The Breast Journal

LETTER TO THE EDITOR

Are All Patients with Ductal Carcinoma In Situ of the Breast Candidates for Radiotherapy after Breast Conservative Treatment? Institute of European Oncology Guidelines

To the Editor:

At present, we know that adjuvant radiotherapy (RT) after breast-conserving surgery (BCS) reduces local recurrence (LR) rates by about 50% in patients with ductal carcinoma in situ (DCIS) of the breast, with no benefits on survival. Comparable reductions were seen for the rise of both invasive and noninvasive LR. Also, nonsignificant long-term toxicity from RT was found (1). This has been demonstrated by well-known randomized trials as NSABP B-17 (2), UK-A-NZ (3), EORTC 10853 (4), SweDCIS (5), and recently confirmed by an update of the same studies (6).

But do all DCIS patients have to undergo RT after BCS? This question was answered with opposing opinions by Buchholz (positively) (7) and Silverstein (negatively) (8). The answer offered by the 2011 St Gallen Consensus Conference (9) was in the negative: most panelists considered that RT could be avoided in elderly women or in patients with low-grade DCIS and clearly negative margins.

On this last point, there is no agreement about the limits of safety related to the width of surgical margins (10) that vary from 10 mm to 1 mm, with intermediate measures of 3 mm, 2–3 mm and 2 mm. On the other hand, DCIS patients with G3 disease and necrosis are generally considered suitable for adjuvant RT, as both of them are associated with higher risk of recurrence (11). Major controversies are related to the need for RT in lower grade disease. Two prospective studies showed contradictory results: in the Dana-Faber Cancer Institute trial the omission of RT resulted in a cumulative LR rate of 12% at 5-year (12). Conversely, the EORTC 10850 trial showed a reduced risk of LR rate in the G1 subgroup after surgery alone, less than 10%, but at a doubled follow-up time, 10 years (4).

Advances in molecular profiling analysis (13) along with the well-known clinical and pathologic parameters might help to improve risk stratification and decision-making. Several studies have investigated the prognostic significance of biomarkers, such as estrogen receptor status, HER2/neu expression, Ki-67-expression (14), but their validation is complex and needs to be tested prospectively in large cohorts of patients.

These previous data justify the still open debate regarding the practice of RT in patients with DCIS. The lack of shared opinions is confirmed if we examine the published surveys on the indications and utilization of RT after BCS. In the UK, patients were significantly more likely to have RT planned (and administered) if they had large (>15 mm), intermediate or high-grade tumors or if central comedo-type necrosis was present (15). In North America, there were strong correlations between the grade of DCIS and margin status and the use of RT (16). Recommendations are in favor of RT as grade increased (more than 97% in G3) and margin width decreased (more than 95% with <10 mm). There were substantial differences in opinion between North America and Europe, as well as in Europe itself, especially regarding low-grade and wide margin lesions, for which Europeans offered observations more often than Americans (56.9% versus 41.2%). Substantial differences by surgeons in surgical treatment, receipt of RT and margin status found by Dick et al. (17) emphasize the importance of the physicians in the quality of care of DCIS. The heterogeneity of the disease accounts for the heterogeneity of treatment and makes the perception of risk and the treatment choices challenging (18).

At the European Institute of Oncology (IEO), in Milan, for more than a decade RT was only administered to DCIS patients with G3, or G2 with comedo-type

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DOI: 10.1111/tbj.12295

necrosis (19), and not administered in cases of G1 neoplasia, or G2 without comedo-type necrosis. In these cases, treated by surgery alone, the observed LR rate was 8% at 6 years (20). Recently, other important cancer-related reports (9,21) also suggested that the same subgroups of DCIS patients could not be candidates for RT after BCS, even though the overview of the randomized trials confirmed a statistical benefit in terms of local control of adjuvant RT not related to histologic grade or presence of comedo-type necrosis (5).

Many other questions related to adjuvant RT in DCIS patients remain open, without a scientific answer. The first relates to the use of a boost RT dose after standard whole breast irradiation (22). A retrospective multicentric study showed that an RT boost dose decreases LR in patients <45 years of age at 10-year follow-up (23). Two multicentric randomized trials assessing the role of the boost are ongoing: the French trial evaluating the impact of a 16 Gy boost after 50 Gy to the whole breast in 25 fractions (Bonbis trial) (24) and the Trans-Tasman Radiation Oncology Group (TROG) investigating the role of the boost dose and of the altered fractionation (25). The latter trial is also designed to test the hypofractionation regimen to the whole breast. The use of large dose/fraction and reduced total dose have shown similar local control and toxicity compared to conventional regimen in invasive breast cancer. Preliminary reports suggest that the hypofractionated RT can be given to DCIS patients (26).

A further open question is related to the use of partial breast irradiation (PBI) in women with DCIS. The Consensus Statement from the American Society for Radiation Oncology (27) agreed that PBI outside a clinical trial can be used to treat small pure DCIS with caution, due to limited data available in the literature, although the American Society Breast Surgeons Registry Trial includes the largest published collection of DCIS patients treated with PBI. At 4.5-year median follow-up, it was possible to observe similar results in DCIS patients treated with PBI, when compared with DCIS patients treated with whole breast irradiation (28). On the other hand, ASTRO panellists strongly recommend the recruitment of patients, including those with DCIS, in the randomized phase III trial of PBI versus WBI (RTOG 0413/NSABP B-39).

In conclusion, the management of DCIS patients is still variable and widely debated. The scientific community is in increasing agreement that the same subsets of patients, with low risk disease (G1, and G2 tumors without comedo-type necrosis) can be candidates to active surveillance only after BCS. On the other hand, the standardization of the adjuvant RT, especially with respect to the role of boost dose and the PBI techniques, still remain an open question that warrants clarification by ongoing studies and new trials.

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