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Locoregional treatments of metastatic internal mammary node following neoadjuvant chemotherapy

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To the Editor: Neoadjuvant chemotherapy (NAC) significantly improves the prognosis for patients with breast cancer with internal mammary lymph node (IMN) involvement,[1] but the locoregional treatment of IMNs including IMN dissection (IMND) and IMN boost irradiation (IMNB) has long been debated,[2] owing to the difficulty in surgical approaches and cardiopulmonary side effects caused by high-dose radiation.[3] To date, the surgical dissection of IMNs is rarely performed; thus, the data regarding survival outcome of IMND is quite limited. In terms of radiotherapy (RT), there is marked discrepancy in radiation dose to IMNs in patients with metastatic IMN following NAC.[4] In this study, we report our institutional experience in the locoregional treatment of metastatic IMN and its impact on prognosis in patients who have undergone NAC.

We retrospectively reviewed the medical records of patients with primary breast cancer who presented with clinically metastatic IMN between January 2014 and December 2020 at Sun Yat-sen University Cancer Center. This study was approved by Institutional Research Ethics Committee of Sun Yat-sen University Cancer Center (No. SL-B2023-612-01), and the requirement for obtaining informed consent was waived. The inclusion criteria were curative surgery and completion of planned NAC and adjuvant RT. The IMN size was determined by measuring the longest diameter of the short axis on cross-sectional imaging. Patients were excluded if they had supraclavicular lymph node metastasis, bilateral breast cancer, distant metastasis, excisional biopsy before NAC, or a history of malignant neoplasms. Patients with missing follow-up data were also excluded.

Data related to patient characteristics (e.g., TNM stage, hormone receptors status, human epidermal growth factor receptor 2 [HER2] status, Ki67, and lymphovascular invasion [LVI]) and therapeutic information were retrieved. The effectiveness of NAC was evaluated by pathological response and Miller–Payne (MP) grading. The pathologic complete response (pCR) was defined as no invasive residual tumor in the breast or lymph nodes (ypT0 or ypTis and ypN0).

NAC consisted of six to eight courses of intravenously administered combined anthracycline-taxane-based therapy, and patients with positive HER2 status all received trastuzumab-based targeted therapy. Curative surgery consisted of the modified radical mastectomy and breast-conserving surgery with clear margins; the axillary lymph node dissection was performed in all patients; IMND was performed based on the surgeon's preference; and most of the procedure was assisted by a thoracoscopy. Adjuvant RT was delivered to the breast/chest wall, infraclavicular, supraclavicular, and internal mammary nodes using three-dimensional conformal radiation (3D-CRT) or intensity modulated radiation (IMRT). A supplemental boost irradiation to the internal mammary nodal chain was delivered in the upper three intercostal spaces at the discretion of the radiation oncologists. Based on the locoregional treatment of IMN, patients were categorized into four groups as follows: IMND–/IMNB–, IMND+/IMNB–, IMND–/IMNB+, and IMND+/IMNB+.

Acute and late adverse events related to RT were recorded according to the toxic effect criteria of the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC). The primary endpoint was overall survival (OS), which was defined as the interval between the date of diagnosis and date of last follow-up (May 2023) or death. Secondary endpoints were disease-free survival (DFS), distant metastasis-free survival (DMFS), and locoregional recurrence-free survival (LRRFS).

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The categorical variables were compared using the chi-squared test, and the Welch's ANOVA was used for continuous variables. The hazard ratio (HR) and 95% confidence interval (CI) were calculated using the Cox proportional hazards regression model. The inverse probability of treatment weighting (IPTW) and propensity score matching (PSM) were used to create well-balanced groups. Subgroup analyses were performed for OS in the IPTW cohort. A 2-sided *P* value <0.05 was considered statistically significant. Analyses were performed using SPSS Statistics, version 26 (IBM Corporation, Armonk, NY, USA) and R-4.2.2 software (The R Foundation for Statistical Computing, Vienna, Austria).

A total of 146 patients were included in this study; 36 (36/146, 24.7%) underwent IMND. The median radiation dose to the breast/chest wall and regional nodes was 50 (range, 45–66) Gy. Of these, 79 (54.1%) patients received IMNB with a median dose of 10 (range, 10–16) Gy. The clinicopathological characteristics of patients in the four treatment arms are summarized in Supplementary Table 1, http://links.lww.com/CM9/C246.

