

Multidisciplinary Approaches to Cancer Symposium

Optimal Adjuvant Treatment for Older Adults with ER+ Breast Cancer: Patients Should Receive Radiation Therapy

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• I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed <u>Assembly Bill (AB) 1195</u>, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed <u>AB 241</u>, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- Will emphasize the importance of shared decision making that incorporates the patient's goals and expectations based on their belief system.
- Elderly patients are often not considered for certain treatments based on their age alone. My presentation will focus on incorporating
 tools that can help us better understand the physiologic age of a patient rather than just their chronological age so that we can make the
 best treatment decisions for them.



- How did we get to this question of omission of radiotherapy? Brief Review and Rad Onc perspectives on:
 - o CALGB 9343
 - o PRIME-II
- Should we view all ER+ breast cancers the same?
- Should we view all patients 65-70 yrs old or older the same?
- What has changed in breast radiotherapy since CALGB 9343/PRIME-II?
- What are the risks/benefits of RT compared to ET?

Goals of Breast Radiotherapy for Conservation Treatment

Invasive breast cancer:

- Maximize local control
- Equivalence to mastectomy
- Prevent Distant Metastases
- Optimize breast cancer/ overall survival
- Maintain sensate and acceptable cosmetic breast appearance

The Safety and Efficacy of Breast Conserving Therapy Established by Phase III Randomized Trials Conducted Over 30 Year ago.

	Yrs	% C	verall Survi	ival
Trial	F/U	BCT	Mastectomy	р
Milan I	20	58	59	NS
NSABP B-06	20	46	47	NS
EORTC 1081	20	39	45	NS
DBCG-82 Tm	20	57.8	50.6	NS

Veronesi, NEJM, 2002 Fisher, NEJM, 2002 Litiere, Lancet Oncol, 2012 Blichert-Toft, Acta Oncologia 2009

EBCTCG Meta-Analyses 2005 & 2011



Improved 10-year Overall Survival and Distant Metastases Free Survival with BCT





van Maaren et al Lancet Oncol 2016

Numerous Phase III Randomized Trials Have Sought to Omit Post Lumpectomy Breast Radiation

			Yrs.				
Tr	rial 🛛	No	F/U	Size (cm)	Surgery	BCS	BCS + RT
	Uppsala-Orebro	381	10	2	Q*	24	8.5
	Milan III	579	10	2.5	Q	23.5	5.8
	NSABP B-06	1262	20	4	L•	39	14
Ontario Clinica	l Oncology Group	837	7.6	3	L	35	11
Scottish Cancer Trials Breast Group		585	7.7	4	L	24.5	5
	Tampere	264	12	2	L	27.2	11.6
	NSABP B-21	1009	8	1	L	16.5 ¹	9.3 2.8 ¹
Toronto-British	Columbia (PMH) ¹	769	10	2	L	13.7	5.1
	BASO II ²	1172	13	2	L	11	3
	CALGB C 9343 ^{1,3}	636	12.6	2	L	10	2
	PRIME-II ⁴	1326	9.1	3	L	9.5	0.9

* Quadrantectomy, • Lumpectomy, ¹ All patients received tamoxifen, ²All Grade I, pN-0, ³ All age≥70 years; ⁴Age≥65 year

CALGB 9343

Eligibility

- RT details
- Breast-conserving surgery with neg. margins
- Age≥70 yrs
- o pT1N0*
- o ER-positive
- N0 on clinical assessment
- Randomization: Tamoxifent+RT versus Tamoxifen alone
- Enrollment period: July 1994-February 1999

- 45 Gy in 25 F to the entire ipsilateral breast by Co-60 or a linear accelerator with maximal energy of 6 MV photons
- The planning volume included 1 cm margin to allow for motion and included the area of the lower axillary nodes (level I/II)
- WBI was followed by a 14 Gy in 7 fraction boost to the tumor bed

Characteristic	Tamoxifen + Irradiation (N=317)	Tamoxifen (N=319)
	no. of women	(%)
Stratification		
Age		
70–74 yr ≥75 yr	139 (44) 178 (56)	146 (46) 173 (54)
Axillary dissection		
No	200 (63)	204 (64)
Yes	117 (37)	115 (36)
Demographic		
Race or ethnic group*		
White	287 (91)	287 (90)
Hispanic	5 (2)	8 (2)
Black	23 (7)	22 (7)
Asian	0	2 (1)
Other	1 (<1)	0
Unknown	1 (<1)	0
Estrogen-receptor status		
Negative	6 (2)	4 (1)
Positive	308 (97)	310 (97)
Unknown	3 (1)	5 (2)
Progesterone-receptor status		
Negative	56 (18)	67 (21)
Positive	251 (79)	245 (77)
Unknown	10 (3)	7 (2)
Size of primary tumor		
≤2 cm	312 (98)	310 (97)

