COMO DISMINUIR O ELIMINAR CARDIO-TOXICIDAD EN IRRADIACION PARA CARCINOMA DE MAMA

Washington
School of Medicine

Carlos A. Perez, M.D.
Former Chairman/Professor Emeritus
Department of Radiation Oncology
Mallinckrodt Institute of Radiology
Siteman Cancer Center
Washington University School of Medicine

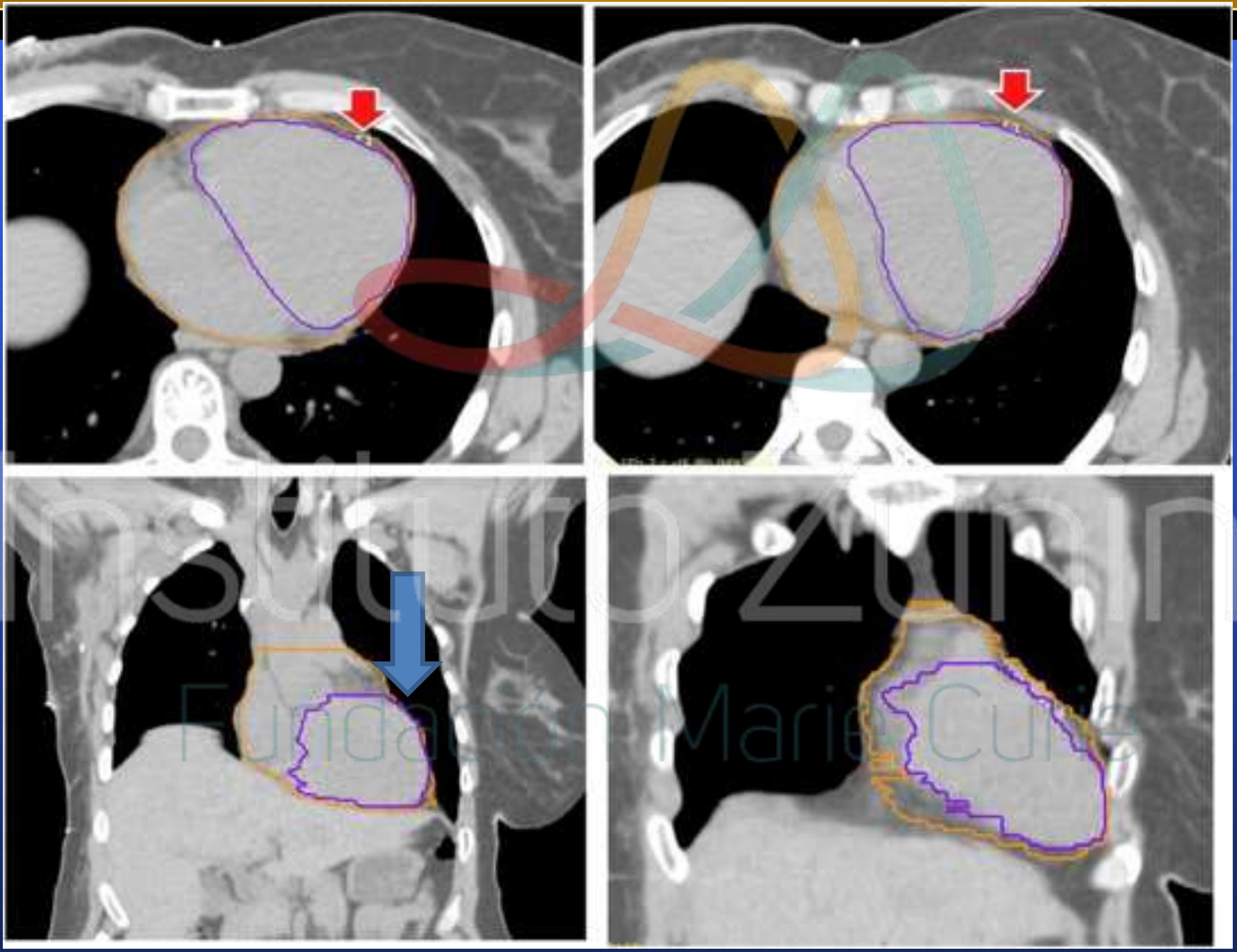
SITEMAN CANCER CENTER
BARNES-JEWISH HOSPITAL • WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

Washington University in St.Louis
School of Medicine

Mentors

perez@radonc.wustl.edu

PROTONS OR PHOTONS IN BREAST CANCER.
Anatomia de Importancia



Contouring of LT Anterior Coronary artery and Cardiac Volumes

Bradley J E et al Int J Radiat Oncol Bio Phys 95: 411, 2016

Breast Conservation therapy:
Standard Whole Breast + Lymphatics Irradiation

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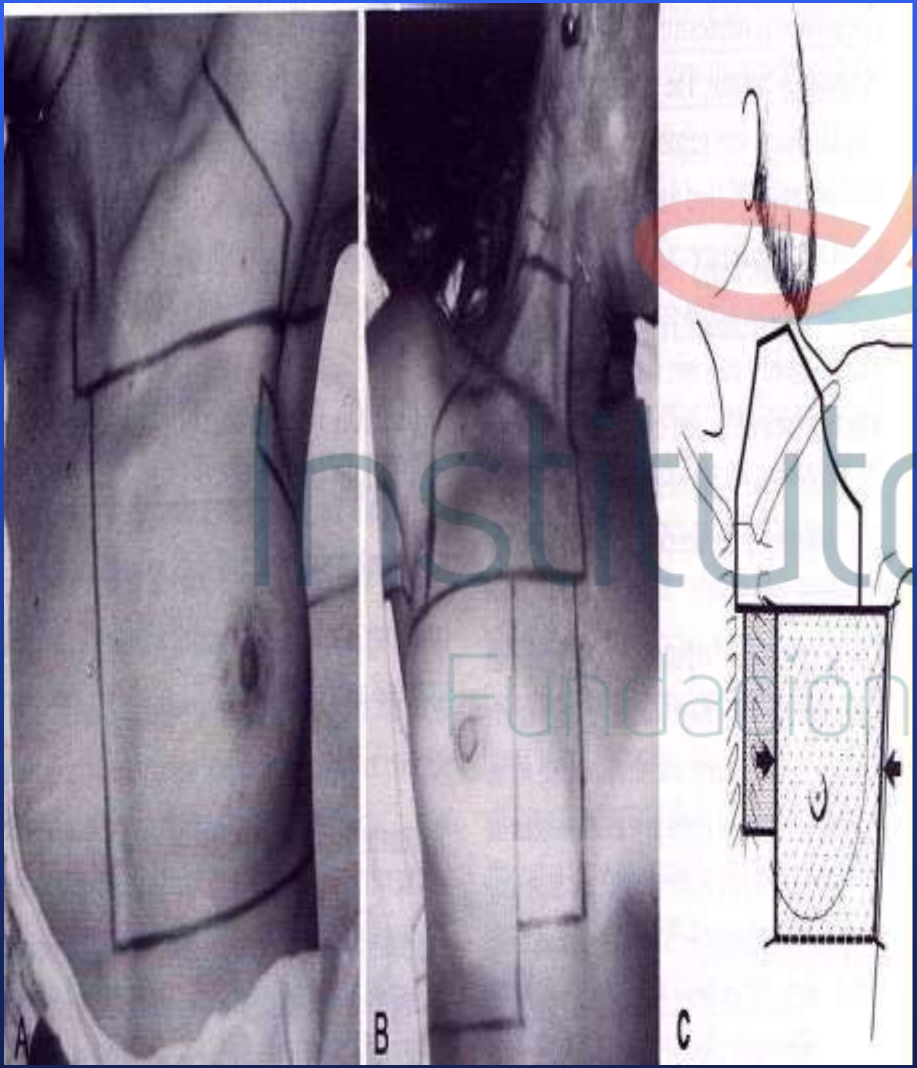

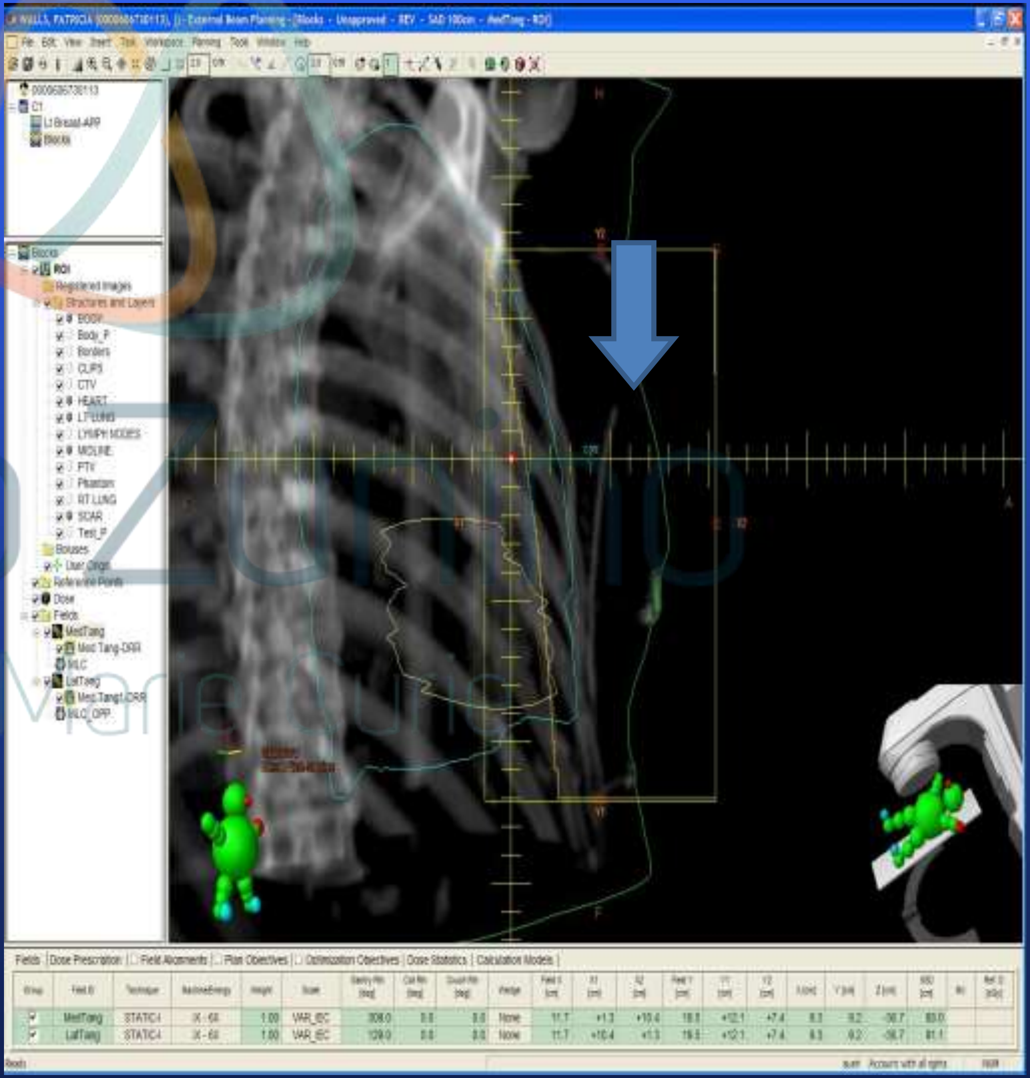

FACTORS ASSOCIATED WITH RISK OF RADIATION CARDIAC TOXICITY

- Volume of Heart irradiated (>5 %)
- Volume of Left Coronary Arteries/ Left Ventricle Irradiated
- Radiation dose (> 5Gy) and dose per fraction
- Radiation Therapy to lymph nodes, especially IMN
- Administration of Anthracyclines, Trastuzumab, Cyclophosphamide, Docetaxel, Aromatase Inhibitors (Anastrozole)
- Patient Age at time of Treatment. Hx of Cardiovascula Disease
- History of Smoking and other Comorbidities

CHEMOTHERAPEUTIC AGENTS AND LEFT VENTRICULAR DYSFUNCTION

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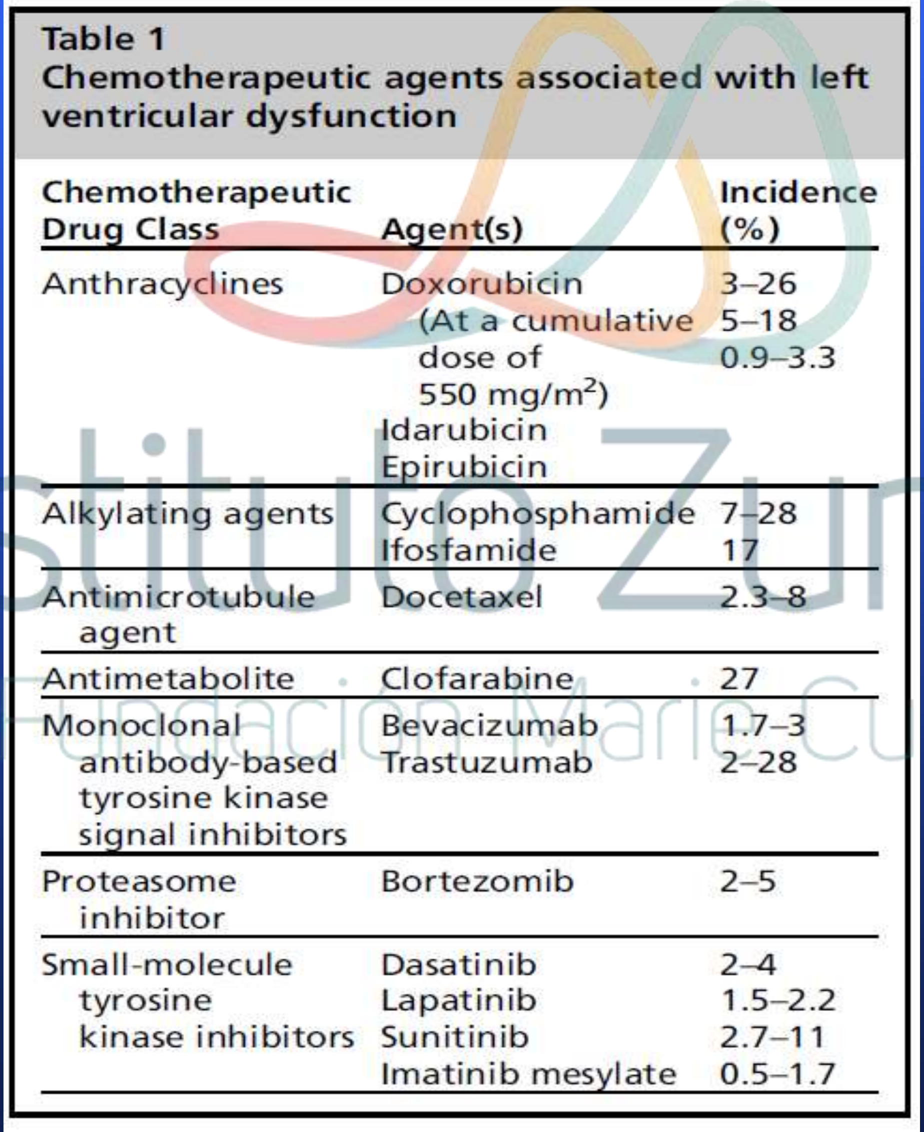

Table 1
Chemotherapeutic agents associated with left ventricular dysfunction

Chemotherapeutic Drug Class	Agent(s)	Incidence (%)
Anthracyclines	Doxorubicin (At a cumulative dose of 550 mg/m^2) Idarubicin Epirubicin	3–26 5–18 0.9–3.3
Alkylating agents	Cyclophosphamide Ifosfamide	7–28 17
Antimicrotubule agent	Docetaxel	2.3–8
Antimetabolite	Clofarabine	27
Monoclonal antibody-based tyrosine kinase signal inhibitors	Bevacizumab Trastuzumab	1.7–3 2–28
Proteasome inhibitor	Bortezomib	2–5
Small-molecule tyrosine kinase inhibitors	Dasatinib Lapatinib Sunitinib Imatinib mesylate	2–4 1.5–2.2 2.7–11 0.5–1.7

POTENTIAL RADIATION-INDUCED INJURY TO HEART

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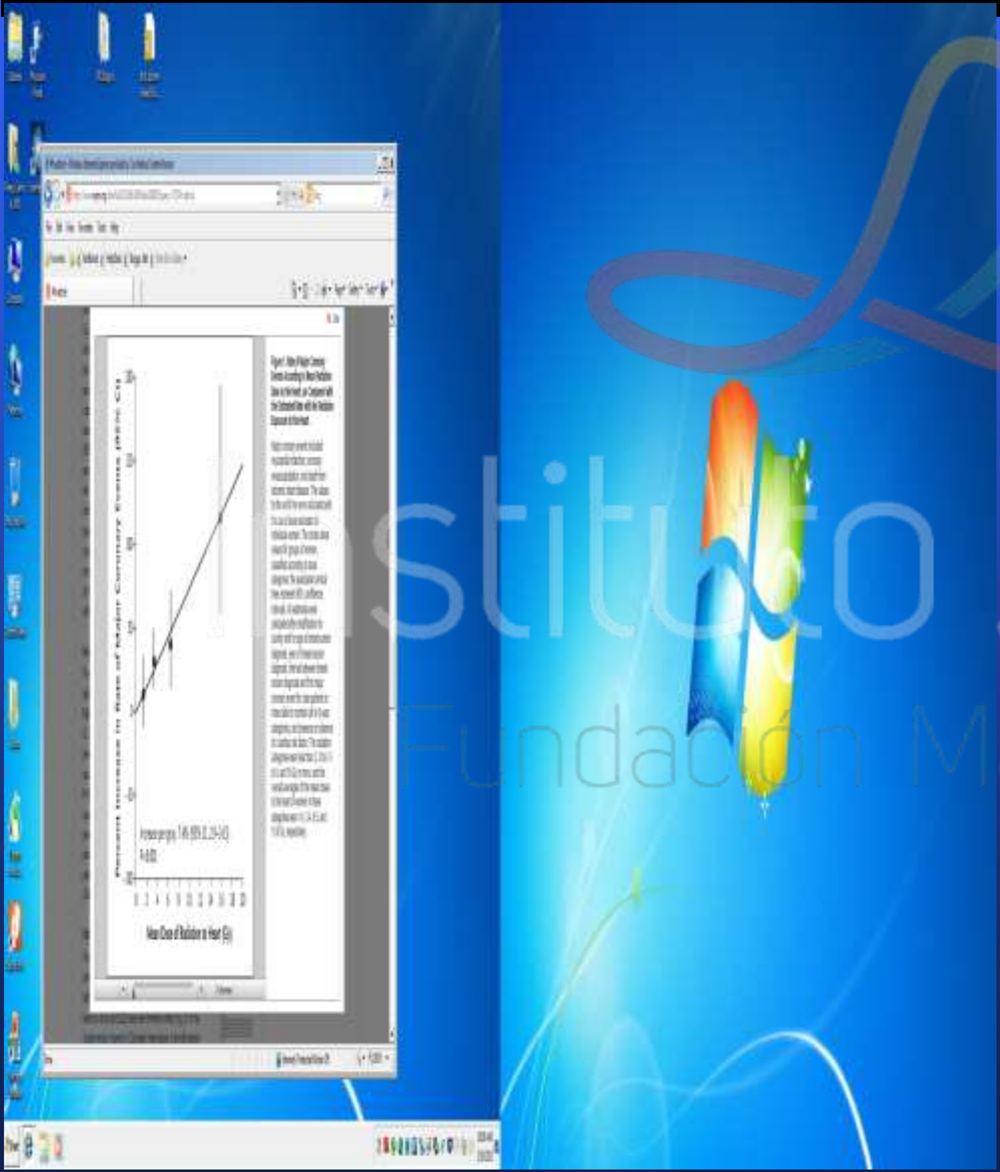
- Arrythmia
- Coronary Artery Stenosis, Ischemia, Angina, Infarction
- (Macro- and Micro-vascular injury, Macrophages)
- Perfusion Defects
- Myocardial damage (Cardiomyopathy, Fibrosis)
- Valvular Injury
- Congestive Heart Failure
- Pericardial Effusion, Pericarditis

HEART DISEASE AFTER RADIATION THERAPY FOR BREAST CANCER



Darby SC et al
N Engl J Med 368: 987. 2013

RISK OF DEATH OR CORONARY DISEASE AFTER RADIATION THERAPY FOR BREAST CANCER

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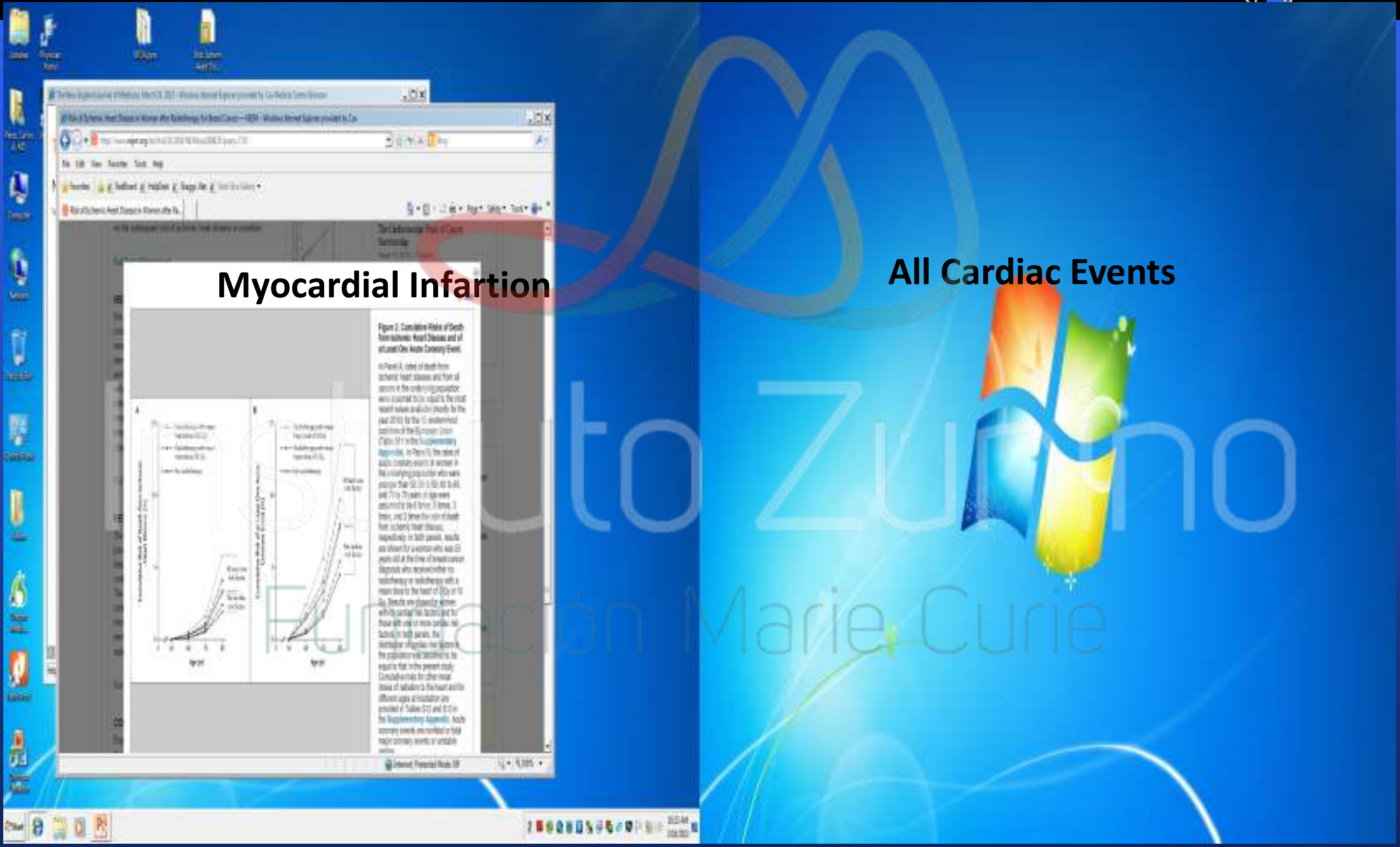

