Po ASTRO 2018:

RAK PIERSI

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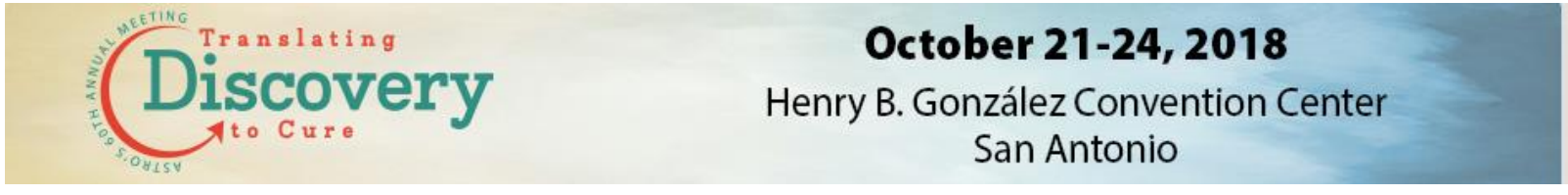


Randomized Trial Evaluating Radiation following Surgical Excision for "Good Risk" DCIS: 12 Year Report from NRG/RTOG 9804

Beryl McCormick, Kathryn Winter, Henry Kuerer, Nour Sneige, Eileen Rakovitch, Barbara Smith, Isabelle Germain, Alan Hartford, Mark O'Rourke, Eleanor Walker, Eric Strom, James Atkins, Lori Pierce, Anthony Pu, Kenneth Sumida, Danny Vesprini, Jennifer Moughan, Julia White

ASTRO October 21, 2018

Background and Rationale

- All prior reported prospective randomized trials comparing radiation (RT) to no RT included patients with both low grade, small, mammographically detected DCIS and larger, higher nuclear grade and symptomatic cases (EORTC, NSABP)
- RTOG 9804 included only "good risk" patients, detected by mammogram, defined by size ≤ 2.5 cm, final margins ≥ 3 mm, and low or intermediate nuclear grade

NRG ONCOLOGY™

„Good risk" DCIS

Primary Objective

In the defined good risk group, was to assess the role of whole breast RT compared to no RT, in decreasing local failure, both invasive and in situ, and preventing the need for mastectomy

NRG ONCOLOGY™

„Good risk" DCIS

Age and Pathology

	Observation (n=317)	RT (n=312)
Age		
< 50	69 (21.8%)	60 (19.2%)
≥ 50	248 (78.2%)	252 (80.8%)
Final Microscopic Margins		
3mm - 9mm	111 (35.0%)	110 (35.3%)
≥ 10mm	50 (15.8%)	51 (16.3%)
Negative by negative re-excision	156 (49.2%)	151 (48.4%)
Mammographic Size of Primary		
≤ 1cm	229 (72.2%)	223 (71.5%)
> 1cm	88 (27.8%)	89 (28.5%)
Nuclei Grade		
NG1	141 (44.5%)	135 (43.3%)
NG2	176 (55.5%)	177 (56.7%)

Whole Breast Irradiation Details

Total Dose	Dose per fraction	# of fractions	n (%)
50 Gy	2 Gy	25	110 (35.3%)
50.4 Gy	1.8 Gy	28	155 (49.7%)
42.5* Gy	2.65 Gy	16	28 (9.0%)
		<16	3 (1.0%)
		>28	1 (0.3%)
No RT			15 (4.8%)

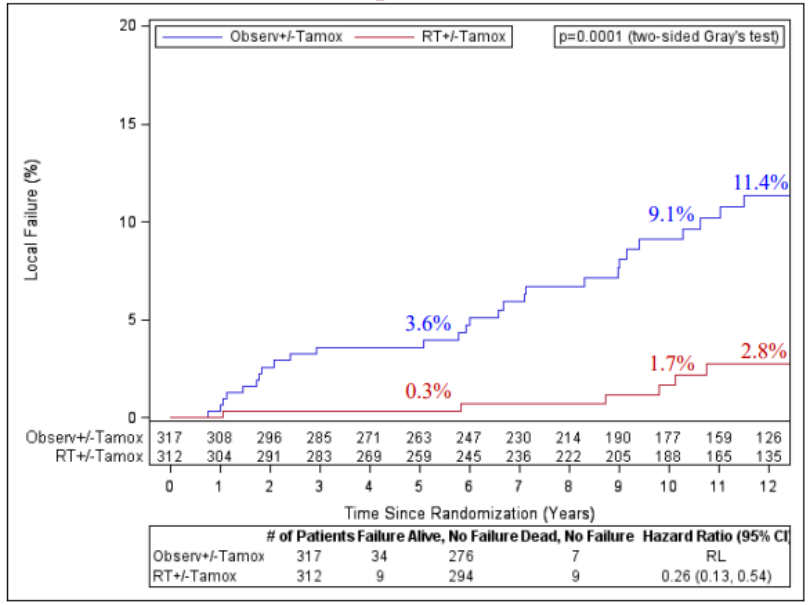
- No Boost

*Added in 12/2001 to allow Canadian NCIC (now CCTG) participation

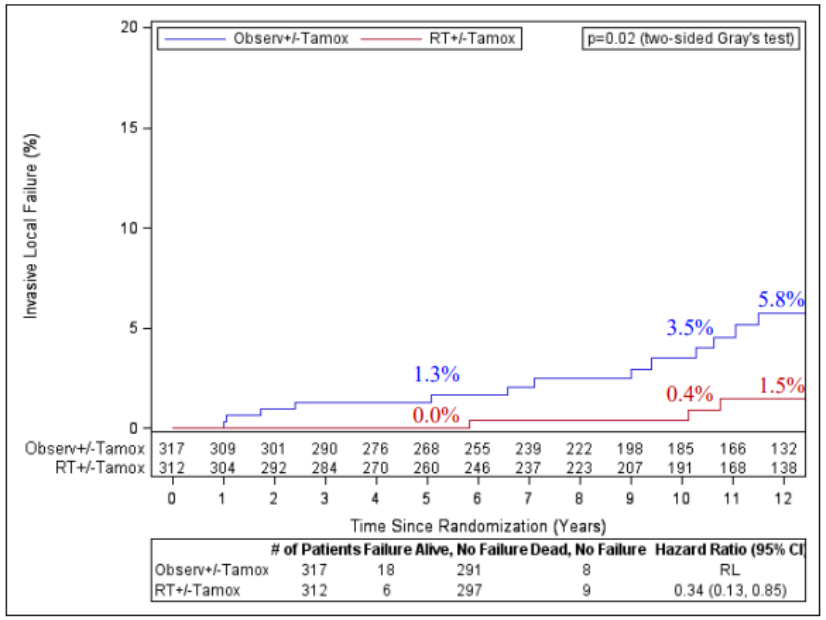
- FINAL TAMOXIFEN USE:

  58% in RT group and 66% in No RT group (p=0.05)

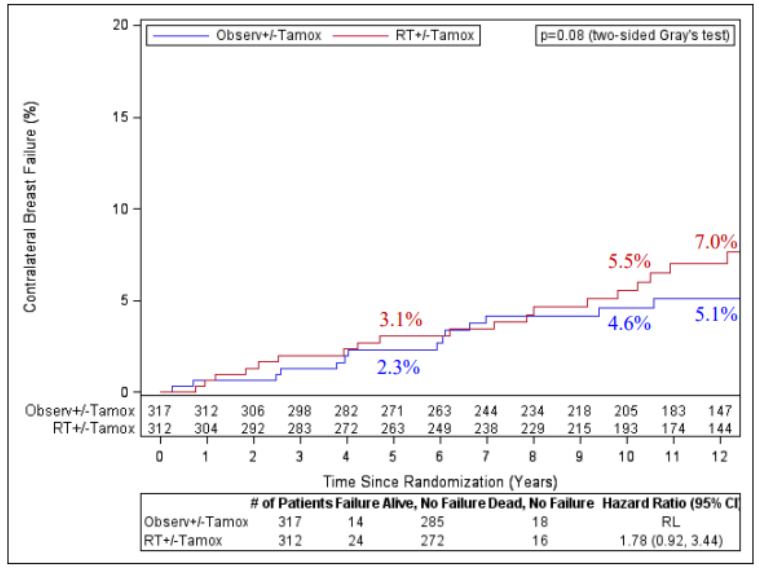
Local Failure: Ipsilateral Breast



Invasive Local Recurrence



Contra-Lateral Breast Events



„Good risk” DCIS

Conclusions

- In this defined “good risk” DCIS population, the addition of whole breast radiation following breast conservation surgery significantly reduced the risk of any local recurrence and of invasive local recurrence
- The larger than expected reduction has yielded meaningful results despite not meeting original targeted accrual
- As with other DCIS trials, NO BOOST was used

For Discussion

- This information should be used to inform a meaningful patient-doctor discussion that includes risks, benefits and the patient’s own degree of comfort, which varies greatly, with regards to local control with and without radiation.
- Endocrine therapy for ER+ DCIS should be part of this discussion.

Inwazyjny rak piersi - Główne koncepcje

- Krótszy czas leczenia – wyższe dawki – hipofrakcjonacja, SBRT

- RT personalizowana
  - przewidywanie tox
  - de-eskalacja dawki RT
  - Wpływ układu immunologicznego

FAST phase III randomised controlled trial of radiotherapy hypofractionation for treatment of early breast cancer: 10-year results (CRUKE/04/015)

Professor Murray Brunt

University Hospitals of North Midlands and Keele University, UK

Joanne Haviland, Mark Sydenham, Hafiz Algurafi, Abdulla Alhasso, Peter Bliss, David Bloomfield, Marie Emson, Andy Goodman, Adrian Harnett, Helen Passant, Yat Tsang, Duncan Wheatley, Judith Bliss, John Yarnold

ASTRO October 2018

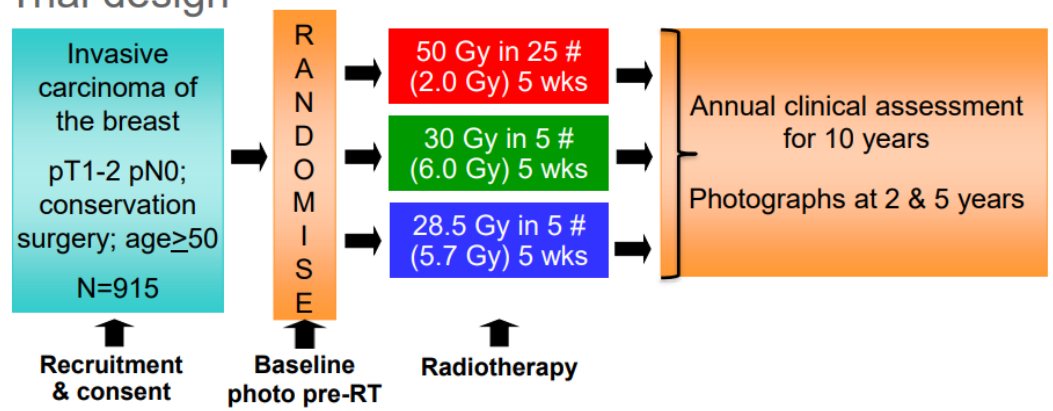
FAST

Aim of FAST trial

To test a 5-fraction regimen of whole breast RT against 25 fractions of 2.0Gy after local excision of early breast cancer in terms of:

