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Editorial

Radiotherapeutic management of the axillae in early stage breast cancer: Perspective of the radiation oncologist

1. The ACOSOG Z0011 study and the MA.20 study: landmark phase III trials

Lymphadenectomy has long been part of the standard treatment for breast cancer in patients with axillary node involvement. Complete axillary lymph node dissection (ALND) provides valuable information for staging as the number of positive nodes is an indicator of risk. Patients with nodal involvement are at high risk of both locoregional recurrence and distant metastasis, and this risk increases with the number of involved nodes. Despite the widely recognized value of ALND in locoregional control and as a prognostic tool, the risk of complications from surgery (lymphedema, seroma, and infection) is significant. An alternative strategy is to perform sentinel lymph node dissection (SLND),¹ which is also useful for staging but with less morbidity.

In cases with 4 or more diseased nodes, axillary radiotherapy is clearly indicated. However, this indication is less certain in cases with 1–3 positive nodes. The decision to irradiate, and the areas to be irradiated, has traditionally depended on other risk factors (tumor size, histological grade, nodal status, hormone receptor status, Ki-67, and HER-2).^{2–6}

However, with the recent publication of the two landmark studies mentioned above,^{7,8} it now appears that it is time to rethink our view of what standard treatment for breast cancer should be. Giuliano et al.⁷ reported the findings of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, a phase III randomized controlled trial (RCT) to evaluate the effect of axillary dissection on survival in women with invasive breast cancer and sentinel node metastasis. The other study, by Whelan et al.,⁸ presented findings from the MA.20 trial carried out by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). The MA.20 study was a multicentric RCT designed to evaluate the value of regional nodal irradiation in early stage breast cancer.

The ACOSOG Z0011 study included clinical stage T1–T2 invasive breast cancer patients with no palpable adenopathy and 1–2 sentinel nodes containing metastases. All patients underwent lumpectomy and tangential-field

radiation therapy,⁹ and were randomized to undergo ALND (10 or more nodes) or no further axillary treatment. Systemic therapy was at the discretion of the treating physician. The primary and secondary endpoints were overall survival (OS) and disease-free survival (DFS). Findings showed no significant between-group differences in OS (91.8% with ALND vs. 92.5% with SLND alone) or DFS (82.2% vs. 83.9%). Given the significant morbidity of ALND, the clear implication of this study is that ALND may be unnecessary in these patients with these characteristics. For radiation oncologists, this change in surgical approach has implications for treatment decisions as we will no longer precisely know the extent of disease spread to the axillary lymph nodes.

The NCIC-CTG MA.20 trial included 1832 women (916 in each group), with a median follow-up of 62 months. The aim was to evaluate the addition of regional nodal irradiation (RNI) to WBI following BCS in women with high risk breast cancer, regardless of sentinel node status. Patients were randomized to WBI or WBI plus RNI to the internal mammary, supraclavicular, and high axillary lymph nodes. Compared to WBI alone, the combined therapy (WBI+RNI) showed an improvement in isolated locoregional DFS, distant DFS, and OS. However, the addition of RNI to WBI resulted in more toxicity (an increase in grade 2 or greater pneumonitis and lymphedema). The authors conclude that additional RNI reduces the risk of locoregional and distant recurrence, improves DFS, and shows a positive trend towards better OS. The results of the MA.20 trial make it clear that adding RNI decreases recurrences in women with early-stage breast cancer. The findings are important because they highlight the value of increasing the radiation field in patients with similar characteristics. Previously, the value of doing this was not clear.^{10,11}

The results of these two studies are welcome news to patients and physicians alike, because far fewer patients will need to suffer from the morbidity (in particular, lymphedema) associated with ALND from a procedure whose value is more prognostic than curative. In fact, recently, the NCCN have updated their guidelines (v1.2112) to bring recommendations in line with the ACOSOG Z0011 findings. The NCCN now recommends that surgically operated (BCS) stage T1/T2 patients

with only 1 or 2 positive sentinel nodes and no previous neoadjuvant chemotherapy not receive ALND.

However, from the perspective of the radiation oncologist, the findings of these two important studies mean that we must now create new guidelines to incorporate the results into our treatment decisions. Moreover, we need to decide what areas of the body should be irradiated in these cases. Traditionally, radiation oncologists have relied on ALND to provide data on the exact number of diseased nodes. This information was then used to select the appropriate radiotherapy approach: when there is a clinically relevant risk, irradiation is performed at the level of the supraclavicular chain and level III axillae.

Until these two studies were published, irradiation was performed only in patients with either 4 or more positive nodal biopsies or, in selected patients with 1–3 node-positive biopsies. However, with the publication of Z0011, it is not clear – at least at present – as to which is the optimal radiation field to use in patients with positive sentinel nodes who have not undergone lymphadenectomy. Haffty et al.¹² believe we should still consider total nodal irradiation in these patients. As these authors point out, less than 1% of patients had regional recurrence in Z0011, even though it was estimated that more than 1 in 4 patients had additional positive nodes (which were not dissected per the study protocol). In addition, chemotherapy likely played an important role in destroying the nodal disease because systemic treatment has been shown to achieve complete response in up to 25% of cases.^{13–15} Another possible reason for the low relapse rate may have been the use of tangential fields through which axillary levels I and II were probably irradiated, even if coincidentally. Haffty and colleagues make an excellent point: we must consider the radiation fields and patient positioning when deciding whether to irradiate additional and larger areas. The Z0011 study does not tell us whether the lower axillae (levels I and II) received a therapeutic dose, but this analysis is being performed now.

