

# Research Progress of Breast Tissue Marker Clips and Their Application in Neoadjuvant Therapy for Breast Cancer

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**Abstract:** Currently, breast cancer being of rapidly increasing incidence rates and as the most commonly diagnosed malignant tumor in breast surgery, has attracted much attention. Neoadjuvant therapy (NAT) has been proved to be beneficial for reducing tumor size and breast-conserving surgery. As a new type of metal localization marker, breast tissue marker clips can be used to precisely locate tumor tissue and improve cure rates. This review focuses on the marker clips and their significance in the diagnosis and treatment of neoadjuvant therapy for breast cancer, hoping to provide more clinical bases for research and promote this technology.

**Keywords:** Breast Tissue Marker Clips; Neoadjuvant Therapy; Breast Cancer; Review

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## Introduction

Being the highest incidence of malignancy among women, breast cancer is seriously threatening their health<sup>[1]</sup>. China's incidence and mortality of this disease rank first in the world, and the burden brought with it continues to increase. Therefore, higher requirements are put forward on the corresponding prevention and treatment measures<sup>[2-3]</sup>. Neoadjuvant therapy (NAT) can reduce the size of breast adenoma, which can not only improve the resectability of inoperable tumors but increase the chances for breast-conserving surgery<sup>[4]</sup>.

A breast tissue marker is a small metal marker, which has different shapes. It can be observed in the imaging system and can be directly placed in breast lesions through percutaneous for long-term lesions marking<sup>[5]</sup>. It has been already proved that placing the tissue marker for patients receiving NAT is helpful, safe, and reliable to locate the tumor<sup>[6]</sup>. Therefore, the application of this technology can increase the accuracy of localization, providing the possible decrease of tumor tissue and even achieving pathological complete response (PCR), which is beneficial for breast-conserving surgery and the therapeutic goal. This article mainly reviews the trend, research progress, clinical application, technical deficiency, and future research direction of breast tissue marker clips in NAT for breast cancer.

## 1. Overview and development of breast tissue marker clips

Breast tissue marker clips are a new accurate localization technology that serves for breast surgery. These clips have small sizes, different shapes and are of good features of tissue fixation. They are usually made of metal materials such as titanium alloy, nickel-chromium alloy, and nickel-free stainless steel, with less body toxicity and anti-anisotropy. It allows these clips to stay in the body for a long term and make full of their unique advantages especially in localizing small lesions.

As research continues, there are different materials in breast tissue markers used by many foreign institutions in various diseases which mainly focus on the application of NAT for breast cancer patients<sup>[7]</sup>. Volleamere et al.,<sup>[8]</sup> indicated in their research that this technique can even be used as an international standard for breast specimen marking.

Furthermore, some scholars believe that compared with metal chips, biodegradable ones are more applicable and have few postoperative complications<sup>[9]</sup>.

They have accurate localization function and considerable clinical significance, but there are still many unsolved issues. At present, the application of this technology is still under exploration in China and has not yet been in a stage of large-scale

clinical use.

## **2. Research progress and clinical significance of breast tissue marker clips in China**

Because marker clips are very small, they were mainly used to locate small breast lesions (diameter <1.0cm) and axillary lymph nodes to precisely locate and completely remove them during operations, in the early clinical stage of breast surgery in China. Most of these small lesions are in the early stage of tumor development, and even if they possibly transform into malignancy, the prognosis is quite good when patients receive surgery at this time. Therefore, it is particularly important to completely remove the lesion when having an accurate location.

1. Locate non-palpable breast lesions and lymph nodes: A study of locating small breast lesions (diameter <1.0 cm) and axillary lymph nodes in Inner Mongolia People's Hospital indicated that 39 lesions and 9 lymph nodes in 31 patients who participated in this study were completely removed, with an average lesions diameter of  $1.2 \pm 0.56$  cm<sup>[10]</sup>. This makes it clear that with the help of the breast localization needle, clinically non-palpable breast lesions and lymph nodes can be completely removed and the early resection rate of malignant lesions can be further improved. Therefore, high-risk breast cancer patients can truly achieve the second-level prevention of early detection, early diagnosis, and early treatment. It is further suggested that a breast localization needle is gradually used in the location of breast lesions and axillary lymph nodes.

In the follow-up practice, many operators found the following problems: the volume of the needle is small and meanwhile, there is no technical support of real-time localization and resection of lesions in the imaging-guided system in China. Statistically, breast markers failed to identify localization in about 5%–20% of cases during surgery<sup>[11]</sup>. Therefore, based on the breast localization needle, it is also necessary to have the assistance of body surface localization to ensure that the operator well-localizes the lesion. The concept of double localization by combination with body mark and puncture was put forward, in the application of puncture combining with body mark to localization of non-palpable breast lesions by the First Affiliated Hospital of Sun Yat-Sen University. It was the first time that the combination was applied in the clinical treatment, which further supplemented and improved the experience of the marker clips in practical application. It also put forward potential problems and standardized the clinical practice of needle localization<sup>[12]</sup>.

2. Auxiliary pathological diagnosis of localization: A clinical study, designed by Xinsteel Center Hospital at Xinyu, Jiangxi Province of China, showed that the pathological diagnosis after resection through localization technology indicated that all cases were malignant, with an accuracy rate of 100%<sup>[13]</sup>. Subsequent research also indicates that the needle can provide precise localization in pathological detection of small lesions, helping effectively detect malignancy in the early stage, which is of great clinical significance in the early prevention and treatment of breast cancer<sup>[14]</sup>.

