

2022

Radiation therapy for older women with early breast cancer: An unnecessary hardship

Lauren E. Shawver

Wayne State University, fn9915@wayne.edu

Follow this and additional works at: <https://digitalcommons.wayne.edu/crp>



Part of the [Medical Education Commons](#), [Oncology Commons](#), [Radiology Commons](#), [Surgery Commons](#), and the [Translational Medical Research Commons](#)

Recommended Citation

SHAWVER LE. Radiation therapy for older women with early breast cancer: An unnecessary hardship. Clin. Res. Prac. Jul 25 2022;8(1):eP2883. <https://doi.org/10.22237/crp/1656633720>

This Clinical Decision Report is brought to you for free and open access by the Open Access Journals at DigitalCommons@WayneState. It has been accepted for inclusion in Clinical Research in Practice: The Journal of Team Hippocrates by an authorized editor of DigitalCommons@WayneState.

Radiation therapy for older women with early breast cancer: An unnecessary hardship

LAUREN E. SHAWVER, B.S., Wayne State University School of Medicine, fn9915@wayne.edu

ABSTRACT A clinical decision report using:

Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial [published correction appears in *Lancet Oncol.* 2015 Mar;16(3):e105]. *Lancet Oncol.* 2015;16(3):266-273. [https://doi.org/10.1016/S1470-2045\(14\)71221-5](https://doi.org/10.1016/S1470-2045(14)71221-5)¹

for an older patient seeking treatment for Stage 1 Ductal Breast Carcinoma.

Keywords: *breast cancer, radiation therapy, older women*

Clinical-Social Context

Josephine Johnson [pseudonym], is an 81-year-old African American woman with a past medical history of hypertension, hypercholesterolemia, and leiomyomas who presented to the clinic for follow-up regarding her recent breast biopsy results. Ms. Johnson denied any complaints; however, her most recent mammogram one month prior identified a 0.4-by-0.4-centimeter suspicious calcification in her left breast, in the 11 o'clock position and 9 centimeters from the nipple. The lesion was biopsied and identified as invasive ductal carcinoma.

When Ms. Johnson presented to the clinic with her daughter, she was concerned and eager to hear from the surgeon. Her sister had been diagnosed and treated for breast cancer, but she could not recall much about her sister's experience. Ms. Johnson did have a friend that had been diagnosed with late-stage breast cancer many years ago. She had watched her friend complete rounds of radiation and "didn't want to go through that," referring to the breast pain and ulcerations of the overlying skin her friend experienced after treatments.

The treating team, Ms. Johnson, and her daughter discussed how her social situation may be impacted by treatment. Ms. Johnson lived with her daughter but was relatively independent in her activities of daily living aside from her daughter assisting her with transportation. She felt supported by her family, but she enjoyed her independence and preferred to not ask for significant help.

Ms. Johnson was informed that based on the size of her tumor, she is most likely Stage 1 Ductal Carcinoma and Estrogen Receptor positive (ER+), Progesterone Receptor positive, and HER-2 Receptor negative, a favorable pathology.²⁻³ The care team recommended a lumpectomy with sentinel lymph node biopsy followed by adjuvant radiation therapy (ART) and adjuvant endocrine therapy (AET). Ms. Johnson was agreeable to the lumpectomy and AET but was hesitant to complete ART.

LAUREN E. SHAWVER, B.S., is a medical student at Wayne State University School of Medicine.



Ms. Johnson's hesitancy to complete radiation therapy stemmed from her dependence on her daughter for transportation to appointments and her recollection of her friend's experience with radiation therapy. Her hesitancy led the team to truly question if ART was necessary in her case or if local recurrence could be prevented with AET alone. A review of UpToDate was performed to evaluate the current treatment recommendations for women with invasive ductal breast carcinoma.

Clinical Question

Does post-lumpectomy radiation decrease local recurrence in older women with early-stage breast cancer receiving adjuvant endocrine therapy?

Research Article

Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial [published correction appears in *Lancet Oncol.* 2015 Mar;16(3):e105]. *Lancet Oncol.* 2015;16(3):266-273. [https://doi.org/10.1016/S1470-2045\(14\)71221-5](https://doi.org/10.1016/S1470-2045(14)71221-5)¹

Description of Related Literature

Guidelines based on staging recommend that women with stage 1 breast cancer should be offered partial lumpectomy with sentinel lymph node biopsy followed by ART and AET.⁴ However, UpToDate cited that women 65 years of age and older with small, less than 3-centimeter, ER+ invasive ductal carcinoma, may not need to complete ART in addition to AET.⁵ Conflicting recommendations from "evidence based" guidelines requires an understanding not only of how the guidelines are constructed, but also the patient to whom the recommendation will be applied.

