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Clip migration after vacuum-assisted breast Biopsy – influencing factors and impact on surgical outcome

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1 INTRODUCTION

1.1 EPIDEMIOLOGY

With around 72,000 new cases per year, breast cancer is one of the most common cancers in women. In addition, more than 6,000 women are diagnosed with breast cancer in situ each year. About 1 percent of all new breast cancer cases affect men (Key, Verkasalo, and Banks 2001).

Based on current incidence rates, approximately one in eight women is expected to develop breast cancer during their lifetime. Almost three out of ten affected women are younger than 55 years at diagnosis. The incidence and mortality rates are still lower in the new federal states than in the old federal states; only among women under 55 have the rates largely converged (Wolf et al. 2011).

Diagnosing, therapy, and supporting patients with breast cancer or its precursors is an interdisciplinary task for everyone involved (L. Wang 2017).

The term breast carcinoma includes all malignant neoplasms of the combined mammary gland. Various histopathological subtypes, as well as invasive carcinomas from non-invasive carcinomas, are differentiated. According to the Robert Koch Institute, 70550 women were diagnosed with Breast cancer in 2020. The mean age at diagnosis was 64.3 years, but 18% of the women were younger than 50 years at the time of diagnosis (Hübner et al. 2020).

Crude incidence has doubled since the 1970s and has been at a similar level since 2002. In 2013, there were 174 new cases per 100,000 women. This development also occurred in other developed western countries like the USA or Scandinavia, while, for example, the incidence rates are significantly lower in Asia. Possible causes, according to the Robert Koch Institute, this long-term increase could include changed diet and exercise habits, the higher number of childless women, the later date of the first birth, and hormone replacement therapy. The rise in incidence rates between 2007 and 2010 was explained by the Robert Koch Institute, most likely due to the introduction of the statutory screening program (Wolf et al. 2011).

After the introduction of the mammography screening program in Germany for women between the ages of 50 and 69 (between 2005 and 2009, depending on the region), the diagnosis rates in the corresponding age group initially rose sharply. Since 2009, however, they have been steadily declining, and in 2016 were only slightly higher than before the screening program. The statistics show that in the screening age group, about 25 percent fewer women are diagnosed with advanced tumors than before the screening introduction. Mammography screening also seems to have impacted breast cancer mortality. From 2003/2004 to 2015/2016, mortality rates decreased by 25.8 and 21.2%, respectively (Katalinic et al. 2020). Mortality rates have declined slightly for women under 70 since 1999, while no significant change was recorded in women 70 years or older. In 2013, 17,853 women died from breast cancer. The 10-year relative survival rate in 2013 was 82% (Wolf et al. 2011)

Since 2005, the age-standardized incidence of carcinomas that have already been diagnosed in the non-invasive stage from approx. 20 to over 40 per 100,000 women. A similar development is recorded worldwide. The same is assumed for the increased incidence of lesions with unclear biological potential (LUBP), some of which are preliminary stages of breast cancer.

1.2 AETIOLOGY AND RISK FACTORS

As with many other cancers, the cause of breast cancer cannot be clearly defined. In addition, it is a heterogeneous disease with different types, which differ in morphology and pathophysiology. However, various risk factors could be identified that allow conclusions to be drawn about the aetiology, but they are particularly relevant for prevention and treatment (Sun et al. 2017).

Especially in women who get diagnosed with breast cancer at a younger age, genetic dispositions play a role. The BRCA1 and BRCA2 (breast cancer genes) are the most crucial risk mutations. However, because one multigenetic occurrence is to be expected, it comes from the familial risk profile also of great importance (Armstrong et al. 2019).

Other potential risk mutations are, for example, the RAD51 or progesterone receptor gene. These are the subjects of current research.

Essential influencers on breast cancer risk, in addition to genetics, are hormonal factors. Women who do not have children, have children late or are on hormone replacement therapy have a higher risk of breast cancer. Lifestyle factors such as a Western diet, low physical activity, or high alcohol may increase the incidence risk (Momenimovahed and Salehiniya 2019).

1.3 SYMPTOMS AND CLINICAL PICTURE

The most important early symptoms are palpable, immovable lumps in the breast and the axilla. In the further course, it comes through connective tissue remodelling skin and nipple retractions, partly due to nipple secretion. Change of the breast size can also occur, as the breast size can get larger due to the tumor and smaller due to shrinkage processes of the connective tissue. If tumor growth continues, it can erode the skin and ulcerate to the outside. Particular forms can occur at the nipple, like M. Paget, or diffuse, like inflammatory breast carcinoma, which can cause inflammatory symptoms such as reddening and pain at an early stage (Burgess, Hunter, and

Ramirez 2001). Characteristic for most carcinomas biopsied stereotactically is the absence of clinical symptoms. For example, intraductal carcinomas have no or minimal invasive components. Due to the invasion of the milk ducts, they are almost always hard to palpate (Tan et al. 2020).

1.4 DIAGNOSTIC IMAGING OF BREAST CANCER

1.4.1 Mammography

Mammography is the most important diagnostic procedure in senology. It is a particular X-ray exam where the X-ray constructs the patient's compressed breast with the soft beam technique. The system is implemented in Germany under the supervision of the German Medical Association and the National Association of Statutory Health Insurance Physicians to ensure the general conditions of the X-ray ordinance and the established quality standards. The quality criteria include a complete picture of the breast, sufficient Chest compression, and exposure of the pectoralis major muscle and the axillary fold. Two standard adjustments are made: The CC (craniocaudal) and MLO (mediolateral oblique) perspectives.

The American College of Radiology (ACR) used the BI-RADS® - Categories (Breast Imaging Reporting and Data System®), a unified Classification for the assessment of mammography, ultrasound, and Magnetic resonance imaging (MRI) introduced in senology. The ACR BI-RADS® Atlas 2016 was published in the 1st edition (D’Orsi, Sickles, and Mendelson 2016) and improved the comparability of the findings of different doctors and the respective modalities and thus facilitated the decision of other diagnostic and therapeutic procedures. It is widely used and is part of the diagnostic chain of the S3 guideline (Strnad et al. 2020). Table 1 in the methods chapter shows the actual classification in a simplified form.

Malignant lesions tend to be blurry on mammography, often depicted spiculated. Architectural defects or skin retractions may accompany this. Grouped or segmental microcalcifications are also considered suspicious, mostly <0.5 mm. According to ACR BI-RADS® guidelines, microcalcifications are classified as amorphous, grossly heterogeneous, finely pleomorphic, or finely described linearly to be regarded as suspicious of malignancy. Monomorphic round or rod-shaped calcifications are more likely than benign to classify. There are also some typical benign findings, such as popcorn-like calcifications in fibroadenomas, vascular calcifications, or peripheral calcifications in oil cysts (Bell and Gossweiler 2023).

An exact statement about the diagnostic accuracy of mammography is complex. It depends not only on patient factors or selection (e.g., age, parenchyma density, hormone status, the prevalence of BRCA mutations, or previous carcinomas) but also on the experience and individual threshold of the examiner (Elmore, Wells, and Howard 1998). The high threshold of the histological examination and biopsy of calcifications has positive predictive value, but only at the expense of a higher false rate of negative findings and vice versa (Heller et al. 2016).

In the current S3 guideline, for women over 40, the sensitivity of the detection of microcalcifications is between 85 and 90% (S3-Leitlinie Mammakarzinom 2021) . In detecting microcalcifications, the sensitivity is exceptionally high and hardly dependent on the X-ray density. However, mammography is pathognomonic only for a few characteristic benign findings, such as oil cysts or calcified fibroadenomas, and for very advanced carcinomas. The specificity in the fatty breast is higher than in glandular and connective tissue. If the fat content is high, malignancies can be diagnosed and ruled out with a relatively high degree of certainty. For this reason, the ACR parenchymal density category is specified for mammography findings.

Due to the hormonal influences on the mammary gland tissue, the sensitivity of mammography is highest for postmenopausal women. Therefore, statutory mammography screening for women between 50 and 69 years of age is introduced. Nevertheless, for women between 40-49 and over 70, mammography is used for early detection and recommended as the primary procedure for clarifying symptoms (Strnad et al. 2020).

1.4.2 Sonography

In addition to mammography, essential imaging procedures in senology are sonography and contrast medium magnetic resonance imaging Breast (Contrast-enhanced MRI Breast), as well as contrast-enhanced mammography and tomosynthesis. Additive processes, mainly combined with mammography, will achieve higher cancer detection rates and more characterization of the Findings (Peintinger et al. 2006).

In the past, breast sonography was only used to differentiate between cystic and solid tumors in the breast. In the meantime, the sonographic examination technique has improved so much that it is possible to work out structural differences that allow conclusions to be drawn about the dignity of the finding. An improved detection rate of mammary tumors and a significant reduction in mortality from breast cancer diseases have been achieved with the mammography screening method commonly used today. However, detecting all breast tumors is not always possible due to the equipment used. Even with large breasts, the examination can cause difficulties. Breast ultrasound can also be performed to clarify unclear changes in the breast. Sonography is a valuable addition to mammography in breast cancer screening but cannot replace it (Jackson 1990).

