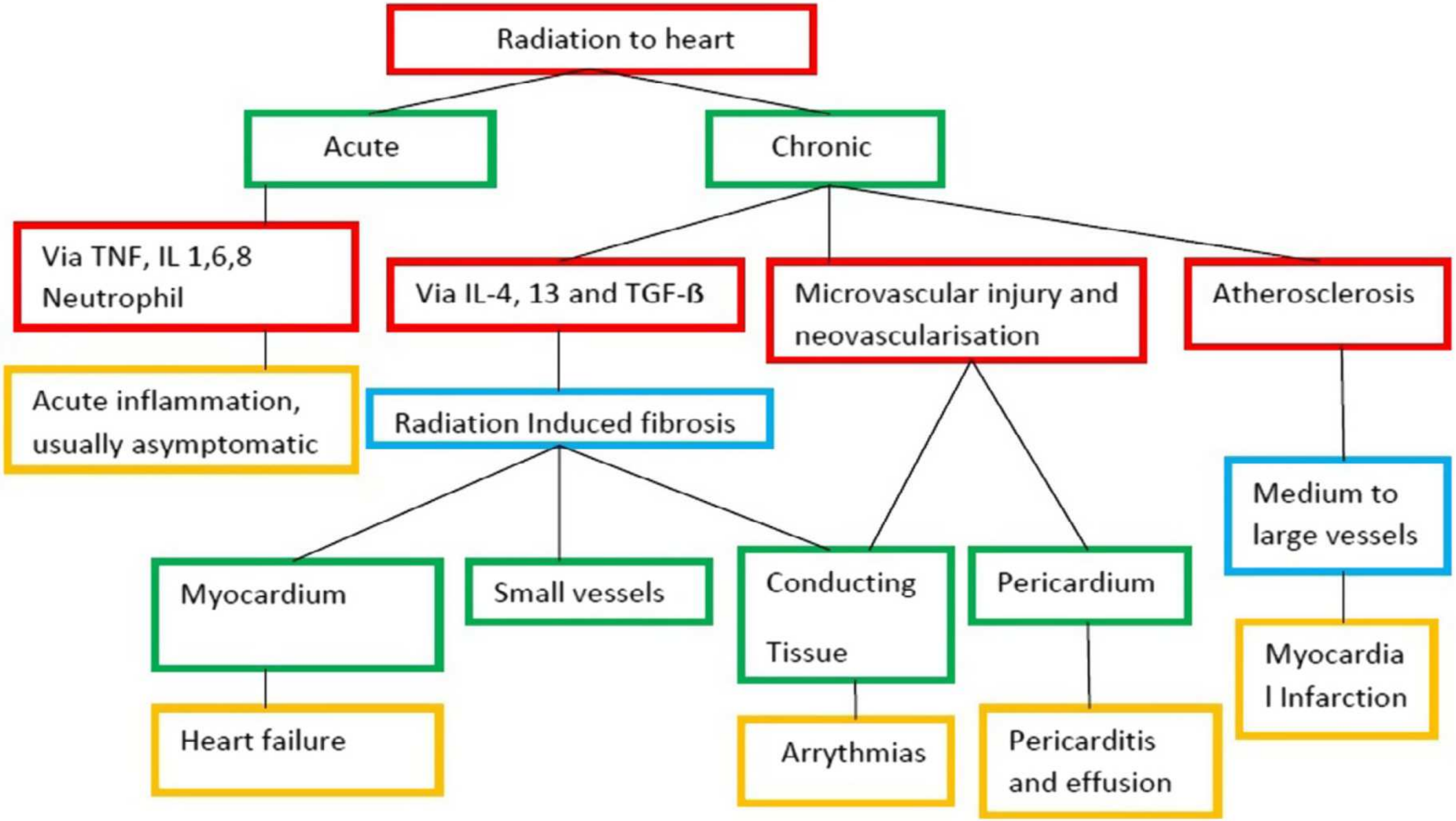


Figure 1 Pathology of RIHD.

Madan et al Journal of the Egyptian National Cancer Institute , 2015

Heart and its component affected by RT

Pericardium	Pericardial thickening
	Pericardial effusion
	Cardiac tamponade
	Constrictive pericarditis
Coronary artery disease	Obstructive lesion in the anterior descending artery
	Obstructive lesion in the coronary ostia
Myocardium	Asymptomatic left ventricular diastolic dysfunction
Valves	Valvular thickening without hemodynamic repercussions
	Aortic stenosis
Cardiac electrical and conduction disorders	Right bundle branch block (more frequent)
	Left bundle branch block
	Complete atrioventricular block
	T-wave flattening or inversion
Great vessels of the chest	Increased carotid *intima*-media thickness
	Chronic baroreflex failure: labile hypertension or orthostatic hypotension
	Aortic calcification
	Stenotic lesions of the subclavian arteries

- Early reactions rare, mostly late effects
- Radiation induced cardiac injuries
  - Pericarditis
  - CCF
  - Restrictive Cardiomyopathy
  - Valvular insufficiency & stenosis
  - CAD: ischemia, infarction

- Basics
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Data Digging

Cardiac Risk RT vs NO RT

Cause-Specific Mortality in Long-Term Survivors of Breast Cancer Who Participated in Trials of Radiotherapy

Trial	XRT			No XRT			SMR_1 / SMR_2		
	O_1	E_1*	SMR_1	O_2	E_2*	SMR_2	SMR_1 / SMR_2	95% CI	P
Radical ± XRT									
Manchester Q[3]	25	16.02	1.56	28	31.28	0.90	1.74	0.97-3.1	.06
Manchester P[3]								1.10-3.8	.02
Oslo I[2]								0.29-2.4	.89
Oslo II[2]								0.95-13.4	.07
Heidelberg[14]								1.02-14.4	.05
Stockholm[5]	8	10.04	0.80	3	9.31	0.32	2.47	0.59-14.5	.28
Subtotal	99	75.68	1.31	67	92.98	0.72	1.82	1.32-2.5	<.001
Simple ± XRT									
Manchester Regional I[15]	13	9.82	1.32	10	8.86	1.13	1.17	0.48-3.0	.86
CRC[4]	35	47.62	0.73	26	52.29	0.50	1.48	0.86-2.6	.16
Edinburgh[6]	4	3.13	1.28	5	3.30	1.52	0.84	0.17-3.9	.94
Subtotal	52	60.57	0.86	41	64.45	0.64	1.35	0.88-2.1	.18
Total	151	136.25	1.11	108	157.43	0.69	1.62	1.25-2.1	<.001

NOTE. SMRs of <1 favor XRT.

*Expected numbers are based on age- and calendar-specific rates for women in England and Wales.

Trials before 1975, Total – 7941,

Cardiac Mortality for patients surviving 10 years N = 4309

Cuzick et al JCO 1994

IHD incidence

Table 2. Comparison of percent ischemic heart disease mortality (with 95% confidence intervals) at 15 years of follow-up between women with left-sided and right-sided breast cancers, stratified by stage of disease at time of diagnosis

	All patients			Patients with in situ/localized disease			Patients with regional disease		
Cohort by year of diagnosis	Left-sided, %	Right-sided, %	*P*	Left-sided, %	Right-sided, %	*P*	Left-sided, %	Right-sided, %	*P*
Overall	8.7 (8.0 to 9.3)	7.5 (6.9 to 8.2)	.07	7.6 (6.7 to 8.4)	6.7 (5.9 to 7.5)	.40	10.2 (9.1 to 11.3)	8.6 (7.6 to 9.6)	.09
1973–1979	13.1 (11.6 to 14.6)	10.2 (8.9 to 11.5)	.02	12.7 (10.3 to 15.2)	9.6 (7.5 to 11.8)	.14	13.3 (11.5 to 15.1)	10.6 (8.9 to 12.3)	.06
1980–1984	9.4 (8.1 to 10.6)	8.7 (7.4 to 10.0)	.64	8.9 (7.2 to 10.5)	8.7 (7.1 to 10.4)	.87	10.0 (7.9 to 12.1)	8.8 (6.8 to 10.9)	.38
1985–1989	5.8 (4.8 to 6.7)	5.2 (4.4 to 5.9)	.98	5.7 (4.5 to 6.8)	4.9 (4.0 to 5.8)	.79	6.0 (4.4 to 7.6)	5.7 (4.1 to 7.2)	.76

Incidence of IHD SEER data

N = 27283 (Left and Right side .13000 each)

Giordano et al Risk of Cardiac Death After Adjuvant Radiotherapy for Breast Cancer : JNCI 2005

IHD incidence

Conclusion

Risk of death from ischemic heart disease associated with radiation for breast cancer has substantially decreased over time

Giordano et al Risk of Cardiac Death After Adjuvant Radiotherapy for Breast Cancer : JNCI 2005

Comparison with historic data

- A review of trials done before1980 to trials after1980
- Weighted mean cardiac morbidity and mortality (including myocardial infarction, ischemic heart disease, cardiovascular disease)
  - 1.28 for trials before1980.
- After 1980,
  - Trials with less than 10 years follow-up had variable or no evidence of increased cardiac morbidity
  - Trials with greater than 10 years follow-up consistently showed increased toxicity

Demirci S et al: Radiation-induced cardiac toxicity after therapy for breast cancer: Interaction between treatment era and follow-up duration. IJROBP 2009

Long-Term Risk of Cardiovascular Disease in 10-Year Survivors of Breast Cancer

Table 4. Multivariable Cox regression analyses for myocardial infarction and congestive heart failure by radiotherapy (RT) field and estimated mean radiation dose to the heart by treatment period*

Treatment period	No. of patients	Estimated mean heart dose, Gy	Dose range, Gy	Myocardial infarction		Congestive heart failure	
				HR (95% CI)†	*P*‡	HR† (95% CI)	*P*‡
1970–1979							
RT fields							
No RT/fields not including heart§	431	≈0	≈0	1.0 (referent)		1.0 (referent)	
Chest wall/breast: right-sided	179	≈3	1.2–3.8	1.76 (0.88 to 3.51)	.11	0.96 (0.57 to 1.63)	.89
Chest wall/breast: left-sided	168	≈7	2.5– 9.0	2.72 (1.38 to 5.38)	.004	1.10 (0.64 to 1.92)	.73
IMC only: right-sided	348	≈7	0.5–11.6	2.59 (1.46 to 4.61)‖	.001	1.44 (0.94 to 2.20)¶	.10
IMC only: left-sided	386	≈9	0.7–15.6	2.00 (1.12 to 3.58)‖	.02	1.61 (1.08 to 2.41)¶	.02
IMC + chest wall/breast: right-sided	158	≈11	2.7–15.4	4.77 (2.43 to 9.35)‖	<.001	2.15 (1.28 to 3.60)¶	.004
IMC + chest wall/breast: left-sided	166	≈15	4.7–18.3	2.59 (1.29 to 5.18)‖	.007	2.29 (1.44 to 3.65)¶	<.001
1980–1986							
RT fields							
No RT/fields not including heart§	261	≈0	≈0	1.0 (referent)		1.0 (referent)	
Breast/chest wall: right-sided	316	≈1.5	1.2–1.6	0.71 (0.29 to 1.74)	.46	0.80 (0.28 to 2.29)	.68
Breast/chest wall: left-sided	395	≈5	2.5–5.3	0.79 (0.36 to 1.72)#	.55	1.16 (0.48 to 2.79)	.75
IMC only: right-sided	359	≈6	0.5–11.6	0.95 (0.46 to 1.93)	.88	1.43 (0.65 to 3.16)	.38
IMC only: left-sided	346	≈7	0.7–15.6	0.94 (0.46 to 1.91)	.86	1.81 (0.84 to 3.92)	.13
IMC + breast/chest wall: right-sided	365	≈9	2.5–14.0	0.80 (0.36 to 1.78)	.58	2.82 (1.27 to 6.29)**	.01
IMC + breast/chest wall: left-sided	376	≈13	4.0–19.9	0.67 (0.30 to 1.52)	.34	2.52 (1.13 to 5.62)**	.02