Thus, in many ways, these findings actually create more uncertainty for radiation oncologists. The indication for radiotherapy is still unclear in patients with positive sentinel node biopsy without ALND.

2. Indication for irradiation in patients with 1–3 positive nodes

Prior to publication in 2005 of the Oxford meta-analysis, which showed a survival benefit of irradiating the supraclavicular area in all patients with involved lymph nodes, this treatment was indicated only in patients with 4 or more positive nodes as determined by ALND. Subsequently, several studies have found a benefit of adding adjuvant RT to surgery and systemic treatment. Among these is the study by Ragaz et al. for the British Columbia Cancer Agency (BCCA).¹⁶ In that RCT, the investigators assessed the impact of locoregional RT in premenopausal lymph node-positive breast cancer patients. These authors found a clear benefit of adjuvant radiotherapy in reducing locoregional recurrences and improved survival. Another similar RCT, carried out by Overgaard and colleagues,¹⁷ assessed the effect of irradiation on survival after mastectomy. Once again, these authors found

a clear benefit: locoregional recurrence alone or with distant metastases was observed in only 9% of the RT group vs. 32% of the chemotherapy group, DFS was better in the RT group (48% vs. 34%), and 10 year OS was also superior (54% vs. 45%).

Of these 2 RCTs, only the one by the BCCA showed that irradiation improved survival in all patients, regardless of the number of positive nodes. For this reason, international guidelines determined that there was insufficient evidence to support irradiating the nodal areas in patients with only 1–3 positive nodes. Until very recently, most consensus and clinical practice guidelines recommended axillary irradiation only in patients with 4+ positive nodes, but not in patients with only 1–3 nodes. The reasoning behind this is that even though radiation might reduce locoregional recurrence, it would be unlikely to improve survival. Overgaard,¹⁸ in response to some critical comments about the first Danish studies, decided to perform a retrospective analysis of the subgroup of node-positive patients from the Danish Breast Cancer Cooperative Group 82 (DBCG 82b and 82c). In that retrospective analysis, the authors only included patients who had had 8 or more nodes removed (a total of 1152 patients). The aim was to evaluate the loco-regional recurrence rate and survival as a function of the number of positive nodes. The authors found that postmastectomy RT yielded an important survival benefit (15 year OS rate of 39% in patients with RT vs. 29% in those without) and this advantage was maintained in patients with 1–3 and 4+ positive lymph nodes. The authors concluded that the indication for RT seems to be at least equally beneficial in patients with 1–3 positive nodes, and they recommended updating guidelines accordingly.

Based on these results, we considered the possibility of performing RT to the supraclavicular chain in patients with 1–3 affected nodes when some other risk factor was present. Currently, there are two randomized trials underway, the SUPREMO (Selective Use of Postoperative Radiotherapy after Mastectomy) and the aforementioned MA.20 (National Cancer Institute of Canada Clinical Trials), both of which aim to clarify the role of RT in patients with intermediate risk who have undergone a radical mastectomy (pT2 N0, grade 3 and/or lymphovascular space invasion and 1–3 positive nodes).

3. Policy for lymph node irradiation at the Catalan Institute of Oncology (Barcelona, Spain)

At our institute we use the following criteria to rule out ALND when the sentinel node biopsy is positive: stage pT1 or pT2 with 1 or 2 positive sentinel nodes; no microscopic involvement of the perinodal fat; BCS; adjuvant conventional breast RT and adjuvant chemotherapy. Within this group of patients, we have defined a series of prognostic factors that determine the type of radiotherapy to be performed: patients >50 years with positive hormonal receptors and histological grade 1 or 2 tumors will undergo radiotherapy with high tangential fields; patients <age 50 or with RH-negative or histological grade III tumors are considered high risk and all nodal chains (levels I, II, III and the ipsilateral supraclavicular area) will be irradiated. Finally, patients with microscopic disease in the sentinel node (pN1_{mic}) do not undergo ALND, nor irradiation of levels I and II.

4. Conclusion

Locoregional treatment of breast cancer is currently undergoing important changes. With the recent publication of MA.20 and the ACOSOG Z0011 studies, we now have two separate RCTs with similar inclusion criteria. Data on the RT fields used in these studies are not yet available and so we must await more data to ultimately decide if all N1 patients should undergo irradiation of the supraclavicular chain and level III. However, the data published to date is surely sufficient to prompt us to seriously consider increasing the volumes to be irradiated in early stage breast cancer. By doing so, we are likely to improve both local control and survival.

Conflict of Interest

None declared.

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