Editorial

Whether adjuvant radiotherapy is desired for postmastectomy patients with T1–T2 tumors and 1–3 positive axillary lymph nodes who received modern systemic therapy?

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The role of postmastectomy radiation therapy (PMRT) for patients with T1–T2 tumors and 1–3 positive axillary lymph node (ALN) metastases of breast cancer is an issue of ongoing debate. The uncertainty and controversy concerning PMRT for this group of patients is mainly due to the discrepancy in the conflicting benefits of locoregional control reported in different trials and in adjuvant systemic treatment eras (1-4).

The meta-analysis updated by the Early Breast Cancer Trialists' Collaborative Group in 2014 revealed an improvement in the 10-year locoregional recurrence (LRR) from 17.4% to 3.4% in patients with breast cancer and 1–3 positive ALNs receiving PMRT and adjuvant systemic therapy (cyclophosphamide, methotrexate, and fluorouracil being the most common drugs) compared with those receiving adjuvant systemic therapy alone (5). However, the majority of clinical trials included in this meta-analysis were conducted in the last 2–3 decades (treatment groups during 1964–1986 in 22 trials of radiotherapy). The ineffective systemic therapy and inadequate axillary lymph node dissections (ALNDs) among these patients might make it difficult to interpret the definite role of PMRT in the era of modern systemic therapy.

A number of studies have reported that the use of modern adjuvant systemic therapy, such as anthracyclines, taxanes, and trastuzumab (for human epidermal growth factor receptor 2-positive breast cancer), reduces LRR rates (11.7% reduction in recurrence in 10 years) and thus improves survival (7.9% reduction in breast cancer–related mortality in 20 years) of patients with breast cancer and 1–3 positive ALNs (6,7). Several retrospective studies have reported relatively low 10-year LRR rates of 6–10% in postmastectomy patients with 1–3 positive ALNs, receiving modern adjuvant systemic therapy without PMRT (8-12). In a retrospective analyses of 1,027 patients with T1–T2 breast cancer and 1–3 positive ALNs from the MD Anderson Cancer Center, McBride *et al.* reported that the use of PMRT was associated with lower 15-year LRR rates (PMRT *vs.* non-PMRT; 3.4% *vs.* 9.5%) in populations in 1978–1997, whereas the PMRT did not reduce the 5-year LRR rates when compared with non-PMRT (2.8% *vs.* 4.2%) in populations in 2000–2007 (11). The possible reason is that in 2000–2007, most postmastectomy patients without PMRT benefited from modern adjuvant systemic therapy and thus had lower LRR rates. Similar results were reported in two large cohort series analyzing mastectomy patients with T1–T2 tumor and 1–3 positive ALNs; the result of Tendulkar *et al.* (10) revealed that the 5-year LRR was 8.9% for patients who did not receive PMRT [79% patients receiving chemotherapy (70% contained taxanes)], while the result of Moo *et al.* from the Memorial Sloan Kettering Cancer Center (13) revealed that 39 (4.4%) of 884 patients

developed LRR [among them, 141 (16%) patients received PMRT]. Given the progress and development of modern adjuvant systemic therapies as well as the improvements in surgical techniques for ALND, the LRR reductions after PMRT may be too small to justify this treatment.

The Breast International Group 02-98 trial was a randomized trial that compared the effect of incorporating docetaxel into anthracycline-based adjuvant chemotherapy {sequential [doxorubicin (A) 75 mg/m^2 ×3 → docetaxel (T) 100 mg/m^2 ×3 → CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) ×3] *vs.* concurrent [AT (50/75 mg/m^2) ×4 → CMF ×3]} with anthracycline-based adjuvant chemotherapy {sequential control (A 75 mg/m^2 ×4 → CMF ×3) and concurrent control [AC (60/600 mg/m^2 ×4 → CMF ×3]} in the disease-free survival (DFS) of patients with T1–T3 tumor and at least one positive ALN breast cancer (included breast conserving surgery and mastectomy), and demonstrated that treatment with sequential docetaxel resulted in significantly better DFS and overall survival (OS) than concurrent doxorubicin-docetaxel and doxorubicin-based control (14,15).