All 10 year survivors N = 4414

Follow up 18 yrs – 942 cardiac events

Hooning et al JNCi 2007

IHD incidence

Conclusion

- Radiotherapy as administered from the 1980s onward is associated with an increased risk of cardiovascular disease. Irradiated breast cancer patients should be advised to refrain from smoking to reduce their risk for cardiovascular disease

- Patients who underwent radiotherapy plus adjuvant chemotherapy (CMF regimen) after 1979 had a higher risk of congestive heart failure than patients who were treated with radiotherapy only (*P* = *0.002)*

Hooning et al JNCi 2007

Oxford Overview - Mortality without recurrence in Radiotherapy trials

	Events	O-E	Hazard Ratio	p
Circulatory disease	**1510**	**77.6**	**1.25 (0.06)**	**0.00003**
Heart disease	1106	60.7	1.27 (0.07)	0.0001
Stroke	345	9.1	1.12 (0.12)	NS
Pulmonary embolism	59	7.8	1.76 (0.36)	0.04
Other causes	**1455**	**6.4**	**1.02 (0.06)**	**NS**
Lung cancer	**156**	**21.7**	**1.78 (0.22)**	**0.0004**
Oesophagus cancer	**23**	**4.9**	**2.40 (0.68)**	**0.04**
Leukaemia	31	2.4	1.40 (0.45)	NS
Soft-tissue sarcoma	7	1.3	2.13 (1.14)	NS
Respiratory disease	241	-1.0	0.98 (0.13)	NS
Other known causes	997	-22.9	0.90 (0.06)	NS
Unspecified cause	**701**	**7.8**	**1.05 (0.08)**	**NS**
Total	**3666**	**91.8**	**1.12 (0.04)**	**0.001**

Slide courtesy – Dr. Ashwini B

Cardiac Adverse Events in Hypofractionation Trials

	START-A				START-B		
	50 Gy (n=749)	41·6 Gy (n=750)	39 Gy (n=737)	Total (n=2236)	50 Gy (n=1105)	40 Gy (n=1110)	Total (n=2215)
Symptomatic rib fracture*							
Reported	5 (0·7%)	8 (1·1%)	9 (1·2%)	22 (1·0%)	17 (1·5%)	24 (2·2%)	41 (1·9%)
Confirmed†	0	0	1 (0·1%)	1 (<0·1%)	3 (0·3%)	3 (0·3%)	6 (0·3%)
Symptomatic lung fibrosis							
Reported	6 (0·8%)	9 (1·2%)	8 (1·1%)	23 (1·0%)	19 (1·7%)	19 (1·7%)	38 (1·7%)
Confirmed†	0	2 (0·3%)	1 (0·1%)	3 (0·1%)	2 (0·2%)	8 (0·7%)	10 (0·5%)
Ischaemic heart disease‡							
Reported	14 (1·9%)	11 (1·5%)	8 (1·1%)	33 (1·5%)	23 (2·1%)	17 (1·5%)	40 (1·8%)
Confirmed†							
Total	7 (0·9%)	5 (0·7%)	6 (0·8%)	18 (0·8%)	16 (1·4%)	8 (0·7%)	24 (1·1%)
Left sided	4 (0·5%)	1 (0·1%)	4 (0·5%)	9 (0·4%)	5 (0·5%)	4 (0·4%)	9 (0·4%)
Brachial plexopathy	0	1 (0·1%)	0	1 (<0·1%)	0	0	0

Data are n (%). *Reported cases include seven after trauma (five in START-A, two in START-B), and ten after metastases (five in START- A and five in START-B). †After imaging and further investigations. ‡26 patients in START-A and 22 in START-B had pre-existing heart disease at enrolment and were excluded.

Table 3: Incidence of other late adverse effects according to fractionation schedule

Joanne S Haviland et al, The lancet 2013

- Basics
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- **Dose volume data**
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Normal Tissue Tolerance– Dose volume data

- Summary of historical landmarks to establish the dose-volume parameters and outcomes

TABLE 13.1 HISTORICAL OVERVIEW OF SUMMARIES OF DOSE/VOLUME/OUTCOME INFORMATION

Report	*Key Contributions*	*Key Shortcomings*
Rubin, 1975[3]	Introduced the concept of $TD_{5/5}$ and $TD_{50/5}$	Minimal dose–volume data
Emami, 1991[1]	Concise summary addressing most clinically meaningful endpoints in a uniform manner Based on available data and expert opinion	Dose–volume relationship based on limited data and, thus, much expert opinion
QUANTEC, 2010[2]	Driven largely by the available 3D dose/volume/outcome data. Systematic review addressing many challenges such as organ delineation and confounding factors such as chemotherapy	Because dose/volume/outcome data on all meaningful clinical outcomes are *not* available, the summary is not able to guide all clinical practice

- QUANTEC– introduced the concept of evaluation of DVH parameters like V*x* (the % of organ receiving >/= *x* Gy)

α/β heart is low (about 1 Gy): fractionation results in substantial sparing effect

Source: Eric J. Hall, Seventh Ed. Ch. 20

Radiation Tolerance Doses– Heart

- Data for 2Gy/ #
- Variation with
    - Age
    - Individual sensitivity
    - Vascular status
    - Other treatment factors

OAR	TD5/5 (Gy)	TD50/5 (Gy)	DVH Vx % or mean dose in Gy	Tolerance dose (Gy)
Heart	1/3 60	70	V40 <30	D_{max} <60
	2/3 45	55	V30 <40–45	
	3/3 40	50	V20 <50	
Lung	1/3 45	65	V30 <10–15	
	2/3 30	40	V20 <25	
	3/3 17.5	24.5	Mean 10	

Practical_Radiotherapy_Planning DOBBS 4th ed.

Radiation Tolerance Doses– Heart

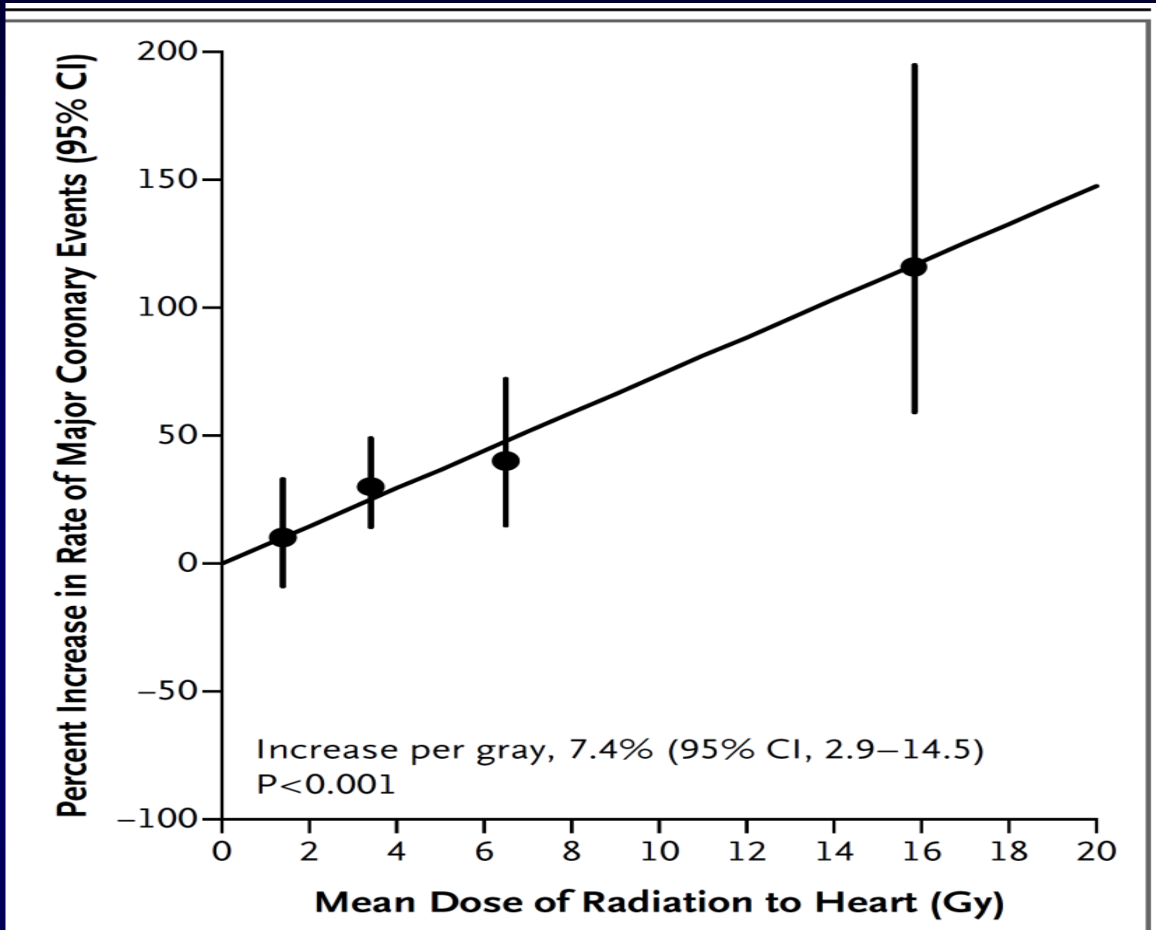
Pericardium	3D-CRT	Pericarditis	Mean dose <26	<15	Based on single study
Pericardium	3D-CRT	Pericarditis	V30 <46%	<15	
Whole organ	3D-CRT	Long-term cardiac mortality	V25 <10%	<1	Overly safe risk estimate based on model predictions

QUANTEC data

Stockholm Breast Cancer Study Group

- Patients: 2168 with major coronary events = 960 (1958 and 2001)
- Matched with population control n = 1205
- Mean dose to Heart
  - Left breast 2.9 Gy
  - Right breast 4.9 Gy
- The percentage increase in risk per gray was similar for women with and those without cardiac risk factors at the time of radiotherapy
- Women irradiated for cancer of the left breast had higher rates of major coronary events than women irradiated for cancer of the right breast (P = 0.002)

Sarah C. Darby et al Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer NEJM 2013



Mean Heart Dose	% Increase in Major Coronary Event
< 2 Gy	10%
2 - 4 Gy	30%
5 - 9 Gy	40%
> 10 Gy	116%

- Rate of Major Coronary Events According to Mean Radiation Dose to the Heart with no apparent threshold
- Each 1 Gy increase leads to 7.4% increased risk $p < 0.001$

Sarah C. Darby et al Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer NEJM 2013

