2014 San Antonio Breast Cancer Symposium: Surgical and Radiation Updates

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Abstracts

1. A Large Prospectively-Designed Study of the DCIS Score: predicting recurrence risk after local excision for ductal carcinoma in situ patients without irradiation (S5-04)
2. The Connecticut Experiment: 4 years of screening women with dense breasts with bilateral ultrasound (S5-01)
3. Final Survival Analysis from the Randomized Women's Intervention Nutrition Study (WINS) Evaluating Dietary intervention as Adjuvant Breast Cancer Therapy (S5-08)

Abstracts

4. Accelerated Partial Breast Irradiation using Intensity Modulated Radiotherapy versus Whole Breast Irradiation: 5-year survival results of a phase 3 randomized trial (S5-03)
5. Underutilization of Hypofractionated Radiation Therapy in Breast Cancer Patients
   a) Utilization of Hypofractionated Radiation Therapy for Early Stage Breast Cancer in Women over 50 years of age (P1-15-02)
   b) The Adoption of Hypofractionated Whole Breast Irradation for Early-Stage Breast Cancer: A national cancer data base analysis (P1-15-03)
   c) Low Utilization of Hypofractionated radiotherapy for the treatment of Early-Stage Breast Cancer in the US (P1-15-10)

A Population-Based Validation Study of the DCIS Score Predicting Recurrence Risk in Individuals Treated by Breast-Conserving Surgery

Rakovitch E, Nofech-Mozes S, Hanna W, Baehner FL, Saskin R, Butler SM, Tuck A, Sengupta S, Elavathil L, Jani PA, Bonin M, Chang MC, Robertson, S, Slodkowska E, Fong C, Anderson JA, Jamshidian F, Cherbavaz DB, Shak S, Paszat L

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2014 San Antonio Breast Cancer Symposium

Background

- DCIS is associated with high survival but treatment is recommended due to risk of recurrence (DCIS or invasive cancer)
  - Breast-conserving surgery (BCS) often followed by radiation
- BCS alone is an option for individuals with low risk of local recurrence
- Traditional clinical and pathologic factors do not reliably identify individuals at low risk of recurrence after breast-conserving surgery
- Biomarkers needed to improve risk assessment of individuals with DCIS treated by breast-conserving surgery

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Oncotype DCIS Score as a Predictor of Local Recurrence: ECOG E5194 Analysis

- E5194, prospective cohort study of selected individuals treated by breast conserving surgery alone (no radiation)
  - ≤ 2.5 cm, nuclear grade 1 or 2
  - ≤ 1 cm nuclear grade 3
  - Resection margins > 3 mm

- 327 cases analyzed to examine the association of the DCIS Score and local recurrence

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ECOG E5194

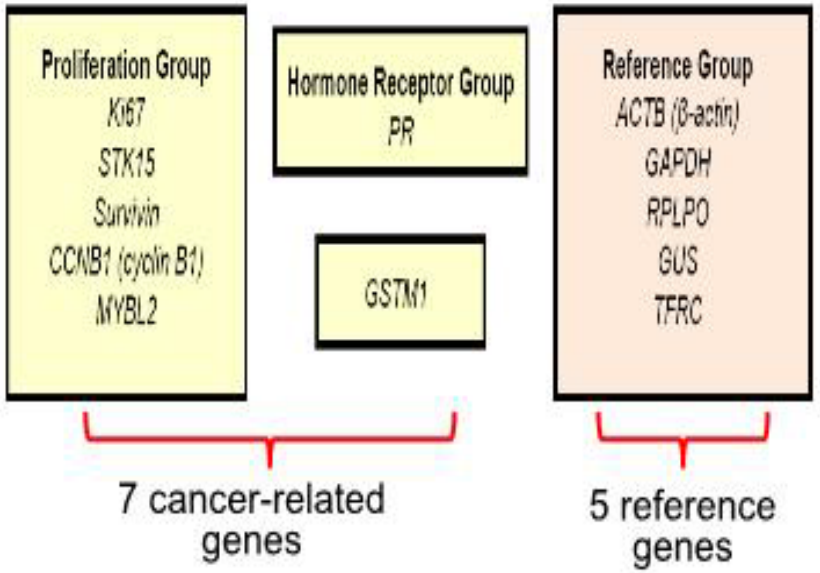
- Median Age 60 yrs (28-88 years)
  - 75% greater than age 50
- Median tumor size:
  - 6mm (Low to intermediate grade)
  - 5mm (High grade)
  - 87% of tumors were less than 1.0cm
- 73% post-menopausal
- Median f/u of 6.2 yrs

Hughes et al. JCO 2009

Oncotype DX DCIS Score

- Multigene expression assay
- 12 of 21 genes from Oncotype DX Recurrence Score
- DCIS Score:
  - Continuous score (0-100)
  - 3 pre-specified risk groups:

Low	< 39
Intermediate	39 – 54
High	≥ 55



- Provides individualized estimates of the 10-year risk of local recurrence in patients with DCIS treated by breast-conserving surgery alone

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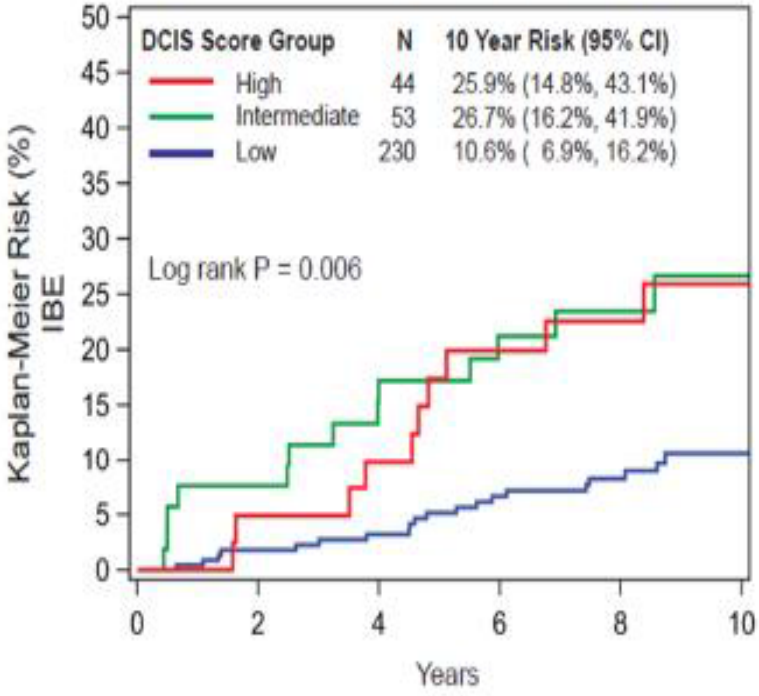
Oncotype DCIS Score as a Predictor of Local Recurrence: ECOG E5194 Analysis

- Ipsilateral local recurrence:
  - DCIS Score HR (per 50 units) = 2.31 (95% CI: 1.15, 4.49,p=.02)
  - Adjusted for tamoxifen
- Ipsilateral invasive recurrence:
  - DCIS Score HR (per 50 units) = 3.68 (95% CI: 1.34, 9.62,p=.01)
  - Unadjusted



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MVA Models of Risk for IBE

	Hazard Ratio (95% CI)	P value
Excluding the DCIS Score		
Tumor size	1.54 (1.14, 2.02)	0.01
Postmenopausal	0.49 (0.27, 0.90)	0.02
Including the DCIS Score		
DCIS Score	2.41 (1.15, 4.89)	0.02
Tumor size	1.52 (1.11, 2.01)	0.01
Postmenopausal	0.49 (0.27, 0.90)	0.02

For study cohort, surgical margins, grade, comedo necrosis, and DCIS pattern, all $p > 0.46$. For tamoxifen, $p = 0.09$.

Solin et al. JNCI 2013

Clinical Relevance

- Ideally, the DCIS score could be used to tell a young, pre-menopausal woman with any size DCIS that she will not need radiation following lumpectomy
- Current data clearly supports the use of DCIS score in post-menopausal women with <1.0cm DCIS
- Can the DCIS score be used in the general population?

Study Objectives

Primary Objective

- To evaluate if the DCIS Score is associated with the risk of **local recurrence** (DCIS or invasive) in patients treated with **BCS alone** with negative margins
  - In ER positive patients (by quantitative RT-PCR)
  - All patients regardless of ER status

Secondary Objectives

- To evaluate if the DCIS Score is independently associated with LR adjusting for significant clinical and pathologic factors
- To evaluate if the DCIS Score is associated with the risk of:
  - Invasive local recurrence
  - DCIS local recurrence

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Study Design

Study population

- Population based cohort of cases diagnosed with pure DCIS in Ontario 1994-2003
- Breast-conserving surgery alone
- Negative resection margins

Statistical Analytical Plan

- Pre-specified study objectives, Laboratory assays, Endpoints
- Oncotype DCIS Score
  - Continuous variable (0 – 100)
  - 3 pre-specified risk groups:

Low	< 39
Intermediate	39 – 54
High	≥ 55

Statistics

- Cox proportional hazards models
- Kaplan-Meier estimates to evaluate 10-year risk of recurrence by DCIS risk group (log rank tests used to compare risk groups)

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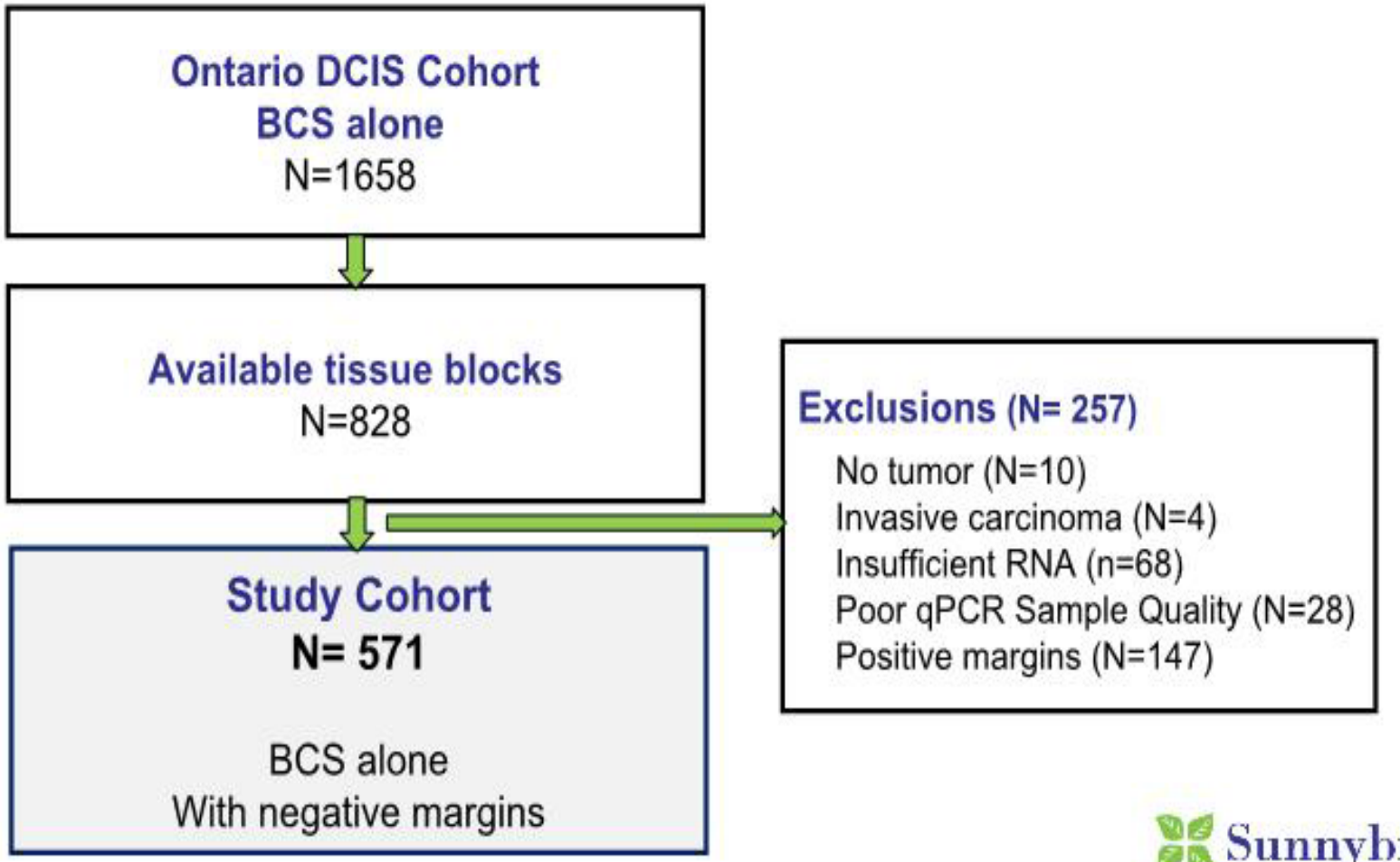
Ontario Cohort



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Patient Characteristics
Ontario Cohort (N=571)

Age ≥ 50 years	459 (81%)
Nuclear Grade	
Low	55 (10%)
Intermediate	332 (58%)
High	184 (32%)
Comedo Necrosis	350 (61%)
Solid Subtype	358 (63%)
Tumor Size	
≤ 10 mm	150 (26%)
> 10 mm	140 (25%)
Missing	281 (49%)
Multifocality*	114 (20%)
ER+ by RT-PCR	541 (95%)
HER2+ by RT-PCR	100 (17.5%)

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*Presence of at least 2 foci of DCIS in the same quadrant at least 5 mm apart
Sikand et al. J Clin Path, 2005

Ontario Cohort Outcomes

- Median follow-up = 9.6 years
- Local recurrence = DCIS or invasive breast cancer in same breast 6 months or more after diagnosis of DCIS
- N=100 local recurrences
  - N=57 invasive
  - N=44 DCIS
- 10 year Kaplan Meier risk of local recurrence = 19.2%

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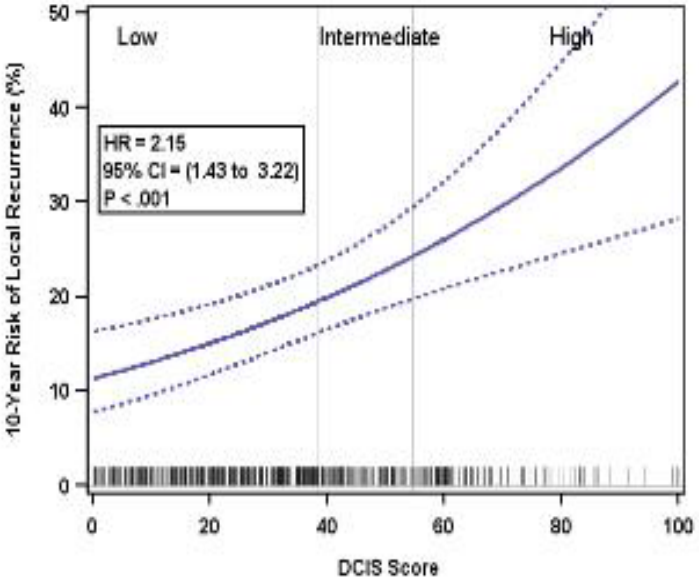
DCIS Score as a Predictor of Local Recurrence: *Univariable Analysis*

Endpoint	HR (95% C.I.)*	*P* value
Local Recurrence in ER+ DCIS	**2.26 (1.41, 3.59)**	<0.001
Local Recurrence in all Patients	**2.15 (1.43, 3.22)**	<0.001

