Should Radiation Be Recommended for Older Women with Breast Cancer? Yes!

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Background

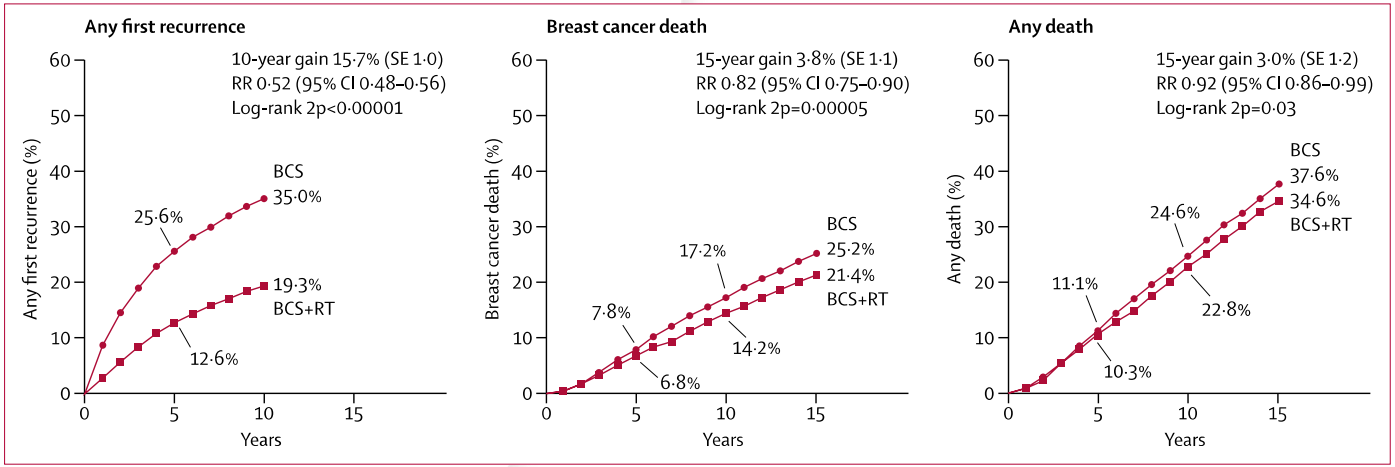
- RT approximately halves the rate of developing ANY disease recurrence
- Reduces breast cancer death by a sixth

The Lancet
Volume 378, Issue 9804, 12–18 November 2011, Pages 1707-1716

Articles

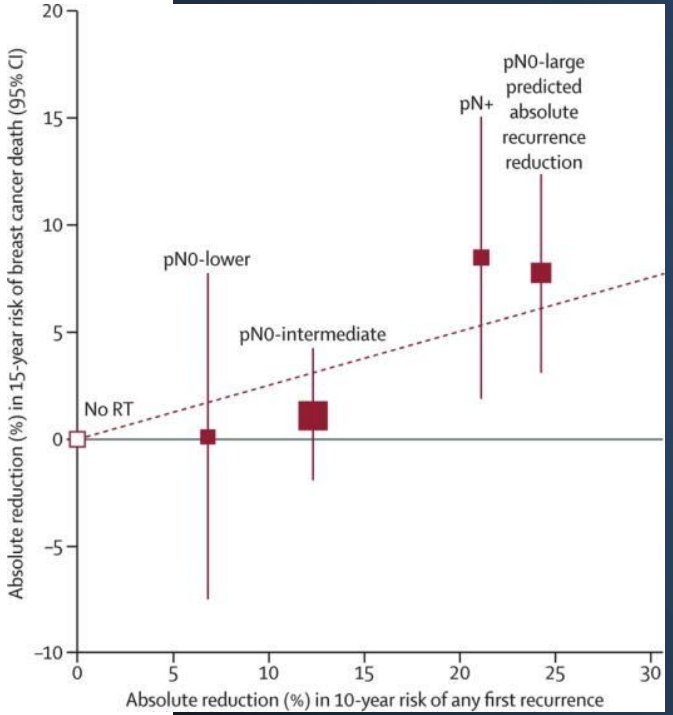
Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) ‡