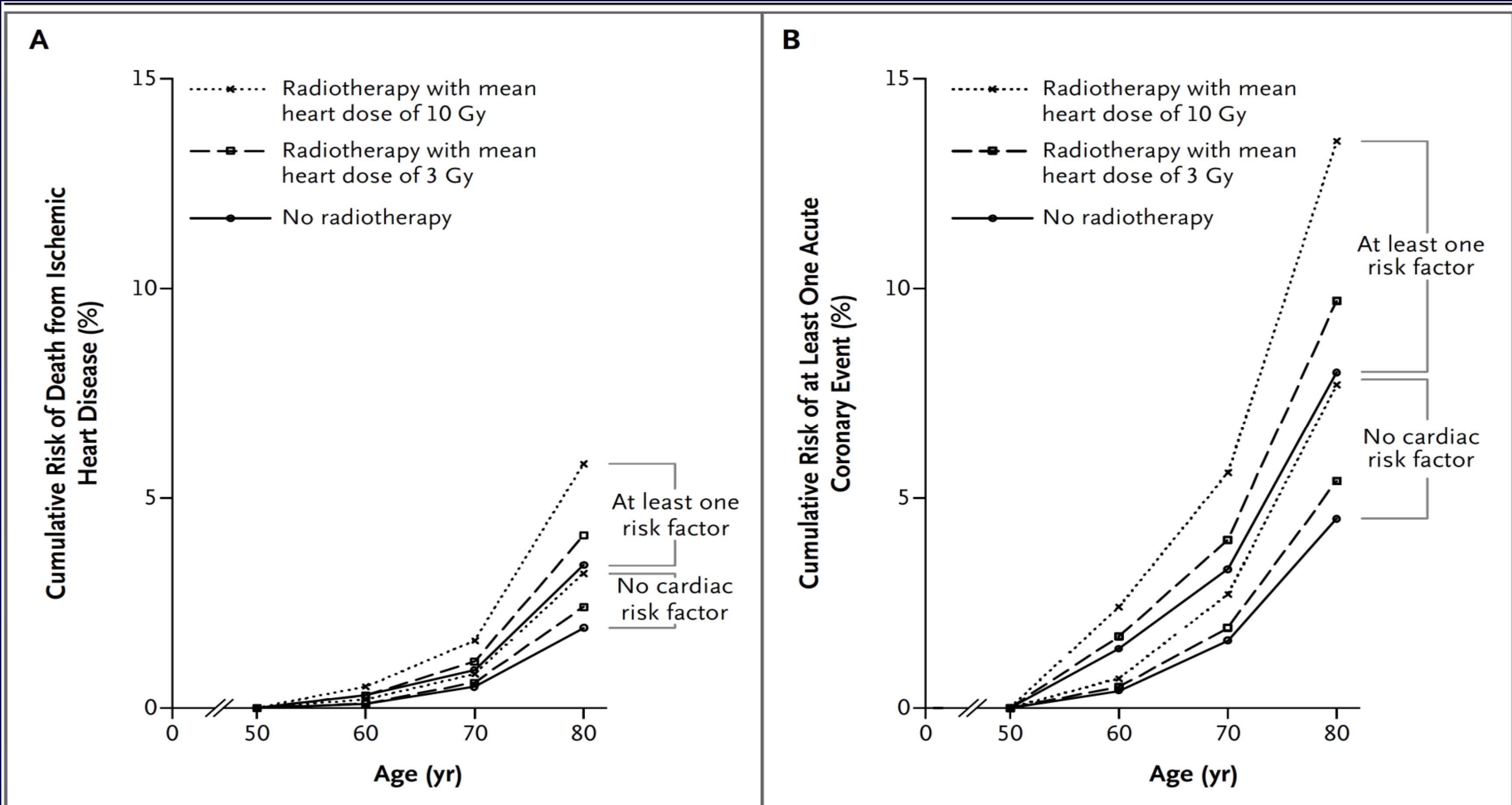


Figure 2. Cumulative Risks of Death from Ischemic Heart Disease and of at Least One Acute Coronary Event.

Post lumpectomy modern radiotherapy techniques significantly decreased the dose delivered to the heart (mean V25 Gy was 5.7% compared to 25% in Stockholm trial

Sarah C. Darby et al Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer NEJM 2013

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)

Sifted focus to mean heart dose but the mean dose effect might differ with age

Sarah C. Darby et al Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer NEJM 2013

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Factors which leads to increase in Heart Dose

Patient Related

- Previous co-morbidity
- Large breasts
- Age / Sex
- Lifestyle
- Smoking/alcohol
- Surgical scar

Treatment Related

Radiotherapy

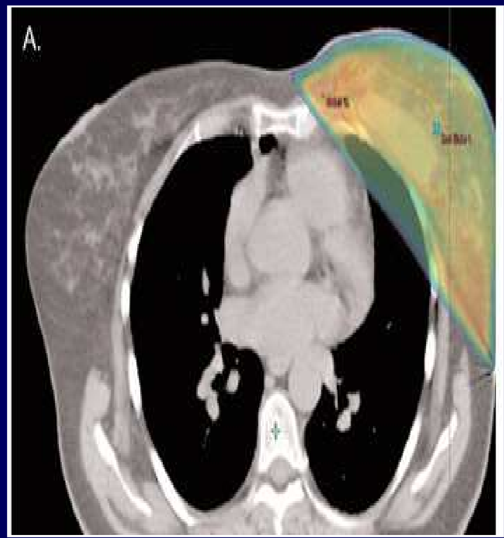
- Cobalt or MV
- Position
- 2D or 3D
- Technique
- QA

Chemotherapy

- Anthracyclins – Type- I cardiotoxicity
- Trastuzumab – Type – II cardiotoxicity
- Hormonal therapy

Technique of Sparing of Heart

- Brest Board
- Prone position
- Heart block
- 3D conformal radiotherapy (3DCRT)
- Intensity modulated Radiotherapy (IMRT)
- Tomotherapy
- Respiratory maneuvers
- APBI
- Proton therapy

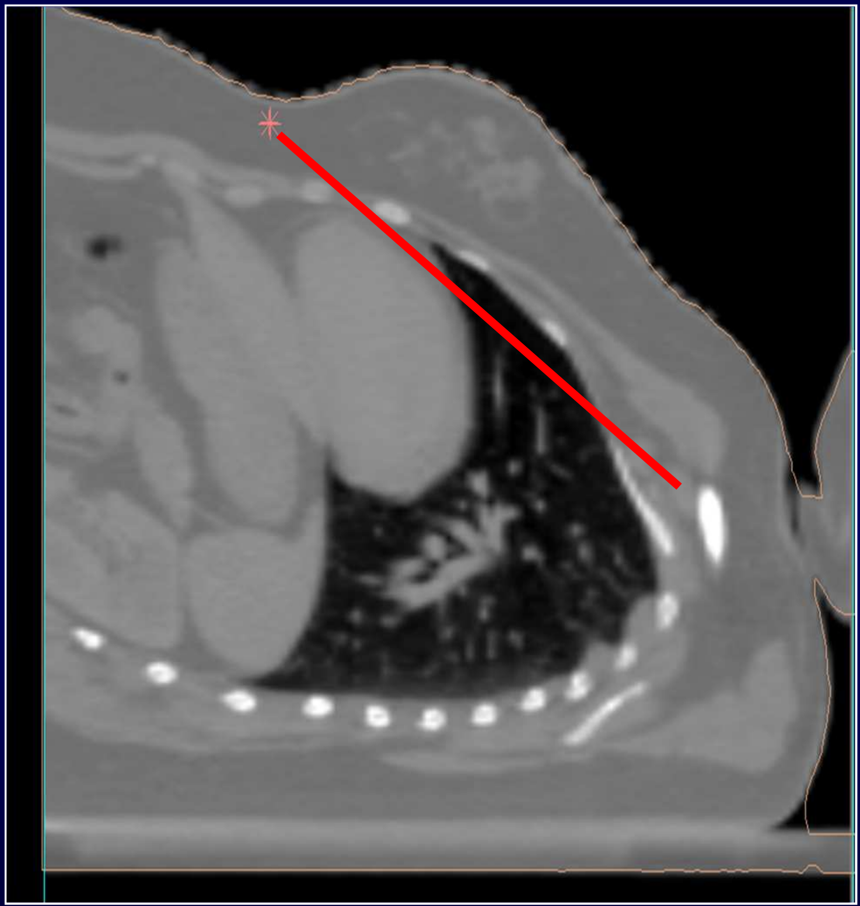


Breast Board

- Improves the angle of treatment along the chest wall to spare the anterior heart
- The tissues of the breast move forward with the slant of the board and higher arm elevation, allowing for less inclusion of tissues deep to the chest wall. [1]
- Improvements in the position have been shown to reduce the mean cardiac dose by as much as 60% and the maximum dose to the heart by 30% in comparison to treatment with flat positioning and collimation [2]
- Proper set up and immobilization can decrease cardiac dose.

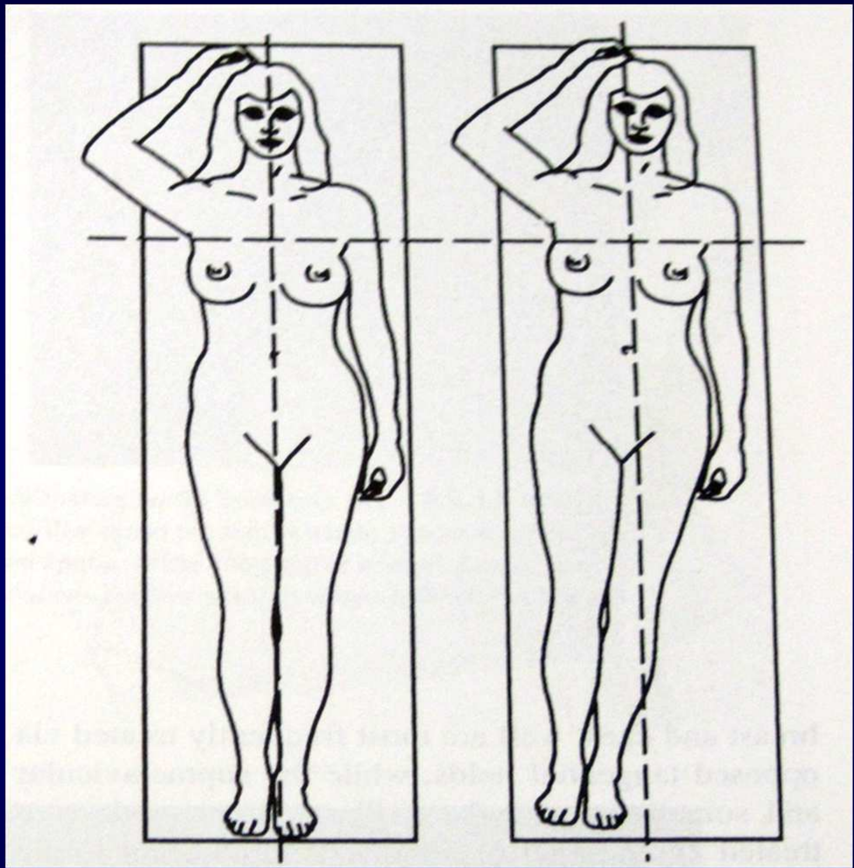
1. Canney PA et al: Reducing cardiac dose in post- operative irradiation of breast cancer patients: The relative importance of patient positioning and CT scan planning. Br J Radiol 1999
2. Canney PA et al: Variation in the probability of cardiac complications with radiation technique in early breast cancer. Br J Radiol 2001