Continuous DCIS Score



* Cox model HRs for a 50 point increase in the DCIS Score

✓ Primary pre-specified endpoints met

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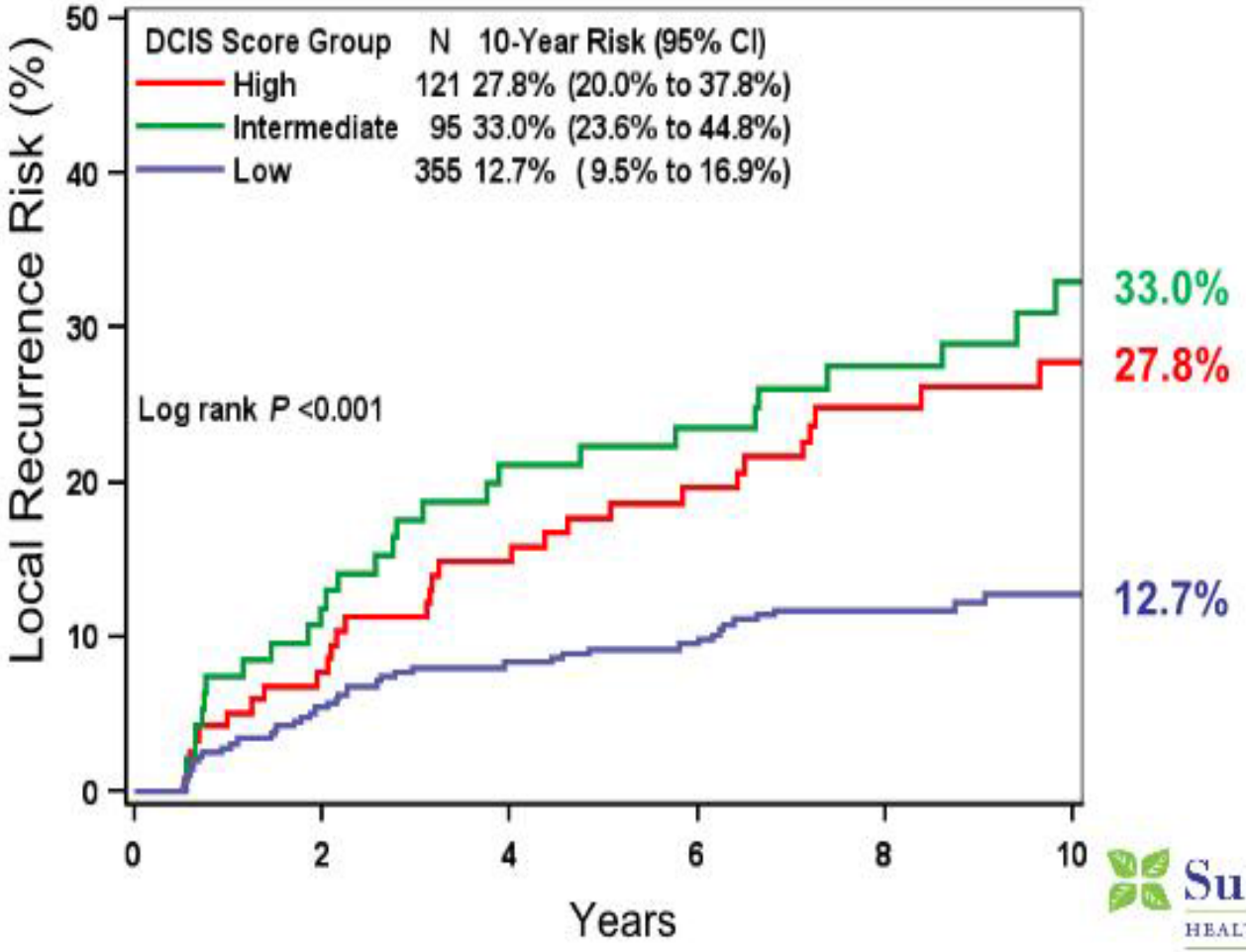
Kaplan-Meier 10-year Risk of Local Recurrence by DCIS Score Risk Group



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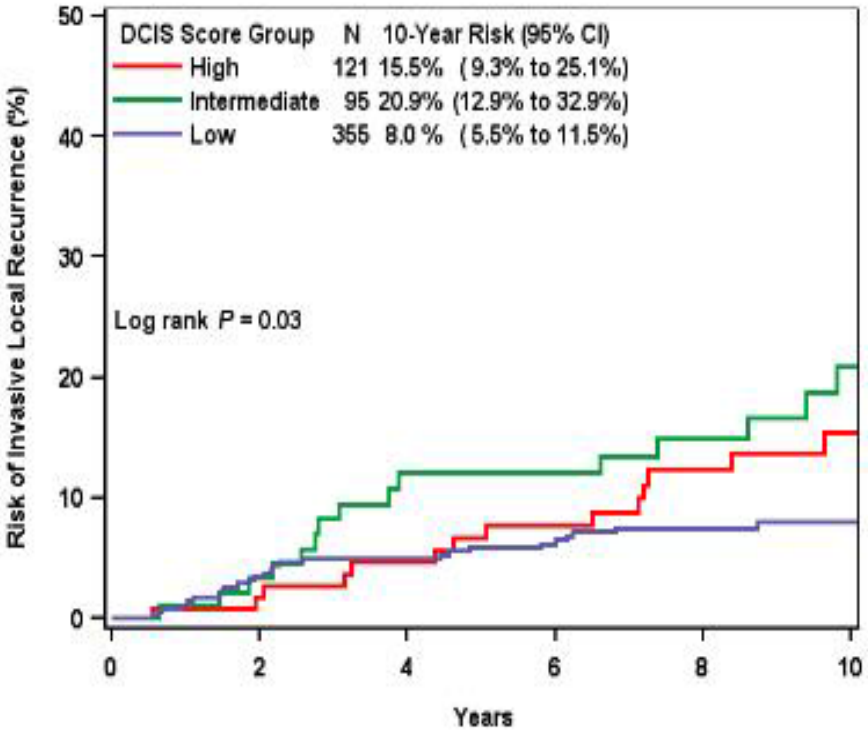
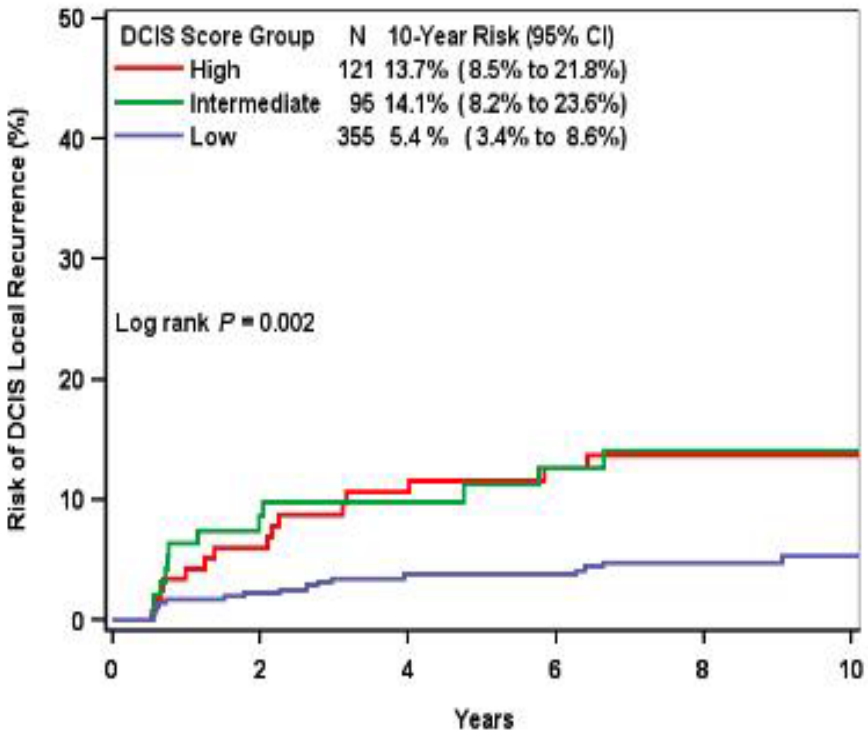
10-year Risk of Invasive and DCIS Local Recurrence by DCIS Score Risk Group

Invasive Local Recurrence



DCIS Local Recurrence



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Factors Associated with Local Recurrence: *Multivariable Analysis*

Characteristic	N	HR (95% C.I.)	*P* value*
DCIS Score /50	**571**	**1.68 (1.08, 2.62)**	**0.02**
Age at diagnosis (yr)			0.03
< 50	110	**1.75 (1.07, 2.76)**	
≥ 50	459	1.0	
Tumor size			0.01
>10mm	140	**2.07 (1.15, 3.83)**	
≤10mm	150	1.0	
Subtype			0.04
Solid	358	**1.63 (0.97, 2.88)**	
Cribriform	175	1.0	
Multifocality*			0.003
Present	114	**1.97 (1.27, 3.02)**	
Absent	457	1.0	

Presence of at least 2 foci of DCIS in the same quadrant at least 5 mm apart
Sikand et al. J Clin Path, 2005

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Conclusion

- DCIS score is associated with the risk of local recurrence and invasive local recurrence in a population of patients with pure DCIS treated with breast conserving surgery alone (no radiation)

Does this study support the use of the DCIS score in the general population?

Take Home Message

- For clinical decision making, not really

Take Home Message

- For clinical decision making, not really
- DCIS score appears a reliable predictor of local recurrence following breast conserving surgery alone (no radiation) in:
  - Women > age 50 (post-menopausal)
  - DCIS size ≤ 1.0 cm
  - *Cribiform subtype*
  - *Unifocal*

San Antonio Breast Cancer Symposium-December 9-13, 2014

Hartford HealthCare

The Connecticut Experiment:
4 Years of Screening Women with Dense Breasts with Bilateral Ultrasound

Jean M Weigert MD FACR
Director of Breast Imaging
The Hospital of Central Connecticut
Mandell and Blau MD's PC
New Britain CT

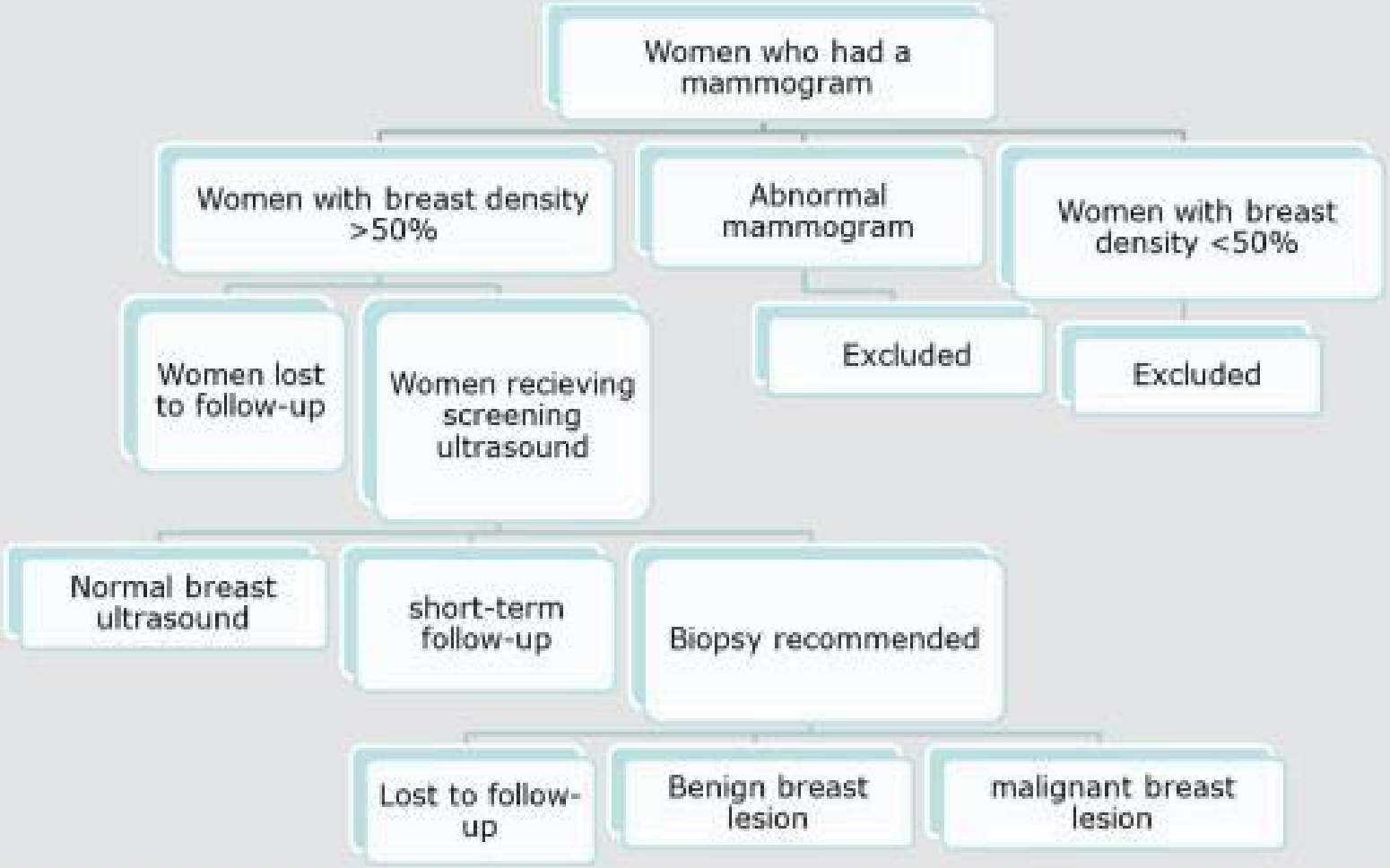
ORIGINAL STUDY

- **Purpose:** To determine if screening breast ultrasound in women with mammographically normal but dense breasts is useful for the detection of breast cancer.
- **Objectives:** Determine PPV, cancer detection rates types of cancers detected including size and node status. Establish ideal screening population, benefits, and risks.

STUDY DESIGN

- Retrospective chart review
- Data was collected on
  - Number of mammograms performed
  - Number of screening breast ultrasounds
  - BIRADS breakdown of ultrasounds
  - Biopsy proven malignancies and high risk lesions.
  - Patient demographics on biopsy proven high risk lesion/malignancy.

SCHEMATA OF DATA COLLECTION



Results

	Year 1	Year 2	Year 3	Year 4
Screening Mammograms	30670	32050	32230	27937
Ultrasounds for Dense Breasts	2706	3351	4128	3331
BIRADS 4 and 5 Ultrasounds	151	180	178	53
Cancers	11	11	13	11
PPV	7.1	6.1	8.1	17.2
# Cancers per 1000 Screened	4.0	3.2	3.2	3.3
% Eligible Screened	22.1	26.1	32.0	28.3

Results

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BIRADS 4 and 5 Ultrasounds	151	180	178	53
Cancers	11	11	13	11
PPV	7.1	6.1	8.1	17.2
# Cancers per 1000 Screened	4.0	3.2	3.2	3.3
% Eligible Screened	22.1	26.1	32.0	28.3

LESION CHARACTERISTICS YEAR 1

Type of Lesion	Size on USG	Histologic Grade	Receptor status	Sentinel Nodes	Age	Risk Factors
IDC	1.5	1	ER/PR+	0	57	cousin
IDC	2.2	2	ER/PR+	1 macro-met	50	none
IDC	1.5	2	ER/PR+	0	48	Mat. grandmother
IDC/ILC	1.2	3	ER?PR+	1 macro-met	61	none
IDC/ILC	1.5	3	ER/PR+	0	57	none
IDC/ILC/DCIS	1.2x0.8	2	ER/PR+	0	49	none
ILC	3.0x3.0	2	ER/PR+	0	50	none
ILC	2.5x2.0	2	ER/PR+	0	78	none
Mucinous colloid	8.0	2	ER/PR+	0	45	none
DCIS	3.7x3.0	2	ER+/PR-	0	50	none
Papillary intra-cystic with DCIS	1.2	2	ER/PR+	0	57	none

LESION CHARACTERISTICS YEAR 4

Type of Lesion	Size on USG	Histologic Grade	Receptor status	Sentinel Nodes	Age	Risk Factors	Prior USG
IDC	1.5	3	ER/PR+	1 macro-met	48	none	
IDC	1.2	3	ER/PR+	1 macr-met	66	none	
IDC	3	2	ER/PR+	1 micro-met	48	none	
IDC/DCIS	2.1	3	ER?PR+	2 macro-met	76	none	
ILC	0.4	2	ER/PR+	0	76	none	2012
ILC	1.2	2	ER/PR+	0	49	none	2011
ILC/LCIS	1.2	2	ER/PR+	0	46	none	
mixed IDC/ILC	1	2	ER/PR+	0	57	uterine	2012
mixed IDC/ILC	1	2	ER/PR+	0	61	prior breast	2011
Tubular	0.4	1	ER+/PR-	0	54	none	
ALH/LCIS	0.4				66	prior breast	

DISCUSSION

- Screening Breast Ultrasound in women with Mammographically Dense breast tissue (> 50%) find Occult Cancers
- This has continued at the same rate/thousand over the first four years since enacting Legislation that mandates informing patients of the breast tissue density and allowing then to choose to have additional imaging with breast ultrasound.
- The PPV has improved indicating that as expected there is a learning curve in deciding which lesions to follow and which to biopsy. Cancers are found in women having yearly USG.
- Overall % eligible women seeking test remains steady at about 30% which may be due to lack of education but more likely cost/insurance issues

LIMITATIONS

Only four years of data-how many years do we need to prove the value of adding Bilateral Breast Ultrasound?

We have many more years of screening mammography and we know that there has been improved mortality. These are the exact same types of cancers.

The absolute Breast Density was not listed for each cancer ie no designation of 50-75% or >75%

This could be considered arbitrary as we didn't have "absolute" density data and don't know if that is relevant.

No Cost analysis was performed to determine the amount to diagnose each additional cancer.