Premise

- Despite advances that reduce the burden and toxicity of modern RT, no treatment is entirely without toxicity or burden
- Not all subgroups attain the same absolute benefit from RT, and survival benefit appears restricted to those with a larger absolute reduction in recurrence risk from RT
- Ideally, we could identify some patients at sufficiently low risk of residual locoregional disease (thanks to advances in radiology, pathology, surgery, and systemic therapy) who might safely avoid RT altogether

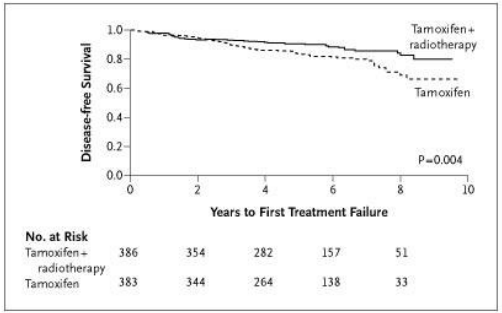


Data: Canadian Trial

- Patients 50+ with T1-2 node-negative breast ca randomized to observation vs RT after BCS and tamoxifen (Fyles et al. NEJM 2004)
  - IBTR 8% vs 1% at 5 years
  - **At 8 years, 18%** vs 4%
  - Planned subgroup analysis of 611 women with T1, receptor-positive tumors: IBTR 6% vs 0.4% at 5 years and 15% vs 4% at 8 years

Tamoxifen with or without Breast Irradiation in Women 50 Years of Age or Older with Early Breast Cancer

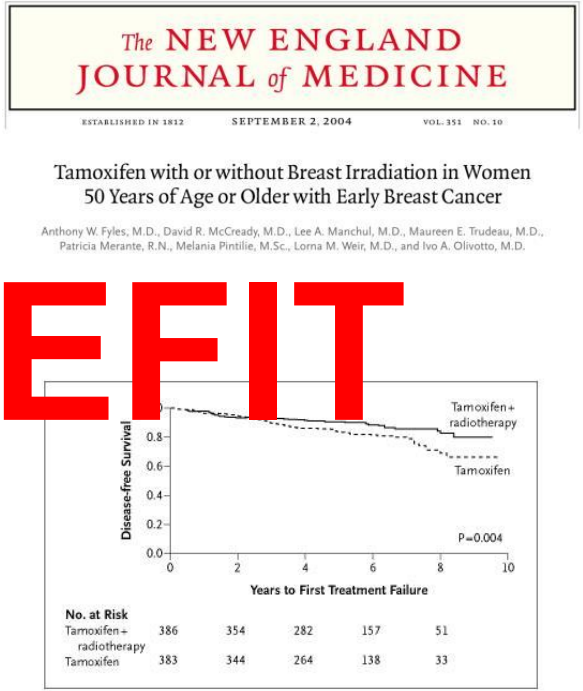
Anthony W. Fyles, M.D., David R. McCready, M.D., Lee A. Manchul, M.D., Maureen E. Trudeau, M.D., Patricia Merante, R.N., Melania Pintilie, M.Sc., Lorna M. Weir, M.D., and Ivo A. Olivotto, M.D.



Data: Canadian Trial

- Patients 50+ with T1-2 node-negative breast ca randomized to observation vs RT after BCS and tamoxifen (Fyles et al NEJM 2004)
  - IBTR 8% vs 1% at 5 years
  - **At 8 years 14% vs 4%**
  - Planned subgroup analysis of 611 women with T1, receptor-positive tumors: IBTR 6% vs 0.4% at 5 years and 15% vs 4% at 8 years

>10% BENEFIT



Data: CALGB 9343

Hughes et al. NEJM 2004, JCO 2013

- Patients
  - 636 women, age 70+
  - Clinical stage I, ER+
- Randomization
  - Tamoxifen +/- RT
- 10-yr LRR **10% vs 2% (favoring +RT)**
- No significant difference in DMs, breast cancer-specific mortality, or all-cause mortality

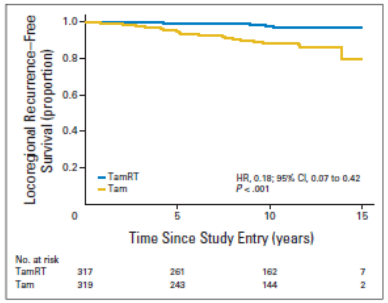


Fig 2. Time to local or regional recurrence. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

