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## THE METAL CLIPS AS BREAST CANCER MARKERS IN ASSESSMENT OF RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY

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The purpose of the study was to investigate the features of using surgical clips as tumor localization markers in patients with breast cancer and influence responses after neoadjuvant chemotherapy. 14 patients (16 lesions) underwent preoperative ultrasonography-guided surgical clip insertion before neoadjuvant chemotherapy. Within the 8–10-day period before surgery follow-up mammography, ultrasonography and magnetic resonance imaging were performed to evaluate treatment response after neoadjuvant chemotherapy. 10 lesions underwent breast conservative surgery, the rest – 6 lesions were treated with modified radical mastectomy. There was no difficulty in the pathological evaluation of a specimen due to inserted surgical clips. The time interval from clip insertion to mammography after procedure and surgery was  $38.1 \pm 12.4$  days and  $115.7 \pm 28.4$  days, respectively. The mean number of inserted clips was  $2.1 \pm 0.8$ . Our results have shown that surgical clips are helpful in visualization of tumors and their localization by various imaging methods, well tolerated and safe for the patient, do not interfere with treatment response after neoadjuvant chemotherapy.

**Key words:** breast malignancy, breast conservative surgery, pathologic complete remission, radiodense marker

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## МЕТАЛЕВІ КЛІПСИ ЯК МАРКЕРИ РАКУ МОЛОЧНОЇ ЗАЛОЗИ В ОЦІНЦІ РЕЗУЛЬТАТІВ НЕОАД'ЮВАНТНОЇ ХІМІОТЕРАПІЇ

Метою дослідження було вивчити особливості використання хірургічних кліпс в якості маркерів локалізації пухлини у хворих на рак молочної залози та впливу на відповідь після неoad'ювантної хіміотерапії. У 14 пацієнтів (16 уражень) перед операцією з приводу неoad'ювантної хіміотерапії було встановлено хірургічну кліпсу під ультразвуковим контролем. Протягом 8–10 днів до операції проводили контрольну мамографію, ультрасонографію та магнітно-резонансну томографію для оцінки відповіді на лікування після неoad'ювантної хіміотерапії. 10 уражень зазнали консервативної хірургії молочної залози, решта – 6 уражень – було проліковано модифікованою радикальною мастектомією. Не було жодних ускладнень у патологічній оцінці зразка через встановлені хірургічні кліпси. Часовий інтервал від встановлення кліпси до проведення мамографії після процедури та операції становив  $38,1 \pm 12,4$  днів та  $115,7 \pm 28,4$  днів, відповідно. Середня кількість вставлених кліпс становила  $2,1 \pm 0,8$ . Наші результати показали, що хірургічні кліпси допомагають візуалізувати пухлини та їх локалізацію різними методами візуалізації, добре переносяться та є безпечними для пацієнта, не впливають на терапевтичну відповідь після неoad'ювантної хіміотерапії.

**Ключові слова:** зляксісне новоутворення молочної залози, консервативна хірургія молочної залози, повна патологічна ремісія, рентгенщільний маркер.

Breast malignancy is one of the most common tumor affecting women, representing 31 % of overall tumors among the female population [14].

Breast cancer (BC) incidence rates have risen in most of the past four decades; during the most recent data years (2010–2019), the rate increased by 0.5 % annually, largely driven by localized-stage and hormone receptor-positive disease. 10 % of the females have the risk of developing breast cancer at some stage in their life [2, 14].

The rate of breast cancer in women is increasing each year while the age at initial diagnosis is shifting to a younger age and the increase in breast cancer incidence is accompanied by an increase in the clinician and researchers concerns in the improvement of diagnostic and therapeutic tools [3]. Treatment options that guide therapeutic choices in patients with primary breast cancer are becoming diversified. New therapies are now being added to conventional chemotherapy regimens, leading to dramatic changes in breast cancer treatment strategies recently [13].