Hughes KS, NEJM 2004

CALGB 9343

Treated Patients	TamRT Arm	Tam Arm	Total
Total	317	319	636
Reautrence	23	42	65
Local or regional ± distant	6	32	38
IBTR alone	2	20	22
Axilla alone	0	5	5
IBTR with axilla	0	1	1
IBTR with distant	4	6	10
Distant alone	17	10	27
Death			
All cause	166	168	334
Breast cancer specific	13	8	21







Hughes KS, JCO 2013

PRIME-II

Eligibility

- RT details
- o Breast-conserving surgery with neg. margins≥1mm
- o Age≥65 yrs
- o pT1-2(≤3cm)
- o pN0 on sentinel node biopsy
- o ER-positive/PRpositive or both
- o Grade 3 or LVSI allowed but not both
- Randomization: Tamoxifen+RT versus Tamoxifen alone
- Enrollment period: April 2003-Dec 2009

- - 40-50 Gy (2.66-2.00 Gyper F in 15-25 F) over 3-5 weeks
 - Permitted a breast 0 oost with electrons of 10-15 Gy
 - o Lymphatics were not to be irradiated

Characteristic	No Radiotherapy (N= 668)	Radiotherapy (N = 658)
Age — yr		
Mean	71.1±5.0	70.8±4.7
Median (IQR)	70 (67–74)	69 (67-73)
Tumor size — no. (%)		
0–1.0 cm	258 (38.6)	265 (40.3)
1.1-2.0 cm	326 (48.8)	319 (48.5)
2.1–3.0 cm	84 (12.6)	74 (11.2)
Excision margins — no. (%)		
<1 mm	10 (1.5)	9 (1.4)
1–5 mm	315 (47.2)	296 (45.0)
>5 mm	227 (34.0)	239 (36.3)
Reexcision [†]	112 (16.8)	110 (16.7)
Unknown	4 (0.6)	4 (0.6)
Tumor grade — no. (%)		
1	271 (40.6)	292 (44.4)
2	368 (55.1)	352 (53.5)
3	23 (3.4)	13 (2.0)
Unknown	6 (0.9)	1 (0.2)
ER status — no. (%)‡		
High	593 (88.8)	601 (91.3)
Low	65 (9.7)	55 (8.4)
Unknown	10 (1.5)	2 (0.3)
Radiotherapy — no./total no. (%)§		
Within 40 to 50 Gy	-	573/584 (98.1)
Boost	-	91/584 (15.6)
	ŀ	(unkler IH, NF.IM 20
	•	

PRIME-II



Kunkler IH, NEJM 2023

PRIME-II





	No RT (n=118)	RT (n=113)
Breast cancer	16	15
Angiocarcinoma	0	1
Cardiac	9	14
Cerebrovascular	5	4
Thromboembolic	2	1
Other cardiovascular	3	1
Lung cancer	7	7
Other respiratory	14	13
Other cancers	20	25
Other causes	11	5
Unknown	31	27

Death due to breast cancer: 31 (18%) Death due to other cancers: 60 (26%) All other causes: 140 (56%)

Is All ER+ Breast Cancer The Same?

- HR+/HER2- breast cancer is a heterogeneous disease that can be divided into a minimum of 2 subtypes: luminal A or luminal B
- We should incorporate tumor biology grade, Ki67, genomic assays if available - into our decision-making process regarding omission of radiation therapy
- Subgroup analysis of the PRIME-II study clearly demonstrates that ER-low tumors derive a large absolute benefit from adjuvant radiation therapy



Is Chronologic Age the Best Tool to Aid with Decision Making Regarding Omitting Therapies?

- PRIME-II, while aiming to enroll women ≥65 years old, had a median age of 70 years old
- CALGB 9343 enrolled a population of elderly patients with multiple comordibities with median age 75 years old and >50% had died within 10 years (only 6% of deaths were attributable to breast cancer)
- Challenge in our practice is making sure that we don't undertreat some of our patients
- In my clinic, I tend to use the Lee/Schonberg index to help estimate the risk of mortality in the next 10 years

