



St. Gallen 2021 Chinese expert perspective of optimal regional management

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Abstract: The 17th St. Gallen International Breast Cancer Conference (SG-BCC) was focused on the challenge and the treatment of early breast cancer and the individual therapies of different patients. The axillary lymph nodes dissection (ALND) with first level or second level had been de-escalated to a sentinel lymph node biopsy (SLNB), and studies about the necessity of axillary surgery were being conducted, which depending on the results, might result in axillary surgery no longer being used. Given the current medical context and the health insurance available in China, we agree with most of the voting results from the SG-BCC panel; however, there are some points with which we hold differing views. SLNB was recommended to patients with ipsilateral breast recurrence and pregnant women in the China Anti-Cancer Association (CACA) Guidelines for Breast Cancer since 2019, and axillary management was still required for patients with sentinel lymph node (SLN) micrometastases since 2017. SLNB is suitable for patients with imaging of 1–2 abnormal axillary lymph nodes (ALNs) in 2021 update. Further, SLNB remains the staging procedure of choice in upfront surgery patients and after neoadjuvant therapy (cN0/cN1). As high nodal pathologic complete response (pCR) in cN0 human epidermal growth factor receptor 2 positive (HER2+) and triple negative breast cancer patients achieve a breast pCR, post neoadjuvant therapy SLNB might be avoided in the future.

Keywords: Breast cancer; sentinel lymph node biopsy (SLNB); regional management; St. Gallen 2021

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The 17th St. Gallen International Breast Cancer Conference (SG-BCC) 2021 was entitled “*Primary therapy of early breast cancer, evidence, controversies, consensus*”, and focused on the challenges and the treatments of early breast cancer, and more specifically, the individual disease situations of different patients. The SG-BCC panel experts came from different countries and spoke on different subjects. These experts held different perspectives on the SG-BCC recommendations. Given the current medical context and the health insurance available in China, we agree with most of the voting results from the SG-BCC

panel; however, there are some points with which we hold differing views. This review outlines the perspectives of Chinese experts on the optimal regional management.

In the session about the challenges and opportunities that have arisen in relation to breast cancer care since SG-BCC 2019, Professor Michael Gnant of the Medical University of Vienna presented de-escalation strategies for breast cancer surgery. In relation to the breast, Gnant stated that radical mastectomy had been improved to a form of modified radical mastectomy, and mastectomy had developed into breast conservation surgery (BCS). Further,

Gnant stated that breast surgery might be not performed in the future but need more clinical evidence of breast surgery omission. In relation to the axilla, axillary lymph nodes dissection (ALND) with first level or second level had been de-escalated to sentinel lymph node biopsy (SLNB), and studies about the necessity of axillary surgery were being conducted, which might result in no axillary surgical staging.

The first BCS was performed at our breast cancer center in 1985. Subsequently, more than 4,000 patients have received this type of surgery. Our breast cancer center is the principal investigation center in China, and it led a multicenter study in which SLNB was used to treat breast cancer instead of ALND from January 2002 to June 2007. This study of 2020 cases confirmed that SLNB could replace ALND in sentinel lymph node (SLN) negative patients with low axillary recurrence. After these results were published, many breast surgeons accepted and performed SLNB in clinical practice. Today, this approach continues to benefit millions of patients every year in China. As a breast surgeon, the challenge is to provide appropriate medical care to patients with breast cancer. In doing this, consideration must be given to the benefits and injuries of any treatment. We have had opportunities to design clinical trials to validate new methods for patients in accordance with evidence-based medicine principles.

The prospective validation study of Morrow *et al.* confirmed that ALND could be avoided in a large majority of the American College of Surgeons Oncology Group (ACOSOG) Z0011-eligible patients without preoperative axillary imaging or routines using of nodal irradiation (1,2). The ACOSOG Z0011 study led us into the SLNB era. However, if SLNB is to be used the following departments are required: the department of surgery, imaging, nuclear, and pathology, the department of radiotherapy to identify the irradiation treatment, and an internal medicine department to make the medication regimens. Thus, a multidisciplinary team is required to perform SLNB. It is only in this way that SLNB can be performed effectively and accurately. SLNB can guide the management of axilla and/or systemic therapy in the era of limited nodal information.