Ultrasound is more sensitive than mammography before gland involution due to the lower breast fat percentage. For women under 40, sonography is recommended as the primary imaging method (Urban et al. 2011).

1.4.3 Magnetic Resonance Imaging

After the creation of the first MRI pictures of a human being in 1977 and the introduction of the first contrast medium, "Magnevist," for MRI in the free trade in 1988, MRI was soon also used initially only in clinical studies - in the field of female breast. In Germany, Heywang-Köbrunner played a vital role in the evaluation of MRI for breast cancer diagnosis. As early as 1986, she published the first results (Wolf et al. 2011) on using contrast-enhanced MRI in breast diagnostics. The technical problems at the beginning of the MRI era consisted, on the one hand of the low temporal resolution of the MR devices of the time and, on the other hand, of the coil technology unsuitable for examining the breasts. Therefore, only static investigations could initially be made, and only one side was imaged. The coils for the simultaneous imaging of both breasts were only developed later. Simultaneous imaging of both breasts with dynamic sequences before and during contrast agent application has been mandatory for many years (S. H. Heywang-Köbrunner 1992).

In addition, if unclear lesions occur, MR-guided biopsies and MR-guided preoperative marking have been performed since the mid-1990s. In this way, if the indication is appropriate, the method's high sensitivity can be used and, similar to sonography, a histological clarification can be carried out in unclear cases (Papalouka et al. 2018; Urban et al. 2011).

MRI of the breast with contrast media is a susceptible method with which even small breast carcinomas and tumor precursors (DCIS) can be diagnosed. With this, tumors not yet visible in X-ray mammography and ultrasound can sometimes be found.

A breast MRI is mainly used for the early detection of breast cancer in women with a high family risk (high-risk patients) or to clarify unclear findings found in mammography or ultrasound (Jackson 1990; C. H. Lee et al. 2010).

MRI is also an examination without radiation exposure. However, it is time-consuming and, in contrast to sonography, only partially risk-free. The use of an intravenous contrast agent is mandatory. Applying a contrast medium can cause contrast agent allergy and is limited in the case of impaired renal function or nephrogenic systemic fibrosis (Lauby-Secretan et al. 2015). In the current S3 guidelines, contrast enhanced MRI is used in the diagnostic and preoperative staging. It is then recommended when uncertainties persist after conventional diagnostics exist and in exceptional cases such as for premenopausal patients or those with a high genetic risk.

In addition, contrast MRI can assess response to neoadjuvant chemotherapy and local recurrence diagnosis.

1.4.4 Tomosynthesis

Tomosynthesis is a further development of traditional mammography. The X-ray tube moves in an arc over the breast. It creates numerous images with a very low radiation dose (on average, only about 10% higher radiation exposure than traditional mammography). In addition to the classic mammography recording, a summation image is calculated from up to 80 projection images (Helvie 2010; Bernardi et al. 2016).

Numerous studies have investigated the use of tomosynthesis in screening instead of 2D mammography. These have revealed that the combination of both methods leads to higher rates of invasive cancer detection and increases the effectiveness of breast cancer screening (Hodgson et al. 2016; Bernardi et al. 2016).

1.5 EARLY DETECTION AND STATUTORY MAMMOGRAPHY SCREENING

Measures for the early detection of breast cancer are part of controversially discussed debate both in the population and in science. According to the current S3 guideline, mammography is the "only method with a proven reduction in breast cancer mortality"(S3-Leitlinie Mammakarzinom 2021) . This is because microcalcifications can be very well detected.

Therefore, between 2005 and 2009, a national law Mammography screening program was introduced. Women between 50 and 69 years old are invited to mammography every two years. Additionally, an annual palpation examination of the breasts and regional lymph nodes for women over the age of 30, as well as instructions for self-examination, are part of statutory early detection (Wolf et al. 2011).

The primary goal of mammography screening is to reduce mortality, which is difficult to calculate due to different methodological approaches and limitations (Wolf et al. 2011). Nevertheless, a reduction in mortality is considered guaranteed. Myers et al. calculated in their review of studies on screening an approximately 20% reduction in mortality in programs worldwide (Bundesärztekammer (German Medical Association) and Instand E.V. 2015). The Euroscreen Working Group assumed a reduction in their calculations up to 31% (or 48% for women screened), and the IARC (International Agency for Research on Cancer) of 23% and 40%, respectively (Yamada et al. 2010; Paci et al. 2014).

Critical authors like Goetzsche et al. estimate a 10-15% reduction. However, they included in their calculations an overdiagnosis rate of 30%. Along with the risk of false-positive results, they justified the criticism of the proportionality of screening (Lauby-Secretan et al. 2015). However, the studies above showed that the rate of overdiagnosis was lower and that wrong positive diagnoses were primarily only followed by non-invasive follow-up examinations (Yamada et al. 2010; Paci et al. 2014). The risks from radiation exposure have also been classified as low compared to the reduction in mortality (Yamada et al. 2010; Paci et al. 2014; Gøtzsche and Jørgensen 2013). In addition to reducing mortality, the secondary goal is to increase patients' quality of life due to early diagnosis and to keep the option of, for example, breast-conserving surgery (Wolf et al. 2011).

Results from the German screening program for mortality reduction should have been introduced sooner. However, it could already reduce the diagnosis of advanced breast cancer stages. This is a surrogate parameter for a successful screening program (Khil et al. 2020). Likewise, declining mastectomy and lymphadenectomy rates could already be observed (Yaffe and Mainprize 2011).

Neither sonography nor Contrast-enhanced MRI is suitable due to the effort involved in investigations and the increased rates of recalls for early detection in the general population (S3Leitlinie Mammkarzinom 2021)(Melnikow et al. 2016). However, for women with elevated breast cancer risk, an increase in carcinoma detection of tumors is detected in the pre-invasive stages. Therefore contrast-enhanced MRI as a screening procedure is recommended (Albert, Schreer, and Arbeitsgruppe der Stufe-3-Leitlinie Mammarkarzinom 2019). Also, comprehensive screening is being considered for other subgroups, such as women with increased Breast density, but still lacks studies of higher evidence classes (Schrodi et al. 2013).

1.6 METHODS OF MINIMALLY INVASIVE DIAGNOSTICS

Image-guided needle biopsy is a safe and accurate non-surgical method to diagnose suspicious abnormal findings at breast imaging, pivotal for adequate decision-making, including treatment planning (Bick et al. 2020; Esserman, Cura, and DaCosta 2004). It is mostly about suspicious microcalcifications, but in rare cases, it is also about architectural defects or small opacities (Melnikow et al. 2016).

With the introduction of mammography screening, the number of histologically clarified findings was precise. An open biopsy performed on the patient represents a significant burden, among other things, due to general anaesthesia (Kimball, Nichols, and Vose 2018). Minimally invasive biopsies have fewer side effects and are cheaper and better available than open biopsies. In addition, the formation of scars in the future can make diagnostic measures more difficult, significantly less. The proportionality to the performance of open biopsies would be in many clarifications with negative results not given, which is why minimally invasive methods were increasingly used and continuously developed (Melnikow et al. 2016). In their meta-analysis, Gruber et al. concluded that by using minimally invasive procedures, 71-85% of open biopsies could be saved, and a significant cost reduction could be achieved (O'Flynn, Wilson, and Michell 2010).

The current S3 guidelines recommend minimally invasive histological confirmation of diagnosis by stereotactic vacuum-assisted breast biopsy (VABB) for microcalcifications without accompanying sonographic findings. Open surgical biopsy should be only considered if a histological confirmation with this minimally invasive procedure is not possible, e.g., due to the location of the lesion or insufficient breast volume (Lebeau et al. 2019).

1.7 TREATMENT OF BREAST CANCER

1.7.1 Operative Treatment

Breast-conserving surgery

Breast-conserving surgery does not carry a higher risk of recurrence for patients than radical breast removal if the tumor has been completely removed (healthy tissue at the edge of the incision in the microscopic examination) and the breast is subsequently irradiated (Veronesi et al. 2002). Whether breast-conserving surgery can be performed depends on the nature of the tumor; cancer must not be too large concerning the breast and must be localized. As a rule, the breast skin and chest wall muscles must not be affected. There should be no other tumors in the breast that are widely separated (Morrow et al. 2001). There should be no additional extensive precancerous breast lesions. Ultimately, breast-conserving surgery must be decided individually for each patient based on imaging, pathologic features, and clinical examination (Urban et al. 2011).

