

How nescience may obscure evidence

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During the last decade, treatment trends for early breast cancer have been fluctuating between opposite extremes. More aggressive regional nodal irradiation (RNI) has been suggested by several recent studies [10, 17], on the other side, the previously unquestioned dogma of axillary dissection as an important part of breast cancer management was gradually abandoned in favor of sentinel node dissection (SLND). While consensus was rapidly achieved for pathologically negative SN, the management of patients with one or two positive SN remained controversial up to the first publication of a randomized study of the American College of Surgeons Oncology Group [3] which specifically addressed the outcome of such patients with ALND vs. none. Even though

limitations of the study were recognized and led to some critical comments [7], current guidelines [8, 14] rapidly adopted the omission of ALND in these selected patients.

Unreckoned insights about the quality of evidence generated by the Z0011-trial were provided by a recent publication on behalf of the Alliance for Clinical Trials in Oncology by Jagsi et al. Briefly, the study [3] (published in 2011) comprised 891 women from 115 institutions with a clinically negative axilla who underwent sentinel node dissection (SLND), revealing 1–2 pathologically affected nodes. Tumor characteristics were pT1 (70%) or pT2 invasive carcinomas, mostly ER+, well-differentiated tumors. Patients were randomized to either axillary dissection (ALND) or

Editorial on Jagsi et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial.

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“no further local treatment”. Adjuvant whole breast irradiation (WBI) with standard tangents was mandatory, third field nodal irradiation was explicitly excluded. No further requirements were made concerning RT technique or quality control. Systemic treatment was left to the discretion of the treating center. The study was terminated after accrual of 891 instead of the originally planned 1900 patients. After a median follow-up of 6.3 years, no difference in OAS and DFS was observed, 5-year locoregional recurrence-free survival rate was 96.7% after SNB alone and 95.7% in patients with ALND. The authors concluded that ALND might no longer be justified in T1–2 tumors even in case of 1–2 positive sentinel nodes.

Speculation evolved, to what extent inadvertent radiotherapy of the axilla had contributed to the low rate of locoregional recurrence. Several studies investigated the dose delivered to the axillary nodes by conventional tangential fields, and explored the possibility of achieving an improved coverage of level I by minor field extensions in cranial direction [1, 11, 15]. Haffty et al. proposed the use of “high tangents” in order to reduce the potentially increased risk of local recurrence for SN-positive patients [4]. This seemed a tempting compromise between RT of the complete axilla and total omission of any local treatment.

In order to quantify the extent of axillary radiation in the Z0011 trial, Jagsi et al. [5] took the attempt to analyze the radiation field design of the Z 0011 study population by requesting the treatment records from the involved radiation oncologists for a central review. Completed case report forms were obtained for 605/856 patients, of those 540 (89%) had received WBI. Additional treatment to the supraclavicular region was recorded in 89 (15%) of these patients in this subgroup. Noteworthy, detailed RT records were only available for 228 patients, of whom 185 (81.1%) received tangents alone. Information about the cranial field border was provided by 142 records. “High tangents” (defined as cranial tangent border ≤ 2 cm from the humeral head) were used in 50% of the ALND patients and 52.6% of the SLND group. Of the 228 patients with records reviewed, 43 (18.9%) received directed regional nodal RT using \geq three fields: 22 in the ALND arm and 21 in the SLND arm. Those receiving directed nodal RT had greater nodal involvement ($p < 0.01$) than those who did not. Overall, there was no significant difference between both treatment arms in the use of protocol-prohibited nodal fields.

The authors (one of whom is the first author of Z0011) commented these finding as “unexpected” [5]. This appears as a benevolent interpretation of a study which is commonly cited as main evidence for a change of practice and turns out to be performed with a substantial amount of previously unrecognized protocol violations.