Two earlier studies (refs. 6 & 7) did perform such an analysis and did not show the cost to be great. After all, what would the cost be compared to finding a cancer at a later stage which costs more to treat and have potentially increased mortality! Clearly more data and analysis is necessary!

CONCLUSION

- The addition of bilateral breast ultrasound to screening mammography in women with mammographically dense breast tissue (>50%) increases the ability to find cancers in this patient population.
- These are predominantly small and node negative unless of high grade.
- Women having repeat ultrasound are now having cancers diagnosed indicating that in this patient population this test should be part of their routine yearly "screening" procedure.

Take Home Message

Screening Breast Ultrasound may help with early detection of cancers in women with dense breasts but appears to be dependent on experience and expertise.

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Final Survival Analyses from the Women's Intervention Nutrition Study (WINS) Evaluating Dietary Fat Reduction as Adjuvant Breast Cancer Therapy

December 12, 2014

RT Chlebowski RT, Blackburn GL

for the Women's Intervention Nutrition Study Investigators

Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center

Beth Israel Deaconess Hospital

Background

- More recent observational studies on dietary fat intake and breast cancer outcome provide mixed results (3 of 6 cohort studies positive).
- Emerging evidence now provides more support for obesity being a lifestyle factor associated with adverse breast cancer outcome.

Makarem et al. Annu Rev Nutr. 2013;33:doi:10.1146/annurev-nutr-112912-095300.
Chlebowski et al. J Clin Oncol 2002;20(4):1128-43.
Demark-Wahnefried et al. Cancer Epidemiol Biomarkers Prev 2012;21(8):1244-59.
Ligibel et al. J Clin Oncol 2013;32(31):3568-74.

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Women's Intervention Nutrition Study (WINS) Evaluating Dietary Fat Reduction in Early Stage Breast Cancer

Eligibility Criteria:

- **Women 48-79 years**
- **Early breast cancer**
- **Primary surgery ± RTx**
- **Systemic therapy (ER^+: tamoxifen/chemotherapy ; ER^-: chemotherapy)**
- **Dietary fat intake > 20% of calories**

(n = 2437)

RANDOMIZE

Dietary intervention:
reduced fat intake
(n = 975)

Control
(n = 1462)

Primary Endpoint: Relapse-free survival

Randomization 60:40 within a year from primary surgery

Accrual 1994 – January, 2001
Intervention ended May 2004

Chlebowski RT, et al. *J Natl Cancer Inst 2006;98:1767.*

WINS: Dietary Intervention

- Goal: Reduce dietary fat intake (target 15% calories from fat), weight loss not an intervention target
- Diet Group: women given a fat gram goal by centrally trained, registered dieticians implementing a low fat eating plan [1, 2]
- Eight bi-weekly individual counseling sessions and subsequent contacts every 3 months
- Monthly group sessions
- Self-monitoring of fat gram intake, unannounced telephone calls
- Control Group: women had dietician contacts every three months

[1] Chlebowski, Rose, Buzzard, et al Breast Cancer Res Treat 20:73-84, 1992
[2] Winters, Mitchell, Smiciklas-Wright, et al J Am Diet Assoc. 104:551-9, 2004

WINS: Baseline Characteristics

	Diet	Control
Age-yrs (SD)	58.6 (7.27)	58.5 (7.61)
Time from 1^0 surgery to entry (SD), d	227 ± 96	221 ± 93
Tumor Size		
Mean (SD), cm	1.93 (0.9)	1.89 (0.9)
Nodal Status		
Negative – (%)	73.1%	72.9%
Mean No. + (SD)	2.0 (1.5)	20. (1.6)

WINS: Baseline Characteristics

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	Diet	Control
ER Status, n	975	1462
Positive	79.0%	81.3%
Negative	21.0%	18.7%
PgR Status, n	967	1452
Positive	67.8%	67.3%
Negative	28.4%	29.0%
Surgery, n	967	1452
Mastectomy	35.5%	29.9%
Breast Conserve	64.5%	70.1%

WINS: Baseline Characteristics

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	Diet	Control
Systemic Rx, n	975	1462
Tamoxifen alone	47.7%	47.4%
Tamoxifen + ChemoRx	38.5%	38.0%
ChemoRx alone	13.9%	14.6%
ChemoRx Regimen, n	505	763
AC	33.5%	31.9%
CMF	53.5%	53.7%
FAC/CAF	7.0%	7.0%
AC → T	6.3%	7.5%

Caloric Intake from Fat (%) at Baseline and Subsequently by Randomization Group

Randomization Group	Percent Caloric Intake from Fat				
	Baseline	12 Mos	36 Mos	60 Mos	72 Mos
Diet	29.6 ± 7.1	20.0 ± 7.8	21.7 ± 8.4	23.2 ± 8.4	23.0 ± 9.2
Control	29.6 ± 6.7	29.2 ± 8.2	30.7 ± 8.7	31.2 ± 8.9	31.4 ± 8.2

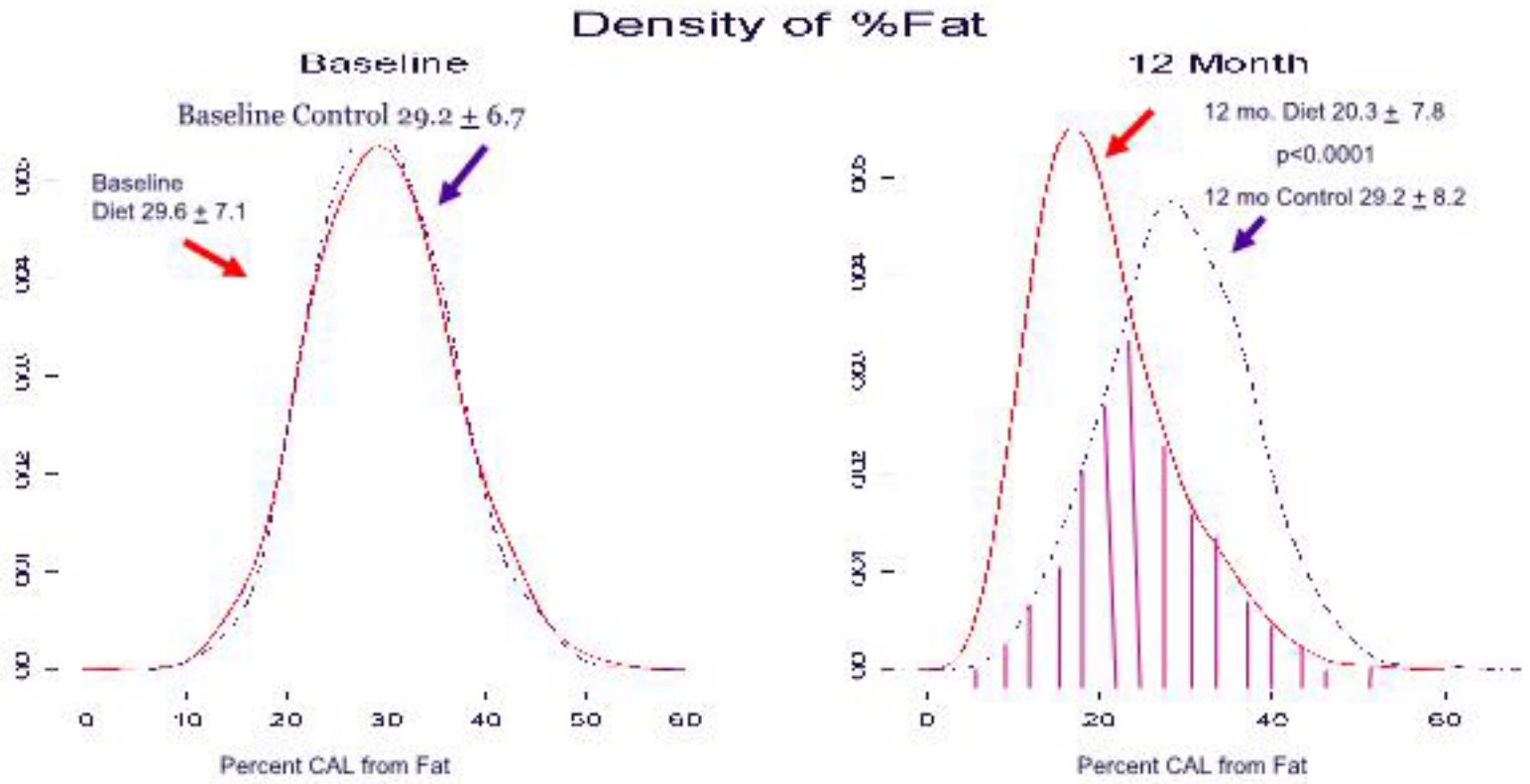
All values, P<.0001 versus control

Reduced caloric intake from fat (%) in Diet Groups

Information on dietary intake was available for 975 and 1461 of women in the dietary intervention group and the control group, respectively, at baseline; for 840 and 1328 women, respectively, at year 1; for 654 and 1077 women, respectively, at year 3; and for 380 and 648 women, respectively, at year 5.

Chlebowski RT, Blackburn GL, Thomson CA, et al J Natl Cancer Inst 2006;98:1767

WINS: % Calories from Fat by Randomization Group



Chlebowski RT, Blackburn GL, Thomson CA, et al J Natl Cancer Inst 2006;98:1767

Change in BMI and Weight by Randomization Group

	Diet Minus Control Group		
Variable	Year 1	Year 3	Year 5
BMI (kg/m^2)	-0.80 (-1.3 to -0.3)	-0.77 (-1.3 to -0.2)	-1.1 (-1.9 to -0.4)
Weight (LBS)	-5.0 (-8.0 to -2.1)	-3.9 (-6.9 to -0.5)	-6.0 (-9.9 to -1.9)

All values, $P < .005$ versus control
Reduced weight and BMI in Diet Group

BMI = Body Mass Index

All values for weight, $P = .005$, intervention versus control Information on weight and BMI was available for all 975 and 1462 women in the dietary intervention group and the control group, respectively, at baseline; for 854 and 1310 at year 1; 698 and 1044 at year 3; and 386 and 998 at year 5.

Chlebowski RT, et al. *J Natl Cancer Inst 2006;98:1767.*

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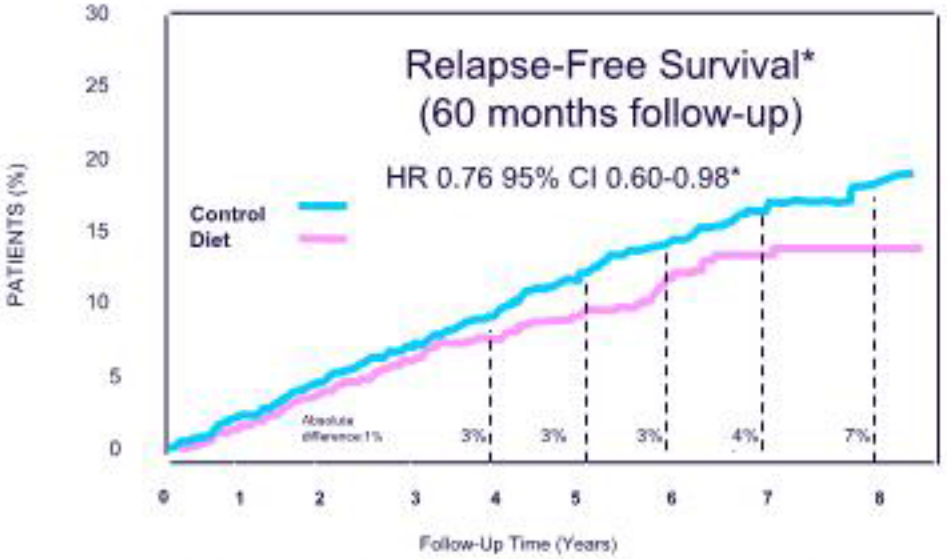
WINS Previously Reported Clinical Outcomes



*p=0.03, from adjusted Cox proportional hazard model

Overall Survival Subgroups (108 months follow-up)		
Group	HR, 95% CI	P-value
All	0.82 (0.64-1.07)	0.146
ER+, PR+	0.90 (0.64-1.28)	NS
ER-, PR-	0.36 (0.18-0.74)	0.003

Funding and intervention ended in May 2004.
Follow-up through 2013 (death registry), 19.4 year maximum

Chlebowski RT, Blackburn GL, Thomson CA, et al J Natl Cancer Inst 2006;98:1767
Chlebowski RT, Blackburn GL, Hoy MK, et al Proc Amer Soc Clin Oncol 26; Abstract 522, 2008

Study Purpose

Using National Death Registry data (DOBsearch.com), the primary purpose was to determine whether a lifestyle intervention targeting fat intake reduction will improve overall survival in early stage breast cancer patients receiving standard breast cancer management after a median follow-up period of 15 years.

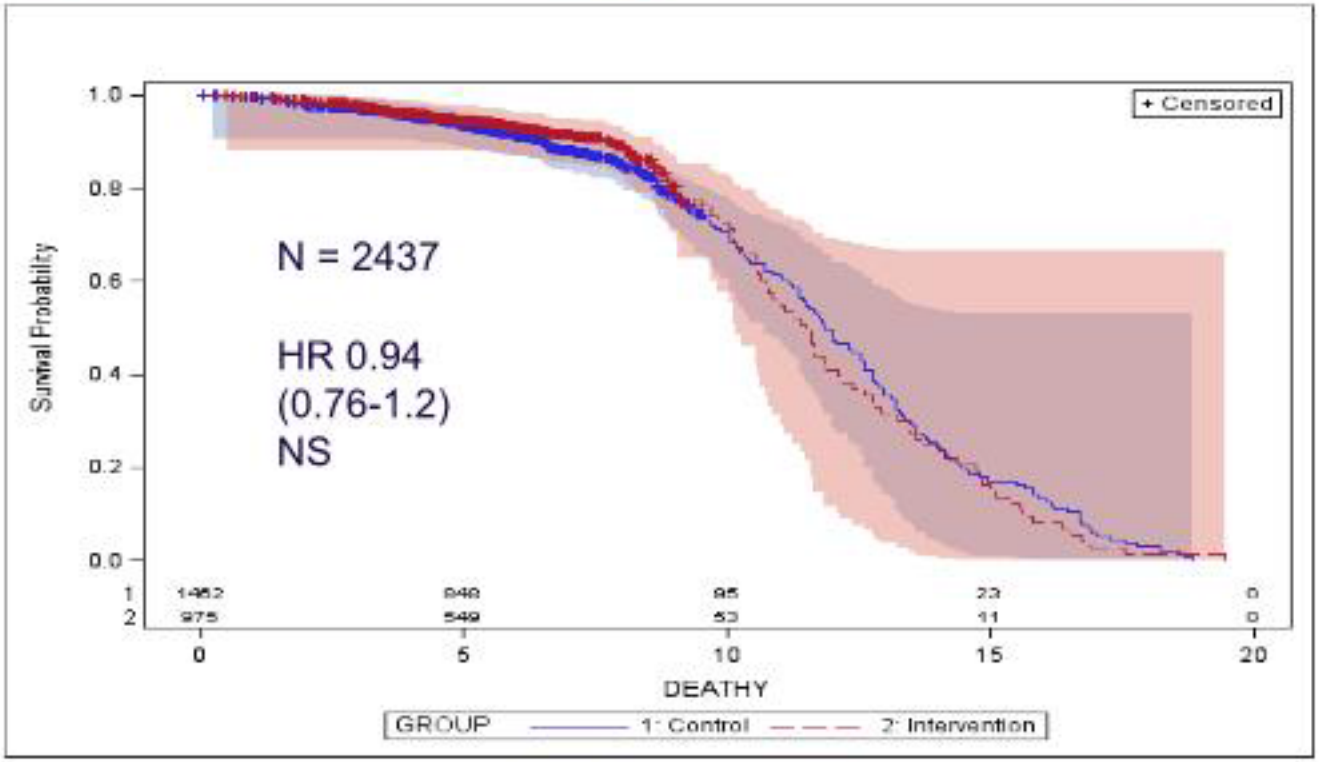
Death Rate by Randomization Group

	Number	Deaths	Percent
Control:	1462	250	17.0%
Diet:	975	133	13.6%

Lower death rate in Diet Group

Hazard ratios (HRs) are reported from Cox proportional hazards models and depicted in Kaplan Meier plots

WINS Survival for All by Randomization Groups



Product-Limit Survival Estimates With Number of Subjects at Risk and 95% Hall-Wellner Ba