Repeat SLNB in patients with ipsilateral breast recurrence

For patients with ipsilateral breast recurrence and in those who have negative nodes on imaging after a previous

treatment of BCS and SLN mapping (N0), the SG-BCC 2021 panelists (67%) recommended a repeat SLNB. Poodt *et al.* found that a repeat SLNB is feasible for 64% of patients and is especially appropriate for patients who have undergone a SLNB previous. With a negative predictive value of 96.5%, the repeat SLNBs appear to be highly specific, and have substantial advantages over ipsilateral ALND in patients with ipsilateral breast recurrence (3). The Invasive Breast Cancer National Comprehensive Cancer Network (NCCN) Guidelines (Version 3, 2020) updated the recommended treatment of local recurrence to an initial treatment of BCS. For patients with a local breast recurrence after BCS who have previously undergone a SLNB, the NCCN guidelines recommend a consideration of repeat SLNB although the accuracy of repeat SLNB in these patients is unproven by clinical trial. For patients with mastectomy, the guidelines do not recommend a repeat SLNB after local recurrence. Notably, repeat SLNBs in patients with ipsilateral breast recurrence has been recommended by the China Anti-Cancer Association (CACA) Guidelines for Breast Cancer since 2019.

Omission axillary surgery in prophylactic mastectomy

In accordance with the Choosing Wisely Campaign of the Society of Surgical Oncology and the NCCN guidelines, the 2021 CACA Guidelines for Breast Cancer will abandon the recommendation of SLNB in prophylactic mastectomy and the omission axillary surgery in contralateral or bilateral prophylactic mastectomy. These recommendations will be removed for the following reasons: the risk of breast cancer in the contralateral breast is very low; SLNB is an invasive method and can produce some adverse reactions; and the incidence of occult breast cancer is low due to the development of a screening technique (4). For these reasons, the risk-to-benefit ratio of SLNB in prophylactic mastectomy is larger than that of omission axillary surgery.

Axillary management is still required for patients with SLN micrometastases

Based on the results of ACOSOG Z0011 study and the International Breast Cancer Study Group (IBCSG) 23-01 trial, NCCN guideline recommend no ALND in 1–2 SLN positive patients performing BCS and whole breast irradiation (WBI) (5). WBI with tangential fields after BCS could lead to substantial axillary irradiation and control the

residual tumor burden in axilla, but (intraoperative) partial-breast irradiation has no therapeutic effect on these residual axillary metastases. In the no ALND group of the IBCSG 23-01 trial, 18.8% (80/425) of BCS patients received intraoperative partial-breast irradiation (5). The 10-year axillary recurrence rate was acceptably low (1.7%, 8/467) in the no ALND group; however, it was 4.5% (6/134) in the group that did not receive axillary management; a figure that was significantly higher than that for patients who did receive axillary management (0.6%, 2/333; $P=0.0024$). The question arises as to whether an axillary recurrence rate as high as 4.5% in patients with only SLN micrometastases should be accepted. To answer this question, consideration must be given to the effective way to control the residual tumor burden in the axilla and decrease the regional recurrence rate if there is no ALND. The results of randomized control trials showed that both WBI after BCS and axillary regional nodal irradiation after mastectomy/BCS could control the residual axillary metastases in patients with SLN positive and no ALND (1,6-8). Moreover, systemic therapy including target therapy could further decrease the risk of local/regional recurrences when the SLN is positive. After the sub-analysis of the omission axillary surgery trials (9-11), a multi-factor forecasting model might be established to identify patients who could benefit from no axillary management as a guideline in clinical practice. At present, axillary management is still required for patients with SLN micrometastases under CACA Guidelines for Breast Cancer since 2017.