- late normal tissue responses
- local tumour control

Trial design



Primary endpoint:
- 2-year change in photographic breast appearance

Secondary endpoints:
- 5-year change in photographic breast appearance
- clinical assessments of late AEs
- ipsilateral local tumour control

FAST

Baseline and treatment characteristics (N=915)

		50Gy/25# N=302 (%)	30Gy/5# N=308 (%)	28.5Gy/5# N=305 (%)
Age (years)	**Mean (SD) [range]**	63.1 (7.2) [50 - 88]	62.9 (7.5) [50 - 84]	62.7 (6.8) [50 - 82]
Grade	**1**	31	37	34
	2	59	52	55
	3	10	11	11
Pathological tumour size, cm	**<1**	30	27	29
	1-2	55	54	52
	≥2	15	19	19
Histological type	**Ductal**	76	78	75
Adjuvant therapy	**None**	13	12	10
	Tamoxifen	75	79	73
	AI	10	8	15
	Tamoxifen → AI	1	1	1

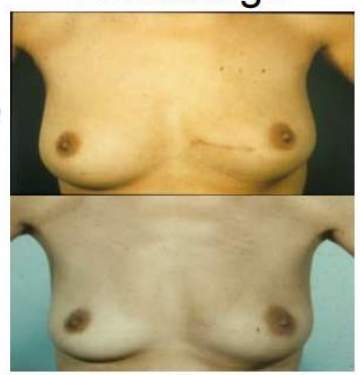
What we mean by' *no change*' and '*marked change*' after breast radiotherapy

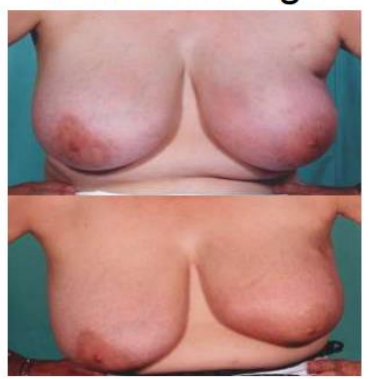
'No change'

'Marked change'

After surgery, before RT…

Years later…



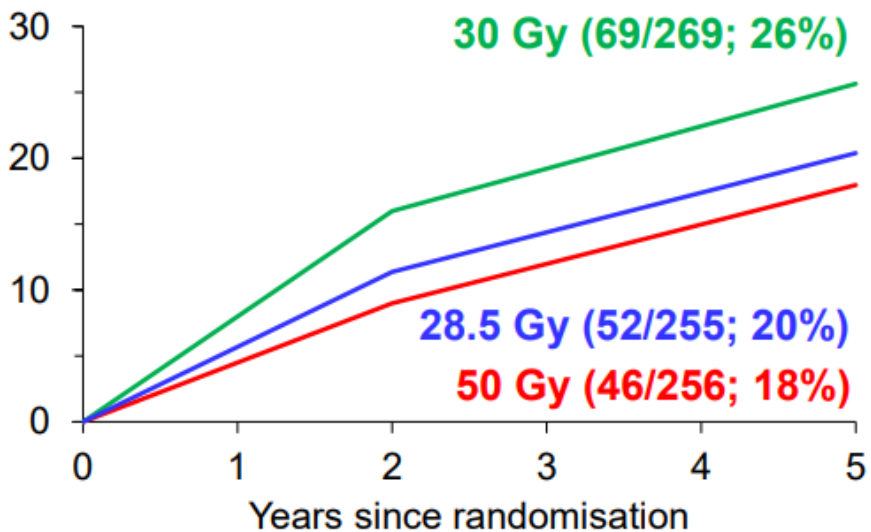


Courtesy of John Yarnold

FAST

Photographic assessment of overall change in breast appearance by 5 years

% with mild / marked change in breast appearance

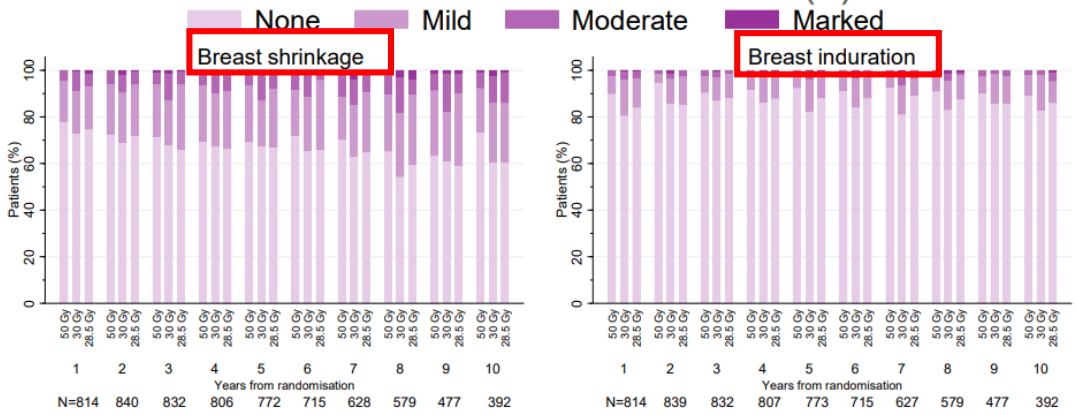


	Difference (95%CI)
30Gy vs **50Gy**	+7.4% (0.3, 16.7) p=0.03
28.5Gy vs **50Gy**	+2.4% (-3.8, 10.8) p=0.47

Marked changes: 2%, 4%, 2%

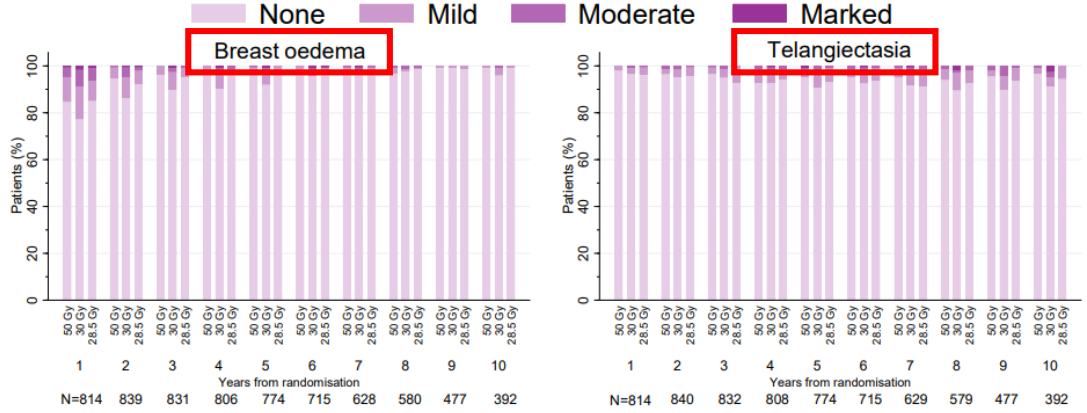
FAST

Clinical assessments of late AE in breast (1)



	OR for moderate/marked shrinkage (95%CI)	OR for moderate/marked induration (95%CI)
30Gy vs 50Gy	1.88 (1.32, 2.67), p<0.001	2.39 (1.31, 4.35), p=0.004
28.5Gy vs 50Gy	1.11 (0.76, 1.64), p=0.59	1.67 (0.89, 3.16), p=0.11

Clinical assessments of late AE in breast (2)



	OR for moderate/marked oedema (95%CI)	OR for moderate/marked telangiectasia (95%CI)
30Gy vs 50Gy	3.70 (1.86, 7.35), p<0.001	2.68 (1.13, 6.34), p=0.02
28.5Gy vs 50Gy	1.92 (0.91, 4.07), p=0.09	0.78 (0.26, 2.35), p=0.66

FAST

Comparison of schedules at 5 & 10 years: any clinically-assessed AE in breast

	5 years; N=774		10 years; N=392	
	% any moderate/ marked AE in breast	Difference compared with 50Gy (95%CI)	% any moderate/ marked AE in breast	Difference compared with 50Gy (95%CI)
50Gy/25#	7%	-	9%	-
30Gy/5#	18%	+10.5% (4.9, 16.1) p<0.001	18%	+9.4% (1.1, 17.6) p=0.04
28.5Gy/5#	10%	+2.4% (-2.5, 7.3) p=0.42	15%	+5.5% (-2.3, 13.3) p=0.23

Relapse and survival at median 10 years' follow-up

	50Gy/25# N=302	30Gy/5# N=308	28.5Gy/5# N=305	Total N=915
Local relapse	3	4	4	11
Regional relapse	2	0	3	5
Distant relapse	17	15	15	47
Death (breast cancer)	30 (7)	33 (8)	33 (10)	96 (25)

Estimate of 10-year local relapse rate: 1.3% (95%CI 0.7, 2.3%)

FAST

- Wnioski
  - Istotne późne AEs – rzadkie
  - AEs po D -28,5Gy /5fr / 5 tyg podobne do tych, obserwowanych po D - 50Gy / 25fr / 5 tyg
  - Niewielkie różnice w częstości i nasileniu AEs po 5 i po 10 latach
  - LR bardzo rzadkie we wszystkich grupach
  - 5 x 5,5 Gy / co tydzień może być rozważona, gdy brak możliwości 3 lub 5 tygodni trwającej RT frakcjonowanej codziennie
  - Badanie UK FAST-Forward aktualnie testowana RT: 5 x 5,5Gy w ciągu 1 tygodnia

Inwazyjny rak piersi - Główne koncepcje

- Krótszy czas leczenia – wyższe dawki – hipofrakcjonacja, SBRT

- RT personalizowana
  - przewidywanie tox
  - de-eskalacja dawki RT
  - Wpływ układu immunologicznego

