



De-Escalation of Multidisciplinary Breast Cancer Care with Cryoablation Therapy: Navigating Novel Therapeutics, Ethics, and Outcomes

Olivia Cheng, MD^{1,2}, and Lauren M. Postlewait, MD, FACS^{1,2}

¹Division of Surgical Oncology, Department of Surgery, Winship Cancer Institute, Emory University, Atlanta, GA; ²Breast Cancer Program, Georgia Cancer Center for Excellence, Grady Health System, Atlanta, GA

With the rapid evolution of technology and therapeutics in the modern era, we increasingly find ourselves questioning the status quo. How can we comprehensively treat disease while minimizing morbidity and optimizing quality of life? In the realm of surgery, for example, the advent of minimally invasive techniques has changed the playing field, allowing surgeons to tackle certain surgical diseases with shorter length of stay, smaller incisions, and quicker recovery times compared with open surgery. However, understanding the role and potential utility of a new intervention becomes more complicated in the field of breast oncology where single interventions typically do not offer optimized outcomes; rather, best practice results from the appropriate combination of multidisciplinary treatment and diagnostic approaches (systemic therapy, surgery, and radiation). Notably, with the advent and maturity of multidisciplinary treatment regimens, breast cancer locoregional treatment has transformed over the years from maximally invasive single therapy (radical mastectomy) in the 1880s to options of breast conservation surgery and less aggressive axillary interventions currently.^{1–4} As new local treatment strategies appear on the horizon, it is imperative to consider the effect they might have on other aspects of multidisciplinary care,

such as decisions regarding systemic therapy or radiation and subsequent long-term cancer outcomes. We must also prioritize individualized, data-driven care with efforts to meet the patient's goals of care, account for the patient's functional status, and consider specific tumor biology.⁵

Evidence is growing to support the feasibility of cryoablation therapy as a potential alternative to the local surgical management of breast cancer in select patients.^{6–8} However, mature data on long-term oncologic outcomes of this approach are not yet available. The American College of Surgeons Oncology Group (ACOSOG) Z1072 trial was a phase II, multicenter study of patients with unifocal invasive ductal carcinoma <2 cm in size. Eighty-six patients received cryoablation treatment followed by surgery and pathologic assessment of the tumor bed. The primary outcome was rate of complete tumor ablation which was 75.9% (90% confidence interval [CI] 67.1–83.2), or up to 92% when multifocal disease outside the ablation field was not defined as an ablation failure.⁷ These results set the stage for cryoablation, suggesting it might be a feasible treatment modality, particularly as part of a multidisciplinary approach to care in patients with smaller tumors. Beyond initial tumor response, investigators of the ICE3 trial are examining 5-year in-breast recurrence rates after cryoablation in patients older than 60 years of age with small (<1.5 cm) hormone receptor-positive, HER2-negative tumors. Interim 3-year analysis in this multicenter, prospective, single-arm, industry-sponsored trial appear promising, with a 2% in-breast recurrence rate in the 194 patients included; however, interpretation and generalizability of these results are limited by the study design, potential selection bias, and no control for other interventions delivered, such as radiation, systemic therapy, or nodal surgery.⁶ As such, the therapeutic role of cryoablation in comprehensive breast care remains uncertain.

This article refers to: Khan S, Cole J, Habrawi Z, Melkus M, Rahman RL. Cryoablation allows the ultimate de-escalation of surgical therapy in select breast cancer patients. *Annals Surgical Oncology*. (2023). <https://doi.org/10.1245/s10434-023-14332-3>.