Mastectomy

Only in a few patients does the entire breast need to be removed: The mammary gland, skin, and enveloping layer of the pectoral muscle (fascia). In many cases, however, the skin can be preserved (so-called "skin-sparing" or skin-saving mastectomy), and in some cases, the nipple can be preserved (so-called "nipple-sparing" mastectomy) (Mallon et al. 2013). A mastectomy becomes necessary when the tumor is too large, tumors are growing at several sites that are distant from each other, the breast skin is affected, breast cancer precursors are present throughout the breast, the tumor cannot be completely removed during a previous operation, and a follow-up operation with preservation of the breast is not possible, or if radiotherapy is not possible (e.g., in the case of old age) if the breast carcinoma is inflammatory ("inflammatory breast carcinoma") or at the request of the patient (Niemeyer et al. 2011).

Removal of the lymph nodes

When breast cancer cells metastasize, that is, when they spread throughout the body from the breast, they usually do so initially through the lymphatic system. The lymphatic channels from the breast open into the ipsilateral axillary lymph nodes. Whereas in the past, these lymph nodes were permanently removed during surgery ("axillary dissection"), it is now standard to remove only the so-called sentinel lymph nodes (SLN) - the first ones on the lymphatic pathway between the breast and the armpit. However, this is only possible if the lymph nodes appear inconspicuous before surgery (Teichgraeber et al. 2020).

If no cancer cells are found during the subsequent fine-tissue examination of the SLN, it can be assumed that the tumor has not yet spread, and thus, there are no metastases in other lymph nodes. If it is found during or after surgery that more than two SLN are affected, at least ten lymph nodes must usually be removed. However, in the case of a maximum of two affected lymph nodes, further removal may not be necessary if radiation and medication are continued after the operation. In a few instances (extensive, palpable lymph node metastases or lymph node metastases that are conspicuous on imaging), more than ten lymph nodes may need to be removed (Jatoi et al. 1999).

In the case of neoadjuvant chemotherapy for clinically nodal-negative breast carcinoma, sentinel biopsy should follow chemotherapy to avoid unnecessary axilla surgery (Kuehn et al. 2013).

1.7.2 Hormonal therapy

About two-thirds of all malignant breast tumors grow depending on female sex hormones, especially estrogen. They are produced in large quantities in the ovaries from menarche to menopause. Nevertheless, other tissues also produce estrogen (Locker 1998).

After the link between breast cancer and hormone action became known, many women had their ovaries removed (ovariectomy) or were irradiated. However, the resulting infertility was very problematic for young patients. The anti-hormone therapies (also called "endocrine therapies") available since the 1970s stop or slow down tumor growth in a medicinal way. After treatment, menstruation often resumes; fertility may be preserved (Abdulkareem and Zurmi 2012).

Like chemotherapy, anti-hormone therapy acts throughout the body ("systemic therapy"). It combats even the smallest tumor metastases that cannot yet be detected with today's options. The cure rate can thus be increased by 30 percent. This positive effect continues for ten years after the therapy has been discontinued (Symmans et al. 2010).

1.7.3 Radiotherapy

High-dose ionizing radiation (e.g., X-rays) damages the genetic material of the irradiated cells. Radiation therapy is used after surgery, i.e., adjuvantly, to destroy tumor cells that may not have been removed and thus prevent a recurrence (Early Breast Cancer Trialists' Collaborative Group 1995).

After breast-conserving surgery, radiotherapy of the remaining breast is currently standard practice because it can significantly reduce the likelihood of cancer recurrence. In low-risk individual cases - if the patient is over 70 years old, has a small HR-positive and HER2-negative tumor without lymph node involvement, and receives endocrine therapy - radiation may not be necessary (Kolberg et al. 2023; Tendulkar et al. 2012).

Radiation is often not required after mastectomy. In this case, radiation is only given in the case of advanced tumors, if the cancer cannot be removed entirely despite this operation, if there is an increased risk of recurrence, or if more than three lymph nodes are affected. If one to three axillary lymph nodes are affected, but the tumor has a low risk, radiotherapy of the chest wall can be omitted (Jacobson et al. 2021).

In rare cases - when the risk of recurrence is low - partial breast irradiation is sufficient, in which only the tumor-bearing part of the breast is irradiated. Radiotherapy can be done during surgery or in the days following (Strnad et al. 2020).

If metastases have been found in the axillary lymph nodes, but the lymph nodes have not been cleared out, or if there are residual tumors in the axilla, the lymph node stations are also irradiated - depending on the findings, in the axilla, at the collarbone or very rarely in the region around the breastbone (Freedman et al. 2000; Budach et al. 2015). The lymphatic drainage channels are also irradiated (Castelo et al. 2020).

In advanced diseases, radiation therapy is also used to treat metastases. In contrast to adjuvant radiotherapy, radiation is no longer used to cure the disease but to relieve symptoms such as pain (Chowdhary et al. 2019).

2 RESEARCH QUESTIONS AND AIM OF THE THESIS

Percutaneous stereotactically guided breast biopsies are often performed to obtain a histological diagnosis of mammographically suspicious lesions such as microcalcifications, areas of architectural abnormalities, or sonographically undetectable lesions (Bick et al. 2020; Huang et al. 2014). Using large-volume needles and vacuum-assisted techniques, stereotactically guided biopsy often results in partial or complete lesion removal. A metallic biopsy marker is placed in the biopsy site at the end of the biopsy procedure to ensure that the biopsy site is clearly visible and can be easily distinguished from other lesions in future mammographic examinations or if subsequent surgery is required. The instant shift of the biopsy marker is observed immediately after the biopsy, and the placement of the marker is related to a phenomenon called the "accordion effect"(Esserman, Cura, and DaCosta 2004). This is thought to be due to decreased pressure in the breast that occurs when the breast is released from the compression required for the stereotactic procedure.

A clip dislocation after vacuum-assisted biopsy occurs in about 13-20% of the cases in clinical practice and is challenging for radiologists and surgeons (Chaveron et al. 2009). It may cause insecurity for the surgeon and radiologist and may increase the need for re-excision or secondary mastectomy.

The primary objective of the present investigations is to identify risk factors for immediate clip displacement in patients with stereotactic vacuum-assisted breast biopsy (VABB).

The secondary aim of the study is to investigate the impact of clip dislocation on the outcome of subsequent surgery.

3 MATERIALS AND METHODS

3.1 STUDY POPULATION

We conducted a retrospective data analysis of all patients who underwent VABB at the interdisciplinary Breast Centre of the University of Rostock Women's Hospital at the Klinikum Suedstadt site. One hundred ninety-two biopsies were performed for 190 patients. Two patients had a biopsy on both sides, resulting in 192 biopsies. In general, BI-RADS®-4 or BI-RADS®-5 findings in the mammography (suspicious microcalcifications, masses <1 cm, architectural distortions) indicated a biopsy (table 1).

This group of patients was biopsied at the Department for Radiology at the Interdisciplinary Breast Centre of the Klinikum Suedstadt Rostock from 22/10/2020 to 31/12/2021 to evaluate a relevant clip dislocation according to various parameters.

Table 1: BI-RADS® classification, a simplified representation based on the German version of the ACR BI-RADS ® Atlas Mammography (D'Orsi, Sickles, and Mendelson 2016)

Category	**Definition**	**Meaning**
0	Additional imaging evaluation and/or comparison to prior mammograms (or other imaging tests) is needed.	Abnormality was detected, but the radiologist needs further diagnostics or must compare the findings with previous examinations.
1	Negative	It means nothing new or abnormal was found.
2	Benign finding	This is also a negative test result (no sign of cancer), but the radiologist describes a finding that is not cancer.
3	Probably benign finding – Follow-up in a short time frame is suggested	A finding in this category has a deficient (no more than 2%) chance of being cancer. It is expected to stay the same over time. However, since it is not proven benign, you will likely need follow-up with repeat imaging in 6 to 12 months and regularly until the finding is known to be stable (usually at least two years). This approach helps avoid unnecessary (Mallon et al. 2013), but if the area does change over time, it still allows for early diagnosis.
4	Suspicious abnormality – Biopsy should be considered	These findings do not look like cancer, but they could be cancer. The radiologist is concerned enough to recommend a biopsy. The findings in this category can have a wide range of suspicion levels. For this reason, this category is often divided further: 4A: Finding with a low likelihood of being cancer (more than 2% but no more than 10%)

		4B: Finding with a moderate likelihood of being cancer (more than 10% but no more than 50%) 4C: Finding with a high likelihood of being cancer (more than 50% but less than 95%), but not as high as Category 5
5	Highly suggestive of malignancy	The findings look like cancer and have a high chance (at least 95%) of being cancer. A biopsy is very strongly recommended.
6	Histopathologically proven malignancy	This category is only used for findings on a mammogram (or ultrasound or MRI) that have already been shown to be cancer by a previous biopsy.

