



Regional Nodal Irradiation in the Modern Era of Breast Cancer Management

By Yazid Belkacemi, MD, PhD, Benjamin D. Smith, MD, Janet K. Horton, MD

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Management of the axilla has undergone a tremendous evolution in recent years. Although surgery has become progressively less invasive, data supporting a larger role and extent of regional nodal irradiation (RNI) have grown. For example, the AMAROS trial (After Mapping of the Axilla Radiation or Surgery) demonstrated that axillary radiation therapy (AXL-RT) can be used as an alternative to completion axillary lymph node dissection (cALND) in node-positive patients, yielding extremely low rates of axillary recurrence and less morbidity than surgical resection (1). Simultaneously, MA.20 and European Organization for Research and Treatment of Cancer (EORTC) trial 2292 reported improvements in disease-free survival (DFS) and distant metastasis-free survival in patients with node-positive, high-risk node-negative, or central/medial tumors RNI (2, 3). Nevertheless, concurrent surgical trials evaluating the omission of ALND in the absence of consistent regional nodal radiation also reported excellent long-term outcomes (4). Similarly, it is not clear that the value of RNI applies equally to all patient subsets. For example, in a planned subset analysis of MA.20, estrogen receptor-positive patients seem to derive a lesser benefit from RNI than their estrogen receptor-negative counterparts. Conversely, in the EORTC trial showing improved outcomes with RNI, a full 44% of the patient cohort had high-risk node-negative disease. This confluence of data suggests that many unresolved issues remain in the optimal prescription of RNI. In this Oncology Scan we highlight some recent reports on this topic that aim to validate the efficacy of AXL-RT as a single modality, enhance the convenience of treatment delivery, and improve patient selection.

Sávolt et al. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla—Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. *Eur J Surg Oncol* 2017. (5)

Summary: The OTOASOR (Optimal Treatment Of the Axilla—Surgery Or Radiotherapy) trial is the second recent trial comparing AXL-RT with cALND in breast cancer patients with 1 to 3 positive sentinel lymph nodes after breast conservation (82%-84%) or total mastectomy (16%-18%). Although more than 1000 patients were included in each arm, only 244 and 230 patients were eligible for the final analysis in the cALND and AXL-RT arms, respectively. Patients in the RNI arm received a total dose of 50 Gy in 25 fractions to the whole breast/chest wall, the 3 levels of the axilla, and the supraclavicular fossa. The internal mammary chain was not considered as a target in this trial. High-risk patients in the cALND arm (≥ 4 nodes or patients with 1 to 3 nodes with high-risk features, such as premenopausal status, lymphovascular invasion, or high-grade tumor) also received postoperative RT.

As in the 2013 publication (6), OTOASOR showed no difference in axillary recurrence at 97 months (2% vs 1.7%, $P = 1$), despite the fact that 38.5% of patients in the cALND arm were found to have additional lymph nodes in the surgical specimen, 22% with 4 or more. Similarly, DFS ($P = .51$) and overall survival ($P = .060$) were not different between the 2 arms. Morbidity, defined as any clinical sign of lymphedema, paresthesia, swelling, arm pain, or impaired shoulder mobility, was higher at 1 year in patients undergoing cALND (15.3%) than in those receiving RNI

(4.7%). For patients treated with both ALND and AXL-RT, 31.5% were noted to have treatment-related morbidity.

Comments: The OTOASOR trial provides additional confirmation that AXL-RT can be used as a less morbid method to control disease in the axilla because no differences were seen in the rates of axillary recurrence or survival. As in AMAROS, the OTOASOR cohort included patients treated with breast conservation as well as mastectomy. It is worth noting that the more aggressive indications for RT after ALND in the OTOASOR trial would be expected to minimize any differences between the 2 arms, particularly because the cALND arm had a higher rate of patients who were premenopausal and had T2-3 tumors. This effect would have been less significant in the more robust AMAROS trial, in which only patients with ≥ 4 lymph nodes received postoperative RT.

A major limitation of the OTOASOR trial is the lack of long-term morbidity data. Despite a median follow-up of 97 months, morbidity outcomes are reported at only 1 year. In the AMAROS trial the significant differences in clinical signs of lymphedema between the AXL-RT and cALND arms were persistent but concurrently decreased in severity over time.