UCSF E-prognosis: https://eprognosis.ucsf.edu/leeschonberg.php

Risk Calculator			
1. How old is your patient?	Select	t	٣
2. What is the sex of your patient?	O Female	0	Male
3. What is your patient's <u>BMI</u> ?	Select	t	٣
4. Which best describes your patient's health in general?	Select		*
5. Does your patient have chronic lung disease, such as emphysema or chronic bronchitis?	⊖ Ye	25 @	No
6. Has your patient ever had cancer (excluding minor skin cancers)?	O Ye	es @	No
7. Does your patient have congestive heart failure?	O Ye	is @	No
8. Does your patient have diabetes or high blood sugar?	⊖ Ye	ès @	No
9. Which best describes your patient's cigarette use?	Select	t	Ŧ
10. Does your patient have difficulty walking 1/4 mile (several city blocks) without help from other people or special equipment?	⊖ Ye	es @	No
11. During the past 12 months, how many times was your patient hospitalized overnight?	Select	t	٣
12. Because of a physical, mental or emotional problem, does your patient need the help of others in handling routine needs such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?	O Ye	25 @	No
13. Because of a health or memory problem, does your patient have difficulty managing money - such as paying bills and keeping trad expenses?	:kof ○ Ye	is @	No
14. Because of a health or memory problem, does your patient have difficulty with bathing or showering?	O Ye	25 @	No
15. Because of a health problem, does your patient have difficulty pushing or pulling large objects like a living room chair?	O Ye	es @	No
T T	otal Lee Index P otal Schonberg I	oints: 0 Index P	oints: 0

Lee Schonberg Index Examples

- Lee Schonberg index predictes all cause 4, 5, 10 and 14 year mortality from community dwelling adults 50 and older
- Both indices have been internall validated in random data sets and are well calibrated across all risk levels
- Lowest possible score (70-74 y/o woman with breast cancer) is Schonberg=3 and Lee=5
- Score for an 80-84 y/o patient with BMI<25, with emphysema, with DM2, former smoker and difficulty pushing objects is Lee=12/Schonberg=14
- My recommendations for treatment would be completely different based on these scenarios

Points	Risk of FIVE YEAR mortality	Risk of TEN YEAR mortality	Risk of FOURTEEN YEAR mortality
0-1	<3%	5% - 11%	19% - 21%
2-3	3% - 6%	9% - 12%	19% - 24%
4 - 5	7% - 8%	15%-21%	27% - 36%
6-7	10% - 12%	26% - 37%	42% - 52%
8 - 9	17% - 27%	37% - 44%	42% - 52%
10-11	26% - 29%	53% - 60%	74% - 78%
12 - 13	37% - 41%	60% - 68%	81%-83%
14 - 15	47% - 52%	74% - 76%	87% - 88%
16 - 17	60%-61%	86% - 87%	100%
≥17	70%	92%	100%
Points	Risk of FIVE YEAR mortality	Risk of TEN YEAR mortality	Life Expectancy (years)
0-1	1% - 2%	2% - 5%	33.1 - 35.4
2-3	2%-4%	7% - 10%	23.7 - 30.1
4-5	6% - 8%	15% - 23%	17.7 - 21.1
6-7	9% - 15%	34% - 43%	12.6 - 14.3
8-9	20%	52% - 58%	8.9 - 10
10-11	28% - 45%	70% - 82%	5.0 - 7.2
12 - 13	44% - 59%	83% - 91%	3.8 - 5.1
≥14	63%	93%	2.9

UCSF E-prognosis: https://eprognosis.ucsf.edu/leeschonberg.php

Listening to Our Patients – Qualitative Research

Antiestrogen Therapy Alone (after a lumpectomy)	Radiation Therapy Alone (after a lumpectomy)	Antiestrogen Therapy and Radiation Therapy Together (after a lumpectomy)
 93 women may not get a breast cancer recurrence 07 women may get a breast cancer recurrence 	90 women may not get a breast cancer recurrence (86 - 93) 10 women may get a breast cancer recurrence (7 - 14) (average range to 8 years of follow-up)	99 women may not get a breast cancer recurrence 01 woman may get a breast cancer recurrence (up to 8 years of follow-up)
В	В	В