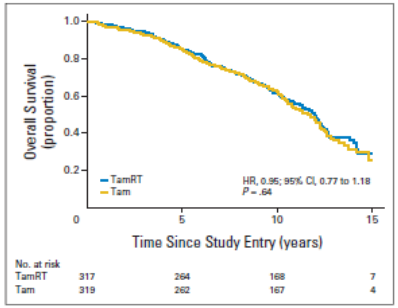


Fig 5. Overall survival. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

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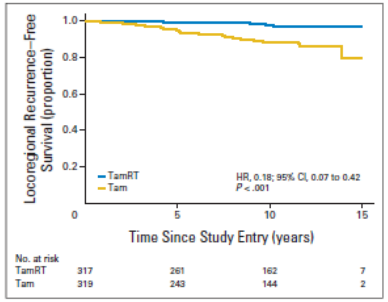
8% BENEFIT



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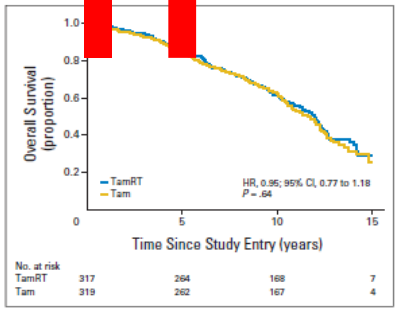
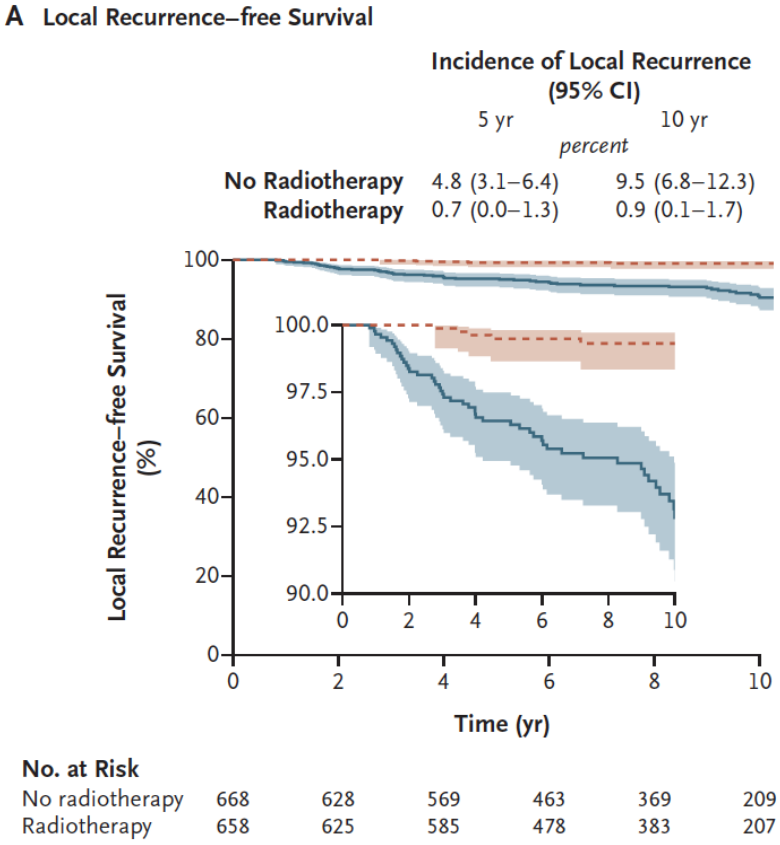


Fig 5. Overall survival. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

The Data: PRIME II

Kunkler et al. Lancet Oncol 2015, NEJM 2023.

- Age 65+, tumors up to 3cm, 1mm margins
- Findings virtually identical to CALGB 9343
  - 5 years (4% vs 1% LR)
  - **10 years (10% vs 1% LR)**
- But **higher recurrence with ER-low (19.1%) or poor ET adherence**
- Few Grade 3 patients