Currently, in China, some publications guide technical development. They recommend that localization markers can also be used in benign breast diseases, but are not yet included in the NCCN Guidelines for the diagnosis and treatment of breast cancer.

## **3. Clinical application of breast tissue marker clips in NAT**

Studies abroad have shown that breast cancer patients who have achieved PCR through NAT before the operation is better than that patient who has not achieved PCR<sup>[15]</sup>. Placement of the clips before NAT can not only accurately locate breast lesions and regional metastatic lymph nodes, but also improve local control rates of breast-conserving surgery patients for five years<sup>[6]</sup>. Therefore, it is suggested to place clips at breast lesions and axillary positive lymph nodes of breast cancer after patients receiving NAT in quite a lot of guidelines and experts' consensus both at home and abroad<sup>[16-17]</sup>.

1. Node-positive patients before receiving NAT: A systematic retrospective study confirmed the necessity and feasibility of sentinel lymph node biopsy before NAT for breast cancer with positive lymph nodes<sup>[18]</sup>. If the sentinel lymph node is negative, axillary lymph node dissection can be avoided during operation. However, the false-negative result is easy to appear after NAT for node-positive patients before NAT, which is not good for the accurate judgment of the operator<sup>[19]</sup>. Foreign scholars' studies have confirmed that the false-negative rates of sentinel lymph node biopsy after NAT can be effectively

reduced by inserting localization clips into biopsy nodules of patients with positive axillary lymph nodes<sup>[11]</sup>. And the research conclusion was also recommended by domestic experts consensus<sup>[17]</sup>.

2. Breast cancer patients who receive NAT: On the one hand, for image-assistance, Hartmann and Rüländ et al.,<sup>[20-21]</sup> reported that the ultrasonic detection rates of breast tumors and axillary lymph nodes after NAT were as high as 83.3% and 100% respectively. On the other hand, as for the surgical margin, the negative rate of patients who received NAT was slightly higher than that of those who did not<sup>[6]</sup>. Generally speaking, placing markers in NAT for breast cancer patients can not only increase the detection rate of B-ultrasound, MRI, and other imaging methods but also improve the accuracy of localization. Moreover, it is beneficial to fully remove lesions in breast-conserving surgery to ensure the negative surgical margin. In other words, ensuring the accurate location of the lesions is the premise to improve the negative rate of the margin during operation. And increasing the negative margin rate can improve the breast-conserving rate, thus reducing the local recurrence rate.

#### **4. Common complications of breast tissue marker clips**

Displacement is the most common complication. A marker clip should be placed within 10 mm within the preset position. Otherwise, it is called displacement which is mainly caused by the accordion effect<sup>[22-24]</sup>. In addition, around 5%–20% of cases may not be able to find the clips during operation, which means they disappear<sup>[25]</sup>. Moreover, bleeding could occur after implantation which may be caused by the coagulation disorders of patients, insufficient time for dressing and compression after the operation, or loosening- or shifting- wrapping. Very few patients have different degrees of complications, such as infection, pneumothorax, and pain after implantation.

#### **5. Technical deficiency and future research direction**

The technology of breast tissue marker clips is, on the one hand, a new one in the field of minimally invasive surgery, and has the function of long-term localization guidance. Meanwhile, it is also an invasive treatment technique and needs further evaluation on whether the safety and stability of the marker clips can meet the corresponding technical standards after it is placed precisely in the breast tissue of the body. On the other hand, benign breast diseases need long-term follow-up and return visits for clinical diagnosis and treatment of breast diseases. It will be the trend of accurate diagnosis and treatment to use the long-term localization advantage of the marker clips to guide the later re-examination and follow-up of patients.

Under the condition that the clinical efficacy has not been evaluated, the long-term therapeutic benefit of this technique has not yet been reflected, and the cost of placing a breast tissue marker clip is high for patients. It needs the support of government departments and medical insurance policies if widely use this technology in future diagnosis and treatment of breast surgical diseases. At the same time, it is also required that provincial and municipal hospitals, especially the grade A tertiary hospitals that offer breast specialties services independently, strengthen the guidance to junior general surgeons on the theoretical knowledge and practical skills related to markers. The research and application of this technology can be brought to basic-level hospitals.

#### **6. Conclusions and prospects**

Being an emerging technology, tissue marker clips were introduced into China after 2015. It can provide different degrees of localization function in dealing with non-palpable breast lesions, breast lump biopsy, mastitis, neoadjuvant treatment of breast cancer and its pre-treatment positive lymph nodes, etc. Its efficacy and importance have been confirmed by domestic and foreign institutions. Implantation has gradually been carried out in clinical practice in dozens of large-scale grade A tertiary hospitals in China.

Fewer developing units are in the stage of exploring and accumulating cases, compared with foreign countries. At present, there is still a lack of standardized guidance and standard operating procedures for the placement of ultrasound-guided marker clips based on NAT of breast cancer in China. In the future development of breast science, it is expected to carry out large-scale, multi-center, and random prospective clinical research, and explore the detailed implantation process to scheme standardization and popularize this minimally invasive technique.

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