Darby SC et al N Engl J Med 368: 987. 2013

HEART DISEASE AFTER RADIATION THERAPY FOR BREAST CANCER

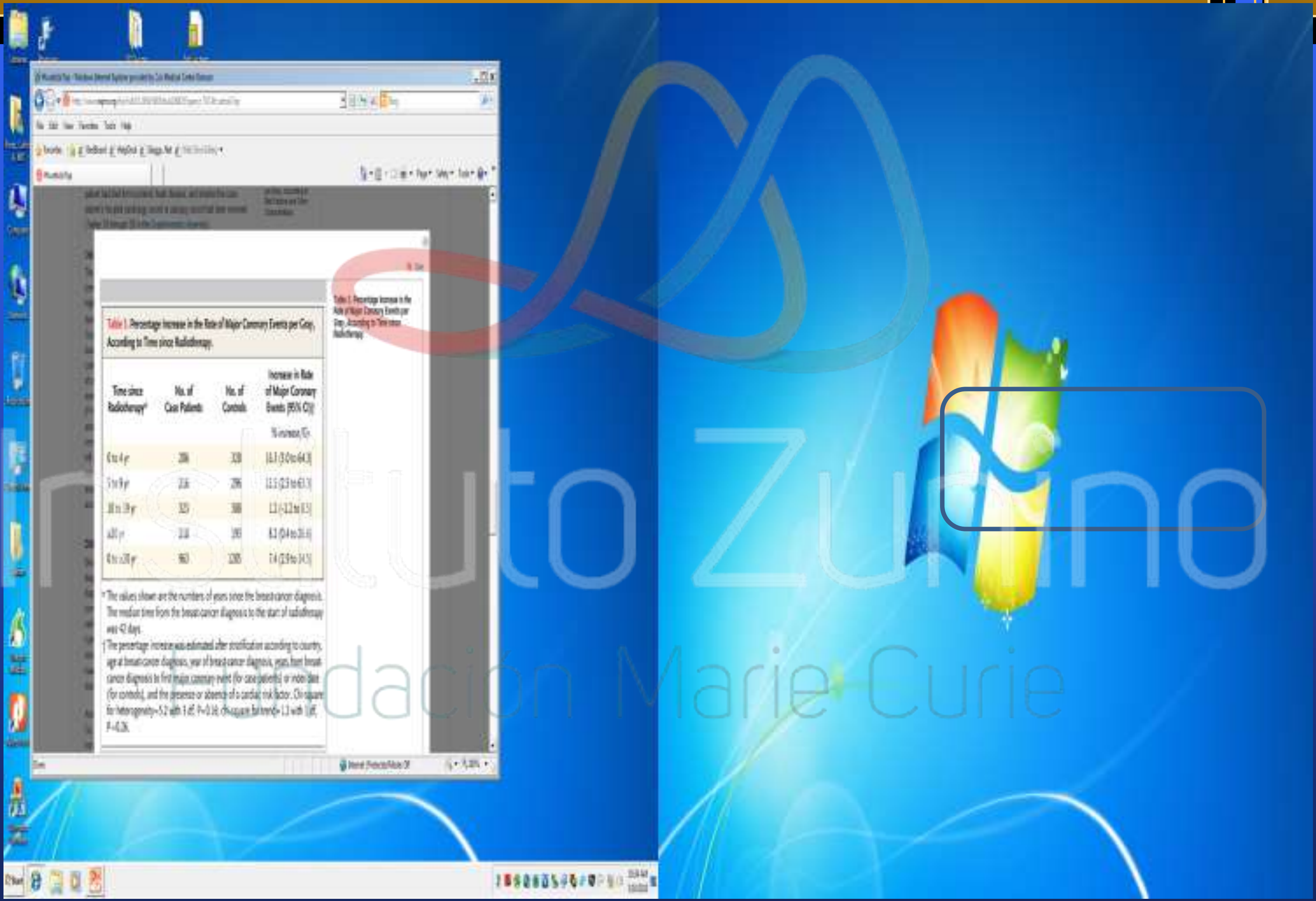

Table 1. Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

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	325	388	1.2 (−2.2 to 8.5)
≥20 yr	216	193	8.2 (0.4 to 26.6)
0 to ≥20 yr	963	1205	7.4 (2.9 to 14.5)

* The values shown are the numbers of years since the breast-cancer diagnosis. The median time from the breast-cancer diagnosis to the start of radiotherapy was 42 days.

† The percentage increase was estimated after stratification according to country, age at breast-cancer diagnosis, year of breast-cancer diagnosis, years from breast-cancer diagnosis to first major coronary event (for case patients) or index date (for controls), and the presence or absence of a cardiac risk factor. Chi-square for heterogeneity=5.2 with 3 df, P=0.16; chi-square for trend=1.3 with 1 df, P=0.26.

Darby SC et al N Engl J Med 368: 987. 2013

PREDICTION OF POST RADIATION ACUTE CARDIAC EVENTS MODEL

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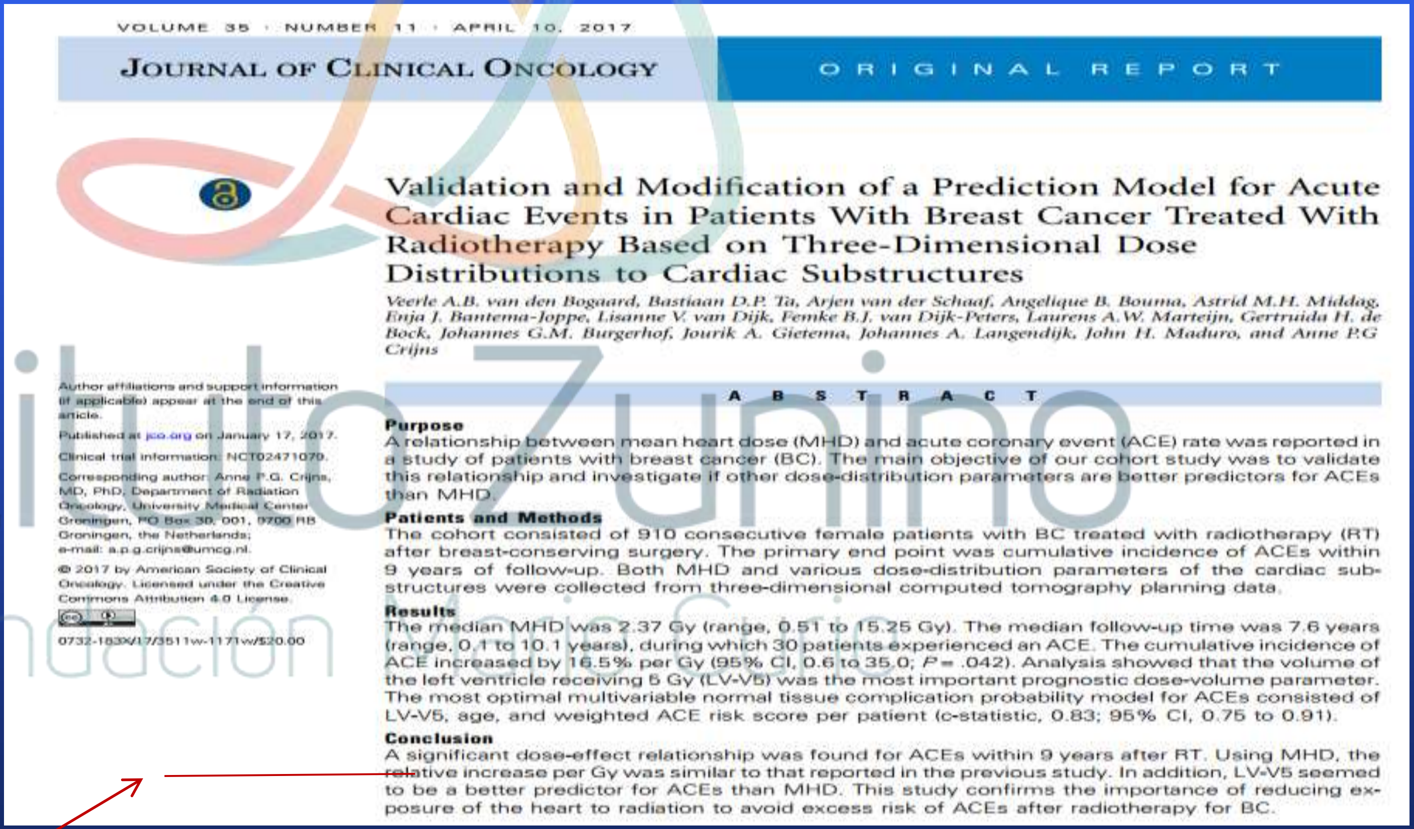
This report agrees with Darby's value of an increase in ACE of 16% per Gy of MHD over the first 9 years following radiation therapy



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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Validation and Modification of a Prediction Model for Acute Cardiac Events in Patients With Breast Cancer Treated With Radiotherapy Based on Three-Dimensional Dose Distributions to Cardiac Substructures

Veerle A.B. van den Bogaard, Bastiaan D.P. Ta, Arjen van der Schaaf, Angelique B. Bouma, Astrid M.H. Middag, Enja J. Bantema-Joppe, Lisanne V. van Dijk, Femke B.J. van Dijk-Peters, Laurens A.W. Marteijn, Gertruida H. de Bock, Johannes G.M. Burgerhof, Jourik A. Gietema, Johannes A. Langendijk, John H. Maduro, and Anne P.G Crijns

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on January 17, 2017.

Clinical trial information: NCT02471070.

Corresponding author: Anne P.G. Crijns, MD, PhD, Department of Radiation Oncology, University Medical Center Groningen, PO Box 30, 001, 9700 RB Groningen, the Netherlands; e-mail: a.p.g.crijns@umcg.nl.

0732-183X/17/3511w-1171w/$20.00

ABSTRACT

Purpose
A relationship between mean heart dose (MHD) and acute coronary event (ACE) rate was reported in a study of patients with breast cancer (BC). The main objective of our cohort study was to validate this relationship and investigate if other dose-distribution parameters are better predictors for ACEs than MHD.

Patients and Methods
The cohort consisted of 910 consecutive female patients with BC treated with radiotherapy (RT) after breast-conserving surgery. The primary end point was cumulative incidence of ACEs within 9 years of follow-up. Both MHD and various dose-distribution parameters of the cardiac substructures were collected from three-dimensional computed tomography planning data.

Results
The median MHD was 2.37 Gy (range, 0.51 to 15.25 Gy). The median follow-up time was 7.6 years (range, 0.1 to 10.1 years), during which 30 patients experienced an ACE. The cumulative incidence of ACE increased by 16.5% per Gy (95% CI, 0.6 to 35.0; *P* = .042). Analysis showed that the volume of the left ventricle receiving 5 Gy (LV-V5) was the most important prognostic dose-volume parameter. The most optimal multivariable normal tissue complication probability model for ACEs consisted of LV-V5, age, and weighted ACE risk score per patient (c-statistic, 0.83; 95% CI, 0.75 to 0.91).

Conclusion
A significant dose-effect relationship was found for ACEs within 9 years after RT. Using MHD, the relative increase per Gy was similar to that reported in the previous study. In addition, LV-V5 seemed to be a better predictor for ACEs than MHD. This study confirms the importance of reducing exposure of the heart to radiation to avoid excess risk of ACEs after radiotherapy for BC.

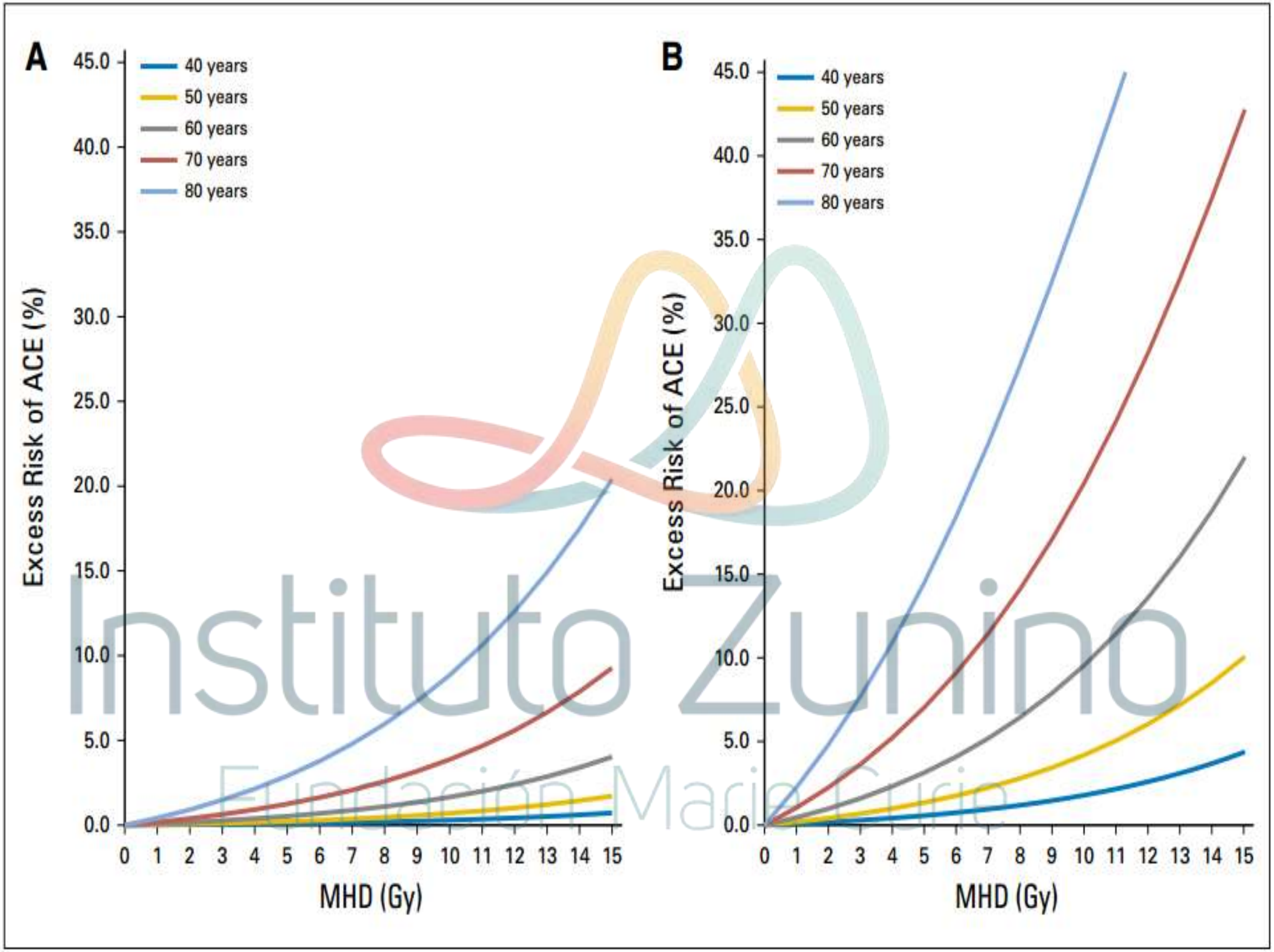

Fig 2. Excess risk of an acute coronary event (ACE) depending on the mean heart dose (MHD) in volume percentage calculated per age category and (A) absence or (B) presence of cardiac risk factors.

CARDIAC MORTALITY AFTER RIGHT-SIDED BREAST IRRADIATION

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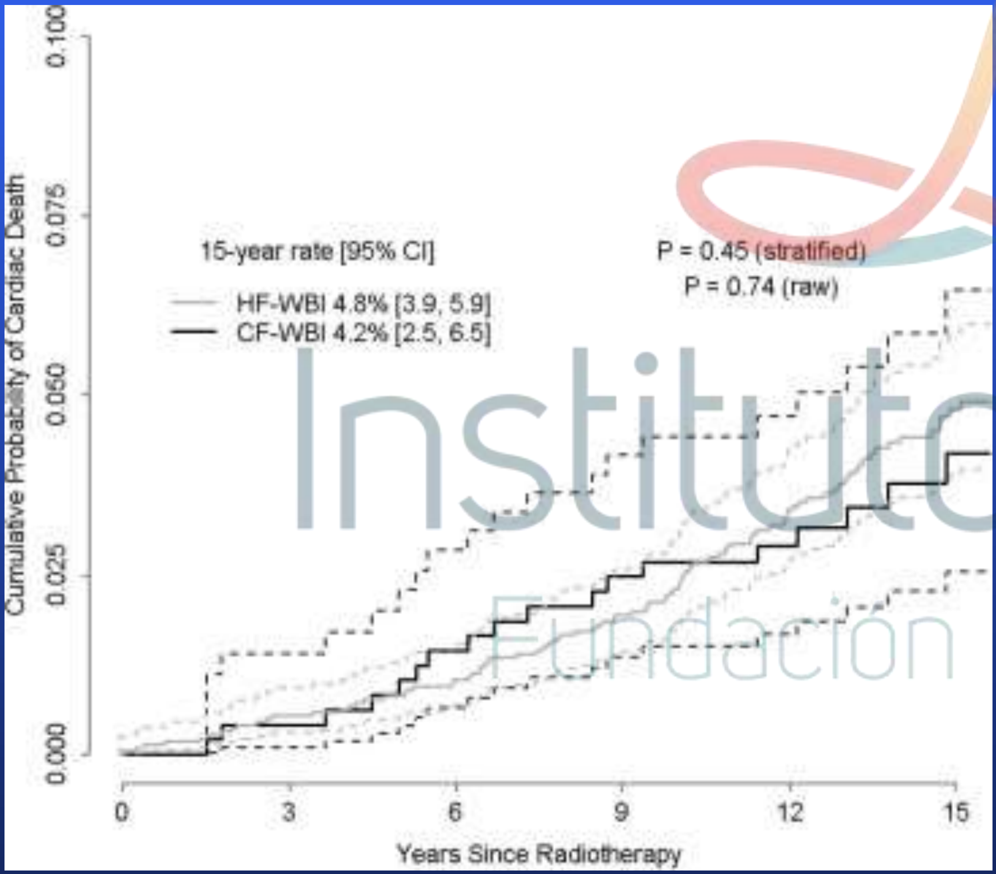
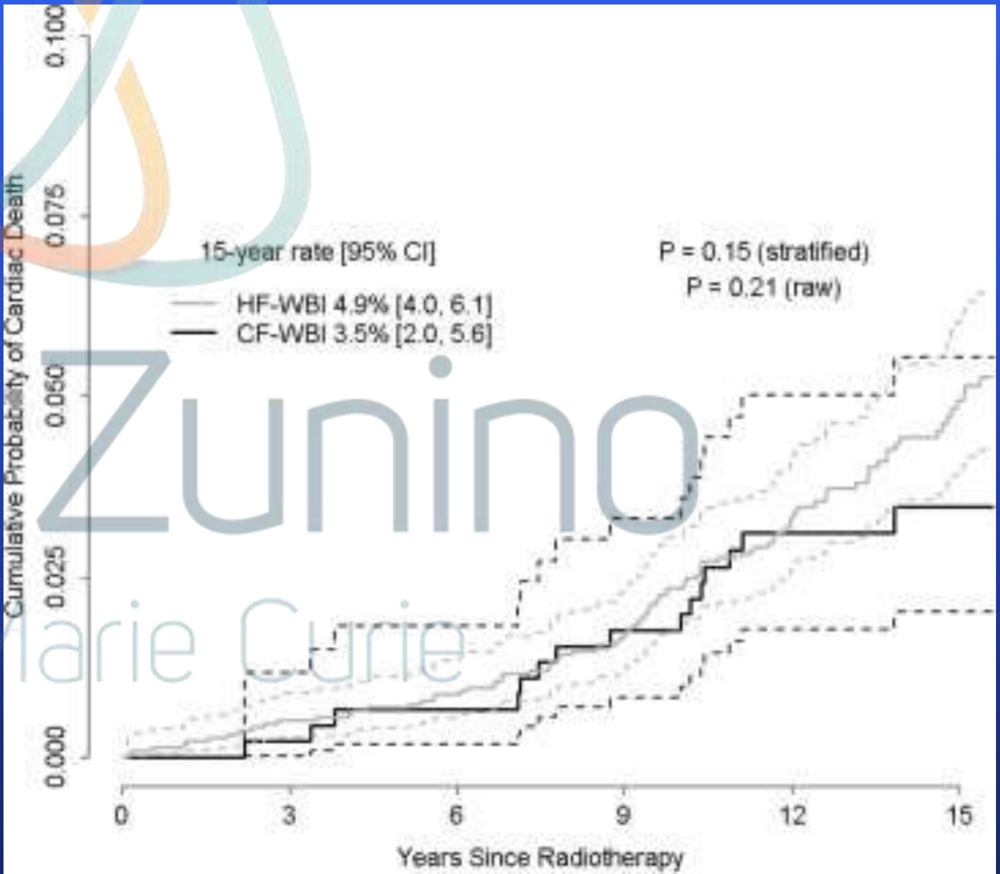
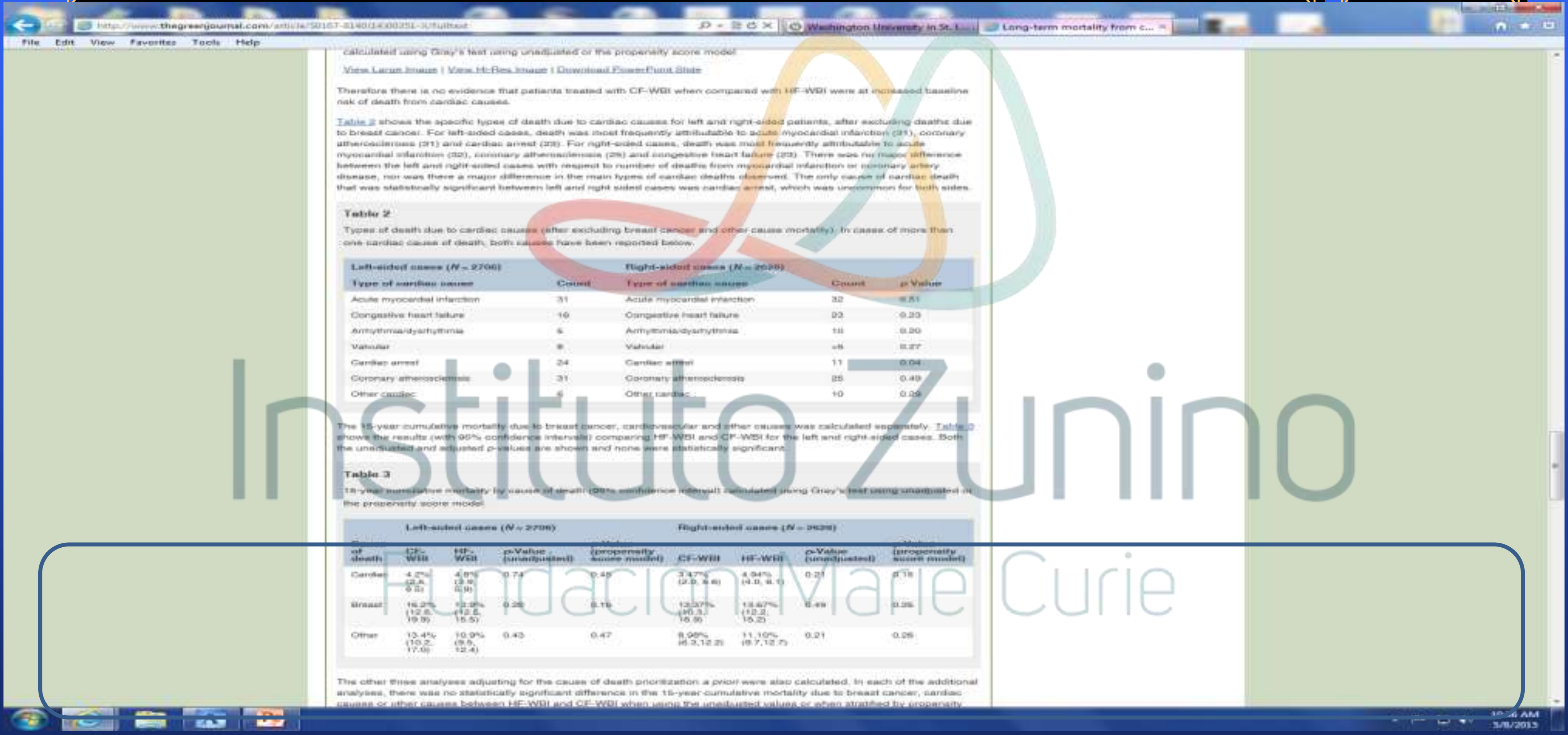




Chan EK et al Radiother & Oncol 114: 73, 2015

CARDIAC MORTALITY AFTER LEFT/ RIGHT-SIDED BREAST IRRADIATION

Washington University School of Medicine



calculated using Gray's test using unadjusted or the propensity score model

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Therefore there is no evidence that patients treated with CF-WBI when compared with HF-WBI were at increased baseline risk of death from cardiac causes.

