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EDITORIAL

Axillary surgery de-escalation for breast cancer in the era of precision medicine

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In the era of precision medicine, the breast cancer surgical treatment field is gradually moving toward a de-escalation model. Through precise preoperative assessments and multidisciplinary decision-making, surgical trauma can be decreased, and patients' quality of life can be improved by ensuring safety. Herein, we explore the axillary de-escalation surgery model for breast cancer.

Axillary region surgical de-escalation in patients with cN0 breast cancer undergoing initial surgery

Sentinel lymph node biopsy (SLNB), a minimally invasive axillary lymph node (ALN) staging technique, has become standard for evaluating ALN metastasis status in patients undergoing initial surgery. These patients have negative axillary examination findings or have lymph nodes that are suspected to be clinically positive but test pathologically negative after fine-needle aspiration. With the development of medical imaging technology and increased patient demand for a better quality of life, potential avoidance of axillary surgery for these patients has become a major research topic. Two recent studies, SOUND and INSEMA, have reported the non-inferiority of omission SLNB in patients with cN0 breast cancer. Whereas approximately 9% and 11% of patients with SLNB in the SOUND and INSEMA studies, respectively, developed 1–3 ALN macrometastases, only 0.4% and 1.0% of patients who did not undergo axillary surgery, respectively, developed axillary recurrence[1,2]. These observations suggested manageable tumor safety profiles with omission of axillary surgery in rigorously screened cN0 patients.

For low-risk hormone receptor-positive/HER-2 negative (HR+/HER2−) patients, omission of minimally invasive axillary surgical staging may affect breast radiotherapy planning. The NCCN guidelines recommend regional lymph node radiotherapy for patients with one to three ALN metastases[3], but this approach led to the under-treatment of approximately 13.7–15.1% of patients who did not undergo SLNB in the SOUND and INSEMA studies. In addition, patients with stage T1 tumors are typical candidates for accelerated partial-breast irradiation (APBI); however, current guidelines specify negative lymph node pathology in patients undergoing APBI. Data from the prospective LUMINA and IDEA studies have suggested that whole-breast radiotherapy can be avoided after breast-conserving surgery (BCS) in HR+/HER2− breast cancer cases in biologically low-risk postmenopausal patients[4,5]. According to the ASTRO and ESTRO guidelines, whole-breast radiotherapy may be omitted after BCS in patients > 70 years old, in patients in stage T1, and in the HR+/HER2− population. However, lymph node status in negative histology was also required in patients in both the LUMINA and IDEA studies, and is specified by the ASTRO guidelines. Therefore, in older patients with HR+/HER2− biologically low-risk breast cancer, adverse effects due to whole-breast radiotherapy and minimally invasive axillary staging must be adequately weighed to determine which treatments patients prefer to reduce and the downstaging site (local and/or regional) that should be prioritized. With ongoing progress in imaging

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technology and artificial intelligence, clinicians can combine the enrollment criteria from the INSEMA and SOUND studies to screen for patients with HR+/HER2− biologically low-risk postmenopausal breast cancer who have histologically negative lymph nodes—the target population for dual de-escalation of whole-breast radiotherapy and axillary surgery after BCS. Therefore, we conducted a multicenter retrospective study in which the lymph node metastasis percentage was 18.9% (70/370) among postmenopausal patients with initial cT1N0 and HR+/HER2− cancers. The enrollment limitations, based on the INSEMA study and the ASTRO guidelines' pathological characteristics, comprised patient age > 70 years, cT1N0 stage, estrogen receptor positivity/progesterone receptor positivity (ER+/PR+), Ki-67 ≤ 20%, and lymph node metastasis in the G1/2 stage population of 11.6% (17/146). This patient subset might achieve a dual de-escalation benefit with omission of whole breast radiotherapy and axillary surgery after BCS. Therefore, precisely predicting the ALN-negative population in the INSEMA study might facilitate axillary surgery de-escalation and the avoidance of whole-breast radiotherapy. We also expect that relevant studies will be able to identify the low-risk population from the SOUND and INSEMA trials, construct models to accurately predict the ALN-negative population, perform a dual de-escalation study on omitting whole-breast radiotherapy and axillary surgical staging, and conduct a prospective randomized controlled trial to validate survival benefits.

Axillary surgery de-escalation after neoadjuvant therapy (NAT) for breast cancer

As NAT efficacy for various molecular breast cancer subtypes is increasingly optimized, the rates of pathological complete remission (pCR) after NAT continue to increase, thereby creating opportunities for downstaging axillary surgery. Several key guidelines, including the NCCN, ASCO, CSCO, and CBCS guidelines for SLNB for breast cancer, recommend that for patients with cN0 stage cancer and patients with clinically abnormal positive lymph nodes, but pathological negativity after fine-needle aspiration or coarse-needle biopsy (cNa/FNA−), if NAT is performed, they should be axillary staged by SLNB after NAT[3,6,7]. Patients with cN0 disease do not require ALN dissection and regional radiotherapy if they have sentinel lymph node negativity after NAT. For patients with macrometastasis, micrometastasis, or isolated tumor cells in a single sentinel lymph node after NAT, axillary radiotherapy is recommended as an alternative to ALN dissection, as reported in the 2021 St. Gallen Consensus, CSCO, and CBCS Guidelines[6,8,9]. Barron et al.[10] on the basis of a retrospective review of 2010–2015 National Cancer Database data, have reported that for patients with HER2+ and triple-negative (TN) breast cancers with tumor diameters ≤ 5 cm and ALN negativity (cT1-2N0), who achieved breast pathological complete remission (bpCR) after completing established neoadjuvant treatment regimens, the risk of ALN positivity (ypN+) is < 2%, thus supporting the rationale for avoiding axillary surgery in this subgroup. The ongoing ASICS study is exploring the feasibility of omitting SLNB in patients with initial axillary-negative HER2+/TN breast cancer who achieve pCR after NAT. We look forward to the publication of their data.

We also conducted a retrospective study reviewing clinicopathological data from patients with HER2+/TN early invasive breast cancer who were initially and clinically negative in the axilla (cT1-3N0M0), and who had completed an established neoadjuvant treatment regimen. Patients seen between January 2019 and December 2024 were included in a multicenter retrospective study. Of the 226 included patients, the percentage achieving ypN0 after postoperative pathological NAT confirmation was 96.5% (218/226). Patients with the HR-/HER2+ subtype achieved the highest ypN0 rate after NAT, at 98.3% (114 of 116). The risk of ypN+ among cN0 patients who achieved bpCR after NAT regimen completion was 2.4% (164/168).

In summary, patients with breast cancer > 70 years old, with cT1N0 stage, ER+/PR+, HER2−, Ki-67 ≤ 20%, and stage G1/2 might achieve dual de-escalation benefits, and might not require whole-breast radiotherapy and axillary surgery after BCS. In patients with cT1N0 and TNBC/HER2+ disease, axillary surgery can potentially be omitted after completion of established NAT, particularly in patients achieving bpCR after NAT. In contrast, given regional healthcare differences, clinical evaluations must consider locally available imaging technology and potential false-negative rates.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Xueying Du, Yongsheng Wang, Zhao Bi.
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