Review of the San Antonio Breast Cancer Symposium

Localized Therapy: Radiation Oncology

ROSWELL PARK COMPREHENSIVE CANCER CENTER

EMPIRE STATE HEMATOLOGY & ONCOLOGY SOCIETY

Simon Fung-Kee-Fung, MD

March 4, 2023

Disclosures

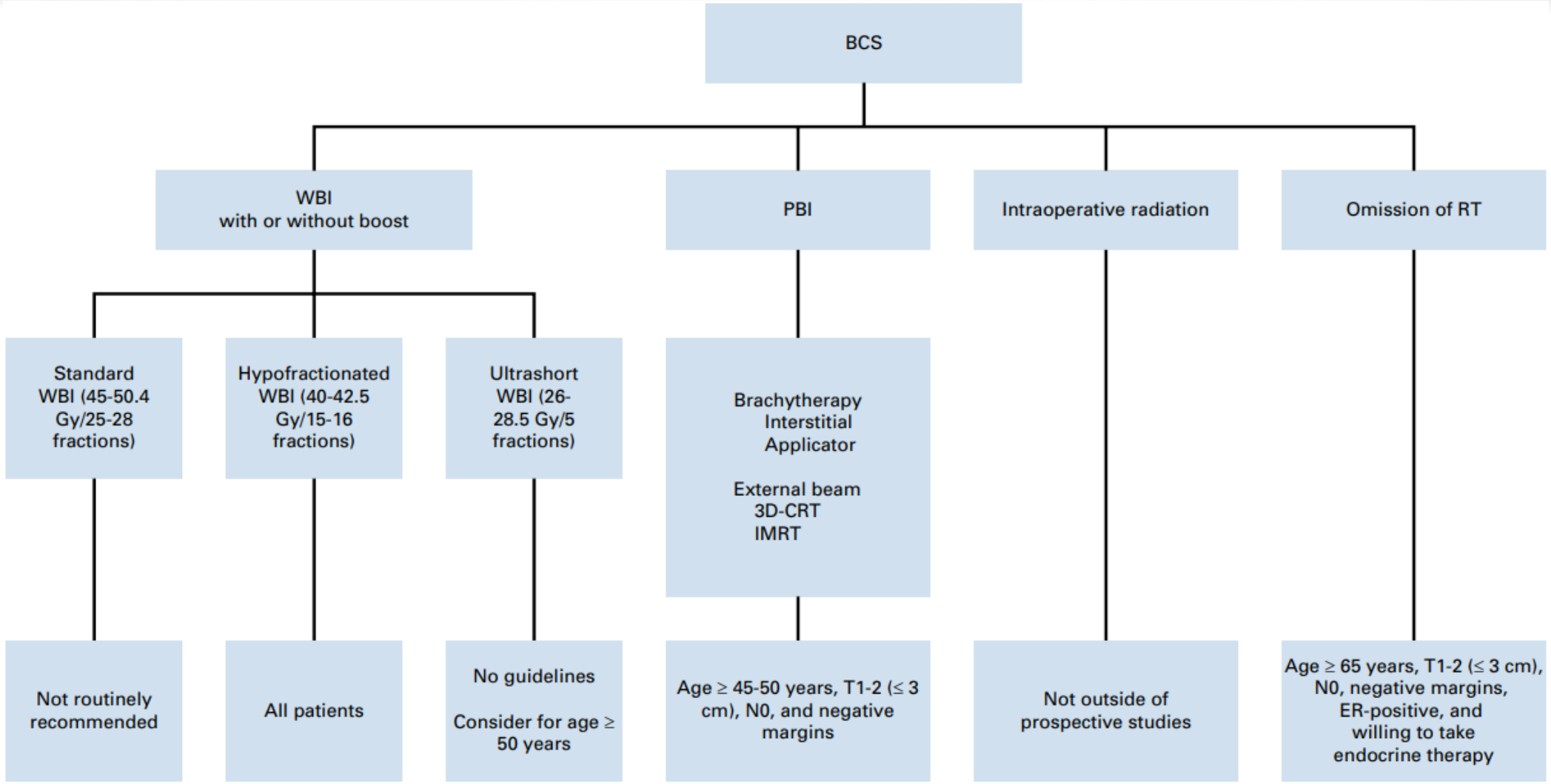
- None

Outline: RT Advances = Less Toxicity

- New Fractionation Schemes (A Review)
  - Early Stage Breast Cancer
  - PostMastectomy Radiation Therapy
- New(ish) Technology
  - VMAT, Protons oh my!

T1-2, N0

EARLY STAGE BREAST CANCER



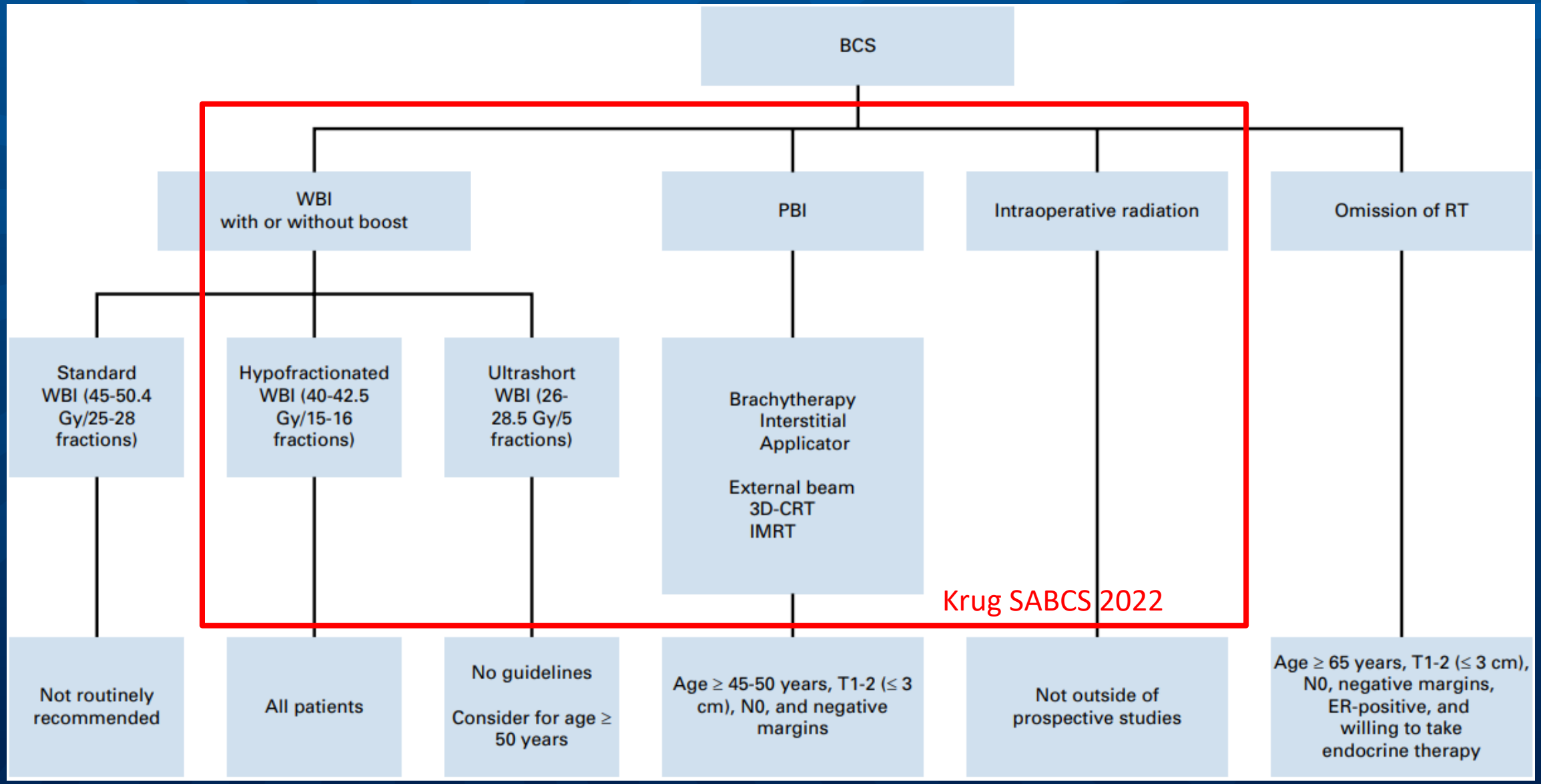
Shah et al JCO Oncol Practice, 2021: 17(12)

UKSH UNIVERSITÄTSKLINIKUM Schleswig-Holstein

CAU Christian-Albrechts-Universität zu Kiel Medizinische Fakultät

RT: How short can it be

PD Dr. med. David Krug
Deputy Director
Department of Radiation Oncology
University Hospital Schleswig-Holstein, Kiel, Germany