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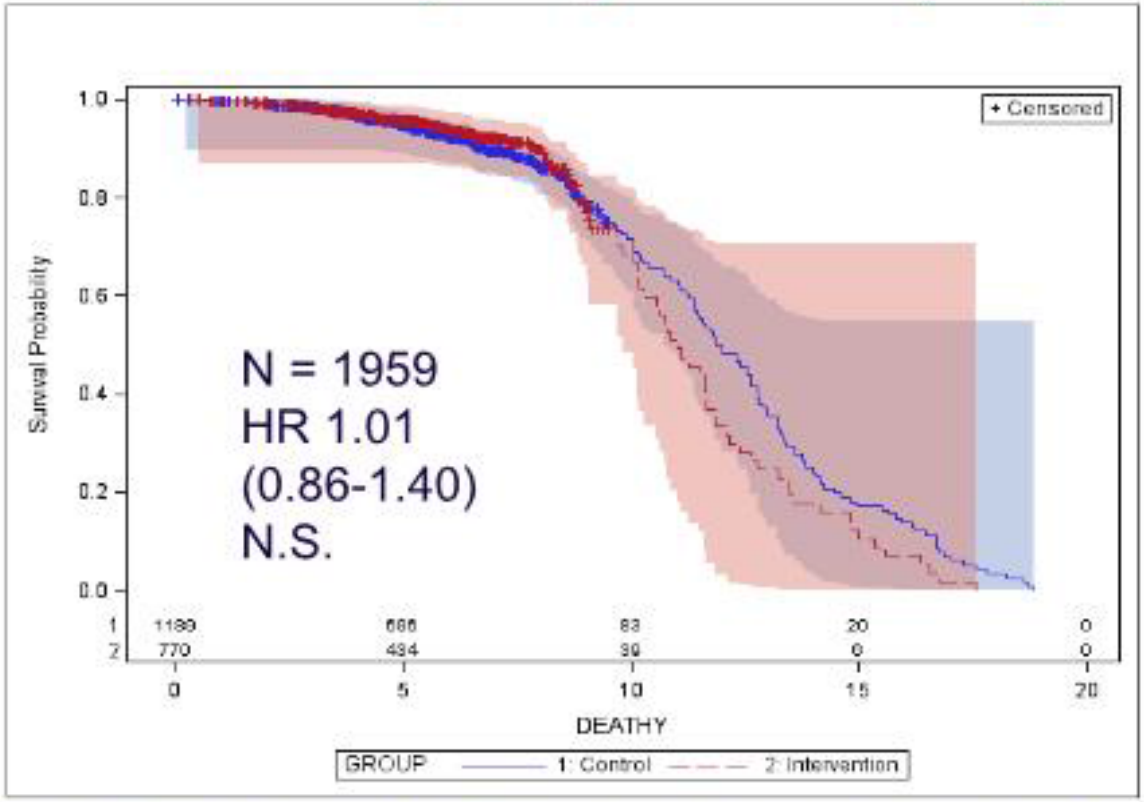
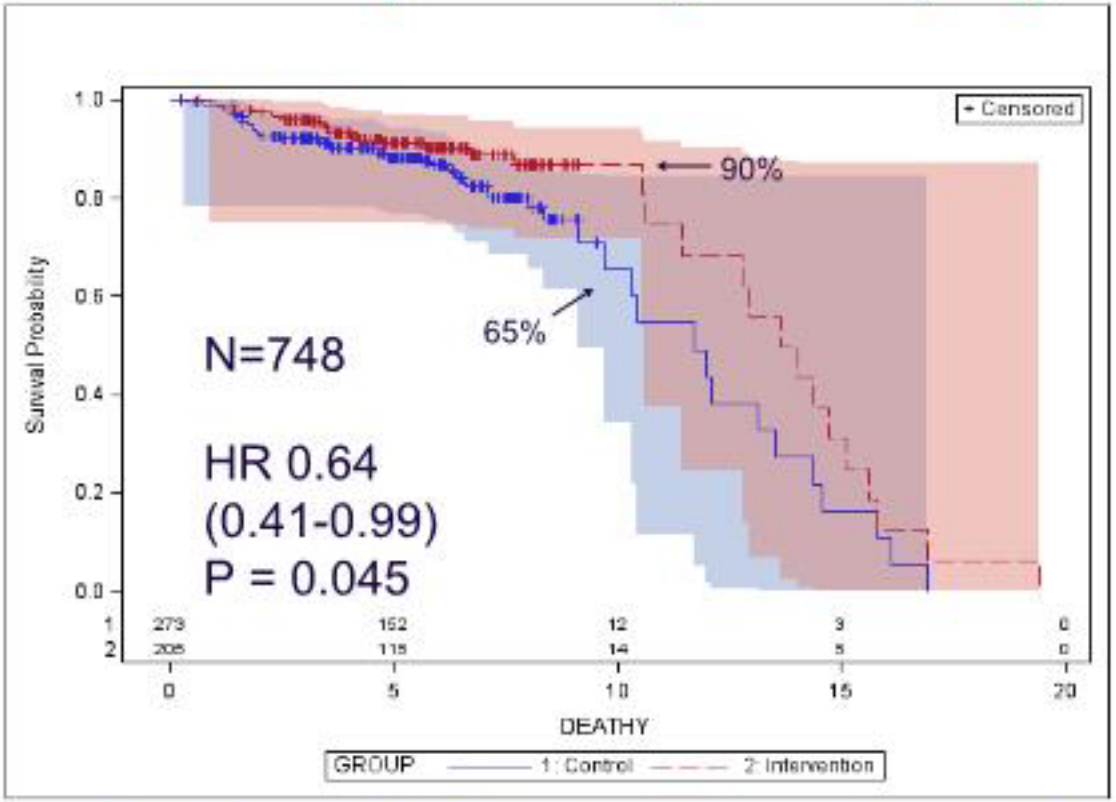
WINS Survival (ER positive) by Group



roduct-Limit Survival Estimates With Number of Subjects at Risk and 95% Hall-Wellner Ba

WINS Survival (ER negative) by Group



Median Survival
11.7 yrs
(9.1-14.4)
vs.
13.6yrs
(10.6-15.1)

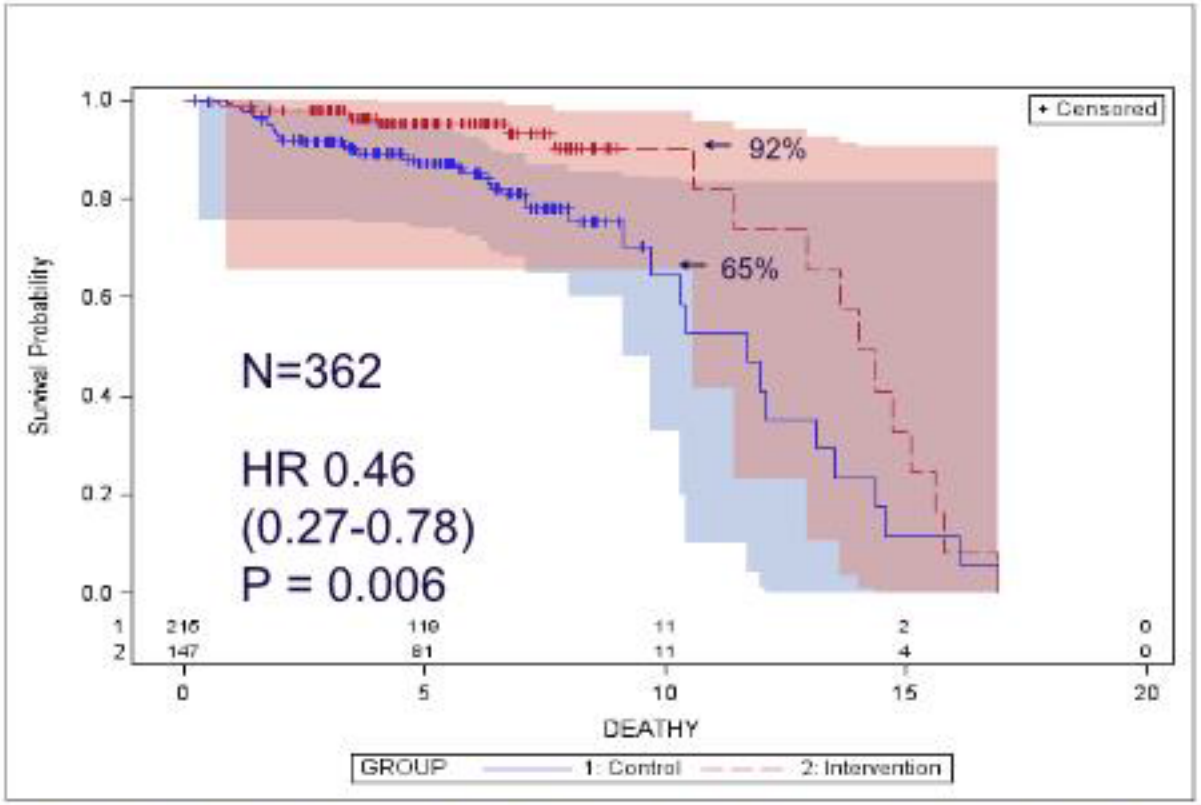
roduct-Limit Survival Estimates With Number of Subjects at Risk and 95% Hall-Wellner Ba

Cumulative Hazard Ratio for Death by Randomization Group Through Follow-up Years ER Negative

Years	HR	(95% CI)	p-value
1-3	0.49	(0.22-1.11)	0.087
1-5	0.71	(0.38-1.30)	0.264
1-7	0.64	(0.37-1.13)	0.127
1-10	0.58	(0.34-0.99)	0.045
1-15	0.69	(0.38-0.97)	0.036
1-20	0.64	(0.41-0.99)	0.045

San Antonio Breast Cancer Symposium, December 9-13, 2014

WINS Survival (ER and PR negative) by Group



Median Survival
11.7 yrs
(9.1-13.5)
vs.
14.0 yrs
(11.4-15.1)

Product-Limit Survival Estimates With Number of Subjects at Risk and 95% Hall-Wellner Ba

Cumulative Hazard Ratio for Death by Randomization Group Through Follow-up Years ER Negative and PR Negative

Years	HR	(95% CI)	p-value
1-3	0.23	(0.07-0.80)	0.021
1-5	0.34	(0.14-0.82)	0.017
1-7	0.32	(0.14-0.73)	0.006
1-10	0.31	(0.14-0.67)	0.003
1-15	0.38	(0.21-0.69)	0.001
1-20	0.46	(0.27-0.79)	0.006

Per SEER, 73% anticipated to be triple negative

Howlader et al. J Natl Cancer Inst 2014 Apr 28;106(5). pii: dju055. doi: 10.1093/jnci/dju055.

Limitations

- Post hoc Analysis
- Exploratory Subgroup Analysis
- Limited/no participant contact after intervention ended
- 1990s breast cancer treatment
- Her2 status unavailable
- No information on cause of death

WINS Conclusions

San Antonio Breast Cancer Symposium, December 9-13, 2014

- A lifestyle intervention targeting fat intake reduction associated with weight loss did not significantly increase overall survival of women with resected breast cancer receiving conventional cancer management.
- Exploratory analyses suggest favorable lifestyle influence on survival in hormone receptor negative subgroups and during active intervention.
- Given emerging evidence, future lifestyle interventions should best target weight loss/maintenance and increased physical activity.

Take Home Message

- Currently, strong and pro-active nutritional support which effectively promotes a low fat diet resulting in weight loss appears to be the only recommendation we can make for potentially preventing breast cancer recurrence in breast cancer patients following definitive treatment for hormone receptor negative tumors

Accelerated partial breast irradiation using intensity modulated radiotherapy versus whole breast irradiation

5-year survival results of a phase 3 randomized trial

Lorenzo Livi

Icro Meattini, Livia Marrazzo, Stefania Pallotta, Gabriele Simontacchi, Calogero Saieva, Vieri Scotti, Carla De Luca Cardillo, Paolo Bastiani, Jacopo Nori, Lorenzo Orzalesi, Simonetta Bianchi

Azienda Ospedaliero Universitaria Careggi

Department of Radiotherapy-Oncology
Florence University
Florence, Italy

PHASE 3 TRIAL DESIGN

ACCELERATED IMRT TO TREAT THE INDEX QUADRANT
30 Gy in 5 fractions (6 Gy/fr in 2 weeks)

versus

STANDARD WHOLE BREAST RADIOTHERAPY
50 Gy + boost 10 Gy in 30 fractions (2 Gy/fr in 6 weeks)

*AFTER CONSERVING SURGERY IN HIGHLY **SELECTED** EARLY BREAST CANCER **PATIENTS***

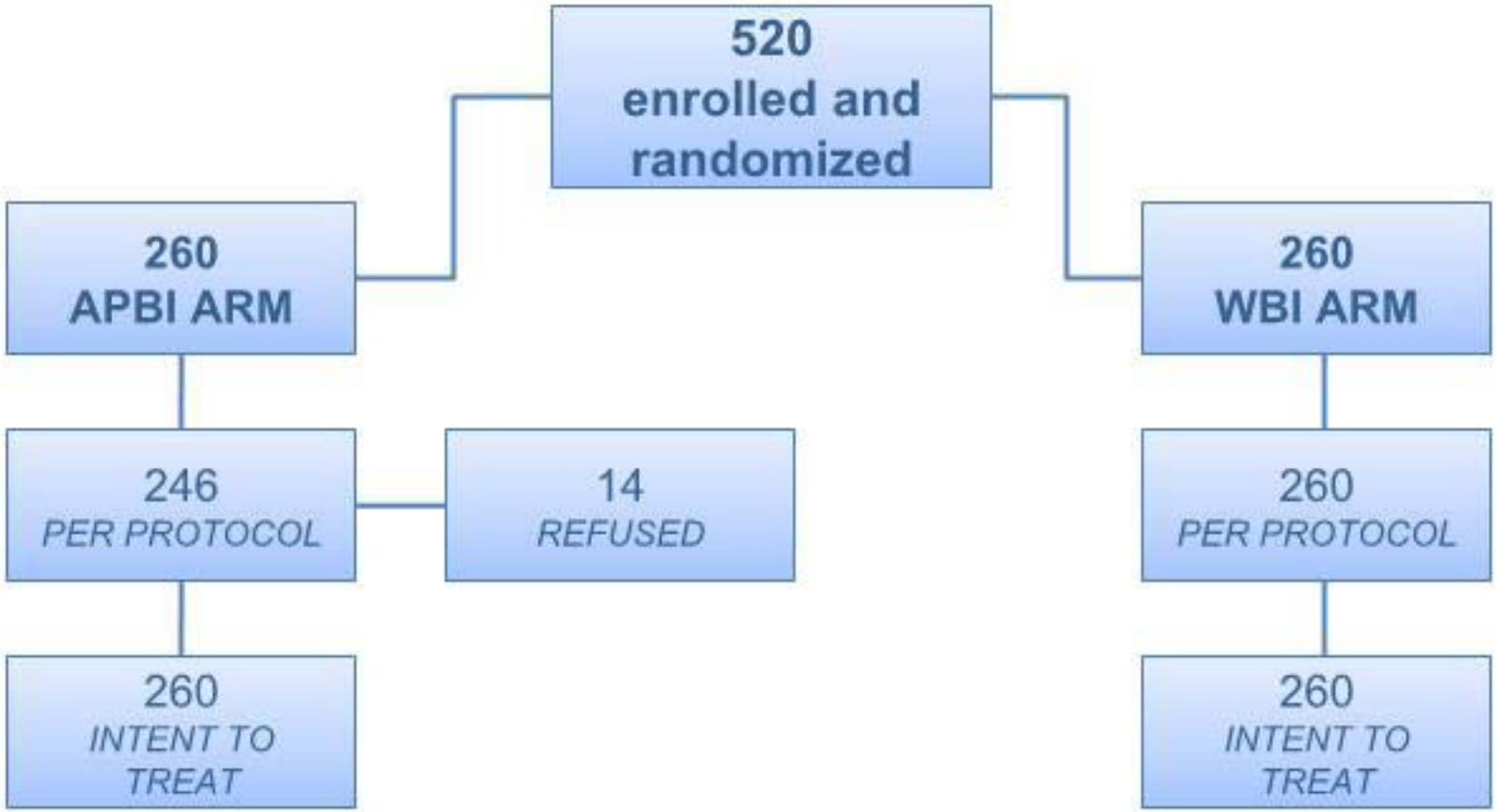
pT < 25 mm
surgical margins > 5 mm
aged > 40 year

Livi et al, IJROBP, 2010

METHODS

- Randomly assigned in a 1:1 ratio to receive WBI or IMRT - APBI
- 80% statistical power *(two-sided p-values <0.05 were considered significant)*
- Primary endpoint: ipsilateral breast tumor recurrences (IBTR)
- Secondary endpoints: treatment toxicity and overall survival (OS)
- Treatment tolerance assessment:
  - RTOG & EORTC scale
  - Harvard Breast Cosmesis scale

