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ORIGINAL ARTICLE – BREAST ONCOLOGY

Debate: Postmastectomy Radiation Therapy in T1/2N1 Disease

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ABSTRACT Although postmastectomy radiation therapy is known to reduce local recurrence in patients with T1/2N1 breast cancer, some have postulated that not all patients require this treatment. In this era of genomic analyses and personalized therapy, clinicians have debated whether the toxicity of post-mastectomy radiation therapy (PMRT) can be avoided for some subsets of patients. However, the data in this regard remain controversial, particularly as surgeons de-escalate the surgical management of the axilla. Several ongoing clinical trials may provide a glimpse into optimal management in this scenario. However, the "right" answer to this debate currently remains unclear.

It is well known that post-mastectomy radiation therapy (PMRT) reduces the rate of chest wall recurrence by approximately two thirds. Some studies also have found a survival benefit with PMRT for node-positive patients.[1,2] Indeed, most professional organizations including the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO), and the Society of Surgical Oncology (SSO) unanimously agree that PMRT reduces the rate of locoregional failure and breast cancer mortality for patients with T1/2 N1 disease.[3] However, radiation therapy is not without potential toxicity, and in the current era of multidisciplinary care, with a focus on personalized therapy and molecular medicine, some debate has surrounded whether PMRT remains mandatory for this population. This report lays out the data both for and against the use of PMRT and the clinical trials that hopefully will help answer this important question.

LOCOREGIONAL CONTROL AND SURVIVAL

For patients with one to three positive nodes, the National Comprehensive Cancer Network guidelines suggest strong consideration of PMRT to the chest wall, supraclavicular and infraclavicular fossae, internal mammary lymph nodes, and any part of the axillary bed at risk.[4] These recommendations and those of ASCO/ASTRO/SSO[3] are based largely on the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).[5]

The EBCTCG study of 22 randomized trials involving 8135 women found that PMRT reduced both recurrence and breast cancer mortality in women undergoing mastectomy for tumors with one to three positive lymph nodes, even when systemic therapy was given.[5] Among the 1133 patients with one to three positive lymph nodes who received systemic therapy, the 10-year local recurrence rate (4.3% vs 21%; $p < 0.001$) and the 20-year breast cancer mortality rate (41.5% vs 49.4%; RR (Relative risk), 0.78; $p = 0.01$) were significantly improved with PMRT. The study also observed a trend toward an improved 20-year any-cause mortality (52.6% vs 55.5%; RR, 0.86; $p = 0.08$).[3]

Given these data, it may be surmised that PMRT should be liberally used in the setting of T1/2N1 breast cancers. However, some have noted that many of the trials in the EBCTCG study were conducted several decades ago. Although these older studies provide long-term follow-up data, they do not include the effects of screening and more modern therapies, both of which may have reduced the actual burden of disease in lymph nodes and may make the impact of PMRT less substantial. Indeed, when McBride et al.[6] compared locoregional recurrence rates between patients who had T1/2 breast cancers and one to three positive nodes treated with systemic therapy but no PMRT in an earlier period (1978–1997) and patients in a later

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period (2000–2007), they found that those with cancers diagnosed in the earlier era had a higher 5-year breast cancer event rate (defined as recurrence or breast cancer-related death) than those with cancer diagnosed in the later period (22% vs 8%; $p = 0.0002$, log-rank). Interestingly, they also found that although PMRT reduced the 5-year rate of locoregional recurrence in the earlier cohort (9.5% vs 3.4%; $p = 0.028$; adjusted hazard ratio [HR], 0.37; $p = 0.038$), it did not appear to benefit patients in the later cohort (2.8% vs 4.2%; $p = 0.48$; adjusted HR,1.41; $p = 0.48$).[6] In fact, in a multivariate analysis that included covariates of the era of diagnosis and PMRT, the era of diagnosis was the most significant factor predictive of locoregional recurrence (adjusted HR, 0.35; $p < 0.001$).[6]

PROGNOSTIC FACTORS/GENOMIC ASSAYS

Perhaps one reason for the improved locoregional outcomes in the more recent era regardless of PMRT has been better systemic therapies. Although the EBCTCG found a benefit from PMRT, even among those who received systemic therapy, our current use of systemic therapies is increasingly being tailored based on tumor biology. Indeed, some have argued that locoregional recurrence may be related to tumor biology and that not all T1/2N1 patients will require PMRT. For example, Leonardi et al.,[7] in evaluating 1281 pT1/T2N0 and 1081 pT1/T2N1 breast cancer patients found that the 10-year cumulative incidence of locoregional recurrence rates was 8.8% in the N0 group and 10.9% in the N1 group. However, young age (<35 years), presence of lymphovascular invasion (LVI), and Ki67 of 20% or more were significant predictors of locoregional recurrence, and patients with two or more of these factors showed an increase in the locoregional recurrence rate to 15% or higher.[7] The authors therefore suggested that PMRT might be reasonably reserved for these patients.