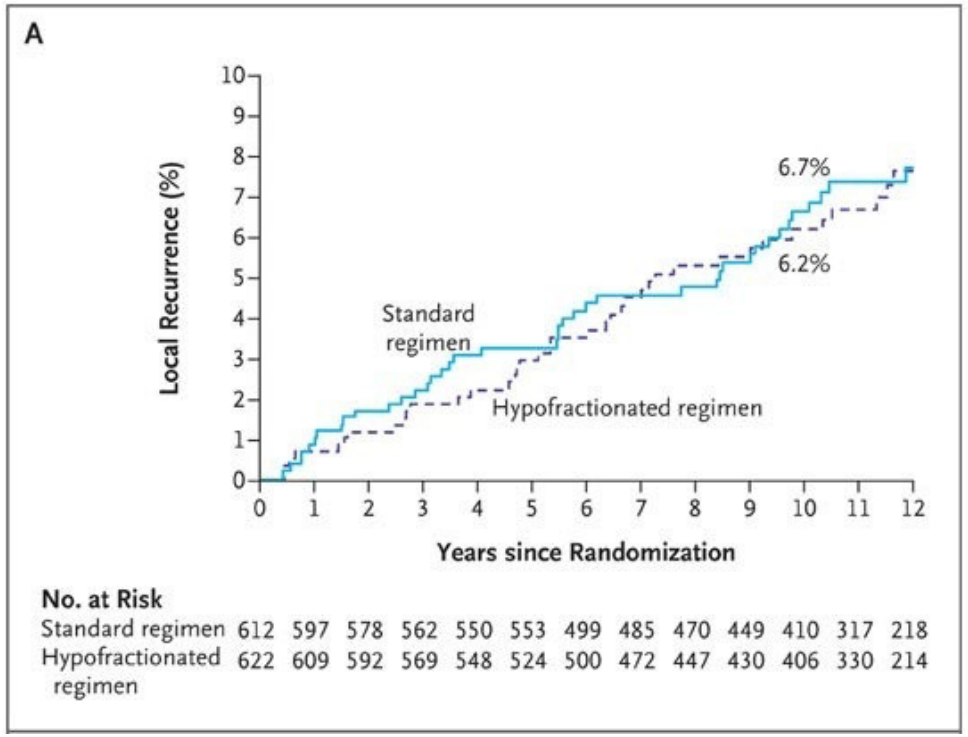


Hypofractionated Whole Breast Irrad. (H-WBI)

Hypofractionation							
Trial	Years of Accrual	No. of Patients	F/U (years)	Radiation Dose	Local Recurrence with SWBI (%)	Local Recurrence with AWBI (%)	Toxicity
Ontario Oncology Group	1993-1996	1,234	12	42.56 Gy/16 fx 50 Gy/25 fx	6.2	6.7	No significant difference cosmetic outcomes (71.3% SWBI *v* 69.8% HWBI)
START-A	1999-2002	2,236	9.3	50 Gy/25 fx 41.6 Gy/13 fx 39 Gy/13 fx (all over 5 weeks)	6.7	5.6 8.1	No difference 50 Gy, 41.6 Gy with moderate or marked normal tissue effects; reduced induration/telangiectasia/edema with 39 Gy *v* 50 Gy
START-B	1999-2001	2,215	10	50 Gy/25 fx 40 Gy/15 fx	5.2	3.8	Breast shrinkage, telangiectasia, and edema significantly lower with 40 Gy

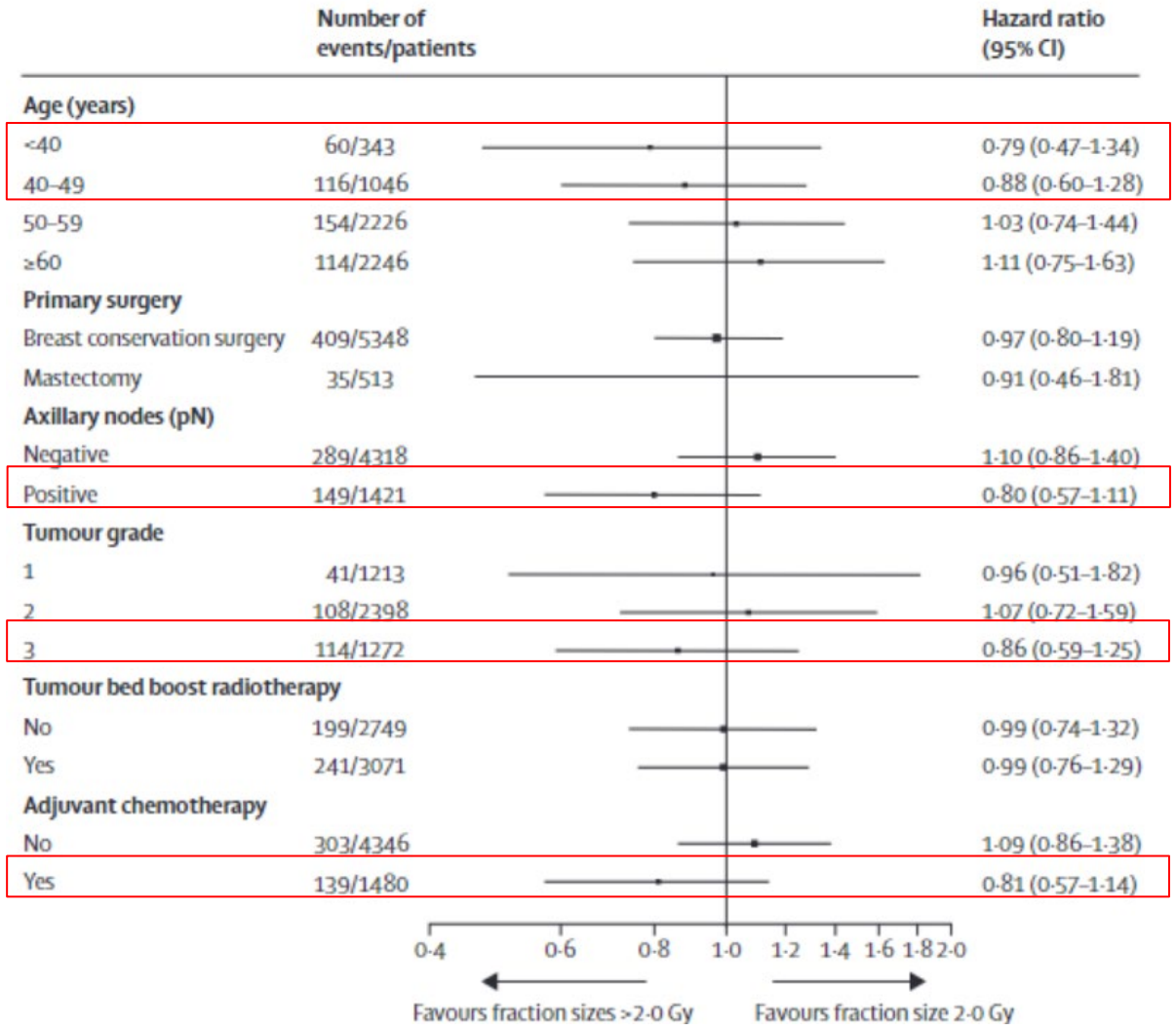
Shah et al JCO Oncol Practice, 2021: 17(12)

Ontario Oncology Group



Whelan et al, NEJM 2010

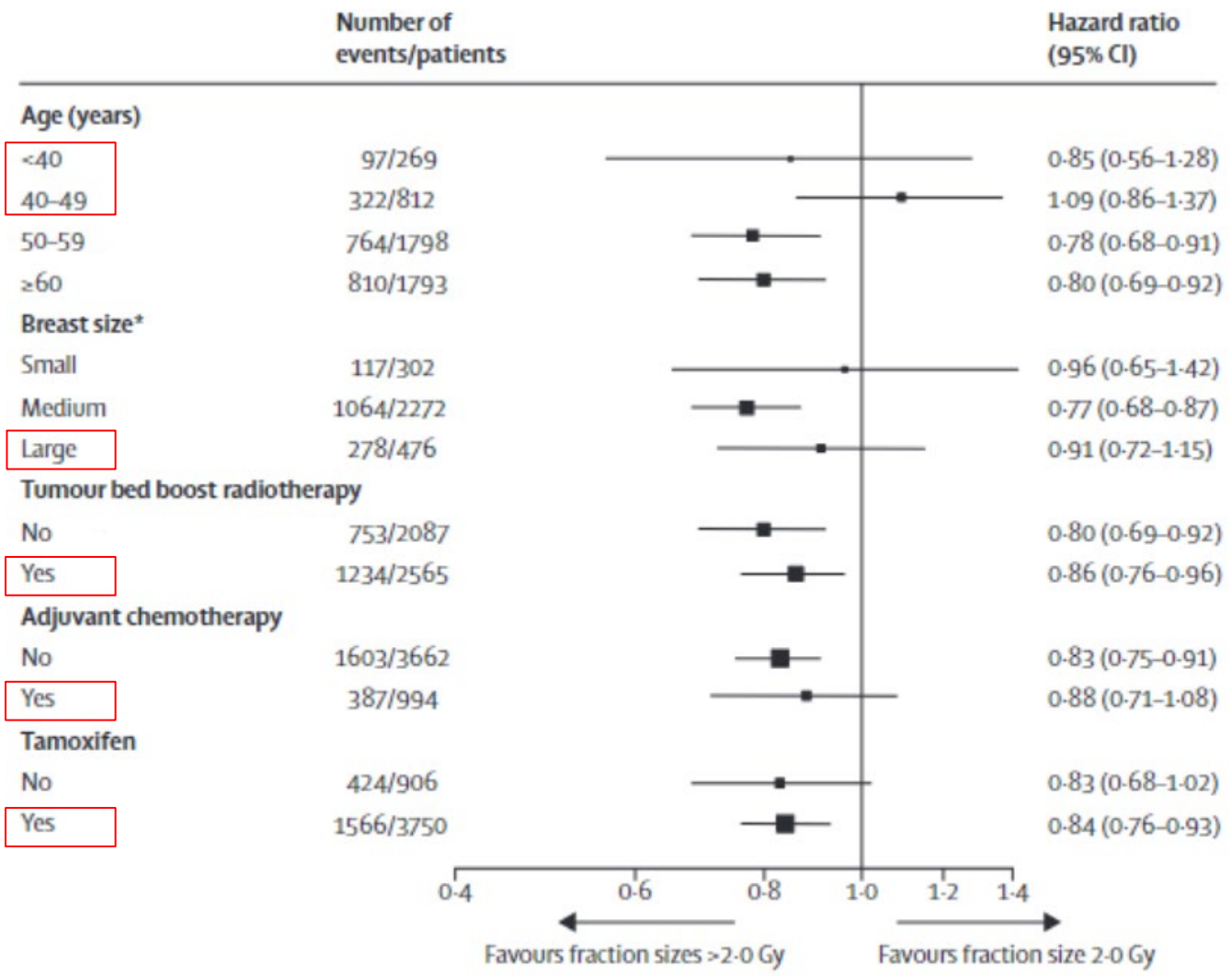
UK START: Meta-Analysis Local-Regional Relapse



