

THE TRANSFORMATION OF AXILLARY SURGERY FOR BREAST CANCER

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Abstract: Breast cancer surgery treatment has a century of development from extended radical mastectomy to modified radical mastectomy and then to breast-conserving surgery. Breast cancer surgery tends to be more and more minimally invasive. Axillary surgery is an important part of breast cancer surgery. Sentinel lymph node biopsy (SLNB) is a common surgical procedure, and axillary lymph node dissection (ALND) is the most common choice for patients with positive sentinel lymph nodes. However, ALND has many sequelae for breast cancer patients, such as postoperative lymphedema, abnormal limb sensation and movement, etc. In the past decade, evidence has shown that it is feasible to avoid ALND in breast cancer with positive sentinel lymph nodes. Some scholars have studied that SLNB combined with axillary radiotherapy is equivalent to ALND. In short, axillary surgery is increasingly tending to be minimally invasive and narrow in scope. This study aims to explore the transformation and future development direction of axillary surgery for breast cancer.

Keywords: Breast cancer; Axillary surgery; SLNB; ALND

1 INTRODUCTION

At the end of the 19th century, Halsted proposed radical mastectomy, which significantly extended the survival time of patients, followed by extended radical mastectomy and modified radical resection, which continued for decades, and both performed axillary lymph node dissection. Axillary lymph node dissection can make a clear pathological stage of lymph nodes for breast cancer and guide subsequent treatment, but after axillary lymph node dissection, patients may have complications such as lymphatic return disorders, paresthesias, and mobility disorders of the affected limb. At the end of the twentieth century, sentinel lymph node biopsy was introduced into breast cancer surgery, followed by a series of clinical trials showing that sentinel lymph node negative patients[1]. The overall survival rate and disease-free survival rate were similar in the Sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) groups. Now, in challenging the traditional notion of tumor-free, the Z0011 trial has shown that sentinel node-positive patients are safe and feasible to be exempt from ALND under certain conditions[2]; There have also been studies on the applicability of sentinel lymph node biopsy after neoadjuvant chemotherapy. The current management of axillary surgery is still in a transitional stage, and it is necessary to find an appropriate balance between reducing the recurrence rate, maintaining tumor safety, and performing staged surgery, but the overall trend of surgical development is to ensure safety while reducing surgical complications. This paper reviews the development status and development trend of axillary surgery for breast cancer.

2 HISTORY OF SENTINEL LYMPH NODE BIOPSY

Since the advent of Halsted surgery, ALND has been the standard axillary surgery for breast cancer patients, and ALND still plays an important role in breast cancer surgery, mainly including: 1. Assessing lymph node status, 2. Preventing axillary recurrence, and 3. Removing positive lymph nodes may improve survival. However, the role of ALND has been gradually changed by several randomized clinical trials, and ALND does not reduce systemic recurrence or improve survival. 1985, American Study Group on Adjuvant Breast and Intestinal Surgery (NSABP) B-04 Clinical Trial.