PHASE III TRIAL CHART



2005-2013 (recruitment closed). *ClinicalTrials.gov Identifier: NCT02104895*

DEMOGRAPHICS

	Whole Breast		Partial Breast	
	N	%	*N*	%
Age				
<50	45	17·8	41	15·8
51-59	70	29·2	61	23·5
60-69	81	31·2	99	38·1
≥70	58	22·8	59	22·6
Pathological tumour stage				
pTis	32	12·3	23	8·8
pT1a	18	6·9	28	10·8
pT1b	88	33·8	98	37·7
pT1c	107	41·2	97	37·3
pT2	5	1·9	14	5·4
Number of positive nodes				
None	213	81·9	232	89·2
1-3	33	12·7	19	7·3
No axillary nodal dissection	14	5·4	9	3·5
Oestrogen receptor				
Negative	11	4·2	12	4·6
Positive	249	95·8	248	95·4
Progesterone receptor				
Negative	25	9·6	28	10·8
Positive	235	90·4	232	89·2
Molecular subtype				
Luminal A	151	72·6	169	79·3
Luminal B	42	20·2	33	15·5
HER2 positive (non-luminal)	13	6·2	6	2·8
Triple negative	2	1·0	5	2·3

TARGET IDENTIFICATION

Surgical Clips

(mandatory)

to CTV identification

⇩

CTV

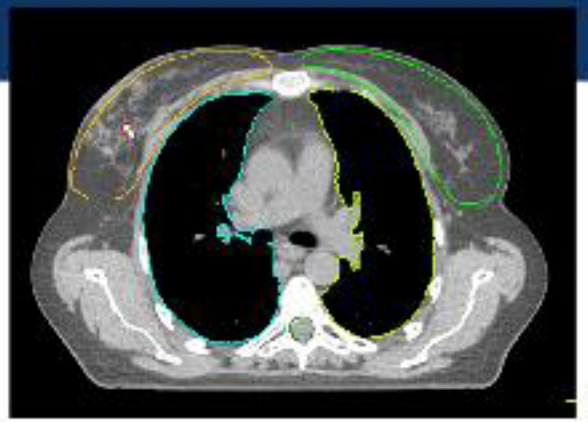
Surgical Clips + 1 cm 3D expansion

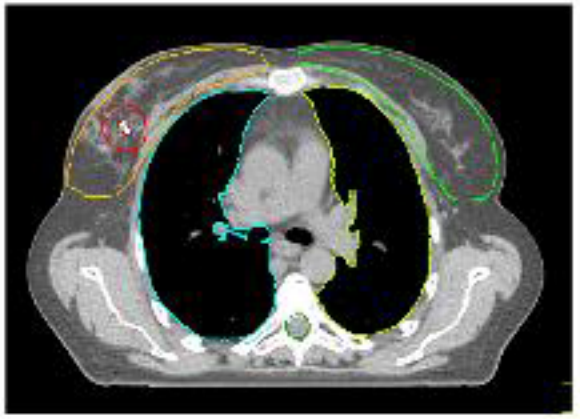
⇩

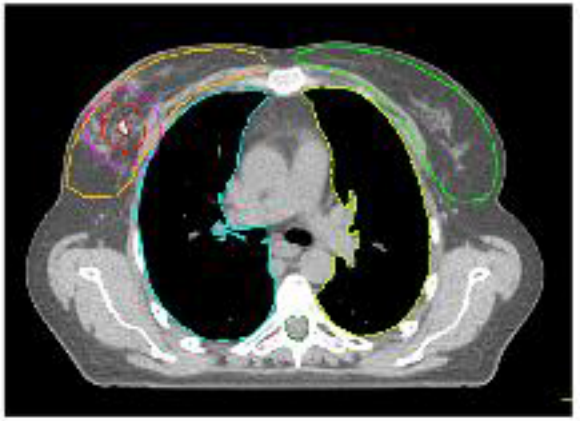
PTV

CTV + 1 cm 3D expansion

(limiting to 3 mm from skin and to 4 mm intrusion in homolateral lung)

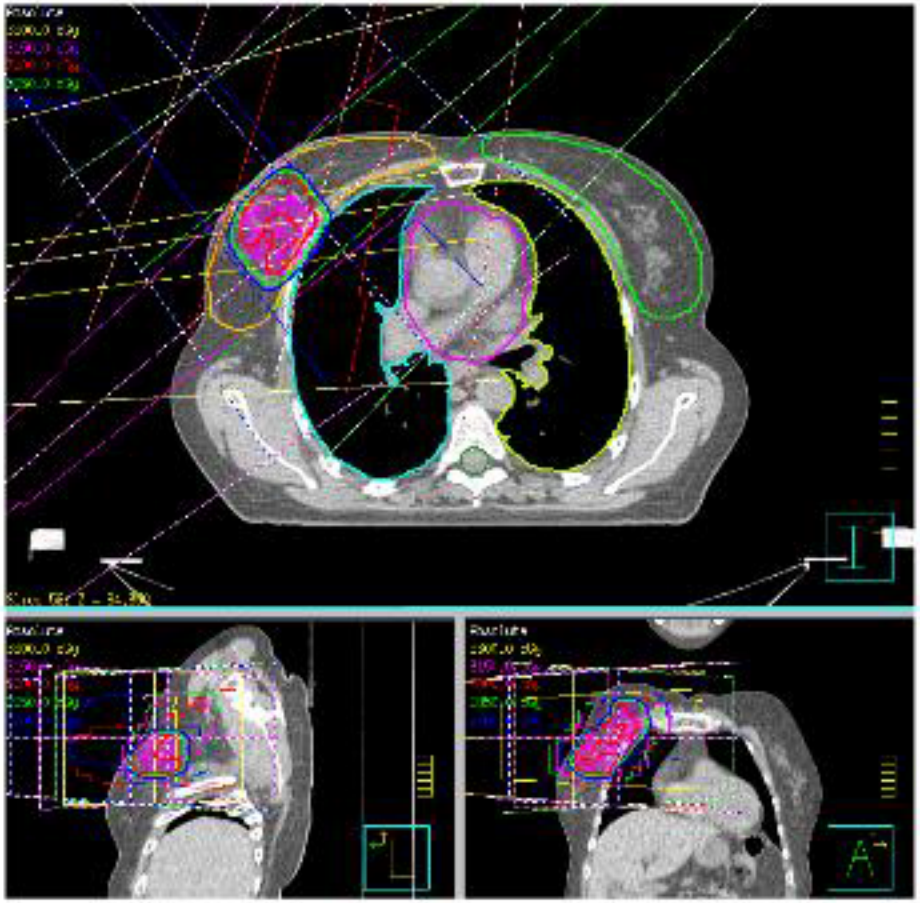






APBI USING S&S IMRT TECHNIQUE

OAR	Constraint
Contralateral Lung	V5 < 10%
Homolateral Lung	V10 < 20%
Heart	V3 < 10%
Homolateral breast (uninvolved tissue)	V15 < 50%
Contralateral Breast	Max 1 Gy in each point



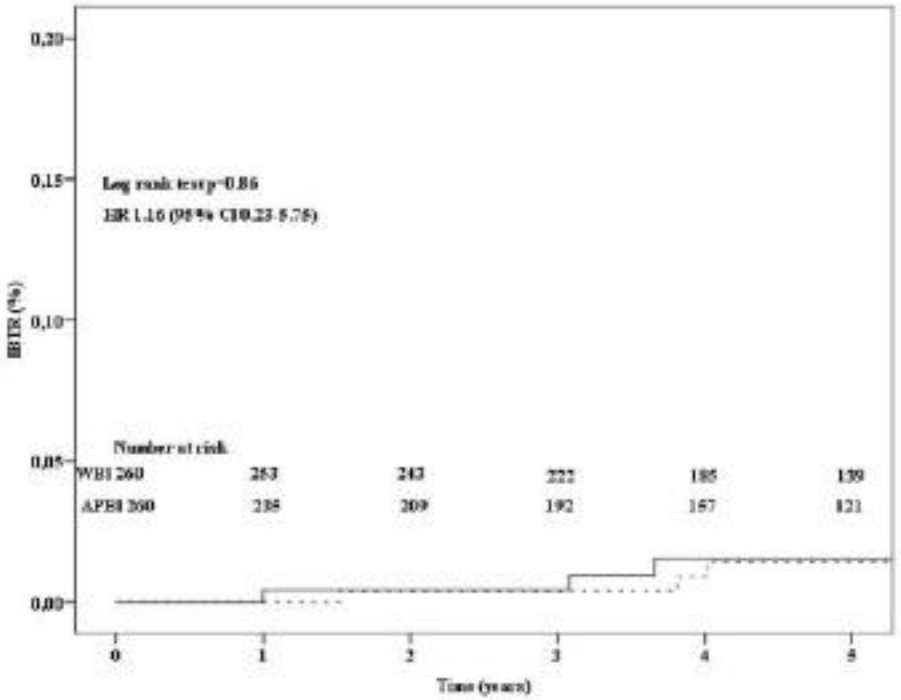
OUTCOME RESULTS

- Median follow-up: 5 years (range 0.6-9.0)
- Mean time to IBTR: 2.9 years (range 1-4)

- No statistically significant difference for:
  - 5-year IBTR rate *(p=0.86)*
  - 5-year distant metastases rate *(p=0.87)*
  - 5 years OS rate *(p=0.057)*

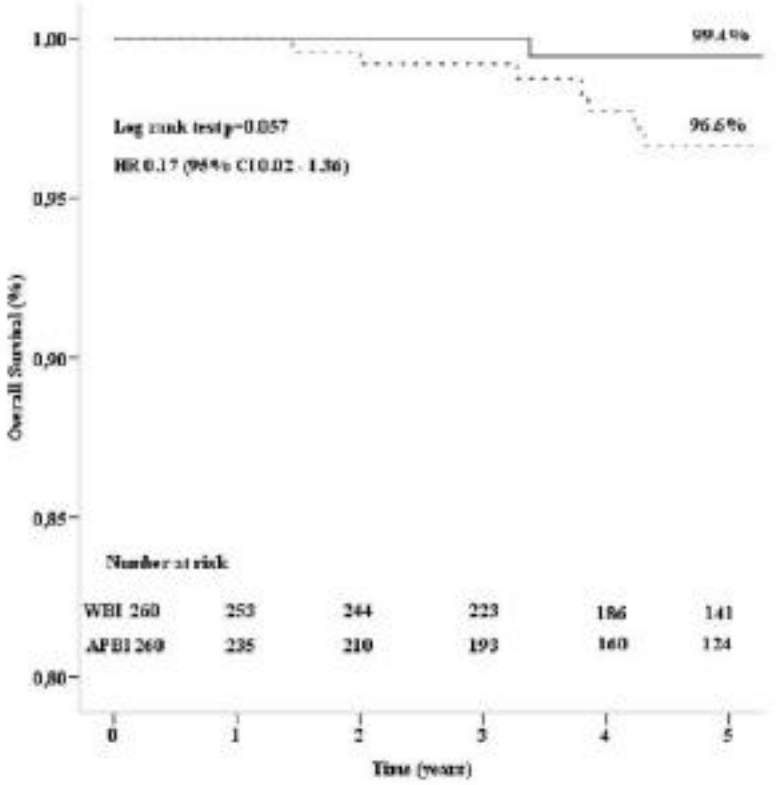
Cumulative incidence of ipsilateral breast tumour recurrence

(intention-to-treat population)



5-year IBTR rate 1,5% in the APBI and 1,4%in the WBI group (log rank test p=0.86)

Overall survival
(intention-to-treat population)



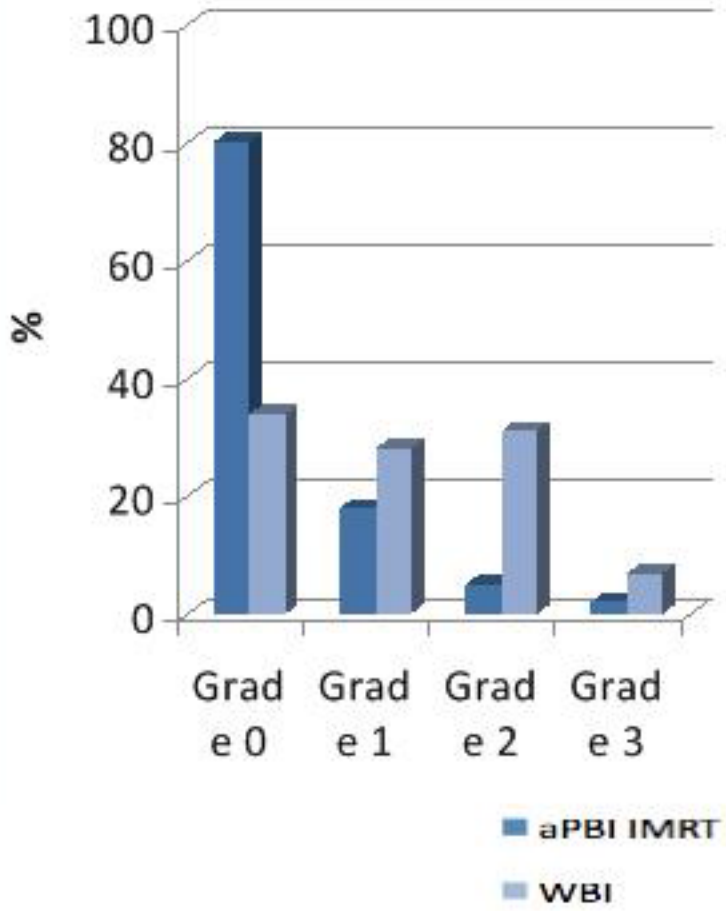
The 5-year overall survival was 96.6% for the WBI and 99.4% for APBI group

SAFETY RESULTS

- Acute adverse events: APBI group showed a statistically significant better safety considering any grade of skin toxicity (p=0.0001)
- No grade 3 toxicity was observed for APBI and WBI group
- Early late side effects, only two cases (0.8%) experienced grade 2 toxicity in WBI group (skin fibrosis)
- Cosmetic result was rated as excellent/good for more than 90% of patients in both groups
- Overall, APBI group showed better outcome to WBI group (p=0.045)

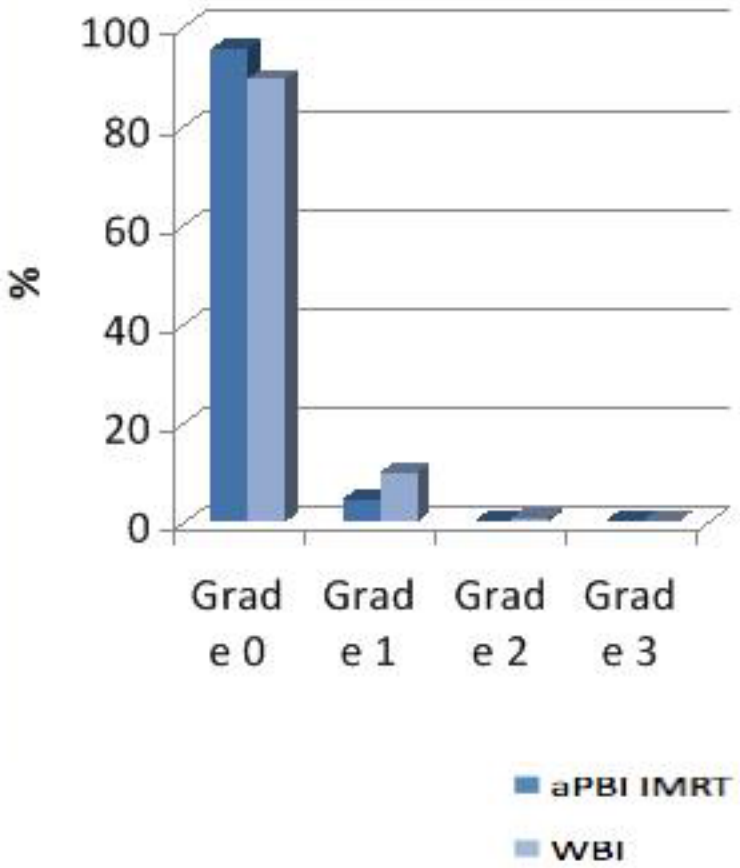
ACUTE TOXICITY RESULTS

	WBI (n:274) N	%	APBI (n:246) N	%	p-value
Any skin toxicity					
None	93	33.9	197	80.1	
Yes, any Grade	181	66.1	49	19.9	**0.0001**
None	93	33.9	197	80.1	
Grade 1	77	28.1	44	17.9	
Grade 2	85	31.1	5	2.0	
Grade 3	19	6.9	0	0	
Grade 4	0	0	0	0	**0.0001**
Grade 0-1	170	62.0	241	98.0	
Grade ≥2	104	38.0	5	2.0	**0.0001**