New Paradigm for SBRT in Breast Cancer

NRG-BR001: A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases

Steven J Chmura, MD, PhD[1], Kathryn A Winter, MS[2], Joseph K Salama, MD[3], Clifford Robinson, MD[4], Thomas M. Pisansky, MD[5], Virginia Borges, MD[6], Hania Al-Hallaq, PhD[1], Martha Matuszak, PhD[7], Sean S Park, MD[5], Victor Gonzalez, MD[8], Yasmin Hasan, MD[1], Jose Bazan, MD[9], Philip Wong, MD[10], Harold A Yoon, MD[11], Janet K Horton, MD[3], Gregory N Gan, MD PhD[12], Michael T Milano, MD, PhD[13], Elin Ruth Sigurdson, MD[14], Jennifer Moughan, MS[2], Julia White, MD[9]

[1] University of Chicago Comprehensive Cancer Center; [2] NRG Oncology Statistics and Data Management Center/ACR; [3] Duke University Medical Center; [4] Washington University in St. Louis; [5] Mayo Clinic; [6] University of Colorado – Anschutz Medical Center; [7] University of Michigan; [8] University of Arizona Medical Center – University Campus; [9] Ohio State University Comprehensive Cancer Center; [10] Centre Hospitalier de l'Université de Montréal; [11] Heartland Cancer Research NCORP; [12] University of New Mexico Comprehensive Cancer Center; [13] University of Rochester; [14] Fox Chase Cancer Center

ASTRO Annual Meeting: 10/24/2018

Oligometastases

- Defined as metastases limited in number/destination organ and volume
- Described by Dr.'s Hellman and Weichselbaum in 1995
- Associated with better prognosis in prospective surgical and early SBRT series
- Translational research supports more indolent biology earlier in the metastatic cascade

Chmura et al, 2018

Hellman and Weichselbaum, J Clin Oncol 13:8 (1995)

Oligometastases (cont'd)

- Predominantly retrospective studies of metastectomy have demonstrated improved outcome in addition to systemic therapy for liver and lung metastasis
- SBRT increasingly used for asymptomatic metastasis securing durable in-field control
- Survey of > 1000 Radiation Oncologists N. America, Europe, ASIA: 61% using SBRT for treatment of OGM
- Can SBRT to all oligometastasis in addition to systemic therapy improve survival?

Chmura et al, 2018

Lewis et al, Am J Clin Oncol 2015

Limited Prospective safety data SBRT >2 metastases

- Prospective trials treated a median of 1.5 metastases

- ***All differ in***
  - IGRT use
  - OAR constraints
  - Dealing with metastases with overlapping PTV
  - Dealing with Prioritization of PTV vs OAR

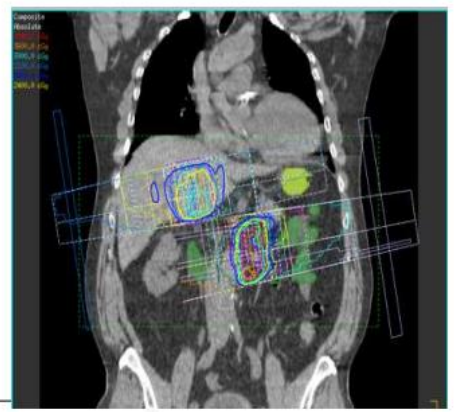


Table 2. Selected Studies of Oligometastatic Patients Treated With Irradiation of All Known Metastases

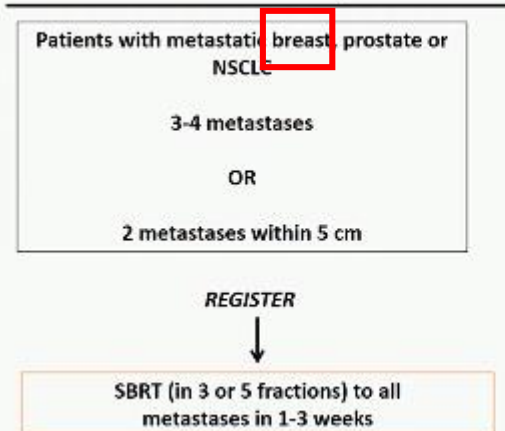
Study	No. of Patients	No. of Metastases per Patient		Dose (Gy)		Follow-Up (months)		Metastasis Control (%)	OS (%)	Toxicity Grade ≥ 3 (%)
		Median	Range	Total	No. of Fractions	Median	Range			
Mt Sinai (New York, NY)[82]	21	1	1-5	40-60	10	10	2-18	1 year: 85	1 year: 75	NA
University of Rochester (Rochester, NY)[41]	121	2	1-5	50	10	85	55-125*	2 years: 67	4 years: 28	1†
University of Chicago (Chicago, IL)[20]	61	2	1-5	24-48	3	21	3-61	2 years: 53	2 years: 57	10†
Vrije University (Brussels, Belgium)[83]	309	2	1-5	40-50	10	12	1-84	2 years: 33	3 years: 32	NS

Abbreviations: NA, not applicable; NS, not stated; OS, overall survival.
*Surviving patients with breast cancer.
†Crude rate.

Salama JK and Milano MT JCO 2014;32:2902--2912

Chmura et al ASTRO 2018

Study Schema/Eligibility



- Metastatic Breast, NSCLC and Prostate pts
- One of 3 criteria:
  - 3-4 radiographically distinct mets
  - 2 radiographically distinct metastases anatomically close (i.e., within ≤ 5 cm)
  - 1 radiographically distinct metastasis, which was anatomically close (i.e., ≤ 5 cm) to a surgically resected metastases
- 30-day washout of systemic therapy prior to SBRT
- Concurrent hormonal therapy and some other standard agents allowed

Chmura et al ASTRO 2018

Patients and Tumor Characteristics

- **42** patients enrolled/**35** evaluable for DLT assessment
  - 60% with 3-4 mets, 20% with 2 anatomically close mets, 6% with 3-4 distinct mets, 2-3 treated with SBRT and other(s) surgically removed
  - Number of distinct mets: 34% two, 60% three, 6% three
  - 69% >/= 60 years old
  - 34% breast
  - Median number of mets treated on trial: **3**

Chmura et al ASTRO 2018

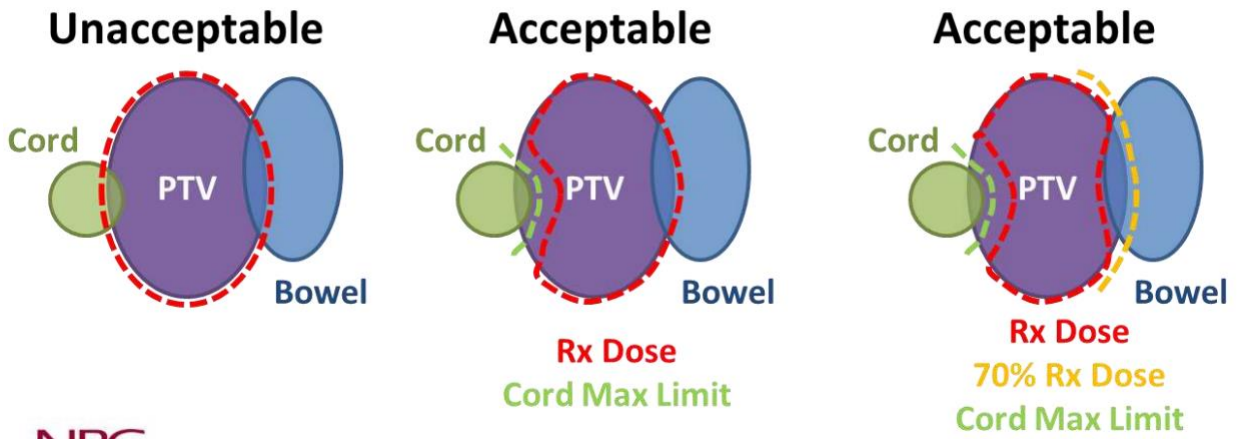
Established starting RT doses/fractions for different sites

Metastatic Location	Initial Starting Dose	Dose De-escalation
Lung – Peripheral	45 Gy (3 fxs)	42 Gy (3 fxs)
Lung – Central	50 Gy (5 fxs)	47.5 Gy (5 fxs)
Mediastinal/Cervical Lymph Node	50 Gy (5 fxs)	47.5 Gy (5 fxs)
Liver	45 Gy (3 fxs)	42 Gy (3 fxs)
Spinal/Paraspinal	30 Gy (3 fxs)	27 Gy (3 fxs)
Osseous	30 Gy (3 fxs)	27 Gy (3 fxs)
Abdominal-pelvic	45 Gy (3 fxs)	42 Gy (3 fxs)

** Because PTVs can overlap with OAR, the protocol provides guidance on what to prioritize in such cases*

Chmura et al ASTRO 2018

NRG-BR001 SBRT Planning: Flexible Prioritization of PTV or OAR



NRG ONCOLOGY™

Al-Hallaq et al. 2016 Nov - Dec;6(6):e291-e298.

Low toxicity for multi-site oligometastatic treatment

Metastatic Location	#Enrolled for DLT Assessment	#Evaluable for DLT Assessment	#DLTs
Bone/Osseous Starting Dose	8	6	0
Spinal/Paraspinal Starting Dose	7	6	0
Peripheral Lung Starting Dose	7	6	0
Abdominal-pelvic Starting Dose	9	7†	0
Central lung Starting Dose	8	7†	0
Liver Starting Dose	9	5	0
Mediastinal/Cervical Starting Dose	7	6	0

Chmura et al ASTRO 2018

#ASTRO18

48 grade ≥ 3 AEs regardless of relationship to treatment in 16 patients

- 7 grade ≥ 3 AEs in 6 patients ***mechanistically related*** to treatment

Mechanistically Treatment-Related AEs

Location(s) to Which Patient Contributed	Adverse Events (attribution)	Days from SBRT start	
Abdominal-pelvic and Liver	Grade 3 Gastric Ulcer (probable)	131	≤ 6 months
Peripheral Lung, Central Lung, and Mediastinal/Cervical	Grade 3 Pneumonitis (probable)	125	≤ 6 months
	Grade 3 Pulmonary fibrosis (possible)	243	> 6 months
Peripheral Lung and Central Lung	Grade 3 Bone pain (definite)	362	> 6 months
Central Lung	Grade 3 Bronchial fistula (definite)	337	> 6 months
Bone/Osseous and Abdominal-pelvic	Grade 3 Fracture [right humerus] (definite)	556	> 6 months
Bone/Osseous and Central Lung	Grade 3 Bronchial stricture (definite)	496	> 6 months

Chmura et al ASTRO 2018

Wnioski

- SBRT 3-4 mts lub 2 położonych blisko siebie – jest bezpieczna
- Późno pojawiające się powikłania – konieczność dłuższej obserwacji
- Badanie dało podstawę do rozpoczęcia badań randomizowanych:
  - NRG-BR002
  - Alliance A09156
  - 7 badań SBRT/immuno