Table 2 shows the specific types of death due to cardiac causes for left and right-sided patients, after excluding deaths due to breast cancer. For left-sided cases, death was most frequently attributable to acute myocardial infarction (31), coronary atherosclerosis (31) and cardiac arrest (23). For right-sided cases, death was most frequently attributable to acute myocardial infarction (32), coronary atherosclerosis (25) and congestive heart failure (23). There was no major difference between the left and right-sided cases with respect to number of deaths from myocardial infarction or coronary artery disease, nor was there a major difference in the main types of cardiac deaths observed. The only cause of cardiac death that was statistically significant between left and right sided cases was cardiac arrest, which was uncommon for both sides.

Table 2

Types of death due to cardiac causes (after excluding breast cancer and other cause mortality). In cases of more than one cardiac cause of death, both causes have been reported below.

Left-sided cases ($N = 2706$)		Right-sided cases ($N = 2628$)		
Type of cardiac cause	**Count**	**Type of cardiac cause**	**Count**	**p Value**
Acute myocardial infarction	31	Acute myocardial infarction	32	0.51
Congestive heart failure	19	Congestive heart failure	23	0.33
Arrhythmia/dysrhythmia	6	Arrhythmia/dysrhythmia	11	0.20
Valvular	8	Valvular	<6	0.27
Cardiac arrest	24	Cardiac arrest	11	0.04
Coronary atherosclerosis	31	Coronary atherosclerosis	25	0.49
Other cardiac	6	Other cardiac	10	0.29

The 15-year cumulative mortality due to breast cancer, cardiovascular and other causes was calculated separately. Table 3 shows the results (with 95% confidence intervals) comparing HF-WBI and CF-WBI for the left and right-sided cases. Both the unadjusted and adjusted p-values are shown and none were statistically significant.

Table 3

15-year cumulative mortality by cause of death (95% confidence interval) calculated using Gray's test using unadjusted or the propensity score model

	Left-sided cases ($N = 2706$)				Right-sided cases ($N = 2628$)			
Cause of death	**CF-WBI**	**HF-WBI**	**p-Value (unadjusted)**	**p-Value (propensity score model)**	**CF-WBI**	**HF-WBI**	**p-Value (unadjusted)**	**p-Value (propensity score model)**
Cardiac	4.2% (2.8, 6.5)	4.8% (3.8, 5.9)	0.74	0.45	3.47% (2.0, 5.6)	4.94% (4.0, 6.1)	0.21	0.18
Breast	16.2% (12.6, 19.9)	13.9% (12.5, 15.5)	0.28	0.16	13.37% (10.3, 16.9)	13.67% (12.2, 15.2)	0.49	0.26
Other	13.4% (10.2, 17.0)	10.9% (9.5, 12.4)	0.43	0.47	8.98% (6.3, 12.2)	11.10% (9.7, 12.7)	0.21	0.26

The other three analyses adjusting for the cause of death prioritization a priori were also calculated. In each of the additional analyses, there was no statistically significant difference in the 15-year cumulative mortality due to breast cancer, cardiac causes or other causes between HF-WBI and CF-WBI when using the unadjusted values or when stratified by propensity

Chan EK et al Radiother & Oncol 114: 73, 2015

Effect of Breast Irradiation on Cardiac Disease in Women Enrolled in BCIRG-001 at 10-Year Follow-Up

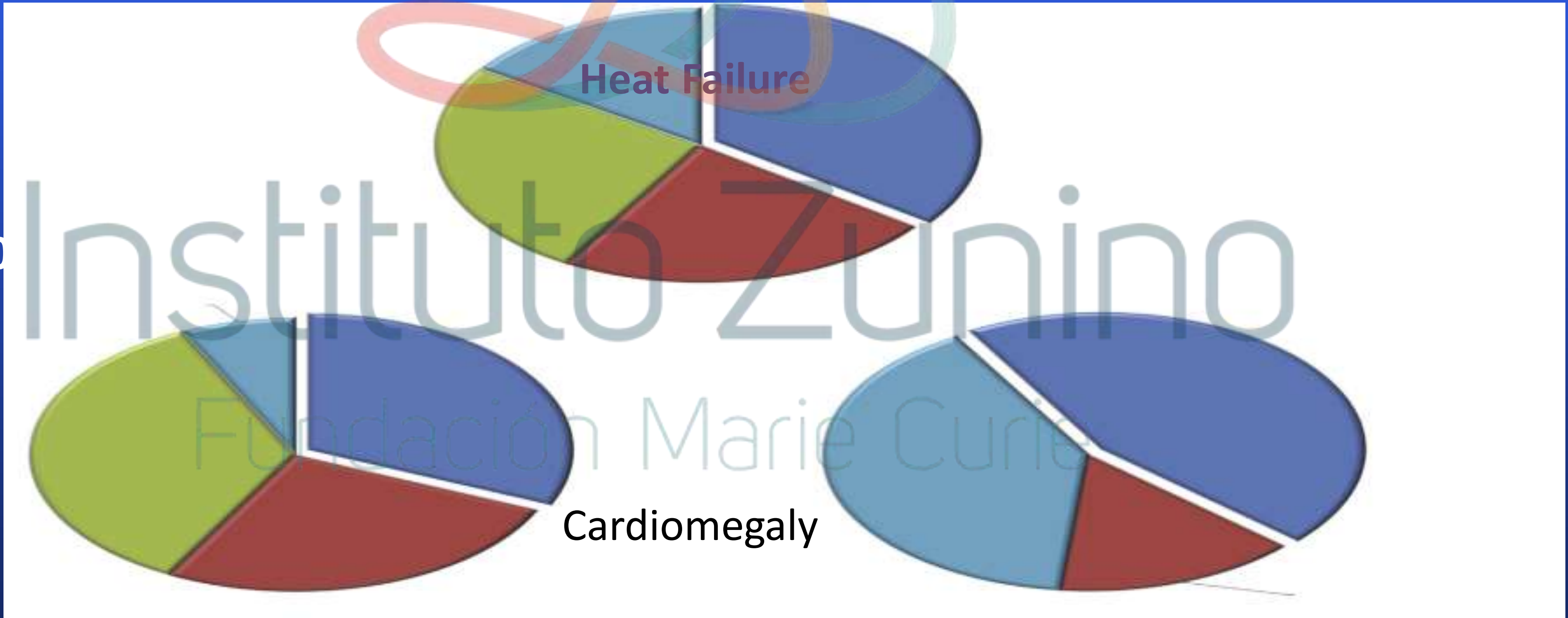
RT PATIENTS

NO RT PATIENTS

Ischemic H D 4

18 Cardiac Disorder 9

Arrhytmia 20



15 Heart Failure/ Cartdiomegaly 3

Wu S P et al Int J Radiat Oncol Bio Phys 99: 541, 2017

Effect of Breast Irradiation on Cardiac Disease in Women Enrolled in BCIRG-001 at 10-Year Follow-Up

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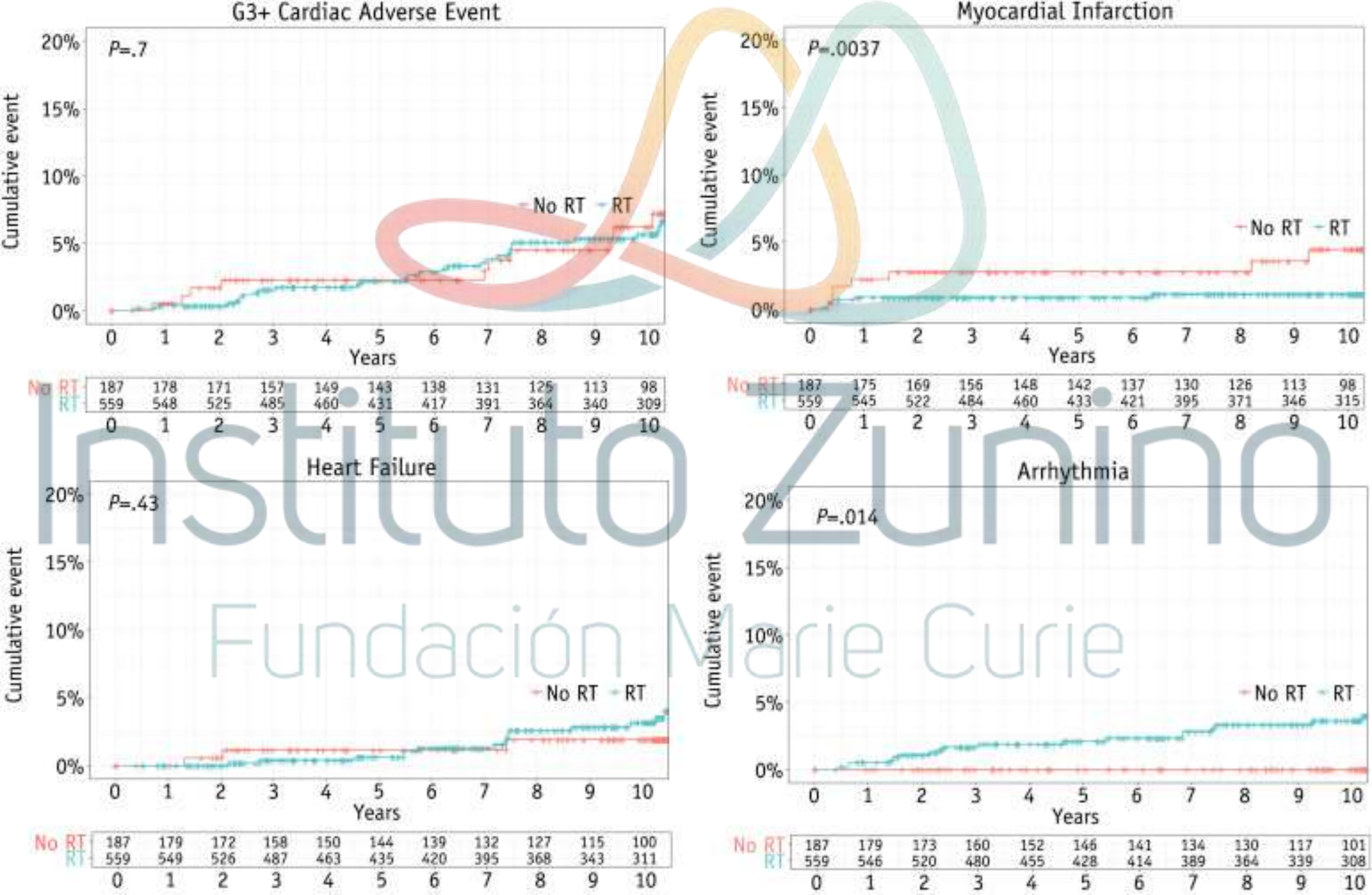
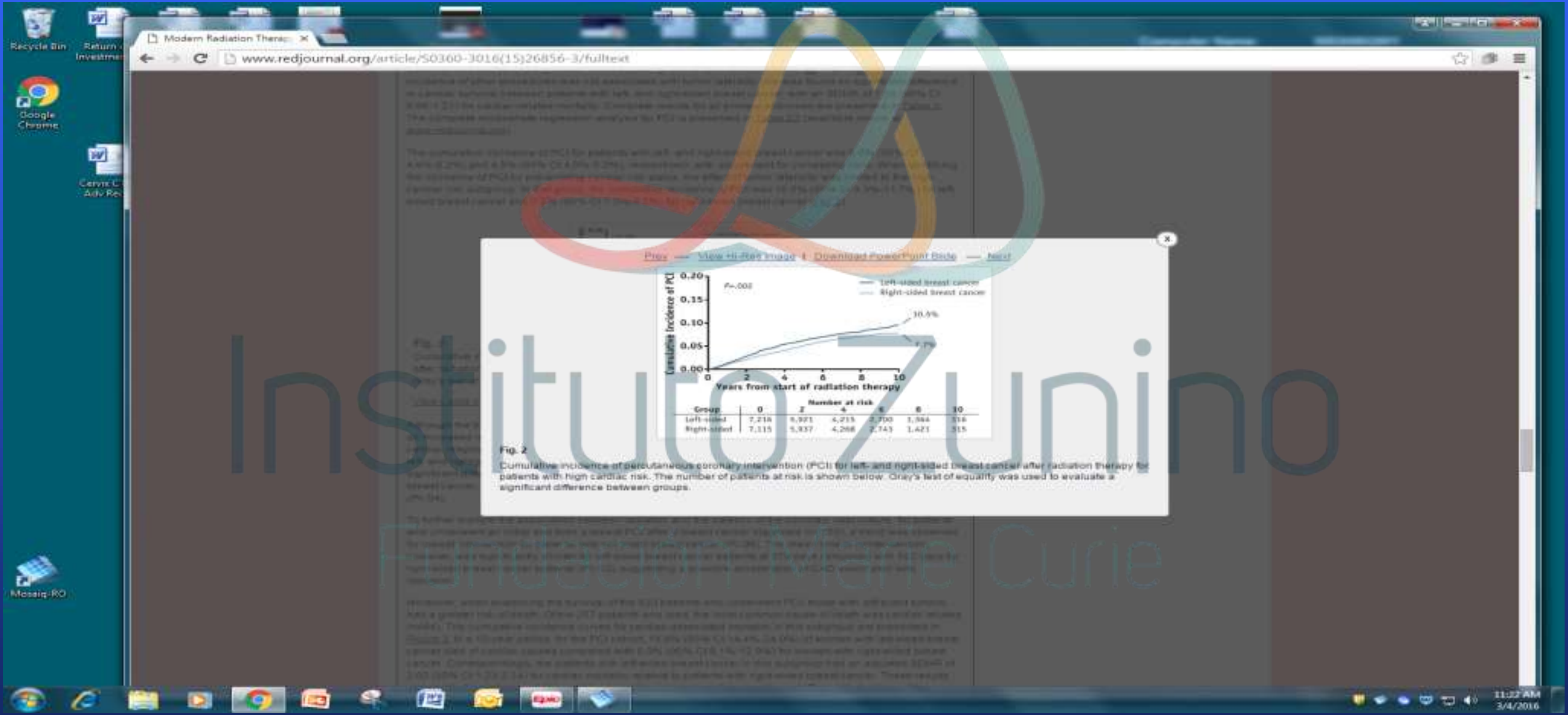


Wu S P et al Int J Radiat Oncol Bio Phys 99: 541, 2017

LEFT BREAST IRRADIATION AND CARDIAC TOXICITY



Number at risk

Group	0	2	4	6	8	10
Left-sided	7,218	5,921	4,215	2,700	1,364	316
Right-sided	7,115	5,937	4,268	2,743	1,421	315

Fig. 2

Cumulative incidence of percutaneous coronary intervention (PCI) for left- and right-sided breast cancer after radiation therapy for patients with high cardiac risk. The number of patients at risk is shown below. Gray's test of equality was used to evaluate a significant difference between groups.

Boero IJ et al Int J Rad Oncol Bio Phys 94: 700, 2016

Association Between Tangential Beam Treatment Parameters and Cardiac Abnormalities After Definitive Radiation Treatment for Left-Sided Breast Cancer

Correa C R et al Int J Radiat Oncol Bio Phys 72: 508, 2008

Association Between Tangential Beam Treatment Parameters and Cardiac Abnormalities After Definitive Radiation Treatment for Left-Sided Breast Cancer

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Total number of patients studied 62

Framingham predicted cardiac event incidence 6/62 (9%) p = 0.001
Actual incidence of cardiac diagnostic study abnormalities 24/62 (3

Coronary artery territory of abnormality
Left anterior descending artery 21/24 (88%)
Left circumflex artery 1/24 (4%)
Right coronary artery 1/24 (4%)
Left circumflex plus right coronary artery 1/24 (4%)

Correa C R et al Int J Radiat Oncol Bio Phys 72: 508, 2008

Association Between Tangential Beam Treatment Parameters Cardiac Abnormalities After Definitive Radiation Treatment for Left-Sided Breast Cancer

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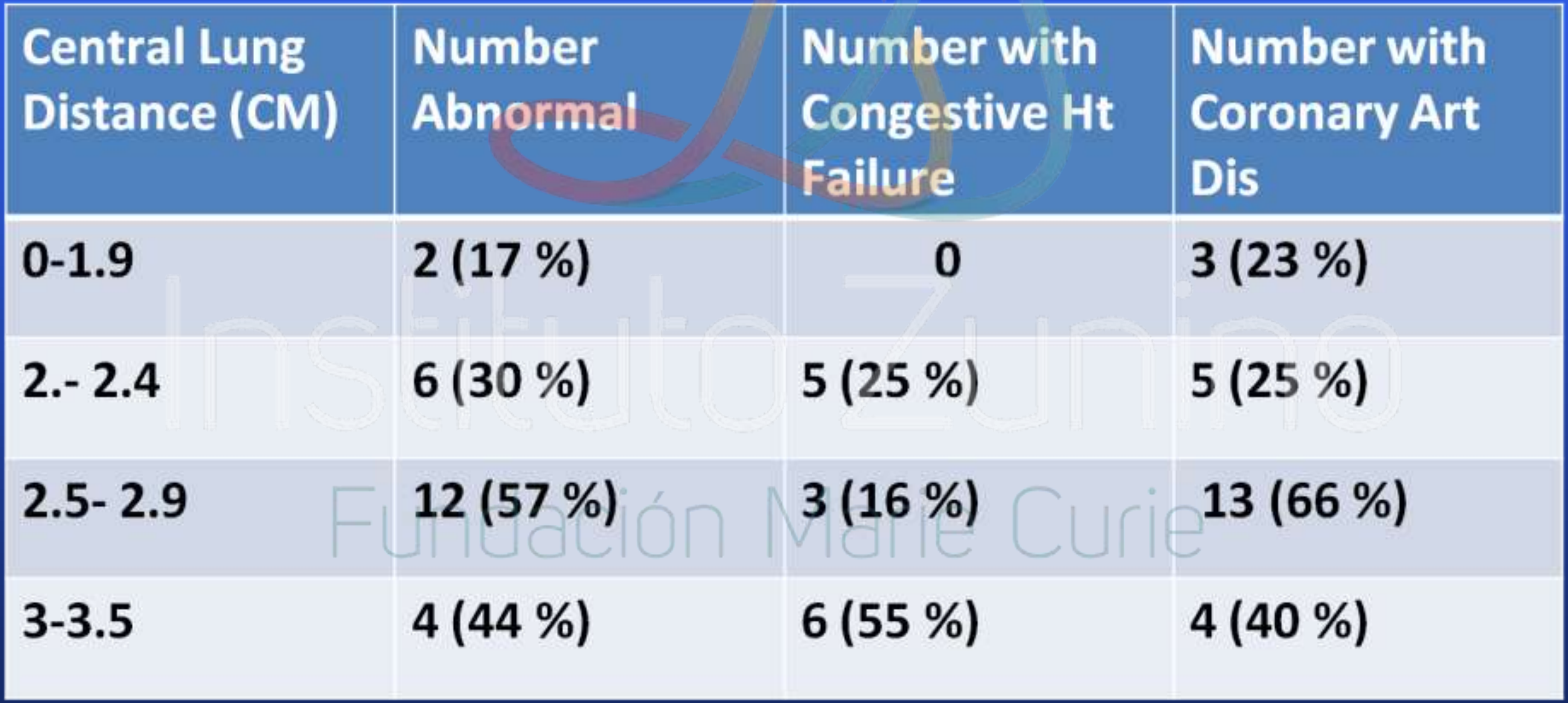
Cardiac Diagnostic Abnormalities



Central Lung Distance (CM)	Number Abnormal	Number with Congestive Ht Failure	Number with Coronary Art Dis
0-1.9	2 (17 %)	0	3 (23 %)
2.- 2.4	6 (30 %)	5 (25 %)	5 (25 %)
2.5- 2.9	12 (57 %)	3 (16 %)	13 (66 %)
3-3.5	4 (44 %)	6 (55 %)	4 (40 %)

Correa C R et al Int J Radiat Oncol Bio Phys 72: 508, 2008

Whole Heart Versus Coronary Artery Dosimetry in Predicting Risk of Cardiac Toxicity Following Breast Radiation Therapy

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52 women with stage III Breast Cancer (36 Left, 16 Right).

Dosimetry to the LAwas calculated based on the individual RT Tmn

Median follow-up time from RT to CTA was 5.1 years .
LAD Dmax was more strongly associated with the onset of any CAC andLAD stenosis (≥25% lumen).

For any CAC, O R was 1.15 and 2.21 for MHD and LAD Dmax, respectively.
For moderate/severe CAC, OR was 1.04 (p=0.24) and 2.57 (p=0.04) for MHD and LAD Dmax, respectively.

LAD Dmax > 10 Gy was a significant threshold for increased odds of developing any CAC (OR 10.21 (p=0.03), moderate/severe CAC (OR 5.21, p=0.04), and LAD stenosis (OR 6.52, p=0.03).

Patel SA et al Int J Radiat Oncol Bio Phys 102 (3): S46, Nov 2018

ECOCARDIOGRAM SCREENING:
:ENFERMEDAD CARDIACA INDUCIDA POR RADIACIÓN

- Screening recomendado (ASE y Europea)
  - » ETT a los 5 años de exposición a RT en aquellos con riesgo
  - » ETT a los 10 años de exposición sin riesgo
  - » Eco stress a los 5 – 10 años después exposición en aquellos con riesgo de enfermedad coronaria

Courtesy, Dr. Hugo Marsiglia

TECHNIQUES TO DECREASE/ ELIMINATE RADIATION CARDIAC INJURY

- Reduce volume of heart irradiated (<5 %)/ Dose to the Heart (< 5Gy)
- Optimize RT Treatment Planning, including use of Electrons
- Use IMRT (Although lower doses to more normal tissue is noted)
- Use Heart Customized Shielding Blocks (Identify Tumor Bed)
- Use Prone Patient Position, Deep Inspiration Breath Holding Techniques
- Selective use of techniques to irradiate Lymph Nodes
- Select Patients for Accelerated Partial Breast Irradiation
- Avoid Concurrent Chemo-Radiation Therapy