Hypofractionation is equivalent to Standard Fractionation in women with high-risk features

Haviland et al, Lancet Oncol 2013

UK START: Marked/Moderate Normal Tissue Effects



Hypofractionation is associated with similar or less Marked / Moderate normal tissue effects than Standard Fractionation

Haviland et al, Lancet Oncol 2013

Moderate Hypofractionation – Std of Care

- ABIM Choosing Wisely (2013)
  - *Don't initiate whole breast radiotherapy as a part of breast conservation therapy in women with early stage invasive breast cancer without considering shorter treatment schedules*.
- ASTRO Guideline RT for Whole Breast (2018)

Table 1 Patients for whom consensus supports use of HF-WBI: A comparison of the 2011 and 2018 ASTRO Guidelines *

Factor	2011 Guideline	2018 Guideline
Age	≥50 years	Any
Stage	T1-2 N0	Any stage provided intent is to treat the whole breast without an additional field to cover the regional lymph nodes
Chemotherapy	None	Any chemotherapy
Dose homogeneity	±7% in the central axis	Volume of breast tissue receiving >105% of the prescription dose should be minimized regardless of dose-fractionation

ASTRO, American Society for Radiation Oncology; HF-WBI, hypofractionated whole-breast irradiation.

FAST(er): Is 5 fractions all we need?

Regimen	Treatment schedule over the course of 5 weeks	$EQD_{2\,Gy}$ ($\alpha/\beta = 3.5$)
Conventional 25 × 2 Gy		50 Gy
START A 13 × 3.0/3.2 Gy [6]		46.1 Gy/50.4 Gy
START B 15 × 2.67 Gy [7]		44.9 Gy
FAST 5 × 5.7/6.0 Gy [27]		47.7 Gy/51.8 Gy
FAST-Forward 5 × 5.2/5.4 Gy [26]		41.1 Gy/43.7 Gy

$EQD_{2\,Gy}$ Dose equivalent delivered in 2 Gy-fractions without time loss-factor.

Krug et al, Strahlenther Onkol 2021; 197:269-280

~~Moderate~~ *ULTRA*- Hypofractionated WBI

Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer

Adrian Murray Brunt, FRCR[1]; Joanne S. Haviland, MSc[2]; Mark Sydenham, BSc Hons[2]; Rajiv K. Agrawal, FRCR[3]; Hafiz Algurafi, FRCR[4]; Abdulla Alhasso, FRCR[5]; Peter Barrett-Lee, FRCR[6]; Peter Bliss, FRCR[7]; David Bloomfield, FRCR[8]; Joanna Bowen, FRCR[9]; Ellen Donovan, PhD[10]; Andy Goodman, FRCR[11]; Adrian Harnett, FRCR[12]; Martin Hogg, FRCR[13]; Sri Kumar, FRCR[14]; Helen Passant, FRCR[6]; Mary Quigley, FRCR[15]; Liz Sherwin, FRCR[16]; Alan Stewart, FRCR[17]; Isabel Syndikus, FRCR[18]; Jean Tremlett, MSc[8]; Yat Tsang, PhD[19]; Karen Venables, PhD[19]; Duncan Wheatley, FRCR[20]; Judith M. Bliss, MSc[2]; and John R. Yarnold, FRCR[21]

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Adrian Murray Brunt, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Churn, Susan Cleator, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Cliona C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita Somaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group*

	FAST	FAST-Forward
Timeframe	2004-2007	2011-2014
Sample Size	915	4096
Dose / Fractionation	50 Gy / 2Gy / 5 weeks 30 Gy / 6 Gy / 5 weeks 28.5 Gy / 5.7 Gy / 5 weeks	40 Gy / 2.67 Gy / 3 weeks 27 Gy / 5.4 Gy / 1 weeks 26 Gy / 5.2 Gy / 1 weeks
Median Follow up	119.8 months	71.5 months
Primary endpoint	Change in photographic breast appearance	Ipsilateral breast tumor recurrence
Inclusion Criteria	pT1-2 (< 3 cm) pN0 Age ≥ 50 years Breast conserving surgery No chemotherapy	pT1-3 pN0-1 Age ≥ 18 years Breast-conserving surgery or mastectomy Approx. 25% adj. chemotherapy
Boost	No	Approx. 25%, 5-8 x 2Gy

Brunt et al, JCO 2020 (FAST), Lancet Oncol 2020 (FAST-Forward)

~~Moderate~~ *ULTRA*- Hypofractionated WBI

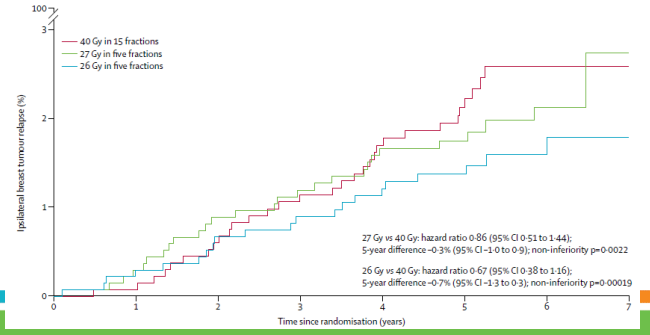
Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer

Adrian Murray Brunt, FRCR[1]; Joanne S. Haviland, MSc[2]; Mark Sydenham, BSc Hons[2]; Rajiv K. Agrawal, FRCR[3]; Hafiz Algurafi, FRCR[4]; Abdulla Alhasso, FRCR[5]; Peter Barrett-Lee, FRCR[6]; Peter Bliss, FRCR[7]; David Bloomfield, FRCR[8]; Joanna Bowen, FRCR[9]; Ellen Donovan, PhD[10]; Andy Goodman, FRCR[11]; Adrian Harnett, FRCR[12]; Martin Hogg, FRCR[13]; Sri Kumar, FRCR[14]; Helen Passant, FRCR[6]; Mary Quigley, FRCR[15]; Liz Sherwin, FRCR[16]; Alan Stewart, FRCR[17]; Isabel Syndikus, FRCR[18]; Jean Tremlett, MSc[8]; Yat Tsang, PhD[19]; Karen Venables, PhD[19]; Duncan Wheatley, FRCR[20]; Judith M. Bliss, MSc[2]; and John R. Yarnold, FRCR[21]

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Adrian Murray Brunt, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Churn, Susan Cleator, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Cliona C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita Somaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group*

	FAST (10 Year Data)			FAST-Forward (5 Year Data)		
	Dose	Frequency	Hazard Ratio (95% CI)	Dose	Frequency	Hazard Ratio (95% CI)
Ipsilateral In-Breast Recurrence	50 Gy	0.7%	-	40 Gy	2.1%	-
	30 Gy	1.4%	HR 1.36 (0.3-6.06)	27 Gy	1.7%	HR 0.86 (0.51-1.44)
	28.5 Gy	1.7%	HR 1.35 (0.3-6.05)	26 Gy	1.4%	HR 0.67 (0.38-1.16)



Brunt et al, JCO 2020 (FAST), Lancet Oncol 2020 (FAST-Forward)

~~Moderate~~ *ULTRA*- Hypofrationated WBI

Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer

Adrian Murray Brunt, FRCR[1]; Joanne S. Haviland, MSc[2]; Mark Sydenham, BSc Hons[2]; Rajiv K. Agrawal, FRCR[3]; Hafiz Algurafi, FRCR[4]; Abdulla Alhasso, FRCR[5]; Peter Barrett-Lee, FRCR[6]; Peter Bliss, FRCR[7]; David Bloomfield, FRCR[8]; Joanna Bowen, FRCR[9]; Ellen Donovan, PhD[10]; Andy Goodman, FRCR[11]; Adrian Harnett, FRCR[12]; Martin Hogg, FRCR[13]; Sri Kumar, FRCR[14]; Helen Passant, FRCR[6]; Mary Quigley, FRCR[15]; Liz Sherwin, FRCR[16]; Alan Stewart, FRCR[17]; Isabel Syndikus, FRCR[18]; Jean Tremlett, MSc[8]; Yat Tsang, PhD[19]; Karen Venables, PhD[19]; Duncan Wheatley, FRCR[20]; Judith M. Bliss, MSc[2]; and John R. Yarnold, FRCR[21]