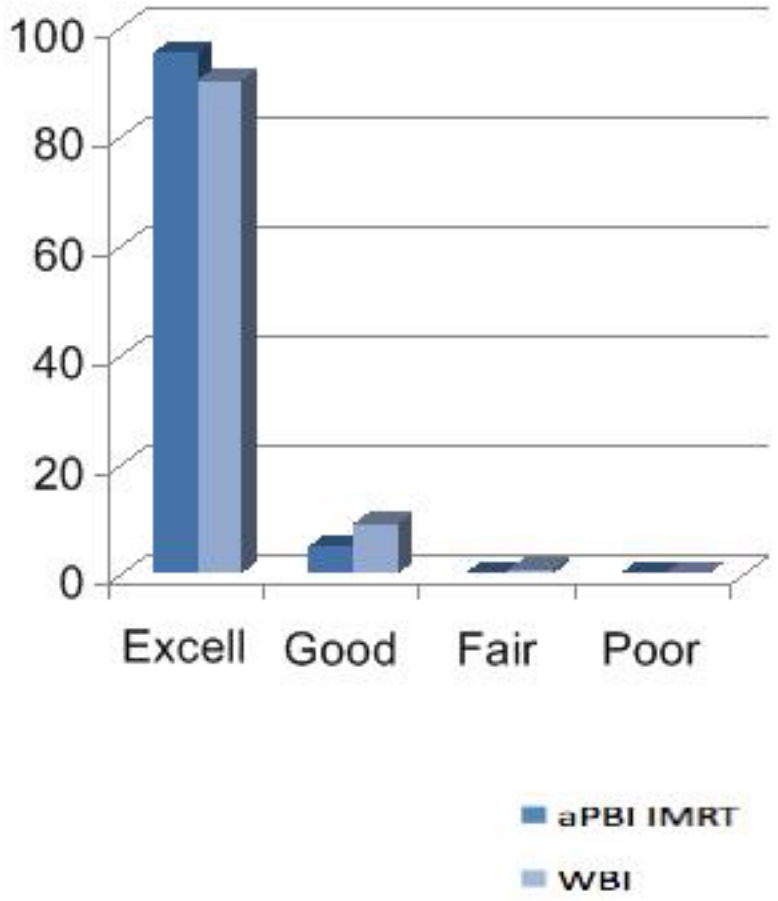
EARLY LATE TOXICITY RESULTS

	WBI (n:274) N	%	APBI (n:246) N	%	p-value
Any skin toxicity					
None	245	89.4	235	95.5	
Yes, any Grade	29	10.6	11	4.5	**0.013**
None	245	89.4	235	95.5	
Grade 1	27	9.9	11	4.5	
Grade 2	2	0.7	0	0	
Grade 3	0	0	0	0	
Grade 4	0	0	0	0	**0.024**
Grade 0-1	272	99.3	246	100	
Grade ≥2	2	0.7	0	0	0.50



COSMESIS RESULTS

- 337 patients **(64.8%)** had a cosmetic evaluation with a **minimum follow-up of 48 months**
- The cosmetic result was rated as **excellent/good** for more than **90%** of patients
- APBI arm showed **better outcome** to WBI arm (p=0.045)



STUDY LIMITATIONS

- Small sample series (overall 520 cases)
- Low IBRT events rate
- Longer follow up needed

Limitations

- No information on dosimetric data for WBI presented or dose constraints used for WBI
- No comparison made between the dose distributions in the WBI vs. APBI cohorts

CONCLUSIONS

- To our knowledge this is the first randomized study using exclusively IMRT technique for APBI delivery
- No statistical difference in terms of IBTR was shown between the two arms at 5-year median follow up
- The APBI group presented significantly better results considering acute, early late, and cosmetic outcome

Take Home Message

- APBI appears to be an option for women with low risk breast cancer but so is hypofractionation and even observation in select cases

Hypofractionation

UK START Trials A and B

TARGIT Trial

Background

- Historically, radiation to the breast or chestwall has been give to a dose of 45 to 50 Gy in 1.8 or 2.0 Gy fractions with or without a boost
- Canadian Phase III study showed 2.67 x 16 fractions equivalent to 50 Gy at 2 Gy per fraction with 12 years of follow-up in Stage I/II node negative patients with less than 25 cm breast separation

Whelan et al. *NEJM* 2010

2011 ASTRO Whole Breast Hypofractionation Consensus Guidelines

- Data support 2.66 Gy x 16 fractions in:
  - pT1/T2 N0 patients
  - $\geq$ 50 years old
  - No Chemotherapy
  - Dose delivered is +/- 7% of the prescribed dose

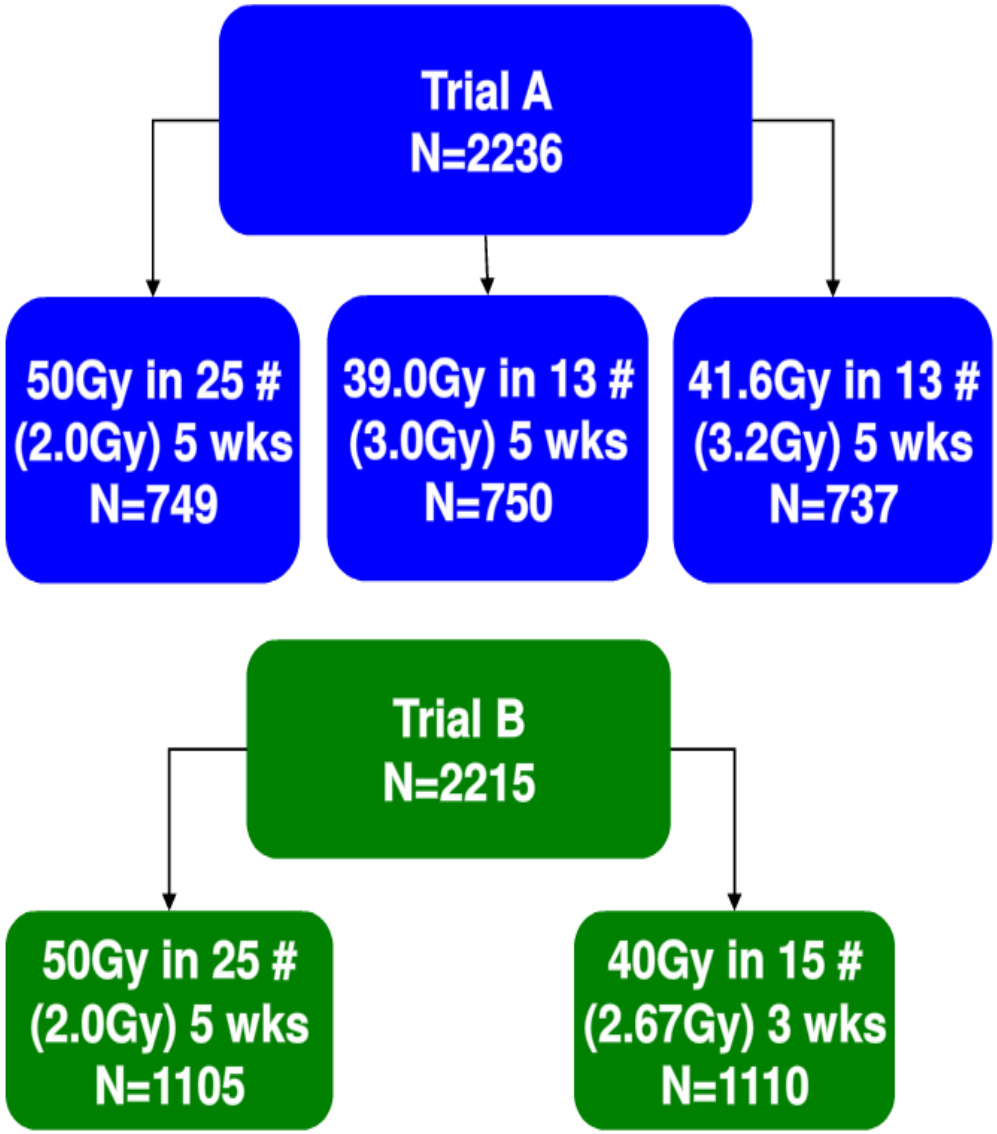
The UK Start (Standardisation of Breast Radiotherapy) Trials: 10-year Follow-up Results

Haviland JS, Agrawal R, Aird E, Barrett J, Barrett-Lee P, Brown J, Dewar J, Dobbs J, Hopwood P, Hoskin P, Lawton P, Magee B, Mills J, Morgan D, Owen R, Simmons S, Sydenham M, Venables K, Bliss JM, Yarnold JR

Haviland et al. *Lancet Oncology* 2013

START Trials: design and endpoints

Women with completely excised invasive breast cancer, T1-3 N0-1 M0



Primary endpoint:
- local-regional relapse

Secondary endpoints include:
- normal tissue effects (assessed by physicians, photographs & patients)
- disease-free & overall survival

Recruitment from 35 UK centres 1999-2002 with QA

Median follow-up:
9.3 years (Trial A)
9.9 years (Trial B)

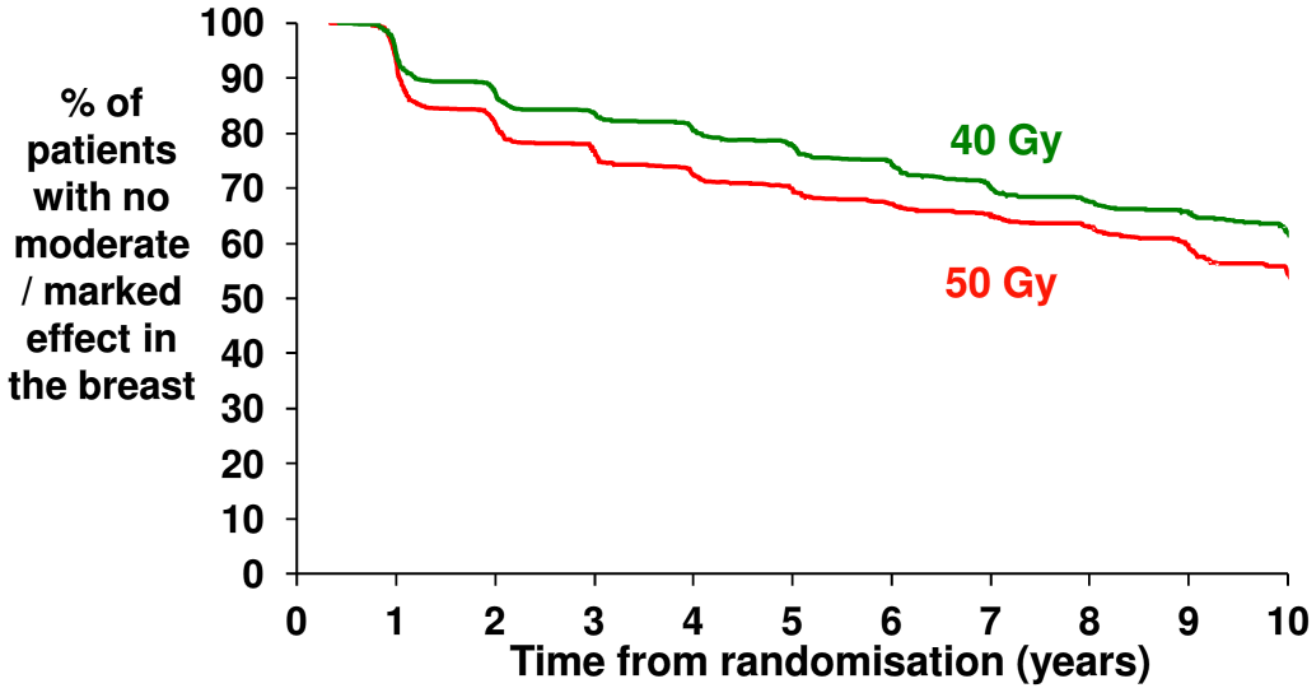
Inclusion Criteria

- pT1-3, N0-1 breast cancer
- Requiring XRT after lumpectomy or mastectomy
- ≥ 1mm surgical margins
- No immediate surgical reconstruction

Common Patient Characteristics

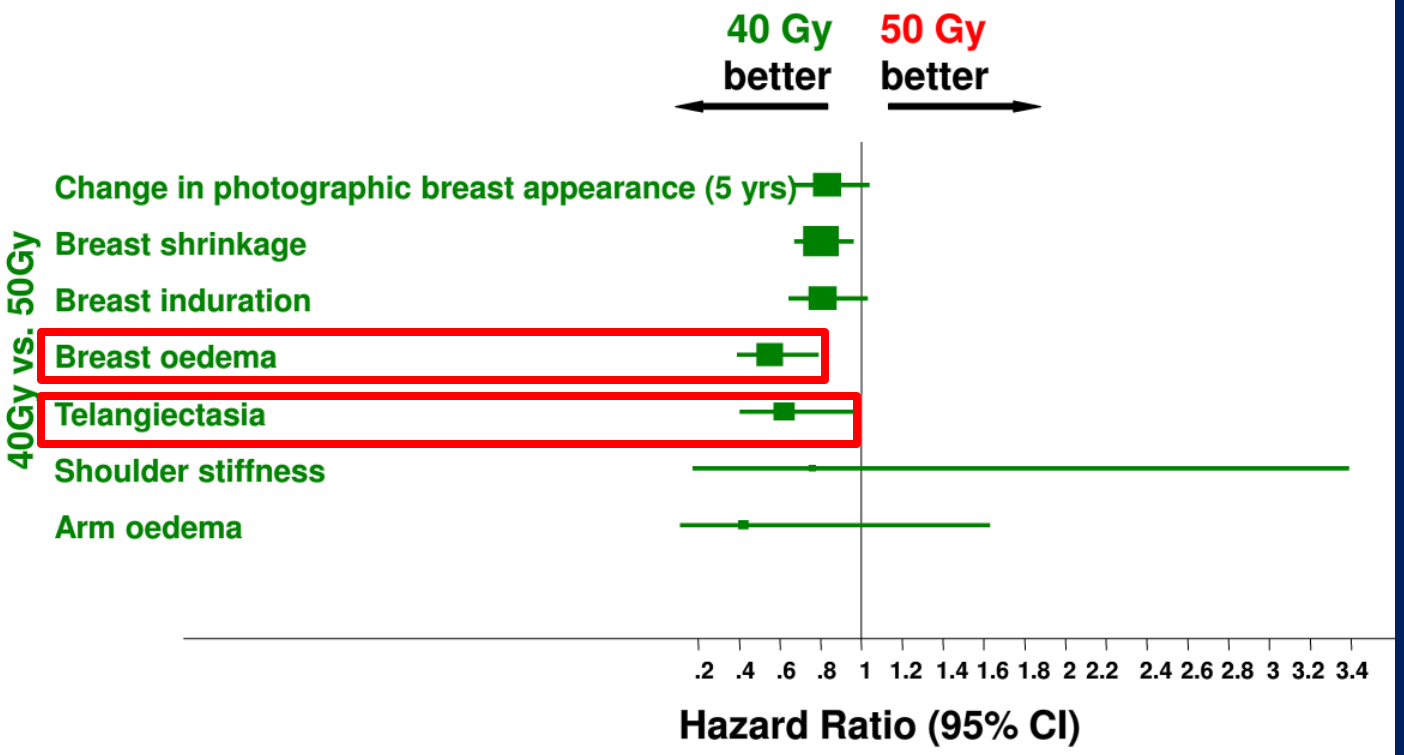
- 80% had tumors <3.0 cm
- ~70% were node negative
- ~70% had low or intermediate grade tumors
- 85% treated with breast conserving surgery
- 85% breast only XRT (no regional nodal XRT)
- ~50% did not receive a boost
- ~70% did not receive chemotherapy
- ~80% received tamoxifen

Trial B: Any moderate/marked effect in the conserved breast (physician assessments)



	Hazard Ratio (95%CI)	Absolute difference at 10 years (95%CI)
40Gy vs. 50Gy	0.77 (0.66-0.89)	-8.1% (-12.4 to -3.7%)

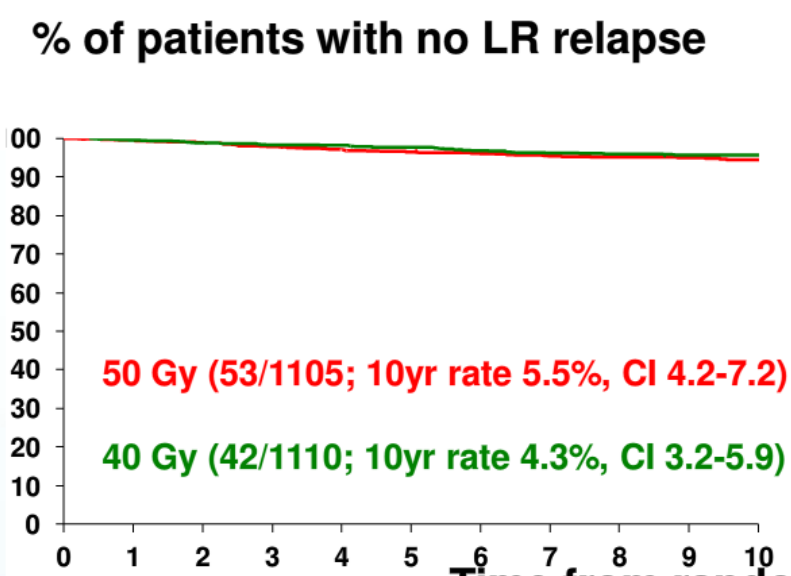
Trial B: Normal tissue effects – individual endpoints (physician assessments)