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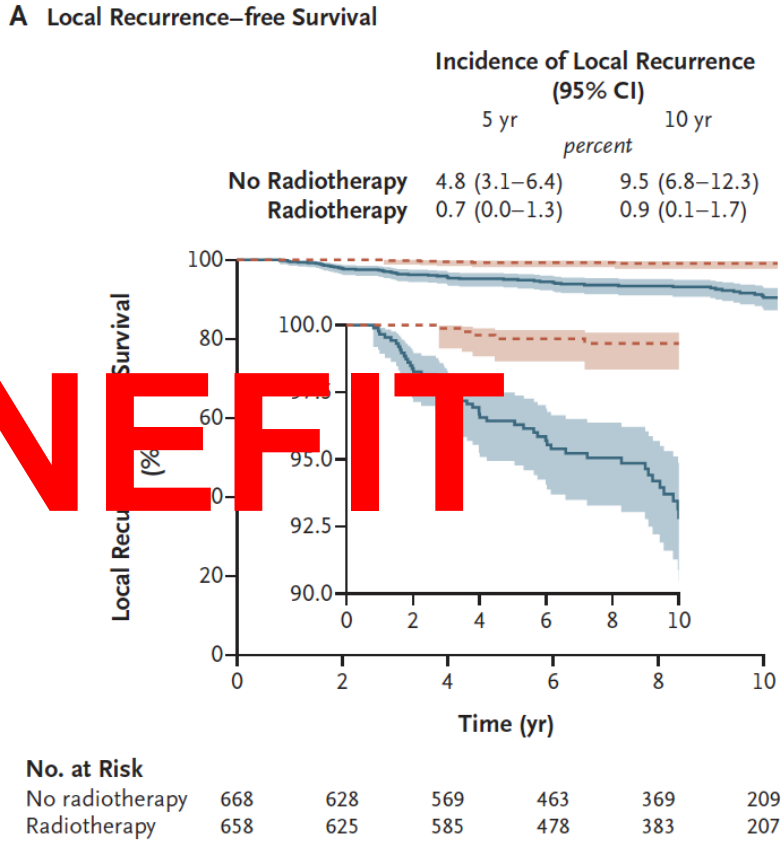
9% BENEFIT



	IDEA	LUMINA	PRECISION	PRIMETIME	EXPERT	Natural	EUROPA	DEBRA
Design	Single arm	Single arm	Single arm	Single arm	Randomized	Randomized	Randomized	Randomized
Years	2015-2018	2013-2017	2016-present	2017-2022	2017-present	2018-present	2021-present	2021-present
Accrual Goal	200	501	672	2400	1167	926	926	1670
Age	≥ 50 ≤ 69	≥ 55	≥ 50 ≤ 75	≥ 60	≥ 50	≥ 60	≥ 70	≥ 50 ≤ 70
T Stage	pT1	pT1	pT1	pT1	pT1	pT1	pT1	pT1
N Stage	pN0, pN0(IHC+)	pN0	pN0, pN0(IHC+)	pN0	pN0, pN0(IHC+)	pN0	cN0, pN0, pN0(IHC+)	pN0
Grade	Any	1-2	1-2	1-2	1-2	1-2	Any if ≤1 cm 1-2 if >1 cm	Any
Biologic criteria	**Oncotype** Score ≤18 **IHC** ER/PR+ HER2-	**IHC** ER≥ 1% PR>20% HER2- Ki67≤13.25%	**PAM-50** Low risk **IHC** ER/PR≥10% HER2-	**IHC** ER/PR+ HER2- **IHC4+C** Very low	**PAM-50** Luminal A ROR ≤60	**IHC** ER≥10% HER2-	**IHC** ER/PR≥10% HER2- Ki67≤20%	**Oncotype** Score ≤18 **IHC** ER/PR≥1% HER2-
Trial Arms	ET	ET	ET	ET	ET vs. ET + RT	ET vs. ET + APBI	ET vs. APBI	ET vs. ET + RT

Biologically Focused Studies

- No long-term results yet

Reflections

- Whether a woman pursues RT depends on her own values/preferences, the expected benefits of RT, and the burden and toxicity of RT
- **Advances in RT have substantially reduced dose to critical normal tissues (e.g., the heart), toxicity, and short-term burden of RT** in recent years, with implications for the risk-benefit ratio, particularly among women with long life expectancies
- The patients eligible for these trials are now also candidates for regimens treating the whole breast or partial breast in **5 fractions or less**