	Benefits Reasons to choose option	How much does it matter to you?	Risks/Side Effects Reasons to avoid option	How much does it matter to you?
Antiestrogens	Antiestrogen therapy alone provides a higher chance of preventing a breast cancer recurrence than choosing the radiation option.	***	Risks: blood clot, stroke, heart problems, osteoporosis (bone loss which can lead to fractures), cataracts in the eye, uterine cancer	* * * * *
	alone Antiestrogen therapy alone provides closer to the same chance of preventing a breast cancer recurrence than choosing the antiestrogen and radiation therapy together option		Side effects: may have hot flashes, night sweats vaginal changes (bleeding, dryness, discharge, itching) joint stiffness or joint pain, weight gain, depression	* * * * *
			Must take a pill each day	***
			Cost of medicine depends on women's own health plan	* * * * *
			(Speak to your doctor about the specific side e and aromatase inhibitors.)	ffects for SERMs
	Other reasons to choose this option:	背负负责责	Other reasons to avoid this option:	资资资资资
Radiation	Radiation therapy alone provides the lowest chance of preventing a breast cancer recurrence compared to choosing the other options(antiestrogen therapy alone or antiestrogen and radiation therapy together)	****	Side effects: breast-pain, edema (swelling), sunburned feeling, rashes, fibrosis (thickening), retraction (shrinking) or skin colour changes, fatigue	****
			May not have radiation again if a recurrence in same area	* * * * *
			Travel to daily treatments for about 5 to 7 weeks	****
			Cost of parking	贫贫贫贫贫
	Other reasons to choose this option:	***	Other reasons to avoid this option	***

Was the decision aid visually appealing?

- The color of the decision aid is very gentle, not offensive.
- The font size is too small and difficult to read. The glossy paper made the decision aid difficult to read; I suggest a matte finish. The background color is not good for the graphics.
- I like the layout.

How satisfied are you with this decision aid?

- · Excellent; I wish I had had this tool when I was deciding.
- It's a wonderful idea because women of this age are not questioning, so this is empowering.
- Although this should not be a replacement for a physician's advice, the decision aid was an excellent tool.
- I feel that the tool would be especially beneficial for women who do not have support.

Listening to Our Patients - Qualitative Research

Perceptions and feelings about cancer treatment options

Wanting treatment over with	"Yeah, because all I wanted was like, let's just get this over with. I don't want to spend the rest of my life on cancer." (Participant 8)
Fearing surgery	"My recovery is always rough post-op—severe post-op nausea, vomiting. So, I wasn't really excited about going under and doing surgery again, going under anesthesia and having surgery so soon." (Participant 20)
Matching treatment with cancer severity	" I Googled about what people do, and I remember reading this article that said women are throwing an atomic bomb at a problem that a firecracker can fix. And talking about having a radical mastectomy, and I'm like, you know what? There's a lot of truth to that. And so I let the fear go and just decided that this is what I want to do. I want to keep my breast." (Participant 1)
Wanting to avoid or minimize surgery	"Because I didn't want the big invasive surgery. I was scared to have surgery, period. I wanted it out of there with less invasive [surgery]." (Participant 17)
Wanting to avoid cancer medications/chemotherapy	"My husband said if the doctor recommends it, then he's in favor of it, but I'm not sure that I am because I have read a lot about the side effects of chemotherapy, how long it takes to get over it and all that. And I'm not sure that I'm signed up for that. So, I guess if the doctor recommends, like, a midpoint, I would say no. But if he said, okay, it's like 100 percent positive, you need it, well then I might think about it." (Participant 3)
Positive views of non-surgical treatment options	"And when I saw the progress [on the Taxol] almost immediately, the tumor started shrinking, and then it was like down to nothing. I couldn't even feel it. It was just bigger than a golf ball before that, you know?" (Participant 8)
Wanting to avoid or minimize radiation therapy	"They wanted me to follow it up with thirty-five radiation treatments. And radiation just isn't something I want to go through thirty-five times. I didn't want to put my body through that." (Participant 1)

Perceptions and feelings about physicians and health care system

Conversations with their physicians about treatment options

Participating in / Directing own care decisions

External conversations with family and friends

Current quality of life and level of support in their daily life

Radiation on CALGB 9343/PRIME-II

	CALGB 9343	PRIME-II
Target	Whole breast+axilla	Whole breast
Technique	2D	3D/simple IMRT
Breast Dose	50 Gy in 25 fractions	40-50 Gy in 15-25 fractions
Boost	Required	Optional
Boost dose	14 Gy in 7 fractions	10-15 Gy in 5-7 fractions
Total duration	32 business days	15-32 business days

Radiation Options Today

	Whole Breast	Whole Breast	Accelerated Partial Breast Irradiation
Target	Whole breast	Whole breast	Tumor bed+1-2 cm
Technique	3D/Simple IMRT	3D/simple IMRT	VMAT or 3D/simple IMRT
Breast Dose	26 Gy in 5 fractions consecutive days	28.5 Gy in 5 fractions once per week	27-30 Gy in 5 fractions on consecutive or non-consecutive days
Boost	No	No	No
Boost dose	N/A	N/A	N/A
Total duration	5 business days	5 business days over 5 weeks	5-8 business days