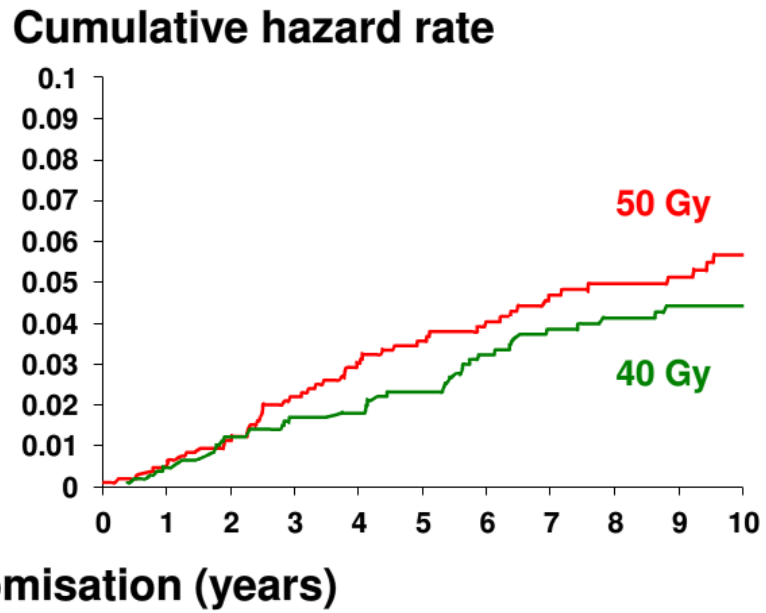


Trials A & B: Other late adverse events

	Trial A			Trial B	
	50Gy	41.6Gy	39Gy	50Gy	40Gy
Symptomatic rib fracture	5 (0.7%)	7 (0.9%)	9 (1.2%)	17 (1.5%)	23 (2.1%)
Symptomatic lung fibrosis	5 (0.7%)	9 (1.2%)	8 (1.1%)	19 (1.7%)	18 (1.6%)
Ischaemic heart disease [left-sided tumours]	17 (2.3%) [8]	10 (1.3%) [4]	9 (1.2%) [5]	25 (2.3%) [10]	22 (2.0%) [11]
Cardiac-related deaths [left-sided tumours]	11 (1.5%) [7]	16 (2.1%) [12]	9 (1.2%) [2]	13 (1.2%) [8]	5 (0.4%) [3]
Brachial plexopathy	0	1 (0.1%)	0	0	0

Trial B: Local-regional (LR) tumour relapse

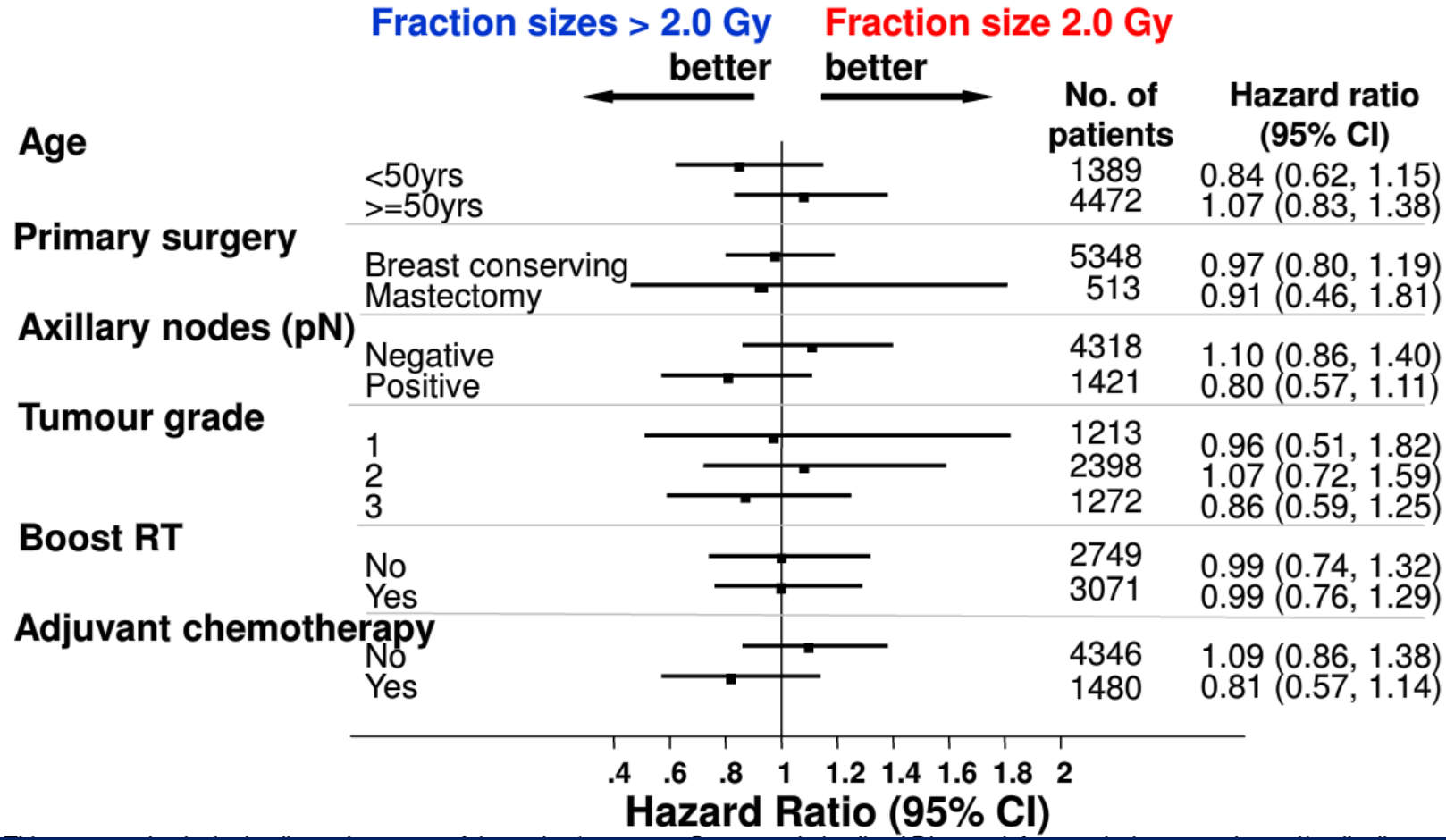




	Hazard Ratio (95%CI)	Absolute difference at 10 years (95%CI)
40Gy vs. 50Gy	0.77 (0.51 – 1.16)	-1.2% (-2.6 to 1.0%)

Meta-analysis of START pilot & START A & B

Subgroup analyses of LR relapse (n=5861)



Conclusions

- Long-term follow-up confirms appropriately-dosed hypofractionated radiotherapy is safe and effective in treatment of patients with early breast cancer
- 41.6 Gy in 13 fxns and 40 Gy in 15 fxns each appear comparable to 50 Gy in 25 fxns in terms of local-regional tumor control and late normal tissue effects.
- These results support the continued use of 40 Gy in 15 fxns as standard of care for women requiring radiotherapy for early breast cancer treated with breast conserving surgery $\geq$ 1mm margins

Utilization of Hypofractionated Radiation Therapy For Early Stage Breast Cancer

a) Utilization of Hypofractionated Radiation Therapy for Early Stage Breast Cancer in Women over 50 years of age (P1-15-02)
b) The Adoption of Hypofractionated Whole Breast Irradation for Early-Stage Breast Cancer: A national cancer data base analysis (P1-15-03)
c) Low Utilization of Hypofractionated radiotherapy for the treatment of Early-Stage Breast Cancer in the US (P1-15-10)

Methods

- National Cancer Data Base – comprehensive oncology outcomes database which captures 70% of all newly diagnosed cancer patients in the U.S.

UPMC CancerCenter
Partner with University of Pittsburgh Cancer Institute

Utilization of Hypofractionated Radiation Therapy for Early Stage Breast Cancer in Women over 50 years of age – A National Cancer Data Base Analysis

Rajagopalan MS[1], Lehocky C[1], Flickinger JC[1], Heron DE[1], Sukumvanich P[2], Kelley JL[2], Ahrendt GM[3], and Beriwal S[1]
Departments of [1] Radiation Oncology, [2] Gynecologic Oncology, and [3] Surgery, University of Pittsburgh Cancer Institute, Pittsburgh, PA

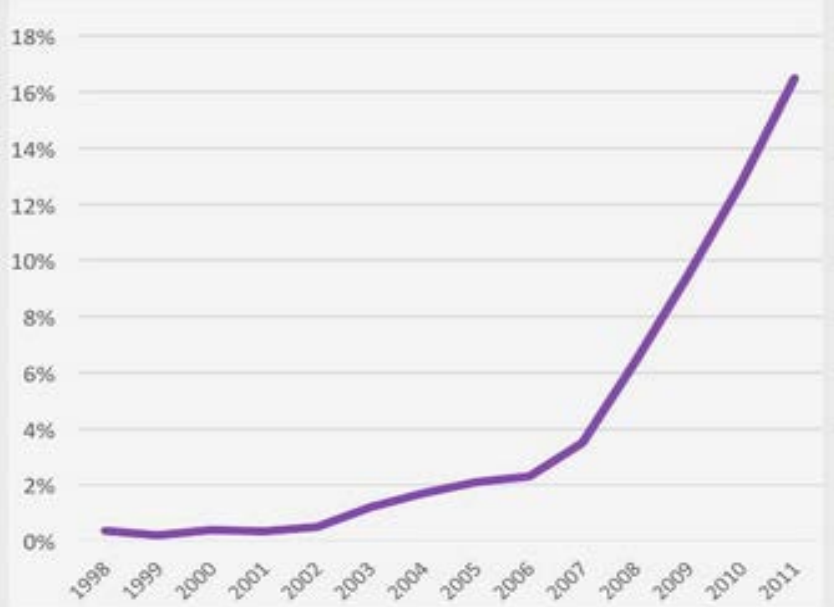


Figure 1. Utilization of HF-WBI by year

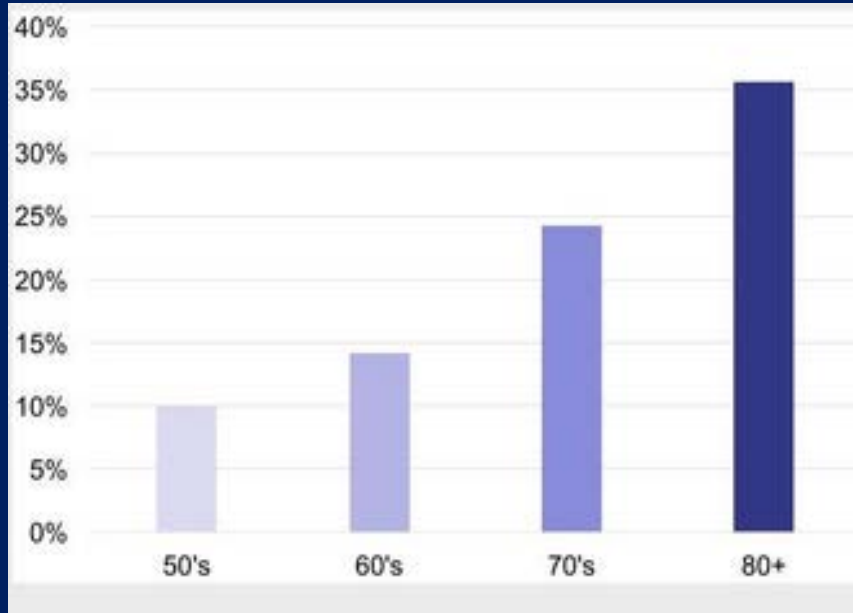


Figure 2. Utilization of HF-WBI in 2011 by age.

MVA: Factors Correlated Increased Use of Hypofractionation

- Later year of Diagnosis
- Advancing age (Decade)
- Treatment in academic center
- Regional location in U.S.
- Lower Grade of Disease
- White race
- Residence in a higher income area ($p<0.001$)
- Greater comorbidity score ($p<0.02$)
- Presence of invasive cancer ($p<0.01$)
- Right-sided disease ($p<0.01$)
- Greater distance from reporting facility ($P<0.001$)

Low utilization of hypofractionated radiotherapy for the treatment of early-stage breast cancer in the US

Yvonne M. Mowery[1], Rachel A. Greenup[2], Kevin Houck[3], Manisha Palta[1], Janet K. Horton[1], Julie A. Sosa[2], E. Shelley Hwang[2], Rachel C. Blitzblau[1]

Departments of [1]Radiation Oncology, [2]Surgery, and [3]Medicine, Duke University Medical Center, Durham, North Carolina, USA

Figure 1. Relative use of radiation treatment fractionation regimen by year

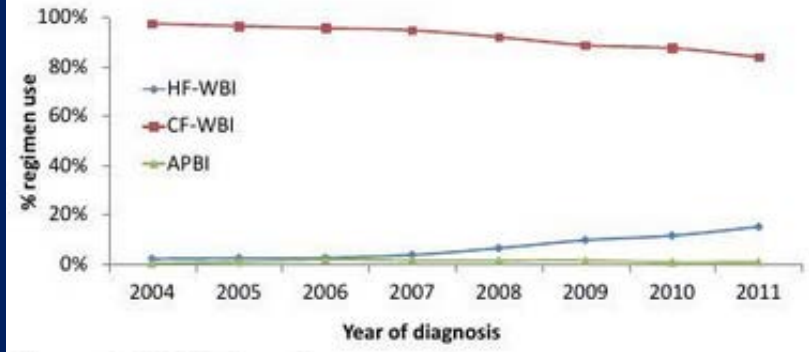


Figure 2. HF-WBI use by year and treatment center type

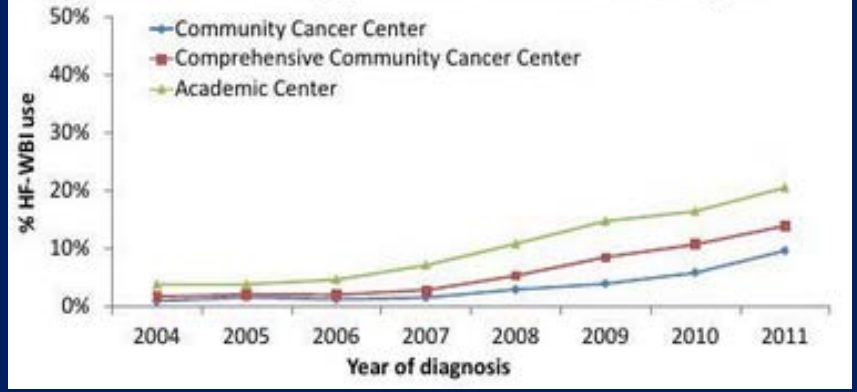
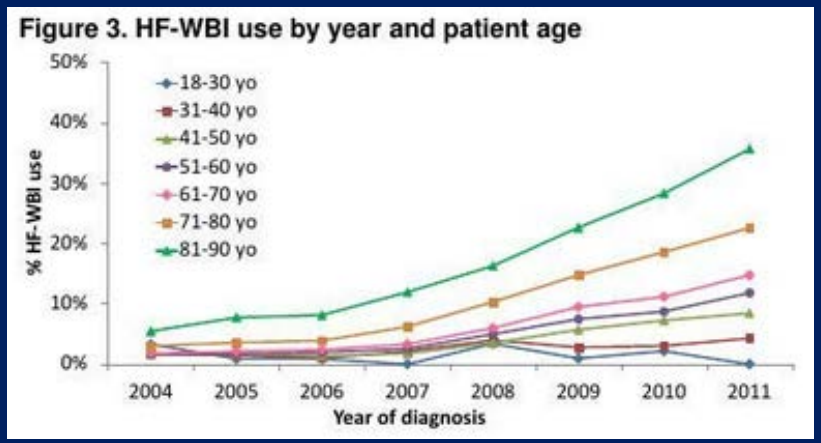


Figure 3. HF-WBI use by year and patient age



MVA: Variables Associated with Hypofractionation Whole Breast Irradiation

Variable	OR	95% CI
Academic Center vs. Community Cancer Center	3.06	2.32 – 4.02
Academic Center vs. Comprehensive Community Cancer Center	1.78	1.53 – 2.08
Patient age, 50-90 vs. 18-49	2.37	1.86 – 3.01
pT2 vs. pT1	0.54	0.46 – 0.63
HER2+ vs. Hormone Receptor +/HER2-	0.75	0.59 – 0.97
ER-/PR-/HER2- vs. Hormone Receptor+/ HER2-	0.66	0.52 – 0.84
Rural vs. urban	2.68	1.69 – 4.24