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Adrian Murray Brunt, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Churn, Susan Cleator, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Cliona C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita Somaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group*

	FAST (10 Year Data)			FAST-Forward (5 Year Data)		
	Dose	Frequency	Hazard Ratio (95% CI)	Dose	Frequency	Hazard Ratio (95% CI)
Ipsilateral In-Breast Recurrence	50 Gy	0.7%	-	40 Gy	2.1%	-
	30 Gy	1.4%	HR 1.36 (0.3-6.06)	27 Gy	1.7%	HR 0.86 (0.51-1.44)
	28.5 Gy	1.7%	HR 1.35 (0.3-6.05)	26 Gy	1.4%	HR 0.67 (0.38-1.16)
Moderate/Marked Normal Tissue Effects Of Breast / Chestwall	50 Gy	33.6%	-	40 Gy	26.8%	
	30 Gy	50.4%	**HR 1.79 (1.37-2.34)**	27 Gy	35.1%	**HR 1.41 (1.23-1.61)**
	28.5 Gy	47.6%	**HR 1.79 (1.37-2.34)**	26 Gy	28.5%	HR 1.09 (0.95-1.27)

Brunt et al, JCO 2020 (FAST), Lancet Oncol 2020 (FAST-Forward)

Moderate or Ultra Hypofrationated WBI

- Moderate Hypofractionated Whole Breast Irradiation
  - Remains SOC in the United States
- Ultra-Hypofractionated Whole Breast Irradiation
  - Appears to have non-inferior in-breast tumor control
  - Some concerns for late toxicity (induration/edema) –FAST fx
  - Longer follow up required (toxicity) –FAST-Forward fx
  - Can be used as an alternative in select circumstances

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

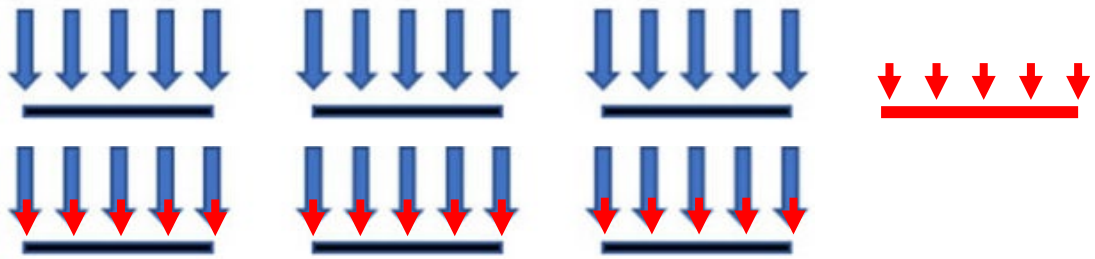
Whole Breast Radiation

- **Target definition is the breast tissue at risk.**
- **RT dosing:**
  - **The whole breast should receive a hypofractionated dose of 40–42.5 Gy in 15–16 fractions; in selected cases 45–50.4 Gy in 25–28 fractions may be considered.**
  - **A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–8 fractions.**
- **Lumpectomy cavity boost can be delivered using enface electrons, photons, or brachytherapy.**
  - **Ultra-hypofraction ated WBRT of 28.5 Gy in 5 (once-a-week) fractions may be considered for selected pts over 50 yrs following BCS with early-stage, node-negative disease, particularly those in whom a boost is not intended.[a,b]**

[a] Alternatively, 26 Gy in 5 daily fractions over one week may be considered, though data beyond 5 years for local relapse or toxicity are not yet available for this regimen. [Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020;395:1613-1626.]
[b] Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of FAST: A randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. J Clin Oncol 2020;38:3261-3272.

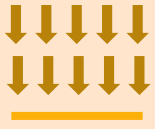
What's New With the Boost?

- Usually Sequential (10 Gy in 4-5 fractions)
- OnGoing Trials – Simultaneous Integrated Boost (SIB) vs Sequential

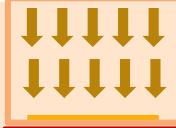


- RTOG 1005 (ASTRO 2022); IMPORT-HIGH (ESTRO 2021)
  - Non-inferiority for ipsilateral in-breast recurrence
  - Toxicity (NS diff in RTOG; Increased marked/mod AE in IMPORT-HIGH)
  - Await publications…

Partial Breast Irradiation (PBI)

Course	Technique	Schedule	Trial(s)	Comments
	EBRT-3D	15 fractions / 3 weeks Daily	IMPORT-LOW	No long-term followup
	EBRT-IMRT	5 fractions / 1.5 weeks QOD	Florence	Non-inferior to WBI IMRT mandated
	EBRT / Brachytherapy	10 fractions / 1 week BID	RAPID, NSABP B39	Worse cosmesis 3D
	IORT photons IORT electrons	1 day	TARGIT ELIOT	Higher LRR than WBI

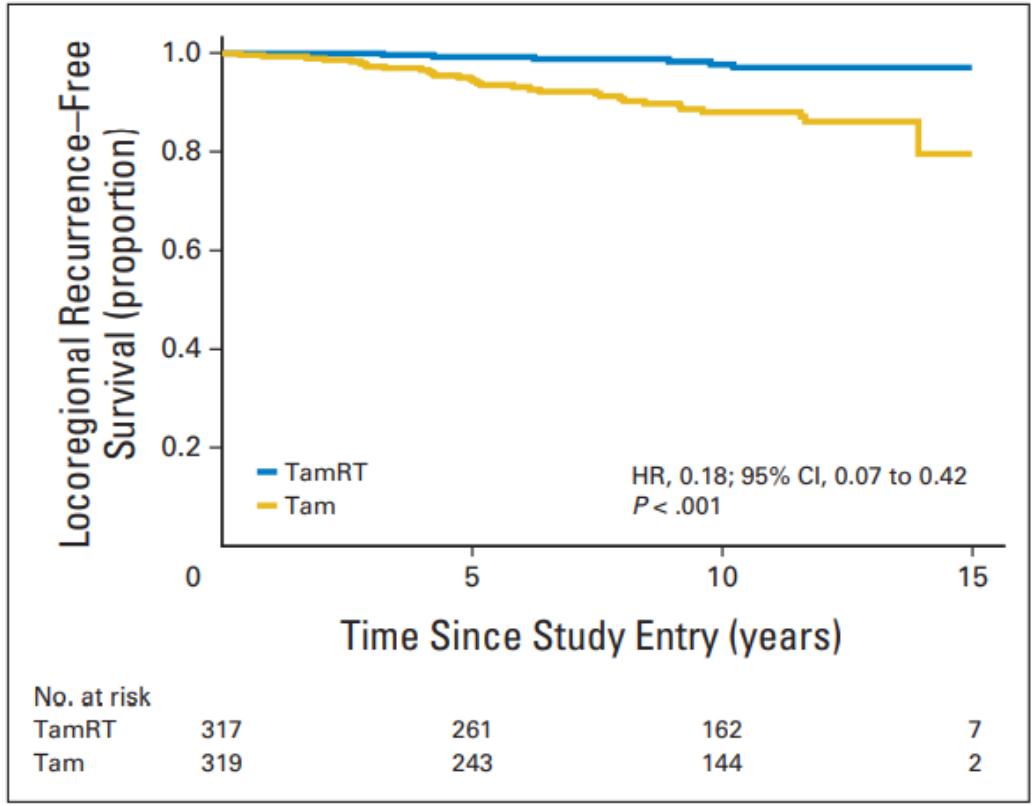
Partial Breast Irradiation (PBI)

Course	Technique	Schedule	Trial(s)	Comments
	EBRT-3D	15 fractions / 3 weeks Daily	IMPORT-LOW	No long-term followup
	EBRT-IMRT	5 fractions / 1.5 weeks QOD	Florence	Non-inferior to WBI IMRT mandated
	EBRT / Brachytherapy	10 fractions / 1 week BID	RAPID, NSABP B39	Worse cosmesis 3D
	IORT photons IORT electrons	1 day	TARGIT ELIOT	Higher LRR than WBI

Differences: A function of Volume, Treatment Technique, Schedule or Radiation Biology?

