Ann Surg Oncol (2023) 30:5309–5311
https://doi.org/10.1245/s10434-023-13665-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ASO PERSPECTIVES

To Radiate or Not to Radiate After Breast-Conserving Surgery–Endocrine Therapy is the Question

Sumana Narayanan, MD, FACS[1], and Roshni Rao, MD, FACS[2]

[1]Division of Surgical Oncology at Mount Sinai Medical Center, Columbia University, Miami Beach, FL; [2]Department of Surgery, Columbia University Medical Center, New York, NY

HISTORY OF OMISSION OF RADIATION AFTER BREAST-CONSERVING SURGERY

Radiation has been a mainstay of treatment after breast-conserving surgery (BCS) for breast cancer for nearly 40 years. The initial landmark trial demonstrating the importance of radiation was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B06 trial.[1] This was a three-arm trial that accrued 2163 stage 1 and 2 patients from 1976 to 1984.[1] These patients were randomized to modified radical mastectomy (MRM), lumpectomy + radiation, or lumpectomy alone. All patients were treated with level I and II axillary lymph node dissection (ALND), and lymph node positive patients were treated with adjuvant chemotherapy.[1] At the 20-year follow-up for this trial, no significant differences were identified between the three trial arms with respect to disease-free survival (DFS), distant disease-free survival, and overall survival (OS).[1] The local recurrence rate (LRR) within the ipsilateral breast was 14.3% with the addition of radiation after lumpectomy, compared with 39.2% in lumpectomy patients without radiation ($p < 0.001$).[1,2] This trial was critical in establishing BCS as a treatment with equivalent survival outcomes as well as confirming the importance of radiation in diminishing local breast cancer recurrence. Another significant trial from the European Organization for Research and Treatment of Cancer (EORTC 10801), which included 868 patients accrued from 1980 to 1986, compared outcomes of MRM operations with a lumpectomy + radiation group.[3,4] Again, there was no significant difference in OS and distant metastasis-free survival between the two groups.[3] There was, however, a lower locoregional recurrence rate in the MRM patients compared with the BCS cohort.[3,4]

As these revolutionary clinical trials allowed BCS with the addition of radiation to become standard practice for many years, more thought has been given to the long-term effects and toxicities associated with radiation, and to situations where it may be excluded without patient detriment. Recently, the PRIME II trial[5] demonstrated that radiation may be safely omitted in women over the age of 65 years with early-stage, hormone-positive breast cancers. We commend the authors on this important practice-changing clinical trial. In this study of 1326 women (accrued from 2003 to 2009), patients were randomized after BCS to whole-breast radiation (40–50 Gy) and no radiation groups.[5,6] Included within the study were women aged 65 years and older with hormone receptor-positive, node-negative, T1/T2 primary breast cancer (with tumors < 3 cm), all of whom were treated with BCS with negative margins.[5] Five years of adjuvant tamoxifen was administered to all patients.[5] At the 10 year follow-up, there were no significant differences in OS, distant recurrence rates, or breast cancer-specific survival (BCSS).[5] There was a significant difference in 10 year LRR between the two groups: 0.9% in the radiation group compared with 9.5% in the no radiation group.[5] These results are consistent with results from the CALGB 9343 trial that included patients ≥ 70 years old, clinical stage I, estrogen receptor (ER)-positive breast carcinomas treated with BCS followed by radiation + tamoxifen or tamoxifen alone.[7] The CALBG 43 study similarly demonstrated no differences in OS, BCSS, or time to mastectomy between groups at 10 years.[7] However, the 10 year LRR was 2% in the radiation + tamoxifen group compared with 10% in the tamoxifen alone arm.[6,7]

First Received: 6 April 2023
Accepted: 8 May 2023
Published online: 23 May 2023

R. Rao, MD, FACS
e-mail: rr3181@cumc.columbia.edu

KNOWN BENEFITS OF ENDOCRINE THERAPY

Endocrine therapy has been an extremely important component to the long-term treatment of patients with ER-positive breast cancers. Endocrine therapy has demonstrated a significant reduction in breast cancer recurrence and breast cancer mortality, which may extend for several years after cessation of treatment.[8] Interestingly, the PRIME II study demonstrated that there was an even more marked difference in LRR in patients who were categorized as "ER low" (0% in the radiation group compared with 19.1% in the no radiation group).[5] The "ER high" group had a less significant disparity between the two groups (1% in the radiation group compared with 8.6% in the no radiation group). Thus, radiation may be more beneficial in preventing LRRs in patients with lower HR positivity who are less likely to benefit from endocrine therapy.