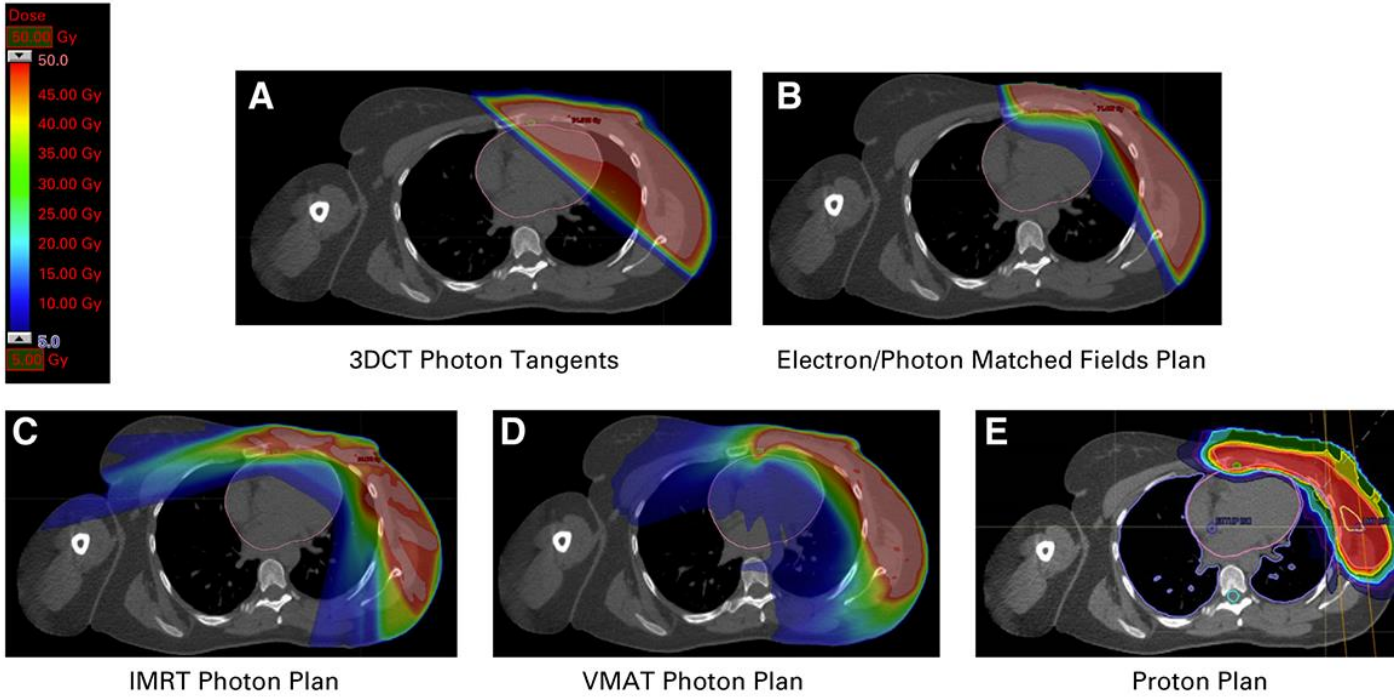
Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 10-year efficacy and late normal tissue effects from a multicentre, open-label, non-inferiority, phase 3, randomised controlled trial and 5-year efficacy results from a randomised axillary substudy

Adrian Murray Brunt, Fay H Cafferty*, Anna M Kirby, Jaymini Patel, Mark A Sydenham, Joanne S Haviland, Susan Griffin, Carlos Chivardi, Helen Fleming, Charlotte E Coles, David J Bloomfield, Charlie Chan, Susan Cleator, Andy Goodman, Clare L Griffin, Cliona C Kirwan, Zohal Nabi, Elinor Sawyer, Navita Somaiah, Isabel Syndikus, Karen Venables, Duncan A Wheatley, John R Yarnold†, Judith M Bliss†*

original reports

Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial

Icro Meattini, MD[1,2]; Livia Marrazzo, MS[2]; Calogero Saieva, MD[3]; Isacco Desideri, MD[1,2]; Vieri Scotti, MD[2]; Gabriele Simontacchi, MD[2]; Pierluigi Bonomo, MD[2]; Daniela Greto, MD[2]; Monica Mangoni, MD, PhD[1,2]; Silvia Scoccianti, MD[2]; Sara Lucidi, MD[1]; Lisa Paoletti, MD[4]; Massimiliano Fambrini, MD[1,2]; Marco Bernini, MD, PhD[2]; Luis Sanchez, MD[2]; Lorenzo Orzalesi, MD[1,2]; Jacopo Nori, MD[2]; Simonetta Bianchi, MD[1,2]; Stefania Pallotta, MS[1,2]; and Lorenzo Livi, MD[1,2]