Neoadjuvant chemotherapy (NAC) is now widely considered the standard of care for breast cancer patients with operable or inoperable tumors. The importance of NAC is determined by decreasing the mortality incidence, increasing overall survival and disease-free survival, assisting in early detection of tumor response to therapy and tumor biology of breast cancers, changing the surgical approach, such as breast conservative surgery (BCS) and converting the inoperable lesions into operable ones [6, 8].

According to numerous studies, success rates for NAC are around 80–90 %. The response of breast cancer to NAC assessed using pathologic complete remission (pCR) and in some patients complete clinical,

radiological and pathological response can be attained following NAC. This pCR may prevent proper localization of any residual tissue by radiologists or surgeons [3, 4, 6].

The accurate and reliable detection of the tumor bed after NAC by radiology and pathology is required in situation, when complete tumor response can be achieved and BCS is considered. In these cases, use of radiodense marker clips has been shown to be an effective and reliable method to identify the region of interest. The clips can be detected by either ultrasound or mammography. They also allow wire marking of an already inserted clip to guide the surgeon to the tumor site [5].

Taking into account above mentioned, international breast cancer specialist panel in 2006 and 2010 announced the importance of radiopaque marker localization into the breast cancer before the start of NAC or before surgical resection (even reconstructive surgery) in patients who received NAC [3].

Application of breast markers adds more progress in the field of interventional radiology in concerns with BC as such clips are inserted using the ultrasound-guided technique [5]. From this point of view, studying the imaging features and outcomes of using radiopaque marker is considered to be helpful for improving techniques of this method.

**The purpose** of the study was to investigate the features of using surgical clips as tumor localization markers in patients with breast cancer and influence on the imaging assessment of treatment responses after neoadjuvant chemotherapy.

**Materials and methods.** The study was performed in the Educational-Therapeutic Clinic of Azerbaijan Medical University.

36 patients who received NAC for breast cancer were under our observation. The decision to apply the clip was made by the attending surgeon individually; patients who agreed to the operation were included in the study. A total of 14 patients underwent preoperative ultrasonography (US)-guided surgical clip insertion to accurately localize the malignant lesion before their scheduled preoperative NAC (mean age,  $42.9 \pm 5.7$  years)

After a course of NAC, patients underwent mammography, US, and magnetic resonance imaging (MRI) to evaluate chemotherapy response before the elective surgery.

The mammographic studies were conducted with standard craniocaudal and mediolateral oblique views of both breasts on a full field digital mammography unit (Fujifilm AMULET s, Japan). All patients underwent real-time gray-scale US scans (LOGIQ P9r4 XD clear, General Electric HealthCare, USA) with two orthogonal planes using a 10–12 MHz linear transducer and dynamic contrast-enhanced MRI (TOSHIBA Vantage Titan 3T, Japan) examinations using a 3.0-T system and a dedicated 7-channel SENSE breast coil.

The initial histological diagnosis of malignant lesion was made through a US-guided 14-gauge core needle biopsy (CNB) at Educational-Therapeutic Clinic of Azerbaijan Medical University. If suspicious axillary lymphatic nodes were found on US, additionally US-guided fine needle aspiration was performed.

In our study disposable surgical clips were used. The technique was as following. A short skin incision was made using local anesthesia. A14/16-gauge coaxial guiding needle was inserted into the center of the malignancy, and the inner stylet was removed under US guidance. The surgical clip was passed through the inserted introducer, and the inner stylet was reinserted to complete the clip placement. The confirmation of the location of the clips by US was conducted at the moment after clip insertion. Mammography after procedure was performed to confirm the correct location of the inserted clips.

Within the 8–10-day period before surgery follow-up mammography, US, and MRI were performed to evaluate treatment response after NAC. In the postoperative period (after surgical excision), specimen mammography was also done to assess clip retrieval and specimen margin. The results were studied and confirmed by a pathologist.

The location of clips, clip migration, the presence of complications (infection, hemorrhage, etc.), and the effect of clips on treatment were assessed. Clip migration was defined as the clip being located outside the proven malignancy at a distance of more than 1 cm.