Similarly, Wang et al.[8] evaluated 1986 breast cancer patients and assigned them a score based on factors they found significant for locoregional recurrence according to multivariate analysis including age, tumor quadrant location, number of positive nodes, LVI, and American Joint Committee on Cancer (AJCC 8th edition) stage. Grouping patients into low-, intermediate- and high-risk groups, they found significant differences in 5-year locoregional recurrence (2.5% vs 5.4% vs 16.2%; $p < 0.001$). Only the latter group benefited with respect to reduction in locoregional recurrence from the use of PMRT ($p < 0.001$), and did so independently of patient age, tumor location, number of positive nodes, LVI, or AJCC 8th-edition stage (HR, 0.23; 95% confidence interval [CI], 0.11–0.49; $p < 0.001$).[8] In the low- to intermediate-risk groups, PMRT had no impact on locoregional recurrence ($p = 0.268$).[8] Indeed, a number of nomograms[9–12] have been developed to identify patients at high risk for locoregional recurrence so that patients at lower risk may be spared PMRT.

Although intuitively, clinicians may see PMRT offering a greater benefit for patients at highest risk of locoregional failure, PMRT still may offer a significant advantage for low-risk patients. For example, Yin et al.[13] stratified 1674 T1/2 patients with one to three positive nodes into low- versus high-risk groups based on age, lymph node ratio, and molecular subtype (all found to have an impact on locoregional recurrence in multivariate analysis). In the low-risk group, which included patients with zero to one negative prognostic features, PMRT still resulted in a statistically significant improvement in 5-year locoregional relapse-free survival (95% vs 98.5%; $p = 0.012$).

Data regarding which patients benefit from PMRT remain inconsistent. For example, although many of these studies point to a potential benefit of PMRT for younger patients, Bhutiani et al.,[14] studying patients in the National Cancer Database (NCDB) who had T1/2 breast cancer with one or two positive nodes, found that PMRT improved overall survival in older patients (≥60 years) after using control for age and tumor grade (RR, 0.62; 95% CI, 0.40–0.93; $p = 0.018$), but had no impact on younger patients. Furthermore, whereas some authors have found that molecular subtype had a significant impact on locoregional recurrence,[15,16] others found that it had no effect and therefore could not be used to guide PMRT decisions.[17]

The concept of using tumor biology to guide the use of PMRT for selected patients with T1/2N1 disease has led clinicians to consider the potential use of genomic assays in this calculus. For example, Goodman et al.[18] found that both the NCDB and the Surveillance, Epidemiology, and End Results (SEER) registry showed a significant interaction between PMRT and the 21-gene recurrence score on overall survival. In their study, PMRT was associated with a longer overall survival for women with a low recurrence score, but had no impact on those with intermediate or high scores, causing the authors to caution against omitting radiation therapy for the low-risk group.

Others have found that the recurrence score could not differentiate between patients could benefit from PMRT and those who could not.[19] Interestingly, although Mamounas et al.[20] found that high a recurrence score predicted a higher risk of locoregional recurrence in general, they found no such association when considering patients who had one to three positive nodes treated with mastectomy. Ultimately, some clarity for the question whether genomic assays can be used to guide PMRT may be obtained through the ongoing TAILOR RT trial, in which estrogen receptor-positive patients with only one

positive axillary node (if a sentinel node biopsy alone was performed) or one to three positive nodes (if an axillary dissection was performed) and an Oncotype DX score lower than 18 will be randomized to PMRT or no PMRT.