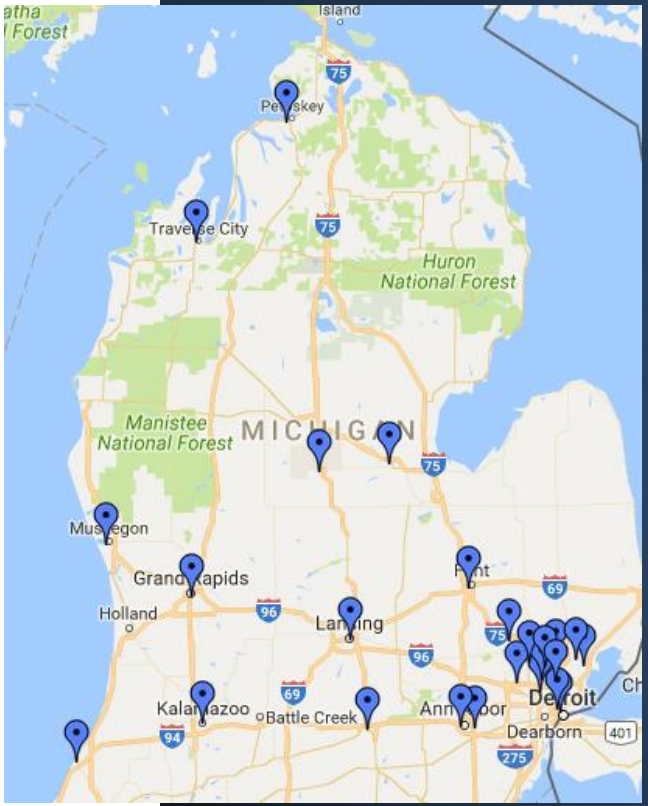


CARDIAC SPARING OF MODERN RT

Torres MA et al. *J Clin Oncol*. 2020;38(20):2299-2309.

Modern Heart Doses

- MROQC statewide quality consortium (Pierce et al. IJROBP 2017)
  - 4688 patients treated with whole breast RT at 20 sites
  - For **left-sided cases treated with moderate hypofractionation, median MHD 1.22 Gy** in 2015
- For context: **Darby NEJM study assessing cardiac toxicity after breast RT had MHD of 4.9 Gy** (including right-sided cases!)



Rethinking the Premise

- How burdensome and toxic really is modern RT?
- In the end, whether a woman chooses to decide to forego a modest disease control benefit depends on the answer to this
- If toxicity and burden are truly minimized, there may be situations in which RT might actually be preferred over certain other treatments that are currently standard...

The Future: Not Reflexive RT Omission But Optimization/Individualization of Care for Each Patient

NEJM Evidence

CURRENT ISSUE

TOMORROW'S TRIAL

Can De-Escalation of Adjuvant Therapy Be Considered for Older Adults with Breast Cancer?

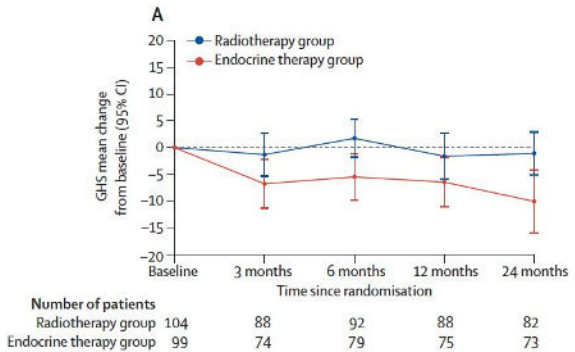
Authors: Manjeet Chadha, M.D., Julia White, M.D., and Reshma Jagsi, M.D., D.Phil. Author Info & Affiliations

Published March 25, 2025 | NEJM Evid 2025;4(4) | DOI: 10.1056/EVIDtt2300358 | VOL. 4 NO. 4

Single-modality endocrine therapy versus radiotherapy after breast-conserving surgery in women aged 70 years and older with luminal A-like early breast cancer (EUROPA): a preplanned interim analysis of a phase 3, non-inferiority, randomised trial