3.2 BIOPSY TECHNIQUE

Most of our patients were biopsied using digital tomosynthesis-guided biopsy. It has already been shown in the literature that digital tomosynthesis-guided biopsy of suspicious lesions can be performed in less time and with less radiation exposure than digital mammography-guided stereotactic biopsy. In addition, digital tomosynthesis-guided biopsy allows the full detector size to be used for imaging and provides immediate information about the depth of the lesion without the need for triangulation, facilitating target lesion recognition and sampling. (Nguyen et al. 2023)(Schrading et al. 2015).

In the VABB, tissue is inserted into the biopsy chamber of a hollow needle, sucked in, and then cut off by a rotating knife. The position biopsy chamber is rotated clockwise between samplings to remove a large and representative tissue volume with one needle position. At the same time, blood can be sucked out of the biopsy cavity to prevent hematomas (Melnikow et al. 2016).

Stereotaxy is a particular calculation method for the depth localization of a finding. For this purpose, a mammographic target recording in -15°, 0°, and +15° is required, which is achieved by tilting the X-ray tube. The required penetration depth can be calculated using a computer-assisted calculation of the needle, which is determined and placed precisely in the lesion. The biopsy can be performed on a mammography device with a stereotaxy function or on a specially made biopsy table. The biopsy table Hologic Affirm® Prone (Hologic Deutschland GmbH, Berlin; Germany) in conjunction with the vertical/orthogonal biopsy approach, in which the needle is advanced perpendicular to the compression plate, in the direction of maximum tissue compression was used. Adequate analgesia must be ensured before starting the vacuum biopsy. The 10G needle is first advanced to the biopsy site after stereotactic localization and, after checking the position, is advanced 19 mm so that the centre of the needle opening is located exactly in the middle of the lesion. The vacuum biopsy needle remains in this position and is rotated clockwise to obtain tissue from the surrounding area. Normally at least 12 cylinders are biopsied and if needed by larger lesions, up to 24 samples were taken. After performing the biopsy two images in lateral and craniocaudal views are done to determine and ensure the correct position of the Clip. Three different brands of the clips were used while performing and collecting our study population Hydromark™, SecureMark® or Tumark®. After vacuum biopsy of microcalcifications, specimen radiography must be carried out using magnification technology. After the vacuum biopsy, the representativeness of the sample was assessed by specimen radiography to document how many cylinders out of the total number of cylinders contained microcalcifications. Then samples have been submitted to the pathologist for further preparations according to the German S3 guidelines for diagnosis and treatment of breast cancer (S3-Leitlinie Mammakarzinom 2021). Appropriate follow-up care and observation of the patients and second look of the biopsied breasts were done by the doctor after at least 30 minutes to ensure appropriate homeostasis. The histopathological findings and the final report must be sent to the referring doctor promptly. The doctor was responsible for complete written and pictorial documentation responsible for the indication and execution of the vacuum biopsy. The written documentation included name and age of the patient, type of the lesion (microcalcification, focal findings, architectural disturbance), localization of the lesion, indication of the vacuum biopsy according and the date the vacuum biopsy was performed.

3.3 HISTOPATHOLOGY OF BREAST LESIONS

3.3.1 Benign findings

The mammary gland comprises 15-25 individual glands whose excretory ducts lead to the nipple. Each consists of several lobules that line the glandular acini. The area of the most peripheral segment of the duct and the lobule becomes referred to as the terminal ductal lobular unit (TDLE) and plays an essential role in the pathogenesis of various mammary lesions, especially breast cancer. Around the individual glands is located the sexually mature female, a fibrous stroma. After menopause, the mammary gland is converted into adipose tissue (Böcker et al. 2012).

Benign changes can be detected histopathologically in up to 90% of women. In particular, the so-called fibrocystic mastopathy (FCM) is so common that some authors consider it to be a physiological variant should be considered. However, there are also benign nonproliferative changes of importance for imaging since the difficulty distinguishing from malignant lesions and sensitivity may be restricted (Sylvia H. Heywang-Köbrunner et al. 2010). Benign proliferative changes without atypia, such as adenosis or certain fibroadenomas (FA), can be associated with a slightly increased risk of breast cancer (Lebeau et al. 2019).

3.3.2 Lesions With Unclear Biological Potential (LUBP)

LUBP is also considered a benign diagnosis. However, they can also act as a precursor (precancerous lesions) for breast cancer. Also, they are often found in biopsies and resected specimens associated with in situ or invasive carcinomas. Biopsies are often inhomogeneous tissues.

Flat epithelial hyperplasia (FEA) and atypical ductal hyperplasia (ADH) are the most commonly associated LUBP with microcalcifications (Saladin et al. 2016). Both have DCIS and invasive ductal carcinoma (IDC) in the glandular cells of the TDLE and are, therefore, considered to be non-obligate precancerous lesions (Sylvia H. Heywang-Köbrunner et al. 2010). The FEA is an atypically modified Columnar cell hyperplasia with enlargement of the glandular acini of the TDLE (D'Orsi, Sickles, and Mendelson 2016).

ADH, on the other hand, already shows the same cell atypia as DCIS grade 1 and can only be reduced by the minor expansion (<2mm, <1 TDLE) of this demarcate (Sylvia H. Heywang-Köbrunner et al. 2010).

Lobular neoplasms that also arise in the TDLE are considered bilateral.

Risk factors and non-obligatory precancerous lesions of the IDC and ILC. It deals with monomorphic and non-cohesive cells with a round nucleus.

LUBP also includes radial scars/complex sclerosing (RN) and papillary lesions (PL). They often appear in combination with intraepithelial proliferation. Other rare LUBPs are Phylloides tumors and various mixed cell entities such as the mucinous lesion (Sylvia H. Heywang-Köbrunner et al. 2010).

3.3.3 Ductal Carcinoma in Situ

DCIS is a malignant neoplasm that spreads from TDLE to the milk ducts. However, it is within the basement membrane. A distinction is made between the DCIS grades 1-3, which are based on the Cell and nuclear morphology and can be distinguished from each other (D'Orsi, Sickles, and Mendelson 2016). Spreading in the milk ducts occurs due to secretion congestion to precipitation and thus to visible microcalcifications in mammography. These are found in 50-75% of DCIS (Ditsch et al. 2020).

3.3.4 Invasive Breast Cancer

Invasive breast carcinomas are classified according to the current WHO classification divided by 2012. At 40-75 %, IDC is the most common type of tumour. It usually has no specific growth pattern and is referred to as a ‘no special type’ (NST). An NST is found in up to 80 % of IDC tumours.

3.3.5 B classification

According to the current guidelines, the histopathological findings of the biopsies are according to the recommendations of the United Kingdom National Health Service Breast Screening Program" (NHSBSP) (Lebeau et al. 2019; Bundesärztekammer (German Medical Association) and Instand E.V. 2015). This so-called B classification is summarized in Table 2 (Lebeau et al. 2019).

Table 2: B Classification

B Category	Definition	Diagnosis
B1	Normal tissue	artifacts, bleeding, microcalcification (<100 µm) in normal terminal ductules, normal breast tissue minimal stromal fibrosis
B2	Benign lesions	Fibroadenoma Usual ductal hyperplasia (UDH) Fibrosis with cysts Sclerosing adenosis Cysts, ductal ectasia Periductal chronic inflammation, Abscess Fat tissue necrosis Microcalcification (>100 µm) Columnar cell lesion without atypia Small papilloma (wholly removed) Apocrine metaplasia Pseuoangiomatous stromal hyperplasia (PASH)
B3	A benign lesion with uncertain biological potential (LUBP)	Atypical ductal Hyperplasia (ADH) Lobular Neoplasia (LN, Ø pleomorphic) Columnar cell lesion with atypia (FEA) Papillary lesion (Papilloma with UDH, larger papilloma) Phyllodes Tumor (PT)

		Fibroepithelial Tumor (suspicious of PT) Radial scar, Complex sclerosing lesion (CSL) Adenomyoepithelioma Pregnancy-like change with atypia Mucocele like lesion Spindle cell stromal Proliferation
B4		It is probably malignant, and evaluation is limited due to technical reasons. At least ADH and DCIS (non-high grade) are not excluded. Papilloma with ADH
B5 B5a B5b B5c B5d	Malignant Non-invasive breast cancer Invasive breast cancer Invasion not excluded Other malignancies	 DCIS, LN (pleomorphic), microinvasion, M. Paget (a) Invasive breast cancer (b) At least DCIS, invasion not excluded (c) Metastasis, Lymphomas, Sarcomas, malignant Phyllodes Tumor (d)

3.3.6 Procedure after minimally invasive diagnostics

The histopathological results have been discussed in a post-interventional multidisciplinary case conference. If only pure normal tissue (=B1) is found in the biopsy, it may be an unrepresentative biopsy and should be re-evaluated. In the case of B2 findings, a control of the mammography after six month is recommended (Sylvia H. Heywang-Köbrunner et al. 2010). When breast carcinoma is diagnosed, the therapy should be determined according to the interdisciplinary tumor conference. The limited locoregional diseases require surgery, possibly with a biopsy of the sentinel Lymph nodes SLNB (in invasive carcinoma) and, depending on the Receptor status carried out a subsequent antiestrogenic therapy. In case of unfavourable tumour biology or advanced stage, neoadjuvant chemotherapy should be carried out before surgery. Breast-conserving surgery is often followed by radiotherapy and systemic therapy (Lebeau et al. 2019; O'Flynn, Wilson, and Michell 2010). While the DCIS in earlier times often used to have a mastectomy (often with radical axillary evacuation), most patients now receive breast-conserving therapy (Bick et al. 2020). An SLNB should only be carried out at the DCIS according to the current S3 guidelines in case of mastectomy. A secondary SLNB (e.g., after a mastectomy) would not be possible. LIN3 is, at this moment, treated similarly to DCIS. In metastatic breast cancer, palliative and supportive therapy should be sought early (Lebeau et al. 2019).