Approximation of prior medial tangent

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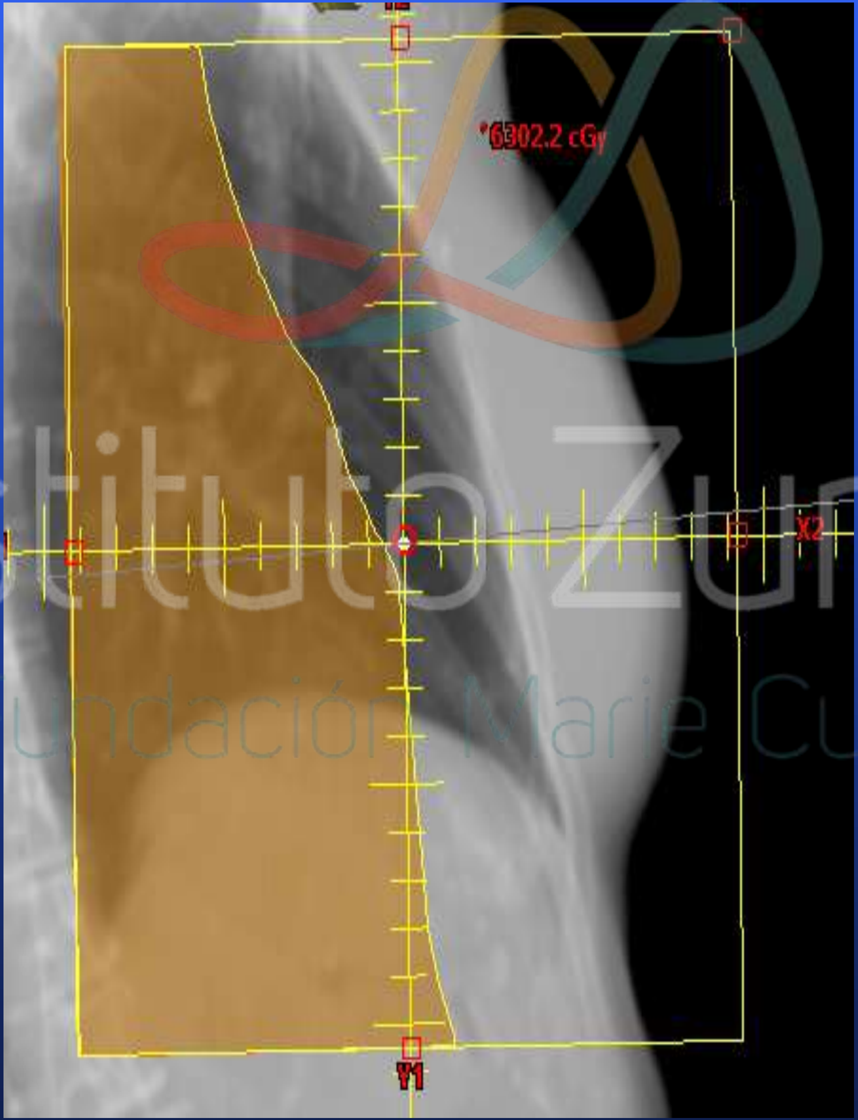
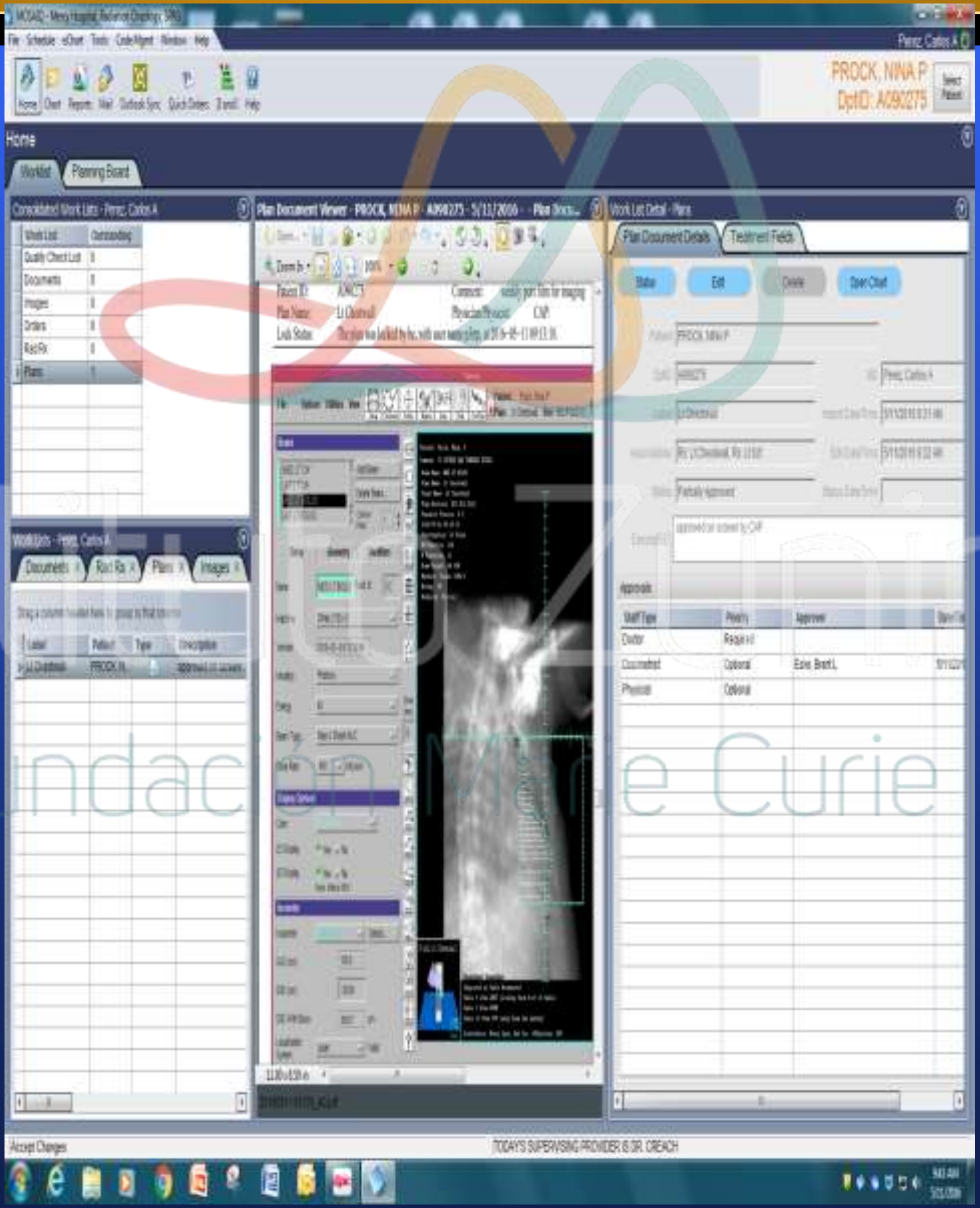


Association Between Tangential Beam Treatment Parameters and Cardiac Abnormalities After Definitive Radiation Treatment for Left-Sided Breast Cancer

Correa C R et al Int J Radiat Oncol Bio Phys 72: 508, 2008

BREAST RT: TECHNIQUE TO AVOID RADIATION DOSE TO THE HEART



PROCK, NINA P
DptID: A090275

Work List Detail - Plans

Staff Type	Priority	Approver
Doctor	Required	
Dosimetrist	Optional	Esler, Brett L
Physicist	Optional	

TODAYS SUPERVISING PROVIDER IS DR. CREACH

BREAST RT: TECHNIQUE TO AVOID RADIATION DOSE TO THE HEART

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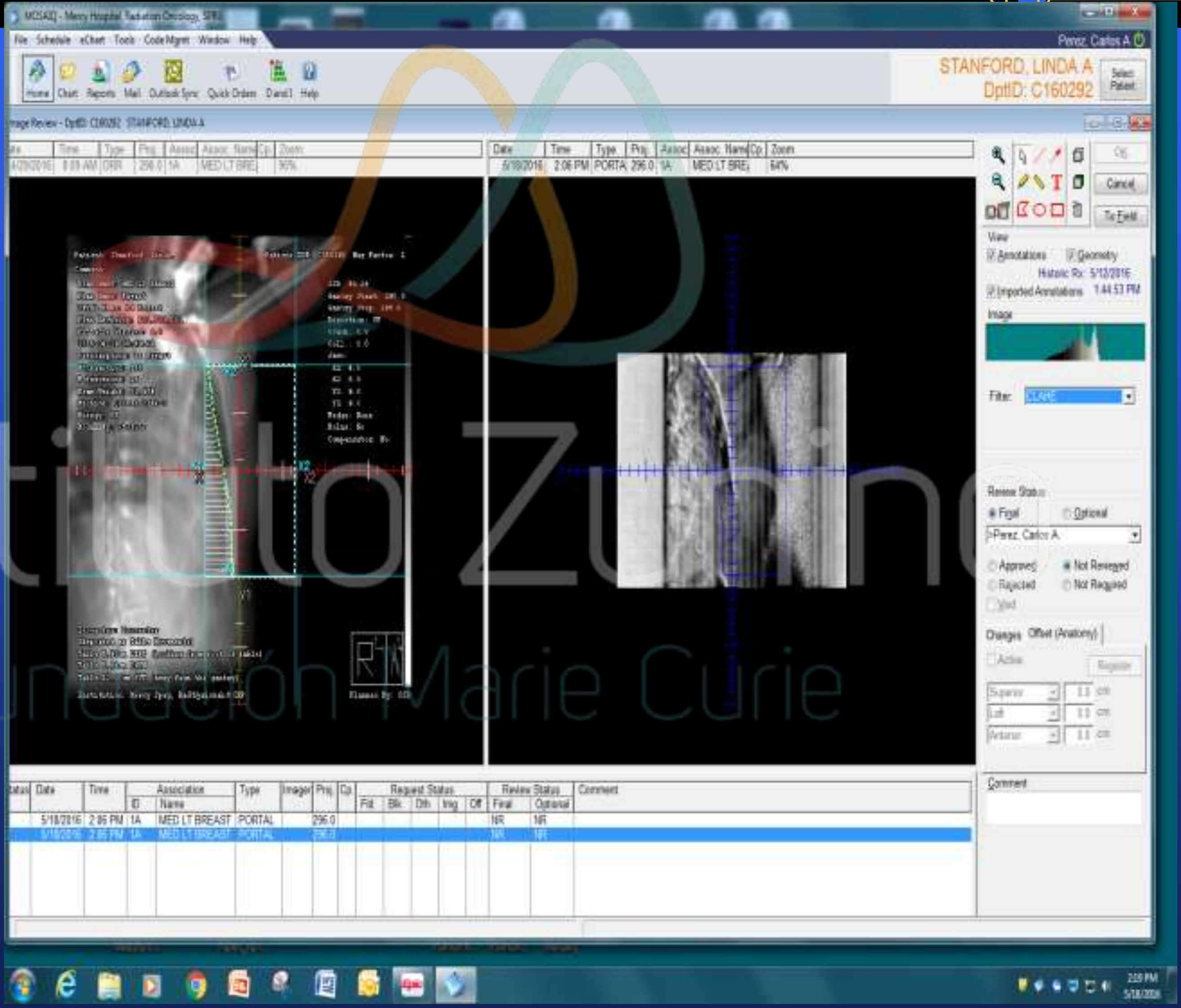
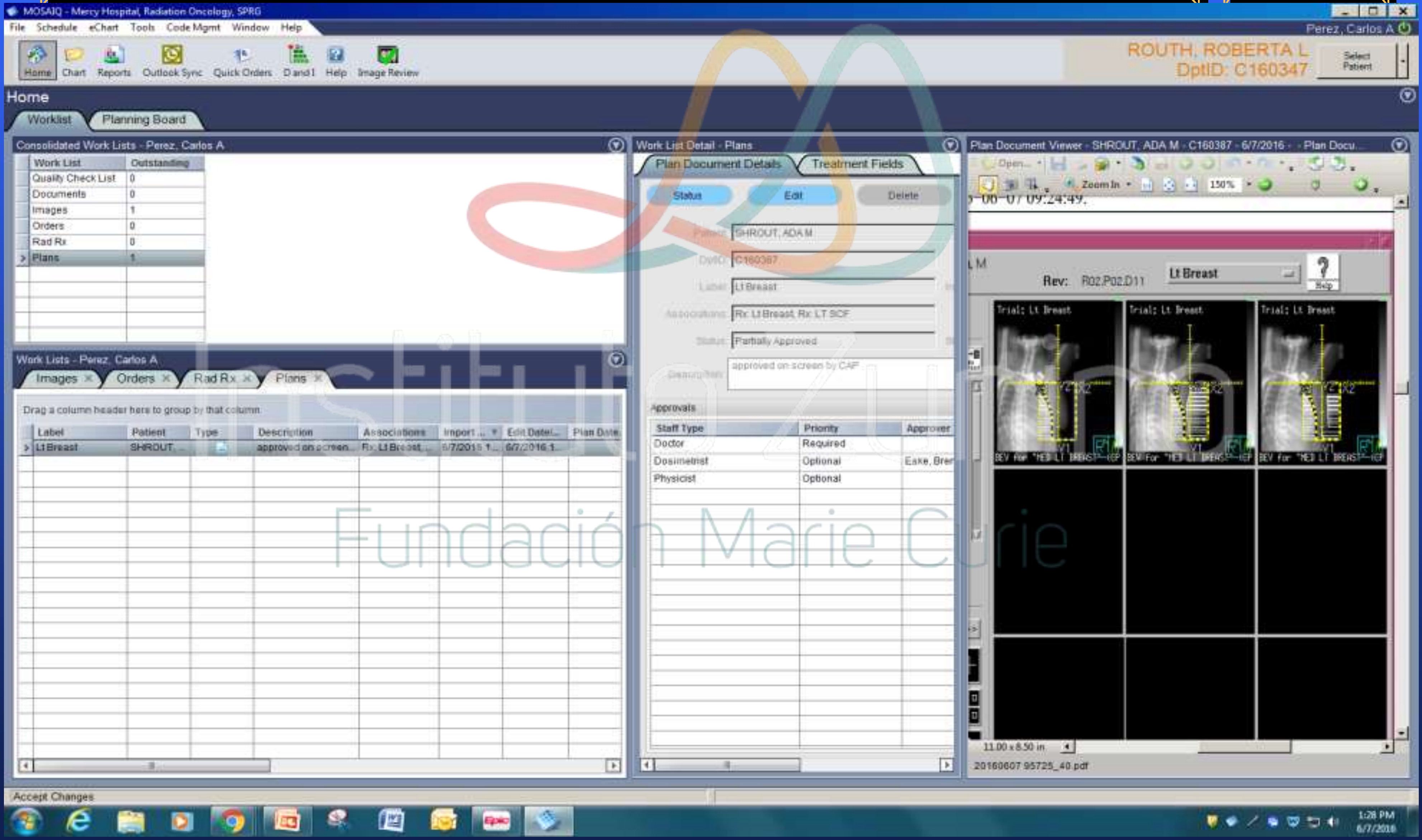


STANFORD, LINDA A
DptID: C160292

Date	Time	Association ID	Association Name	Type	Proj	Review Status Final	Review Status Optional
5/18/2016	2:06 PM	1A	MED LT BREAST	PORTAL	296.0	NR	NR
5/18/2016	2:05 PM	1A	MED LT BREAST	PORTAL	296.0	NR	NR

LEFT BREAST 3D CONFORMAL SEGMENTED RADIATION THERAPY



Work List	Outstanding
Quality Check List	0
Documents	0
Images	1
Orders	0
Rad Rx	0
Plans	1

Patient: SHROUT, ADA M
DptID: C160387
Label: Lt Breast
Associations: Rx: Lt Breast, Rx: LT SCF
Status: Partially Approved
Description: approved on screen by CAF

Approvals

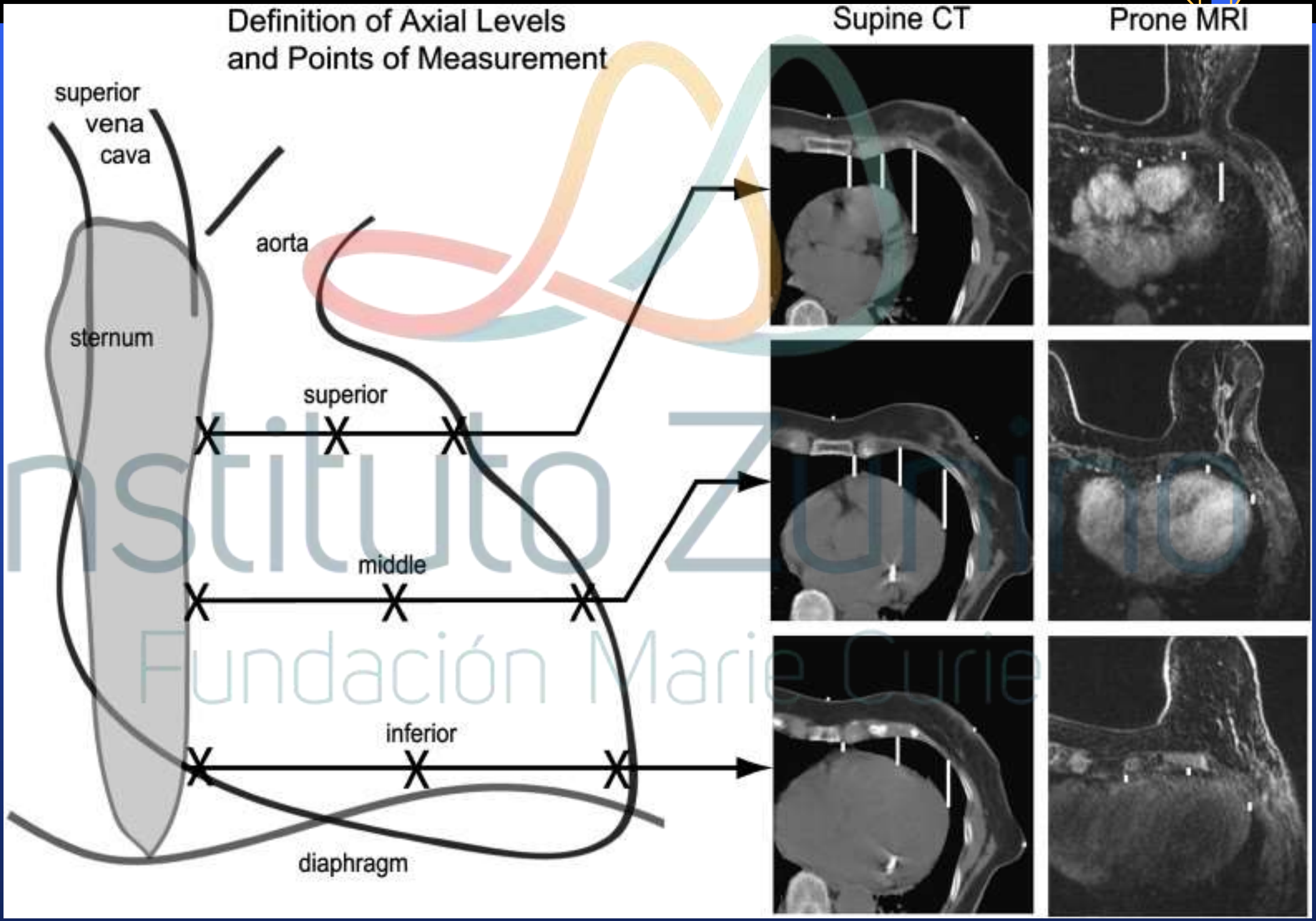
Staff Type	Priority	Approver
Doctor	Required	
Dosimetrist	Optional	Eske, Bren
Physicist	Optional	

Label	Patient	Type	Description	Associations	Import ...	Edit Date/...	Plan Date
Lt Breast	SHROUT,		approved on screen...	Rx: Lt Breast, ...	6/7/2016 1...	6/7/2016 1...	

PRONE POSITION BREAST IRRADIATION

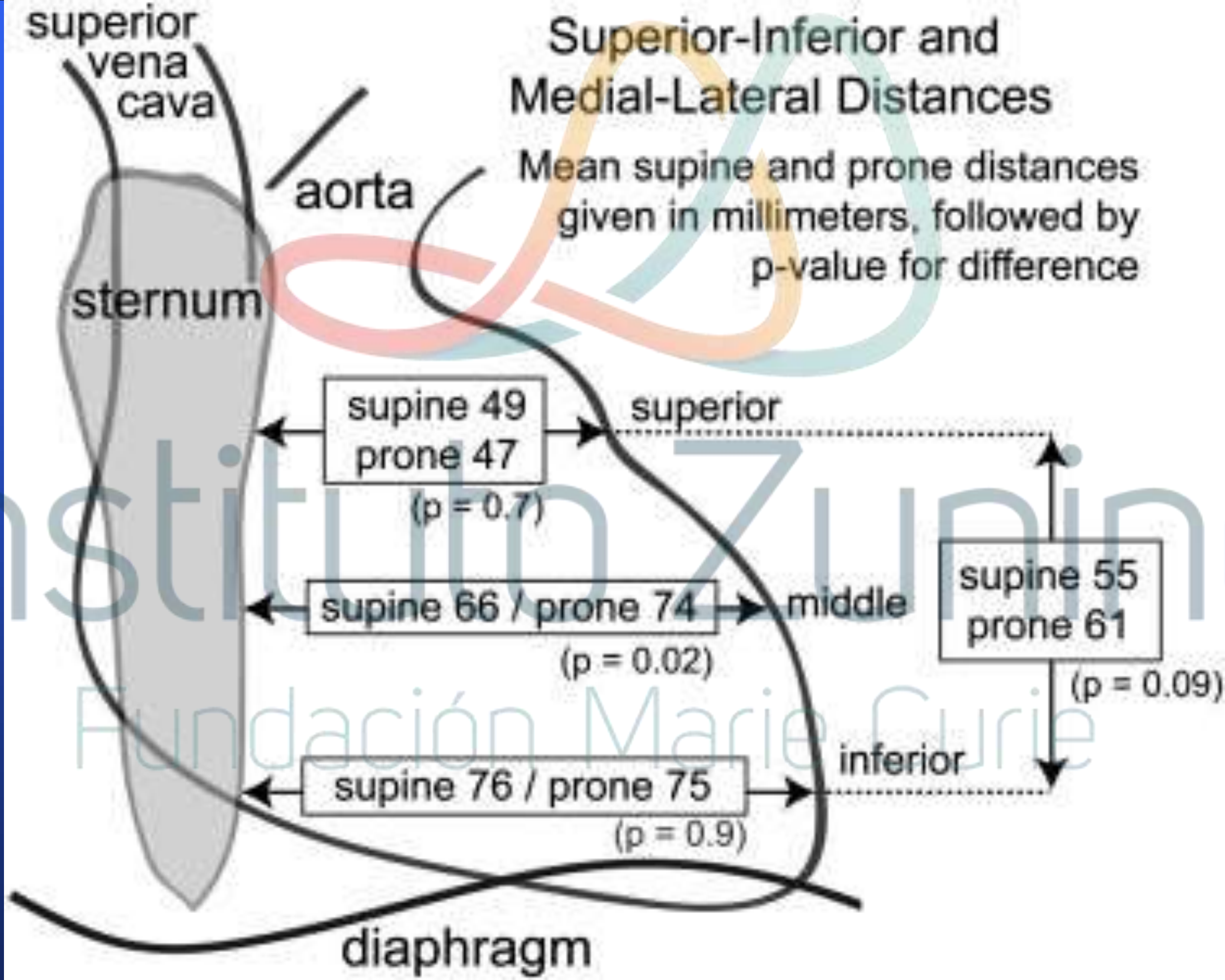
Merchant TE, McCormick B
Int J Rad Oncol Bio Phys
30: 197, 1994

PRONE POSITIONING CAUSES THE HEART TO BE DISPLACED ANTERIORLY WITHIN THE THORAX:



Chino, Marks LB Int J Radiat Oncol Bio Phys 70: 916, 2008

PRONE POSITIONING CAUSES THE HEART TO BE DISPLACED ANTERIORLY WITHIN THE THORAX:



Chino, Marks LB Int J Radiat Oncol Bio Phys 70: 916, 2008

BREATHING CONTROL TECHNIQUES

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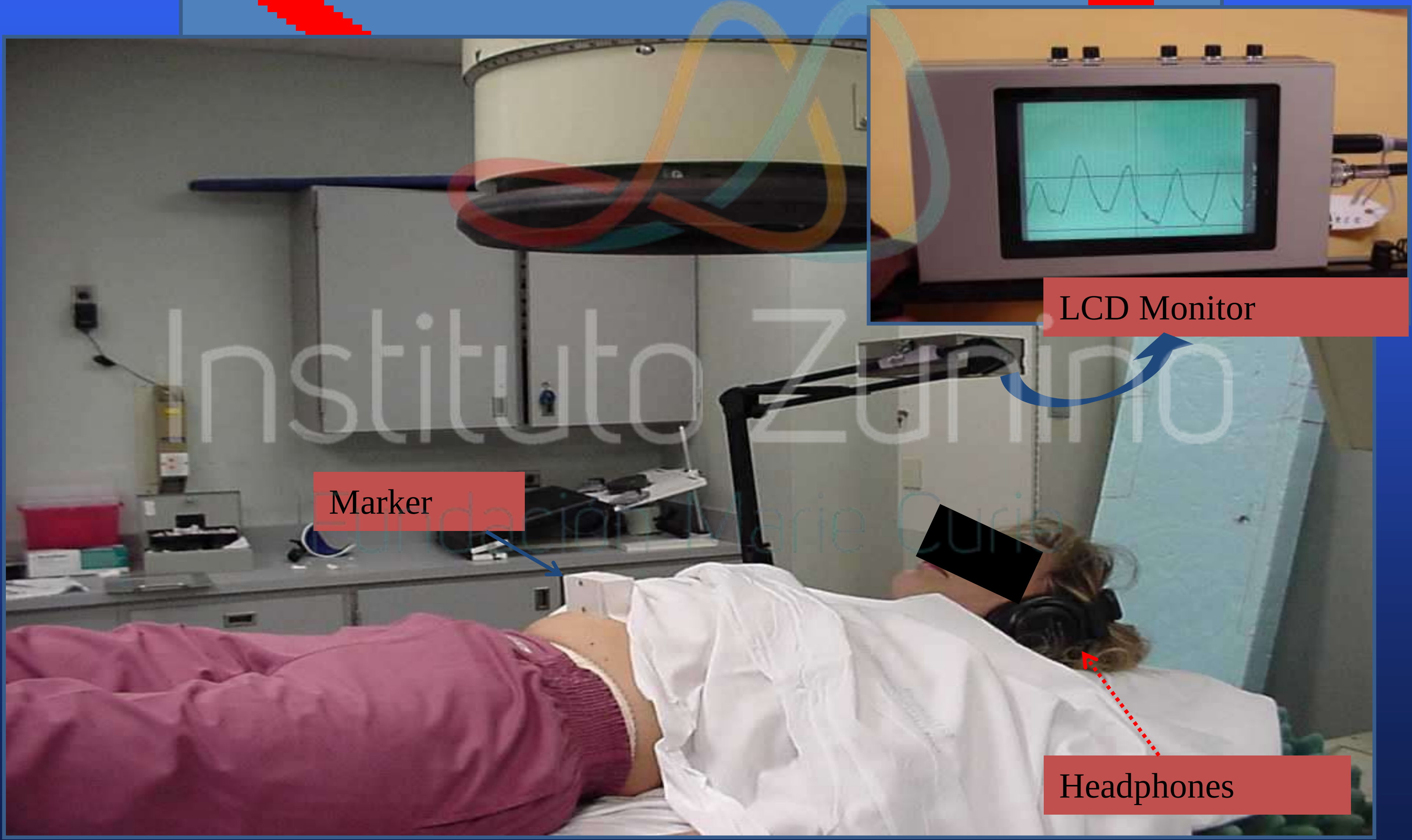

Randomized Comparison of Radiation Therapy Techniques in Management of Node-Positive Breast Cancer: Primary Outcomes Analysis

Of 62 patients randomized, 54 who completed all follow-up procedur
were analyzed.
Mean doses to the ipsilateral lung, left ventricle, whole heart, and
left anterior descending coronary artery were lower with IMRT-DIBH;
The percent of left ventricle receiving ≥5 Gy averaged 15.8% with sta
radiotherapy and 5.6% with IMRT-DIBH (P < .001).
SPECT revealed no differences in perfusion defects in the left anterio
descending coronary artery territory, the study's primary endpoint,
but did reveal statistically significant differences (P = .02) in left vent
ejection fraction (LVEF), a secondary endpoint.