The results of the 10-year study showed that immediate ALND in clinically axillary node-negative patients did not improve survival[3]; A 25-year follow-up study also confirmed that ALND did not reduce systemic recurrence rates or improve survival [4]. SLNB was introduced into the surgical treatment of breast cancer by Krag et al. in 1993 [5], and then NSABP B-32 large randomized clinical trial randomized 5611 patients were randomly divided into ALND group and ALND group only when the sentinel was positive, and there was no difference in the 8-year overall survival rate and disease-free survival rate between the two groups, indicating that SLNB only for SLN-negative patients was safe [1]. Then the ALMANAC clinical study enrolled 1031 patients with clinical axillary node-negative breast cancer were randomly divided into SLNB and ALND groups, and were followed up for 1 year, and the results showed that the SLNB group could reduce the incidence of upper limb complications and improve the quality of life[6]. Based on a series of similar findings, the 2005 ASCO guidelines recommend that early breast cancer patients with clinically negative axillary lymph nodes can be exempted from ALND if SLN is negative, and routine SLNB is recommended for patients with clinically negative axillary lymph nodes [7]. The results show that more and more breast cancer patients undergo SLNB in recent years, and a 2016 study by the Breast Center of Heidelberg University in Germany showed that the proportion of SLNB increased from 10.3% in 2003 to 76.4% in 2016 [8]. Even though SLNB has been widely used, the false negative rate of SLNB is objective, so how can we minimize the false negative rate of SLNB? Related tests such as ALMANAC Trialists, in this experiment, blue staining and radioisotope double tracing method was used to perform SLNB. The results showed that the false negative rate of patients with one SLN removed was 10.1%, and that of two SLN was 8.5%, while that of patients with more than or equal to three SLN was 1.1%. In addition, Bonneau et al surveyed 144517 breast cancer patients who underwent SLNB from the SEER database in 2014 and concluded that removal of at least three SLNs could reduce the false negative rate and had a higher 5-year survival rate [9,10], Therefore, the false-negative rate of SLNB is related to tracer, number of SLNs, and surgical experience of surgeons. At present, guidelines have also put forward requirements for the diagnosis and treatment of SLNB, the detection rate of SLNB should not be less than 90%, and the false negative rate should not be higher than 10%. Therefore, surgeons are advised to use double tracer method for SLNB [11]. SLNB has been accepted and recognized by clinicians after 20 years of development. About internal mammary SLNB, studies have shown that the metastasis rate of the internal mammary SLNs is as follows 18.0% ~ 33.0%, of which 90.0% ~ 98.0% of patients had axillary lymph node metastasis and 2.0% ~ 10.0% had only internal mammary lymph node metastasis [12-14]. Therefore, SLNB can evaluate the lymph node status of most breast cancer patients, and internal mammary lymph node biopsy has been abandoned by most surgeons, and SLNB has become the standard surgical method for clinically negative patients with early-stage breast cancer.

3 AXILLARY SURGERY FOR SENTINEL NODE-POSITIVE BREAST CANCER

The NSABP B-32 trial has demonstrated that it is safe and feasible for sentinel node-negative breast cancer patients not to undergo ALND, but for patients who are clinically axillary negative but pathological sentinel lymph node positive, especially those with less than two positive lymph nodes, the need for axillary lymph node dissection is currently controversial. The International Breast Cancer Research Group IBCSG23-01 trial was designed to address the question of whether patients with single or multiple sentinel lymph node micrometastases (≤ 2 mm without extracapsular extension) could avoid ALND [15]. In this study, 934 breast cancer patients with SLN biopsies with micrometastases were randomly assigned to either no longer undergo surgery or continue with ALND. After 5 years, the disease-free survival rates in the SLN biopsy group and ALND group were 87.8% and 84.4%, respectively. Similarly, the AATRM trial randomly divided patients with clinically negative axillary but micrometastases on SLNB into the observation group or the ALND group, with a median follow-up of 5 years, and there was no significant difference in disease-free survival between the two groups (Observation group: 2.5%; in the; ALND group: 1%) [16]. The data from the IBCSG23-01 trial and the