Overall, OTOASOR adds to the growing body of literature suggesting that the morbidity of a cALND is not routinely needed to ensure excellent outcomes in pN1 patients treated with modern breast cancer therapies.

Khan et al. Hypofractionated postmastectomy radiation therapy is safe and effective: First results from a prospective phase II trial. *J Clin Oncol* 2017. (7)

Summary: This phase 2 single-arm study was designed to evaluate a short course of hypofractionated postmastectomy radiation therapy (PMRT), in which all therapy to the chest wall and nodal areas was completed in 15 days. Among the 69 patients included, 67 women with stage IIA to IIIC breast cancer were eligible for analysis. Patients received a dose of 36.63 Gy in 11 fractions of 3.33 Gy (equivalent dose in 2 Gy fractions for a total dose of 45 Gy) to the chest wall and regional lymph nodes, followed by an optional chest wall boost of 13.32 Gy in 4 fractions (equivalent dose in 2 Gy fractions for a total dose of 15 Gy). The primary endpoint was freedom from any grade ≥ 3 acute or chronic toxicity. Forty-one patients had a breast reconstruction; related complications were not included in evaluation of the primary endpoint.

After a median follow-up of 32 months, no grade 3 toxicities were reported. Grade 2 skin toxicity was observed in approximately one-quarter of the patients (16 of 67; 24%). Two patients experienced an isolated chest wall recurrence, for a 3-year rate of 10.8%. The 3-year estimated distant recurrence-free and overall survivals were 90.3% and 92%, respectively. The total rate of implant loss or failure was 24% (9 of 38) and largely attributable to infection. The unplanned surgical correction rate was 8% (3 of 38), for a total complication rate of 32%. The authors

concluded that this hypofractionated schedule offered high local control and low toxicity.

Comments: Data on hypofractionation in the PMRT setting are lacking owing to concerns of potential toxicity when irradiating regional lymph nodes or reconstructed breasts. In the United Kingdom Standardisation of Breast Radiotherapy (START) trials, only 15% and 8% of patients in START A and B, respectively, were treated with hypofractionation (at a lower dose per fraction) after mastectomy. Similarly, only 13% and 7% of patients, respectively, received surgery plus hypofractionated RT for management of the regional lymphatics (8, 9). Given the paucity of data, this small trial provides an early proof of principle for the extension of hypofractionated RT to a wide range of clinical scenarios. The fractionation schedule does depart, for unclear reasons, from the 15 to 16 fraction regimens now widely practiced for breast conservation in Canada, Europe, and to some extent the United States. In the upcoming phase 3 trial evaluating this concept further, the Canadian regimen of 42.56 Gy in 16 fractions will be utilized.

Of note, no brachial plexopathy was seen in this study, albeit with short follow-up. The dose was constrained to a maximum of 107% in the supraclavicular/axillary volumes, but the brachial plexus was not specifically contoured for evaluation. Brachial plexopathy is quite rare but can present many years after radiation. Though this trial notes no early signals of increased plexopathy, very large numbers of patients followed over many years will be required to determine the impact of this regimen on the brachial plexus with confidence.

This is the first dedicated trial of hypofractionated PMRT reported from North America. Conversely, in low- and middle-income countries, hypofractionation is widely and routinely used owing to a lack of RT means to treat all patients. Recently Bellefqih et al from Morocco reported 19%, 12%, 31%, and 6% of hyperpigmentation, telangiectasia, fibrosis, and grade ≥ 2 lymphedema, respectively, in high-risk node-positive patients treated with 42 Gy in 15 fractions to nodal areas. They did not observe any late lung and heart toxicity or plexopathy after 64 months of follow-up. Though a measure of caution is warranted in the application of this approach before the availability of level I evidence, it is appropriate that early long-term data on this approach will likely come from countries where the absence of RT may do more harm than the uncertainties of hypofractionation (10).