Jagsi R et al Int J Radiat Oncol Bio Phys 101: 1149, 2018

Radiation Effect on Late Cardiopulmonary Toxicity: An Analysis Comparing DIBH versus Prone Techniques for Breast Treatment

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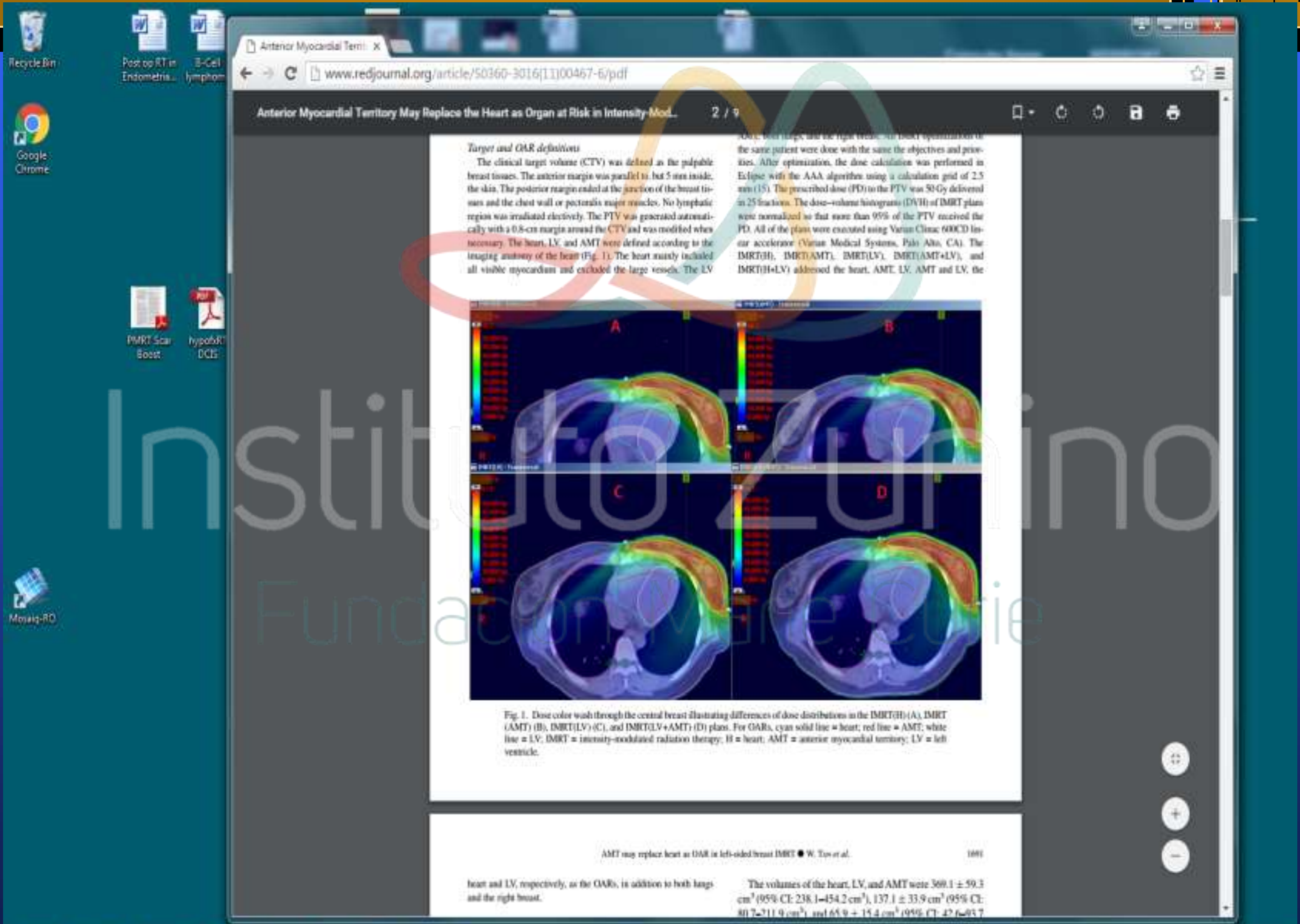
School of Medicine

34 patients with left-sided DCIS or breast cancer who have undergone lumpectom
and breast irradiation, enrolled on a prospective trial comparing prone breast with
supine DIBH planning (NCI-2017-00219).
Patients underwent CT simulation in both positions, and two treatment plans
were generated for each patient.
Mean heart dose was 79.7 cGy and 76.5 cGy (p=0.37),
Estimated mean) absolute (EMA) risk of death from IHD by age 80 was 0.1%
for both plans (p = 1.0).
EMA absolute risk of at least one radiation-related ACE by age 80 was 0.3%
for both plans (p = 0.6).

There was no observed difference in mean cardiac dose between supine DIBH and
prone techniques, and a low absolute risk of both radiation-related ACE and
risk of death from IHD.

Yan S X et al Int J Radiat oncol Bio Phys 102 (Suppl 3): e616, 2018

ANTERIOR MYOCARDIAL TERRITORY IN IMRT FOR LT-SIDED BREAST CANCER



Target and OAR definitions

The clinical target volume (CTV) was defined as the palpable breast tissues. The anterior margin was parallel to, but 5 mm inside, the skin. The posterior margin ended at the junction of the breast tissues and the chest wall or pectoralis major muscles. No lymphatic region was irradiated electively. The PTV was generated automatically with a 0.8-cm margin around the CTV and was modified when necessary. The heart, LV, and AMT were defined according to the imaging anatomy of the heart (Fig. 1). The heart mainly included all visible myocardium and excluded the large vessels. The LV

the same patient were done with the same the objectives and priorities. After optimization, the dose calculation was performed in Eclipse with the AAA algorithm using a calculation grid of 2.5 mm (15). The prescribed dose (PD) to the PTV was 50 Gy delivered in 25 fractions. The dose–volume histograms (DVH) of IMRT plans were normalized so that more than 95% of the PTV received the PD. All of the plans were executed using Varian Clinac 600CD linear accelerator (Varian Medical Systems, Palo Alto, CA). The IMRT(H), IMRT(AMT), IMRT(LV), IMRT(AMT+LV), and IMRT(H+LV) addressed the heart, AMT, LV, AMT and LV, the

Fig. 1. Dose color wash through the central breast illustrating differences of dose distributions in the IMRT(H) (A), IMRT (AMT) (B), IMRT(LV) (C), and IMRT(LV+AMT) (D) plans. For OARs, cyan solid line = heart; red line = AMT; white line = LV; IMRT = intensity-modulated radiation therapy; H = heart; AMT = anterior myocardial territory; LV = left ventricle.

AMT may replace heart as OAR in left-sided breast IMRT ● W. Tan et al. 1691

heart and LV, respectively, as the OARs, in addition to both lungs and the right breast.

The volumes of the heart, LV, and AMT were 369.1 ± 59.3 cm^3 (95% CI: 238.1–454.2 cm^3), 137.1 ± 33.9 cm^3 (95% CI: 80.7–211.9 cm^3), and 65.9 ± 15.4 cm^3 (95% CI: 42.6–93.7

Tan W et al Int J Rad Oncol Bio Phys 83: 1689, 2012

ANTERIOR MYOCARDIAL TERRITORY IN IMRT FOR LT-SIDED BREAST CANCER

Fig. 3. Comparison with IMRT(H): changes of Vn% to the heart (A), AMT (B), LV (C), and left lung (D) in the IMRT(LV), IMRT(AMT), and IMRT(LV+AMT) plans. IMRT = intensity-modulated radiation therapy; H = heart; AMT = anterior myocardial territory; LV = left ventricle; L lung = left lung. V 5%, V10%, V15%, V20%, V30%, and V40% = percent volume receiving 5 Gy, 10 Gy, 15 Gy, 20 Gy, 30 Gy, and 40 Gy or more.

Fig. 4. Mean Vn% of the heart (A), AMT (B), LV (C), and left lung (D) in the IMRT(LV), IMRT(AMT), and IMRT(LV+AMT) plan. IMRT = intensity-modulated radiation therapy; AMT = anterior myocardial territory; LV = left ventricle; L lung = left lung; Vn% = percent volume receiving n Gy or more.

with the use of lower energy, the overdosage volume unusually fell near the surface, corresponding to the anterior portions of the heart, particularly the right atrium, right ventricle, and right coronary artery (25). Three-dimensional dose reconstruction of the anterior mantle field technique using cobalt-60 typically resulted in relative maximum doses of 120% and 150% in the anterior cardiac structures (25). With the use of opposing photon beams of 4- to 6-MV energy, doses were estimated to be 2.5–6% higher than the manually calculated prescribed dose (26). Similarly, in postoperative breast RT for left-sided patients, a significant amount of the anterior part of the heart, where atherosclerosis is the most frequent cause of ischemic heart disease, will be irradiated to deliver the

chain, and for all techniques used to treat these targets, the mean LAD dose (approximately 22 Gy) exceeded the heart dose. The circumflex coronary artery is located in the posterior myocardium and generally received lower doses than either the LAD or the right coronary arteries. The mean circumflex dose from tangential RT was <0.1–8 Gy (12, 30, 31).

In more recent RT used for early-stage breast cancer in conjunction with BCS, the mean irradiated heart volume that received at least 25 Gy ranged from 5.7% to 11.9%, and the 0% to 5% of the left ventricle exposed to radiation received approximately 25 Gy (32, 33).

In breast IMRT, the intermediate and high doses to the heart decreased at the cost of an increasing low dose-

Tan W et al Int J Rad Oncol Bio Phys 83: 1689, 2012

ANTERIOR MYOCARDIAL TERRITORY IN IMRT FOR LT-SIDED BREAST CANCER

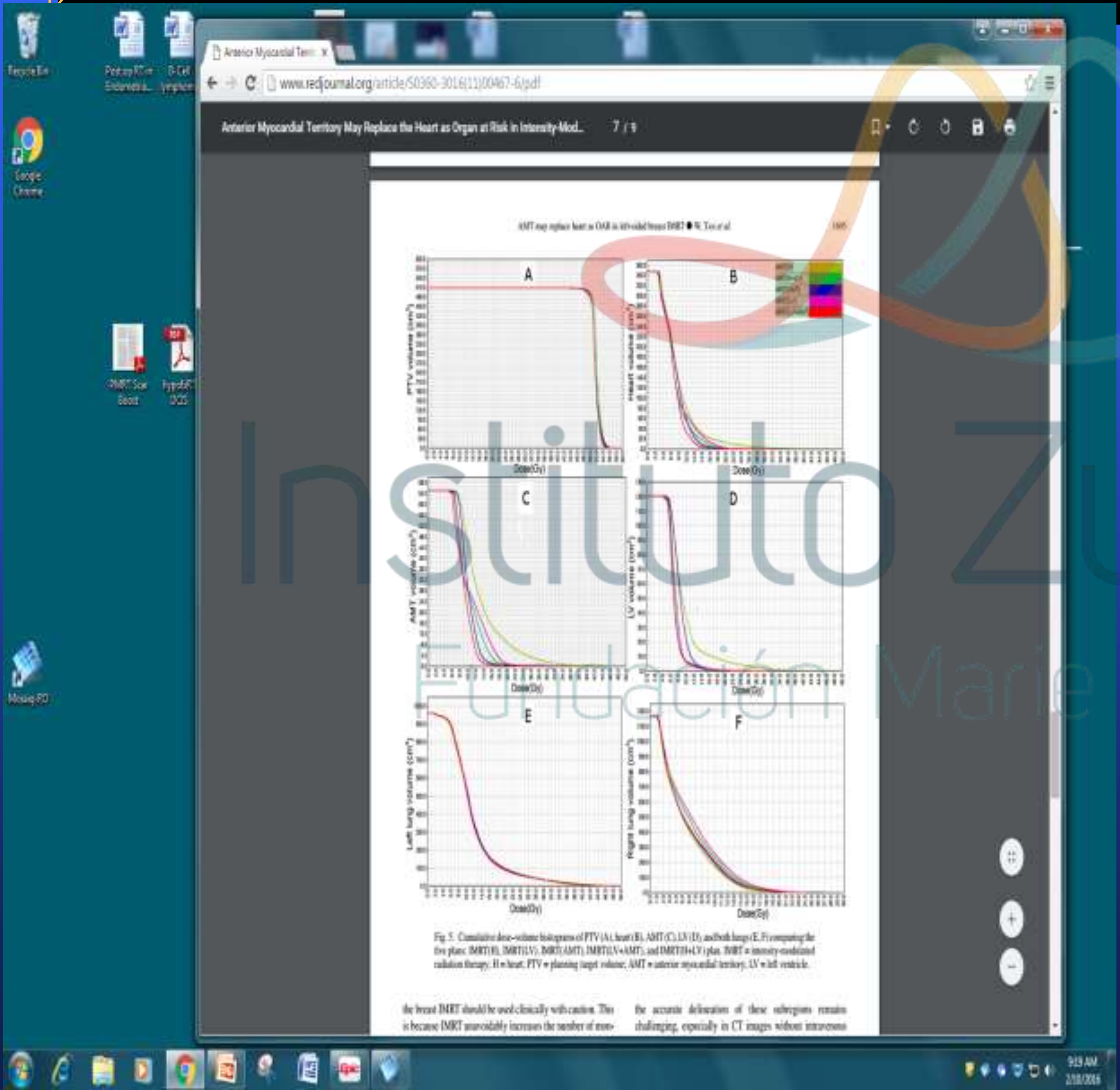


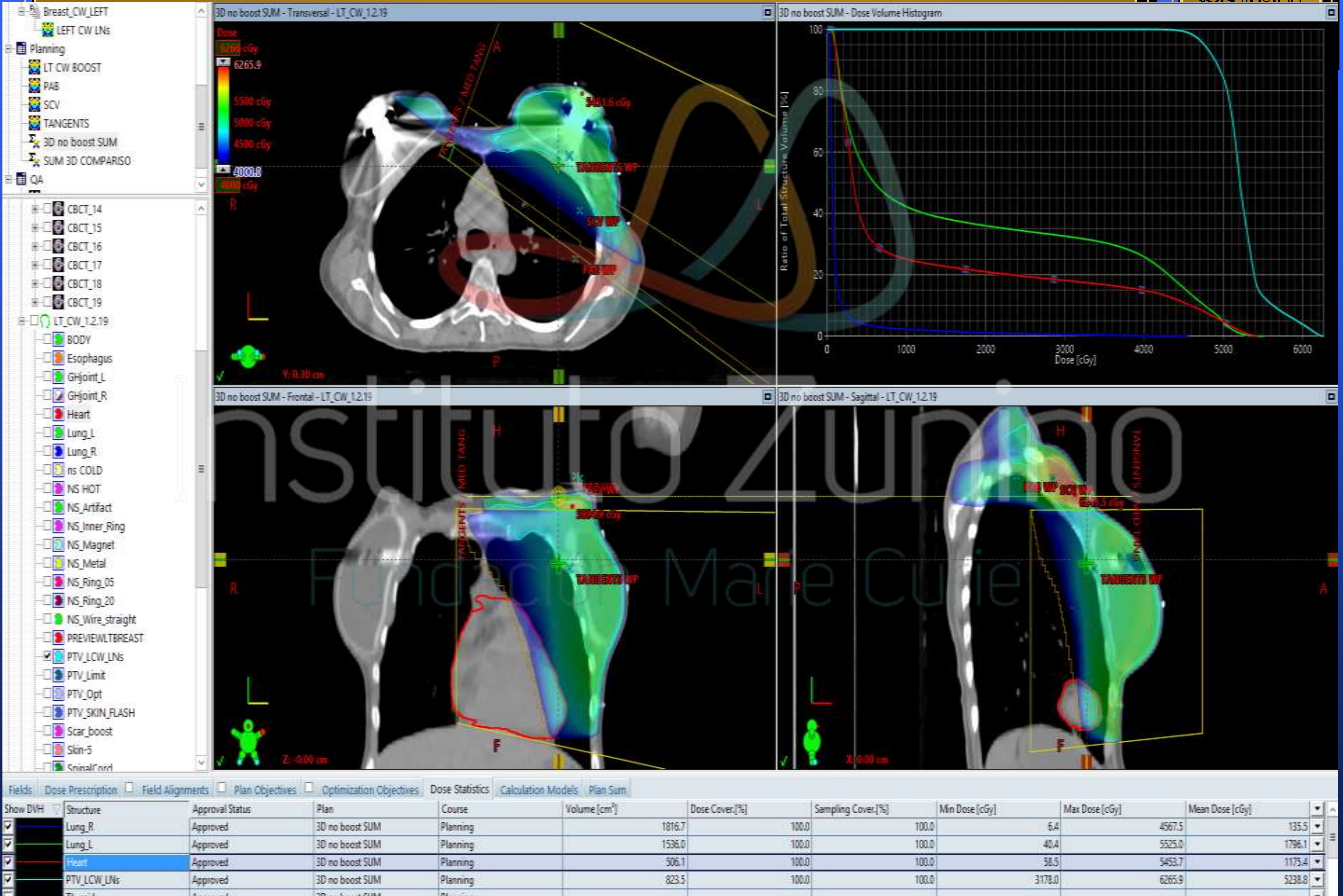
Fig. 5. Cumulative dose-volume histograms of PTV (A), heart (B), AMT (C), LV (D), and both lungs (E, F) comparing the five plans: IMRT(H), IMRT(LV), IMRT(AMT), IMRT(LV+AMT), and IMRT(H+LV) plan. IMRT = intensity-modulated radiation therapy; H = heart; PTV = planning target volume; AMT = anterior myocardial territory; LV = left ventricle.

the breast IMRT should be used clinically with caution. This is because IMRT unavoidably increases the number of mon-

the accurate delineation of these subregions remains challenging, especially in CT images without intravenous

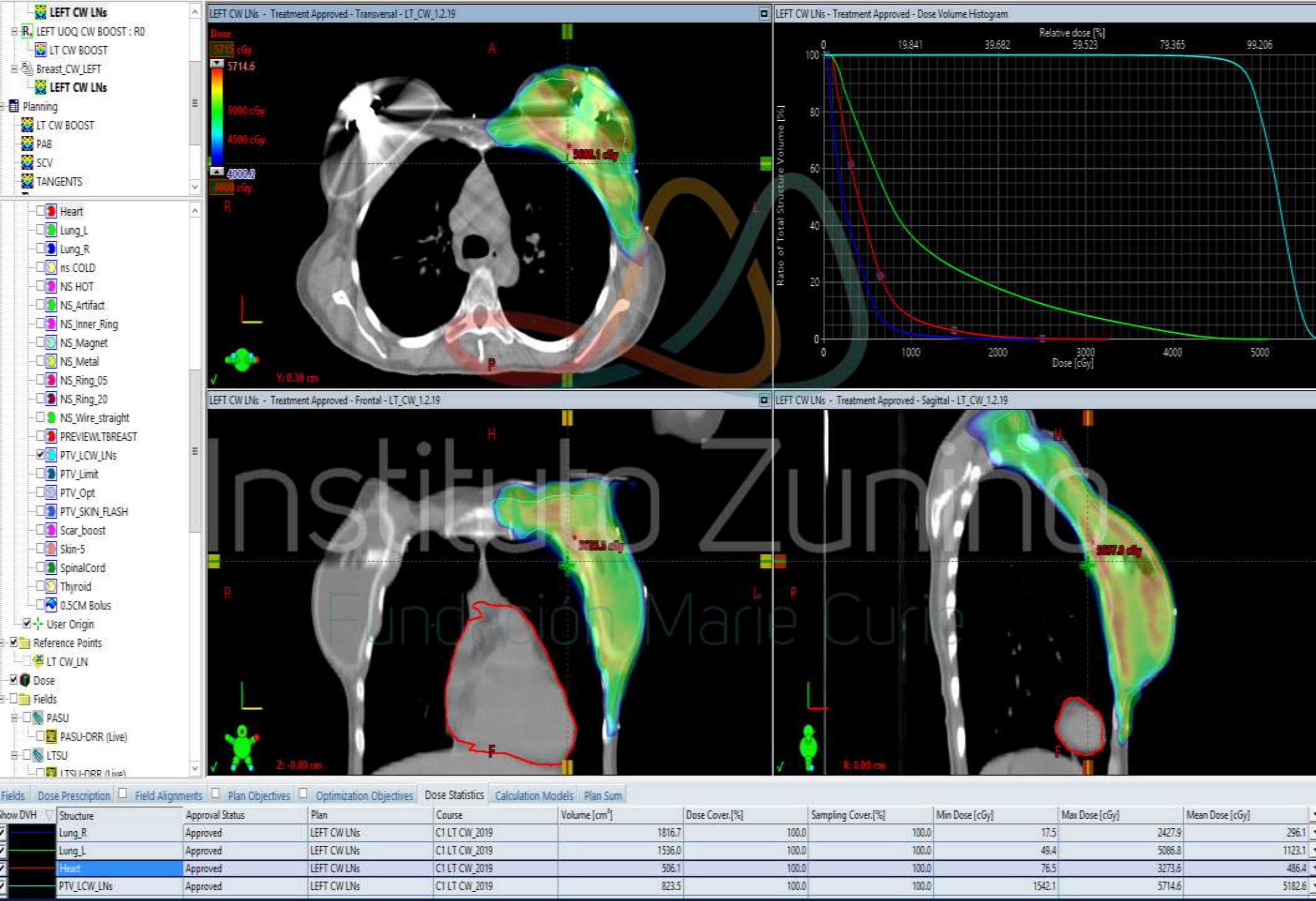
Tan W et al
Int J Rad Oncol Bio Phys
83: 1689, 2012

Comparison 3D plan: Note that the medial tangent is a partially deep tangent and enters through the contralateral tissue expander



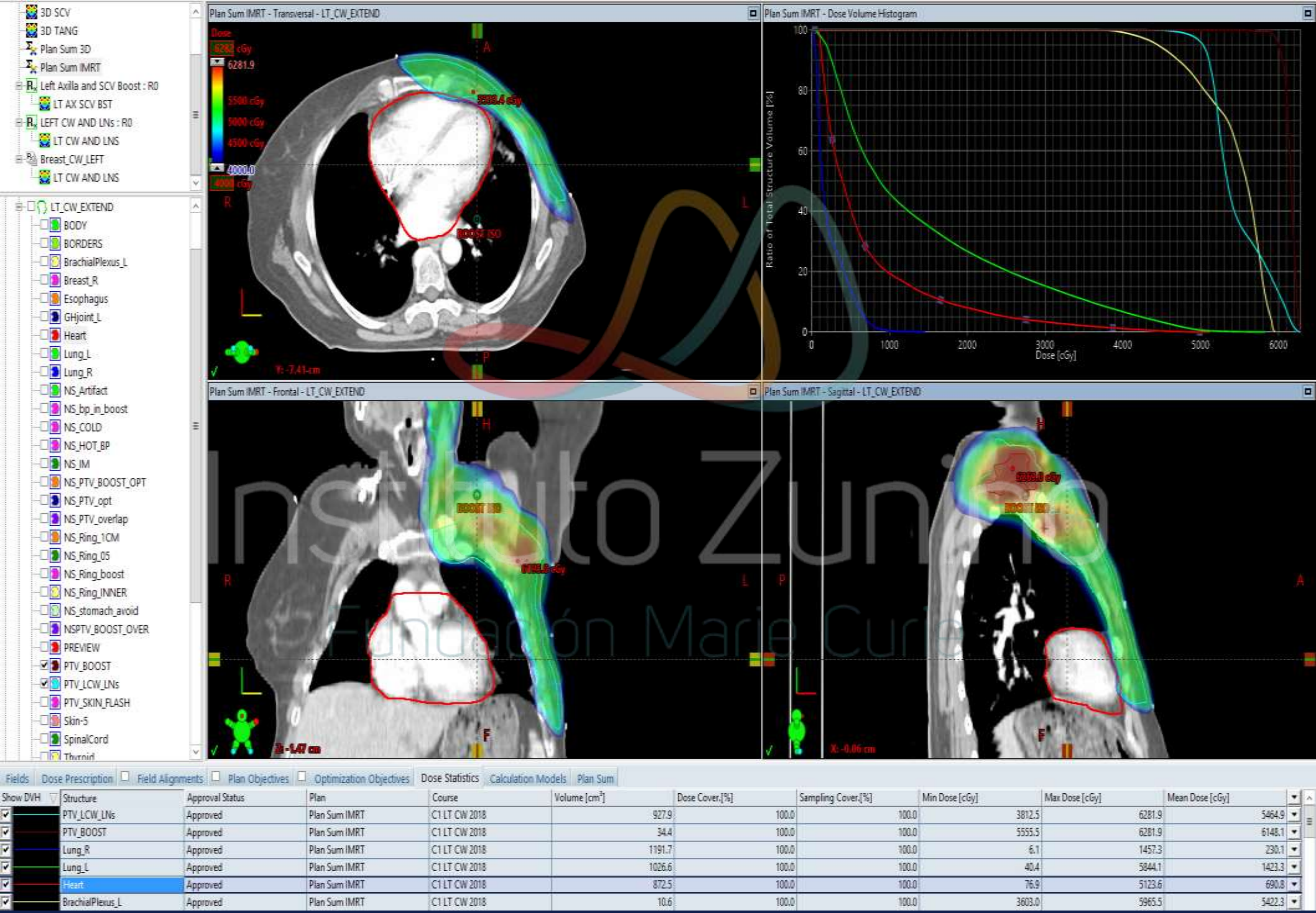
Show DVH	Structure	Approval Status	Plan	Course	Volume [cm^3]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑	Lung_R	Approved	3D no boost SUM	Planning	1816.7	100.0	100.0	6.4	4567.5	135.5
☑	Lung_L	Approved	3D no boost SUM	Planning	1536.0	100.0	100.0	40.4	5525.0	1796.1
☑	Heart	Approved	3D no boost SUM	Planning	506.1	100.0	100.0	58.5	5453.7	1175.4
☑	PTV_LCW_LNs	Approved	3D no boost SUM	Planning	823.5	100.0	100.0	3178.0	6265.9	5238.8

IMRT treatment plan results in improved lung and cardiac sparing.