AATRM trial provide evidence for the safety of exempting axillary lymph node dissection for early breast cancer patients with micrometastasis of sentinel lymph nodes. For patients with macrometastasis of sentinel lymph nodes, the ACOSOG-Z0011 trial enrolled 891 breast cancer patients with clinically negative axillary lymph nodes and positive sentinel lymph nodes 1-2. 446 patients underwent SLNB only and 445 underwent ALND. The median follow-up was 6.3 years. The 5-year overall survival rates of the SLND group and the ALND group were 92.5% and 91.8%, respectively; the 5-year disease-free survival rates were 83.9% and 82.2%, respectively; and the 5-year local recurrence rates were 1.6% and 3.1%, respectively. There was no statistically significant difference in the 5-year overall survival rate, disease-free survival rate, and local recurrence rate between the two groups [2]. Based on the above data, the 2015 ASCO guidelines recommend that axillary lymph node dissection can be waived for breast cancer patients who meet the Z0011 trial criteria (breast-conserving surgery, T1 or T2, clinically negative axillary nodes, and 1-2 sentinel lymph node metastases) [9]. The Z0011 trial has revolutionized the traditional concept that ALND should be performed routinely on SLN-positive patients. Although the current guidelines suggest that ALND can be exempted if the Z0011 trial conditions are met, there are still many controversies. In actual application, there are not many breast cancer patients who meet the Z0011 trial criteria. A multicenter retrospective clinical study in the Netherlands analyzed 11,031 patients with early invasive breast cancer, of whom only 558 met the Z0011 criteria and could be exempted from ALND, accounting for only 5.1% of the total number of breast cancer patients [17]. The above clinical trials were all conducted on patients with clinically negative axillary early breast cancer, and no studies were conducted on cases with clinically positive axillary disease. In 2018, the TAXIS clinical trial conducted a study on patients with clinically positive axillary breast cancer (18). The clinical trial aimed to study the effect of tailored axillary surgery (TAS) surgery. Tailored axillary surgery refers to SLNB & removal of all suspicious lymph nodes & axillary radiotherapy, and its therapeutic effect is no less than ALND. The first case was enrolled in the trial in August 2018, and the final results are yet to be announced. However, for most breast cancer patients, the current standard treatment for patients with clinically positive axillary disease or SLN-positive breast cancer is still ALND, and there is still no unified standard and consensus.

4 ALTERNATIVE TREATMENT FOR AXILLARY SURGERY

At present, the majority of sentinel node-positive breast cancer patients still need to undergo ALND, although ALND can completely remove lymph node lesions and assess lymph node metastasis status. However, it also has side effects such as lymphedema of the upper extremities and motor sensory dysfunction, reduced quality of life for breast cancer patients. Now that there is a lot of evidence that adjuvant therapy can heal some of the remaining metastatic lymph nodes, is reducing the scope of surgery a trend in axillary surgery in the future? The success of the ACOSOG-Z0011 trial is unquestionable, however the trial has been questioned for several reasons [18]. One reason for this is that many cases in the SLNB observation group received radiation therapy, but the SLNB group in the trial was defined as "no further axillary treatment", which can be understood as "No axillary dissection and no axillary radiation therapy" [19]. There are many scholars who believe that the Z0011 trial can do so well because the patients in the SLNB observation group are undergoing breast radiation therapy. The armpits were also accidentally treated with radiotherapy[20-22]. But when Reshma Jaggi tried to collect radiotherapy records from 891 patients in the Remodeling Z0011 trial, only 29% of the cases were well documented[23]. Therefore, we do not know the specific radiotherapy data for Z0011. The EORTC AMAROS clinical trial and the OTOASOR clinical trial complement this shortcoming [24,25], both of these trials investigating clinically axillary-negative but sentinel-positive breast cancer randomized to ALND group or SLNB and axillary radiotherapy group. There was no significant difference in the 5-year axillary recurrence rate between the two groups, suggesting that total axillary radiation therapy is an effective alternative to ALND. The ALND group of these two trials had about 32.8% of cases and 38.5% of positive nonsentinel lymph nodes, respectively, and we can

extrapolate that the axillary radiotherapy group also had such a high proportion of positive lymph node residuals. And the local recurrence rates were similar in the ALND and axillary radiotherapy groups, and there is no doubt that residual positive axillary lymph nodes are sensitive to axillary radiotherapy. Although, we cannot ignore the role of systemic adjuvant therapy, which has been shown to achieve an axillary pathological complete response (pCR) rate of about 20% to 50% in patients with node-positive breast cancer[26,27]. Perhaps the combination of the adjuvant therapy and axillary radiation therapy will be more effective in controlling the local recurrence rate of the axilla. In summary, further research is still needed to confirm how to choose the appropriate treatment regimen for sentinel node-positive breast cancer patients, and from the current research, the direction of axillary radiotherapy as an alternative to ALND is promising.