Omission of Radiotherapy

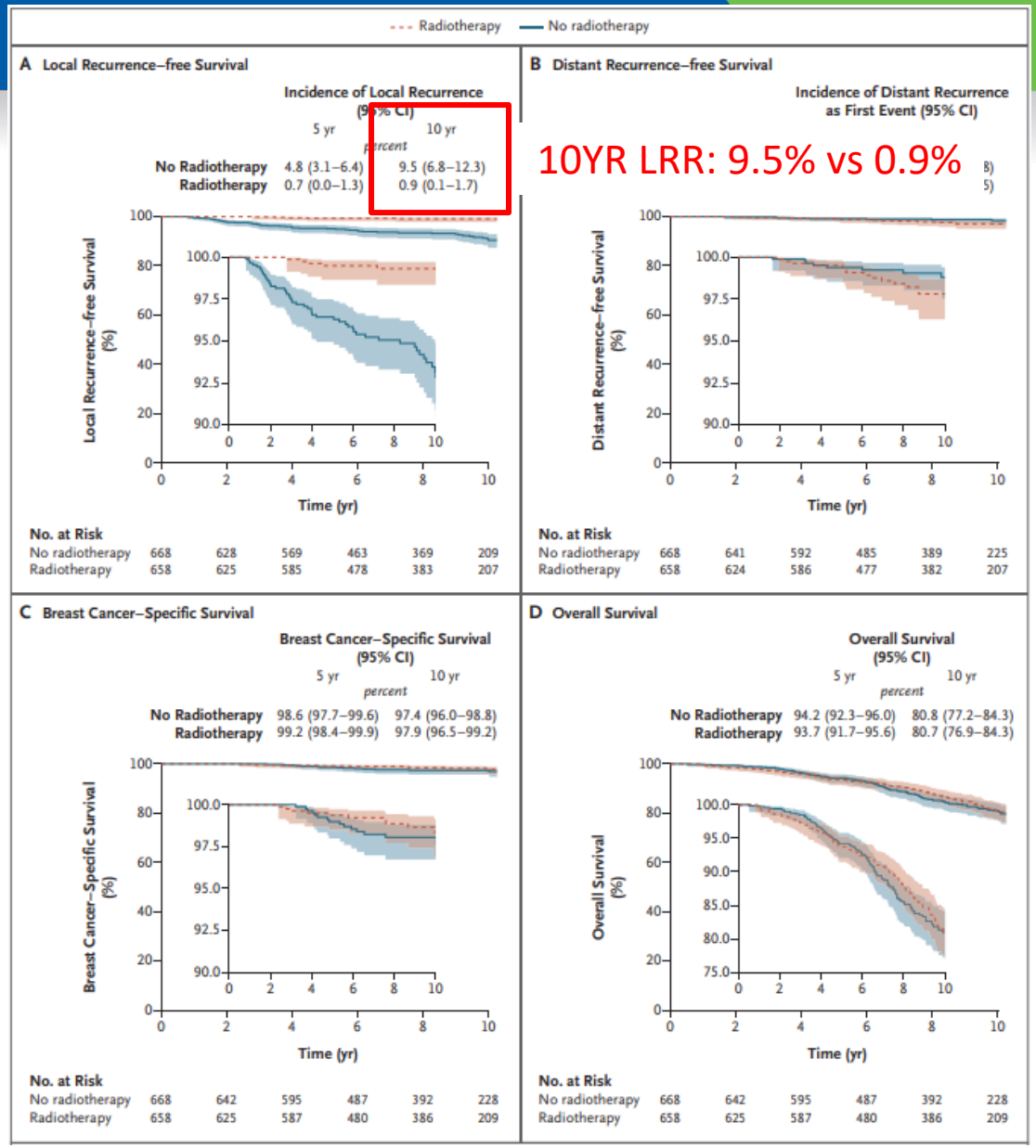
- CALGB 9343
  - 70+ years old T1N0, ER+
  - Tam alone vs TamRT
- At 10 years
  - LRR 9% vs 2%
  - No difference in OS, BCaSS
  - No difference in Time to DM or Mastectomy



Hughes, et al. JCO 2013

PRIME II: Omission

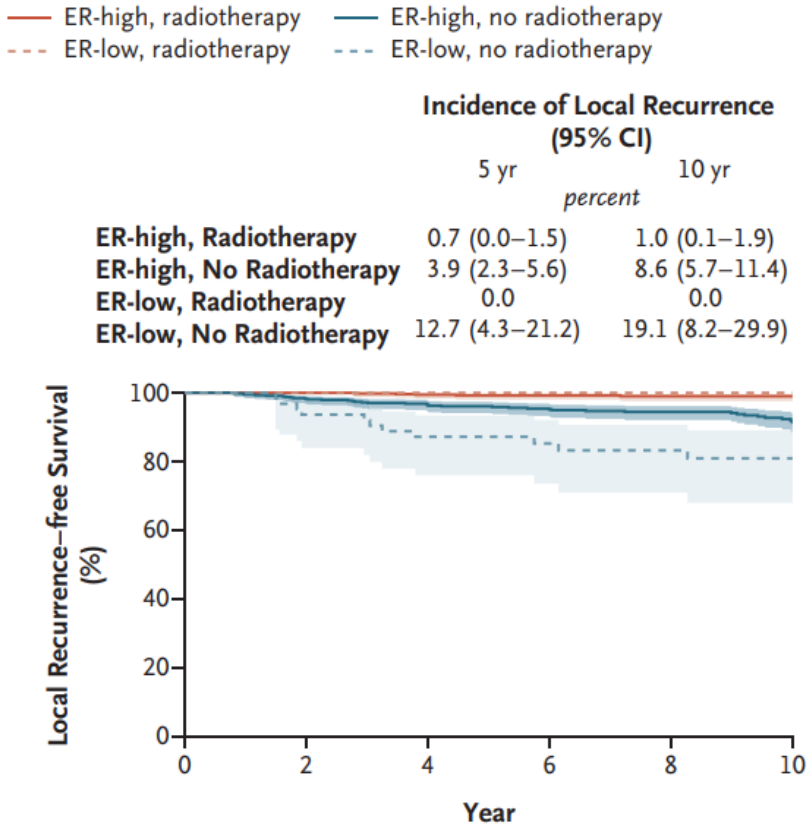
- 65 or older
- T1-2, ≤ 3cm
- pN0 surgical axillary staging
- ER+ or PR+
- G3 or LVI allowed (~5%)
- Margins ≥ 1mm
- Tamoxifen recommended
- Randomized:
  - WBI vs Omission
  - LRR 0.9% vs 9.5%
  - OS, DRS, BCS no difference



Kunkler et al, NEJM 2023, 388;7

PRIME II: Omission

- RT could be omitted safely in
  - Women over 65, grade 1-2, ER+(high)
  - AND can take ET for 5 years
- BUT
  - ET adherence an issue
    - Higher LRR in pts unable to complete 5 y
  - ER-low?
    - Few numbers, but perhaps RT has a greater benefit (LRR 0% vs 19.1%)
- Is 5 fractions RT worth omitting?



Kunkler et al, NEJM 2023, 388;7

Ongoing Trials

- NRG Oncology BR-007 (aka DEBRA trial)
  - 50-69 years old, </= 2cm, N0, ER+
  - With OncotypeDX RS </= 18
  - Endocrine Therapy +/- Radiotherapy (WBI+Boost or PBI-IMRT)
- EUROPA
  - 70+ years old, pT1N0 G1-2, non-lobular, ER+
  - Endocrine Therapy alone vs Radiotherapy alone

- There is not yet a biomarker to *PREDICT* benefit of RT…

ROSWELL PARK
COMPREHENSIVE CANCER CENTER

San Antonio Breast Cancer Symposium®, December 6-10, 2022

Validation of Profile for the Omission of Local Adjuvant Radiotherapy (POLAR) in a meta-analysis of three randomized controlled trials of breast conserving surgery +/- radiotherapy

Karlsson Per, Fyles A, Chang SL, Arrick B, Baehner F, Malmström P, Fernö M, Holmberg E, Sjöström M, Liu F-F, Cameron DA, Williams LJ, Bartlett JMS, Dunlop J, Caldwell J, Loane JF, Mallon E, Piper T, Jack WJ, Kunkler I, Feng FY, Speers CW, Pierce LJ, Bennett J, Taylor KJ.

For the SweBCG91RT-, Princess Margaret- and Scottish Conservation RT-trial groups

Per Karlsson, MD, Sahlgrenska Comprehensive Cancer Center, Gothenburg, Sweden

Gene discovery and algorithm development in SweBCG91RT

POLAR: a 16-gene mRNA-based signature

- Gene Discovery
- Identified gene sets associated with locoregional recurrence in cohort of stage I-II, N0 invasive breast cancer patients with ER+/HER2- tumors, not treated with radiotherapy
- Gene set themes included immune response and proliferation

Marker Symbol	Marker Name
AGR2	Anterior Gradient 2, Protein Disulphide Isomerase
B4GALT1	Beta-1,4-Galactosyltransferase 1
CLDN7	Claudin 7
EZR	Ezrin
GNG11	G Protein Subunit Gamma 11
JUN	Jun Proto-Oncogene
MMP11	Matrix Metallopeptidase 11
PKIB	CAMP-Dependent Protein Kinase Inhibitor Beta
PRPS1	Phosphoribosyl Pyrophosphate Synthetase 1
PSMD10	Proteasome 26S Subunit, Non-ATPase 10
SH3BP5	SH3 Domain Binding Protein 5
SLC16A3	Solute Carrier Family 16 Member 3
SLC7A11	Solute Carrier Family 7 Member 11
SPP1	Secreted Phosphoprotein 1
TNNT1	Troponin T1, Slow Skeletal Type
UBE2E1	Ubiquitin Conjugating Enzyme E2 E1

Courtesy of Dr. Karlsson

Methods

Clinical validation of POLAR signature

- Clinical validation was performed in 3 clinical trials of patients randomized to +/- whole breast radiotherapy following breast conserving surgery
- A patient-level meta-analysis was performed in the subset of node-negative patients who had ER-positive, HER2-negative tumors (N=623)