© Society of Surgical Oncology 2024

First Received: 8 September 2023

Accepted: 28 November 2023

Published online: 7 January 2024

L. M. Postlewait, MD, FACS
e-mail: lauren.postlewait@emory.edu

In their study entitled 'Cryoablation allows the ultimate de-escalation of surgical therapy in select breast cancer patients', Khan et al. report outcomes from a single-institution, single-arm, prospective study that included 32 patients aged ≥ 50 years with early-stage, hormone receptor-positive, HER2-negative invasive ductal carcinoma < 1.5 cm with luminal A subtype who underwent cryoablation instead of surgical local therapy between 2017 and 2023.⁸ Twenty-eight patients were under 70 years of age. Sentinel lymph node biopsy was omitted in all but one patient, thereby completely eliminating surgery in most of the cohort. All patients were prescribed adjuvant endocrine treatment, and only six patients received adjuvant radiation therapy. The average follow-up was 15 months, and the patients reported one recurrence during the study period, which was in the ipsilateral axilla of a patient who underwent cryoablation as her only treatment modality. One death was reported and attributed to reasons unrelated to cancer or cancer therapy. Based on these results, the authors concluded that "cryoablation of the primary tumor foregoing sentinel node biopsy offers an oncologically safe and feasible minimally invasive office-based procedure option in lieu of surgery in patients with early-stage, low-risk breast cancer".⁸

These results appear promising and contribute to the growing foundation of evidence that supports further study of cryoablation as a potential treatment modality in breast cancer care. However, recognizing limitations of study design and level of evidence (sample size, duration of follow-up, variability in protocol, selection bias, and lack of a comparative arm), one cannot make definitive conclusions that support widespread change in clinical practice from these data. Although the highest rate of breast cancer recurrence occurs 1–2 years after treatment, recurrence is still common 5–10 years or longer post-treatment, particularly for patients with hormone receptor-positive tumors.⁹ Allowing for more extended follow-up time in the cohort studied by Khan et al. would provide more clinically pertinent recurrence information after cryoablation.⁸ The interplay and implications of multiple simultaneous de-escalations must also be considered. Radiation was omitted in most of the patients included in the study.⁸ Data from the PRIME II and CALGB 9343 randomized controlled trials support considering omission of radiation in patients aged 65–70 years or older with positive prognostic tumor features after breast-conserving surgery with planned endocrine therapy, weighing a slight increased risk of local recurrence as part of shared decision making with the patient.^{10,11} For patients older than 55 years of age undergoing breast conservation for invasive cancer with favorable tumor biology, results from the LUMINA study suggest acceptable 5-year local recurrence rates with omission of radiation.¹² However, there are limited data to support omission of radiation for patients of any age who are undergoing cryoablative therapy for local

control, particularly considering the findings of multifocal residual disease in the surgical specimen after cryoablation in ACOSOG Z1072.⁷ For the axilla, national guidelines support considering omission of sentinel lymph node biopsy in patients ≥ 70 years of age with favorable tumor biology (Choosing Wisely campaign).⁴ However, for patients studied by Khan et al., sentinel lymph node biopsy was omitted in the majority of the patients who were under 70 years of age, which likely influenced adjuvant multidisciplinary decision making. Implications of this omission are not accounted for in this small cohort with limited follow-up. Furthermore, Khan et al. propose that a non-surgical approach with cryoablation would be particularly helpful for older patients to avoid the risk of anesthesia and surgery. However, the importance of endocrine therapy is also highlighted as part of this comprehensive care in this frail population. The additional question that comes to mind for small, low-risk tumors in older frail patients is whether endocrine therapy alone would be a sufficient lifelong palliative treatment compared with a curative-intent approach with cryoablation plus endocrine therapy.^{13,14} Further study is needed to assess both oncologic outcomes and quality of life.

The therapeutic armamentarium in the field of breast cancer continues to evolve. Preliminary data on cryoablation coupled with adoption of this practice within part of the breast care community suggest a potential clinical equipoise between cryoablation and breast surgery for local treatment in select patients. This equipoise justifies further study to objectively evaluate this treatment modality. Ideally, as we continue to explore this approach, next steps would be to design and conduct a comparative, randomized controlled trial to definitively understand the therapeutic value of cryoablation and describe the risks and benefits compared with standard of care. However, it must be acknowledged that, in reality, randomized clinical trials are expensive, can take decades to come to fruition, and are not always feasible to pursue. Nonetheless, when considering potential new therapeutic approaches in research as part of clinical practice, the ethical principles of beneficence, non-maleficence, patient autonomy, and justice should be considered.¹⁵ We need to clearly define the subset of patients who would benefit the most without harming those who may not. Regarding clinical trials and the implementation of new treatments, we must be transparent in conversations with patients, allowing them autonomy in shared treatment decision making, especially when long-term treatment data are lacking, and the treatment's role in the context of multidisciplinary care algorithms is not well defined.