A straightforward treatment strategy or set for LUBP algorithm is currently lacking. Surgical excision and a radiological Follow-up observation with and without chemoprevention are possible(Lauby-Secretan et al. 2015). According to the current S3 guideline, therapy planning should be interdisciplinary cooperation (Lebeau et al. 2019). Everyone should be involved in the decision; relevant factors are included, including the radiological findings, the representativeness of the biopsy, histopathological features, and other risk factors for breast cancer and concomitant diseases of the patients (Sylvia H. Heywang-Köbrunner et al. 2010).

3.4 EVALUATION OF CLIP MIGRATION

For evaluation of clip migration, we reviewed mammograms before and after biopsy and measured the distance of the clip from the biopsy site in 3 planes. Post-biopsy mammograms were compared to prebiopsy two-view mammograms, and the larger distance in the two-view mammography was evaluated and collected.

A clip dislocation for a distance smaller than 10 mm was considered irrelevant. A clip location for a distance of more than 10mm increases the likelihood of a positive margin at excision after needle localization and is therefore considered relevant (Lehman and Shook 2003).

In reviewing the mammograms, breast density was also assessed according to the ACR classification. The levels are 4 different Levels of breast density (A) almost entirely fatty, (B) scattered areas of fibroglandular density, (C) heterogeneously dense, and (D) extremely dense.

3.5 DATA REVIEW

Many factors were compared to assess if they significantly affected the clip dislocation, like age, breast thickness, access and direction of the biopsies, Clip type, severity of bleeding, number of samples, and histology of the biopsied lesions (Sakamoto et al. 2018).

The data were taken from the patients' records and systematized pseudonymously in a table (Microsoft Excel). For the evaluation, the data were transferred into the statistical program SPSS. The following information was taken from the files:

- Patients age (years)
- Breast thickness (mm)
- Number of samples

- The direction of access (lateromedial, mediolateral, craniocaudal, from below)
- Clip type:
    - Hydromark™ (Devicor Medical Products, Inc., Quickborn, Germany)
    - SecureMark® (Hologic Deutschland GmbH, Berlin; Germany)
    - Tumark® Vision (Hologic Deutschland GmbH, Berlin; Germany
- Bleeding intensity (minor, moderate, severe)
- Histopathological findings
- Surgical procedures and outcomes

The R-Classification

The R classification, adopted in 1987 by the UICC, denotes the absence or presence of residual tumors after treatment(Hermanek and Wittekind 1994). The residual tumor may be localized in the primary tumor area and/or as distant metastases. The R classification considers clinical and pathological findings. A reliable classification requires the pathological examination of resection margins. The R classification has considerable clinical significance, mainly being a strong predictor of prognosis. General and specific procedures for performing pathological R classification on resection specimens of different organs will be described. New methods in R classification comprise imprint cytology, cytological examination of ascites, and examination of bone marrow biopsy. The importance of these methods will have to be established in the future (O'Flynn, Wilson, and Michell 2010).

According to the AJCC:

- R0 - no cancer cells were seen microscopically at the primary tumor site.
- R1 - cancer cells present microscopically at the primary tumor site.
- R2 - Macroscopic residual tumor at primary cancer site or regional lymph nodes. It does not include metastatic disease identified but not sampled during surgery.

3.6 STATISTICAL ANALYSIS

The statistical analysis was done with the IBM SPSS Statistics Version 27. First, a descriptive evaluation was conducted in which the quantitative data were described using minimum, maximum and mean values. For the qualitative characteristics, the absolute and relative frequencies were given.

Cross tables were created and the Pearson's Chi² test and Fisher's exact test were carried out to test the qualitative correlations for statistical significance. The Chi² test is used to test non-metric variables for independence. If the variables are independent of each other, there is no significant difference between the two variables examined ($p>0.05$). The Fisher exact test is used with four-item tables.

A significance level with a probability of error of $p<0.05$ was set for all statistical tests.

The quantitative characteristics were tested for normal distribution using the Kolmogorov-Smirnov test. Most of the variables tested did not have a normal distribution (Kolmogorov-Smirnov test: $p<0.05$), so non-parametric tests were used. The Mann-Whitney U test is a non-parametric test, which tests two independent samples for significant differences.

4 RESULTS

4.1 CHARACTERIZATION OF THE STUDY COLLECTIVE

One hundred ninety-two biopsies were performed for 190 patients. Two patients had a biopsy on both sides, resulting in 192 biopsies for 190 patients. This group of patients was collected in our breast unit from 22/10/2020 to 31/12/2021. The patient's ages ranged from 38 to 86 years (the median was 60.8). The average thickness of the breasts in the patients ranged from 27 to 92 mm (median = 53 mm). In 190 (98.5%) patients, the target lesion type was calcification; in two (1.5%) patients, the target lesion type was a mass. The breast density was divided into four groups according to the BI-RADS reporting system. The levels are (from left to right) A: almost entirely fatty, B: scattered areas of fibroglandular density, C: heterogeneously dense, and D: extremely dense. The first group (A) was 29 of the total number of patients the second group (B) of patients was 88 of the total number of patients, the third group (C) of patients was 70 out of the total number of patients, and the fourth group (D) of patients was 5 out of the total number of patients.

The direction of biopsy was done in four directions: lateromedial, craniocaudal, mediolateral, and from below (caudocranial). Of all patients, 82 (42.7%) had a lateromedial direction biopsy, 48 (25.0%) patients had a craniocaudal direction biopsy, 38 (19.8%) patients had a mediolateral direction biopsy, and 24 (12.5%) patients had a biopsy done by a craniocaudal direction biopsy from below (caudocranial).

The study included the brand of the Clip to see whether it affected the displacement of the Clip after the biopsy (59). Twenty (10.4%) of the patients did not have a clip, 55 (28.6%) of the patients were given a clip of the brand Hydromark™, and 75 (39.1%) of the total number of patients were given a clip from SecureMark®. Finally, the remaining 42 (21.9%) patients used the clip Tumark® Vision.

Of all our patients, 123 (64.0%) had a histological diagnosis of a B2 lesion, 19 (9.9%) patients had a histological diagnosis of a B3 lesion, 41 (21.4%) patients had a histological diagnosis of a B5a lesion, and 8 (4.2%) of patients whose histological diagnosis was B5b, and finally 1 (0.5%) of the total number of patients whose histological diagnosis was B5c.

No surgery was necessary for 124 (64.6%) of all patients. Eighteen (9.4%) of the patients did the Excisional biopsy, 37 (19.3%) of the total patients had breast-conserving surgery, and the remaining 13 (6.8%) of the total number of patients underwent a mastectomy. The patient's characteristics are summarized in Table 3.

Table 3: Clinical and mammographic findings data (n=192)

Variable/Category	Value
Age (years) [a]	60.8 (38-86)
Breast thickness (mm) [a]	53.0 (27-92)
Target lesion type	
calcification	190 (98.5)
mass	2 (1.5)
Breast density	
A	29 (15.1)
B	88 (45.8)
C	70 (36.5)
D	5 (2.6)
The direction of compression/view	
lateromedial	82 (42.7)
craniocaudal	48 (25.0)
mediolateral	38 (19.8)
caudocranial	24 (12.5)
Clip type/brand	
No clip	20 (10.4)
Hydromark™	55 (28.6)
SecureMark®	75 (39.1)
Tumark®Vision	42 (21.9)
Histological diagnosis	
B2	123 (64.0)
B3	19 (9.9)
B5a	41 (21.4)
B5b	8 (4.2)
B5c	1 (0.5)
Primary surgery	
none	124 (64.6)
Excisional biopsy	18 (9.4)
Breast-conserving surgery	37 (19.3)
mastectomy	13 (6.8)

Unless otherwise indicated, data represent the number of cases with percentages in parentheses

[a] Data are indicated as means with ranges in parentheses

4.2 FACTORS INFLUENCING CLIP DISPLACEMENT AFTER STEREOTACTIC VACUUM-ASSISTED BIOPSY

Twenty patients did not receive a clip because some refused the application of the clip, and for some of them, there was no indication. They are excluded from the target table. Clinical and mammographic parameters with potential influence on the accuracy of clip placement at the biopsy site are summarized in Table 4 (n=172).