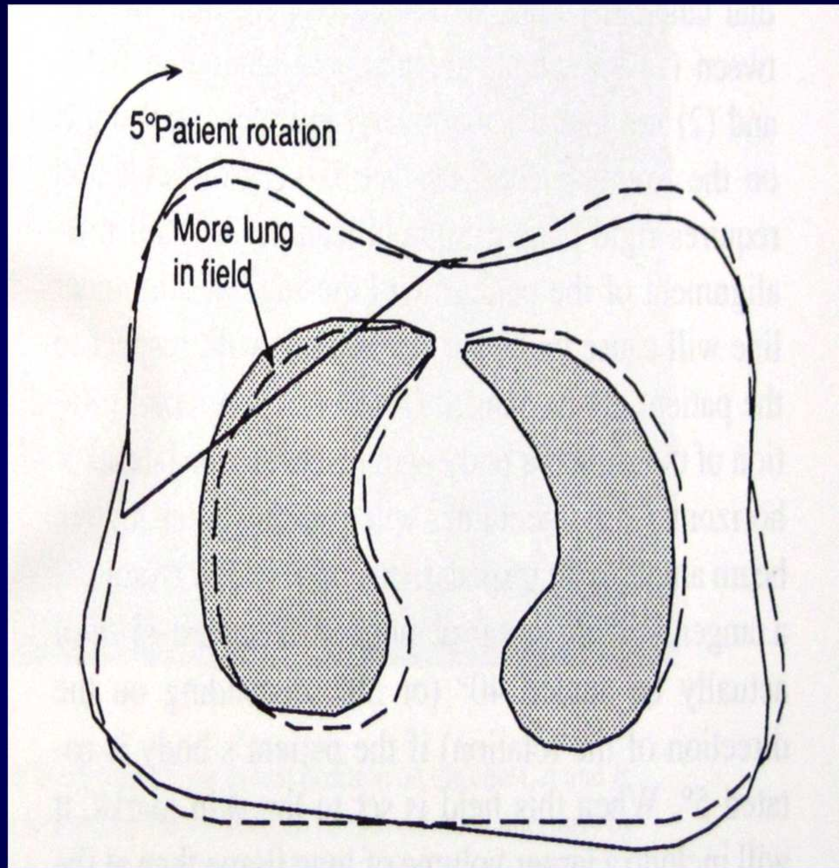
Breast Board



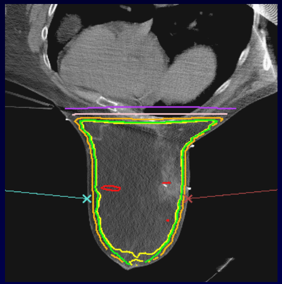
Breast Board

Importance Of Positioning





A small misalignment of the pt. on the couch will have the same effect as if the couch were angled

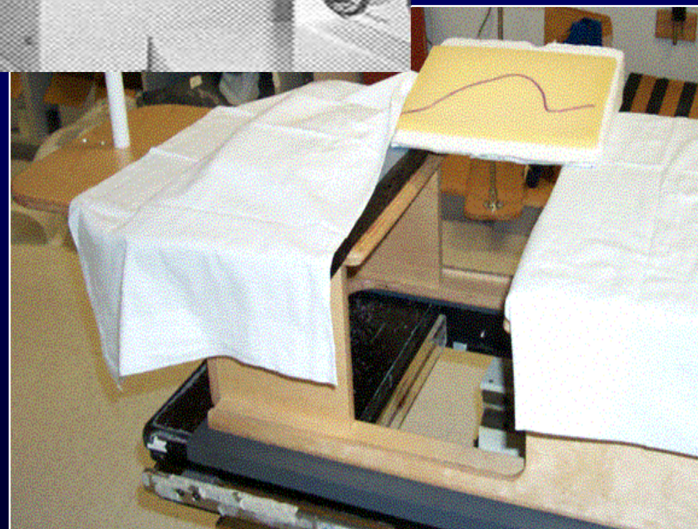


Prone Position

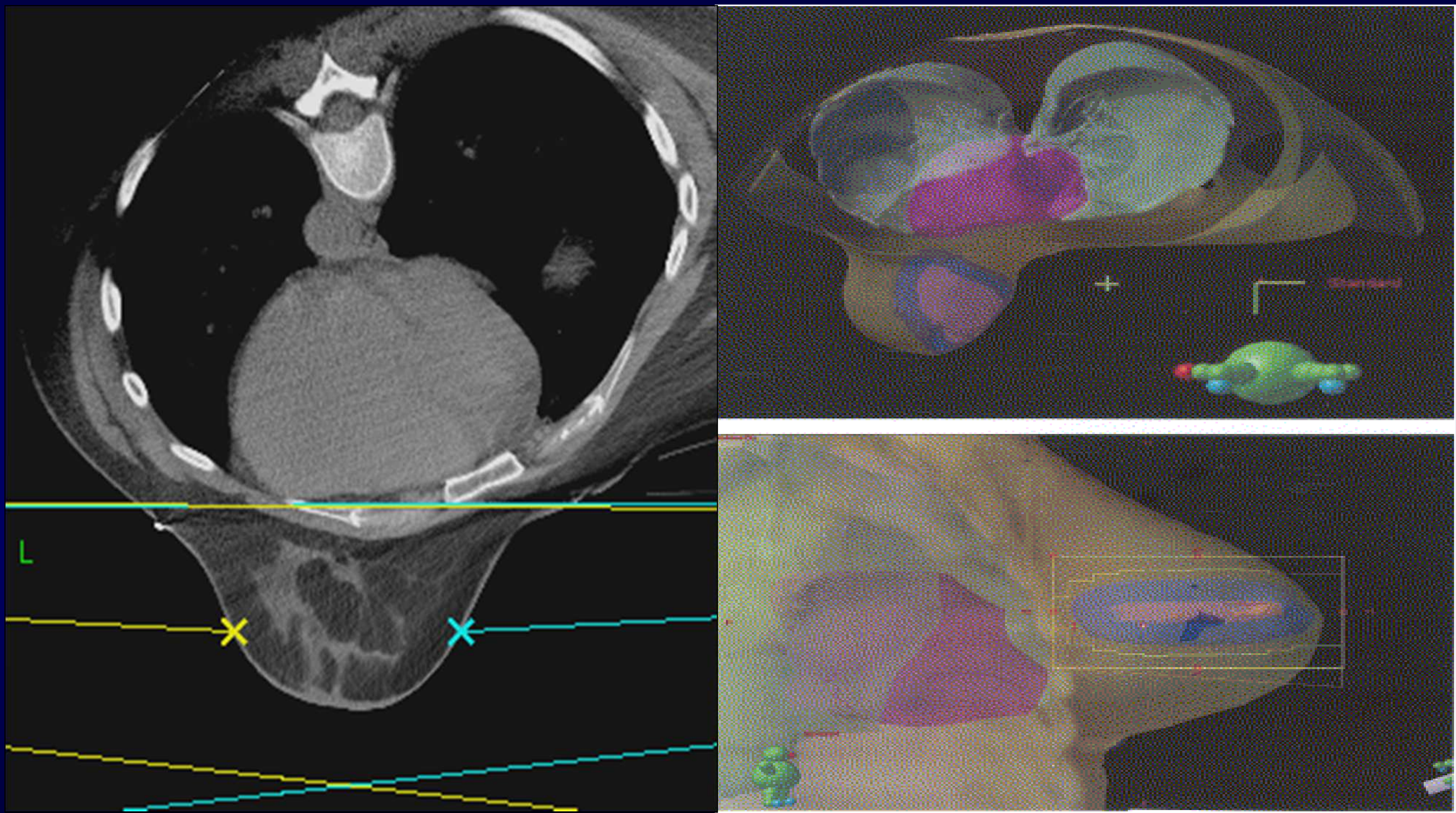
- An alternative to improve cardiac positioning and dose homogeneity throughout the breast.
- Review 200 women simulated with both prone and supine positioning
- Prone positioning decreased the volume of heart in the field for 85% of the patients (with only15% of women having lower cardiac volume with standard supine treatment).
- The reduction in cardiac volumes was 87% (8.8-1.3cm3).
- Although the benefit in women with < 750 cm^3 volume breasts did not reach statistical significance
- Women of all breast volumes had a reduction in cardiac volume with the greatest effect noted in larger breast volumes

Formenti SC et al: Prone vs supine positioning for breast cancer radiotherapy. J Am Med Assoc, 2012