Risks/Benefits of RT vs. Endocrine Therapy

Radiation	Endocrine Therapy
1 week to 1.5 weeks	5-10 years daily
Side Effect Profile	Side Effect Profile
Dermatitis	Vaginal dryness
Fatigue	Hair thinning
Breast swelling/discomfort	Bone mineral density loss
Chronic Breast fibrosis Impaired cosmesis Pulmonary/cardiac complications Secondary malignancies	Alterations in mood Vaginal Bleeding (tamoxifen) Uterine cancers (tamoxifen)
Reduces in-breast recurrence	Reduces both contralateral and ipsilateral risk of breast cancer
No effect on distant recurrence in low-risk disease	~50% relative reduction in distant recurrences

CITY OF HOPE Optimal Adjuvant Treatment for Older Adults with ER+ Breast Cancer: Patients Should Receive Radiation Therapy

Optimal Monotherapy: Retrospective Data

Outcomes of T1 and T2 patients.

Characteristic	BCS Alone n(%)	BCS + RT n(%)	BCS + ET n(%)	BCS + RT + ET n(%)	Total n(%)	p-Value
Number of patients	130	378	161	497	1166	
Median Follow-up (range, months)	67.6 (2.9-168.2)	75.1 (4.4–168.4)	69.6 (5.2-163.1	88.2 (4.5-169.3)	79.1 (2.9-169.3)	0.031
Local Recurrence Disease Progression/Recurrence T1 T2	70(54) 25(19) 19(17) 6(33)	9(2) 17(4) 11(3) 6(25)	10(6) 15(9) 10(8) 5(14)	6(1) 35(7) 19(5) 16(13)	95(8) 92(8) 59(6) 33(16)	<0.0001 <0.0001 <0.0001 0.141
Other Cancer	26(20)	59(16)	20(12)	39(8)	144(12)	
Death Breast Cancer Other Cancer Other Cause/Unknown	70(54) 4(6) 11(16) 55(79)	68(16) 5(7) 14(21) 49(72)	89(12) 7(8) 11(12) 71(80)	115(8) 17(15) 24(21) 74(64)	342(12) 33(10) 60(18) 249(73)	⊲0.0001

Recurrence-Free Survival



Joseph K, Radiother. Oncol. 2021

Event	All Patients (n = 888)		RT only (n = 118)		HT only (n = 233)		RT + HT (n = 398)		(n = 134)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Locoregional recurrence	27	3.0	5	4.2	7	3.0	3	0.8	12	9.0
Local (in breast) only	24	2.7	5	4.2	6	2.6	1	0.3	12	9.0
Regional only	2	0.2	0	0.0	1	0.4	1	0.3	0	0.0
Local and regional	1	0.1	0	0.0	0	0.0	1	0.3	0	0.0
Distant recurrence	11	1.2	4	3	1	0.4	3	0.8	3	2.2
Death ^a	65	7.3	10	8.5	16	6.9	18	4.5	20	14.9
Breast cancer	3	0.3	1	0.8	0	0.0	1	0.3	1	0.7
Other	62	7.0	9	7.6	16	6.9	18	4.5	19	14.2





- HR+/HER2- patients from MINDACT trial with T1N0 disease
- 509 pts with no adjuvant systemic treatment matched to
 509 patients that received only ET
- 76% of patients 50-70 years old
- 95% genomic low-risk

Lopes Cardozo JMN, Ann Oncol. 2022

Optimal Monotherapy: Ongoing Trials



Meattini I, Journal of Geriatric Oncology, 2020

REaCT-70	Risks and benefits of hormonal therapy in patients with low risk breast cancer who are 70 years of age and older.
ClinicalTrials.gov: NCT04921137	Principal Investigator(s): Dr. Marie-France Savard

- Age≥70 yrs old with HR+/HER2-, pN0 tumors with
 - Grade 1 tumors≤5cm, or
 - Grade 2 tumors≤3cm, or
 - o Grade 3 tumors ≤1 cm
- Patients randomized to 5 yrs of ET vs. no ET
- Outcomes: assessment of AEs/toxicity and HR-QOL

Summary

- The optimal treatment of elderly patients with HR+/HER2- breast cancer should be guided by tumor biology, assessment of lifespan, and the patient's voice
- Radiotherapy has a pronounced benefit on in-breast tumor control, even in patients with estrogen-low tumors
- Given the tremendous advances in breast radiotherapy delivery, RT is no longer poses the same burden as it did 30 years ago
- Future quantitative studies in elderly HR+/HER2- patients should look at identifying the optimal monotherapy (RT vs. ET) or de-escalating ET in these patients given the significant duration and side effects of current ET regimens
- As treatment options for breast cancer patients continue to evolve, there is an increasing role for qualitative research studies to help tailor a patient's treatment plan based on optimizing cancer outcomes and their own desires