Show DVH	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑	Lung_R	Approved	LEFT CW LNs	C1 LT CW_2019	1816.7	100.0	100.0	17.5	2427.9	296.1
☑	Lung_L	Approved	LEFT CW LNs	C1 LT CW_2019	1536.0	100.0	100.0	49.4	5086.8	1123.1
☑	Heart	Approved	LEFT CW LNs	C1 LT CW_2019	506.1	100.0	100.0	76.5	3273.6	486.4
☑	PTV_LCW_LNs	Approved	LEFT CW LNs	C1 LT CW_2019	823.5	100.0	100.0	1542.1	5714.6	5182.6

IMRT TO LEFT CHEST WALL AND REGIONAL LYMPH NODES

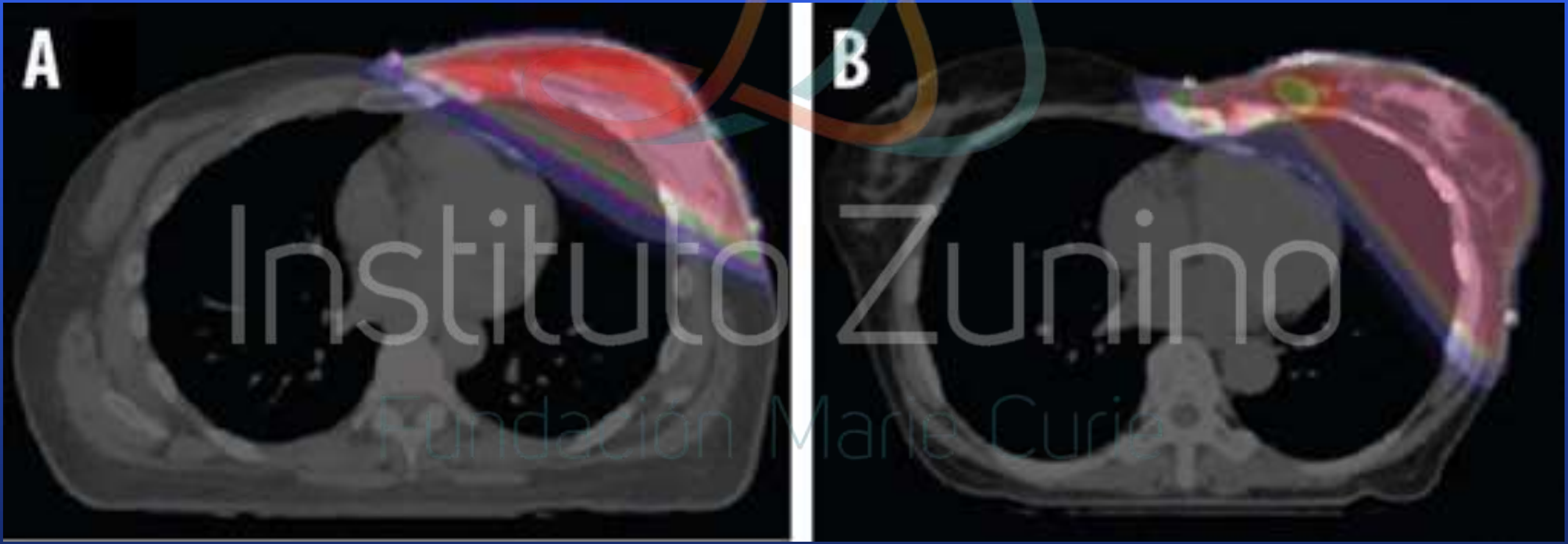


Show DVH	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑	PTV_LCW_LNs	Approved	Plan Sum IMRT	C1 LT CW 2018	927.9	100.0	100.0	3812.5	6281.9	5464.9
☑	PTV_BOOST	Approved	Plan Sum IMRT	C1 LT CW 2018	34.4	100.0	100.0	5555.5	6281.9	6148.1
☑	Lung_R	Approved	Plan Sum IMRT	C1 LT CW 2018	1191.7	100.0	100.0	6.1	1457.3	230.1
☑	Lung_L	Approved	Plan Sum IMRT	C1 LT CW 2018	1026.6	100.0	100.0	40.4	5844.1	1423.3
☑	Heart	Approved	Plan Sum IMRT	C1 LT CW 2018	872.5	100.0	100.0	76.9	5123.6	690.8
☑	BrachialPlexus_L	Approved	Plan Sum IMRT	C1 LT CW 2018	10.6	100.0	100.0	3603.0	5965.5	5422.3

RT TECHNIQUES IN LEFT BREAST CANCER

3D-CRT TANGENTIAL BEAMS

IM PORTAL (PHOTONS-EB) AND TANGENTIALBEAMS



Dess RT et al Int J Radiat Oncol Bio Phys 99: 1146, 2017

TOMO-DIRECT SIMULTANEOUS INTEGRATED BOOST IN LEFT BREAST CANCER

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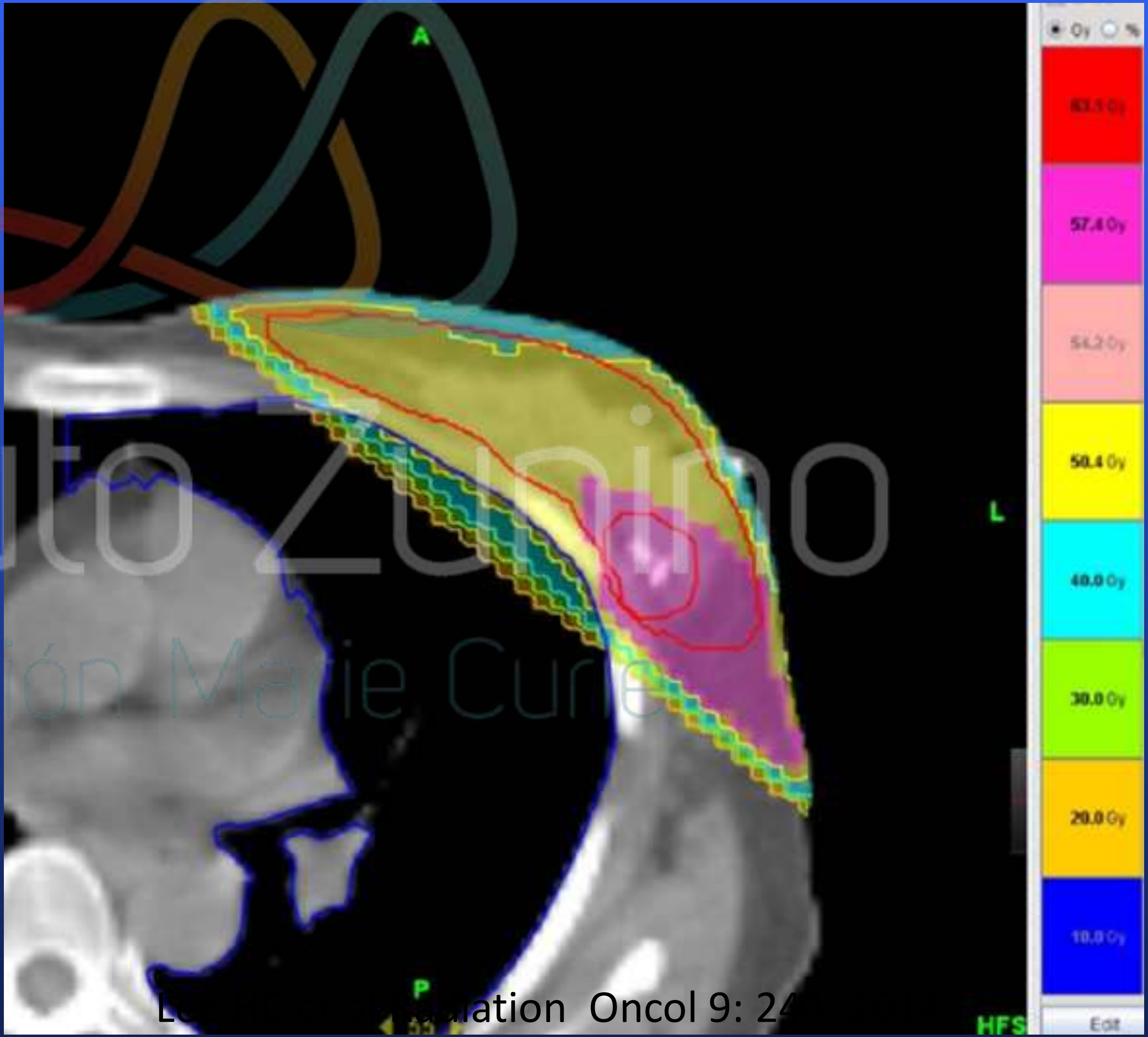
(B)

Figure 1 (See legend on next page)



Le [illegible] ation Oncol 9: 24

VIEWRAY RADIATION THERAPY

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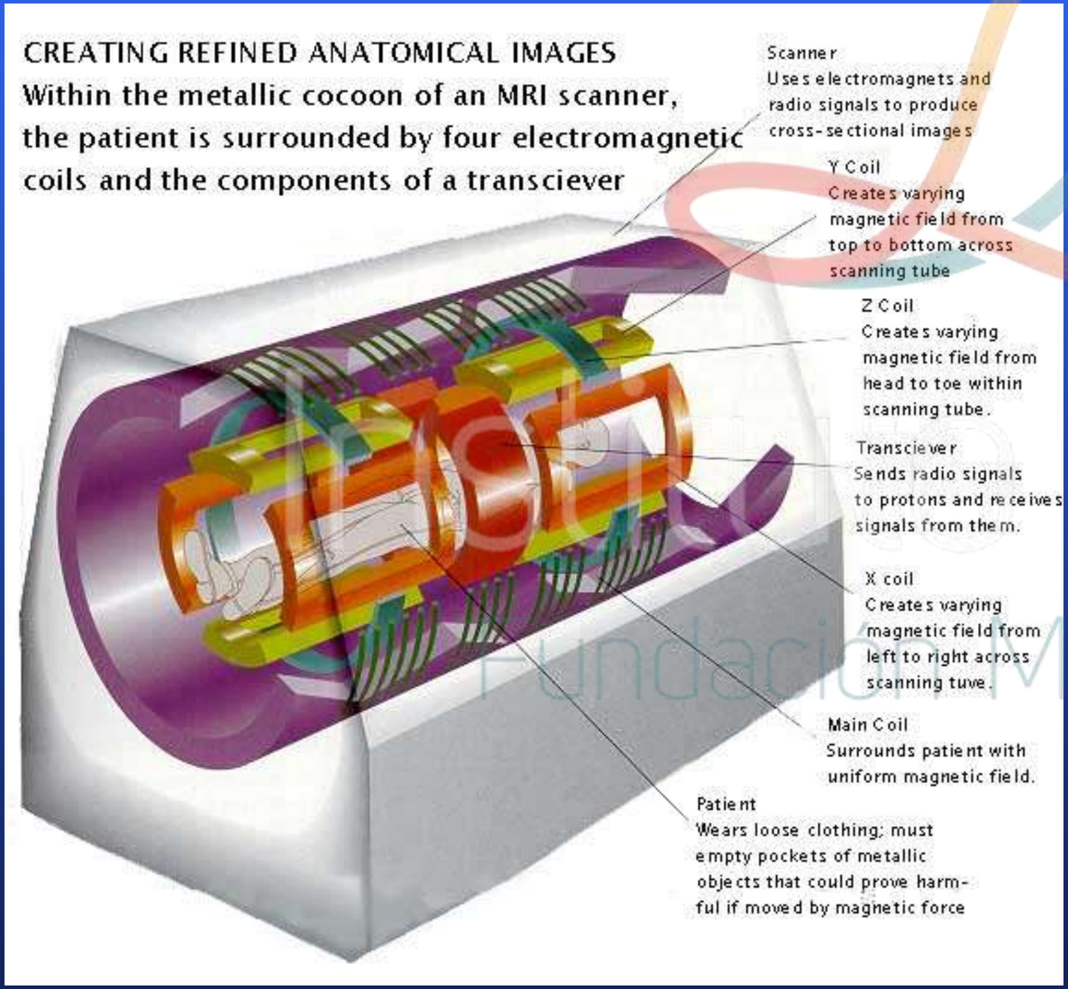


CREATING REFINED ANATOMICAL IMAGES

Within the metallic cocoon of an MRI scanner, the patient is surrounded by four electromagnetic coils and the components of a transciever

Scanner
Uses electromagnets and radio signals to produce cross-sectional images

Y Coil
Creates varying magnetic field from top to bottom across scanning tube

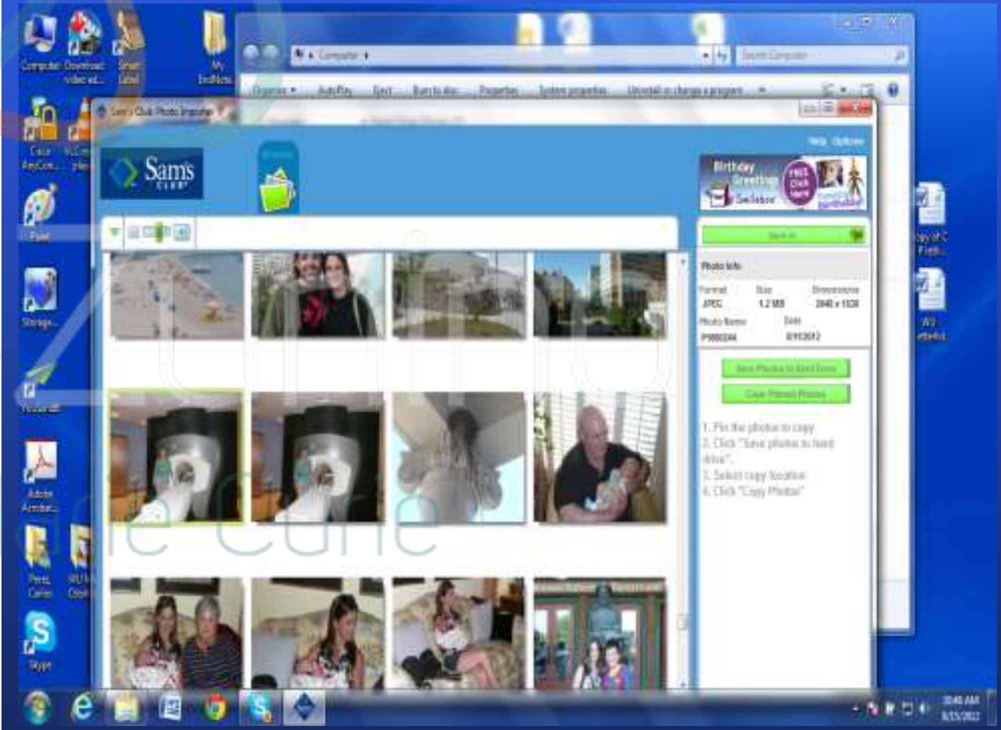
Z Coil
Creates varying magnetic field from head to toe within scanning tube.

Transciever
Sends radio signals to protons and receives signals from them.

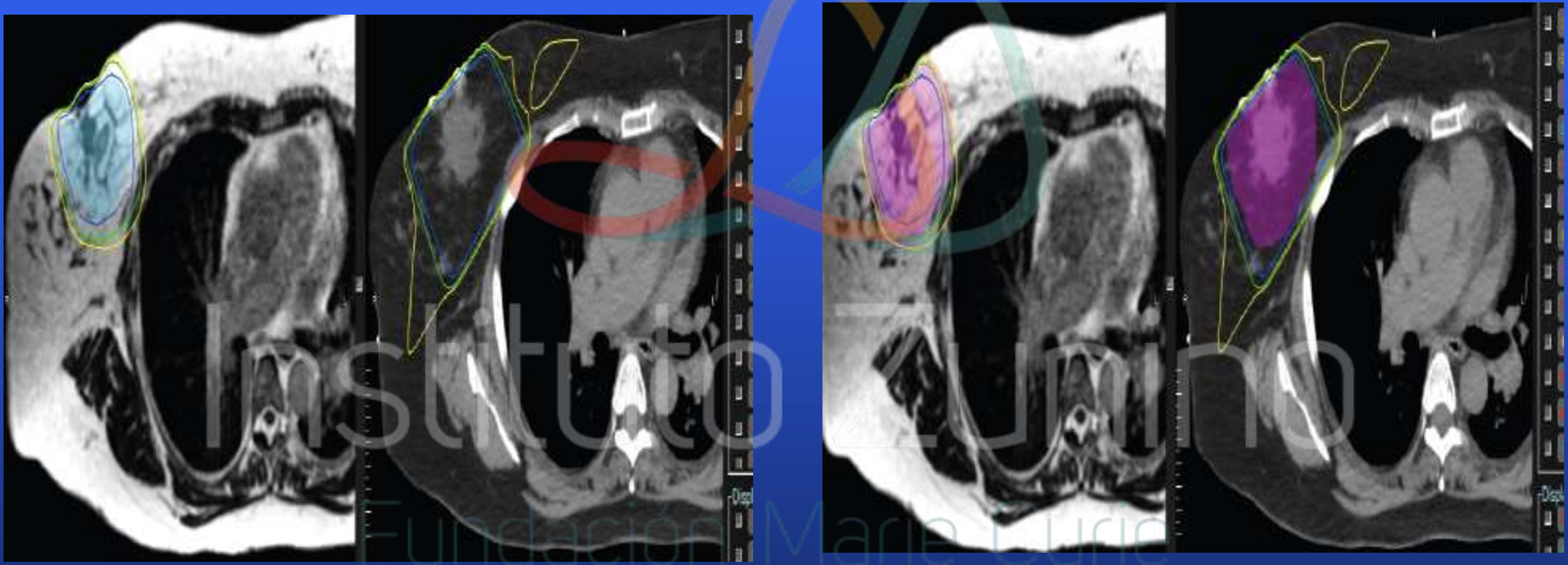
X coil
Creates varying magnetic field from left to right across scanning tuve.

Main Coil
Surrounds patient with uniform magnetic field.

Patient
Wears loose clothing; must empty pockets of metallic objects that could prove harmful if moved by magnetic force



VIEWRAY F0R PARTIAL BREAST IRRADIATION



Left panel: ViewRay planning MRI for partial breast radiation. Aqua colorwash: target volume (130 cc). Right panel: Traditional planning CT for the same patient (290 cc,).