RESPONSE TO NEOADJUVANT CHEMOTHERAPY

The use of neoadjuvant therapy is increasing (particularly among triple-negative and human epidermal growth factor receptor 2 (HER2)-positive patients)[21,22] and often results in a downstaging of disease. Some have postulated that the response to neoadjuvant therapy could be used to define a subset of patients who could be spared PMRT. For example, Mamounas et al.,[23] in an analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and B-27 trials, found that for patients treated with mastectomy, clinical tumor size and lymph node status before neoadjuvant therapy and pathologic lymph node status after neoadjuvant therapy were independent predictors of 10-year locoregional recurrence rates.

For patients with tumors 5 cm in size or smaller who were clinically node-positive before neoadjuvant chemotherapy, the 10-year rates of chest wall and regional lymph node recurrence were higher if they continued to have positive lymph nodes at the time of surgery (10.6% vs 6.4%) than if they had a pathologic complete response in both the breast and axilla (0% for both 10-year chest wall and lymph node recurrence). Interestingly, however, for patients who converted to lymph node negativity but did not have a pathologic complete response in the breast, the rate of regional lymph node recurrence was higher than for those who remained lymph node-positive (8.1%), whereas the chest wall recurrence rate was lower (2.7%).[23]

Other studies have found that PMRT significantly improved relapse-free survival for T1/2N1 patients who underwent neoadjuvant chemotherapy independently of age and clinical stage regardless of response (HR, 0.411; 95% CI, 0.175–0.968; $p = 0.042$).[24] Also, for the subset of patients who achieved a pathologic complete response, the 5-year local recurrence-free survival and 5-year recurrence-free survival were significantly higher for patients who received PMRT (97.2% vs 77.8%; $p = 0.026$) than for those who did not (94.8% vs 77.7%; $p = 0.006$).[24]

Ultimately, prospective data may clarify the role of radiation therapy after a pathologic complete response for patients who have clinical T1-3N1 breast cancer treated with mastectomy, a question currently being evaluated by the NSABP B-51/RTOG 1304 trial. At the same time, however, the Alliance A011202 trial is asking the question whether axillary node dissection is required for node-positive patients who become clinically node-negative after neoadjuvant chemotherapy. In that trial, patients found to have a positive node on final pathology are randomized to axillary dissection or no axillary dissection. However, all the patients in this trial will receive regional nodal irradiation.

LYMPHEDEMA RISK

Finally, any benefit of PMRT must be weighed against its risks, with lymphedema posing as one of the most important risks. Without question, the addition of regional lymph node irradiation significantly increases the rate of lymphedema, particularly for women who may have undergone an axillary node dissection.[25,26] One study found that the rate more than doubled with the addition of radiation therapy (14.1% vs 33.4%; $p < 0.001$).[27] Other studies have found a more modest increase in lymphedema rates with the addition of radiation therapy after axillary dissection (30.1% vs 24.9%; HR, 1.20; $p = 0.49$).[28]

Because axillary dissection does not improve survival,[29] there has been a move toward de-escalating local therapy, particularly in the axilla. Local control, however, remains important. Despite the exclusion of patients with mastectomy in the American College of Surgeons Oncology Group (ACOSOG) Z-0011 trial,[30] some have postulated that avoiding axillary node dissection for patients with positive sentinel nodes after mastectomy may reduce the rate of lymphedema.[26] Although only 9% of the patients ($n = 86$) in the International Breast Cancer Study Group (IBCSG) 23-01 trial underwent mastectomy,[31] the rate of axillary recurrences in the total cohort of patients who underwent a mastectomy in this trial (regardless of randomization to axillary dissection or not) was 2% at 10-years. This led the authors to surmise that clinicians may be able to avoid axillary dissection for these patients, particularly if radiation therapy is given.[31]

Furthermore, the After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) trial (which also included mastectomy patients) randomized node-positive patients to either axillary dissection or axillary radiotherapy and demonstrated that the 5-year axillary recurrence rates were similar in the two arms of the study (0.43%; 95% CI, 0–0.92 for the axillary dissection arm vs 1.19%; 95% CI, 0.31–2.08 for the radiation arm).[32] Importantly, the AMAROS trial also demonstrated that the rates for clinical signs of lymphedema were significantly lower for the patients treated with radiotherapy than for those who had surgery (11% vs 23% at 5 years; $p < 0.0001$).[32] Thus, despite the move toward de-escalation of therapy across disciplines (medical oncology, radiation oncology, and surgery), which method or methods might be best suited for given patients must be carefully assessed.