Prone Breast Board



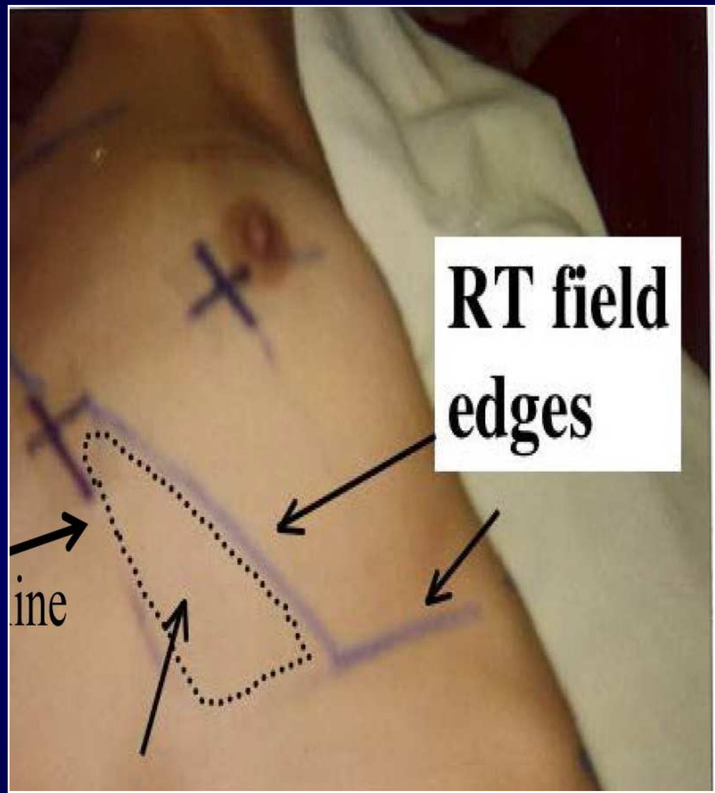
Prone Position



Goodman 2002, MSKCC

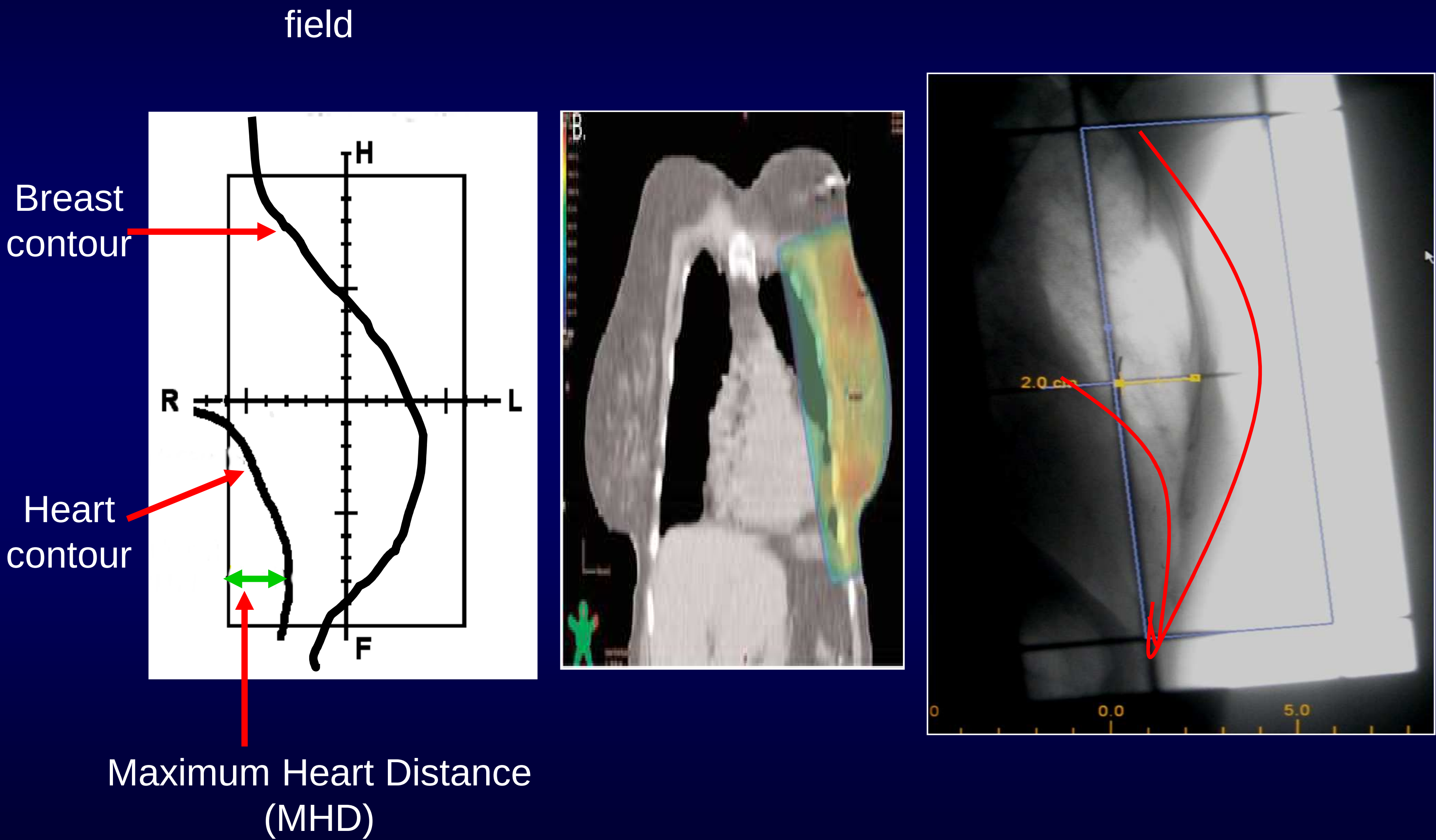
Heart Block

- Customized blocks
- May be appropriate, particularly in patients with well-visualized surgical beds.
- Average percentage of breast tissue that may be under dosed is 2.8%.
- Overall, local recurrence rates were not significantly different between patients with field heart blocks vs those without blocks.

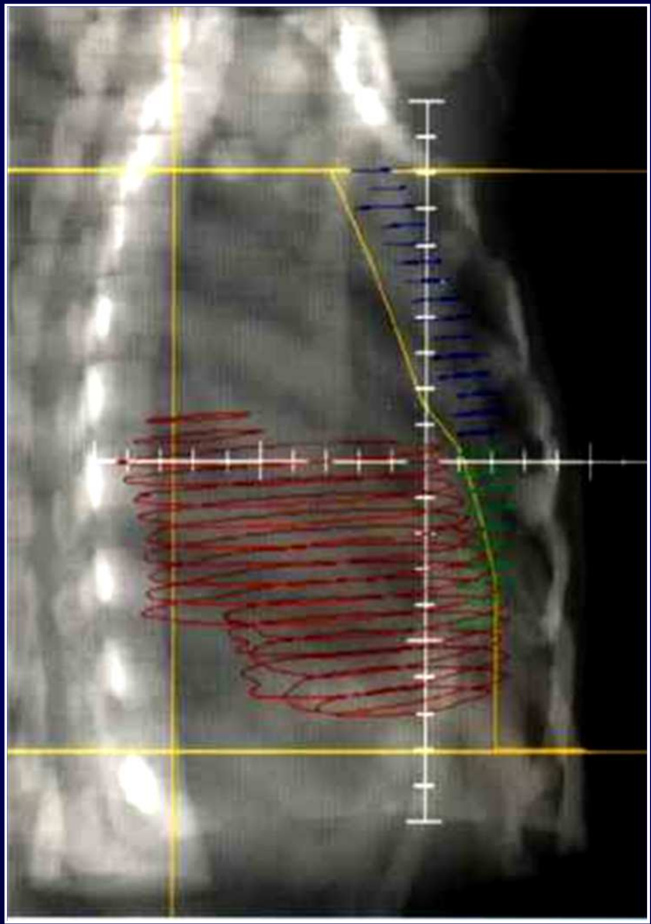


Raj KA et al: Is there an increased risk of local recurrence under the heart block in patients with left-sided breast cancer? Cancer J 1, 2006

Heart Block


field
Breast contour
Heart contour
H
R
L
F
Maximum Heart Distance (MHD)
2.0
0.0
5.0

Heart Block



Marks IJROBP 1994

Left side RT

- Intact Breast
  - Superior tumor
    - Heart Block
  - Inferior Tumor
    - Tangent angle
    - DIBH
    - Electron Patch

- Mastectomy
  - Tangent angle
  - DIBH
  - Electron

Newer RT techniques

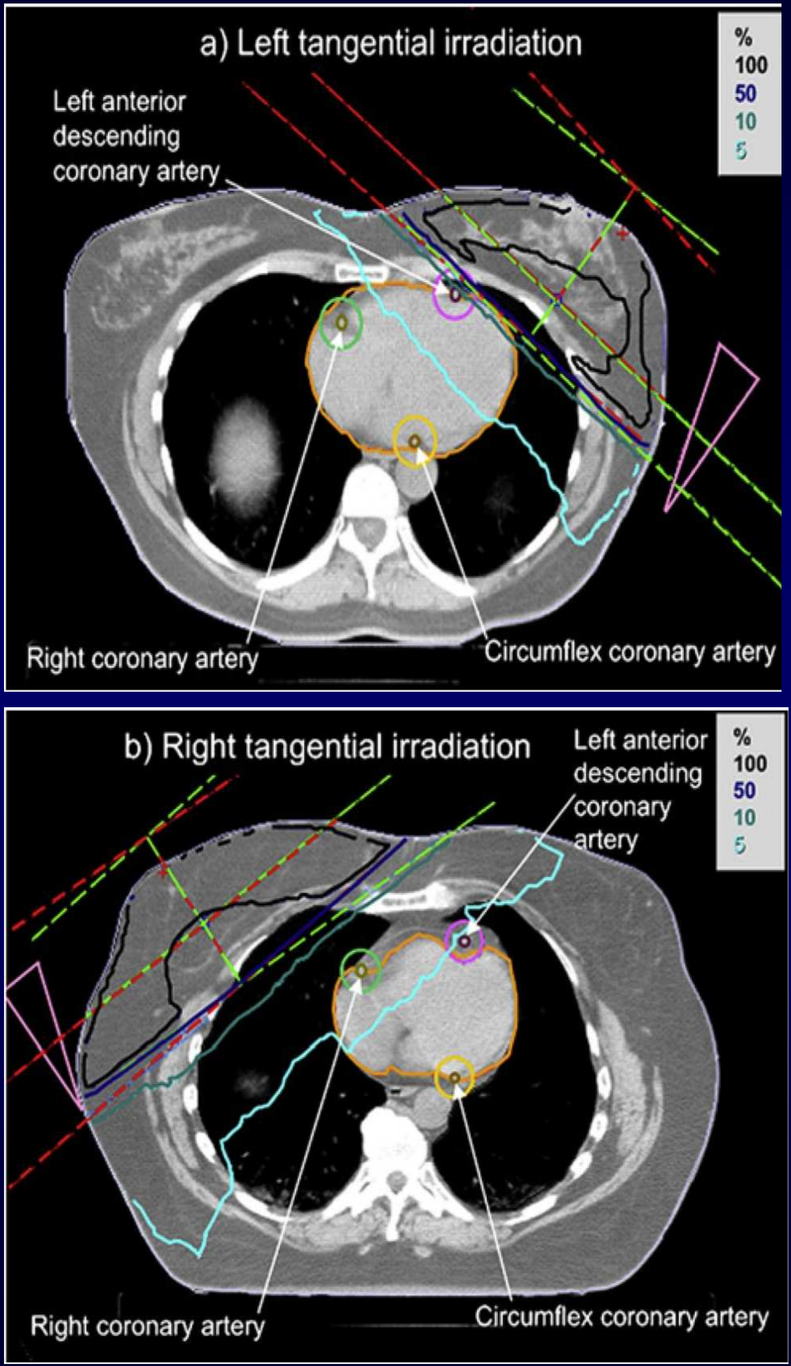
- Technological advancements in the RT technique has improved over the time
- Shift from orthovoltage cobalt to MV
- 2D to 3D planning
- Improvement in PTV coverage
- Decrease in OAR doses
- Use of 3 DCRT, IMRT, Helical Tomotherapy

Challenges in defining Heart volumes in RT

- Uncertainities to delineate the Heart on CT imaging

  - Anatomical challenge: Close proximity / intersection of borders with Great Vessels, Liver, Diapragm and Stomach

  - Physiologic Movements: Different regions move in different degrees and directions during cardiac cycle and respiration



- n=50
- Approximately half of the patients irradiated with left tangential radiotherapy received doses of ≥ 20 Gy to a small part of the anterior heart, which usually included the LAD coronary artery.
- Most of the heart volume, including the right and circumflex coronary arteries, received scattered irradiation alone, and mean heart dose was approximately 2 Gy for left-sided irradiation

Taylor et al, Cardiac dose from tangential breast cancer radiotherapy in The year 2006 IJROBP -2007

Calendar period	Heart	LAD coronary artery	Right coronary artery	Circumflex coronary artery
Mean dose (Gy)				
1970s (Sweden) (4)	13.3	31.8	9.1	6.9
1990s (Sweden) (4)	4.7	21.9	2.0	2.8
2006 (United Kingdom)	2.3	7.6	2.0	1.8
Mean dose (% tumor dose)				
1970s (Sweden) (4)	26.6	63.6	18.2	13.8
1990s (Sweden) (4)	9.4	43.8	4.0	5.6
2006 (United Kingdom)	5.8	19.0	5.0	4.5

	Heart	LAD coronary artery	Right coronary artery	Circumflex coronary artery
Average mean dose (SD)* (Gy)				
Left-sided irradiation	2.3 (0.7)†	7.6 (4.5)†	2.0 (0.3)	1.8 (0.3)
Right-sided irradiation	1.5 (0.2)	1.6 (0.2)	2.0 (0.3)	1.2 (0.1)
Average maximum dose (SD)* (Gy)				
Left-sided irradiation	30.7 (10.8)†	35.2 (8.8)†	2.5 (0.3)	2.4 (0.4)
Right-sided irradiation	2.6 (0.3)	1.9 (0.2)	2.5 (0.4)	1.5 (0.2)