PARTIAL BREAST IRRADIATION

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- External Beam :
  - 3D Conformal / Intensity Modulated (IMRT)
  - Tomotherapy / Topotherapy

-Intra Operative
  - Electron Beam
  - X-Ray beam
  - Interstitial brachytherapy

- Brachytherapy:

  Interstitial:
  - Low Dose
  - High Dose

Partial Breast Radiation

Washington University School of Medicine

Interstitial implants

ACCELERATED PARTIAL BREAST RT- Washington University, St, Louis, USA

Grouping Outcome

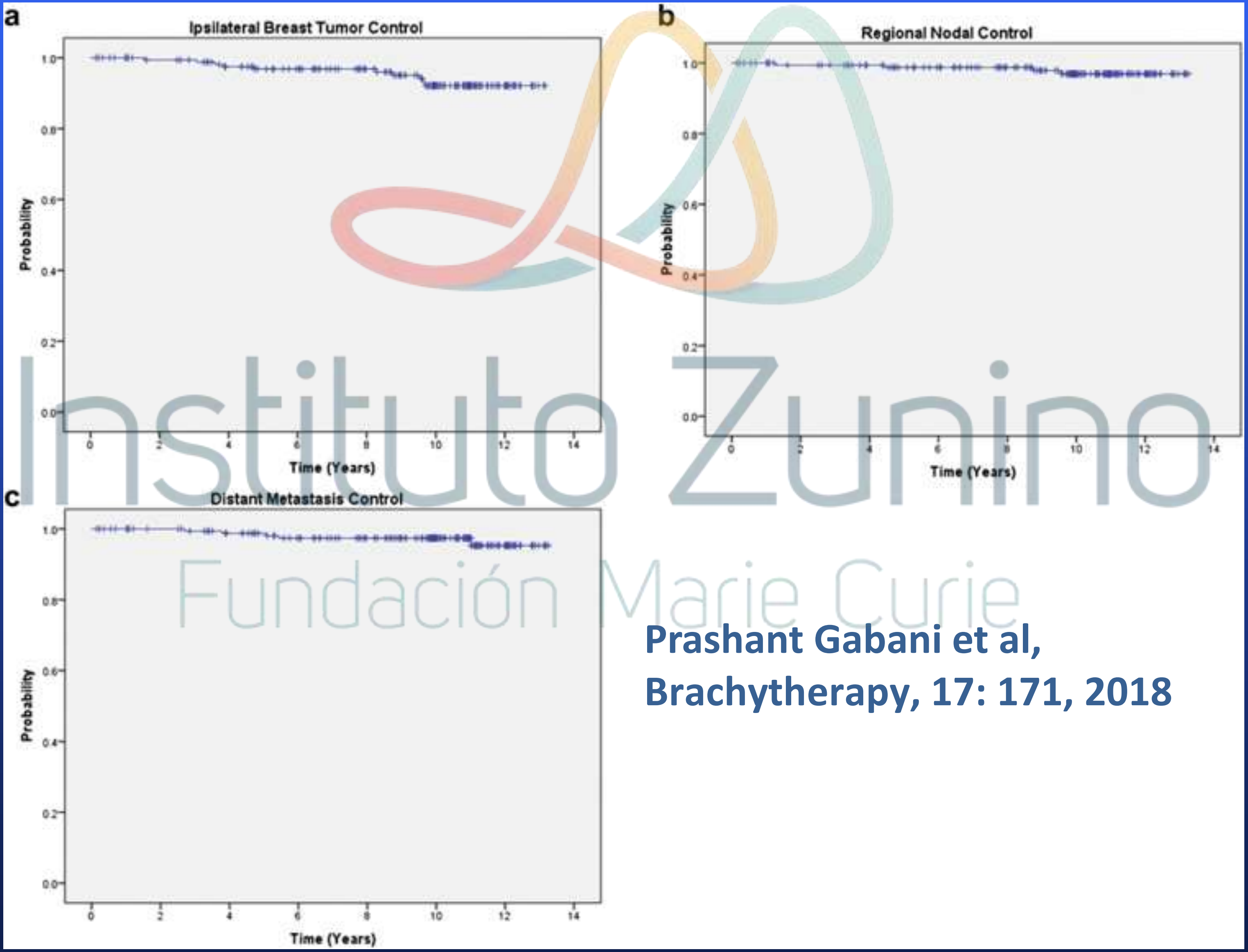
	Suitable (%)N 5 63	Cautionary (%) N 5 86	Unsuitable (%) N 526	
I BTC	92.	1 90.2	100	0.462
RC	100.0	95.0	95.2	0.271
CSS	98.3	98. 5	87.8	0.075
OS	85.4	79.3	76.8	0.587

ASTRO 5 American Society for Radiation Oncology; CSS 5 cancerspecific survival;
IBTC 5 yr ipsilateral breast tumor control; OS 5 yr overall survival; RC regional control;

Prashant Gabani et al, Brachytherapy 17: 171, 2018

ACCELERATED PARTIAL BREAST RT- Washington University, St, Louis, USA

Washington School of Medicine



Prashant Gabani et al,
Brachytherapy, 17: 171, 2018

Single Fraction High-gradient Partial Breast Irradiatio with MRI_Guided Radiation Therapy (ViewRay)for Low-risk Stage 0 and I Breast Carcinoma

FINAL_3D_LUOQ_BREAST_7-24-15 Created: 07/24/2015 14:17 Modified: 07/24

Plan Approval: rak3183

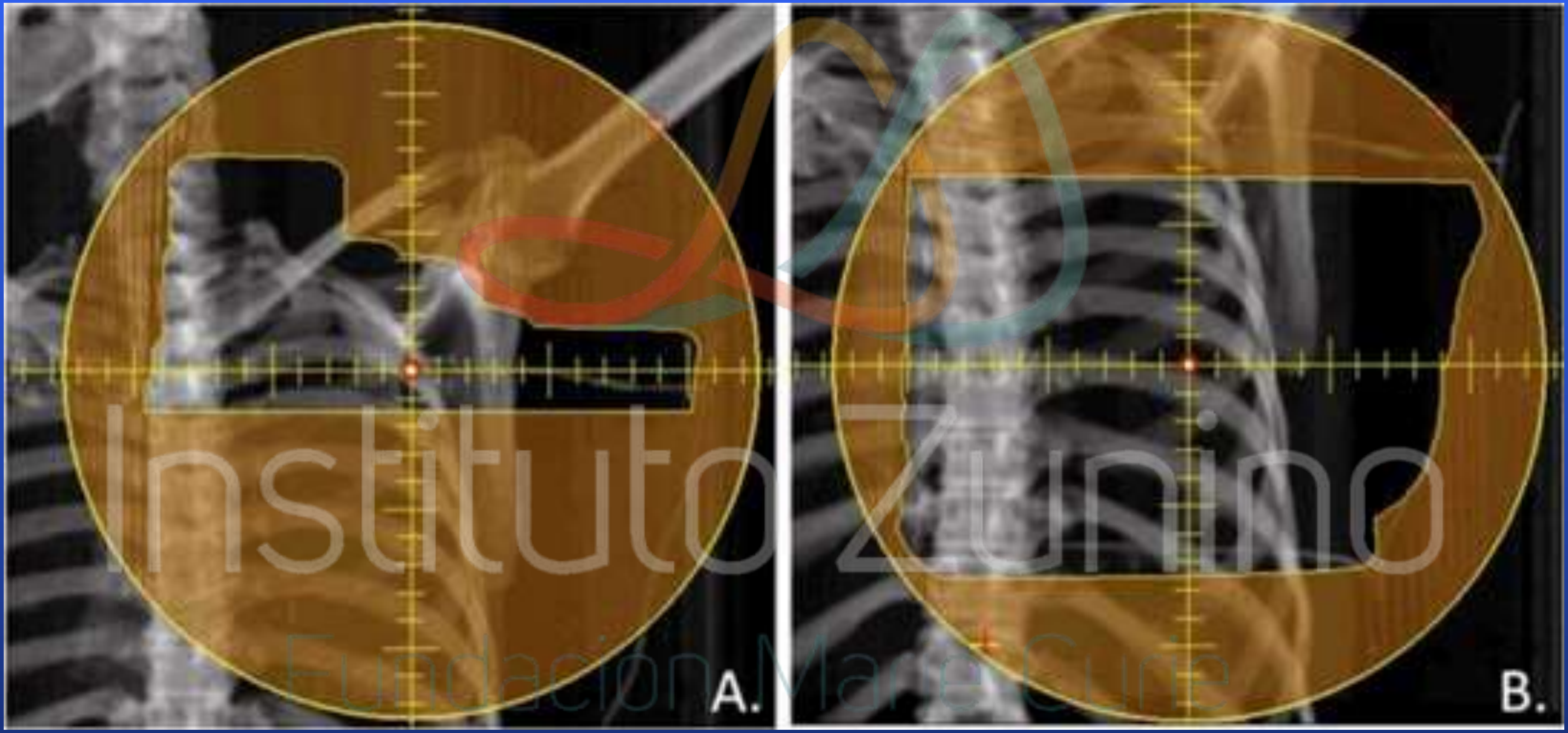
Contour Approval: rak3183

Registration Approval: None

Software Version: ViewRay™ System-3.6.0.240

Equipment Model: VIEWRAY IGRT 7

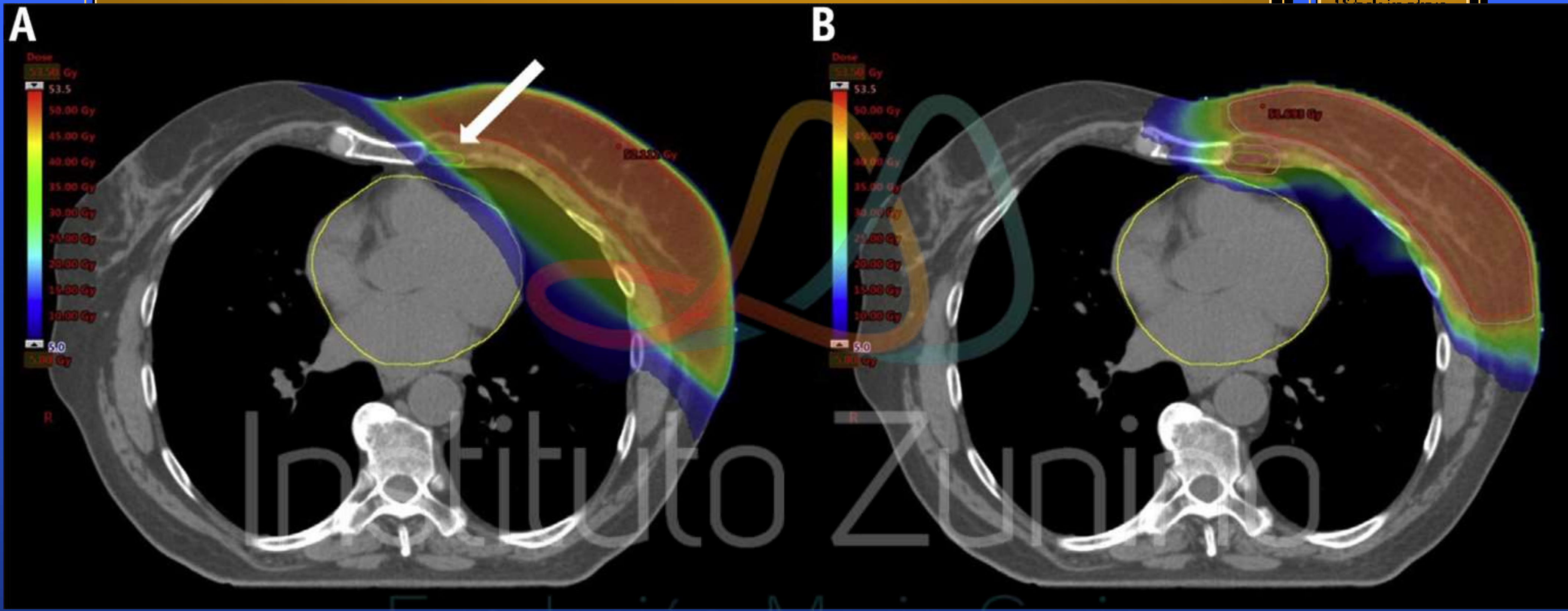
COMPARISON OF PROTONS AND PHOTONS IN BREAST CANCER



Examples of Protons Treatment Volumes

Bradley J E et al Int J Radiat Oncol Bio Phys 95: 411, 2016

PROTONS VS PHOTONS IN BREAST CANCER



Photons

Protons

Stick, L B et al Int J Radiat Oncol Biol Phys, 97:761, 2017

COMPARISON OF PROTONS AND PHOTONS IN BREAST CANCER

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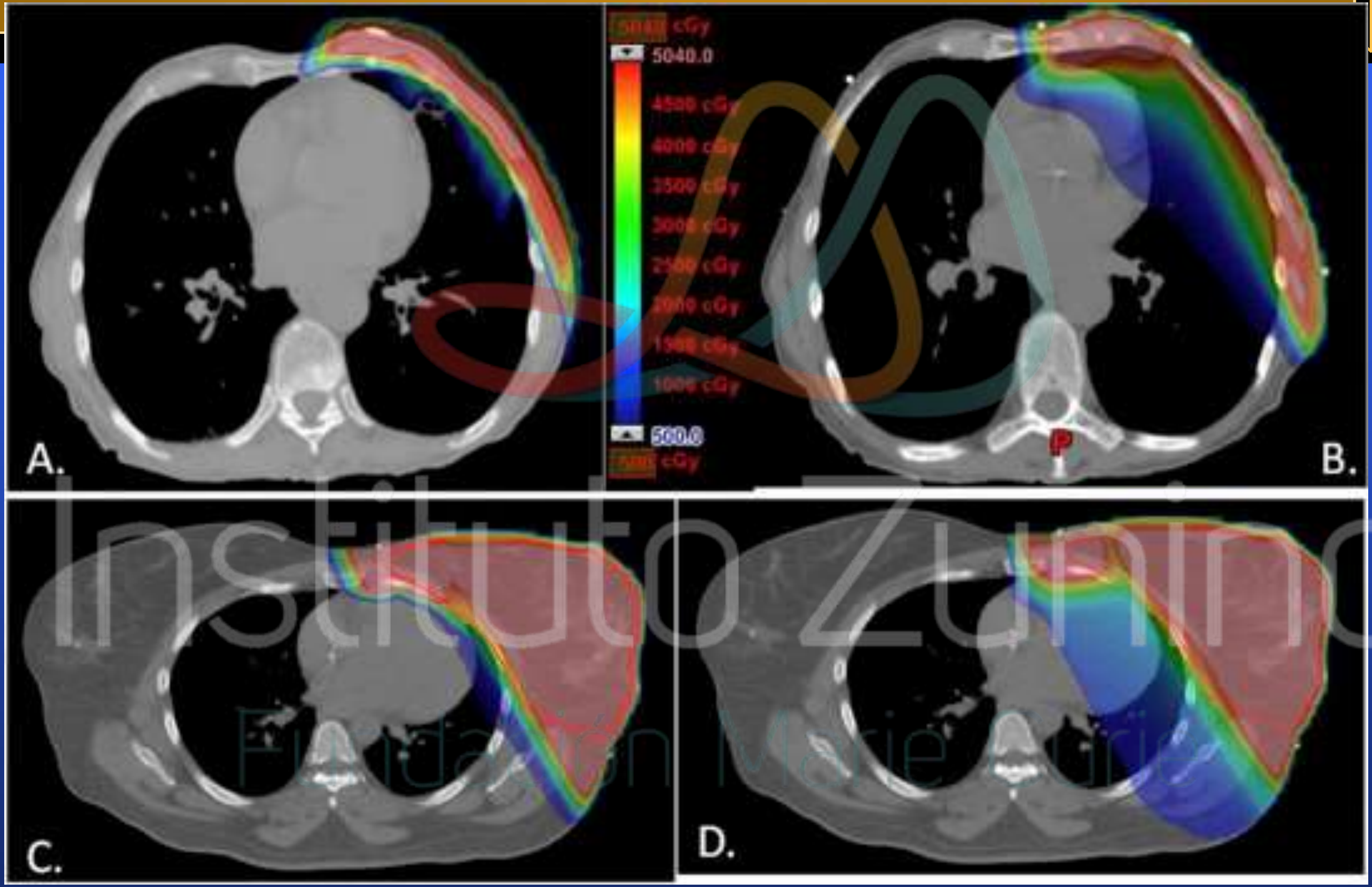
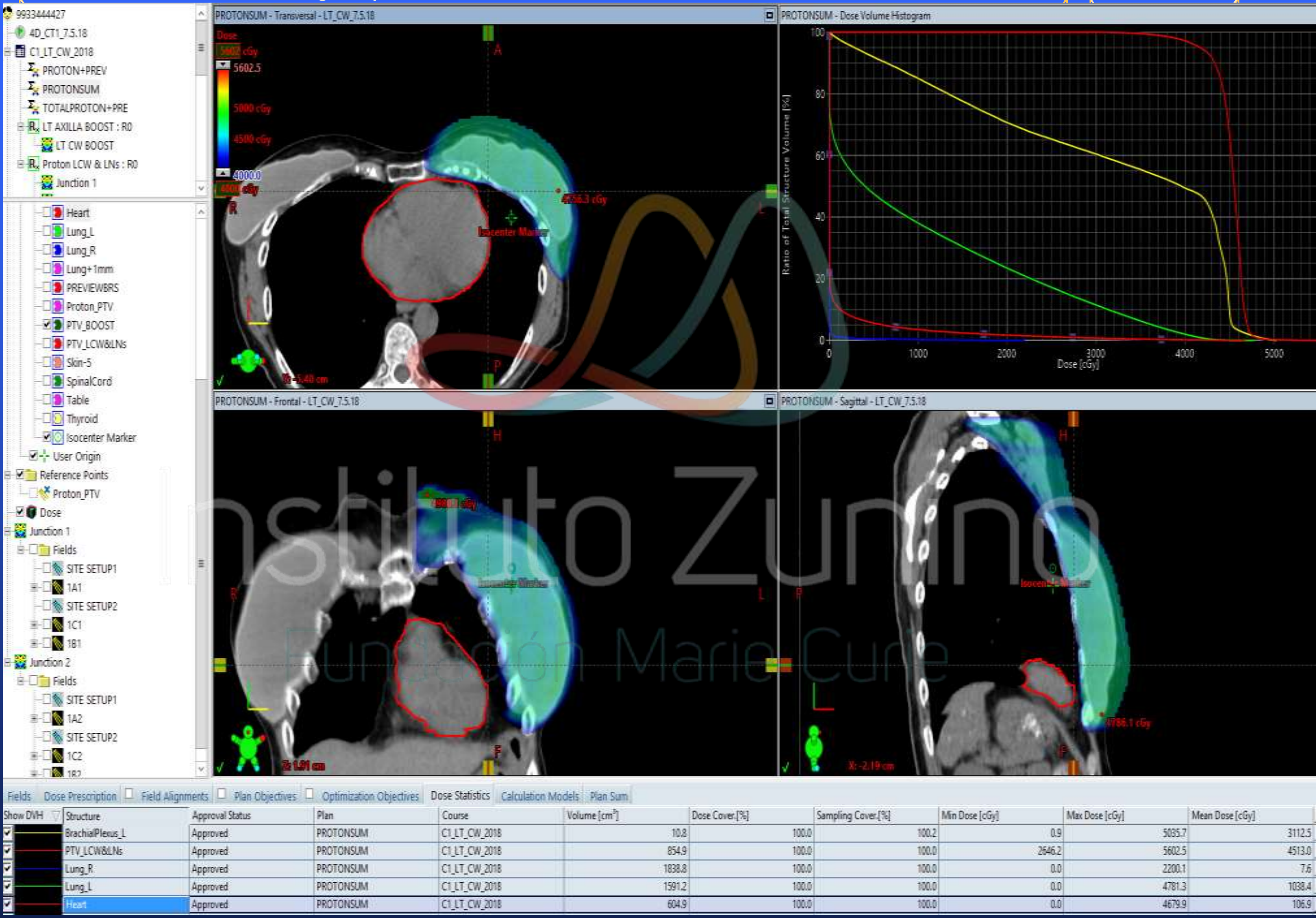


Key: Chest wall A- Protons, B Electrons and Photos, Whole Breast C Protons D Photons

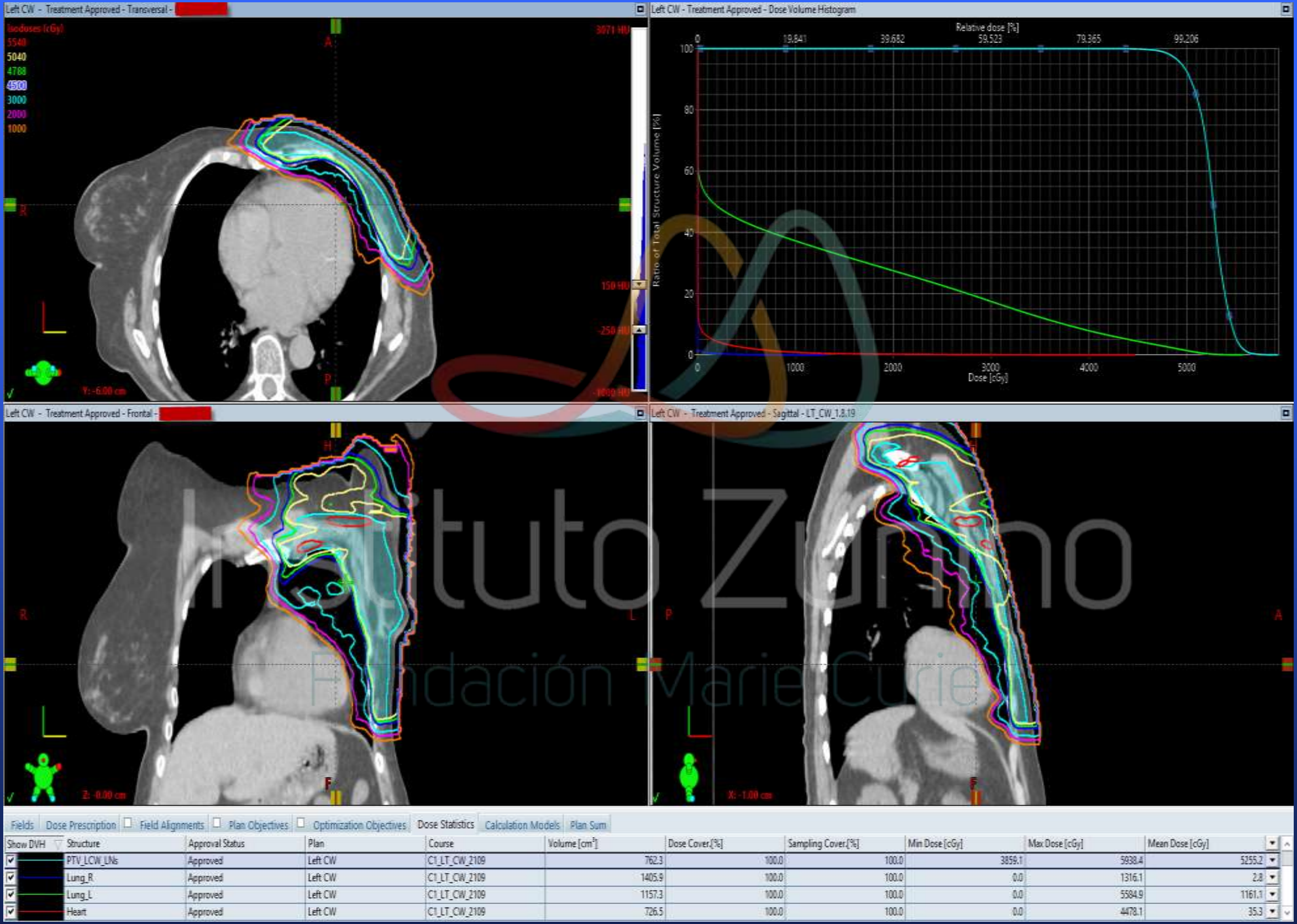
Bradley J E et al Int J Radiat Oncol Bio Phys 95: 411, 2016

Proton radiation therapy to the left chest and regional nodes in the setting of prior left breast radiation treatment.



Show DVH	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑	BrachialPlexus_L	Approved	PROTONSUM	C1_LT_CW_2018	10.8	100.0	100.2	0.9	5035.7	3112.5
☑	PTV_LCW&LNs	Approved	PROTONSUM	C1_LT_CW_2018	854.9	100.0	100.0	2646.2	5602.5	4513.0
☑	Lung_R	Approved	PROTONSUM	C1_LT_CW_2018	1838.8	100.0	100.0	0.0	2200.1	7.6
☑	Lung_L	Approved	PROTONSUM	C1_LT_CW_2018	1591.2	100.0	100.0	0.0	4781.3	1038.4
☑	Heart	Approved	PROTONSUM	C1_LT_CW_2018	604.9	100.0	100.0	0.0	4679.9	106.9

Proton radiation therapy on the RADCOMP study



Left CW - Treatment Approved - Transversal - [redacted]

Left CW - Treatment Approved - Dose Volume Histogram

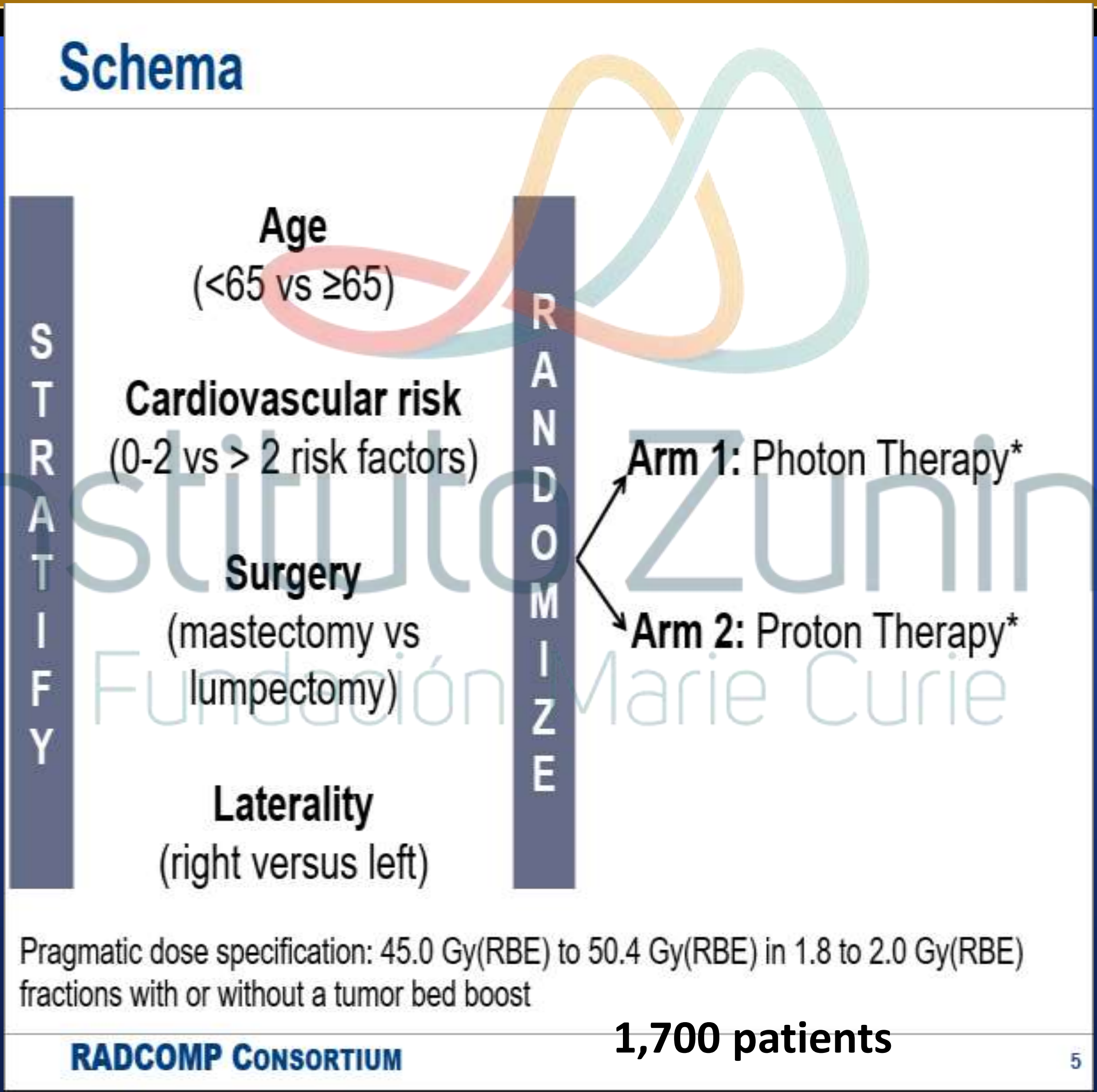
Left CW - Treatment Approved - Frontal - [redacted]