4.2.1 Age

Age had no relation to clip displacement from the biopsy site as if all ages of 172 patients ranged from 38 to 86 years with an average of 60.7 years; of the 142 patients with clip displacement <1 cm, their ages ranged from 38-84 years with an average of 60.5 years, while the age of 30 patients with clip displacement ≥1 cm ranged between 45 and 86 with an average of 61.4 years (p=0.913).

4.2.2 Breast thickness

Breast thickness did not correlate with the displacement of the biopsy clip from its place. The breast thickness of 172 patients ranged from 27 to 92 mm, averaging 50.2 mm. Among the 142 patients with clip displacement <1cm, the breast thickness ranged from 31 to 92 mm with an average of 54 mm, while in the 30 patients with clip displacement ≥1 cm, the thickness of their breasts ranged between 27 and 84 mm with an average of 49.3 mm (p=0.74).

4.2.3 Breast density

The results showed that category A of breast density contains 15.1% of the total patients. 92.3% did not have clip displacement, while 7.7% had clip displacement. In category B of breast density, which contains 47.7% of the total number of patients, 78.8% did not have clip displacement, and 22% had clip displacement. In category C of breast density, which contains 34.9% of the total number of patients, 83.3% did not have clip displacement, and 16.7% had clip displacement. Moreover, in category D of breast density, which contains 2.3% of the total number of patients, 100% did not have clip displacement. Therefore, breast density was not strongly related to the dislocation of the biopsy clip (p=0.29).

4.2.4 Direction of sampling

The direction of sampling affected the clip's location. Of the total number of patients, 41.3% of the sampling was taken using lateromedial direction. The result was that 76.1% of them did not cause clip displacement. In comparison, 23.9% of the patients had a clip displacement. The craniocaudal beam path was used in 25% of patients, and the result was that 81,4% of them had no clip displacement, while 18.6% had clip displacement. Of all biopsies, 20.9% were sampled by mediolateral beam path, and the result was that 88.9% had no clip displacement, while 11.1% of patients had clip displacement. Finally, 12.8% of the total number of patients were sampled using the direction from below (caudocranial), and the result was that 95.5% of them did not cause clip displacement. In comparison, 0.5% of patients experienced clip displacement (p=0.129).

4.2.5 Type of clip

Radiopaque markers are commonly deployed following breast biopsies to indicate the location of the targeted lesion. A frequently encountered complication is the displacement of these markers. This study compared the degree of displacement among three newer generation markers after stereotactic core needle biopsy.

The brands of the clip also had a slight effect on the change of clip location. When we used the Hydromark™ quality for 32% of the total number of patients, the result was that 76.4% did not have clip displacement, while 23.6% had clip displacement. Furthermore, when we used the quality of SecureMark® for 43.6% of the total number of patients, the result was that 85.3% did not have clip displacement, while 14.7% experienced clip displacement. Moreover, when we used the quality of Tumark®Vision for 24.4% of the total number of patients, the result was that 85.7% did not have clip displacement, while 14.3% of them experienced clip displacement (p=0.34)

4.2.6 Intensity of bleeding

Our results showed that the presence of severe Bleeding after biopsy was accompanied with slightly higher migration rates of the Clips. Of all patients, 52.3% suffered from minor bleeding, 81.1% did not have clip displacement, and 18.9% had clip displacement. Also, 43% of patients suffered from moderate bleeding, 85.1% did not have clip displacement, and 14.9% had clip displacement. Finally, 4.7% of the patients suffered from severe bleeding, 75% did not have clip displacement, and 25% had a clip dislocation (p=0.674).

Table 4: Clinical and mammographic parameters influencing the accuracy of clip placement at biopsy site (n=172)

		Clip displacement		
	Total	<1 cm (n=142)	≥1 cm (n=30)	p-value
Age (years) [a]	60.7 (38-86)	60.5 (38-84)	61.4 (45-86)	0.913*
Breast thickness (mm) [a]	53.2 (27-92)	54.0 (31-92)	49.3 (27-84)	0.74*
Number of samples [a]	11.9 (6-24)	11.9 (6-24)	12.1 (6-24)	0.787*
Breast density				0.29**
A	26 (15.1)	24 (92.3)	2 (7.7)	
B	82 (47.7)	64 (78.0)	18 (22.0)	
C	60 (34.9)	50 (83.3)	10 (16.7)	
D	4 (2.3)	4 (100)	0 (0)	
The direction of compression/view				0.129**
lateromedial	71 (41.3)	54 (76.1)	17 (23.9)	
craniocaudal	43 (25.0)	35 (81,4)	8 (18.6)	
mediolateral	36 (20.9)	32 (88.9)	4 (11.1)	
From below (caudocranial)	22 (12.8)	21 (95.5)	1 (4.5)	
Clip type/brand				0.340
Hydromark™	55 (32.0)	42 (76.4)	13 (23.6)	
SecureMark®	75 (43.6)	64 (85.3)	11 (14.7	
Tumark®Vision	42 (24.4)	36 (85.7)	6 (14.3)	
Bleeding				0.674
minor	90 (52.3)	73 (81.1)	17 (18.9)	
moderate	74 (43.0)	63 (85.1)	11 (14.9)	
severe	8 (4.7)	6 (75.0)	2 (25.0)	

Unless otherwise indicated, data represent the number of cases with percentages in parentheses
a Data are indicated as means with ranges in parentheses
* Mann-Whitney U-test; **Pearson-chi-squared test

4.3 COMPARISON OF HISTOPATHOLOGICAL FINDINGS AND SURGICAL OUTCOMES IN PATIENTS WITH OR WITHOUT CLIP DISPLACEMENT

4.3.1 Histopathological findings

Histopathological findings showed that diagnosis of benign disease (B2) was within 64% of the total number of patients, of whom 7.3% did not contain a clip, 74.8% did not get clip displacement, and 17.9% did clip displacement.

A lesion of uncertain malignant potential (B3) was found in 19/192 (9.9%) of the biopsies. Of them,10.5% were not clipped, 73.3% did not have clip displacement, and 15.8% had clip displacement.

The diagnosis of intraductal carcinoma of the breast (B5a) included 21.4% of the total number of patients, 19.5% of whom had no clip, 68.3% did not have clip displacement, and 12.3% had clip displacement.

In eight of 192 biopsies (4,2%), an invasive breast cancer (B5b) was found. One of them did not have a clip. In seven biopsies, clip displacement <1cm was observed, while no clip displacement > 1cm occurred in any category B5b. Among all biopsies, one was diagnosed as B5c. This one did not show any clip displacement >1 cm. Histopathological findings are summarized in table 5.

Table 5: Histopathological results depending on clip placement (n=192)

			Clip displacement		
	Total	No clip	< 1 cm	≥1 cm	p-value
Histopathological findings					0.680*
B2	123 (64.0)	9 (7.3)	92 (74.8)	22(17.9)	
B3	19 (9.9)	2 (10.5)	14 (73.3)	3 (15.8)	
B5a	41 (21.4)	8 (19.5)	28 (68.3)	5 (12.3)	
B5b	8 (4.2)	1 (12.5)	7 (87.5)	0 (0)	
B5c	1 (0.5)	0 (0)	1 (100)	0 (0)	
total	192	20	142	30	

Data represent the number of cases with percentages in parentheses.
* Pearson-chi-squared test

4.3.2 Outcome of surgery

Of the 192 biopsies, 64.6% did not require surgical excision.

An excisional biopsy followed eighteen biopsies (9,4%). Of them, 5.6% had no clip, 83.3% had no clip displacement, and 11.1% had clip displacement.

Breast-conserving surgery was performed for 37 (19.3%) of the total number of biopsies, of whom 83.8% had no clip displacement, 8.1% had clip displacement >1 cm, and 8.1% had no clip.

Of the 192 biopsies, 6.8% underwent a mastectomy, 53.8% were not clipped, 38.5% did not have clip displacement, and 7.7% had clip displacement.

Specimen radiography was done for 56 cases. In 47 of them, the clip was detected, but nine specimens did not include the clip. Of the latter, clip displacement was present in 3 out of 9 cases, whereas only 3 out of 47 with a clip detected had a clip displacement >1 cm (p=0.046).

Data on immediate re-excision were available for 55 cases. Immediate re-excision was performed in 11 of 55 cases, of which one patient had no clip, 8 had no clip displacement and 2 had clip displacement. In contrast, among the 44 cases without immediate excision, only three were with clip displacement, 38 were without, and three did not have a clip (p=0.470).