Recently, the results of a secondary analysis of the Breast International Group 02-98 trial reported by Zeidan *et al.* specifically focused on the LRR of breast cancer patients who underwent mastectomy and had T1–T2 and N1 disease with and without PMRT (16). In this subgroup analysis, the 10-year LRR rates of patients with PMRT and those without PMRT were 2.5% and 6.5%, respectively (P=0.05) (16). This result is mainly contributed from that women in the PMRT group who randomized to anthracycline treatment without docetaxel had a lower 10-year LRR rate than those in the non-PMRT group (3.4% *vs.* 9.1%, P=0.02) (16). However, the 10-year LRR rates of patients randomizing to receive adjuvant docetaxel-containing regimen were not significantly different from those with and without PMRT (2.0% *vs.* 5.3%, P=0.08) (16). Furthermore, the addition of PMRT did not have a significant impact on the OS or breast cancer-specific survival (16). This result is in line with those reported in the abovementioned series, highlighting that the lack of PMRT can significantly decrease the LRR in women with T1–T2 and N1 breast cancer receiving anthracycline and taxane-based chemotherapy (8-13).

Whether PMRT decreases the LRR in patients with T1–T2 and N1 breast cancer, consisting of the heterogeneous biological components and disease status, remains unclear and debatable. Hence, the latest published St. Gallen consensus statement recommended that PMRT can be omitted in subgroups of patients with favorable biological profiles (17). Several retrospective studies have tried to identify the possible risk factors associated with a high risk of LRR for postmastectomy patients with T1–T2 and N1 breast cancer without PMRT; however, the results were inconsistent (8-12). In our retrospective analyses of postmastectomy patients with T1–T2 and N1 breast cancer (most patients received anthracycline- or taxane-based regimen or both) but without PMRT, we identified that young age (≤40 years), tumor larger than 3 cm, and presence of extensive intraductal components were significant risk factors for LRR determined multivariate analyses (18). We further revealed that patients with triple-negative breast cancer (TNBC) had a higher 5-year LRR rate (10.6%) than those without this disease (4.2%) (P=0.05) (18). In a prospective randomized trial of postmastectomy patients with stages I–II and TNBC, Wang *et al.* demonstrated that patients receiving adjuvant chemotherapy plus PMRT had a better 5-year OS than those who received chemotherapy alone (90.4% *vs.* 78.7%, P=0.03) (19). Chen *et al.* also reported that PMRT was closely associated with a longer DFS but not with LRR-free interval in patients with T1–T2N1 and TNBC (20). These results suggest that adjuvant chemotherapy cannot be used to overcome the inferior local control in TNBC patients after mastectomy without adjuvant radiotherapy. However, another study showed that the outcomes of patients with TNBC are associated with a higher isolated LRR rate [adjusted hazard ratio (HR): 14.10, 95% confidence interval (CI): 2.97–66.90%] despite the use of PMRT (21). Therefore, further prospective studies are warranted to assess whether TNBC patients with T1-2N1M0 disease can benefit from PMRT in terms of locoregional control and survival gain.

It is notable that as shown the BIG 02-98 trial (16), among patients who did not receive PMRT, the number of failures in the chest wall [n=10 (2.9%)] and regional nodes [n=8 (2.3%)] were not different. However, in the BIG 02-98 trial, the supraclavicular recurrence was defined as distant recurrence, whereas the supraclavicular recurrence is currently considered as regional recurrence. Our previous finding showed that recurrences occurred in the chest wall (26.3%) and in regional nodes (including the supraclavicular, axillary, and internal mammary nodes; 57.9%) in the patient group who did not receive PMRT (18). Indeed, the commonly used modern PMRT techniques including irradiation of chest wall and regional lymphatics (supraclavicular with and without internal mammary node chains) can lessen cardiac exposure to irradiation (3,22).