Gingras et al. Regional nodal irradiation after breast conserving surgery for early HER2-positive breast cancer: Results of a subanalysis from the ALTO trial. *J Natl Cancer Inst* 2017. (11)

The Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation (ALTO) trial is a previously reported (12) phase 3 adjuvant trial randomizing HER2-positive breast

cancer patients to 1 of 4 arms: trastuzumab alone, lapatinib alone, trastuzumab followed by lapatinib, or concomitant trastuzumab and lapatinib for 1 year. Although the primary endpoint was DFS, in the present analysis Gingras et al evaluated the impact of RNI on DFS in node-positive patients. A total of 1664 patients were included, of whom 878 (52.8%) received RNI to the axilla, supraclavicular region, and/or internal mammary chain. Patients in the RNI group had a higher nodal burden and more tumors larger than 2 cm.

After a median follow-up of 4.5 years, DFS was 84.3% in the RNI group and 88.3% in the non-RNI group. Regional recurrence rates were quite low, with no clear differences between those receiving or not receiving RNI. In multivariable analysis there was no statistically significant association between RNI and DFS. Thus, the authors conclude that the routine use of RNI in patients with node-positive HER2-positive disease receiving targeted therapy should be questioned.

Comments: The primary objective of this retrospective analysis was to evaluate whether results observed in the RNI trials (MA.20 and EORTC 22922) conducted in the pre-trastuzumab era are applicable to HER2-positive breast cancer treated with anti-HER2-targeted therapies. The findings of Gingras et al suggest that RNI has no significant impact in optimally treated HER2-positive patients. However, a number of potential biases must be considered. In this cohort of ALTTTO patients, 55% of patients in the RNI group had ≥ 4 lymph nodes involved. This is a much higher-risk population than those included in the MA.20 and EORTC 22922 trials, and competing risks may mask a potential benefit from RNI. In addition, selection for RNI, target volumes, and doses were not mandated by the ALTTTO protocol, making the application of RNI quite heterogeneous. Finally, distant recurrence was significantly worse in the RNI patients (12% vs 5%), again highlighting the imbalances in these groups that make it difficult to determine the true impact of RNI.

In the era of modern systemic therapy, the role for RNI in patients with node-positive HER2-positive disease who receive contemporary anti-HER2 treatment is unclear. The impact of targeted therapy on local recurrence has been clearly documented (13), and the very low rates of regional recurrence in this report are encouraging. However, given the historic increased risks of recurrence associated with this tumor subtype in the pre-trastuzumab era, omission of RNI in node-positive HER2-positive breast cancer patients

must be done with caution and, most appropriately, on clinical trial.

References

1. 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;15:1303-1310.
2. Poortmans PM, Struikmans H, Bartelink H. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015;373:1879-1880.
3. Whelan TJ, Olivetto IA, Levine MN. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015;373:1878-1879.
4. 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;305:569-575.
5. Savolt A, Péley G, Polgár C, et al. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla—Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. *Eur J Surg Oncol* 2017;43:672-679.
6. Sávolt A1, Musonda P, Mátrai Z, et al. Optimal treatment of the axilla after positive sentinel lymph node biopsy in early invasive breast cancer. Early results of the OTOASOR trial. *Orv Hetil* 2013;154:1934-1942.
7. Khan AJ, Belkacemi Y. Hypofractionated postmastectomy radiation therapy is safe and effective: First results from a prospective phase II trial. *J Clin Oncol* 2017;35:2037-2043.
8. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. *Lancet Oncol* 2008;9:331-341.
9. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial. *Lancet* 2008;371:1098-1107.
10. Bellefqih S, Elmajjaoui S, Aarab J, et al. Hypofractionated regional nodal irradiation for women with node-positive breast cancer. *Int J Radiat Oncol Biol Phys* 2017;97:563-570.
11. Gingras I, Holmes E, De Azambuja E, et al. Regional nodal irradiation after breast conserving surgery for early HER2-positive breast cancer: Results of a subanalysis from the ALTTTO trial. *J Natl Cancer Inst* 2017;109.
12. Piccart-Gebhart M, Holmes E, Baselga J, et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: Results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. *J Clin Oncol* 2016;34:1034-1042.
13. Yin W, Jiang Y, Shen Z, Shao Z, et al. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: A meta-analysis of published randomized controlled trials. *PLoS One* 2011; 6:e21030. doi: 10.1371/journal.pone.0021030. Epub 2011 Jun 9.