The data obtained were analyzed by the descriptive statistical methods (mean, standard error, frequency, percentage, and minimum and maximum).

**Results of the study and their discussion.** Distribution of BC types was as follows: according to immunohistopathological measurements the majority number of cases were invasive ductal carcinoma, ductal carcinoma in situ, and invasive carcinoma of no special type. 2 patients had bilateral cancer. Assessment of results after NAC showed, that finally there were 9 residual invasive carcinomas of no special type, 3 invasive ductal carcinomas, and 4 ductal carcinomas in situ.

10 lesions underwent BCS, and the rest – 6 lesions were treated with modified radical mastectomy.

Image-guided localization or skin marking was performed in 5 patients. There was no difficulty in the pathological evaluation of a specimen due to inserted surgical clips. The majority of patients had T1 tumors (n=8, 57.1 %), and 42.9 % (n=6) had T2 tumors.

The time interval from clip insertion to mammography after procedure and surgery was  $38.1 \pm 12.4$  days and  $115.7 \pm 28.4$  days, respectively. The mean period between clip placement and preoperative follow-up imaging was  $118.4 \pm 29.8$  days for US,  $114.8 \pm 31.2$  days for mammography, and  $119.1 \pm 32.7$  days for MRI. The mean number of inserted clips was  $2.1 \pm 0.8$  (range: 1–4).

On US, the inserted clips were visualized as linear hyperechogenic structures with or without posterior shadowing (Fig. 1).

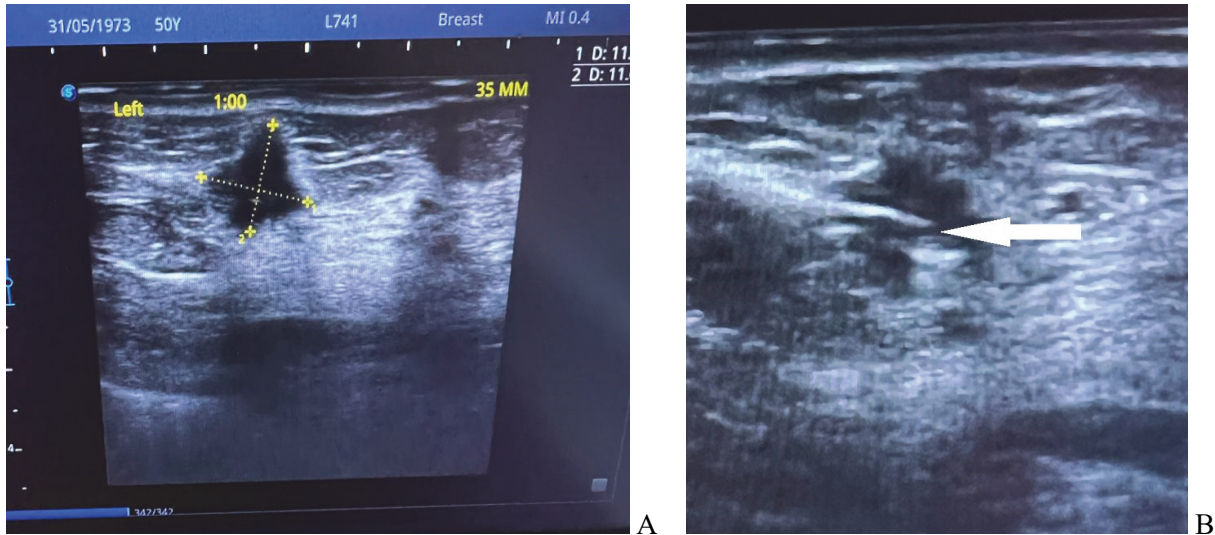


Figure 1. Preoperative ultrasonography (US)-guided surgical clip insertion. A – Visualization of tumor by US. B – The clip insertion (on US images, the coaxial needle (arrows) is visible as an echogenic white line and the clips show a linear hyperechogenic structure in the center of the proven tumor.