Surgical margins were determined to be ≥1 mm. Any surgical margin < 1 mm was deemed positive, and patients underwent re-excision as appropriate.

Table 6: Surgical outcome depending on clip placement (n=192)

			Clip displacement		
	Total	No clip (n=20)	< 1 cm (n=142)	≥1 cm (n= 30)	p-value
Primary surgery					
none	124 (64.6)	9 (7.3)	91 (73.4)	24 (19.4)	
Excisional biopsy	18 (9.4)	1 (5.6)	15 (83.3)	2 (11.1)	
Breast-conserving surgery	37 (19.3)	3 (8.1)	31 (83.8)	3 (8.1)	
mastectomy	13 (6.8)	7 (53.8)	5 (38.5)	1 (7.7)	
Specimen radiography	56				0.046*
Clip included	47 (83.9)		44 (93.6)	3 (6.4)	
Clip not included	9 (16.1)		6 (66.7)	3 (33.3)	
Immediate re-excision	55				0.470*
No	44 (80.0)	3 (6.8)	38 (86.4)	3 (6.8)	
Yes	11 (20.0)	1 (6.8)	8 (72.4)	2 (18.2)	

Surgical margins	55				0.057*
Free	44 (80.0)	3 (6.8)	39 (88.6)	2 (4.5)	
Affected	11 (20.0	1 (9.1)	7 (63.6)	3 (27.3)	

Data represent the number of cases with percentages in parentheses.
* Fisher's exact test

4.3.3 Secondary surgery

Of the 68 patients who underwent primary surgery, no further surgery was necessary in 54 cases. Six patients underwent the re-excision, five underwent secondary mastectomy (±SLNB), and three underwent SLNB alone (table 7).

Table 7: Secondary surgery (n=68)

	n	%
None	54	79.4
Re-excision	6	8.8
Mastectomy (±SLNB)	5	7.4
SLNB alone	3	4.4

SLNB sentinel lymph node biopsy

4.3.4 Histopathological findings, clip placement and residual microcalcifications

In a vacuum-assisted biopsy, the microcalcification group is either completely removed or residual calcifications remain. Depending on the histopathological diagnosis and the resulting need for surgery, it is investigated whether residual calcification was present in the case of clip migration.

Of the 19 B3 lesions, only six were without residual microcalcifications, one with a clip displacement >1 cm. Among the 50 B5a-c lesions, two had complete removal of microcalcifications, and none of the latter had a clip displacement >1 cm (Table 8).

Table 8: Histopathological results according to clip displacement and the presence of residual microcalcifications (n=192)

				Clip displacement

Histopathology	Residual microcalcification	total	No clip	< 1 cm	≥1 cm
B2	No	68	1 (1.5)	55 (80.9)	12 (17.6)
	Yes	55	8 (14.5)	37 (67.3)	10 (18.2)
B3	No	6	0 (0)	5	1
	Yes	13	2 (15.4)	9 (69.2)	2 (15.4)
B5a-c	No	2	0 (0)	2 (100)	0 (0)
	Yes	48	9 (18.8)	34 (70.8)	5 (10.4)

Data represent the number of cases with percentages in parentheses

5 DISCUSSION

5.1 STUDY POPULATION

Stereotactic vacuum-assisted biopsy is an established method in early breast cancer detection to confirm the histological diagnosis of BI-RADS category 4 and 5 findings that are only visible by mammography. If the suspicious lesion, e.g. microcalcification, has been entirely removed by biopsy, a clip is inserted to mark the biopsy site. Previous studies described clip migration after stereotactic vacuum-assisted biopsy in about 12-13% (Jain et al. 2017; Uematsu et al. 2012). Clinically significant clip migration represents a challenge for radiologists and surgeons for subsequent surgery and may worsen the patient's outcome. The aim of this study was, therefore, to identify causes of relevant clip migration. Furthermore, the impact of a clinically relevant clip migration on subsequent surgery has been investigated. To this purpose, we performed a retrospective study of 192 stereotactic vacuum-assisted breast biopsies at the Breast Centre of the University of Rostock at Klinikum Südstadt. from 22/10/2020 to 31/12/2021. Of these, 172 were clipped within the biopsy cavity. Clinically relevant clip migration >1 cm occurred in 17.5% of cases. The Meta-Analyse of Lee et al. 2022 included 3.347 clips after vacuum-assisted breast biopsy from eight retrospective and one prospective study; the average rate of clip migration was 26,8%, range: 14.1-33.3% (Lee et al., 2022) and other studies showed a clip migration rate of 11.8% (Tari et al. 2023) and up to 20 % (Liberman 2000). Our study shows a lower migration rate than the average of the previous studies with a migration rate of 17.5% (Tari et al. 2023; Liberman 2000).

5.2 CAUSES OF CLIP DISLOCATION

Several studies and one recent meta-analysis have shown that clip migration after vacuum-assisted breast biopsy is significantly more frequent in low breast density (fatty breasts), especially the immediate clip migration rate after the biopsy (Huang et al. 2014; Teichgraeber et al. 2020; Jain et al. 2017; J. Wang, Chien, and Lee 2020; I. T.-L. Lee et al. 2022). In the recent meta-analysis by Lee et al a strong correlation of clip migration in globally fatty breast tissue was shown (RR 2.00, 95%CI 1.43; 2.80, $p<0.001$) (Lee et. al., 2022). In contrast, in our study low breast density did not correlate with increased clip migration rate. The rate of significant clip migration was lowest in patients with breast density A at 7.7%, compared to breast density B at 22% and C at 16.7%.

However, we must mention that the decision of the breast density category according to ACR categories A and B is very subjective and can vary according to the examiner. However, no study has more than 50% of the population with fatty breast ACR A and B. The present study is the first to include more than 62% of the population with ACR categories A and B. Moreover, when it comes to the direction of the biopsy, our study showed nonunique results compared to the previous studies and literature that showed that the direction of the biopsy had no role in clip migration (Huang et al. 2014; Teichgraeber et al. 2020; Jain et al. 2017; J. Wang, Chien, and Lee 2020; I. T.-L. Lee et al. 2022). According to our results, there was no clear evidence that the direction of the biopsy could increase the risk of clip displacement. Our results show that the different directions of the biopsy had no significant effect.

Only a few studies exist on the correlation between breast thickness and clip migration. In the retrospective study by Uematsu et al. (2012) on 204 patients with stereotactic VABB, the breast thickness was the only factor that was predictive of a significant movement of the clip. They found that thin breasts tended to have greater clip movement (Uematsu et al. 2012). In our study, breast thickness had no significant influence on clip migration, although the group with clip migration >1cm tended to have less breast thickness (54.0 vs. 49.3 mm, p=0.74).

The previous study of Jain et al. showed that the number of samples did not affect Clip dislocation (Jain et al. 2017). In our study, 12 samples were always taken in accordance with the guidelines, so that no statement is possible on the influence of the number of samples upon the rate of clip migration.

Compared to previous studies, the bleeding rate in our patients was slightly higher than in those studies. In our study we could show that whether minor or major bleedings did affect clip migration (Pinkney, Mychajlowycz, and Shah 2016; Jain et al. 2017). Even the presence of visible Hematoma or severe haemorrhage was not associated with a significantly increased risk of clip displacement for more than one centimetre.

Regarding the different brands of the clips used in the biopsies, a prospective study by Pinkney al al. comparing the displacement of four commercially available breast biopsy markers revealed that the rate of clip migration was lower using the Clips of SecureMark® and Tumark®Vision than the rate of migration that happened using Hydromark™ (Pinkney, Mychajlowycz, and Shah 2016). The largest study on the type of clip was published by Yen et al. (2018) with 2112 patients. They compared surgical clips with commercially available clips (SenoMark, SecureMark®, Hydromark™). The results revealed the superiority of the commercial clips, which had a lower migration rate (38% vs. 27-28%). Only one study found that a T-shaped clip and a heterogeneous composition of the breast had a protective effect on clip migration (Jain et al., 2017). Coated versus uncoated clips also did not reveal any significant influence.

Some authors assume that coated clips have lower migration rates. In the current study, there was no difference in the migration rate for different clips, non-coated (SecureMark®) and coated (Hydromark™, SecurMark), evenly placed (Shah et al, 2018). In our study, Hydromark™ exhibited the greatest mean clip displacement, followed by SecurMark® and Tumark®Vision, although these differences did not reach statistical significance ($p = 0.34$).