The literature review began with a search of PubMed using the terms "breast cancer" and "older women" which returned 2082 results. Adding "irradiation" to the search terms yielded 37 results. Further specifying the term "irradiation" as "irradiation" OR "radiation," identified 274 results. Between 2011 and 2021, there were 160 publications including 6 clinical trials and 4 randomized control trials (RCT). Three of these clinical trials and RCTs explored outcomes related to adjuvant therapy.

Khan et al. was an observational study of 1,449 patients over 70 years old with early-stage breast cancer enrolled in the American Society of Breast Surgeons registry trial.⁶ This study compared ART to AET and found similar levels of recurrence after 5 years.⁶ The standard of care for older women with stage 1 breast cancer following lumpectomy is ART and AET. This study was excluded because the control group was only offered ART and not the standard-of-care, AET and ART. Meattini et al. is a proof-of-concept paper for the RCT, the EUROPA study, which also compared AET to ART.⁷ Meattini et al. discusses the background and methods for the proposed study. Because this study was a proof-of-concept paper and did not include any outcomes, this publication was excluded. The remaining publications in the literature search did not include outcomes related to the recurrence of disease and therefore were excluded.⁸⁻¹⁰

On PubMed, through identification of related articles to Kunkler et al., discussed below, Hughes et al. was additionally considered. Hughes et al. conducted a RCT comparing AET with or without ART.¹¹ This study included 636 women 70 years or older with breast cancer smaller than 2 centimeters. However, the AET used in this trial was tamoxifen, a selective estrogen receptor modulator (SERM), instead of aromatase inhibitors, the standard of care AET for postmenopausal women.¹¹ The team recommended an aromatase inhibitor for AET to Ms. Johnson. Therefore, this study was excluded because this made comparison difficult.

Kunkler et al. conducted a RCT comparing AET with or without ART in older women with early breast cancer following lumpectomy.¹ This trial included 1326 women 65 years or older with breast cancer that was smaller than 3 cm in greatest dimension. This study allowed the care team to choose the AET, SERMs or aromatase inhibitors, based on their evaluation of the patient and their disease. This study found that although only AET had a statistically significant increase in disease recurrence, mortality rates from breast cancer at 5 years between the two groups were similar. This study was relevant to Ms. Johnson because she was a woman older than 65 years old and was diagnosed with early-stage breast cancer. Kunkler et al. was the most relevant and applicable study to Ms.



Johnson because it was the only paper that included women receiving adjuvant aromatase inhibitor therapy.¹¹ Additionally, compared to Hughes et al. the study was more recent and included more participants.^{1,11} Based on the SORT criteria, the evidence for ART in older women with early stage breast cancer has a Strength of Recommendation level B based on the limited quality and quantity of clinical trials.¹²

Critical Appraisal

Kunkler et al. describes a prospective RCT comparing adjuvant therapies in older patients with early breast cancer.¹ This study enrolled women 65 years or older with ER+ T1-2, N0, M0 breast cancer following partial-mastectomy with clear margins ($\geq 1\text{mm}$) and negative lymph nodes. Patients with a history of another malignancy other than non-melanoma skin cancer were excluded from the trial. Patients were enrolled from 2003 to 2009 at 76 sites across four countries, the United Kingdom, Greece, Australia, and Serbia.

A total of 1326 women were randomized 1:1 into two groups of adjuvant therapy – radiation therapy (658 patients) and no radiation therapy (668 patients). Both groups received AET. Patients were followed for up to 10 years with a median follow-up of 5 years. No blinding occurred in this study. The primary outcome was ipsilateral breast tumor recurrence. Secondary outcomes were breast cancer-free survival rates, overall survival rates, contralateral breast cancer, and development of distant metastasis.

For the radiation therapy group, unilateral recurrence was 1.3% as compared to 4.1% in the non-radiation therapy group ($p=0.0002$). Therefore, Kunkler et al. calculated the hazard ratio to be 5.19 ($p=0.0007$). Interestingly, Kunkler et al. identified that there was no difference in survival benefit with ART with no statistical significance in overall 5-year survival ($p=0.34$). In the radiation therapy group, 40 women died, four from breast cancer. In the no radiation therapy group, 49 women died, eight from breast cancer. Therefore, this study argues that ART may not be necessary to improve survival even with a statistically significant increase in local recurrence.