DE-ESCALATION OF THERAPY

Although clinicians preferring to de-escalate PMRT suggest that radiation therapy planning is complex and that radiation (particularly for left-sided lesions) may adversely affect the heart and lungs, with modern-day techniques of deep inspiration breath-hold and intensity-modulated radiation therapy, these risks can be minimized. Furthermore, axillary surgery is not without its risks as well. The rates of numbness, pain, and shoulder dysfunction may be significant compared with the less morbid sentinel node biopsy.[33,34] The question of which method for ensuring local control can be sacrificed remains a matter of debate.

Those who argue for de-escalation of PMRT also point out the increased complications observed in the setting of immediate reconstruction. However, lymph node surgery also has been found to increase complications in the setting of immediate reconstruction. For example, Baker et al.[35] found that among patients who underwent axillary surgery, the incidence of postoperative complications (per breast) was 35.9%, versus 25.6% for those who did not have concomitant axillary surgery. Sentinel node biopsy and axillary dissection were similar in terms of breast complications in this setting.[35]

CONCLUSION

Both radiation or surgery have some toxicity, and both confer some benefit in terms of local control. The question then is how therapy can be can optimally de-escalated and for whom. Ongoing clinical trials should eventually give us some insight into this question. Until then, this remains a controversial issue. The only clear "right" answer is to contribute to the accrual of these trials to help us find the true right answer.

REFERENCES

1. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst*. 2005;97:116–26.
2. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. *Radiother Oncol*. 2007;82:247–53.
3. Recht A, Comen EA, Fine RE, et al. Postmastectomy radiotherapy: an American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology focused guideline update. *J Clin Oncol*. 2016;34:4431–42.
4. NCCN. NCCN Clinical practice guidelines in oncology (NCCN guidelines). *Breast Cancer*. 2021;4:2021.
5. McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet*. 2014;383:2127–35.
6. McBride A, Allen P, Woodward W, et al. Locoregional recurrence risk for patients with T1,2 breast cancer with 1–3 positive lymph nodes treated with mastectomy and systemic treatment. *Int J Radiat Oncol Biol Phys*. 2014;89:392–8.
7. Leonardi MC, Scognamiglio IR, Maisonneuve P, et al. Mastectomy alone for pT1-2 pN0-1 breast cancer patients: when postmastectomy radiotherapy is indicated. *Breast Cancer Res Treat*. 2021;188:511–24.
8. Wang S, Wen G, Tang Y, et al. Effectiveness of the AJCC 8th-edition staging system for selecting patients with T1–2N1 breast cancer for post-mastectomy radiotherapy: a joint analysis of 1986 patients from two institutions. *BMC Cancer*. 2020;20:792.
9. Wang J, Tang Y, Jing H, et al. Risk stratification for prediction of locoregional recurrence in patients with pathologic T1–2N0 breast cancer after mastectomy. *BMC Cancer*. 2020;20:1132.
10. Tang Y, Zhang YJ, Zhang N, et al. Nomogram predicting survival as a selection criterion for postmastectomy radiotherapy in patients with T1 to T2 breast cancer with 1 to 3 positive lymph nodes. *Cancer*. 2020;126(Suppl 16):3857–66.
11. Luo C, Zhong X, Deng L, Xie Y, Hu K, Zheng H. Nomogram predicting locoregional recurrence to assist decision-making of postmastectomy radiation therapy in patients with T1–2N1 breast cancer. *Int J Radiat Oncol Biol Phys*. 2019;103:905–12.
12. Li M, Yue J, Wan X, et al. Risk-adapted postmastectomy radiotherapy decision based on prognostic nomogram for pT1-2N1M0 breast cancer: a multicenter study. *Front Oncol*. 2020;10:588859.
13. Yin H, Qu Y, Wang X, et al. Impact of postmastectomy radiation therapy in T1–2 breast cancer patients with 1–3 positive axillary lymph nodes. *Oncotarget*. 2017;8:49564–73.
14. Bhutiani N, Egger ME, Stromberg AJ, Bhutiani IK, Ajkay N, McMasters KM. Identifying factors impacting the efficacy of postmastectomy radiotherapy in patients with early-stage breast cancer and one to two positive lymph nodes. *J Surg Oncol*. 2020;122:128–33.
15. Scheer AS, Zih FS, Maki E, Koch CA, McCready DR. Postmastectomy radiation: should subtype factor into the decision? *Ann Surg Oncol*. 2016;23:2462–70.
16. Tseng YD, Uno H, Hughes ME, et al. Biological subtype predicts risk of locoregional recurrence after mastectomy and impact of postmastectomy radiation in a large national database. *Int J Radiat Oncol Biol Phys*. 2015;93:622–30.
17. Moo TA, McMillan R, Lee M, et al. Impact of molecular subtype on locoregional recurrence in mastectomy patients with T1–T2 breast cancer and 1–3 positive lymph nodes. *Ann Surg Oncol*. 2014;21:1569–74.
18. Goodman CR, Seagle BL, Kocherginsky M, Donnelly ED, Shahabi S, Strauss JB. 21-Gene recurrence score assay predicts benefit of post-mastectomy radiotherapy in T1–2 N1 breast cancer. *Clin Cancer Res*. 2018;24:3878–87.
19. Zhang WW, Tong Q, Sun JY, et al. 21-Gene recurrence score assay could not predict benefit of post-mastectomy radiotherapy in T1–2 N1mic ER-positive HER2-negative breast cancer. *Front Oncol*. 2019;9:270.
20. Mamounas EP, Liu Q, Paik S, et al. 21-Gene recurrence score and locoregional recurrence in node-positive/ER-positive breast cancer treated with chemo-endocrine therapy. *J Natl Cancer Inst*. 2017;109(4):djw259.
21. Zeidman M, Schmidt H, Alberty-Oller JJ, et al. Trends in neoadjuvant chemotherapy versus surgery-first in stage I HER2-positive breast cancer patients in the National Cancer DataBase (NCDB). *Breast Cancer Res Treat*. 2021;187:177–85.