Inwazyjny rak piersi - Główne koncepcje

- Krótszy czas leczenia – wyższe dawki – hipofrakcjonacja, SBRT

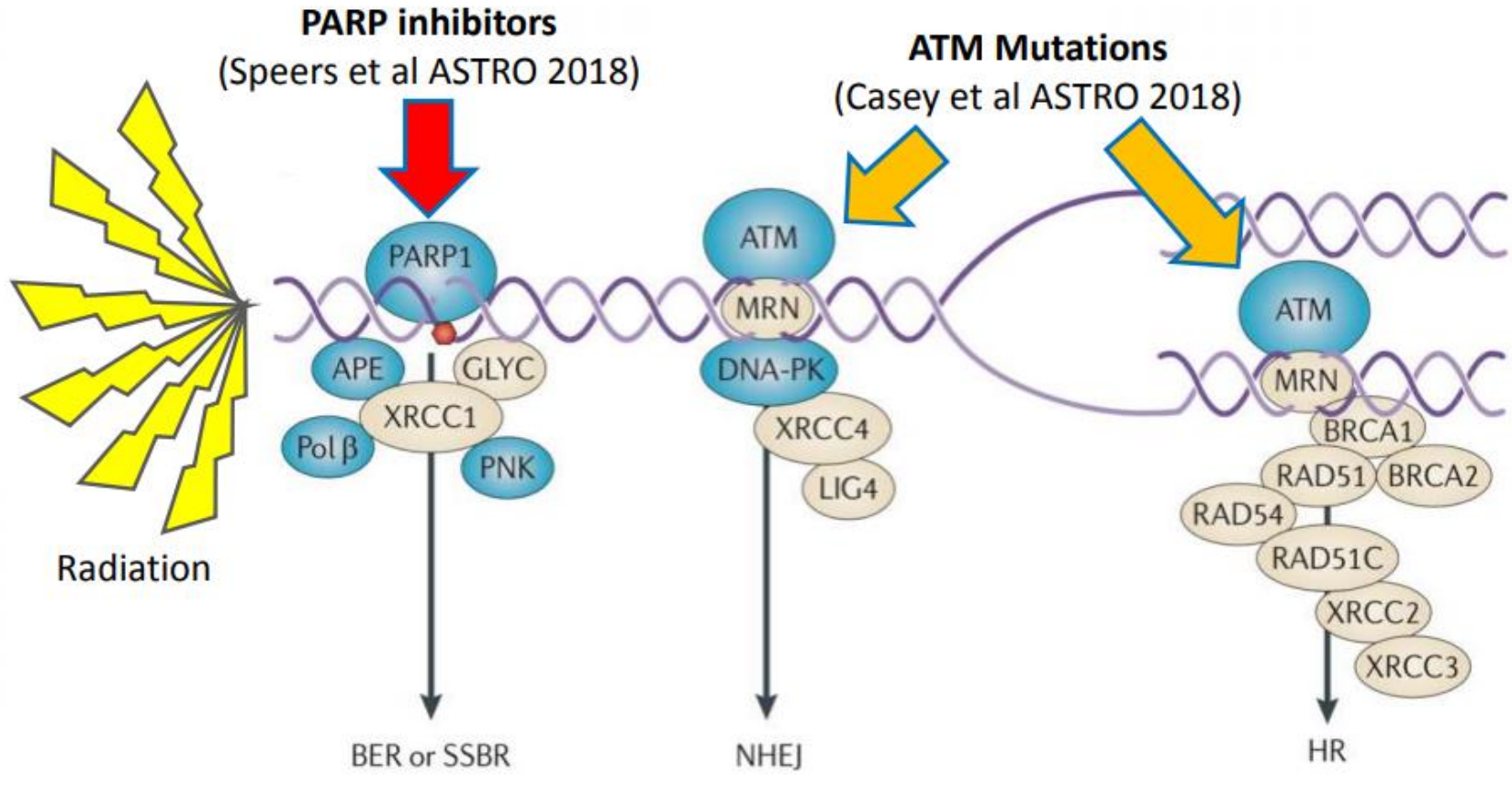
- RT personalizowana
  - przewidywanie tox
  - de-eskalacja dawki RT
  - Wływ układu immunologicznego na efekty leczenia

RT - Miecz o dwóch ostrzach:

- Co dzieje się wewnątrz napromienionej komórki – uszkodzenie DNA
  - DDR: PARP, ATM

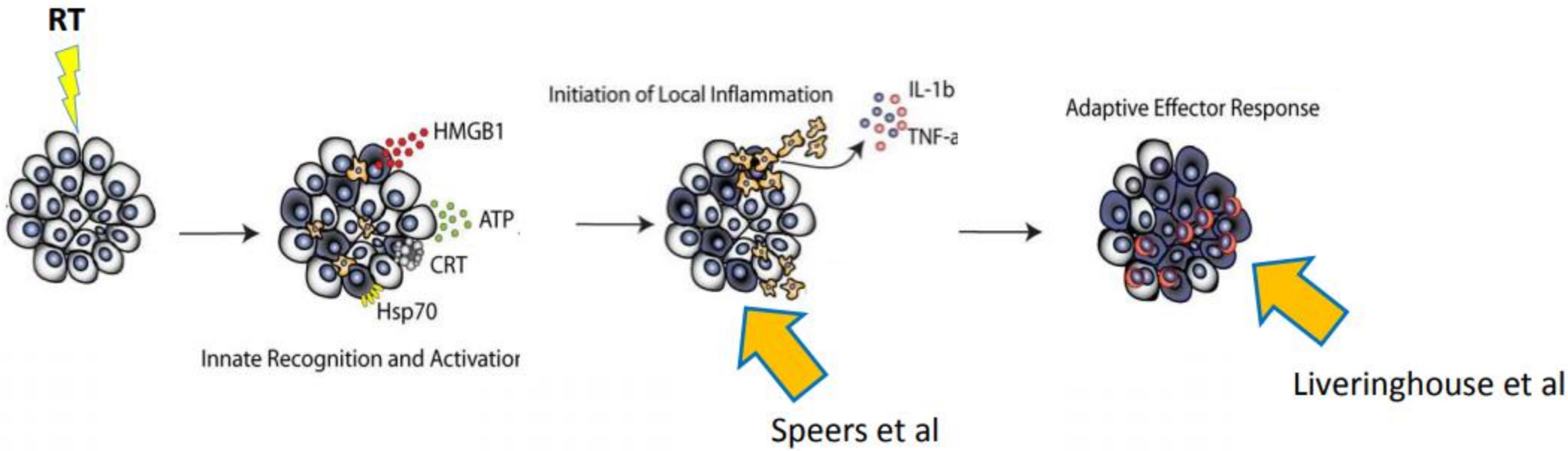
- Co dzieje się poza komórką napromienianą: odpowiedź guz/gospodarz na napromienioną (uszkodzoną) komórkę - zapalenie

Cell-Intrinsic Effects of Radiation (DNA Damage)



Begg et al *Nat Rev Cancer* 2011

Cell-Extrinsic Effects of Radiation (Inflammation)



Shiao et al *Genes Dev* 2011

Gene expression changes predict acute and late toxicity to combined PARP1 inhibition and radiation (RT) in high risk breast cancer patients- results of the biomarker analysis of TBCRC 024.

Corey Speers MD, PhD

on behalf of Ben Chandler, Eric Olsen, Leah Moubadder, Dafydd G Thomas, Meilan Liu, Kent A. Griffith, Jennifer R. Bellon, Wendy A. Woodward, Janet K. Horton, Alice Ho, Beth Overmoyer, Michael Sabel, Anne F. Schott, Felix Y. Feng, Lori J. Pierce*, Reshma Jagsi*and the Translational Breast Cancer Research Consortium

Clinical Context

- Local chest wall recurrence of breast cancer after mastectomy is high in select subsets
  - women with inflammatory breast cancer
  - TNBC with residual disease following neoadjuvant chemotherapy
- More effective locoregional therapies represent critical unmet clinical need→ radiosensitization strategies.

Speer et al ASTRO 2018

- PARPi (Veliparib) preferentially radiosensitizes breast cancer (vs. normal) cells with enhancement ratios up to 2.3
- This radiosensitization is independent of intrinsic BC subtype or BRCA mutational status
- Similar radiosensitization was also demonstrated in Inflammatory Breast Cancer (IBC) models

TBCRC 024: A Multicenter Phase 1 Study of Veliparib Administered Concurrently With Chest Wall and Nodal Radiation Therapy in Patients With Inflammatory or Locoregionally Recurrent Breast Cancer

Reshma Jagsi, Kent Griffith, Jennifer Bellon, Wendy Woodward, Janet Horton, Alice Ho, Felix Feng, Corey Speers, Beth Overmoyer, Michael Sabel, Anne Schott, Lori Pierce for the Translational Breast Cancer Research Consortium

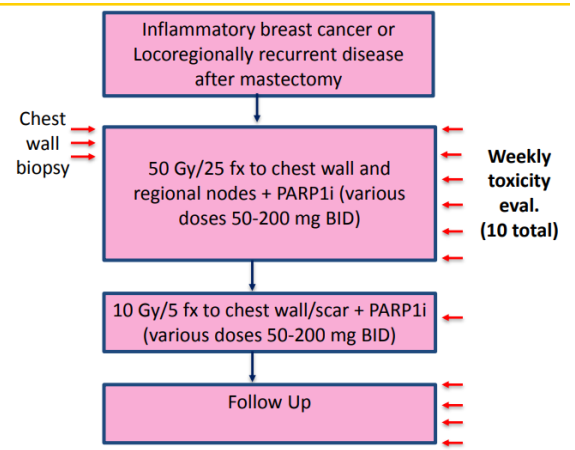
ROGEL CANCER CENTER
MICHIGAN MEDICINE

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Duke Cancer Institute

DANA-FARBER CANCER INSTITUTE

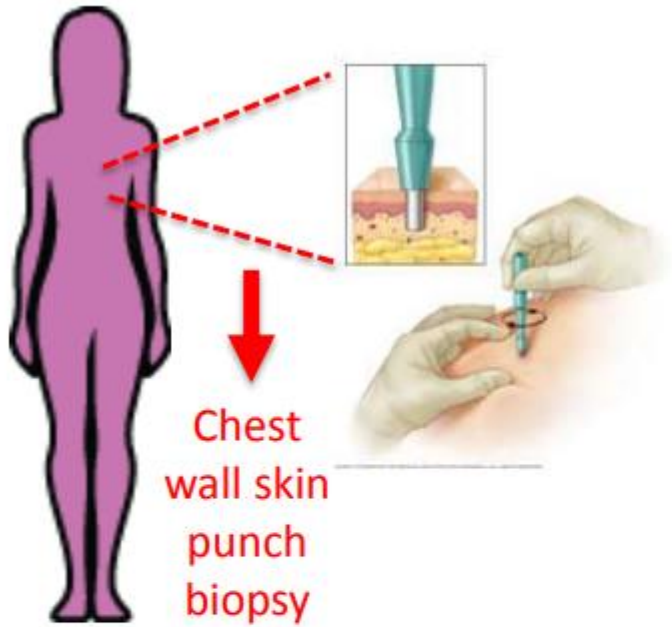
- Sample: 30 Patients with chest wall recurrences or inflammatory breast cancers
- Approach: TITE-CRM
- Endpoints/Measures: acute MTD evaluated based upon the incidence of confluent moist desquamation or other severe CTCAE toxicity
- 10 week observation window for DLTs