The EORTC (European Organization for Research and Treatment of Cancer) 22922 trial demonstrated that the regional nodal irradiation (internal mammary and medial supraclavicular lymph node irradiation) group significantly improved the DFS (P=0.02) and OS (P=0.06) compared with that of the non-regional nodal irradiation group (23). However, the EORTC 22922 trial enrolled a large number of breast-conserving patients (76.1%), and 12.5% of them had more than four positive ALNs (23). In a subgroup analysis of the EORTC 22922 trial, the regional nodal irradiation did not contribute to the significant improvement in OS (HR 0.91, 95% CI. 0.72 to 1.15) in postmastectomy patients (23). Whether irradiation of comprehensive regional nodal lymphatics would improve DFS in this group of patients with PMRT remains unclear.

Of note, current evidences regarding the issue on omitting PMRT in patients with T1–T2 and N1 breast cancer were derived from studies or trials on ALND. However, for patients who underwent simple mastectomy and with 1–3 positive sentinel lymph nodes, performing further ALNDs or regional irradiation remains a challenge for physicians in clinical practice. The AMAROS trial randomized T1–T2 breast cancer patients with positive sentinel nodes (99% had 1–3 positive nodes) following ALND or axillary irradiation (included supraclavicular lymphatics) (24). The 5-year axillary recurrence rates were similar in both arms, that is, 0.43% in the ALND group and 1.19% in the axillary irradiation group. By contrast, the 5-year lymphedema rates for ALND and axillary irradiation group were 23% and 11%, respectively. Notably, in the population of the AMAROS trial, only 18% of the patients underwent mastectomy. In view of the lack of category 1 evidence and the current recommendation from the consensus and guidelines regarding the use of PMRT (17,25), the omission of PMRT is not applicable to postmastectomy patients who only had 1–3 positive sentinel nodes without completion of ALND.

Overall, postmastectomy patients with T1–T2 and N1 disease receiving modern adjuvant systemic treatment without PMRT have a low LRR rate. In patients with high-risk factors, such as young age, presence of extracapsular extension, or lymphovascular invasion and triple-negative subtype, the decision to administer PMRT should be discussed with the patients to inform them about the possibility of gaining locoregional control and the risk for developing cosmetic, cardiac, and pulmonary toxicities. Two ongoing randomized studies could provide evidences that may clarify theses controversies and thus help clinicians decide whether to deliver PMRT in this patient cohort or not. The TAILOR (biomarker low-risk node-positive breast cancer) RT trial explored the role of regional node irradiation for patients whose age ≥40 years after breast conservation surgery (BCS) or mastectomy (Clinicaltrials.gov identifier: NCT03488693). The main inclusion criteria of TAILOR RT trial included 1–3 positive ALNs after BCS or mastectomy and axillary dissection or only 1–2 positive ALNs after BCS and sentinel lymph node biopsy. The eligible patients must have positive estrogen receptor (>1%) and negative human epidermal growth factor receptor 2 (HER2) tumors, and the Oncotype DX recurrence scores less than 18. The primary end point of TAILOR RT trial is to compare the breast cancer recurrence-free interval between patients who received regional RT and those without RT. The SUPREMO (selective use of postoperative radiotherapy after mastectomy) trial is a phase III randomized trial assessing whether PMRT can decrease the LRR in patients with intermediate risk breast cancer (Clinicaltrials.gov identifier: NCT00966888) (26). The intermediate risk of breast cancer included T1–T2 and N1 tumor, T2 and ALN-negative tumors that were grade 3 and/or lymphovascular invasion, or T3N0 tumors, independent of pathological features. Currently, with the paucity of the results of available randomized trials of such patients, the use of individualized and multi-disciplinary approach to deliver PMRT in women with T1–T2 and N1M0 breast cancer should be considered.

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Footnote

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