We did not reveal any evidence of clip migration during mammography after procedure, preoperative final follow-up mammography, and in surgical specimens (Fig. 2).

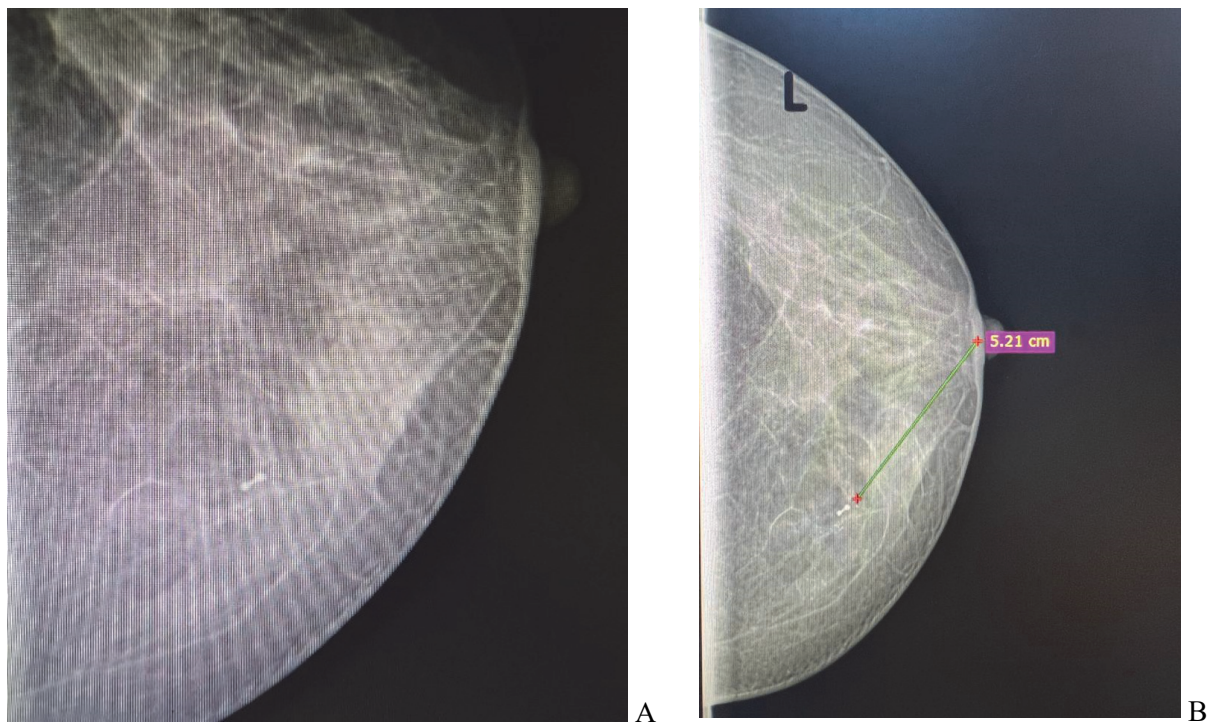


Figure 2. Mammography of a 39-year-old woman who underwent US-guided surgical clip insertion due to left breast cancer. A – Follow-up mammography after clipping procedure (metal clips in the center of the proven malignant mass). B – At preoperative final follow-up mammography, the clips were located in the proven malignant mass without signs of clip migration or other complications.

In addition, there were no patient complained of unfavorable sensation or pain and complication related to the clip insertion within the observation period.

On MRI the clips were detected as small signal voids. It should be noted, that there was no difficulty in evaluating the treatment response to neoadjuvant chemotherapy using both US and MRI.

In this study we assessed visualization possibility of clips as breast markers for different radiological methods in patients with BC.

Evaluation of tumor localization and neoadjuvant chemotherapy response, confirmed by US, mammography, and MRI, is important even if pCR is accomplished [5]. We did not have cases of pCR after NAC, in most cases (56.3 %) partial response to NAC was noted.