Taylor et al, Cardiac dose from tangential breast cancer radiotherapy in The year 2006 IJROBP -2007

IHD incidence

Table 2. Comparison of percent ischemic heart disease mortality (with 95% confidence intervals) at 15 years of follow-up between women with left-sided and right-sided breast cancers, stratified by stage of disease at time of diagnosis

	All patients			Patients with in situ/localized disease			Patients with regional disease		
Cohort by year of diagnosis	Left-sided, %	Right-sided, %	*P*	Left-sided, %	Right-sided, %	*P*	Left-sided, %	Right-sided, %	*P*
Overall	8.7 (8.0 to 9.3)	7.5 (6.9 to 8.2)	.07	7.6 (6.7 to 8.4)	6.7 (5.9 to 7.5)	.40	10.2 (9.1 to 11.3)	8.6 (7.6 to 9.6)	.09
1973–1979	13.1 (11.6 to 14.6)	10.2 (8.9 to 11.5)	.02	12.7 (10.3 to 15.2)	9.6 (7.5 to 11.8)	.14	13.3 (11.5 to 15.1)	10.6 (8.9 to 12.3)	.06
1980–1984	9.4 (8.1 to 10.6)	8.7 (7.4 to 10.0)	.64	8.9 (7.2 to 10.5)	8.7 (7.1 to 10.4)	.87	10.0 (7.9 to 12.1)	8.8 (6.8 to 10.9)	.38
1985–1989	5.8 (4.8 to 6.7)	5.2 (4.4 to 5.9)	.98	5.7 (4.5 to 6.8)	4.9 (4.0 to 5.8)	.79	6.0 (4.4 to 7.6)	5.7 (4.1 to 7.2)	.76

Incidence of IHD SEER data

N = 27283

Giordano et al Risk of Cardiac Death After Adjuvant Radiotherapy for Breast Cancer : JNCI 2005

Modern era shows great promise for reduced cardiac toxicity, although it is likely be decades before we can say this with certainty

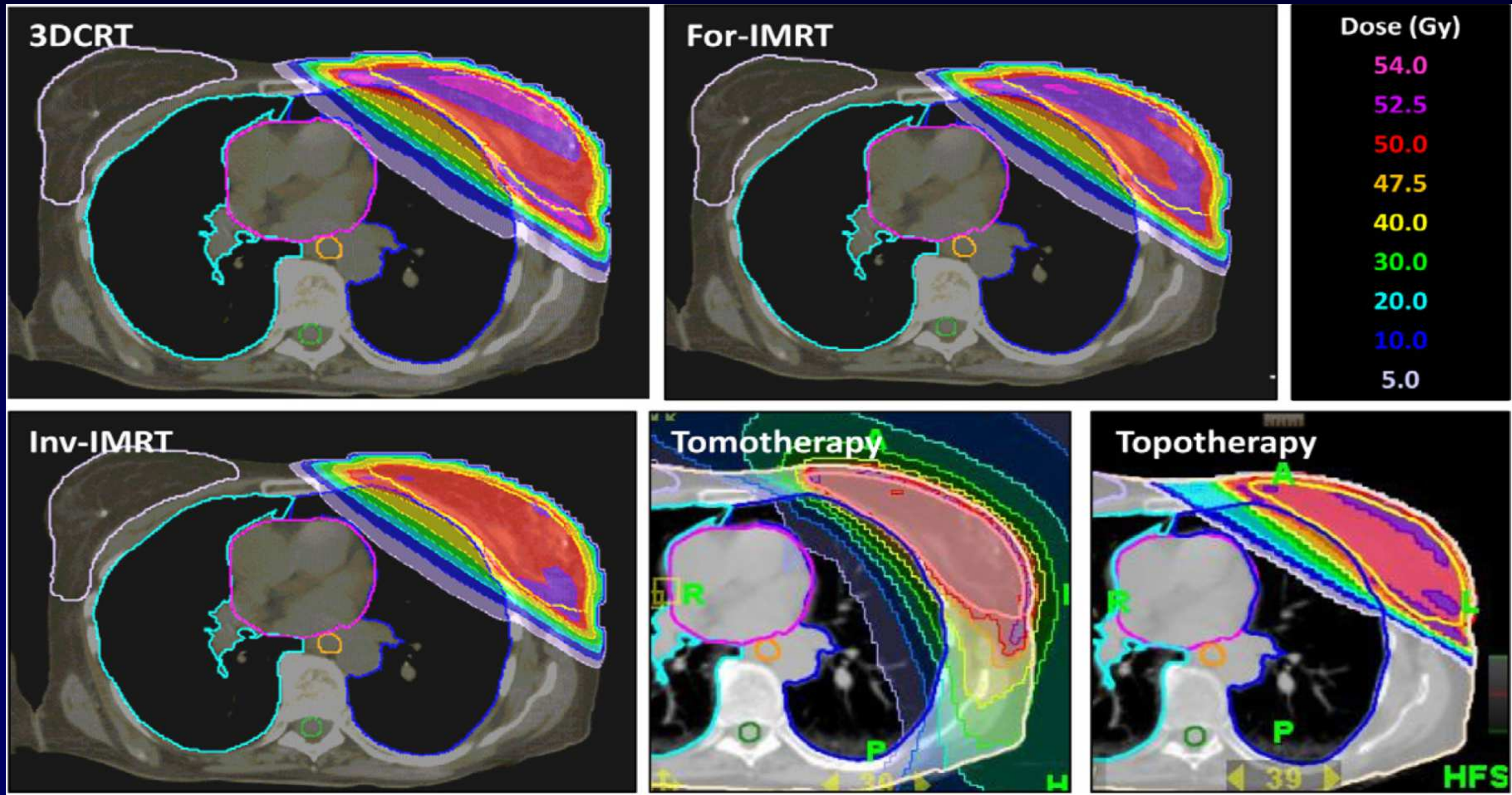
Comparison of different techniques

Comparison of normal tissue dose volume metrics as a function of plan modality.

Metric	3DCRT	For. IMRT	Inv. IMRT	Tomotherapy	Topotherapy	p-Value
Heart						
D_{mean} (Gy)	2.6 ± 0.9	2.3 ± 0.9	1.9 ± 0.8	3.9 ± 1.3	1.9 ± 0.7	0.002
D_{max} (Gy)	50.8 ± 3.5	49.1 ± 5.0	44.0 ± 7.2	33.9 ± 7.7	46.1 ± 5.9	<0.001
V_5 (%)	7.6 ± 3.5	6.6 ± 3.5	5.0 ± 3.1	26.5 ± 18.4	4.7 ± 2.7	0.003
V_{10} (%)	4.2 ± 2.5	3.8 ± 2.4	2.5 ± 2.0	4.8 ± 4.4	3.3 ± 2.2	0.354
V_{20} (%)	2.0 ± 1.6	2.2 ± 1.7	1.2 ± 1.4	0.5 ± 0.4	1.6 ± 1.4	0.010
V_{50} (%)	0.3 ± 0.5	0.1 ± 0.2	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1	<0.001

10 patients with left breast RT

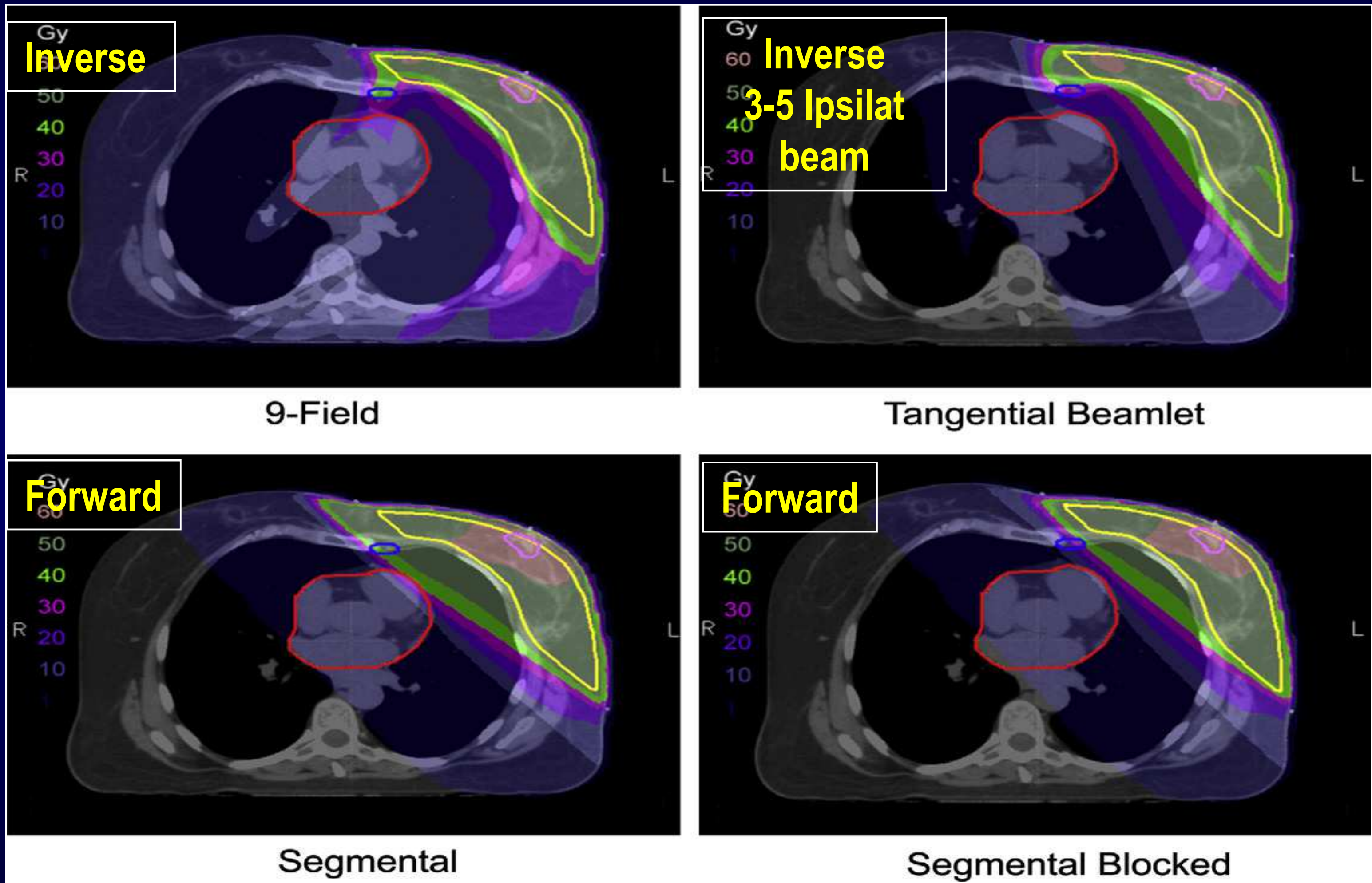
Leah K. Schubert et al Dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and topotherapy, radiotherapy & Oncology 2011



Results: Target max doses were reduced with for-IMRT compared to 3DCRT, which were further reduced with HT, topotherapy, and inv-IMRT. HT resulted in lowest heart and ipsilateral lung max doses, but had higher mean doses. Inv-IMRT and topotherapy reduced ipsilateral lung mean and max doses compared to 3DCRT and for-IMRT.

