The time of sentinel lymph node biopsy and neoadjuvant chemotherapy in clinical negative axilla breast cancer: before or after?

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Neoadjuvant chemotherapy (NAC) refers to systemic cytotoxic drug therapy for nondistant metastatic tumors before surgery, which is also known as preoperative chemotherapy or induction chemotherapy [1]. Pathologic complete response (pCR) is an independent prognostic factor, and several studies indicated that pCR was associated with molecular subtype [2–5]. In a woman who presented with a clinically node-negative (cN₀) disease and received NAC, sentinel lymph node biopsy (SLNB) is thought to be appropriate [6,7]. Before the start of AMAROS and ACSOG Z0011 trials, SLNB should be performed after NAC. But since the results of AMAROS and ACSOG Z0011 trials appeared, axillary lymph node dissection (ALND) could be avoided for patients with ≤ 2 positive sentinel lymph nodes (SLNs) if they would receive axilla radiotherapy [8,9]. So, the optimal time of SLNB and NAC in patients with cN₀ disease remains uncertain. For cN₀ patients, 2017.V1/V2 NCCN breast cancer clinical practice guidelines recommend that it is feasible to perform SLNB before or after NAC, while 2018.V1/V2 NCCN guidelines have changed that SLNB preferably be performed after NAC [10,11]. In 2017, St Gallen Expert Consensus and conference, 95.7% of experts recommended SLNB for cN₀ patients undergoing NAC. But the opinions were not consistent for the optimal time to perform SLNB and NAC. Sixty percent of experts supported SLNB should be performed after NAC, while 20% of experts believed that it was suitable for SLNB before NAC. The remaining experts supported that it is appropriate to perform SLNB before or after NAC [12,13].

The accurate assessment of the primary axillary tumor burden is the biggest advantage of the SLNB prior to NAC. It could accurately assess the primary tumor burden and help to guide the NAC regimen. At the same time, it is a gut feeling that performing an SLNB before the start of NAC for cN₀ patients will reduce the morbidity more compared with an SLNB after NAC [14,15]. The 2019.V1 NCCN guide suggested that ALND will be a standard treatment for patients with any positive SLNs when they receive SLNB after NAC, including micro-metastasis and isolated tumor cells [13]. According to the results of the AMAROS and ACSOG Z0011 test, if axillary radiotherapy is accepted, ALND can be avoided for patients with less than two positive SLNs. The NSABP B-32 study and AMAROS trial found that about 30% of cN₀ patients undergoing SLNB before NAC were SLNs positive [8,16]. ACOSOG Z0011 trial showed that among patients with cT1–2N0 breast cancer undergoing upfront BCS and planned whole breast radiation therapy, ALND was warranted for three or more positive SLNs. According to the ASCOG Z0011 trial and the AMAROS trial, about 80% of cN₀ patients (SLNs positive) were those of one to two SLNs positive who were eligible for receiving whole breast radiotherapy or axillary radiotherapy after mastectomy to avoid ALND, which made about 94% (30% multiplied by 80% plus 70% was 94%) of patients avoid ALND.

Based on the application of ACOSOG Z0011 trial criteria, Pilewskie [17] made a retrospective study and result showed that receipt of NAC compared with upfront BCS remained significantly associated with higher odds

of ALND in the hormone receptor positive/HER-2 negative (HR+/HER2-) subtype (hazard ratio [HR]: 3.35; $p < 0.001$), whereas NAC versus upfront mastectomy remained significantly associated with lower odds of ALND in the HER2+ and TN subtypes (HR: 0.19, $p < 0.001$; HR: 0.25, $p = 0.007$, respectively) [13]. And in our study, we thought that combined with the results of AMAROS and ASCOG Z0011 trial, the rate of avoiding ALND when performing SLNB after NAC was associated with the axillary pCR (apCR) rate after NAC. Our recent study showed that in patients with cN₀ disease, the rate of pathological lymph node positive (ypN₊) after NAC was 19.4% (13/67), and it was 28.1, 13.3 and 10.0%, respectively, among HR+/HER2-, HER2+ and TN patients [13]. The rates of ypN₀ after NAC in patients with HER2+ and TN were 90.0% (18/20) and 86.7% (13/15), respectively, which were significantly higher than HR+/HER2- patients (71.8%, 23/32).

Since patients with cN₀ disease were unable to assess axillary status effectively and the sample size was small, we predicted the apCR of cN₀ patients after NAC by evaluating the apCR of patients with clinical node positive (cN₊) disease [13]. Gentile *et al.* found that the rates of apCR after NAC in cN₊ patients with HER2+ (with targeted therapy) and TN were 63.0 and 41.0%, respectively, which were significantly higher than that of HR+/HER2- patients (17.0%, $p < 0.001$). At the same time, we also found apCR after NAC was significantly associated with molecular subtypes. The apCR rate was 21.2, 53.6 and 58.2%, respectively among patients with HR+/HER2-, TN and HER2+ subtypes. Based on the AMAROS and ASCOG Z0011 trial, there will be 94% of cN₀ patients who could avoid ALND (30% multiplied by 80% plus 70% was 94%) if performing SLNB before NAC [6]. For cN₀ patients with HR+/HER2- subtype, if performed SLNB after NAC, there will be 76.4% of patients could avoid ALND (30% multiplied by 21.2% plus 70% was 76.4%). On the contrary, the apCR was high in TN and HER2+ patients with cN₀ disease after NAC; using the same method, those patients might have more chance (30% multiplied by 53.6% plus 70% was 86.1%, and 30% multiplied by 58.2% plus 70% was 87.5%, respectively) to avoid ALND compared with HR+/HER2- patients.

Although TN (94 vs 86.1%) and HER2+ (94 vs 87.5%) patients performing SLNB prior to NAC had more chance to avoid ALND compared with SLNB after NAC, NAC had another advantage that it could offer an opportunity to evaluate the efficacy of chemotherapy on primary tumor *in vivo*. Furthermore, the residual tumor burden after NAC could assess prognosis of patients and guide future treatment, and it was a more meaningful predictor of local/regional recurrence than before NAC. Although there were 7–8% of TN and HER2+ patients could benefit from avoiding ALND when performed SLNB prior to NAC, the total pCR after NAC could have more pronounced effect on prognosis among these patients. The total pCR in TN and HER2+ patients after NAC could also be used as a surrogate marker for long-term survival to better assess prognosis, whereas the total pCR in HR+/HER2- patients have little thing to do with long-term survival benefit.

At the same time, our result showed that ypN₀ after NAC was significantly correlated with molecular subtypes of the breast tumor in initial cN₀ patients ($p < 0.001$). The rate of ypN₀ after NAC in cN₀ patients was 80.6%, especially in patients with HER2+ (90.0%) and TN (86.7%), making it possible to selectively avoid axillary surgery after NAC, which would contribute to reduce postoperative complications, improve patient quality of life and reduce medical costs.

In conclusion, the clinical nodal staging and molecular subtypes should be considered when choosing optimal time to perform SLNB following NAC. Combining the apCR in different molecular subtypes of cN₊ patients and excellent loco-regional control of AOSOG Z0011 and AMAROS trials in cN₀ patients, it would be preferable to perform SLNB prior to NAC to reduce the risk of ALND for cN₀ patients with HR+/HER2-. SLNB after NAC for cN₀ patients with HER2+ and TN could better avoid ALND. In view of the high ypN₀ rate after NAC in cN₀ patients, axillary surgical staging might be selectively eliminated, especially in patients with HER2+ and TN breast cancer.

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