Despite the appeal to de-escalate breast cancer care to completely nonoperative modalities, simultaneous de-escalation of breast surgery, axillary surgery, and radiation on a large scale without high-level data to support oncologic safety merits serious consideration. Thoughtful,

randomized, large scale clinical trials to analyze the role of cryoablation in the appropriate patient population through a stepwise approach before applying it to the general population with significant de-escalation would be an optimal approach, comprehensively addressing clinical and ethical considerations.

DISCLOSURE Olivia Cheng and Lauren M. Postlewait have no disclosures to declare in relation to this work.

REFERENCES

1. Fisher B, Wolmark N, Redmond C, Deutsch M, Fisher ER. Findings from NSABP Protocol No B-04: comparison of radical mastectomy with alternative treatments. II. The clinical and biologic significance of medial-central breast cancers. *Cancer*. 1981;48(8):1863–72.
2. 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 Eng J Med*. 2002;347(16):1233–41.
3. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (alliance) randomized clinical trial. *JAMA*. 2017;318(10):918–26.
4. Society of Surgical Oncology. Choosing Wisely. Rosemont, IL: Society of Surgical Oncology; 2020.
5. Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA*. 2019;321(3):288–300.
6. Fine RE, Gilmore RC, Dietz JR, et al. Cryoablation without excision for low-risk early-stage breast cancer: 3-year interim analysis of ipsilateral breast tumor recurrence in the ICE3 trial. *Annals Surg Oncol*. 2021;28(10):5525–34.
7. Simmons RM, Ballman KV, Cox C, et al. A phase II trial exploring the success of cryoablation therapy in the treatment of invasive breast carcinoma: results from ACOSOG (Alliance) Z1072. *Annals Surg Oncol*. 2016;23(8):2438–45.
8. Khan S, Cole J, Habrawi Z, Melkus M, Rahman RL. Cryoablation allows the ultimate de-escalation of surgical therapy in select breast cancer patients. *Annals Surg Oncol*. 2023;30(13):8398–403. <https://doi.org/10.1245/s10434-023-14332-3>.
9. Colleoni M, Sun Z, Price KN, et al. Annual hazard rates of recurrence for breast cancer during 24 years of follow-up: Results from the international breast cancer study group trials I to V. *J Clin Oncol*. 2016;34(9):927–35.
10. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol*. 2015;16(3):266–73.
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):2382–7.
12. Whelan TJ, Smith S, Parpia S, et al. Omitting radiotherapy after breast-conserving surgery in luminal A breast cancer. *N Eng J Med*. 2023;389(7):612–9.
13. Mustacchi G, Milani S, Pluchinotta A, De Matteis A, Rubagotti A, Perrota A. Tamoxifen or surgery plus tamoxifen as primary treatment for elderly patients with operable breast cancer: the GRETA trial group for research on endocrine therapy in the elderly. *Anticancer Res*. 1994;14(5b):2197–200.
14. Chakrabarti J, Kenny FS, Syed BM, Robertson JF, Blamey RW, Cheung KL. A randomised trial of mastectomy only versus tamoxifen for treating elderly patients with operable primary breast cancer-final results at 20-year follow-up. *Crit Rev Oncol/Hematol*. 2011;78(3):260–4.
15. Postlewait LM, Singh P. Ethical questions of surgical trials: an evidence-based approach. In: Lonchyna VA, Kelley P, Angelos P (eds). *Difficult Decisions in Surgical Ethics*: Springer; 675–687 (2022).

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.