Leah K. Schubert et al Dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and topotherapy, radiotherapy & Oncology 2011

IMRT techniques



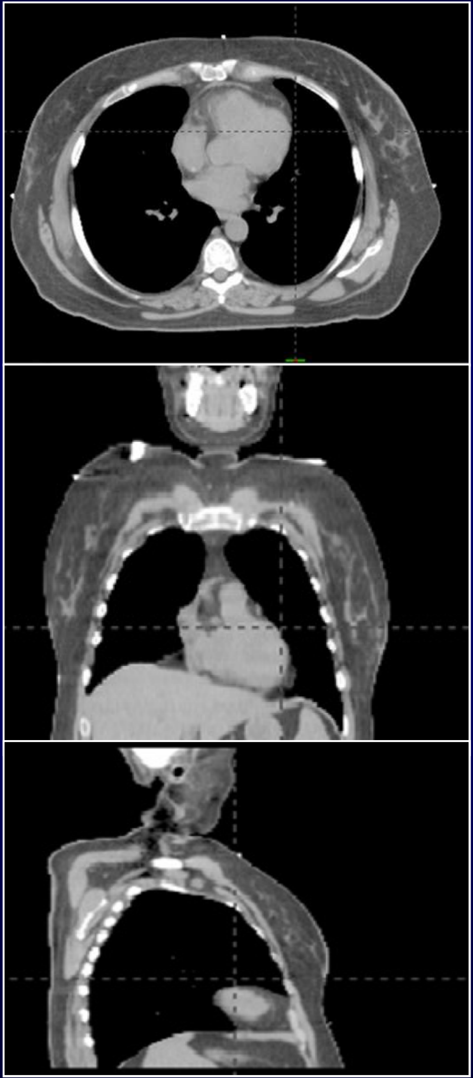
Reshma Jagsi et al; evaluation of 4 different technique of IMRT; IJROBP 2010

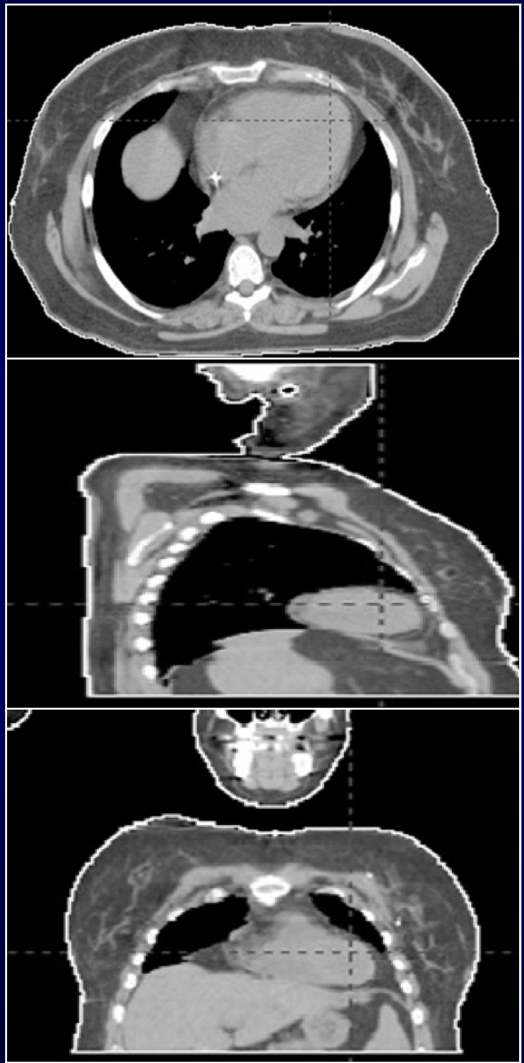
Structure	Mean estimate for 9-field technique (SD)	Mean estimate for segmental technique (SD)	Mean estimate for heart blocked segmental technique (SD)	Mean estimate for tangential beamlet technique (SD)
Heart				
Mean dose (Gy)	7.18 (1.21)	4.10 (1.46)	1.91 (0.33)	2.60 (1.33)
V2 (%)	99.94 (0.20)	47.76 (14.70)	37.63 (12.71)	51.47 (31.87)
V5 (%)	80.18 (16.63)	12.47 (6.18)	3.40 (1.33)	10.15 (13.27)
V10 (%)	11.49 (7.32)	7.11 (4.10)	0.55 (0.39)	2.46 (3.32)
V20 (%)	0.31 (0.36)	4.84 (3.11)	0.03 (0.06)	0.40 (0.79)
V30 (%)	0.01 (0.02)	3.34 (2.38)	0.005 (0.01)	0.05 (0.17)
LAD artery				
Mean dose (Gy)	11.23 (1.53)	20.59 (8.46)	6.00 (1.63)	5.44 (2.38)
Max dose to 1% volume (Gy)	19.32 (4.29)	46.60 (14.50)	14.22 (5.34)	9.81 (5.17)

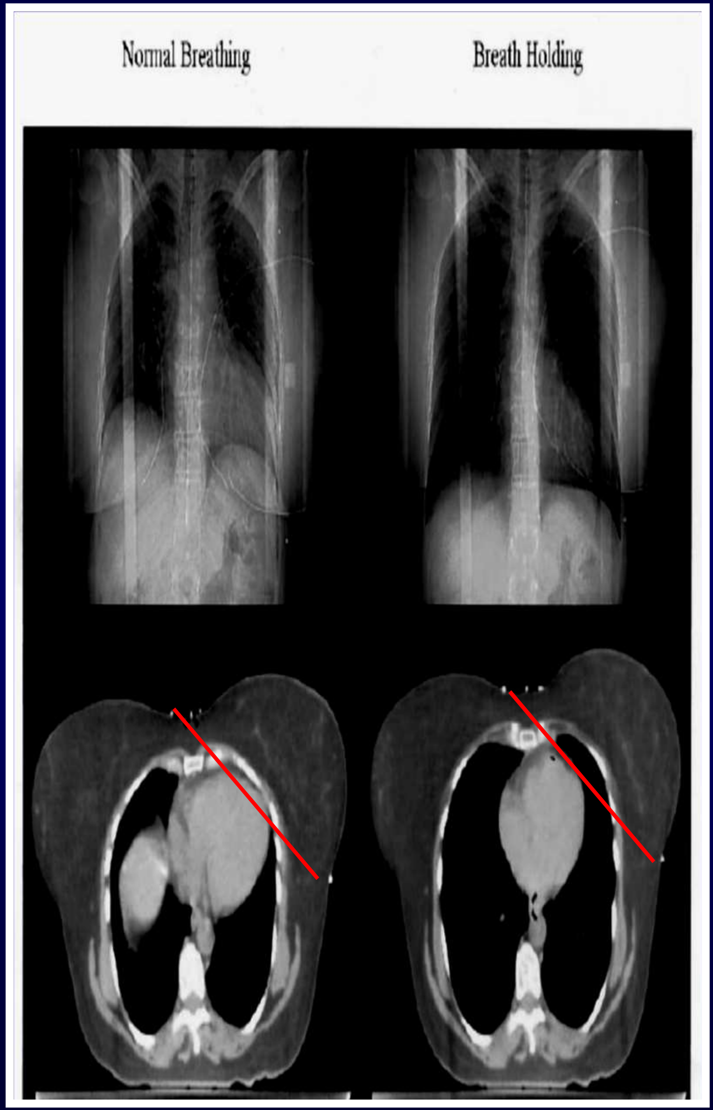
Dosimetric comparision

Reshma Jagsi et al; evaluation of 4 different technique of IMRT; IJROBP 2010

Gating and Deep Inspiration Breathing Techniques







DIBH

Active Breathing

Gating and Deep Inspiration Breathing Techniques

- Deep inspiration breath hold (DIBH) involves gating radiation to deliver treatment when the least volume of heart is in the field
- Inferior and posterior displacement of the cardiac silhouette caused by near maximal inspiration (Fig. 1)
- ~ 50% cases Heart could be entirely removed from the field and that cardiac volumes were reduced by approximately 80% [1]
- Comparisons of techniques found that median heart volume receiving greater than 50% of the dose was decreased from19% to ≤ 3% with either inspiratory gating or DIBH [2]

1. Lu HM et al: Reduction of cardiac volume in left- breast treatment fields by respiratory maneuvers :ACT study. IJROBP 2000
2. Korreman SS *et al:* Breathing adapted radiotherapy for breast cancer Comparison of free breathing gating with the breath-hold technique. Radiother Oncol 2005

Gating and Deep Inspiration Breathing Techniques

- Active breathing may be combined with treatment modalities such as fixed gantry IMRT as well. The reduction in V30 using DIBH for deep tangent IMRT plans was on average13% - 3% [1]
- With active breathing techniques, there is an average reduction of 5% to the volume near the left anterior descending (LAD) receiving 20Gy or more when using fixed gantry angle IMRT over 3D-conformal radiation therapy (CRT) [2]

1. Remouchamps VM et al: Significant reductions in heart and lung doses using deep inspiration breath hold with active breathing control and intensity-modulated radiation therapy for patients treated with locoregional breast IJROBP 2003
2. Mast ME et al: Left-sided breast cancer radiotherapy with and without breath-hold: Does IMRT reduce the cardiac dose even further ? Radiother Oncol 2013

VBH (Voluntary Breath Hold)
vs
Prone

Estimated breast volume of >750 cm3

Frederick R. Bartlett UK Heart Spare Study Radiotherapy and Oncology 2015

VBH (Voluntary Breath Hold)
vs
Prone

- All cardiac dose parameters (Gy) were statistically significantly lower with VBH than prone treatment

