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Adjuvant Regional Nodal Irradiation Recommendations After ACOSOG Z0011 (Alliance) Trial Results: "Our Doubts and Uncertainties Maybe Traitors for Undertreated Patients"

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Predicting breast cancer (BC) outcome based on sentinel lymph node (SLN) status without axillary lymph node dissection (ALND) is an area of uncertainty in patients with limited SLN involvement. These uncertainties automatically influence the decision-making on adjuvant regional nodal irradiation (RNI). The updated clinical practice guidelines report from the American Society of Clinical Oncology on the use of SLN for patients with early-stage BC concluded that women without SLN metastases and those with 1-2 metastatic SLNs receiving whole breast irradiation (WBI) should not undergo ALND. Women with SLN metastases who will undergo total mastectomy (TM) should be offered ALND. These recommendations are mainly based on randomized trials.[1-3] However, several concerns remain including the short follow-up periods of these trials and the uncertainty of axilla coverage by the tangential fields (TgFs) irradiation, especially with 3-D conformal techniques.[4]

In the ACOSOG Z0011 trial, the 6-year outcome after breast conserving surgery (BCS) plus whole breast radiotherapy (WBRT) was equivalent in patients who underwent SLN biopsy (SLNB) only and in those further treated with ALND that previously had ⩽2 positive SLNs on SLNB. This equivalence was attributed to the potential cure of axillary residual disease with systemic therapy and radiotherapy (RT).[2] While radiation parameters and dose distribution in the axilla were not reported in the initial publication, Jagsi *et al.* tried to provide more details on RT technique in their subsequent publication.[2,5] Unfortunately, these data are unable to dispel the ambiguity of RNI usefulness in the patients' profiles included in the Alliance trial. Thus, the authors could not respond to questions posed by other scientists regarding the control of residual disease using TgFs and the ability of these fields in covering axillary volumes and delivering a tumoricidal dose to potential residual disease. Analyses concerned 605 patients among whom RT data were only available for 228 patients (37%). Finally, analysis of axilla coverage by TgFs concerned only 142 patients (23%). While dose evaluation was not possible, and dose distribution is unknown, the authors highlighted the fact that 43 patients received directed regional nodal RT using 3 fields. Therefore, this study could not draw any conclusion on whether additional RNI was necessary or beneficial for these patients.[5] The only conclusion made was that most patients received TgFs alone and some also received direct nodal irradiation via a third field. These data do not confirm the original conclusion on the impact of TgFs and systemic therapy on the axillary residual disease control mentioned in the first report.[2] Indeed, response should be linked to the dose distribution analysis and demonstration of whether the level of dose is considered as tumoricidal or not. In our recent reports, we showed that TgFs allow only a limited dose to levels I-II and to SLNB area when only using standard TgFs (STgFs).[4,6] In case of SLN

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involvement and no further ALND, using high TgFs (HTgFs) to cover the SLNB area was mandatory because of a higher risk of non-SLN involvement that depends on the anatomic location of SLN and its degree of involvement.[6-8]

Several reports have indicated that axillary nodal coverage depends on the upper TgFs border. Studies using STgFs showed axilla contents underdosage with about only 50% of level I and 20-30% of level II receiving 95% of the prescribed dose.[4] Krasin *et al.* showed that only 1 out of 25 patients received 50Gy in level I of the axilla, and no patient had an adequate coverage of rest of the axilla.[9] Orecchia *et al.* reported that only one out of 15 patients received 40Gy in the axilla in a context of significant volume reduction.[10] Our group showed that the SLNB area was completely covered by the TgFs, independently from its size, in only 48% of the patients. The average dose in the SLNB area was 33Gy. However, a significantly higher dose was delivered using HTgFs. The average dose is considered as non-tumoricidal in at least the partially suitable (34Gy) and unsuitable (8Gy) groups.[6]

We concluded that from a radiation oncology view, in patients with SLN involvement and no further ALND, the use of direct fields could be considered rather than TgFs as suggested in ACOSOG Z011 trial for an adequate coverage of the axilla. Regarding the survival benefit obtained recently with RNI, our doubts and uncertainties maybe traitors for undertreated patients and compromise their outcome.

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