We agree that in spite of these violations, the non-inferiority of SNB compared to ALND is corroborated, none-

theless without supporting the assumption that positive SN have no impact on prognosis [2]. The reverse has been recently indicated by the results of a subgroup analysis of the NSABP-B 32 trial which was originally also designed to evaluate whether SLND alone was equivalent to complete ALND, albeit in primarily SN-negative women. Tissue blocks of SN obtained from patients with pathologically negative SN were centrally re-evaluated and occult metastases were detected in 15.9%. Follow-up showed a small but significantly worse outcome of those patients with occult metastases compared to those who remained negative. The absolute difference in 5-y OAS was 1.2% ($p = 0.03$), DFS even 2.8% ($p = 0.02$) [16]. Several large retrospective cohort studies showed a similar trend even for microscopically positive nodes [6, 9].

Jagsi et al state that their observations “should not be taken to suggest that nodal RT administered to patients in the Z 0011 study was necessary or beneficial”. They substantiate this statement by stressing that a subgroup had not been irradiated at all (about 11% in both arms). Should the reader take this further protocol violation as evidence that local treatment is dispensable for SN positive patients? In fact, the analysis demonstrated that the vast majority of the women *did* receive local treatment – as relevant radiation doses were delivered to the axilla. The ability of radiation to sterilize axillary metastases has recently been demonstrated by the EORTC 10981–22023 AMAROS study comparing ALND vs. dedicated axillary radiotherapy in pathologically positive SN. The 5-year axillary recurrence rate was 0.54% after ALND and 1.03% after RT. As the rate of lymphedema was significantly lower, the authors suggested RT as a standard instead of ALND in this situation [12].

In this context, it seems worth mentioning, that two large randomized trials recently provided evidence indicating that regional nodal irradiation (RNI) not only improves local control but also reduces metastases and prolongs survival. The EORTC 22922-10925 [10] study included 4,004 women stage with mostly pT1–2 tumors (95%) and either involved axillary LN and/or a medially located primary tumor. Patients were randomized to receive postoperative RT either with or without RNI. After 10 years, patients with RNI had a small but significant improvement of 1.6% in OAS and 3% in disease-free as well as metastases-free survival (MFS). The positive impact of RNI on MFS has also been indicated by the NCIC-CTG MA.20 trial [17]. The study included 1,832 women with mostly 1–3 positive axillary nodes (85%) and 10% with negative nodes. Patients were randomized after breast conserving surgery and ALND to either WBI or WBI and additional RNI. The 5-year disease free survival (DFS) was significantly improved by 5.4% in the RNI-group ($p = 0.003$). This difference is twice as high as the absolute benefit in terms of

local control (2.3%) and therefore hypothetically attributable to the prevention of distant metastases.

In summary, the question how to best manage SN-positive patients without ALND remains unresolved, even if omission of ALND is justifiable. As the authors finally emphasize, their findings must not be extrapolated to patients without any axillary radiation dose coverage, for instance, in case of prone breast treatment or partial breast irradiation. One important conclusion should be to require dose volume histograms routinely for WBI treatment plans [13]. Jagsi et al. [5] deserve merit for their attempt to quantify the radiation dose of the axilla in order to estimate the potential contribution of inadvertent RT to the outcome of Z0011. Unfortunately, the results of their survey rather obscure than elucidate the issue.

The paper is in so far extraordinary as it provides remarkable insights into the pitfalls of interpreting “evidence” and illustrates that the label “randomized study” should not mislead to draw premature conclusions. It is reassuring that in the last sentence of the paper the authors conclude “that given the findings of our study, it is not unreasonable to also consider additional nodal treatment in selected patients”.

At least, a definitely agreeable statement!

Compliance with ethical guidelines

Conflict of interest M.-L. Sautter-Bihl, F. Sedlmayer, W. Budach, J. Dunst, P. Feyer, R. Fietkau, W. Haase, W. Harms, M.D. Piroth, R. Souchon, F. Wenz, R. Sauer declare no conflict of interest.

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