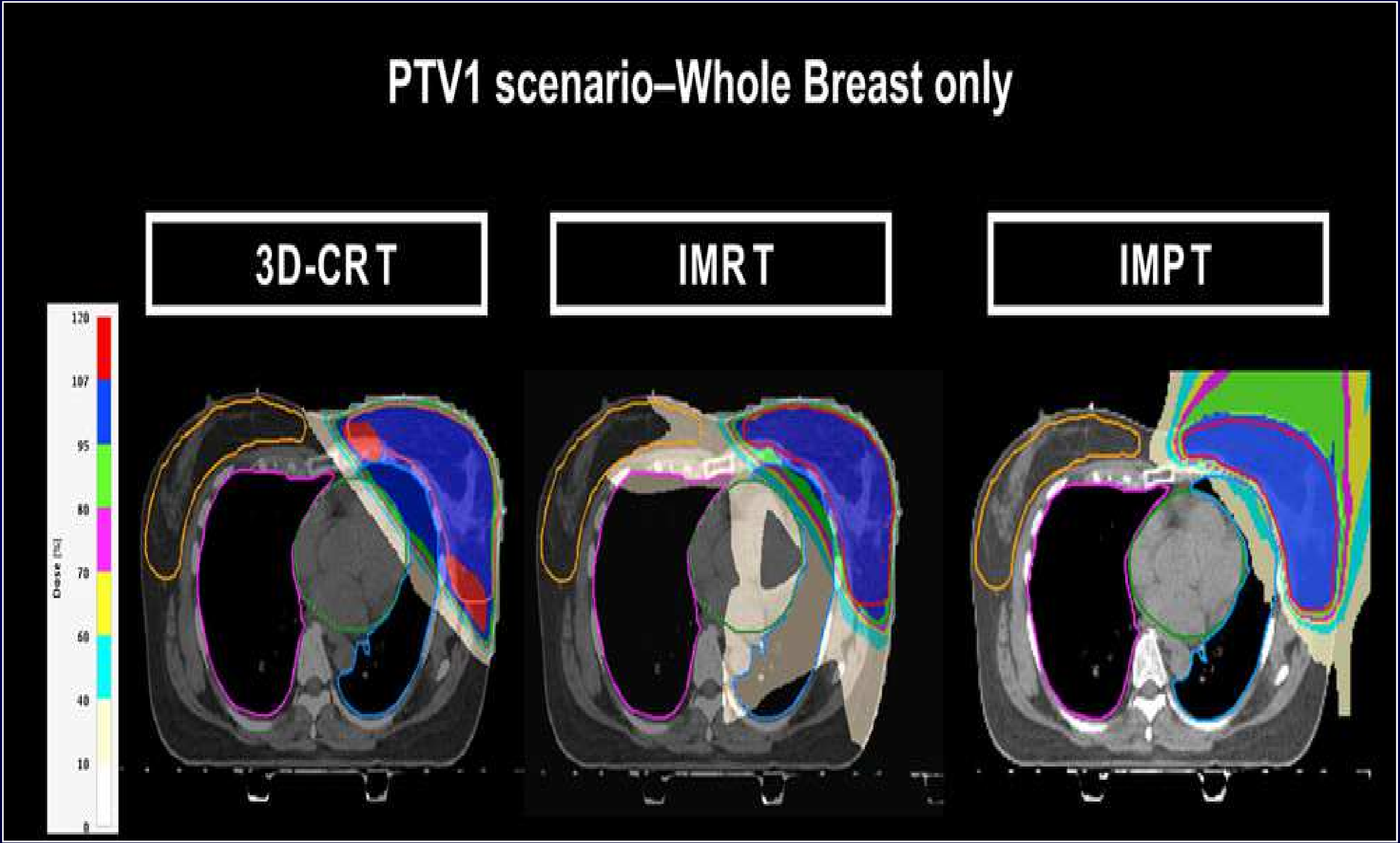
- Heart NTDmean 0.44 [0.38–0.51] vs. 0.66 [0.61–0.71] ($p < 0.001$)

- LAD NTDmean 2.9 [1.8–3.9] vs. 7.8 [6.4–9.2] ($p < 0.001$)

- LADmax 21.0 [15.8–26.2] vs. 36.8 [35.2–38.4] ($p < 0.001$)

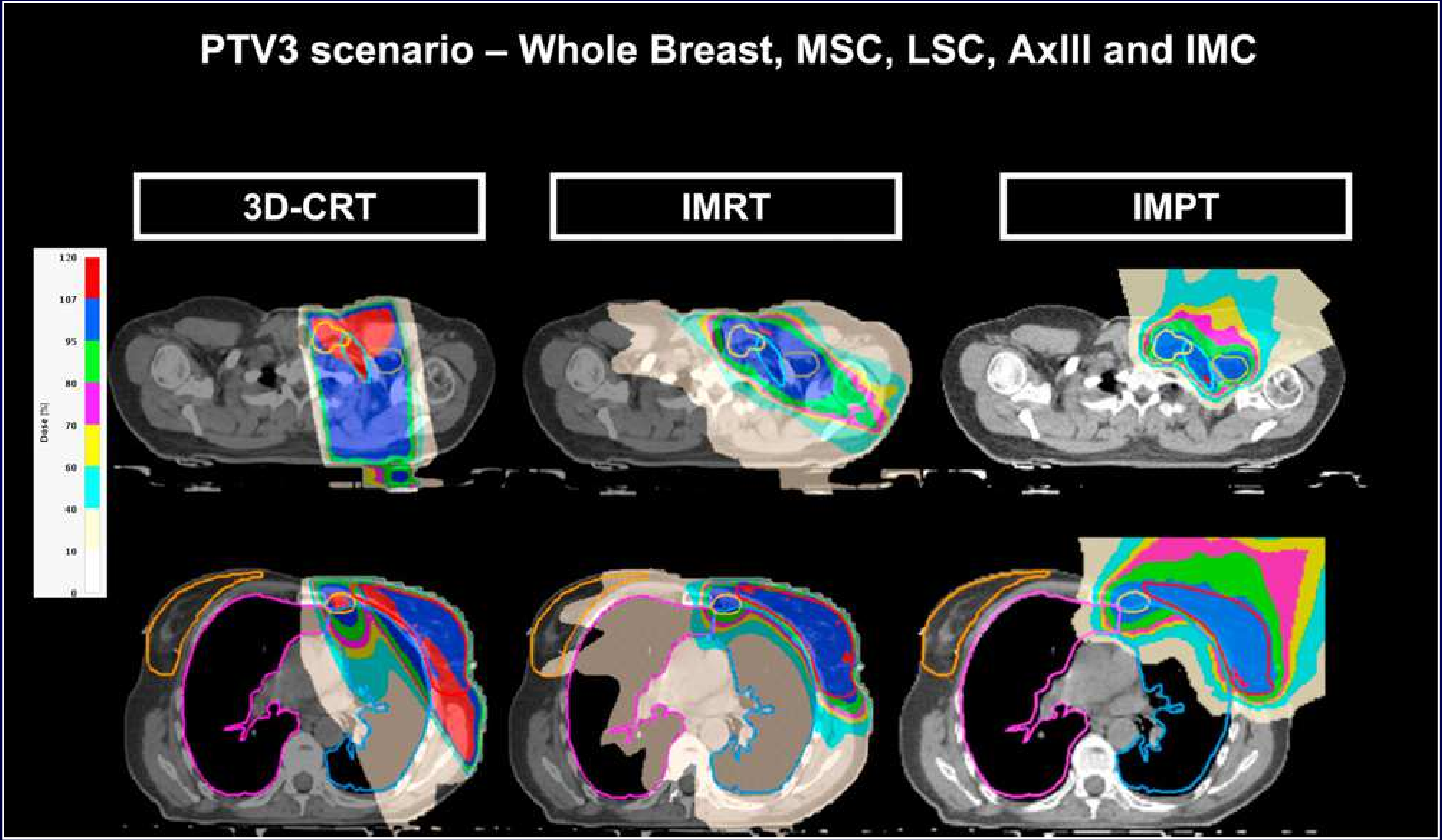
Frederick R. Bartlett UK Heart Spare Study Radiotherapy and Oncology 2015

Proton Therapy



Carmen Ares, Proton Therapy , IJROBP - 2010

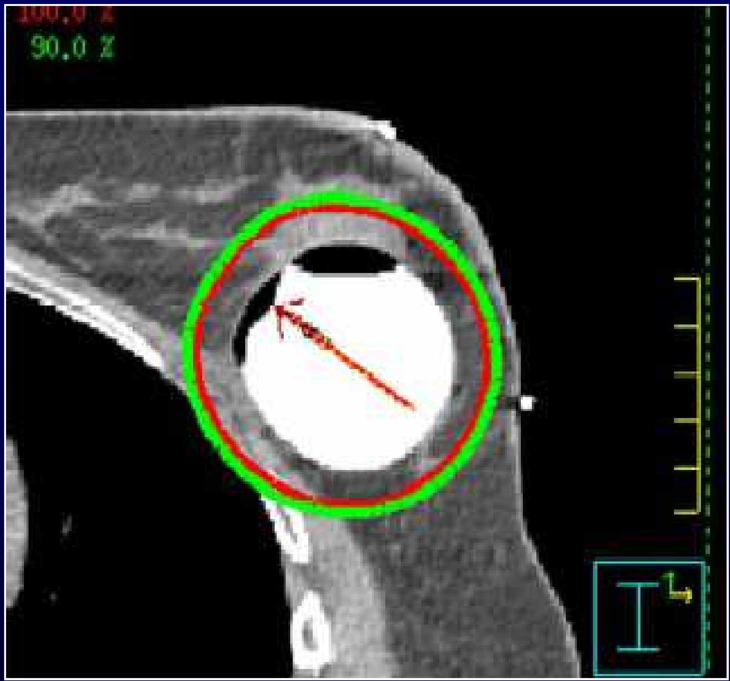
Proton Therapy

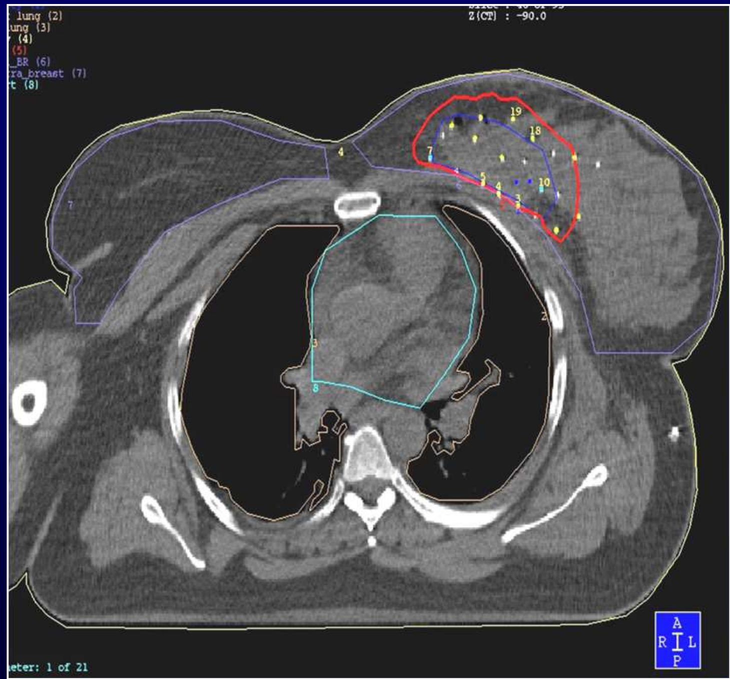


Carmen Ares, Proton Therapy , IJROBP - 2010

APBI

- Accelerated Partial breast irradiation
- As the dose is limited to tumor bed cavity and rapid dose fall off
- The cardiac morbidity and risk is very low





- Basics
- Pathophysiology
- Evidence of RIHD
- Dose volume data
- Ways to improve
- Clinical data
- **Future perspective**

Future perspective

- Incorporation of specialties such as cardio-oncology in the patient management and long-term follow-up are opportunities to identify high-risk patients earlier
- Biomarkers of cardiotoxicity – cardiac troponins,natriuretic peptides,and proposed early markers of cardiac injury markers, such as heart-type fatty acid-binding proteins and glycogen phosphorylase isoenzyme BB.
- Cardiac Stem cell

Conclusion

- RIHD is known toxicity of breast RT
- Data clearly states the adverse effects of RT on heart
- Recent advanced techniques of RT has reduced the cardiac doses significantly
- Further long term follow up data will be needed to analyze effect of newer techniques
- Use proper techniques and doses to spare the heart as much as possible
- All patients should be treated with CT simulation plans
- For centers doing 2D plans minimize MHD to <1cm

Thank you