SLNB is suitable for patients with imaging of 1-2 abnormal axillary lymph nodes (ALNs)

In the post-Z0011 era, the question arises as to whether SLNB is suitable for cT1-2N0 patients with imaging of 1-2 abnormal ALNs and confirmed by fine needle aspiration cytology (FNAC) or core-needle biopsy (CNB). In a retrospective analysis of such patients treated at our center, 1, 2, and more than 2 positive ALNs were found in 42.9% (42/98), 15.3% (15/98), and 41.8% (41/98) of patients, respectively, after ALND. Among these cases, 40 patients received a SLNB followed by an ALND, and the false-negative rate (FNR) of SLNB was 0% with 1-3 positive SLNs detected. Positive non-SLNs were 0, 1, 2, 3, and more than 3 in 65% (26/40), 7.5% (3/40), 2.5% (1/40), 5% (2/40), and 20% (8/40) of patients, respectively. In the European Organisation for Research and Treatment of Cancer (EORTC) 10981-22023 and the Z0011 trials,

positive non-SLNs were found in 32.8% and 27.3% of patients with clinically negative axilla, respectively (2,8). In relation to patients with imaging of 1-2 abnormal ALNs and confirmed by FNAC/CNB, our retrospective analysis indicated that SLNB was still accurate (FNR: 0%), and up to 65% of cases had no positive non-SLN. As the non-SLN positive rate and tumor burden were higher than that of the whole population in the EORTC 10981-22023 and Z0011 trials, the results show that the regional radiation of the EORTC 10981-22023 model is more suitable for regional control than that of the Z0011 model. Thus, SLNB is suitable for patients with imaging of 1-2 abnormal ALNs (as confirmed by preoperative ALN FNAC/CNB). Notably, this indication is recommended in the 2021 CACA Guidelines for Breast Cancer. However, larger cohort analyses and prospective multicenter trials are required to validate this approach. Further, a nomogram based on tumor size, pathology, and molecular subtype to predict the ALN tumor burden and guide effective axillary management is essential.

Genomic tests could be applied to patients with 1-2 positive SLNs without ALND

A majority of the SG-BCC panelists (79%) rejected the indication for chemotherapy in postmenopausal patients if their genomic risk according to the clinical criteria of the 70-gene test or the 21-gene test was low and/or their recurrence score was ≤ 25 (12-14). In the era of limited nodal information, the first results from the RxPONDER (Rx for Positive Node, Endocrine Responsive breast cancer) trial suggested that Oncotype DX could be applied to patients with 1-2 positive SLNs without ALND, which constituted 37.4% of the intent-to-treat population. However, no specific research has been conducted on how to apply genomic tests precisely to hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) patients with 1-2 positive SLNs without ALND. To construct a nomogram using the multicenter retrospective data to predict precisely which HR+/HER2- patients with 1-2 positive SLNs could be subjected to genomic tests (≤ 3 positive lymph nodes), a retrospective analysis was undertaken of 18,600 stage I-III breast cancer patients treated with SLNB at Shandong Cancer Hospital, Fudan University Shanghai Cancer Center and West China Hospital. Our nomogram was based on a multicentric database, showed good accuracy, and could assist oncologists to determine precisely which

HR+/HER2- breast cancer patients with 1–2 positive SLNs without ALND could undergo genomic tests. Notably, the value of the area under the curve was 0.804 [95% confidence interval (CI): 0.681–0.812; $P < 0.001$]. Thus, improvements and the expansion of the role of genomic assays in selecting patients for systemic therapy will obviate the need for axillary surgery and inform most systemic treatment decisions.