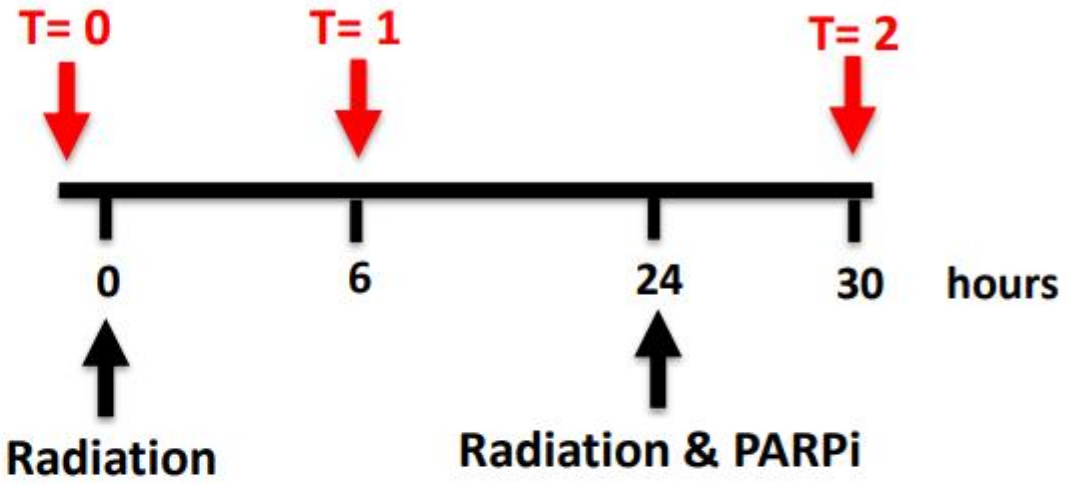


TBCRC 024: A Multicenter Phase 1 Study of Veliparib Administered Concurrently With Chest Wall and Nodal Radiation Therapy in Patients With Inflammatory or Locoregionally Recurrent Breast Cancer

Reshma Jagsi, Kent Griffith, Jennifer Bellon, Wendy Woodward, Janet Horton, Alice Ho, Felix Feng, Corey Speers, Beth Overmoyer, Michael Sabel, Anne Schott, Lori Pierce for the Translational Breast Cancer Research Consortium

- Maximum tolerated dose of veliparib in conjunction with standard chest wall and nodal RT: 200 mg bid (final estimate of toxicity 24%, less than the 30% predicted)
- No grade 4 or 5 events
- Although severe acute toxicity did not exceed 30% even at the highest tested dose, over half of patients developed hyperpigmentation at 1 year (55%) and nearly half of surviving patients (47%) demonstrated grade 3 adverse events at 3 years
- This underscores the importance of long-term monitoring of toxicity in trials of radiosensitizing agents.
- 3 yr local control improved (94%) **BUT** distant control remains an issue (57%)

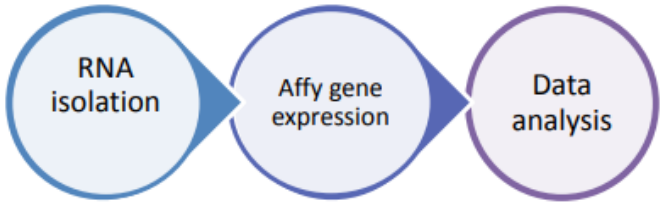




Skin punch biopsies from the irradiated field were taken from patients at:

1. baseline (pretreatment T=0)
2. 6 hrs after first fraction of RT alone (T=1)
3. Veliparib started with second fraction RT and a third punch taken 6 hrs after the second fraction of RT (T=2)

Skin Punch Specimen



paired linear models with probeset filtering on variance at <0.2. Significant probesets defined as fold change ≥1.5, adjusted p-value <.05, FDR 5%.

↑increased expression
↓decreased expression

- **31 genes whose expression was significantly different 6 hrs after RT; 54 genes differed after combined treatment**
  - Diffentially expressed genes including those associated with DNA damage repair (↑ATM, ↑XPC, ↑MDM2, ↑APOBEC3C ↑POLH, ↑CyclinG1) and proliferation (↓Ki67, ↓ASPM, ↓TP53TG1).
- **67 genes were associated with acute toxicity (within 10 weeks)**
  - including overrepresentation of ↑miRNAs associated with gene repression—many of these genes associated with wound response.
- **63 non-overlapping genes were associated with late toxicity (1-3 years)**
  - Genes associated with ↑metabolism, ↑inflammation, and ↓DNA damage

- Ostra toksyczność nie wiązała się z późną toksycznością

- Po raz pierwszy zidentyfikowano w materiale biopsyjnym ze skóry:
  - po RT - zmiany w ekspresji szybko odpowiadających genów
  - Geny związane z ostrą reakcją popromienną i późną toksycznością – przewidywanie toksyczności?
  - Wyniki muszą być zewnętrznie zwalidowane

Clinical Trials Combining RT with PARP Inhibitors

- **SWOG 1706 (Jagsi)**: Phase 2 trial of RT +/- **olaparib** in inflammatory breast cancer patients (n=300); post-neoadjuvant, post-surgery.
- **MSKCC (Khan):** RT + **rucaparib** in TNBC patients with residual disease; post-neoadjuvant chemotherapy, post-surgery.
- **MGH/Dana-Farber (Ho, Bellon):** RT + **niraparib** in TNBC patients with Incomplete Pathologic Response following Neoadjuvant Chemotherapy.

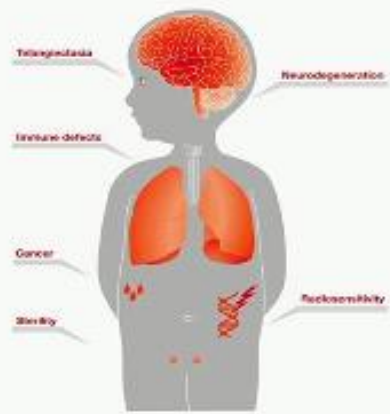
Memorial Sloan Kettering Cancer Center

Pathogenic mutations in *ATM* enhance radio-sensitivity & local control in patients with primary and metastatic breast cancer

D. L. Casey, K. L. Pitter, J. Setton, L. Z. Braunstein, M. E. Robson, J. Reis-Filho, B. Weigelt, C. Lu, S. N. Powell, T. A. Chan, N. Lee, and N. Riaz

Ataxia-Telangiectasia

- Syndrome of Ataxia-Telangiectasia (A-T) first described in the 1920s
- Exquisite radiosensitivity of patients with A-T was observed in the 1960s
- Subsequent discovery of the Ataxia-Telangiectasia-Mutated (*ATM*) gene, which is now known to play a key role in the DNA damage response (DDR) pathway

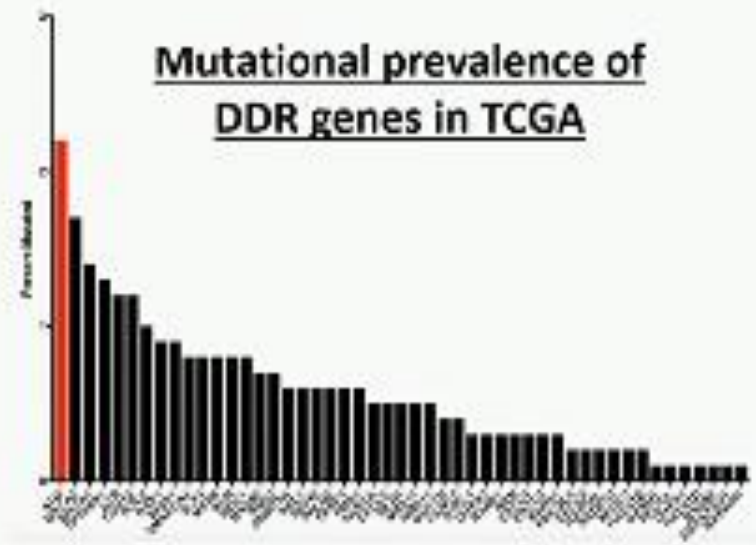


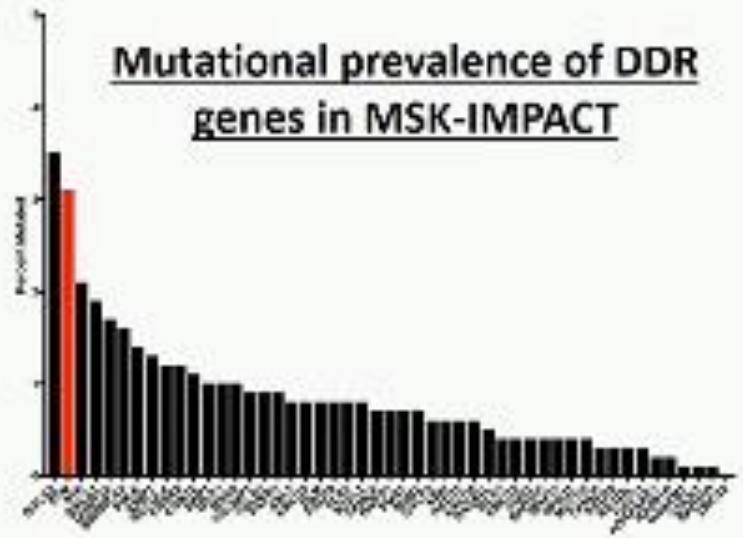
Germline vs Somatic *ATM* Mutations

	Germline Homozygous (A-T)	Germline Heterozygous (Breast Cancer Predisposition)	Somatic Mutation (Phenotype ?)
			