5 AXILLARY SURGERY AFTER NEOADJUVANT CHEMOTHERAPY

SLNB is the gold standard for axillary lymph node staging in early-stage breast cancer, and neoadjuvant chemotherapy (NAC) is the standard treatment option for patients with locally advanced and inflammatory breast cancer. But now NAC can be used not only for patients with locally advanced disease, there is also an increasing use of NAC, as it can make breast-conserving patients who cannot conserve breast. However, most current guidelines are based on surgical pathology prior to adjuvant therapy. Preoperative NAC poses a challenge to clinicians, especially for axillary surgery. For patients with clinical axillary lymph node negative (cN-) before NAC, studies have shown that the detection rate and false negative rate of SLNB before and after NAC are consistent. Moreover, SLNB after chemotherapy can reduce the number of SLN positives, reduce unnecessary axillary dissection, and reduce complications after ALND, and the recurrence rate and survival rate are similar[28,29]. At present, most experts believe that SLNB after NAC is safe and feasible, and the 2016 ASCO clinical practice guidelines have also been updated to provide SLNB for early breast cancer patients receiving preoperative NAC [30]. For patients with clinical axillary positive (cN+) before NAC, studies have shown that NAC can increase the pCR rate of axillary positive lymph nodes from 20% to 50%. In theory, these patients do not need axillary dissection, but what is the false negative rate of SLNB in patients with axillary positive breast cancer after NAC? In the ACOSOGZ1071 trial, 701 breast cancer patients with axillary lymph node metastasis and NAC were enrolled in this trial, and the false negative rate of SLNB was 12.6% [31]; Similar trails, such as the SENTINA trails, had a false-negative rate of 14.2% for SLNB [32]; Compared with the false negative rate of SLNB in early breast cancer patients without NAC, a 2016 Meta analysis of sentinel lymph node biopsy by Niebling showed that the false negative rate of double tracer SLNB was 2.6% [33]. The false negative rate of these two trials is relatively high, and the high false negative rate will inevitably leave out many breast cancer patients who must implement ALND. Therefore, at present, there is a great controversy about whether to perform SLNB with axillary lymph nodes positive before NAC. However, in order to reduce the false negative rate of SLNB after neoadjuvant chemotherapy, Anderson proposed a new technique-targeted axillary dissection (TAD), that is, puncture biopsies of all suspected metastatic lymph nodes before neoadjuvant chemotherapy. Radioactive iodine 125 particles were placed in the lymph nodes with pathologically confirmed metastasis. after the completion of NAC, patients underwent axillary surgery with X-ray films to selectively remove the lymph nodes labeled by iodine-125 particles [34]. This is a new technique that can be used to remove all suspicious lymph nodes in a targeted manner and reduce the false-negative rate of SLNB. One study recruited 208 breast cancer patients who underwent NAC with TAD before operation, and then the false negative rate of SLNB decreased from 10.1% to 1.4%. [35].

6 PROSPECTS FOR FUTURE AXILLARY SURGERY

SLNB has opened a new era for axillary surgery for patients with early-stage breast cancer, and the development direction of breast cancer surgery is minimally invasive and aesthetic, and so is axillary surgery. Nowadays, there are many screening methods, and more and more early breast cancer patients are being detected. There are also many systemic adjuvant treatments for breast cancer, and the treatment effect is also very obvious. Since systemic adjuvant treatment is also effective for the axilla, too much surgery will only reduce the patient's quality of life. It is worth discussing whether the scope of axillary surgery can be further reduced, even for patients with clinically negative axillary findings, can SLNB be abandoned based solely on negative imaging findings [36]. Perhaps even if the axillary tumor is clinically positive, the same therapeutic effect as ALND can be achieved by simply removing all suspicious lymph nodes and receiving systematic and standardized treatment. The TAXIS trial is currently conducting a phase III clinical study on clinically axillary-positive breast cancer, and the results will take some time to verify. But we hope that TAS surgery and axillary radiotherapy can bring similar therapeutic effects to ALND, and have a higher quality of life.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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