SLNB after neoadjuvant therapy in patients with cN0 and cN1 transforming to ycN0

The concept of neoadjuvant therapy is accepted as a standard approach in China as soon as adjuvant therapy is indicated under the same treatment regimens. It could improve the rate of BCS and offer an opportunity to evaluate the efficacy of chemotherapy and/or target therapy on primary tumors *in vivo*. It is also an ideal platform to detect differences in the shrinkage mode of the primary tumor in patients with different molecular subtypes. The neoadjuvant therapy platform was used to evaluate the optimal timing of SLNB in axilla and/or internal mammary after neoadjuvant therapy at our breast cancer center. The majority of the SG-BCC panelists agreed that SLNB for axillary staging after neoadjuvant therapy in patients with clinical negative ALNs (cN0) and with cN1 convert to ycN0. Although it is different in the identification rate, accurate rate, and operation times of SLNB before and after neoadjuvant therapy, SLNB after neoadjuvant therapy could provide more information of residual nodal disease and guide the identification of adjuvant treatment especially for patients with HER2+ and triple negative subtypes. If SLNs are identified positive after neoadjuvant chemotherapy and dual target therapy in patients with HER2+ subtype, the adjuvant treatment should choose T-MD1 therapy. In the triple negative subtype, patients with SLN positive after neoadjuvant chemotherapy should receive adjuvant chemotherapy or target therapy to improve survival. Due to the high rates of nodal pathologic complete response (pCR) in HER2+ and triple negative subtypes, SLNB after neoadjuvant therapy have more chance to replace ALND in patient with SLN negative. Our results showed that the nodal pCR after neoadjuvant therapy was 83.8% in patients with cN0 and the FNR of SLNB was 0 when more than 1 SLN were found and the clipped nodes were removed (15). Based on the identification rate and accuracy rate of SLNB before and after neoadjuvant therapy, SLNB after neoadjuvant therapy has been recommended in patients

with cN0 since the 2017 CACA Guidelines for Breast Cancer. The 2021 CACA Guidelines for Breast Cancer updates that the adaptation of SLNB including patients with cN1 transforming to ycN0.

Local-regional management of residual ALN disease after neoadjuvant therapy

As part of the local-regional management of residual ALN disease after neoadjuvant therapy, the majority of the SG-BCC panelists agreed that axillary radiation therapy should replace ALND, specifically, 1 of 3 SLNs macrometastases (52%), 1 of 3 SLNs micrometastases (72%), 1 of 3 SLNs identified isolated tumor cells (88%). Furthermore, the majority of the SG-BCC panelists (73%) agreed that ALND was always indicated following neoadjuvant therapy when the residual disease was identified in SLN. The Alliance A11202 study is evaluating the role of axillary radiotherapy and ALND in patients with cN1 but finding SLN residual disease. After the results of the Alliance A11202 study publication, the voting results of SG-BCC panelists will be consistent and CACA Guidelines for Breast Cancer will be updated.

Targeted axillary dissection in patients with neoadjuvant therapy

In patients who have cytologically or histologically proven cN1 at presentation, who have a good clinical response, and who will receive radiation therapy, including of the axilla, the majority of the SG-BCC panelists (85%) agreed that ALND may be avoided if a clipped node is present. In relation to targeted axillary dissection, 60% of the SG-BCC panelists agreed that targeted axillary dissection is an appropriate option for standard ALND, and 90% of the SG-BCC panelists agreed that targeted axillary dissection is an option in cN1 patients with clipped or marked initially involved node(s) who converted to cN0 before surgery. The question arises as to whether it is necessary to find more than 3 SLNs after neoadjuvant therapy with targeted axillary dissection. We hope that the SG-BCC panelists will vote on this issue in 2023.

In conclusion, SLNB remains the staging procedure of choice in upfront surgery patients after neoadjuvant therapy (cN0/cN1). Ongoing trials examining the omission of SLNB in cT1-2N0 patients with negative axillary imaging are likely to lead to less axillary surgery in the future. As high nodal pCR in cN0 HER2+ and triple negative breast

cancer patients achieve a breast pCR, post neoadjuvant therapy SLNB might be avoided in the future.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/tbcr-21-16>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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