Incidence:	**~1/40,000**	**~1/200**	**~1/30**

ATM is the Most Commonly Mutated DDR Gene in the TCGA in Breast Cancer

2,5-3%

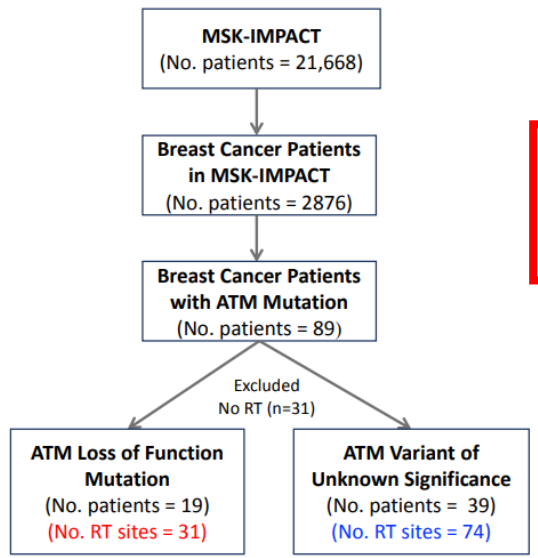




Aim

To determine if breast cancers with somatic ATM mutations have a radiosensitive phenotype

MSK-IMPACT: Breast Cancer



A) No Mutation

B) LoF Mutation: Any mutation that results in a truncating or non-functional protein

C) VUS Mutation: Missense mutation not known to cause a dysfunctional protein

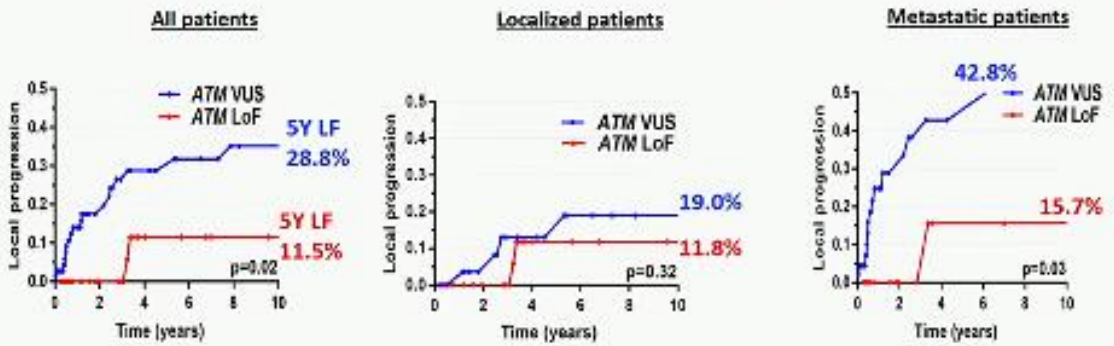
Only 2 patients (3%) in our cohort had a known germline *ATM* mutation

Patient Characteristics

	ATM LoF N=19 pts / 31 sites	*ATM* VUS N= 39 pts / 74 sites	*p*
Age at RT			
Mean	52.4	53.8	0.30
Extent of disease at RT			
Localized	15 (48)	29 (39)	0.38
Metastatic	16 (52)	45 (61)	
Gross disease at time of RT			
No	15 (48)	33 (45)	0.72
Yes	16 (52)	41 (55)	
RT dose (BED, Gy)			
Mean	53.9	50.6	0.33
Receptor status			
ER+/PR+/HER2	15 (48)	56 (76)	0.01
ER+/PR+/HER2+	4 (13)	8 (11)	
ER-/PR-/HER2-	12 (39)	9 (12)	
ER-/PR-/HER2+	0 (0)	1 (1)	

The more profound the damage, the greater the impact on therapeutic responses to RT

Data on local failure rates mirrors in vitro studies where ATM loss has greater RT sensitivity (Li et al *Oncol Rep* 2017, Khanna et al *Oncogene* 1993)



Casey et al ASTRO 2018

Palliative Response and Toxicity

- Patients with LoF mutations who were treated palliatively were more likely to experience lasting symptomatic relief from RT than patients with VUS (p=0.009)
- No differences in grade ≥2 acute toxicity after RT among patients with LoF mutations vs VUS

Casey et al ASTRO 2018

- Zmiany w genach DDR, w tym *ATM* są częste u chorych na raka piersi
  - Ok 30 % - mutacje w DDR
  - 3% chorych – mutacja w genie *ATM*

- U chorych z mutacją genu *ATM* typu LoF– lepsza LC niż u chorych z mutacją typu missense

- Ostra i późna tox podobna po RT

- LoS mutacja genu *ATM – nowy marker radiowrażliwości u chorych na raka piersi*
  - *leczenie personalizowane?*
  - *De-esklacja dawki RT?*

Locoregional Recurrence is Associated with Genomic Down-regulation of the Immune Response in Women with Locally Invasive Breast Cancer

C.L. Liveringhouse[1], J.D. Purcell[2], M.N. Mills[1], R. Diaz[2] and T.J. Robinson[2]

[1]University of South Florida, Tampa, FL [2]Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL

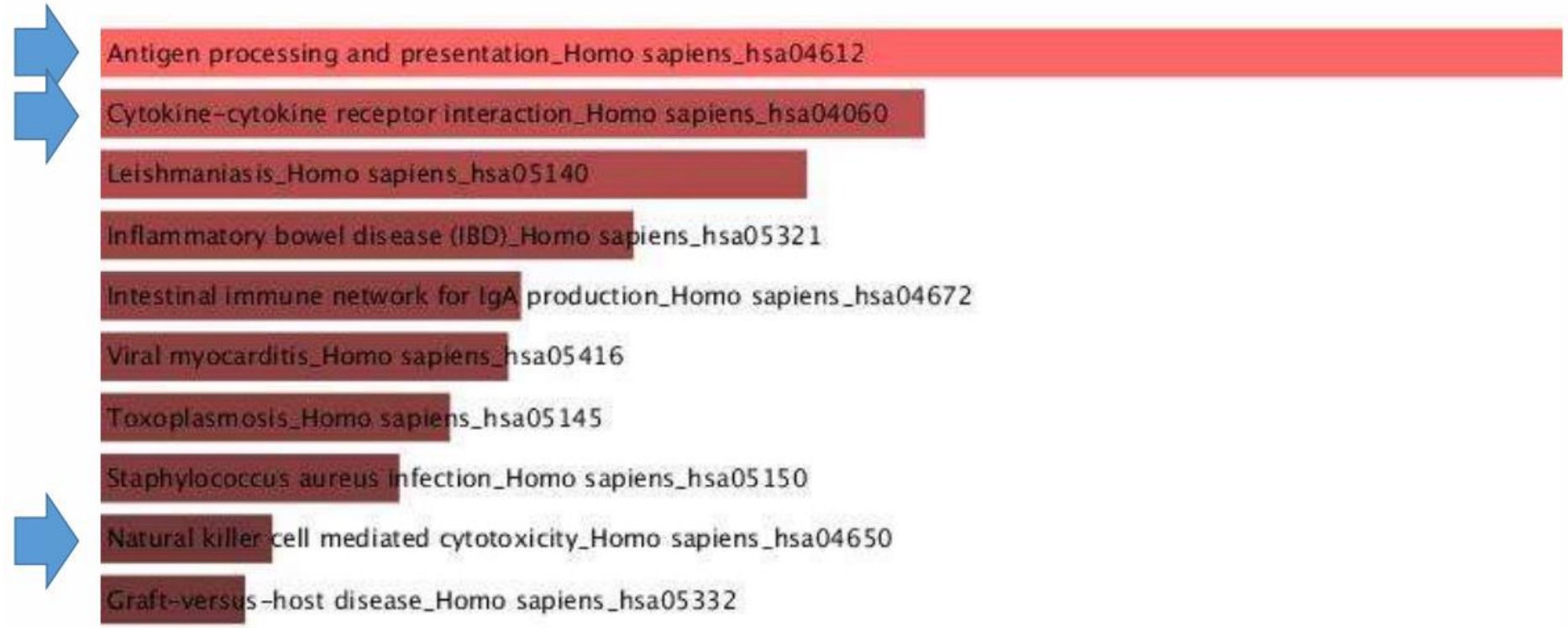
Variable	Overall (N=588)	ER- (n=145)	ER+ (n=443)	P
Primary Treatment:				0.200
Mastectomy Alone	214 (36.4%)	61 (42.1%)	153 (34.5%)	
Mastectomy + PMRT	115 (19.6%)	20 (13.8%)	95 (21.4%)	
Lumpectomy + WBRT	238 (40.5%)	59 (40.7%)	179 (40.4%)	
Chemotherapy:				<0.001
Yes	345 (58.8%)	121 (83.4%)	224 (50.7%)	
Herceptin:				
Yes	85 (14.7%)	29 (20.4%)	56 (12.8%)	

588 chorych, ER+ i ER- profilowanie genetyczne

- 241 genes associated with LRR in ER- (P<0.001)
- 203 genes associated with LRR in ER+ (P<0.001)

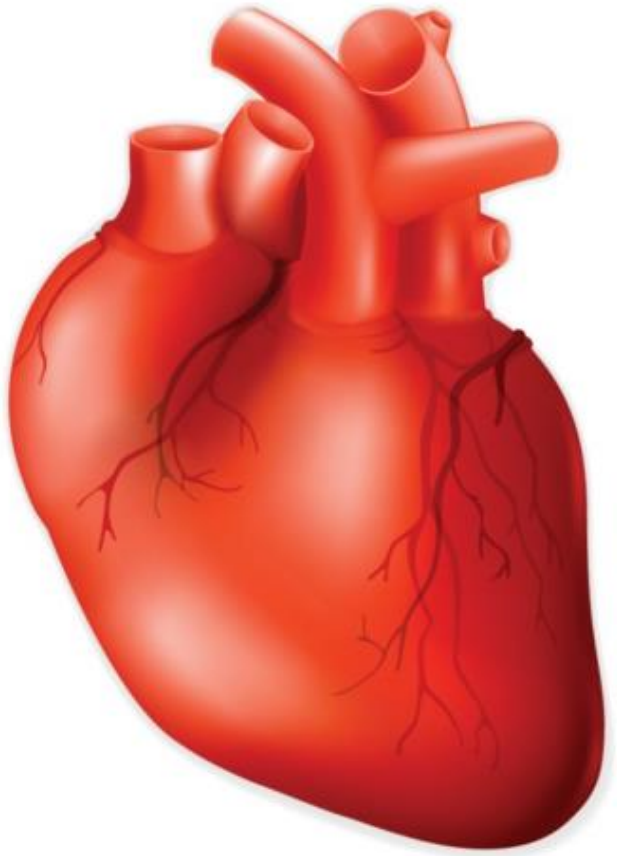
- Pathway analysis of up-regulated genes associated with LRR in ER+ tumors