In our practice, various precautionary measures have been taken to minimise the rate of clip migration. The paddle compression release was performed slowly to avoid accordion effect. Immediately after the needle was removed and paddle compression released, manual compression was applied to the biopsy sites in the direction of needle insertion to avoid the formation of hematomas and bleeding and the to minimize the risk of clip migration accompanied by significant bleeding or formation of a hematoma. (Weaver et al., 2021)

5.3 IMPACT OF CLIP MIGRATION ON PATIENT OUTCOMES

Within our 192 biopsies were no recorded cases of false negative biopsies with an accuracy rate of 100%, which is almost like previous studies. For example the Study of Jackman, Marzoni, and Rosenberg et al. 2009 showed out of 1121 11gauge vacuum biopsies an accuracy percentage of 99.55%, and the multicentre study of Kettritz et al. 2004, which included 2874 patients showed an accuracy rate of 99.5% with one recorded false negative biopsy out of the 2874 biopsies.

In our study, 64% of patients were diagnosed with benign disease (B2), 9.9% with lesions of uncertain malignant potential (B3), 21.4% with intraductal carcinoma of the breast (B5a) and 4.2% with invasive breast cancer (B5b). In our study, the rate of B3 lesions of 9.9% is significantly lower than in the study by Saladin et al. 2016, which described a rate of 17.0% and a rate of malignancies (invasive and non-invasive) of 21.5% in a total of 9153 VABB. However, this study included stereotactic as well as sonographically guided and MR-guided VABB (Saladin et al. 2016). Our study revealed that of the B3-B5 lesions with clip dislocation, only one B3-lesion was without residual microcalcifications. Therefore, wire-assisted surgery was not possible in this patient. Since histologically it showed a radial scar, a wait-and-see approach was possible. The follow-up examinations after 12 and 24 months revealed no new lesion on mammography.

For 64.6% of the total biopsies, no subsequent surgery was necessary. Compared to the study of Sigal-Zafrani et al. (2008) a higher rate of our patients (64.4% vs. 54%) were not primarily operated (Sigal-Zafrani et al. 2008). This is because almost two thirds of the biopsies in our study revealed benign histologies. However, this also means that the VABB saved those patients an open surgical procedure.

Breast-conserving surgery or excisional biopsy was performed in 28.6% of all biopsies, while a mastectomy was performed in 6.8%. Specimen radiography was done for 56 cases. In forty-seven of them, the clip was detected, and nine did not include the clip. Our study revealed that with subsequent surgery, clip migration >1 cm was associated with a higher rate of negative specimen radiography. Of the latter, clip displacement was present in 3 out of 9 (66.7%) cases, whereas only 3 out of 47 (93.6%) with a clip detected had a clip displacement >1 cm (p=0.046). All nine missing clips were removed during the immediate re-excision. Therefore, in none of our 56 cases the clip was missed.

The consequences of missing clips were described in the study of Green et a. (2021). The research group included 43 women [5% of the cohort; 95% confidence interval (CI) 3.9-7.2] with a missing clip. The positive margins were comparable (7.17 % of cases; 29, 15 % of 196 cases in the control group; p = 0.96). In eleven women (33%), a residual clip was visible on postoperative mammography; in four cases a percutaneous biopsy of the clip was successful, all without residual tumour. There was no significant difference in the rate of re-excision (14 % vs. 8 %, p = 0.23) or local or distant recurrence.

In our study, immediate re-excision was performed in 11 of 55 cases (20%). The rate of clip migration >1 cm was higher in the cohort with immediate re-resection than in the cohort without re-resection (18.2% vs. 6.8%), but the difference was not statistically significant (p=0.470). Our data showed the same re-excision rate that mentioned in the previous literature depending on the specimen radiography (Van Riet et al. 2021)

Of the 68 patients who underwent primary surgery, no further surgery was necessary in 54 cases. Six patients underwent the re-excision, 5 underwent secondary mastectomy (±SLNB), and 3 underwent SLNB alone. Here, the percentage of the patients who needed a re-operation (re-excision, mastectomy, or SLNB) was also lower than the percentage in the previous literature (Bundred et al. 2016).

As documented, out of the 55 Patients who underwent surgeries, re-excision was indicated in 11 cases due to affected surgical margins. Our results reveal a marginal significant influence of clip migration on the rate of affected margins. In 3 of 11 patients (27.3%) with affected margins, clip migration >1 cm was present, whereas in free margins, clip migration was observed in only 4.5% (p=0.057). Ignoring the inaccurately located clip and using sonography or mammography-assisted internal breast landmarks and confirmation of the correct location of the marker with the help of mammography in two views or sonography led to avoiding misguidance of the surgeons. This approach conforms to the previous literature. (Birdwell and Jackman 2003).

5.4 STRENGTHS AND WEAKNESSES OF THE STUDY

Our study is the first to systematically address surgical management and outcome after clip dislocation. We showed that, in most cases, the biopsy region can be safely removed even after clip dislocation.

Our study considered age, breast side, clip brand, breast thickness, compression applied on the breast, direction, and number of samples. We also had a large population of 192 patients, which makes our results reliable. However, only 30 patients had a clip migration >1 cm. As a result, the factors influencing clip migration possibly did not achieve any significant differences.

One of the weaknesses of our study was that we considered the whole breast's density and not the regional inhomogeneity in the biopsy location. We also did not consider the location of the suspected lesion in the breast or the depth of the lesion in relation to the skin or chest wall. We also eliminated the presence of hematomas after biopsies and included the severity of bleeding.

6 SUMMARY

Previous studies have shown that clip movement after vacuum-assisted stereotactic biopsy is not uncommon and ranges from 13 to 33% (I. T.-L. Lee et al. 2022). The recent study shows a migration rate of 15.6%. Previous studies have also investigated the mechanisms of clip migration, the causes and changes in clip position due to breast anatomy or lesion size and shape, changes in clip position after reduction mammoplasty, and clip displacement with different clips.

The current research shows that neither the type of clip nor age, the direction of biopsy, and breast density had an influence on clip dislocation. Despite that, some studies showed that the number of samples, breast composition, and fat density significantly affect clip migration, but our study showed different results. In our study, we probably had more patients with microcalcification (190 out of 192 biopsies), and in only two cases was the target lesion mass. Unfortunately, the local heterogeneity surrounding the lesion was not included and tested in the current study, and instead of that, we have, like many previous studies, the breast density.

The presence of severe bleeding after the vacuum-assisted breast biopsies was accompanied by slightly higher rates of Clip migration (25%) than in the case of minor (18.9%) or moderate bleeding (14.9%). So, appropriate haemostasis and control of bleeding can be beneficial in reducing clip dislocation, especially in patients with a higher risk of bleeding.

The histopathological findings revealed that the diagnosis of benign disease (B2) was found in 64% of all patients. A lesion of uncertain malignant potential (B3) was diagnosed in 9.9% of the biopsies, whereas intraductal carcinoma of the breast (B5a) was diagnosed in 21.4 %. In eight of 192 biopsies (4,2%), an invasive breast cancer (B5b) was recorded.

Based on the diagnosis of a B3-B5 lesion, 68 (35.4%) patients underwent primary surgery. Of them 28.6% underwent excisional biopsy or breast conserving surgery, while 6.8% underwent primary mastectomy. In 5 of 55 patients with breast conserving procedures, clip migration >1 cm was present. In the majority of cases with clip migration >1 cm (n=24), no surgery was necessary due to a B2 lesion. One patient with clip migration >1 cm underwent a mastectomy.

In the patients with breast-conserving procedures and clip dislocation > 1 cm, residual microcalcifications were present in four out of five cases. Therefore, a wire-guided operation could be performed in these four women. Only in one patient with a biopsy-proven radial scar (B3-lesion) was safe wire-guided surgery not possible due to the lack of residual microcalcifications in the case of relevant clip migration. After 24 months of follow-up, this patient revealed no new lesion on mammography.

To date, there is no data on the effects of immediate clip migration on a subsequent operation. Our study revealed that with subsequent surgery, clip migration >1 cm was associated with a higher rate of negative specimen radiography (33.3% vs. 6.4%, p=0.046). We also revealed that relevant clip migration was associated with a higher rate of affected margins. In 3 of 11 patients (27.3%) with affected margins, clip migration >1 cm was present, whereas in free margins, clip migration was observed in only 4.5% (p=0.057).

Our routine of examining the patients preoperatively, ignoring the inaccurately located clip, and using sonography or mammography-assisted internal breast landmarks to confirm the correct location of the marker preoperatively, using mammography in two views or sonography, was helpful in avoiding the surgeons' misguidance and minimizing the need for re-operation.

We think that further examination of the factors we did not take into consideration in our study like the local inhomogeneities according to the location of the lesion and the depth of the least in relation to skin and chest wall could be helpful to determine the relevancy of such factors and their effect.

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9 DECLARATION OF SELF-EMPLOYMENT

I hereby declare that I have written this thesis entitled: Clip migration after vacuum-assisted breast biopsy - influencing factors and impact on surgical outcome independently and without outside help, that I have not used any sources and tools other than those specified and that I have labelled the passages taken from the sources and tools used as such, either literally or in terms of content.

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