Editorial

Postmastectomy radiation therapy in women with T1–T2 tumors and 1 to 3 positive lymph nodes: analysis of the breast international group 02-98 trial

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In case of patients affected by breast cancer with more than 4 positive lymph nodes (LNs), postmastectomy radiation therapy (PMRT) has been widely adopted to reduce local relapse (1,2). Some controversies are still present regarding the use of PMRT for patients with 1–3 positive LNs. The updated meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published in 2014 regarding the effects of PMRT, performed additional analyses on 1.133 patients were affected by breast cancer with 1–3 positive LNs receiving axillary dissection and chemotherapy (3). The latter meta-analysis showed that the 10-year rate of locoregional failure was 21.0% and 4.3% for patients who received radiation therapy or not, respectively (P=0.001). The 10-year rate for any recurrence (locoregional or distant) was 45.5% and 33.8% without PMRT and with irradiation (P=0.001), and the respective 20-year rates of breast cancer mortality were 49.4% and 41.5% (P=0.01; relative risk, 0.78), respectively. The trials included in the EBCTCG meta-analysis were conducted in the 1970s and 1980s and chemotherapy used, was cyclophosphamide, methotrexate, and fluorouracil (CMF); or methotrexate plus fluorouracil; or single-agent cyclophosphamide or melphalan (Data Supplement Table 1) (3).

The Danish trial reported the results of patients with 1–3 positive LNs treated with mastectomy and without PMRT (4). The study showed the half of loco-regional failure rates at 10 years in the group that received an anthracycline-based adjuvant therapy compared with CMF-based chemotherapy control group. Furthermore, the CLG B 9344 study (5) reported an incremental locoregional benefit of taxane chemotherapy. On this basis, the aim of the recent study published by Zeidan and colleagues (6), is to identify the real benefit of PMRT for patients with T1–T2 breast cancer and 1–3 positive LNs in the era of anthracycline and taxane-based adjuvant chemotherapy (7). To achieve this goal, the authors analyze retrospectively 684 women with pT1–2 pN1 (1–3 LNs) enrolled in the Breast International Group (BIG) 02-98 trial (8) and treated with mastectomy and an axillary with at least 8 LNs dissection. The findings of the study showed a benefit outcome in terms of loco-regional recurrences in the radiotherapy group, but some considerations should be highlighted.

Inclusion criteria

In this subgroup of patients, the main considered variable was the PMRT delivery, in particular, 337 women received PMRT and 347 did not. Considering the trial design, the choice of giving PMRT, the treatment volumes and prescription doses were arbitrarily managed by each participating center in the study. Moreover, considering that this trial was designed to test four different chemotherapy schedules and the patients randomly assigned to 1 of the 4 treatment arms in a 1:1:2:2 ratio, the subgroup of cases analyzed for the declared aim could be affected in a notable way by these different and heterogeneous therapeutic choices. Nevertheless, the inclusion criteria of this analysis were very relevant to the goal, reducing the risk of bias

linked to retrospective patient selection.

All inclusion criteria were correctly respected in the results and the two comparative groups (PMRT and no-PMRT) were quite balanced in the patients and disease characteristics, except for tumor size and number of positive LNs. In fact, in no-PMRT group a smaller proportion of patients presented a pT2 disease compared to the PMRT group (59% *vs.* 67%, P=0.04), likewise the number of positive LNs equal to 3 in PMRT group was higher than no-PMRT group and this difference was strongly statistically significant (33% *vs.* 18%, P<0.001). Thus, based on tumor staging, the patients in the PMRT group were at higher risk of relapse.

Treatment and results

In line with the aim, the primary objective of the study was to examine the efficacy of PMRT on locoregional recurrence (LRR), breast cancer-specific survival (BCSS) and overall survival (OS) at 10 years. The median follow-up of this analysis was 9 years (range, 1 month–12 years), adequate for a 10-year actuarial estimate of the considered rates, but not so long to draft definitive results.

Regarding radiotherapy, in most cases the treatment volume covers the chest wall and regional node (including supraclavicular LNs) (7) to achieve the best local disease control. The Table 1 of the study (6) reported that 92% of patients were irradiated on chest wall, 74% on supraclavicular LNs, 45% on internal mammary LNs, and 24% on axillary LNs. The number of LRRs was low, 26 events on the entire population of 684 patients. Of those, 6 were in the PMRT group and 20 in the no-PMRT group. The 10-year LRR was lower in the PMRT group: 2.5% (95% CI, 1.0–6.0%) *vs.* 6.5% (95% CI, 4.2–9.9%) (HR 0.29; 95% CI, 0.12–0.73, P=0.005). However, in the definition of locoregional control, the recurrence in the supraclavicular area was defined as distant recurrence. In this way, the data of the local disease recurrence at this area is not provided, going to confuse with a framework of distant metastasization and potentially weakening the effectiveness of the same local treatment.

The benefit, in terms of local control, of PMRT was greater for patients who receive adjuvant chemotherapy without taxane, with 10-year LRR rates of 3.4% (95% CI, 0.7–15.1%) and 9.1% (95% CI, 4.8–16.8%) for the PMRT group and no-PMRT group, respectively (HR 0.20; 95% CI, 0.04–0.92, P=0.02). In patients who receive chemotherapy with taxane, 10-year LRR rates were 2.0% (95% CI, 0.8–5.3%) and 5.3% (95% CI, 2.9–9.3%), respectively, for the PMRT group and no-PMRT group (HR 0.37; 95% CI, 0.12–1.18, P=0.08). No significant differences in BCSS (84.3% and 83.9%) or OS (81.7% and 78.3%) were observed receiving or not the PMRT. These results, according with EBCTCG meta-analysis (3), suggest that PMRT in women with T1–T2 breast cancer and 1–3 positive LNs improves the local control disease even if they receive anthracycline and taxane-based adjuvant chemotherapy. The advantage would seem greater in the group without taxane. The lack of a significant impact of PMRT on BCSS or OS, is probably due to the use of this type of systemic therapy compared to older schemes such as CMF, allowing to achieve a better disease control out-field.

Certainly, the major limitation of this study (6) such as previous published (3), is the lack of a correct stratification of patients for breast cancer subtypes according to biomarker (Ki67 and HER2 status) and hormone receptors status, that allow to estimate the disease biological aggressiveness (9). This important disease aspect associated with tumor size, axillary LNs burden (number of positive LNs, nodal ratio, and size of nodal tumor deposits), tumor grade, lymphovascular invasion, and patient characteristics (age and comorbidity conditions) could be predictive of local recurrence risk, life expectancy and complications risk.

In conclusion, in light of these findings, the ASCO-ASTRO-SSO guidelines (10) and St. Gallen consensus statement (11) recommend to omit PMRT in women affected by breast cancer pT1–T2, 1–3 positive LNs, and a favorable biological profile. The results of ongoing SUPREMO trial, that randomized patients with to 1–3 LNs to either chest wall radiation or observation, might help to determine (12) which patient subcategories are most likely to benefit from PMRT when modern systemic therapy is used. The decision to use PMRT should be made in a multidisciplinary fashion through discussion among providers from all treating disciplines early in a patient's treatment course.

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