Notable weaknesses of this study were related to AET. This study allowed patients to be placed on any AET at the discretion of their provider. Further, this study names Tamoxifen, a SERM, as the recommended AET. The current standard of care AET for ER+ breast cancer in postmenopausal women is aromatase inhibitors.² In postmenopausal women, aromatase inhibitors are more effective than SERMs at decreasing recurrence rates in ER+ breast cancer.¹³ Because Kunkler et al. did not provide data on the AET each patient received, it is unclear whether this could have impacted outcomes.

Another limitation of this study is the lack of data on HER-2 receptor status. Recent research has shown that HER-2 positivity is significant for poor clinical response.¹⁴ Because HER-2 receptor status was not analyzed, it is unclear if this could have affected the results.

This study was conducted in the United Kingdom, Australia, Greece, and Serbia and did not report race and ethnicity as patient characteristics. Additionally, this study had some attrition bias with overall attrition of 78.5% at 5 years. Kunkler et al. does not provide any rationale for the attrition. Given that this study includes an older participant group, the poor attrition may be due to morbidity related to breast cancer or other health problems leading to loss of follow-up.

This study was not blinded to patients or providers. Requiring patients to attend sham ART sessions would have been an unnecessary burden to patients. However, blinding providers and researchers could have strengthened this study. This study was conducted with an intention to treat analysis. This study was registered with ISRCTN without deviation from the treatment protocol and was funded by the Chief Scientist Office (of Scotland) and the Breast Cancer Institute. Kunkler et al. is a SORT Level 2 Evidence.¹²

Clinical Application

Following National Comprehensive Cancer Network guidelines, Ms. Johnson was offered a treatment plan of a lumpectomy and axillary sentinel lymph node biopsy followed by AET and ART.² However, based on Kunkler et al., ART may not provide enough additional protection against local recurrence to outweigh the consequences of radiation. The patients included in this trial represent Ms. Johnson as an older woman with early-stage ER+ breast cancer anticipating lumpectomy followed by adjuvant therapy. Therefore, Ms. Johnson could be offered AET

without ART. Ms. Johnson was presented with both plans, AET only or AET with ART, and she ultimately chose to complete AET only.

Ms. Johnson was hesitant about radiation therapy as she had watched her friend undergo an aggressive radiation regimen and suffer. She understood that the radiation schedule proposed to her would likely be less aggressive, but she continued to have concerns about the side effects. Ms. Johnson was informed that although there may be minimal benefits to radiation, risks of harm from radiation included fatigue, pain, and skin changes. AET only allowed Ms. Johnson more independence in her treatment, so she did not have to depend on her daughter to attend additional appointments. For Ms. Johnson, the possible harm of not completing ART increases her risk of local recurrence but does not increase her mortality risk. The patient was informed of this risk and believed that it was outweighed by the physiological and emotional stress of completing ART on herself and the weight on her daughter.

New Knowledge Related to Clinical Decision Science

Clinical Decision Science allows for individualized medicine. This clinical decision report is based on Ms. Josephine Johnson, an 81-year-old female presenting with Stage 1 Ductal Carcinoma of the left breast following routine screening mammogram. This report highlights how the risks and benefits of completing treatments must evaluate social impact in addition to health outcomes.

This Clinical Decision Report highlights that the patient's familiarity with and experiences of recommended treatments plays an important role in clinical decisions. This is an important enough consideration that it might be wise to ask every patient what they know about and what their experience has been with recommended treatments. It is not only the experience of the clinician, but also the experience of the patient that were determinative for this clinical decision. In the absence of direct patient experience with treatments, patients often say, "You're the doctor, you decide." This Clinical Decision Report highlights the need to explore the individual patient's values and needs prior to making a doctor making such a clinical decision.

Again, this Clinical Decision Report highlights the fallibility of "evidence based" guidelines.

For older women with early-stage breast cancer, research shows a significant but small benefit of ART to prevent recurrence. However, without an impact on mortality, the toll on patients must be considered. Every patient is unique, and the burden of radiation therapy depends on the patient and their overall health, interest in therapy, and social situation. For some patients, their overall health prognosis due to other significant comorbidities may not project any benefit from aggressive treatment. Further, social situations may create boundaries including transportation, monetary costs, and time that may substantially impact a patients cost-benefit analysis of aggressive treatment.

