Lymph Node Radiotherapy Instead of Extended Axillary Surgery – the New Standard?

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Keywords

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Summary

Breast cancer treatment has undergone major changes in the last 20 years. Specifically, the role of axillary lymph node dissection has changed from radical axillary dissection with excision of a high number of lymph nodes to sentinel lymph node biopsy (SLNB). This paradigm shift is associated with a controversial debate regarding the significance of axillary staging, the need for surgery, and the role of radiotherapy. Looking ahead, lymph node staging and axillary treatment might shift from SLNB and/or axillary dissection to ultrasound-guided needle biopsy and irradiation of regional lymph nodes in order to reduce treatment-related sequelae in early-stage breast cancer.

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Decreasing Axillary Staging

In previous years, the number of positive lymph nodes was an important criterion to indicate systemic therapy [1]. However, recently, biological markers and tumor biology have been rapidly gaining importance [2].

Halsted's hypothesis of radical mastectomy included the removal of the breast, the major and minor pectoralis muscle, as well as the ipsilateral axillary lymph nodes [3]. However, despite being lymph node-negative, 30% of patients developed locoregional relapse and even distant metastases [4].

The NSABP B-04 trial randomized 1,079 patients to radical mastectomy with axillary radiotherapy (ART), mastectomy with axillary dissection (AD), or mastectomy alone with observation of the axilla. The 10-year results showed a 17.8% axillary recurrence rate in patients with untreated axillae compared to 1.4% in those who underwent AD and 3.1% in those with ART [5]. Still, AD remained the treatment of choice for axillary management, mainly because the number of involved nodes guided the decision regarding adjuvant systemic therapy.

However, due to improved screening, the prevalence of axillary metastases has decreased. Considering the high risk of surgical morbidity, with a lymphedema incidence of up to 50% after 20 years, and the increasing importance of biological markers, extensive surgical treatment became more and more questionable [6–11].

Sentinel lymph node (SLN) biopsy (SLNB) represents an opportunity to reduce axillary morbidity while obtaining lymph node staging. Several trials have proven the safety of omitting AD in the case of a negative SLNB. In a systematic review published in 2010 with over 15,000 patients, the axillary recurrence rate was 0–3% at a mean follow-up of 34 months [12].

In the NSABP B-32 trial with more than 5,600 patients with early breast cancer, more than 3,900 patients were SLN-negative and did not undergo further axillary treatment. The remaining SLN-positive patients were randomized to 2 groups: AD versus observation. Among the 3 groups, no differences in overall survival (OS), disease-free survival (DFS), and locoregional control could be found [13].

With the introduction of SLNB, the rate of lymph node positivity went up to 30%. The more detailed pathology workup [14, 15] identified a higher number of small tumor foci. However, initially, the clinical impact of these small foci remained unclear [15]. Therefore, the IBCSG 23-01 and the AATRM trial randomized patients with SLN micrometastases to either further axillary surgery or observation. In both studies, regional failure and OS were statistically equivalent between groups [16, 17].

Axillary Radiotherapy: An Alternative Option for the Adjuvant Axillary Management of Breast Cancer

For a long time, the usage of regional lymph node irradiation in early breast cancer was very restrictive. Most international guidelines advised radiotherapy of the lymphatics only in the case of more than 3 positive lymph nodes. The commonly recommended treatment volume merely encompassed the supraclavicular fossa. This cautious approach was mainly based on insufficient data regarding the benefit of additional lymph node irradiation in terms of survival and the supposed risk of side effects such as lymphedema and plexopathy. A meta-analysis demonstrated an average incidence of treatment-related lymphedema in up to 20% of patients with early breast cancer [18]. The pooled data identified the extent of axillary surgery as the leading risk factor for lymphedema. These findings were confirmed in a large population-based cohort of nearly 1,800 breast cancer patients [19]. The authors found no lymphedema events within the group of patients without any axillary surgery. However, the 5-year incidence of lymphedema increased with the degree of surgery from 5.3% in the case of SLNB to 15.9% in the case of AD ($p < 0.001$). In multivariate analysis, radiotherapy, chemotherapy, and obesity were identified as additional factors further increasing the risk of lymphedema in conjunction with any axillary surgery.

Therefore, complete omission of AD in the case of positive SLNB has been the next progressive step in order to reduce treatment-related side effects. The ACOSOG-Z0011 and the AMAROS trial randomized patients with limited numbers of positive SLN [20, 21] comparing AD to no further therapy or non-invasive treatment. The ACOSOG-Z0011 trial recruited 891 patients treated with breast-conserving therapy followed by adjuvant systemic treatment and tangential radiotherapy. Irradiation of the lymphatics was not permitted per protocol. Regarding OS and regional control, AD showed no additional benefit. The AMAROS trial compared AD versus ART in over 1,425 SLN-positive patients after breast-conserving surgery or mastectomy. Likewise, this trial reported no additional benefit of surgery compared to non-invasive treatment. However, the surgical approach led to an almost 2-fold increase in lymphedema compared to radiotherapy.