Parent Trial	Setting	Enrollment	Stage, Tumor size	Age Limitation	Nodal status	Surgery	Systemic Therapy	RT
SweBCG91RT[4] N=1178	Sweden	1991-1997	Stage I-IIA	None	N0	BCS	8% with HT or CT	±WBRT 48-54 Gy, 24-27 fractions
Princess Margaret[4] N=769	Canada	1992-2000	Stage I-II, tumor <5cm	≥50	N0	BCS	100% tamoxifen 20mg daily / 5 years	±WBRT 40 Gy, 16 fractions With boost
Scottish Conservation Trial[5] N=589	Scotland	1985-1991	Stage I-II, tumor <4cm	≤70	~18% N+	BCS	According to receptor status. HR+ received tamoxifen 20mg daily / 5 years	±WBRT 50 Gy, 20-25 fractions With boost

4. Sjöström, M et al. Development and Validation of a Genomic Profile for the Omission of Local Adjuvant Radiation (POLAR) in breast cancer. J Clin Oncol (in press)

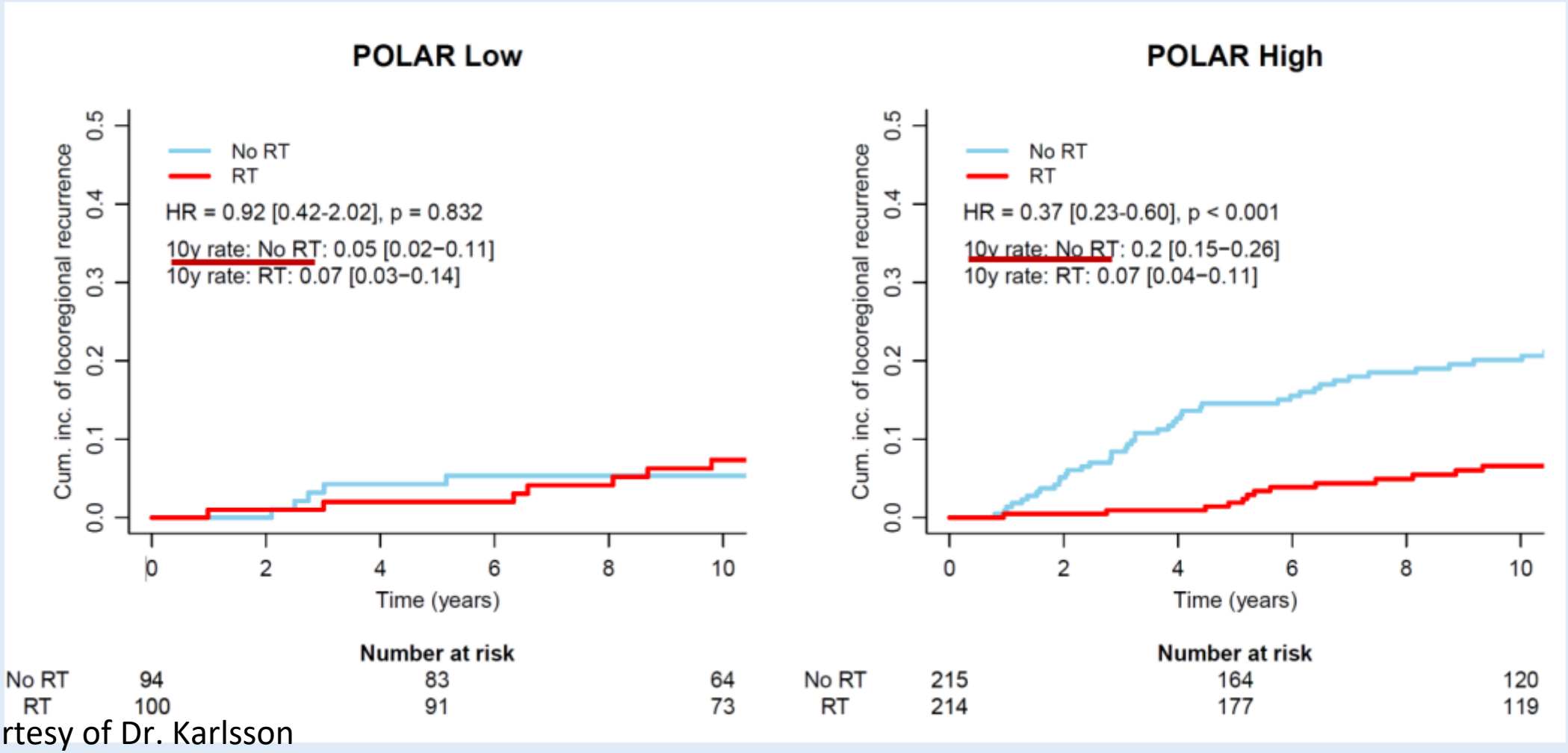
5. Taylor, KJ et al. Validation of Profile for the Omission of Local Adjuvant Radiotherapy (POLAR) in early-stage invasive breast cancer patients of the Scottish Conservation Trial, SABCS 2022 Poster P4-02-12

Courtesy of Dr. Karlsson

Results

Effect of RT in POLAR Low vs High

Cumulative incidence of LRR in POLAR Low vs High, stratified by treatment arm (N=623)



Courtesy of Dr. Karlsson

Results

POLAR prognosticates for locoregional recurrence

Univariable and multivariable Cox proportional hazards models on time to LRR in no RT arm (n=309)

		Univariable		Multivariable	
Variable		HR (95%CI)	P-value	HR (95%CI)	P-value
POLAR (continuous, standardized)		1.53 (1.24-1.91)	<.001	1.43 (1.12-1.82)	0.005
Age	<50	Reference		Reference	
	50-59	0.64 (0.37-1.13)	0.122	0.61 (0.33-1.14)	0.121
	60-69	0.53 (0.30-0.93)	0.028	0.45 (0.24-0.84)	0.012
	≥70	0.28 (0.11-0.73)	<.001	0.17 (0.05-0.59)	0.005
Tumor size	T1	Reference		Reference	
	T2	1.05 (0.52-2.11)	0.890	1.12 (0.50-2.51)	0.777
Grade	1	Reference		Reference	
	2	1.48 (0.78-2.80)	0.228	1.40 (0.71-2.79)	0.333
	3	1.91 (0.92-3.97)	0.083	1.10 (0.47-2.60)	0.820
Molecular groupings (approximated by IHC)	LUMA	Reference		Reference	
	LUMB	1.26 (0.78-2.03)	0.353	1.37 (0.80-2.33)	0.248

Courtesy of Dr. Karlsson

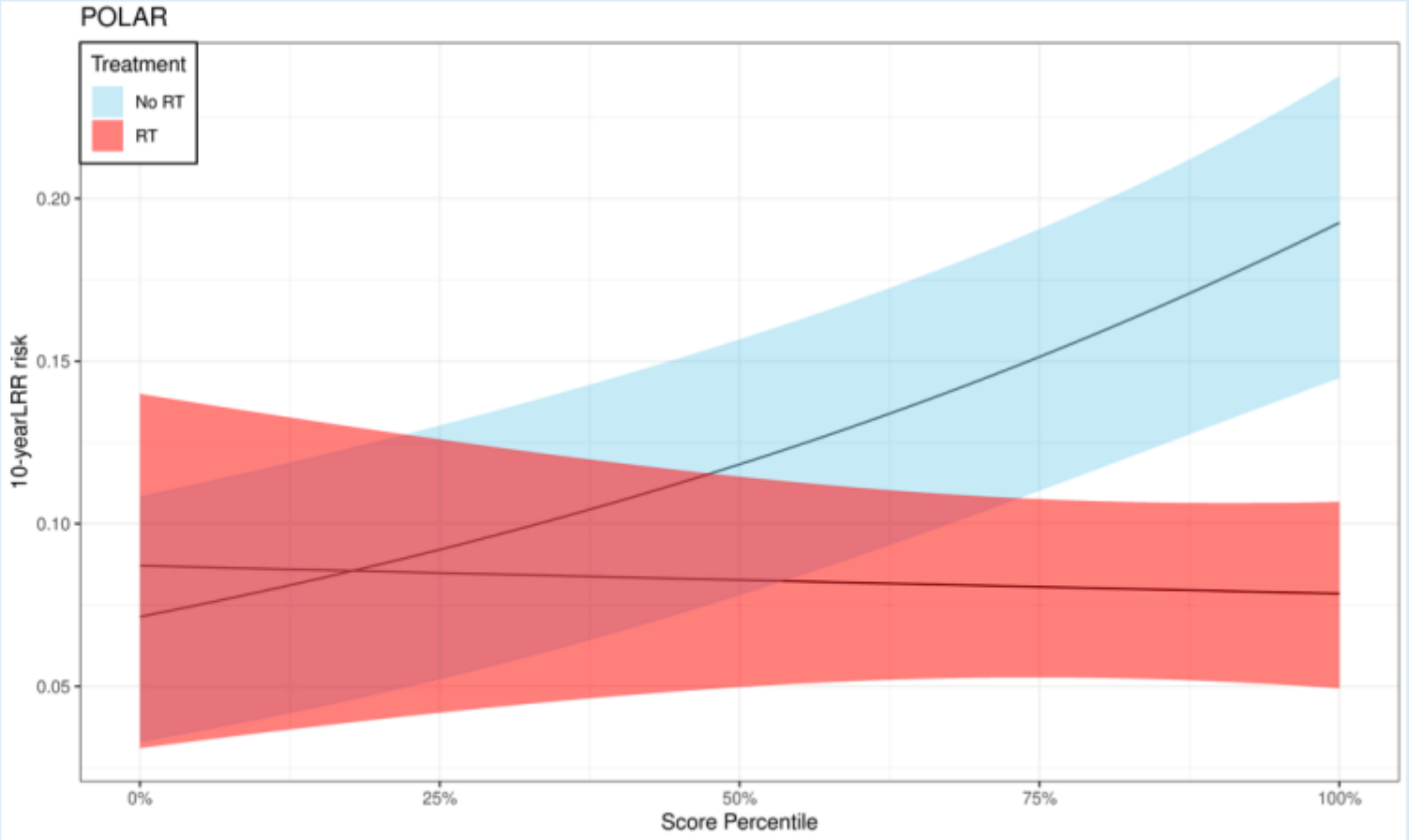
Results

POLAR x RT interaction analysis

Cox PH model with POLAR x RT interaction term (N=623) and 10-year LRR risk

POLAR score was predictive of RT benefit. Patients with a low POLAR score show no apparent benefit from RT