Finally, the benefit of screening, diagnosing, and treating elderly women with early-stage breast cancer must be considered. Without substantial impact on quality of life and mortality, should we be screening elderly women for breast cancer? When overdiagnosing and overtreatment does not benefit patients, we place a substantial burden on patients which can worsen health outcomes, and place significant psychosocial stress on patients and their families. As physicians, we must consider these consequences when initiating "harmless" screenings. Ms. Johnson's overall health and quality of life may not have been impacted if she was not screened, diagnosed, and treated for her new-onset breast cancer.

Conflict Of Interest Statement

The author declares no conflicts of interest.

References

1. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial [published



- correction appears in *Lancet Oncol.* 2015 Mar;16(3):e105]. *Lancet Oncol.* 2015;16(3):266-273. [https://doi.org/10.1016/S1470-2045\(14\)71221-5](https://doi.org/10.1016/S1470-2045(14)71221-5)
2. Amin MB, Edge SB, Greene FL, et al. (Eds.). *AJCC (American Joint Committee on Cancer) Cancer Staging Manual*. 8th ed. Springer; 2018.
 3. Gradishar WJ, Anderson BO, Abraham J, et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2020;18(4):452-478. <https://doi.org/10.6004/jnccn.2020.0016>
 4. Taghian A, Merajver S. Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer. *UpToDate*. Uptodate; 2021. Accessed 19 September 2021. <https://www.uptodate.com/contents/overview-of-the-treatment-of-newly-diagnosed-invasive-non-metastatic-breast-cancer>
 5. Taghian A. Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer. *UpToDate*. UpToDate; 2021. Accessed 19 September 2021. <https://www.uptodate.com/contents/adjuvant-radiation-therapy-for-women-with-newly-diagnosed-non-metastatic-breast-cancer>
 6. Khan AJ, Vicini FA, Beitsch P, et al. Local control, toxicity, and cosmesis in women >70 years enrolled in the American Society of Breast Surgeons accelerated partial breast irradiation registry trial [published correction appears in *Int J Radiat Oncol Biol Phys.* 2013 Mar 15;85(4):899]. *Int J Radiat Oncol Biol Phys.* 2012;84(2):323-330. <https://doi.org/10.1016/j.ijrobp.2011.12.027>
 7. Meattini I, Poortmans PMP, Marrazzo L, et al. Exclusive endocrine therapy or partial breast irradiation for women aged ≥70 years with luminal A-like early stage breast cancer (NCT04134598 - EUROPA): Proof of concept of a randomized controlled trial comparing health related quality of life by patient reported outcome measures. *J Geriatr Oncol.* 2021 Mar;12(2):182-189. <https://doi.org/10.1016/j.jgo.2020.07.013>
 8. VanderWalde NA, Martin MY, Kocak M, et al. Randomized phase II study of a home-based walking intervention for radiation-related fatigue among older patients with breast cancer. *J Geriatr Oncol.* 2021;12(2):227-234. <https://doi.org/10.1016/j.jgo.2020.09.013>
 9. Presutti R, D'Alimonte L, McGuffin M, et al. Decisional support throughout the cancer journey for older women diagnosed with early stage breast cancer: a single institutional study. *J Cancer Educ.* 2014;29(1):129-135. <https://doi.org/10.1007/s13187-013-0558-x>
 10. Soulos PR, Yu JB, Roberts KB, et al. Assessing the impact of a cooperative group trial on breast cancer care in the medicare population. *J Clin Oncol.* 2012;30(14):1601-1607. <https://doi.org/10.1200/JCO.2011.39.4890>
 11. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol.* 2013;31(19):2382-2387. <https://doi.org/10.1200/JCO.2012.45.2615>
 12. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *The Journal of the American Board of Family Medicine.* 2004;17(1):59-67. <https://doi.org/10.3122/jabfm.17.1.59>
 13. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet.* 2015;386(10001):1341-1352. [https://doi.org/10.1016/S0140-6736\(15\)61074-1](https://doi.org/10.1016/S0140-6736(15)61074-1)
 14. Schettini F, Pascual T, Conte B, et al. HER2-enriched subtype and pathological complete response in HER2-positive breast cancer: A systematic review and meta-analysis. *Cancer Treat Rev.* 2020;84:101965. <https://doi.org/10.1016/j.ctrv.2020.101965>