With a median follow-up of 47.5 months, 30 (30/146, 20.5%) patients died and 53 (53/146, 36.3%) patients developed disease recurrence, including 49 (49/146, 33.6%) cases of distant metastasis and 32 (32/146, 21.9%) of locoregional relapse. The 5-year OS, DFS, LRRFS, and DMFS rates were 75.6%, 61.0%, 75.5%, and 65.4%, respectively. Multivariable analysis of survival outcomes is shown in Supplementary Table 2, http://links.lww.com/CM9/C246. Regarding the impact of locoregional treatment, the OS (HR: 0.35, $P = 0.033$), DFS (HR: 0.48, $P = 0.040$), and LRRFS (HR: 0.35, $P = 0.043$) were improved in the IMND–/IMNB+ group, compared with those in the IMND–/IMNB– group [Figure 1]. However, the patients treated with both IMNB and IMND did not exhibit better OS (HR: 0.89, $P = 0.866$) or DFS (HR: 1.59, $P = 0.390$).

Patients were further divided into IMNB ($n = 79$) and non-IMNB ($n = 67$) groups. At the time of analysis, 19 (19/67, 28.4%) patients in the non-IMNB group and 11 patients (11/67, 13.9%) in the IMNB group had died. No Grade 3 or higher radiotoxicity was observed in either group. There were seven patients presented with radiation pneumonitis within 6 months after treatment, but the difference was not statistically significant between the groups treated with IMNB or without IMNB. Only one patient in the non-IMNB group had cardiac disorder presented as systolic dysfunction, whose symptoms disappeared after medication. No significant differences in the other toxic effect rates were observed between the two groups.

Compared with the non-IMNB group, the IMNB group showed a 15.6% improvement in the 5-year OS rates, but this improvement was not statistically significant (67.4% *vs*. 83.0%; HR: 0.39, $P = 0.052$). There was no significant difference in DFS, DMFS or LRRFS between the two groups [Supplementary Table 3, http://links.lww.com/CM9/C246]. For the PSM analysis, 104 patients were matched 1:1 into the IMNB and non-IMNB groups. The patient characteristics between the two groups were not statistically different [Supplementary Figure 1 and Supplementary Table 4, http://links.lww.com/CM9/C246]. The survival outcomes of patients were not improved by IMNB in the PSM cohort [Supplementary Table 3, http://links.lww.com/CM9/C246]. After the IPTW adjustment, all available covariates were well balanced between the two groups (all $P > 0.05$), and the standardized mean differences (SMDs) were all less than 10% [Supplementary Figure 1 and Supplementary Table 4, http://links.lww.com/CM9/C246]. In the IPTW cohort, the patients in the IMNB-treated group had better OS (5-year OS 80.1% *vs*. 68.3%; HR: 0.54, $P = 0.040$), DFS (HR: 0.63, $P = 0.033$) and LRRFS (HR: 0.51, $P = 0.020$) than those in the non-IMNB group. Distant recurrences were similar between