The randomized, single-center OTOASOR study compared AD and ART and yielded similar results in $< cT3$ SLNB-positive patients. After 8 years of follow-up, there was no statistical difference in axillary recurrence or DFS between the 2 treatment arms [22].

However, is radiotherapy at all beneficial in patients with low-volume lymph node metastases? In fact, a meta-analysis by Budach et al. [23] confirmed this in 2015. The authors pooled the data of 3 randomized trials: MA.20, EORTC-22922/10925, and a French trial [24–26]. The major eligibility criterion of all 3 trials was $pN+$. The MA.20 also included lymph node-negative patients with a high risk for recurrence, while the EORTC and the French trial included lymph node-negative patients with a medial or central tumor location. The primary endpoint was OS, secondary endpoints were DFS and distant metastasis-free survival (DMFS). MA.20 and EORTC-22922/10925 both showed an improvement in DFS and, interestingly, DMFS, but no significant impact on OS. However,

the meta-analysis of Budach et al. [23] showed that additional radiotherapy to the internal mammary and/or supraclavicular lymph nodes resulted in significantly improved OS and DFS; however, the absolute benefit was low.

The influence of the extent of nodal irradiation was also demonstrated by the DBCG-IMN study [27] which was performed as a population-based approach with radiotherapy to the internal mammary chain in addition to the supraclavicular fossa for right-sided breast cancer only. The results demonstrated improved OS for the extended treatment volume. However, the significant improvement in the 8-year survival rate was only found in premenopausal patients. Tumor biology seems to influence the importance of the extent of nodal irradiation.

Discussion

The increasing number of patients diagnosed with early breast cancer and their excellent prognosis have resulted in less invasive treatments in order to decrease late sequelae. The evidence for omission of AD without impairment of local control and OS is still weak. The ACOSOG Z0011 trial seemed to prove its safety as presented by the authors in the 10-year update [28]. However, the study had several limitations. The trial was underpowered to reach statistical significance concerning its primary endpoint, OS, and the dropout rate almost reached 20% [29]. In the AD arm, micrometastases (< 2 mm) were identified in only 37.5% of the patients compared to 44.8% in the SLNB group ($p = 0.046$). Furthermore, an analysis of the 228 available radiotherapy plans revealed a substantial amount of protocol violations. In the SLNB-only arm, more than 18% of the patients received prohibited irradiation of the axilla or the supraclavicular fossa, and almost 50% of the patients were treated with 'high tangential fields' increasing the dose to the axillary level II.

The American Society of Oncology, the St. Gallen Consensus, and the recently updated Germany Cancer Society guidelines advise to omit AD in the case of 1–2 positive lymph nodes. For patients with more than 2 positive lymph nodes, radiotherapy is considered as an alternative to surgery.

The authors of a systematic review and meta-analysis concluded that SLNB only is an adequate treatment for patients with up to 2 micrometastases. For those patients with macrometastases in the SLNB, omission of AD is a feasible option provided that the patients receive adequate adjuvant treatment including adjuvant radiotherapy to the breast [30].

A further step towards reducing late sequelae could be the omission of surgical intervention in the clinically negative axilla altogether.

The ongoing German INSEMA trial is investigating a restrictive axillary staging in clinically node-negative early breast cancer patients [31].

The results of the SOUND trial might lead to the replacement of any open surgical staging by ultrasound-guided core or needle biopsy of negative or sonographically suspicious lymph nodes for early breast cancer smaller than 2 cm [32].

The ongoing POSNOC trial may finally answer the question whether or not further axillary treatment, AD, or ART should be the treatment of choice for SLN-positive breast cancer patients [33]. However, this study is not expected to complete accrual before 2018.

Conclusion

Considering i) the evidence proving the importance of nodal irradiation, ii) the low rates of toxicity compared to extensive surgery, and iii) the absence of randomized trial results demonstrating in which cases additional axillary treatment can be safely omitted, we believe that ART is a safe and less toxic alternative to AD.

The role of radiotherapy to the axilla in the setting of complete clinical response of initially positive axillary lymph nodes after ne-

oadjuvant radiotherapy remains less clear. The ALLIANCE A011202 trial (ClinicalTrials.gov: NCT01901094) might clarify this role. The trial is still recruiting patients presenting with cT1–3 cN1 and clinical complete remission after neoadjuvant chemotherapy. These patients undergo SLNB before randomization to axillary clearance or radiotherapy. Ongoing trials such as SERC/IPC 2012-001 (ClinicalTrials.gov: NCT01717131) in France, SENOMAC (ClinicalTrials.gov: NCT02240472) in Sweden, and BOOG 2013-07 (ClinicalTrials.gov: NCT 0211682) in the Netherlands currently investigate the same topic of omitting axillary surgery. The results of these trials are expected in 2027–2029.

Disclosure Statement

The authors do not have any conflicts of interest to declare.

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