Due to widely using NAC as an effective treatment method in early diagnosed cases of BC, in patients with inflammatory BC and those in whom residual disease may prompt a change in therapy, breast marker placement has become routine, especially in cases that may need additional excision based on the pathological findings [7].

According to ESMO Clinical Practice Guidelines [10], marking the tumour bed with clips in a standardised way facilitates accurate planning of the radiation boost field, if it is indicated. Currently, achievable low local recurrence rates [ $<0.5$  % per year (with a target of  $<0.25$  %) and  $\leq 10$  % overall at very long-term follow-up] should be maintained. Our results suggest all above mentioned. The limitation of our study was a small number of patients, which required further researches.

In this research, all clips inserted as tissue markers were removed with the primary BC tissue at the moment of surgery. Surgical clips were placed via a commercial coaxial guiding needle used in the CNB of the breast. This procedure was easy to perform, and clip insertion in our patients required less than 5 minutes. The similar results with easily using surgical clips to replace commercial breast markers has been reported in several previous studies [12, 14]

The authors showed effective results with no complications, don't interfere with the patients' imaging and of the significant low cost compared to the commercial ones. Soliman AH, et al (2018) also emphasized the low cost of using surgical clips compared special breast markers [12]. We did not evaluate the cost of the procedure: it will be the purpose of our further works.

Despite the fact that in our work we did not register any problems with visualization related to clips the other researchers reported about controversial results. So, Kim WH, faced a challenge in US-guided dual-localization technique suggested in this study. Although clips were easily placed in all cases, without significant complications, 21 % of clips were not clearly visible on ultrasound examination performed after neoadjuvant chemotherapy. Despite the available information about the hyperechoic characteristics of metal clips, which make them clearly visible against the background of the hypoechoic cortex of the axillary node before neoadjuvant chemotherapy, as NAC develops, the cortex becomes thinner, which makes it difficult to differentiate the clip from echogenic fat cords. Thus, using a different type of clip can help visualize using the ultrasound examination. The authors suggested that this can be seen as an approach to marking target nodes [5]. It should be noted that the study of Kim WH, et al, had a similar limitation like ours: a small number of cases observed. So, the clarification of this problem needs additional studies. On the other hand, the study above mentioned had a strength which is that the investigators performed tattooing after NAC for the nodes clipped before NAC, which allowed them to evaluate internodal relationships as well as the technical feasibility of the approach.

One of the important problems is the migration of surgical clips [9, 11]. It can be a real limitation due to related complications. Usually, clips are inserted into the center of the tumor mass, out of fat tissue. Thus, the chance of clip migration should be lower because of the higher tissue resistance. Clip migration may occur immediately after biopsy or may be seen on later follow-up mammograms. The migrated clip is usually found within the breast. Ang BWG, et al, described a rare case of delayed clip migration to the skin, following a magnetic resonance guided biopsy of the breast [1].

Despite the mean time period from clipping to surgery of approximately 4,5 months (range, 51–146 days), there were no cases of clip migration in our study as confirmed on all imaging methods. Moreover, there was no case of complications related to clip insertion.

A number of studies report that radiopaque markers are useful for tumor localization as well as for evaluating tumor response after neoadjuvant chemotherapy without compromising radiological multimodal evaluation, including magnetic resonance imaging [4, 9, 11].

In our work we can assess tumor response to NAC and confirm the clip location by using multimodality imaging studies; the clips were visualized as a radiopaque metal density on radiography, and as a hyperechogenic linear structure with or without posterior shadow on ultrasound examination.

The limitation of our study was the small number of patients (only 14), which did not allow to provide a reliable overall generalization from the study results. Further studies are required for continued assessment of this method.

### Conclusion

There were not any cases of pCR after NAC in our work, in most cases (56.3 %) partial response to NAC was noted. Our results have shown that surgical clips are useful visualization of tumors and their localization by various imaging methods, well tolerated and safe for the patient, do not interfere with treatment response after neoadjuvant chemotherapy. There was no difficulty in the pathological evaluation of a specimen due to inserted surgical clips, so, method can be successfully used for detection.

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