22. Riedel F, Hoffmann AS, Moderow M, et al. Time trends of neoadjuvant chemotherapy for early breast cancer. *Int J Cancer*. 2020;147:3049–58.
23. Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. *J Clin Oncol*. 2012;30:3960–6.
24. Wang Q, Zhao J, Han X, et al. Is there a role for post-mastectomy radiotherapy for T1–2N1 breast cancers with node-positive pathology after patients become node-negative pathology following neoadjuvant chemotherapy? *Front Oncol*. 2020;10:892.
25. Kim M, Kim SW, Lee SU, et al. A model to estimate the risk of breast cancer-related lymphedema: combinations of treatment-related factors of the number of dissected axillary nodes, adjuvant chemotherapy, and radiation therapy. *Int J Radiat Oncol Biol Phys*. 2013;86:498–503.
26. Miller CL, Specht MC, Skolny MN, et al. Risk of lymphedema after mastectomy: potential benefit of applying ACOSOG Z0011 protocol to mastectomy patients. *Breast Cancer Res Treat*. 2014;144:71–7.
27. Johnson AR, Kimball S, Epstein S, et al. Lymphedema incidence after axillary lymph node dissection: quantifying the impact of radiation and the lymphatic microsurgical preventive healing approach. *Ann Plast Surg*. 2019;82:S234–41.
28. Naoum GE, Roberts S, Brunelle CL, et al. Quantifying the impact of axillary surgery and nodal irradiation on breast cancer-related lymphedema and local tumor control: long-term results from a prospective screening trial. *J Clin Oncol*. 2020;38:3430–8.
29. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med*. 2002;347:567–75.
30. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011;305:569–75.
31. Galimberti V, Cole BF, Viale G, et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23–01): 10-year follow-up of a randomised, controlled phase 3 trial. *Lancet Oncol*. 2018;19:1385–93.
32. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15:1303–10.
33. Peintinger F, Reitsamer R, Stranzl H, Ralph G. Comparison of quality of life and arm complaints after axillary lymph node dissection vs sentinel lymph node biopsy in breast cancer patients. *Br J Cancer*. 2003;89:648–52.
34. Kell MR, Burke JP, Barry M, Morrow M. Outcome of axillary staging in early breast cancer: a meta-analysis. *Breast Cancer Res Treat*. 2010;120:441–7.
35. Baker NF, Baecher KM, Hart AM, Styblo TM, Carlson GW, Losken A. The impact of axillary node surgery on outcomes following immediate breast reconstruction. *Breast J*. 2020;26:2170–6.