W rakach piersi ER /-/ zmniejszona ekspresja genów odpowiedzialnych za odpowiedź immunologiczną - związana z LRR



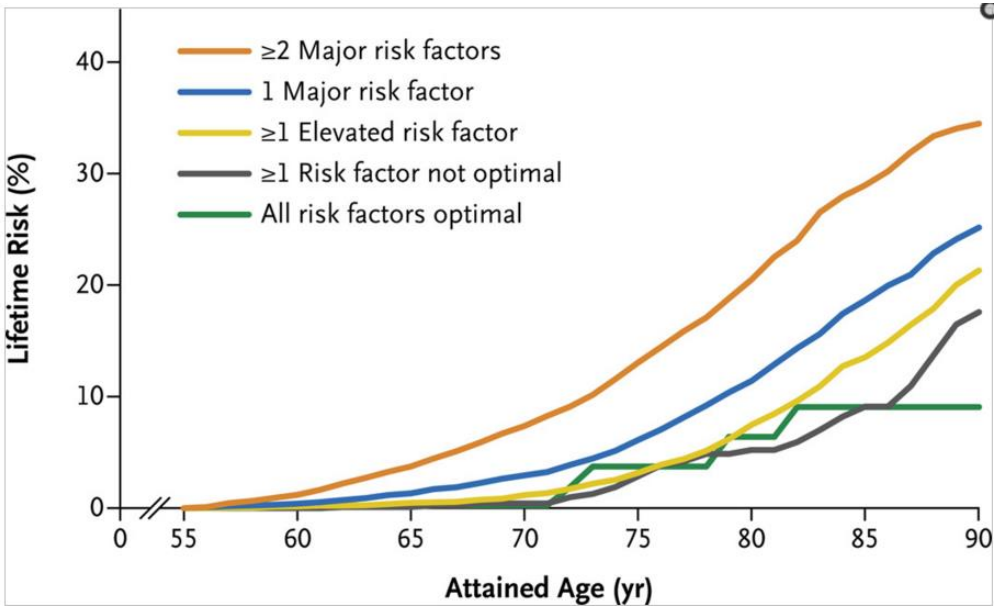
- Pathway analysis of down-regulated genes associated with LRR in ER- tumors

Toksyczność - serce



Ryzyko choroby niedokrwiennej serca

- Cukrzyca
- nadRR
- Wysoki cholesterol
- Papierosy



- Wzrost z 1,5-9% do ok. 30%

N Engl J Med. 2012 January 26; 366(4): 321–329.

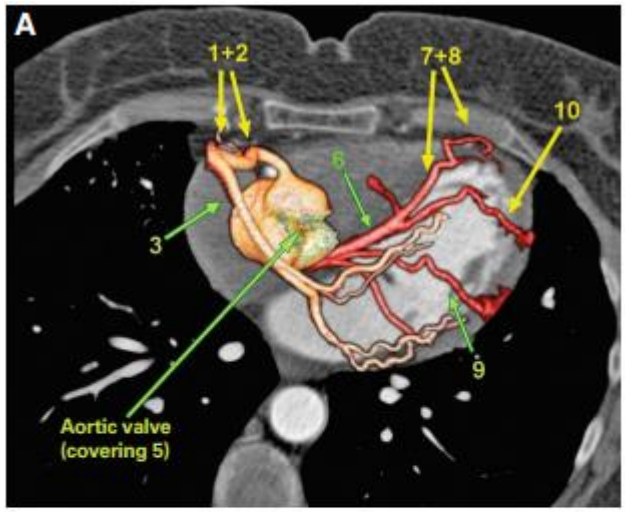
VOLUME 30 · NUMBER 4 · FEBRUARY 1 2012

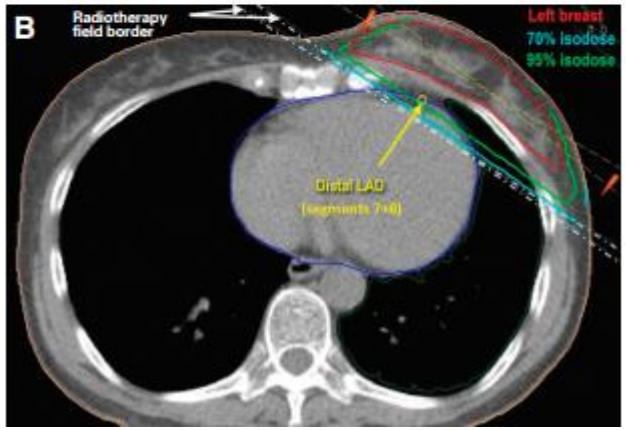
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Distribution of Coronary Artery Stenosis After Radiation for Breast Cancer

Greger Nilsson, Lars Holmberg, Hans Garmo, Olov Duvernoy, Iwar Sjögren, Bo Lagerqvist, and Carl Blomqvist





Location of Coronary Events From RT

- Swedish breast cancer cohort from 1970 – 2003
- Coronary angiography 1990 - 2004

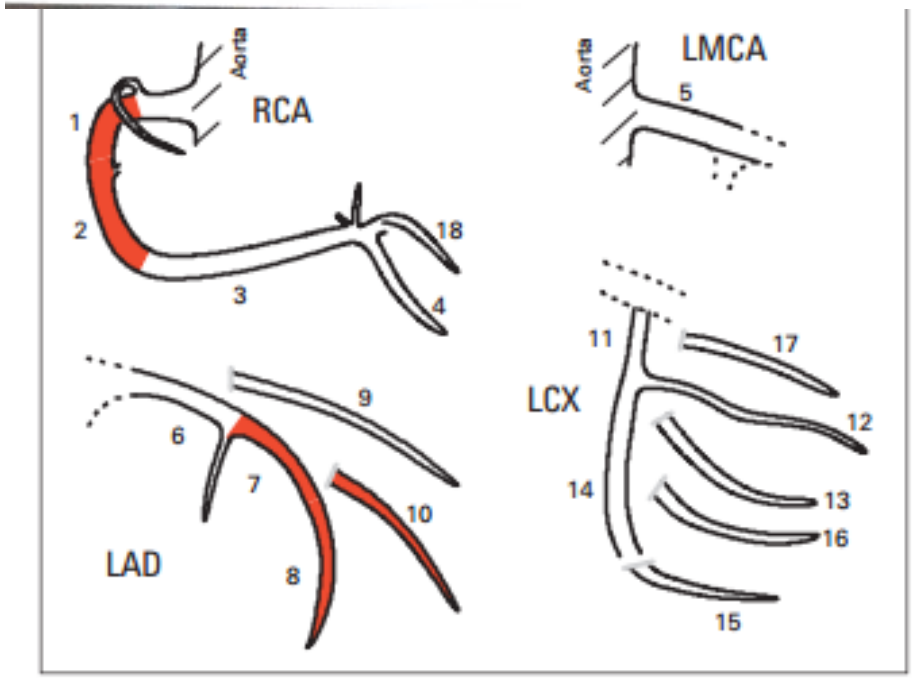
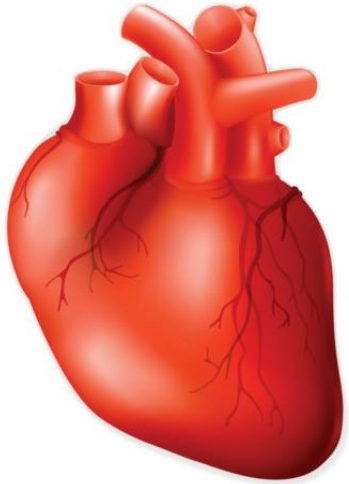


Fig 1. Segments of coronary arteries with hotspot areas highlighted. LAD, left anterior descending artery; LCX, left circumflex artery; LMCA, left main coronary artery; RCA, right coronary artery.



Comparing whole heart versus coronary artery dosimetry in predicting the risk of cardiac toxicity following breast radiation therapy

Sagar A. Patel, Syed S. Mahmood, Trinh Nguyen, Beow Y. Yeap, Rachel B. Jimenez, Nandini M. Meyersohn, Tomas G. Neilan, Shannon M. MacDonald

Department of Radiation Oncology, Division of Cardiology and Cardiovascular Imaging

Massachusetts General Hopsital, Boston MA

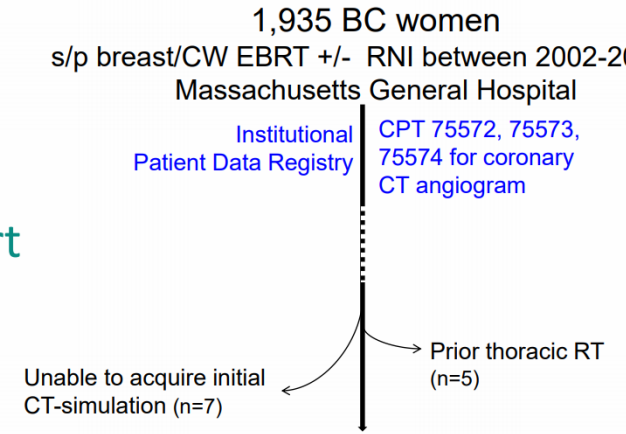
- Radiation-induced heart disease, especially in left-sided breast cancer treatment, is well established.
- Population-based analyses[1,2] in women treated with breast RT have shown that dose to the whole heart and left ventricle predict the risk of major adverse cardiac events (MACE).
  - **MHD constraint predominates clinical practice**
- Accelerated left anterior descending artery (LAD) atherosclerosis has been associated with prior left-sided breast RT[3,4] and may be a major driver of cardiac morbidity.