The PRIME II trial utilized tamoxifen as the adjuvant endocrine therapy, which is a somewhat unusual choice in postmenopausal women.[5] This is especially true given the reduction in recurrence rates and 10-year breast cancer mortality in postmenopausal women treated with aromatase inhibitors compared with those treated with tamoxifen.[9] Additionally, tamoxifen has been associated with an increased risk of thromboembolic disease and uterine cancer, as well as other adverse effects such as hot flashes, which may compromise compliance with therapy.[8]

PARTIAL BREAST RADIATION AS A TREATMENT MODALITY

Partial breast radiation (PBR) has been introduced as an alternative treatment to whole breast radiation (WBR) for patients with early stage breast cancer. Potential advantages described include shorter treatment time and similar survival outcomes and LRR, with comparable toxicity and cosmesis.[2,10,11] The PRIME II trial did not include much discussion as regards to partial breast radiation, except for noting some limitations such as the need for localization and potential issues associated with quality assurance compared with WBR.[5] This group takes the view that adjuvant endocrine therapy is the primary competitor to WBR in reducing the risk of recurrence; however, no studies have included the impact of PBR on these patients.[5] The ongoing EUROPA trial aims to address this by comparing patients older than 70 years receiving BCS for T1N0 tumors randomized to adjuvant PBR alone versus endocrine therapy alone.[12] The outcomes of this study will examine patient-reported quality-of-life scores, as well as evaluate differences in local and distant control, adverse event rates, and impact on BCSS and OS.[12] This will probably be fundamental in determining the treatment modality that is likely to have the least adverse impact on quality of life without compromising recurrence rates or survival in older breast cancer patients.[12]

A PERSONAL STEPPED TRIAL

Despite the clear evidence of improved oncologic outcomes with adjuvant endocrine therapy, compliance and completion of currently recommended regimens has continued to be less than ideal.[13] Studies reveal high attrition rates, and data indicate only 40–60% of patients may in fact be completing this recommended therapy.[14,15] Discontinuation of endocrine therapy is multifactorial and influenced by side effects as well as perceptions of the benefit of the treatment.[15,16] In contrast, analysis reveals excellent compliance with adjuvant radiation therapy, with reports of > 80% of all patients completing the advised course.[17,18]

Given the current multidisciplinary management of breast cancer, an approach that incorporates a discussion with all specialties prior to surgical intervention would allow the patient to understand the risks and benefits of the omission of each therapy and then make an informed decision regarding what is an acceptable risk of recurrence for that individual. Additionally, a short, well-timed course of endocrine therapy, in the neoadjuvant setting or the immediate postsurgical setting, may allow a patient to evaluate their tolerance of endocrine therapy, but still receive timely radiation therapy if they experience adverse side effects that would lead them to noncompliance with a multiyear course. Conversely, if they find the endocrine therapy quite manageable, this would allow for a great deal of comfort with omitting radiation for suitable tumor types.

GENOMICS TO DECIDE

With continued advancements in the understanding of tumor biology, the final answer on the de-escalation of radiation therapy clearly lies in the (likely not very distant) future. Similar to optimizing chemotherapy benefit with the use of genomic analysis,[19,20] potentially prolonging endocrine therapy for higher-risk patients,[20] and the use of simulation modeling,[21] there are ongoing efforts to allow for more carefully considered assessments of the benefit of radiation therapy.[22,23] Recently, Sjöström et al.[24] utilized samples from two different completed randomized trials that evaluated the benefit of radiation therapy after BCS to develop and validate a Profile for the Omission of Local Adjuvant Radiation (POLAR). POLAR is a 16 gene assay that stratifies patients as low risk of local LRR with omission of radiation versus high risk of LRR with omission of radiation.[24] This promising work is planned for transition into clinical trials and would potentially provide a molecular signature for radiation recommendations.[24] Future assays would also likely need to include an assessment of radiation sensitivity of the tumor

and potentially radiation toxicity predictions for individual patients.[25]

Above all, in modern medical care, a shared decision-making approach, where the tolerance of recurrence risk versus potential adverse reactions from medical interventions will allow for optimal outcomes for the individual patient with their goals "… governed by the balance of light…".[26]

DISCLOSURE None.