Variable	HR [95% CI]	p-value
POLAR	1.54 [1.24-1.91]	0.00008
Radiotherapy	1.06 [0.46-2.45]	0.89
POLAR : Radiotherapy	0.64 [0.44-0.94]	0.022



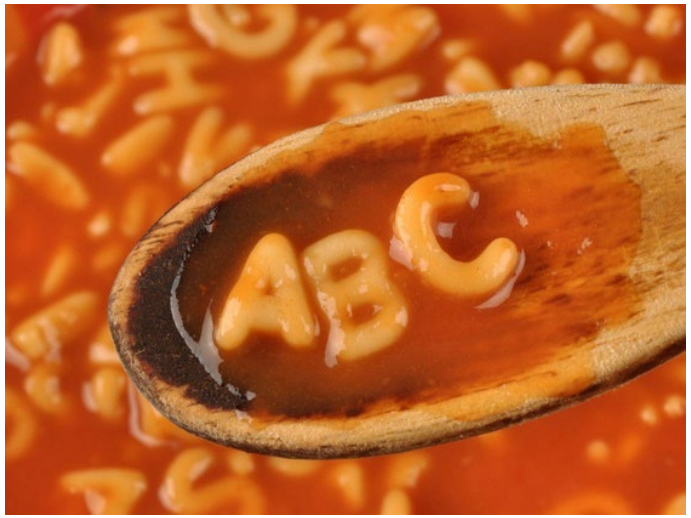
Courtesy of Dr. Karlsson

Summary: POLAR Signature

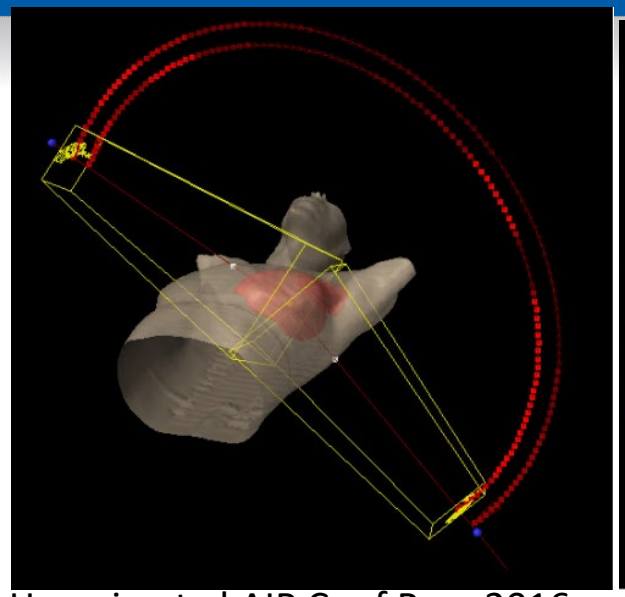
- Patient-level Meta-Analysis Validation of Genomic Signature
- POLAR is Prognostic
  - Significant Factor for Local Recurrence Risk on Uni- & Multi-variate Analysis
- POLAR is Predictive
  - Test for interaction between POLAR and RT as a predictive classifier of benefit from RT was positive, p = 0.022
- BUT
  - About half (354/623) of patients from SweBCG91-RT trial that developed POLAR
  - Need Contemporary patients (8% SweBCG91-RT received HT or CT)
  - Need Prospective trials

Advances in RT- NEW(ish) Technology

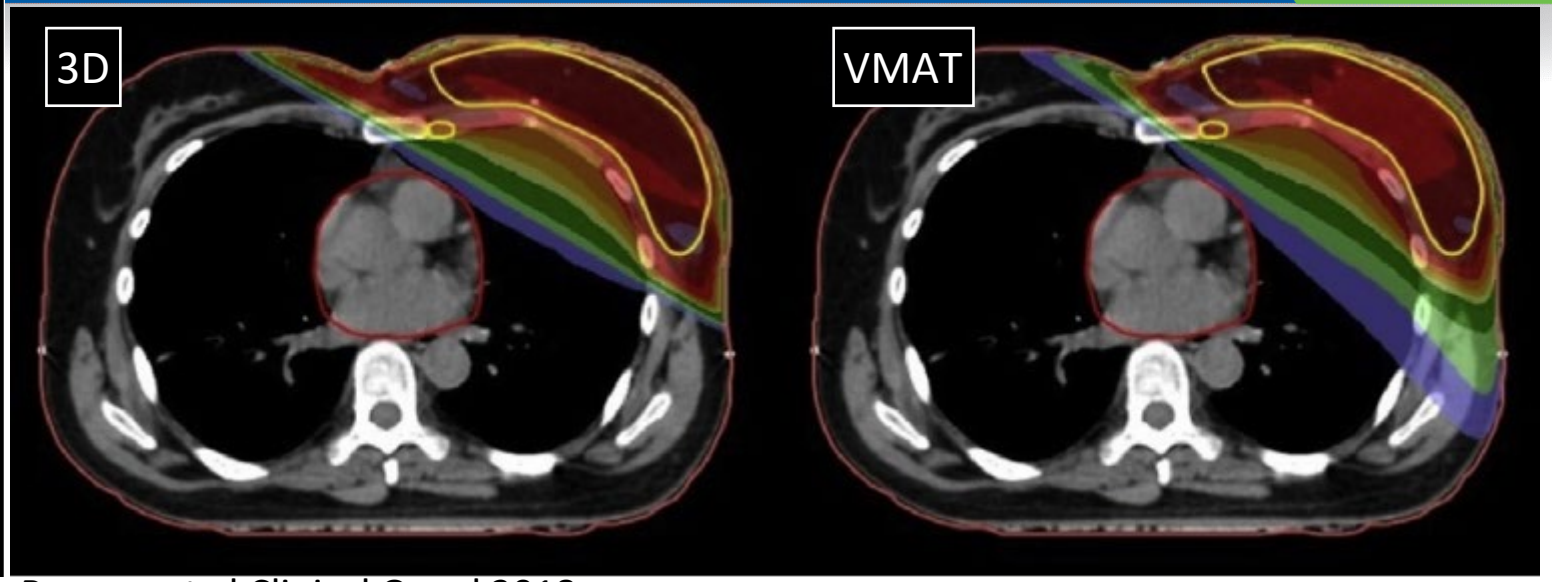
- VMAT
  - APBI
  - LABC / Difficult anatomy
- Proton Therapy
  - TBD



From 3D to IMRT / VMAT



Hossain et al,AIP Conf Proc 2016

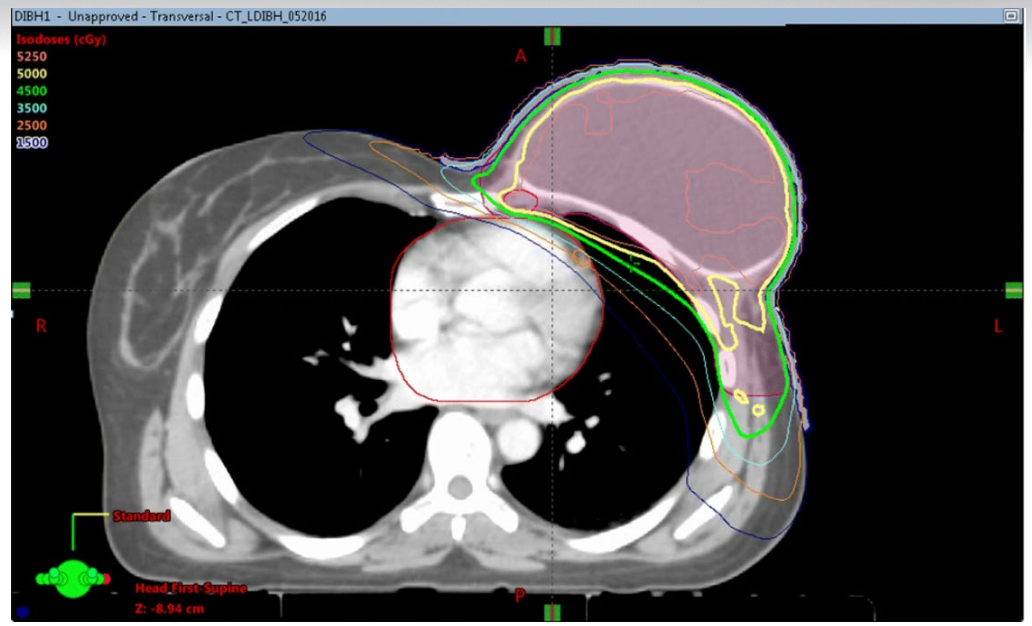


Ranger, et al Clinical Oncol 2018

- Volumetric Modulated Arc Therapy
  - Better conforms HIGH dose(s)
  - Worse low dose(s) distribution