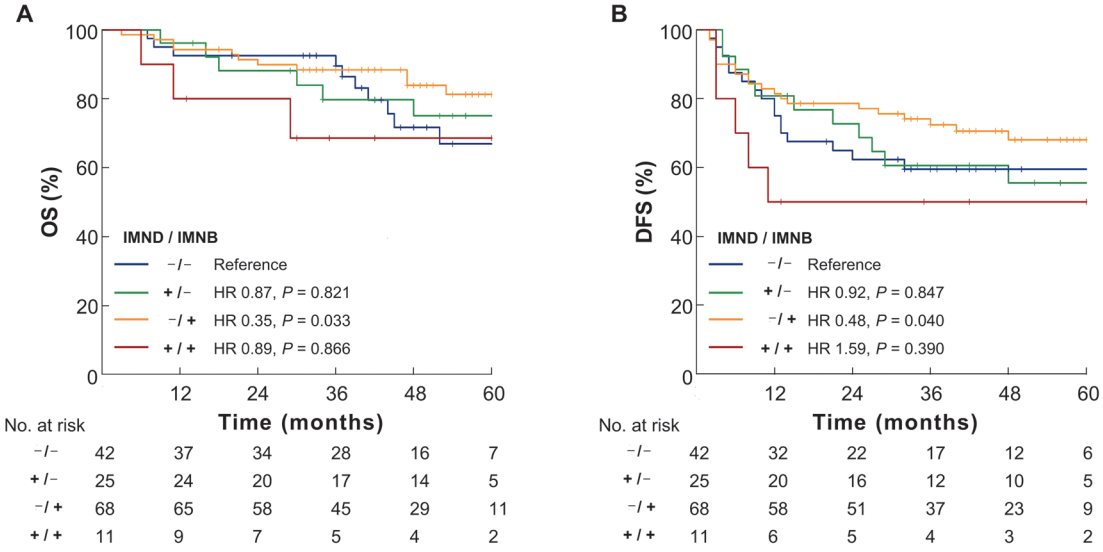

Figure 1: Survival curves of patients receiving different locoregional treatments of IMN. The OS (A) and DFS (B) were improved in the IMND–/IMNB+ group, compared with those in the IMND–/IMNB– group. However, the patients treated with both IMNB and IMND did not exhibit better OS or DFS. DFS: Disease-free survival; HR: Hazard ratio; IMN: Internal mammary lymph node; IMNB: Boost of irradiation to IMN; IMND: IMN dissection; OS: Overall survival.

the two groups (HR: 0.78, $P = 0.275$) [Supplementary Table 3, http://links.lww.com/CM9/C246].

Subgroup analyses of the IPTW cohort showed that the impact of IMNB on OS varied according to T stage, response to NAC, and receipt of IMND. The benefit was observed in patients with larger tumors (cT3-4) (HR: 0.38, $P = 0.007$) and non-pCR status (HR: 0.55, $P = 0.033$). Furthermore, patients in the non-IMND group also tended to benefit from IMNB (HR: 0.38, $P = 0.004$). Interestingly, the impact of IMNB on OS was not affected by the molecular subtype [Supplementary Figure 2, http://links.lww.com/CM9/C246].

With modern imaging modalities, IMN metastasis is more frequently observed. Even after NAC, there were still 13% of patients presenting with residual IMN,[5] suggesting that IMN should not be neglected or undertreated. Several clinical trials showed that RT of internal mammary area for high-risk patients with breast cancer could significantly improve OS and DFS.[6,7] Although the presence of metastatic IMN is an indication for radiation therapy to the lymphatic chain,[8] the optimal RT dose to IMN after NAC has not been established due to the lack of compelling evidence.

In the study by Andring *et al*[2], 97% of patients underwent an additional IM nodal boost after NAC. They treated high-risk undissected IMNs with 60 Gy and gross residual disease with 66 Gy. As a result, they found an acceptable survival outcome with a 5-year OS of 74%. In our study, 54.1% of patients received IMNB, and the 5-year OS was 75.6%, which was similar to that reported by Andring *et al*[2]. Furthermore, our survival analyses in the unadjusted cohort showed that the OS and LRRFS were improved in the IMND–/IMNB+ group, compared with the IMND–/IMNB– group. After the IPTW adjustment, IMNB not only reduced the risk of local relapse but also improved the 5-year OS, suggesting that a boost radiation to IMN (median dose 10 Gy) may provide better outcomes.

The ongoing NSABP B-51/RTOG 1304 trial questioned the necessity of adjuvant RT to the regional lymph nodes in patients with clinically positive but pathologically negative axillary lymph nodes after NAC. In this context, the question arises whether we should stratify RT to IMN according to the response to NAC. Our subgroup analyses showed that the impact of IMNB on OS varied according to the response of NAC. Patients who did not achieve pCR tended to benefit from the IMNB.

This study has several limitations. First, it was a retrospective study performed at a single institution, allowing for potential selection bias. Second, although the prognostic impact of IMNB was further assessed in the PSM and IPTW cohorts, there were some confounding factors that could not be balanced, including the missing data on the salvage treatment after recurrence. Therefore, the findings of subgroup analysis performed in the IPTW cohort should be interpreted with caution. To better investigate the survival benefit of IMNB, a randomized controlled trial is needed, and it is imperative to ensure the utmost homogeneity in surgery, neoadjuvant, and adjuvant therapy.

In conclusion, this study provides important information on outcomes and prognostic factors for patients with clinically metastatic IMN after multimodality treatments, especially with regard to the locoregional management of IMN after NAC. Future studies should focus on identifying patients who would most benefit from IMN boost irradiation as well as on optimizing the boost irradiation dose.

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Conflicts of interest

None.

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