Icro Meattini, Maria Carmen De Santis, Luca Visani, Marta Scorsetti, Alessandra Fozza, Bruno Meduri, Fiorenza De Rose, Elisabetta Bonzano, Agnese Prisco, Valeria Masiello, Eliana La Rocca, Ruggero Spoto, Carlotta Becherini, Gladys Blandino, Luca Moscetti, Riccardo Ray Colciago, Riccardo A Audisio, Etienne Brain, Saverio Caini, Marije Hamaker, Orit Kaidar-Person, Matteo Lambertini, Livia Marrazzo, Calogero Saieva, Tanja Spanic, Vratislav Strnad, Sally Wheelwright, Philip M P Poortmans, Lorenzo Livi*, on behalf of the EUROPA Trial Investigators†*

- BASO II trial (Blamey et al. Eur J Cancer 2013)
  - 10y LR: 22% after neither adjuvant therapy; 8% with RT alone; 8% with tamoxifen alone; 2% with both
- Ontario cohort study (Goldberg et al. BCRT 2019)
  - 5y LR 9.4% after neither adjuvant therapy, 1.4% with RT alone, 3.1% with ET alone, 0.9% with both



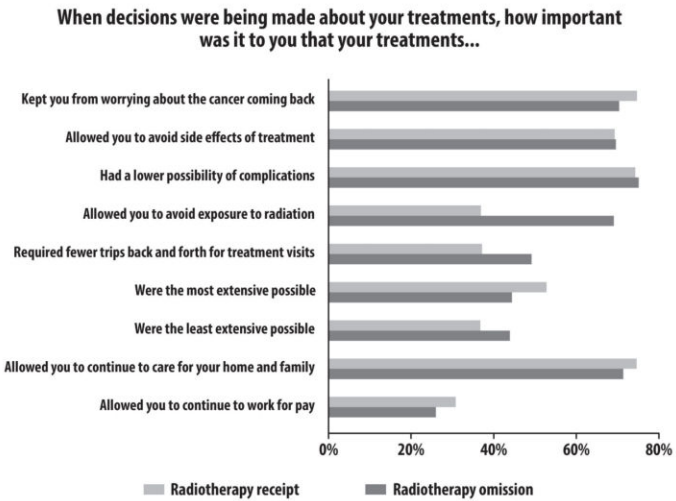
Patients' Values and Preferences Should Inform Decisions

Cancer
An International Interdisciplinary Journal of the American Cancer Society

Original Article | Free Access

Patient views and correlates of radiotherapy omission in a population-based sample of older women with favorable-prognosis breast cancer

Dean A. Shumway MD, Kent A. Griffith MPH, MS, Sarah T. Hawley PhD, MPH, Lauren P. Wallner PhD, MPH, Kevin C. Ward PhD, MPH, Ann S. Hamilton PhD, Monica Morrow MD, Steven J. Katz MD, MPH, Reshma Jagsi MD, DPhil ... See fewer authors



Medical Decision Making
Volume 40, Issue 4
May 2020
Pages 407-550

ARTICLE

Eliciting Medical Maximizing-Minimizing Preferences with a Single Question: Development and Validation of the MM1

Thinking About How Much Healthcare You Prefer to Get: What Type Are You?

Sometimes, medical action is clearly necessary, and sometimes it is clearly NOT necessary. Other times, reasonable people differ in their beliefs about whether medical action is needed.

In situations where it's not clear, do you tend to lean towards **taking action** or do you lean towards **waiting and seeing** if action is needed?

Importantly, there is no "right" way to be.

Please answer on the 1-6 scale below:

I strongly lean toward waiting and seeing	I lean toward waiting and seeing	I somewhat lean toward waiting and seeing	I somewhat lean toward taking action	I lean toward taking action	I strongly lean toward taking action
1	2	3	4	5	6
○	○	○	○	○	○

Summary

- A subset of select older women with ER+, small, node-negative cancers can reasonably consider RT omission, **BUT they must willing to tolerate a higher risk of LRR**
- **Most informed candidates for RT omission choose to receive what is now a 5-day course of therapy that is well-tolerated by the overwhelming majority in order to reduce the risk of local recurrence by 8%**
    - **Not all older women are candidates for RT omission**
    - **Those who were not represented** on these trials or have high-risk factors (high grade, lower ER, disinclination to adhere to ET) should **strongly be encouraged** to receive RT