VMAT

Riou et al, Radiat Oncol 2015

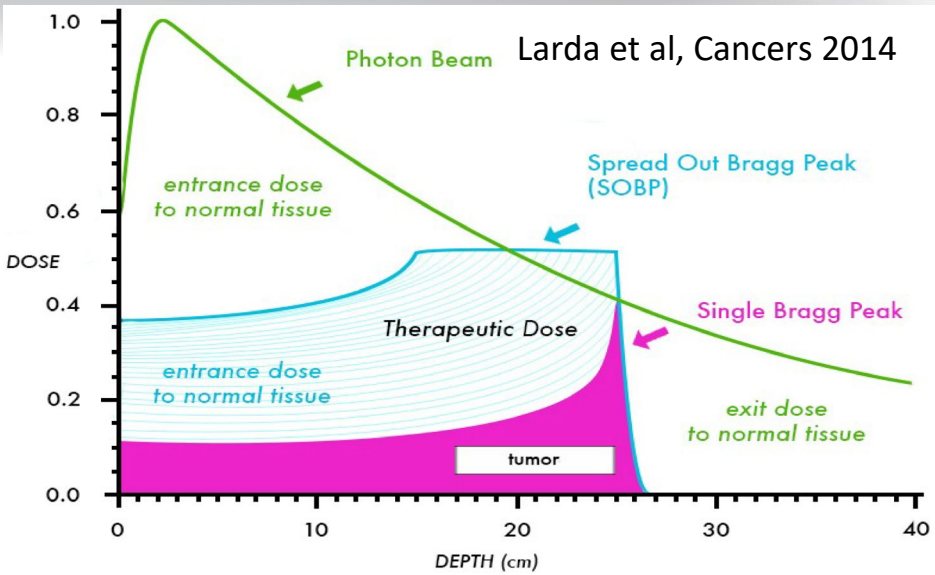


Dumane et al, Radiat Oncol 2018

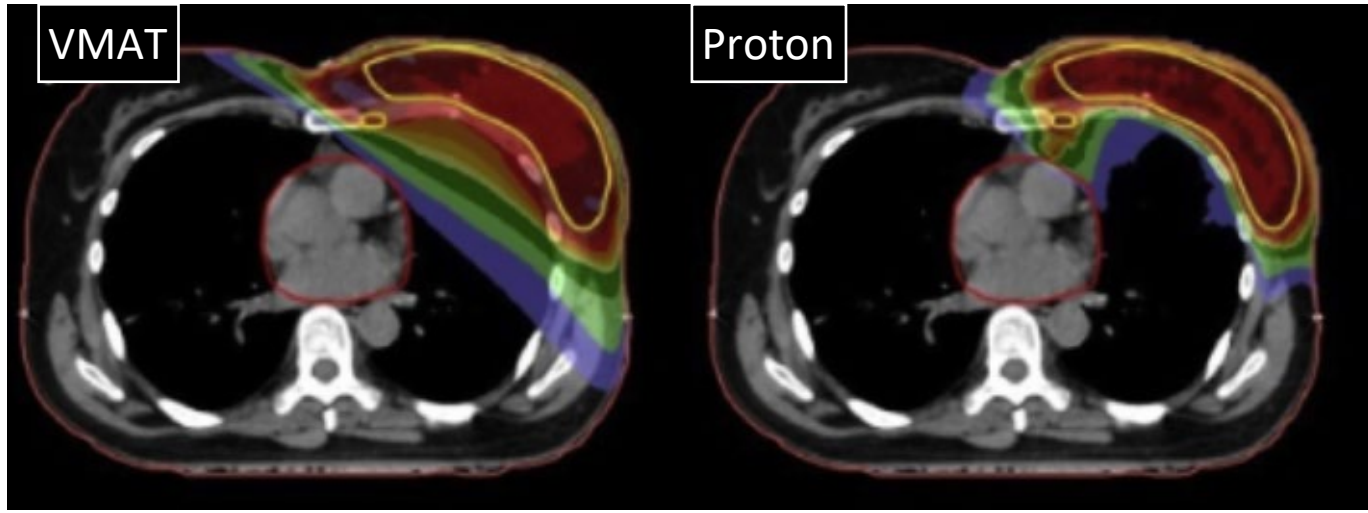
- Not Routine!
- Roles: APBI, Difficult anatomy,LABC, Re-RT
- Art of Tradeoffs – More low-dose to heart, contralat breast, lung

Proton Therapy

- Dose deposit at Bragg Peak
  - Sharp fall-off distally
  - Depth a function of energy
  - Reduces “exit dose” to normal tissues



Larda et al, Cancers 2014



Ranger, et al Clinical Oncol 2018

Ph II Study – Protons for BrCa + RNI

- 69 patients treated with RNI (63 left breast)
- 1^ endpoint: gr3+ pneumonitis or any gr4 toxicity
- Median age 45 years old; 94% stage II-III / 93% mastectomy / 99% chemotherapy

	Dose, Gy (RBE), Median (range)		
Target Structures	**Mean**	**Minimum**	**Maximum**
Chest wall/breast (n = 71)	49.9 (44.9-51.5)	39.6 (24.4-49.1)	52.5 (47.2-61.7)
Internal mammary nodes (n = 71)	48.8 (40.7-62.3)	40.1 (14.3-53.0)	52.3 (45.4-66.8)
Supraclavicular fossa (n = 66)	46.0 (43.8-51.2)	40.5 (32.0-49.1)	48.8 (46.0-57.6)
Axilla, level 1* (n = 43)	47.6 (42.0-52.1)	42.9 (37.0-49.4)	51.6 (46.7-58.2)
Axilla, level 2 (n = 62)	47.5 (44.1-51.8)	42.7 (30.1-49.4)	51.5 (46.8-55.7)
Axilla, level 3 (n = 68)	47.0 (44.6-51.6)	42.1 (32.7-50.0)	51.1 (46.9-61.8)
Avoidance structures			
Heart (n = 69)	0.50 (0.10-1.70)	0.10 (0.01-0.10)	16.6 (4.20-46.4)
LAD (n = 65)	1.16 (0.09-12.0)	0.10 (0.01-1.50)	4.70 (1.10-42.2)
Ipsilateral lung dose (n = 69)	7.72 (2.39-13.8)	0.10 (0.01-0.10)	45.9 (39.3-58.6)
Ipsilateral lung, V20 (n = 69)	14.5% (8.76-22.24)	—	—

Jiminez et al, JCO 2019

Ph II Study – Protons for BrCa + RNI

Toxicity	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)
Acute			
Skin dermatitis	10 (14)	57 (83)	2 (3)
Dysphagia	19 (28)	5 (7)	0
Fatigue	38 (55)	24 (35)	0
Subacute/late			
Hyperpigmentation	36 (52)	—	—
Telangiectasia	11 (16)*	—	—
Atrophy	1 (1)*	—	—
Lymphedema	1 (1)	0	0
Seroma	0	0	1 (1)
Infection	0	0	1 (1)
Radiation pneumonitis	3 (4)	1 (1)	0
Rib fracture	5 (7)	0	0

NOTE. n = 69.
*All telangiectasia/atrophy were observed in the three-dimensional passively scattered protons cohort.

- Rate of grade 3 radiation pneumonitis was 0%
- Overall toxicity was limited, BUT notable is the rate of rib fracture (7%)!

Jiminez et al, JCO 2019

MAYO CLINIC

Phase 2 randomized trial of conventional versus hypofractionated post-mastectomy proton radiotherapy

Robert W. Mutter, MD
Associate Professor
Department of Radiation Oncology
Mayo Clinic, Rochester, MN
mutter.robert@mayo.edu

Ph II Study: PMRT Dose with Protons

- 88 Patients, randomized
  - PMRT with Protons
  - 50 Gy /25 vs 40 Gy / 15

Dosimetric outcomes	25 fraction N = 41	15 fraction N = 41
Heart mean	0.54 Gy	0.49 Gy
Ipsilateral lung V20 Gy	13.9%	8.6%

- 1^ Endpoint: 24 month complication rate of 15 fraction proton PMRT is acceptable (non-inferior) to 25 fractions
- Results: No significant difference in complication rates
  - Non-inferiority could not be established; Sample size?

Mutter et al, SABCS 2022

Ongoing Trials

- RadCOMP — ClinicalTrials.gov Identifier: NCT02603341
  - Ph III: Protons vs Photons
  - Target accrual ~1300 pts (90% accrued)

- RT-CHARM (Alliance A221505) — ClinicalTrials.gov Identifier: NCT03414970
  - PMRT With Breast Reconstruction
  - Ph III: Standard (25 fractions) vs Hypofractionation (16)
  - Completed accrual 900 pts

Conclusions

- Advances in Radiotherapy
  - Dose / fractionation (Less!)
  - Target (Partial Breast)
  - Personalized Biomarker (POLAR)
  - Technology (VMAT, Proton)
- Less Toxicity
  - Improved Therapeutic Ratio!

Thank you!