1. Darby SC, et al. *N Eng J Med* 2013; 368(11):987-98
2. van den Bogaard V, et al. *J Clin Oncol* 2017; 35(11):1171-78
3. Correa et al. *J Clin Oncol* 2007; 25:3031-37
4. Nilsson et al. *J Clin Oncol* 2011; 30:380-86

Aim

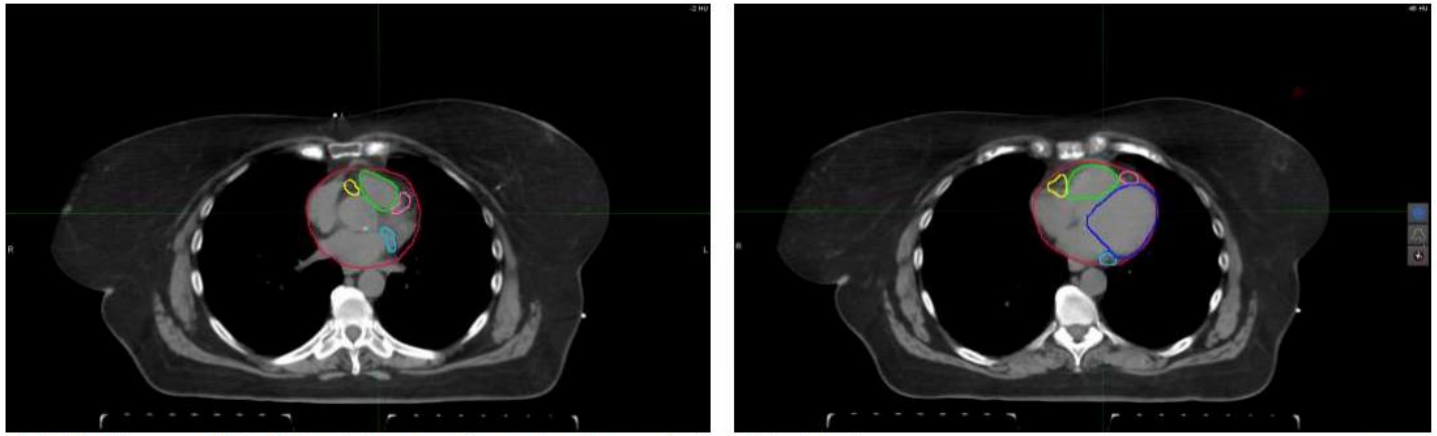
- Investigate cardiac substructural dose-volume predictors of MACE using validated[1-3] non-invasive cardiac imaging (i.e. coronary CT angiogram) as surrogate endpoint
  - Compare the strength of relationship between whole heart dose versus LAD dose and onset of toxicity

Study Cohort



Methods: Exposure

- Cardiac substructures were retrospectively contoured on original CT simulation per RADCOMP cardiac atlas; reviewed by cardiac radiologist
- EQD2 to these structures were calculated based on individual plan used for treatment ($\alpha/\beta = 2$ for myocardium/coronary vessels§)



§ Schultz-Hector et al. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with radiobiologic data? *Int J Radiat Oncol Biol Phys* 2007; 67:10-18.

Tętnica wieńcowa przednia zstępująca

Zwapnienia, zwężenie

Results Part A: coronary calcification

Heart	Crude (95% CI)	*p*	Adjusted (95% CI)	*p*
Mean	1.07 (0.95-1.20)	0.30	1.04 (0.95-1.23)	0.24
V5	1.26 (0.86-1.86)	0.24	1.16 (0.88-2.09)	0.16
V10	1.28 (0.74-2.21)	0.38	1.26 (0.76-2.35)	0.30
V20	1.28 (0.61-2.67)	0.52	1.23 (0.62-2.77)	0.47

LAD Artery	Crude (95% CI)	*p*	Adjusted (95% CI)	*p*
Dmax	2.08 (0.92-4.70)	0.08	2.40 (1.00-5.61)	**0.05**

LAD stenosis

Heart	Crude (95% CI)	p	Adjusted (95% CI)	p
Mean	1.16 (0.99-1.34)	**0.06**	1.21 (1.01-1.46)	**0.04**
V5	1.81 (1.07-3.07)	**0.03**	1.85 (1.11-3.14)	**0.02**
V10	2.31 (1.07-4.98)	**0.03**	2.22 (1.09-5.09)	**0.03**
V20	1.84 (0.86-3.94)	0.12	2.06 (0.88-4.87)	0.09

LAD Artery	Crude (95% CI)	p	Adjusted (95% CI)	p
Dmax	4.32 (1.36-13.66)	**0.01**	6.03 (1.48-23.41)	**0.01**

Aim #2

- Identify a mean heart dose and LAD Dmax DVH threshold for onset of CAC and LAD stenosis

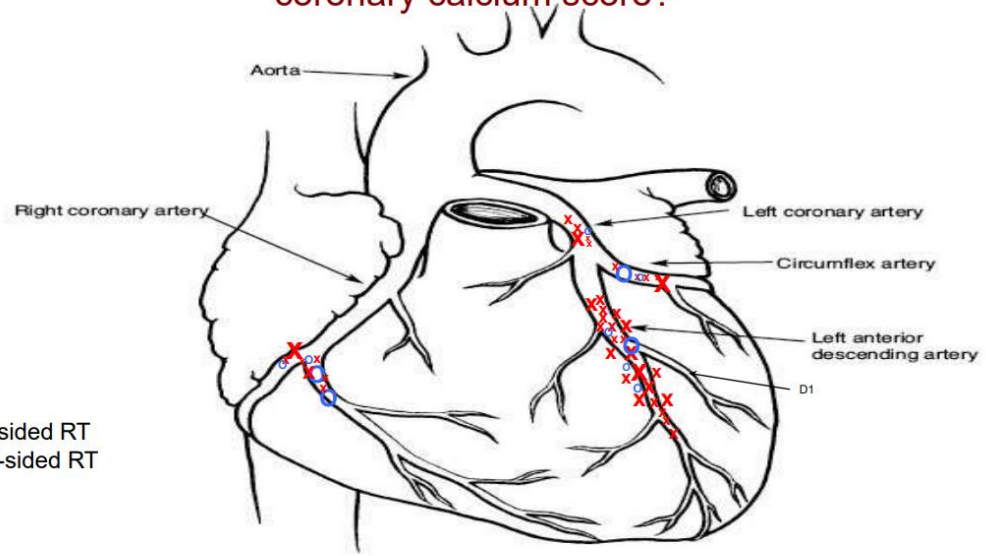
Coronary calcification

Heart Mean	Crude (95% CI)	p	Adjusted (95% CI)	p
> 1 Gy	1.34 (0.32-5.63)	0.68	1.54 (0.36-8.34)	0.49
> 2 Gy	2.46 (0.66-9.20)	0.18	2.84 (0.68-11.80)	0.15
LAD Dmax				
> 10 Gy	5.32 (1.06-16.70)	**0.04**	5.21 (1.16-18.36)	**0.04**

LAD stenosis

Heart Mean	Crude (95% CI)	p	Adjusted (95% CI)	p
> 1 Gy	2.90 (0.91-9.14)	0.08	4.24 (1.00-9.51)	**0.05**
LAD Dmax				
> 10 Gy	6.38 (1.42-28.63)	**0.01**	6.52 (1.39-19.67)	**0.03**

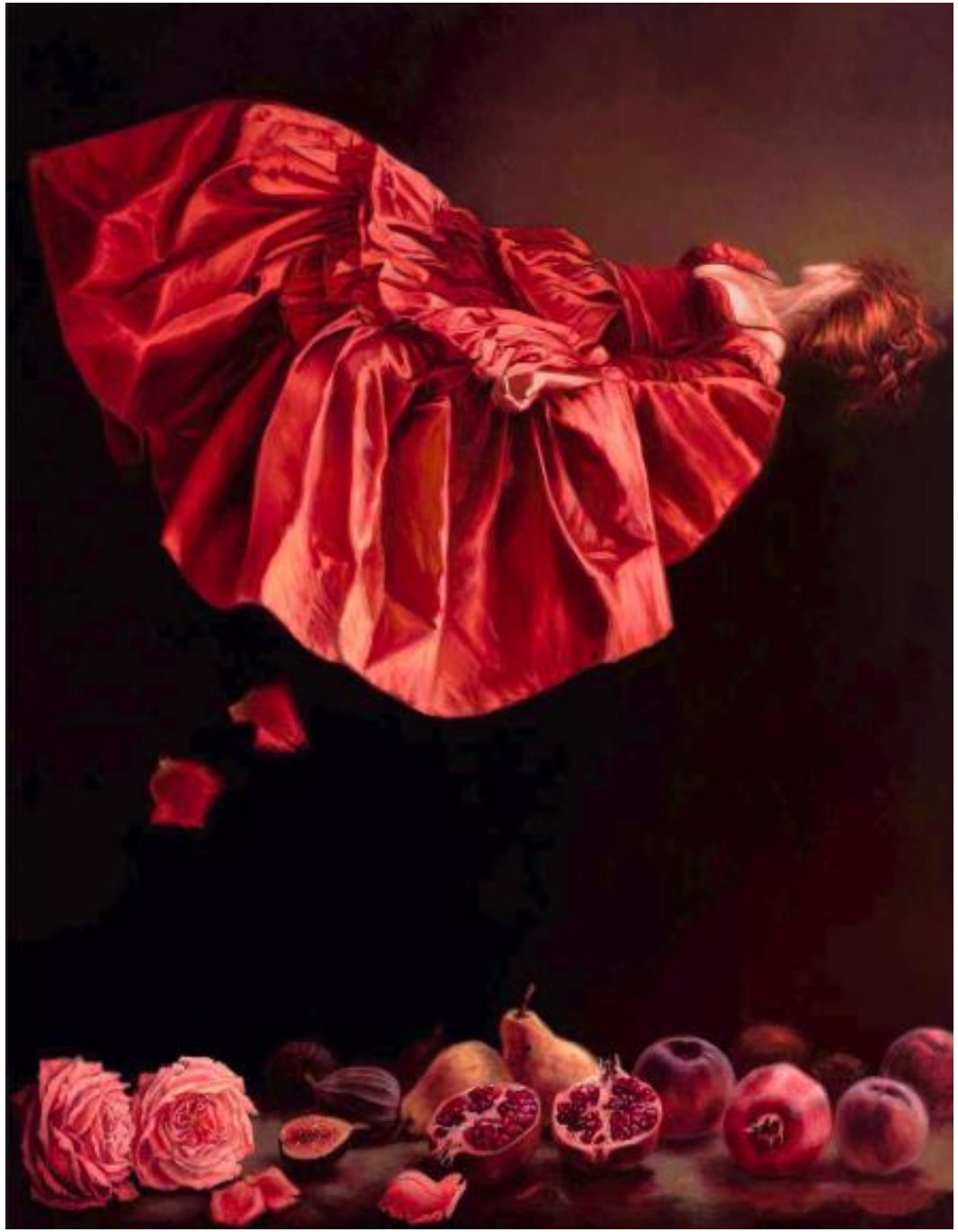
Why may LAD dosimetry be a valid predictor for total coronary calcium score?



Total CAC score is dominated by LAD calcification

Conclusions

- LAD D_{max} had a stronger association with incidence of CAC and LAD stenosis than MHD and may be a better predictor of late MACE
- LAD should be routinely evaluated as an avoidance structure for left-sided breast RT planning
- If prospectively validated, LAD Dmax <10 Gy may serve as a clinical parameter to minimize late cardiac toxicity



Obraz Joanny Sierko-Filipowskiej