The Adoption of Hypofractionated Whole Breast Irradiation for Early-stage Breast Cancer: a National Cancer Data Base Analysis

Elyn H. Wang BS[1], Sarah S. Mougaian MD[1,2,3], Pamela R. Soulos MPH[2], Charles E. Rutter[1,3,4], Suzanne B. Evans MD MPH[1,3,4], Bruce G. Haffty MD[5], Cary P. Gross MD[1,5,6], James B. Yu MD[1,3,4]

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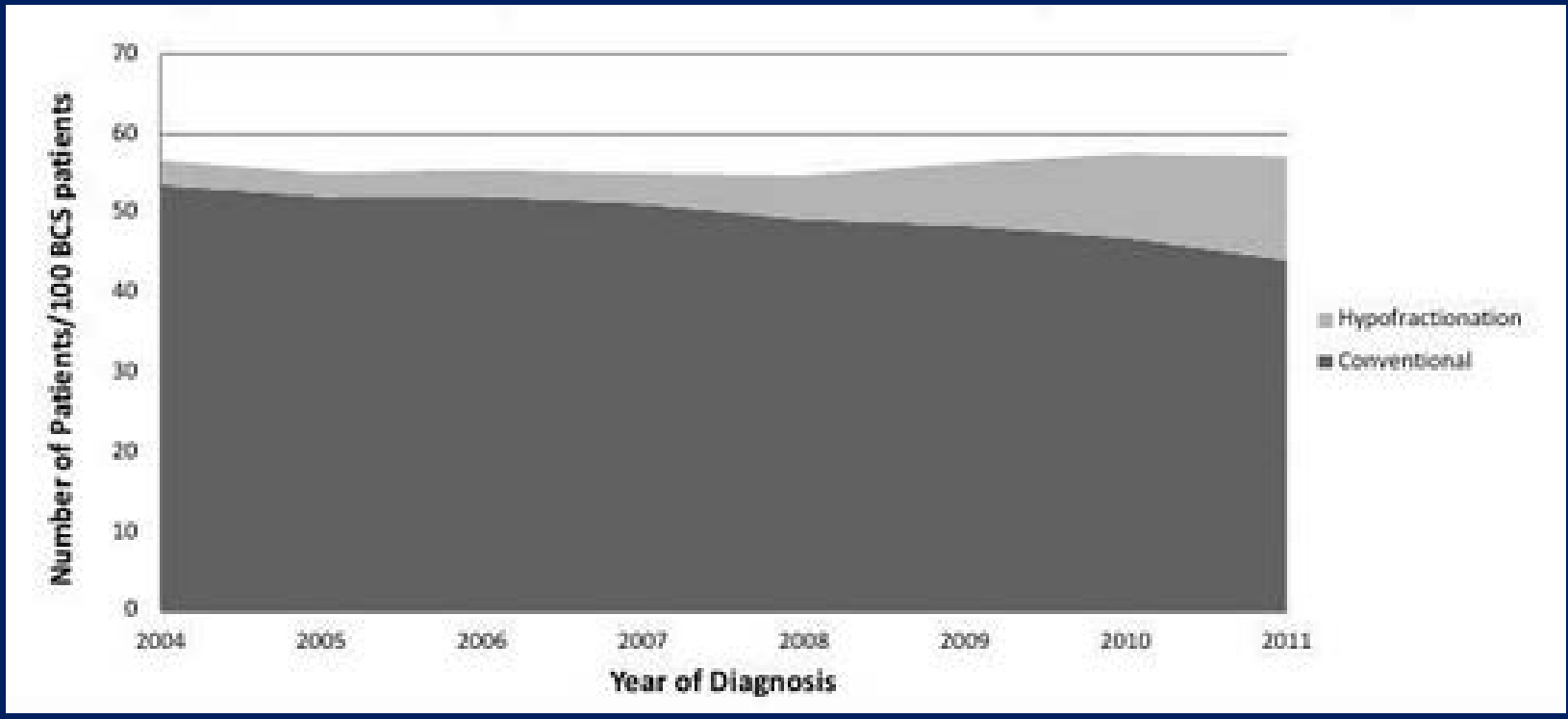

Results

- Hypofractionation was less likely to be used in patients with high risk disease, such as increased tumor size ($p<0.001$) or poorly differentiated histologic grade ($p<0.001$).

Published in final edited form as:
JAMA. 2014 December 17; 312(23): 2542–2550. doi:10.1001/jama.2014.16616.

Uptake and Costs of Hypofractionated vs Conventional Whole Breast Irradiation After Breast Conserving Surgery in the United States, 2008–2013

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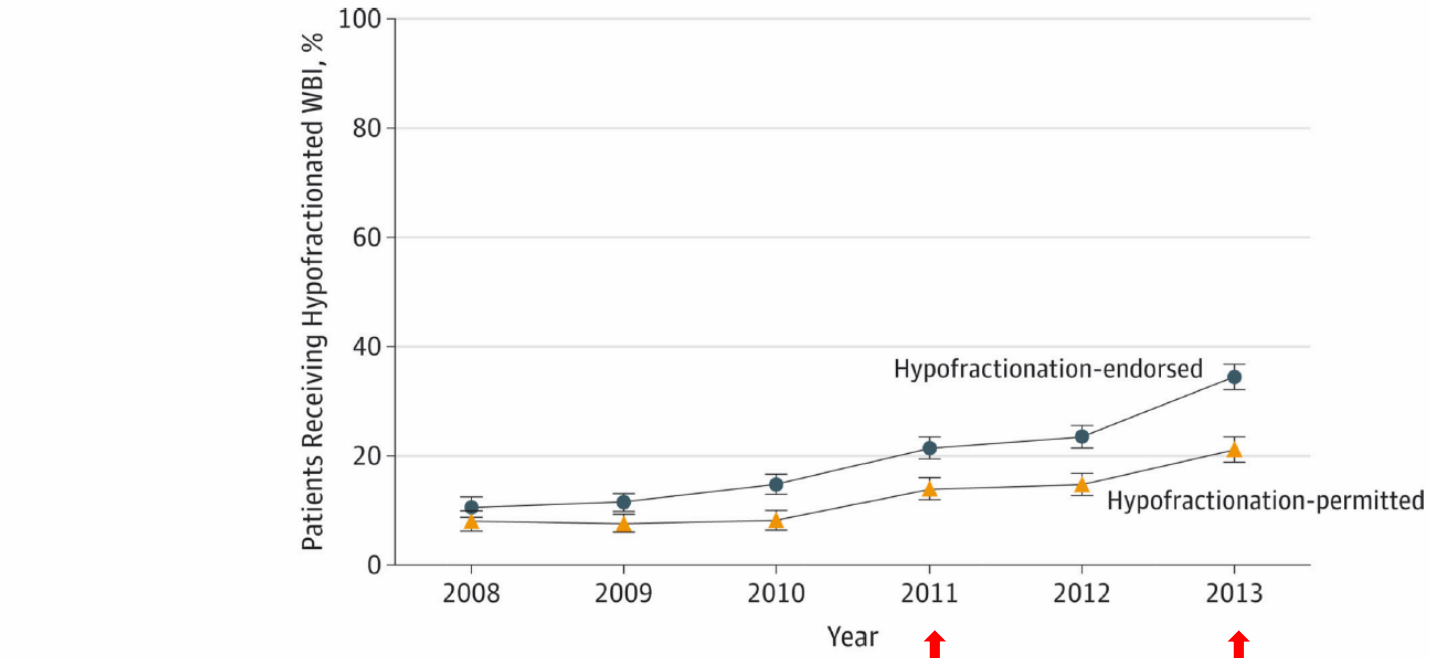
Methods

- Health Core Integrated Research Database
  - Links medical and pharmacy claims and eligibility files
  - 14 commercial health plans across the U.S.
  - 9.2 million adult women
  - Includes claims data for commercial payer and Medicare Advantage enrollees

Results



Total No. of patients						
Hypofractionation-endorsed	1091	1468	1450	1595	1695	1625
Hypofractionation-permitted	666	1221	1190	1253	1211	1178

Figure 2.
Hypofractionated Whole Breast Irradiation After Breast Conserving Surgery Among Patients With Early-Stage Breast Cancer in 14 Commercial Health Plans, 2008 to 2013

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Factors Associated With Hypofractionated vs Conventional Whole Breast Irradiation (WBI) in the Hypofractionation-Endorsed Cohort

	No. (%) of Women			Adjusted OR (95% CI)[a]	*P* Value
	Total	Conventional WBI	Hypofractionated WBI		
Year, 2008–2013[b]	8924			1.4 (1.3–1.4)	<.001
Patient Factors					
Age at radiotherapy start, y					
50–54	1745 (19.6)	1477 (84.6)	268 (15.4)	1 [Reference]	
55–59	1933 (21.7)	1596 (82.6)	337 (17.4)	1.1 (0.9–1.4)	.17
60–64	2201 (24.7)	1777 (80.7)	424 (19.3)	1.3 (1.1–1.6)	.003
65–69	1121 (12.6)	867 (77.3)	254 (22.7)	1.6 (1.3–1.9)	<.001
70–74	803 (9.0)	614 (76.5)	189 (23.5)	1.7 (1.4–2.2)	<.001
≥75	1121 (12.6)	791 (70.6)	330 (29.4)	2.5 (2.0–3.0)	<.001
Modified Deyo-Charlson Comorbidity Index[c]					
0	5647 (63.3)	4536 (80.3)	1111 (19.7)	1 [Reference]	
1	2141 (24.0)	1704 (79.6)	437 (20.4)	0.9 (0.8–1.1)	.30
2	713 (8.0)	571 (80.1)	142 (19.9)	0.8 (0.7–1.0)	.05
≥3	423 (4.7)	311 (73.5)	112 (26.5)	1.1 (0.8–1.3)	.68
Radiotherapy technique					
Non-IMRT	8096 (90.7)	6518 (80.5)	1578 (19.5)	1 [Reference]	
IMRT	828 (9.3)	604 (72.9)	224 (27.1)	1.5 (1.3–1.8)	<.001
Practice setting					
Freestanding facility	3029 (33.9)	2499 (82.5)	530 (17.5)	1 [Reference]	
Outpatient hospital	5895 (66.1)	4623 (78.4)	1272 (21.6)	1.4 (1.3–1.6)	<.001
Geographic Factors (by Zip Code of Residence)					
US Census region					
Northeast	2289 (25.6)	1782 (77.9)	507 (22.1)	1 [Reference]	
Midwest	1906 (21.4)	1526 (80.1)	380 (19.9)	0.9 (0.8–1.1)	.35
South	2039 (22.8)	1651 (81.0)	388 (19.0)	1.0 (0.9–1.2)	.93

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Health Care Expenditures and Out-of-pocket Expenses for Patients With Early-Stage Breast Cancer in 14 Commercial Health Plans

	Whole Breast Irradiation, Adjusted Mean (95% CI), US $		Differences, Adjusted Mean (95% CI), US $[a]	*P* Value
	Hypofractionated	Conventional		
Hypofractionated-Endorsed Cohort				
Commercial plan paid expenditures				
Total[b]	28 747 (27 345 to 30 221)	31 641 (30 446 to 32 883)	2894 (1610 to 4234)	<.001
Radiotherapy-related[c]	12 622 (12 053 to 13 218)	16 961 (16 358 to 17 585)	4338 (3709 to 4991)	<.001
Patient out-of-pocket expenses				
Total[b]	2215 (2012 to 2438)	2233 (2075 to 2404)	19 (−155 to 207)	.84
Radiotherapy-related[c]	617 (536 to 710)	746 (668 to 832)	128 (46 to 221)	<.001
Hypofractionated-Permitted Cohort				
Commercial plan paid expenditures				
Total[b]	64 273 (60 500 to 68 282)	72 860 (69 599 to 76 283)	8587 (5316 to 12 017)	<.001
Radiotherapy-related	14 974 (14 160 to 15 837)	19 762 (18 928 to 20 632)	4785 (3984 to 5623)	<.001
Patient out-of-pocket expenses				
Total[b]	3278 (2954 to 3638)	3421 (3158 to 3706)	143 (−121 to 429)	.30
Radiotherapy-related[c]	519 (415 to 648)	619 (520 to 736)	100 (3 to 215)	.04

Take Home Message

- Hypofractionation appears to be underutilized in the United States

Why?

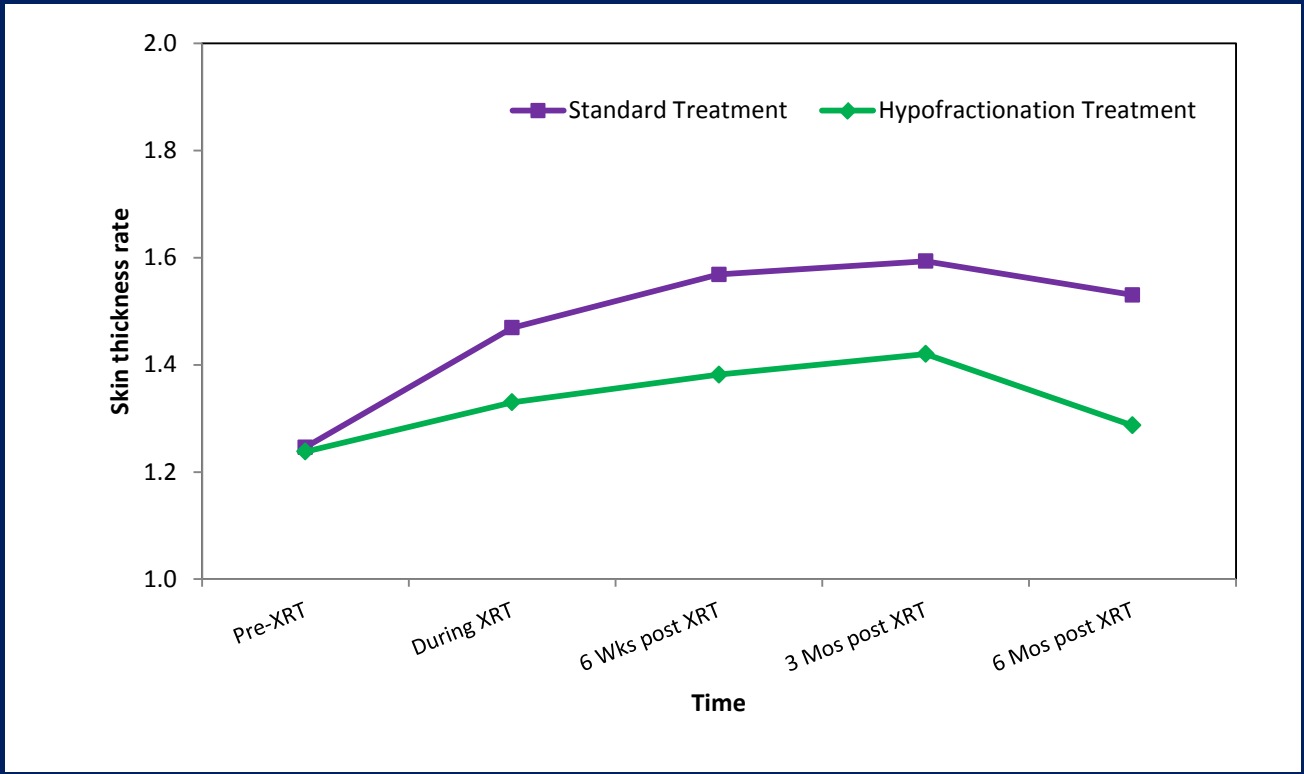
Lingering Questions

- Is the 3 week regimen safe and effective for Stage III breast cancer patients or women who have tumors >3.0 cm?
- Can we use the 3 week dose in women needing SCV XRT?
- Does receptor status impact the efficacy of the 3 week course?
- What is the appropriate boost dose in these patients?
- Is it safe in the following patients:
  - Non-Caucasian patients
  - Large breasts
  - Patients treated with chemotherapy

Emory Study

- Phase I/II Simultaneous Integrated Boost Study for breast cancer patients with one or more of the following factors:
  - Previously treated with chemotherapy
  - Women with large breasts (>25 cm separation)
  - Women <50 years old
- 2.66 Gy x 15 fractions (39.9 Gy to the breast) and simultaneous built in boost to the cavity (48 Gy)
- Protocol has been expanded to include N1 patients needing regional nodal XRT (supraclavicular treatment) and post-mastectomy patients

Skin Thickness Results



Compared with patients receiving standard treatment, patients receiving hypofractionated treatment experienced lower skin toxicity during XRT, 6 weeks, 3 months and 6 months post XRT.

Thank You