Left CW - Treatment Approved - Sagittal - LT_CW_1.8.19

Fields | Dose Prescription | ☐ Field Alignments | ☐ Plan Objectives | ☐ Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

Show DVH	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑	PTV_LCW_LNs	Approved	Left CW	C1_LT_CW_2109	762.3	100.0	100.0	3859.1	5938.4	5255.2
☑	Lung_R	Approved	Left CW	C1_LT_CW_2109	1405.9	100.0	100.0	0.0	1316.1	2.8
☑	Lung_L	Approved	Left CW	C1_LT_CW_2109	1157.3	100.0	100.0	0.0	5584.9	1161.1
☑	Heart	Approved	Left CW	C1_LT_CW_2109	726.5	100.0	100.0	0.0	4478.1	35.3

RADCOMP TRIAL COMPARING PROTONS TO PHOTONS IN LOCALIZED BREAST CANCER



Schema

STRATIFY

Age
(<65 vs ≥65)

Cardiovascular risk
(0-2 vs > 2 risk factors)

Surgery
(mastectomy vs lumpectomy)

Laterality
(right versus left)

RANDOMIZE

Arm 1: Photon Therapy*

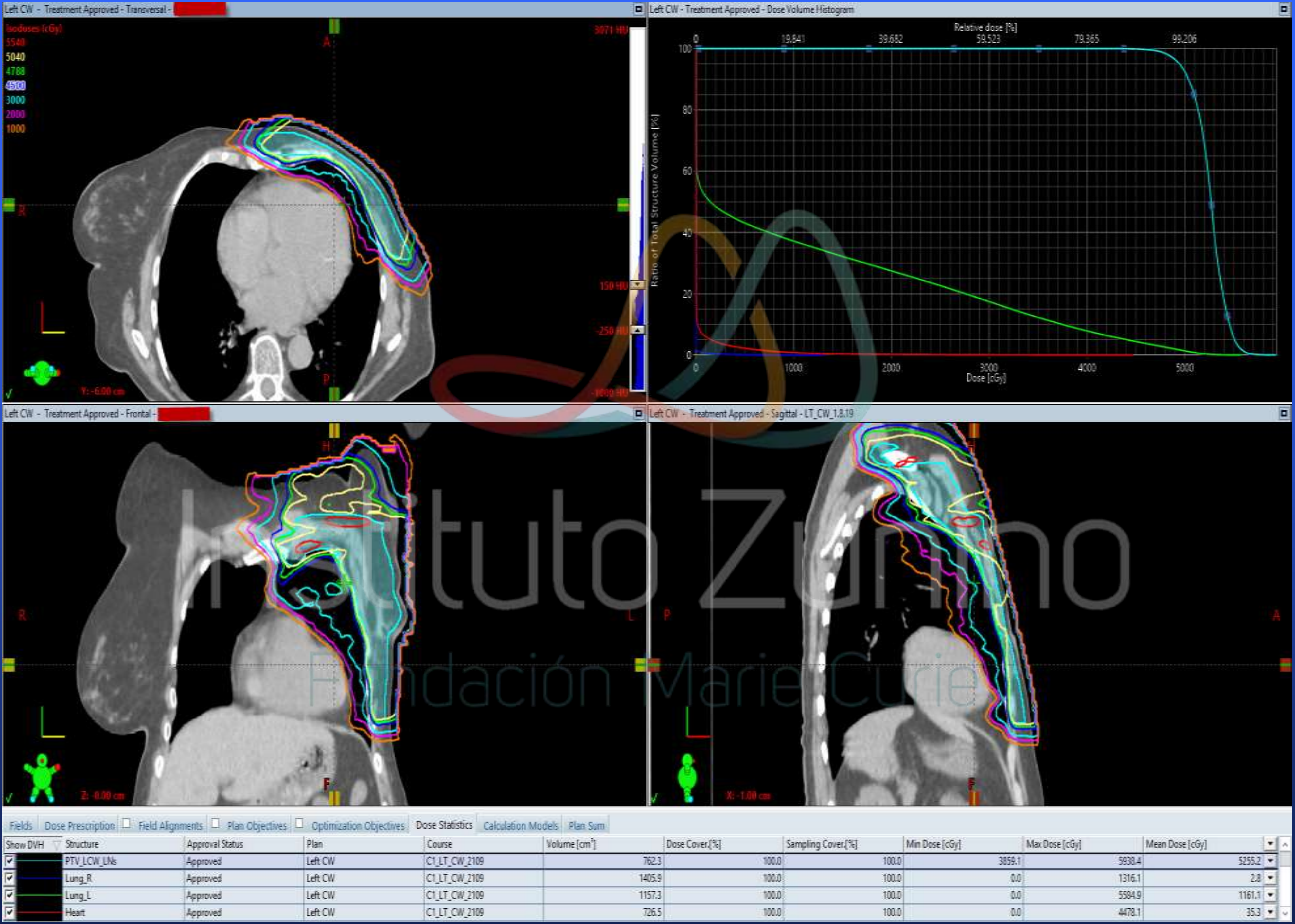
Arm 2: Proton Therapy*

Pragmatic dose specification: 45.0 Gy(RBE) to 50.4 Gy(RBE) in 1.8 to 2.0 Gy(RBE) fractions with or without a tumor bed boost

1,700 patients

RADCOMP CONSORTIUM

Proton radiation therapy on the RADCOMP study



Show DVH	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑	PTV_LCW_LNs	Approved	Left CW	C1_LT_CW_2109	762.3	100.0	100.0	3859.1	5938.4	5255.2
☑	Lung_R	Approved	Left CW	C1_LT_CW_2109	1405.9	100.0	100.0	0.0	1316.1	2.8
☑	Lung_L	Approved	Left CW	C1_LT_CW_2109	1157.3	100.0	100.0	0.0	5584.9	1161.1
☑	Heart	Approved	Left CW	C1_LT_CW_2109	726.5	100.0	100.0	0.0	4478.1	35.3

COST EFFECTIVENESS (CE) OF PROTONS IN BREAST CANCER

Proton RT was not CE in women without CRFs or a mean heart dose (MHD) <5 Gy.
Base-case analysis noted cost-effectiveness for proton RT in women with ≥1 CRF at approximateminimum MHD of 6 Gy with a willingness-to-pay threshold of $100,000/quality-adjusted life-year.
For women with ≥1 CRF, probabilistic sensitivity analysis noted preference of proto
for an MHD ≥5 Gy with a similar willingness-to-pay threshold.

Referral for proton therapy may be cost-effective for patients with ≥1 CRF in patine
whom photon plans are unable to achieve an MHD <5 Gy.

Given the assumed benefit that reduced MHD would connote a lower risk of CHD
preference for proton therapy in younger patients is owing to more time living
free of CHDcompared with older patients with shorter baseline life expectancies.
The analysis did suggest greater benefit for proton RT in 50-year-old women ove
40-year- old women this phenomenon is a function of outcomes data from Darby

Mailhot Vega RB et al Int J Radiat Oncol Bio Phys 95: 11,2016

)

COST EFFECTIVENESS OF PROTONS IN BREAST CANCER

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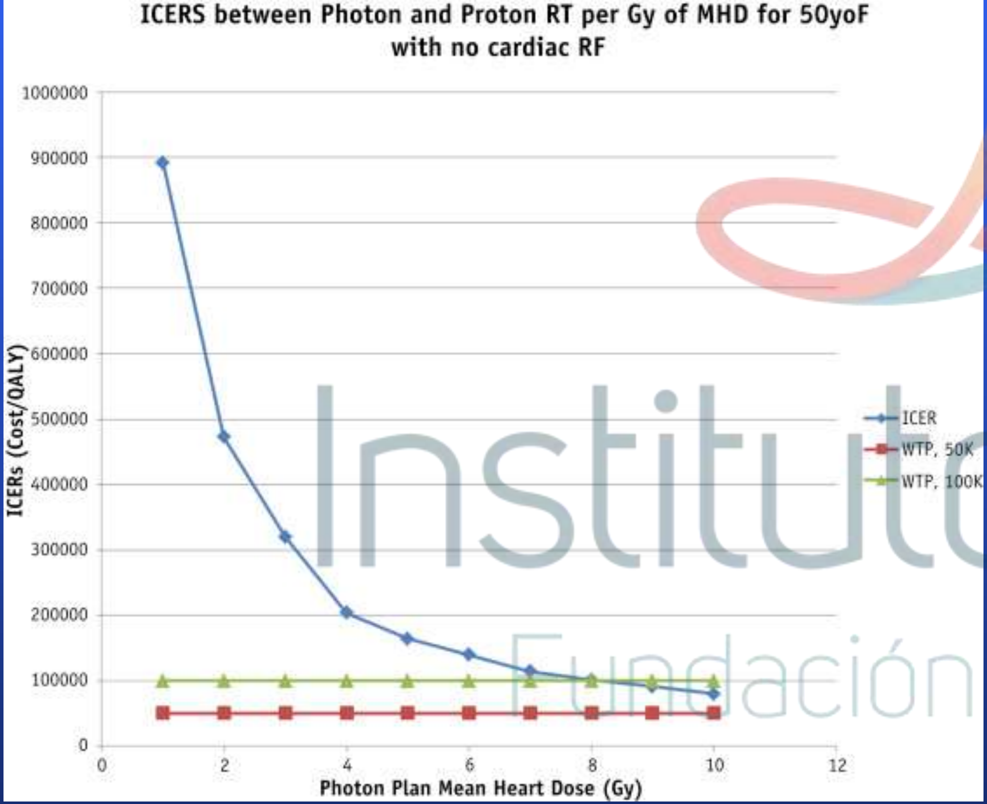
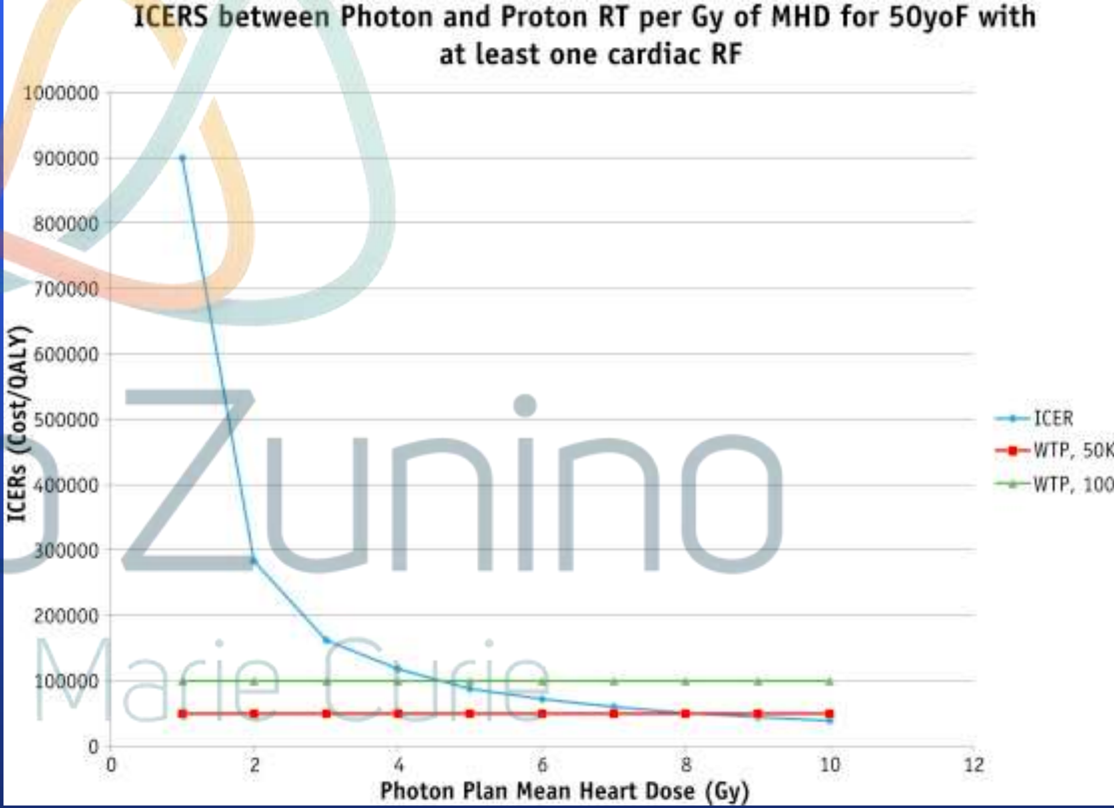

ICERS between Photon and Proton RT per Gy of MHD for 50yoF with no cardiac RF


ICERS between Photon and Proton RT per Gy of MHD for 50yoF with at least one cardiac RF

Mailhot Vega RB et al Int J Radiat Oncol Bio Phys 95: 11, 2016

Cardiac Toxicity is Not Increased 25 Years After Treatment of Early-stage Breast Carcinoma With Mastectomy or B C T From the National Cancer Institute Randomized Trial

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- Among BCT pts, radiation central lung distance >3 cm was similar for right- versus left-sided tumors (35.7% vs. 50.0%, p = 0.48). Cardiac interventions (CABG or PCI) occurred in 4 MRM and 3 BCT pts. Framingham 10-yr risk of MI was similar between arms. Diastolic function, including peak filling rate (p = 0.29) and diastolic volume recovery (p = 0.28), was similar in between arms. No pt had evidence of myocardial fibrosis. One pt in each arm had pericardial thickening. Among BCT pts, cardiac structure and function were similar for right or left tumors. BCT pts had no increase in visible atherosclerosis (HR = 1.12, p = 0.80) or luminal stenosis >50% (HR = 0.64, p = 0.62). Prevalence, severity and distribution of atherosclerosis were not different in BCT pts for right- or left-sided radiation, including LAD (close proximity to the chest wall, received the highest RT dose) (38.9% vs. 33.3%, p = 0.73).

Chemotherapy pts trended towards more visible atherosclerosis independent of

Siimone CB et al Int J Radiat Oncol Bio Phys 84: S35, 2012

A Randomized Comparison of Radiation Therapy Techniques in Management of Node-Positive Breast Cancer: Primary Outcomes Analysis

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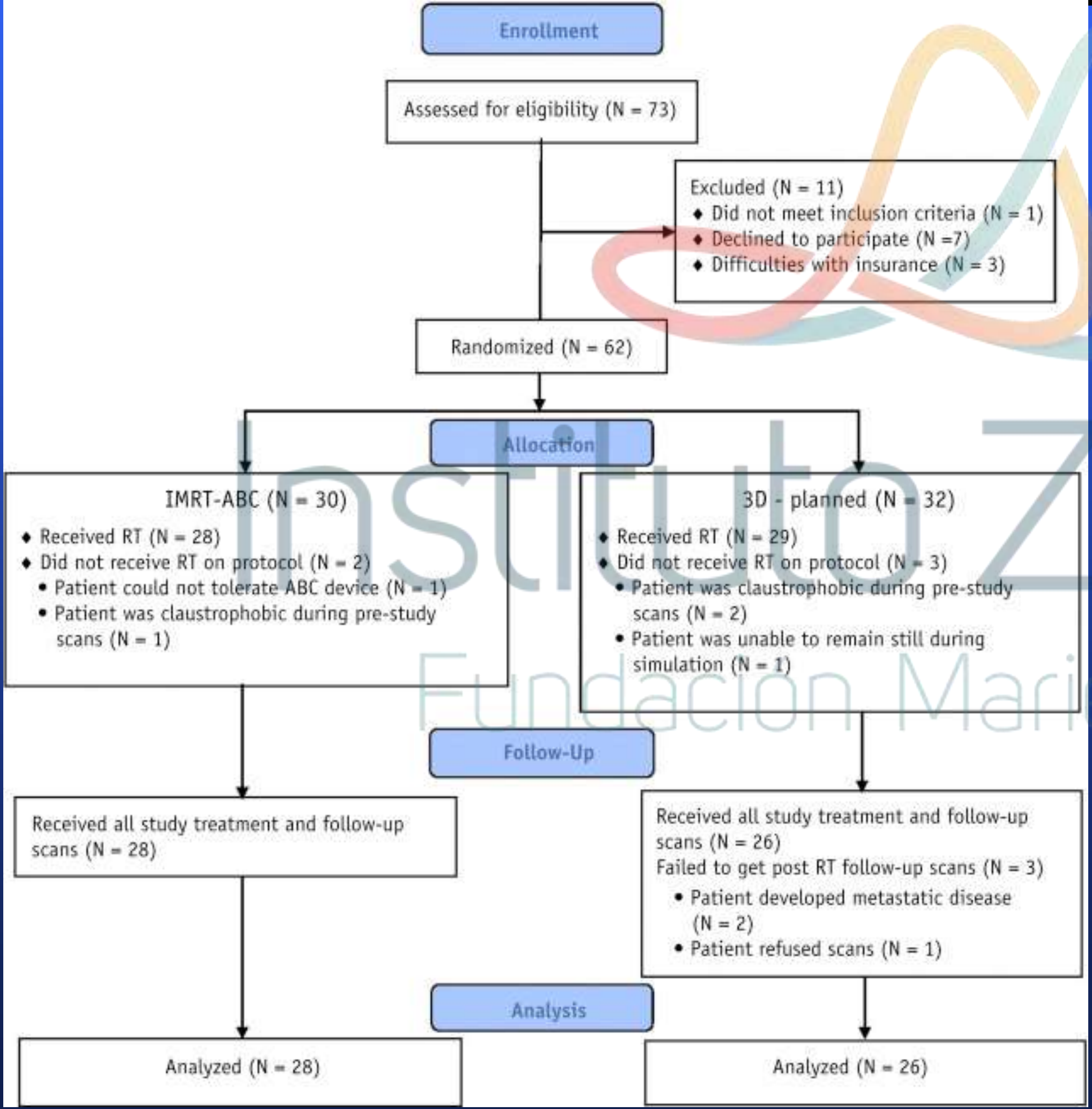

Enrollment

Assessed for eligibility (N = 73)

Excluded (N = 11)
- Did not meet inclusion criteria (N = 1)
- Declined to participate (N =7)
- Difficulties with insurance (N = 3)

Randomized (N = 62)

Allocation

IMRT-ABC (N = 30)
- Received RT (N = 28)
- Did not receive RT on protocol (N = 2)
  - Patient could not tolerate ABC device (N = 1)
  - Patient was claustrophobic during pre-study scans (N = 1)

3D - planned (N = 32)
- Received RT (N = 29)
- Did not receive RT on protocol (N = 3)
  - Patient was claustrophobic during pre-study scans (N = 2)
  - Patient was unable to remain still during simulation (N = 1)

Follow-Up

Received all study treatment and follow-up scans (N = 28)

Received all study treatment and follow-up scans (N = 26)
Failed to get post RT follow-up scans (N = 3)
- Patient developed metastatic disease (N = 2)
- Patient refused scans (N = 1)

Analysis

Analyzed (N = 28)

Analyzed (N = 26)

Jagsi R et al
Int J Radiat Oncol Bio Phys
101: 1149, 2018

Randomized Comparison of Radiation Therapy Techniques in Management of Node-Positive Breast Cancer: Primary Outcome Analysis

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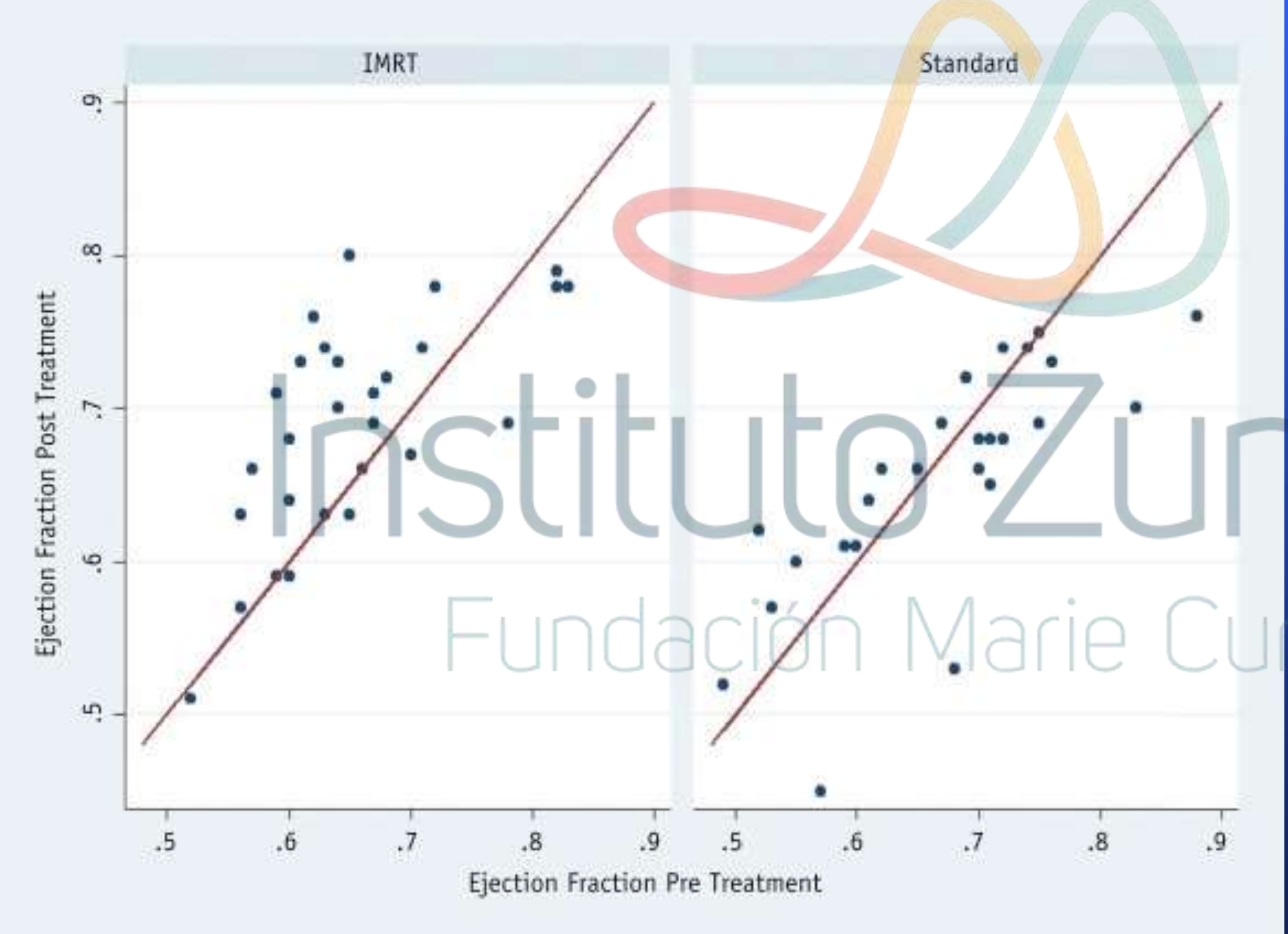

Jagsi R et al
Int J Rad Oncol Bio Phy
101: 1149, 2018

RADIATION-INDUCED CARDIAC TOXICITY IN PATEINTS TREATED FOR BREAST CANCER

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Conclusions

- Risk Factors that increase incidence of these events
- Screening Recommended in Hi-Risk Patients
- Limit Radiation dose to less than 5 Gy (Heart and
- Coronary vessels
- Limit Volume of Heart irradiated to less than 5 %
- Use Modern Radiation Therapy Techniques
- Follow patients (20 years or longer) and when indicated evaluate Cardiac Function (Perfusion/ other studies)

MUCHAS GRACIAS POR VUETRA ATENCION Y ESPLENDIDA HOSPITALIDAD

Washington
School of Medicine