REFERENCES

1. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347:1233–41.
2. Valente SA, Shah C. The landmark series: adjuvant radiation therapy for breast cancer. *Ann Surg Oncol*. 2020;27:2203–11.
3. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst*. 2000;92:1143–50.
4. Litiere S, Werutsky G, Fentiman IS, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol*. 2012;13:412–9.
5. Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in early breast cancer. *N Engl J Med*. 2023;388:585–94.
6. Purswani JM, Hardy-Abeloos C, Perez CA, Kwa MJ, Chadha M, Gerber NK. Radiation in early-stage breast cancer: moving beyond an all or nothing approach. *Curr Oncol*. 2022;30:184–95.
7. 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;31:2382–7.
8. Early Breast Cancer Trialists' Collaborative G, Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*. 2011;378: 771–784.
9. Early Breast Cancer Trialists' Collaborative G. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386: 1341–1352.
10. Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer*. 2015;51:451–63.
11. Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet*. 2017;390:1048–60.
12. 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;12:182–9.
13. Hershman DL, Shao T, Kushi LH, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat*. 2011;126:529–37.
14. Wallace AS, Keene KS, Williams CP, et al. Radiation therapy utilization in Medicare beneficiaries with early-stage breast cancer. *Cancer*. 2018;124:475–81.
15. Lambert LK, Balneaves LG, Howard AF, Chia SK, Gotay CC. Understanding adjuvant endocrine therapy persistence in breast cancer survivors. *BMC Cancer*. 2018;18:732.
16. Bluethmann SM, Murphy CC, Tiro JA, Mollica MA, Vernon SW, Bartholomew LK. Deconstructing decisions to initiate, maintain, or discontinue adjuvant endocrine therapy in breast cancer survivors: a mixed-methods study. *Oncol Nurs Forum*. 2017;44:E101–10.
17. McClelland S 3rd, Burney HN, Zellars RC, Ohri N, Rhome RM. Predictors of whole breast radiation therapy completion in early stage breast cancer following lumpectomy. *Clin Breast Cancer*. 2020;20:469–79.
18. Lamm R, Woodward SG, Varshney K, et al. A comparison of timely completion of hypofractionated and traditional adjuvant radiation therapy in early-stage breast cancer: evidence of impact on reducing racial and socioeconomic disparities. *Surgery*. 2022;172:31–40.
19. Kalinsky K, Barlow WE, Gralow JR, et al. 21-Gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med*. 2021;385:2336–47.
20. Andre F, Ismaila N, Allison KH, et al. Biomarkers for adjuvant endocrine and chemotherapy in early-stage breast cancer: ASCO guideline update. *J Clin Oncol*. 2022;40:1816–37.
21. Chandler Y, Schechter C, Jayasekera J, et al. Simulation modeling of breast cancer endocrine therapy duration by patient and tumor characteristics. *Cancer Med*. 2022;11:297–307.
22. Ouattara D, Mathelin C, Ozmen T, Lodi M. Molecular signatures in ductal carcinoma in situ (DCIS): a systematic review and meta-analysis. *J Clin Med*. 2023;12.
23. Chevli N, Haque W, Tran KT, et al. 21-Gene recurrence score predictive for prognostic benefit of radiotherapy in patients age >/= 70 with T1N0 ER/PR + HER2- breast cancer treated with breast conserving surgery and endocrine therapy. *Radiother Oncol*. 2022;174:37–43.
24. Sjostrom M, Fyles A, Liu FF, et al. Development and validation of a genomic profile for the omission of local adjuvant radiation in breast cancer. *J Clin Oncol*. 2023;41:1533–40.
25. Feng H, Wang H, Xu L, et al. Prediction of radiation-induced acute skin toxicity in breast cancer patients using data encapsulation screening and dose-gradient-based multi-region radiomics technique: a multicenter study. *Front Oncol*. 2022;12:1017435.
26. Shakespeare W, Herzberg MJ. Shakespeare's The tragedy of Hamlet, prince of Denmark. Boston, New York etc. D.C.: Heath and Company, 1934.