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# BENIGN BREAST LESIONS – ANALYSIS BY ARTIFICIAL INTELLIGENCE AND REMOVAL BY VACUUM-ASSISTED EXCISION

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# Benign breast lesions – analysis by artificial intelligence and removal by vacuum-assisted excision

Thesis for Doctoral Degree (Ph.D.)

By

Athanasios Zouzos

The thesis will be defended in public at Rolf Luft Auditorium, Anna Stecksens gata 53, CMM L1:00, Karolinska University Hospital, on Friday April 4<sup>th</sup>.

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This work is dedicated to my wife and child, for the countless hours of their patience, to my parents and brother for formatting my character, and to all my tutors who encouraged and believed in me.



## Popular science summary of the thesis

In 1986, the National Board of Health and Welfare in Sweden recommended screening mammography for women 40–74 years of age. Mammography has since become the modality of choice for the detection of breast cancer. Worldwide participation in diverse breast cancer screening mammography programs has been proven to significantly reduce breast cancer mortality. In Sweden, the current nationwide participation rate is > 80%, indicating great acceptance of the screening initiative.

In addition to the clear advantage of early breast cancer detection, widespread screening mammography has highlighted many other benefits, including less radical treatment, improved quality of life, and reduced societal costs.

Along with the detection of breast cancer, mammography can detect several other lesions in the breast that are benign or of uncertain malignant potential. The detection of such lesions has increased over the last decade with advancements in digital mammography equipment. Approximately 10% of screening findings are of uncertain malignant potential, which can lead to unnecessary work-ups involving biopsy and surgery.

The introduction of artificial intelligence (AI) for mammographic image analysis has proven beneficial to screening programs by further increasing the sensitivity of mammography, with the goal of reducing false-positive rates. Our first study investigated the grading of previous biopsies with an artificial AI-computer-aided detection (CAD) system.

Furthermore, the introduction of larger biopsy needles for work-ups based on radiographic findings has been proven to reduce false-negative rates and may allow for the removal of the entire specimen without the need for surgery. Our second and third studies investigated the effects of needle size on the outcomes of vacuum-assisted excisions of breast lesions, as well as patient experience during those procedures. Our fourth study reported the pathological appearance of our previous findings across repeated sampling with the goal of better understanding lesions that are suitable for minimally invasive excision.

# Abstract

Following advances in diagnostic imaging modalities over the last decade, lesions of uncertain malignant potential have been increasingly diagnosed, primarily through mammography and sonography. These diagnoses, however, increase patient anxiety and result in an abundance of work-ups, including biopsies for radiologists, and often lead to unnecessary surgery.

One modern field of research is the integration of artificial intelligence (AI) based computer-aided detection (CAD) systems into various types of equipment to improve their accuracy. Our first study (Study 1) investigated the grading of previous benign biopsies using an AI-CAD system that has been integrated into mammography.

Another modern field of research has been the use of larger bore needles in breast biopsies, such as vacuum-assisted biopsy needles with an outer diameter of up to 7G (4.6 mm). These needles can provide a sufficient tissue sample with which to obtain a more accurate diagnosis, while at the same time allowing the operator to completely excise the specimen under local anesthesia. Our second study (Study 2) investigated how needle size affected the time and results of the excision procedure. Our third study (Study 3) evaluated the procedure from the patients' perspective, documenting their experiences and any eventual adverse effects after the procedure. Our fourth study (Study 4) compared the first diagnostic pathology report to the reports obtained post-excision to identify lesion characteristics that would help determine which lesions are more susceptible to excision with a larger needle.

In Study 1 we retrospectively applied a commercial AI-CAD system (Insight MMG, version 1.1.4.3; Lunit Inc.) to a dataset of screening mammograms from 10,889 women. We divided the study population into three groups: women who did not undergo a biopsy, those who underwent a biopsy before or after screening mammography (with benign results), and those who were diagnosed with breast cancer. The AI system flagged all women above the cutoff threshold, which was defined as 0.4 on a scale of 0.0 to 1.0. The percentages of women flagged were as follows: 3.5% for healthy women without a biopsy, 11% for those with benign biopsy findings, and 84% for those with breast cancer ( $P < 0.001$ ). The AI-CAD system flagged a much larger proportion of women who underwent a biopsy than those who did not; however, the flagging rate was not any higher than that of the radiologists.



In Study 2 we performed a randomized controlled trial to compare the excision completeness and efficacy of the vacuum-assisted excision (VAE) procedure using 7G and 10G vacuum needles. We enrolled 208 patients, and after withdrawal of consent, the trial population included 194 patients. There were no differences in procedure time ( $P = 0.126$ ) or excision completeness ( $P = 0.109$ ) between procedures performed using 7G and 10G needles. Of the 127 patients who attended the 24-month follow-up, 88% (112/127) had lesions completely excised, with no statistically significant difference between the 7G and 10G needles.

In Study 3 we administered a questionnaire to all of the patients included in Study 2. Patient acceptance of the procedure and short- and long-term complications were also documented. We calculated the total hospital costs of the VAE procedures and compared them with those of open surgical excision (OSE), the previous standard of care for surgical excision. There were no significant differences in pain levels ( $P = 0.713$ ), complications ( $P = 0.724$ ), or patient acceptance of the procedure between the 7G and 10G needle groups ( $P = 0.401$ ). Approximately 97% (173/178) of the patients would recommend the procedure to others, and the total hospital procedural cost of VAE was estimated to be 60% lower than that of OSE.

In Study 4 we retrospectively examined the results of the pathology reports of all patients included in Study 2; however, we excluded patients who did not have a cytological or histopathological diagnosis prior to the VAE, during which tissue samples were placed in one, two, or three successive containers, starting at the core of the lesion and moving outwards to the normal tissue. The results of the diagnostic reports from the initial biopsy (cytology and/or histology) were compared with those from the tissues obtained during the VAE. The discrepancy between the diagnoses of fine needle aspiration (FNA) specimens and those from VAE was 38%, while that for core needle biopsy (CNB) was 29%. The upgrade rate to cancer was most common after a diagnosis of atypical ductal hyperplasia (ADH) on CNB.

In conclusion, this thesis provides new knowledge on how to improve the performance of AI-CAD systems and broadens our understanding of we can improve the performance of AI. This confirms the necessity for alternative solutions to surgery for the diagnosis and treatment of undetermined lesions and

provides data to support a separate personalized approach for different lesion types.

## List of scientific papers

- I. **Athanasios Zouzos**, Aleksandra Milovanovic, Karin Dembrower, Fredrik Strand

Effect of Benign Biopsy Findings on an Artificial Intelligence–Based Cancer Detector in Screening Mammography: Retrospective Case-Control Study

*JMIR AI 2023 | vol. 2 | e48123 | p. 7*

- II. **Athanasios Zouzos**, Irma Fredriksson, Andreas Karakatsanis, Iliana Aristokleous, Theodoros Foukakis, Fredrik Strand

Effect of needle size on outcomes of vacuum-assisted excision of breast lesions. A randomized controlled trial

*European Journal of Radiology 183 (2025) 111895*

- III. **Athanasios Zouzos**, Irma Fredriksson, Andreas Karakatsanis, Fredrik Strand

Patient experience and healthcare cost aspects of vacuum-assisted excision of breast lesions. A report from the Swedish VAE randomized clinical trial

*Manuscript*

- IV. **Athanasios Zouzos**, Irma Fredriksson, Andreas Karakatsanis, Johan Hartman, Fredrik Strand

Variation in pathological appearance across repeated sampling from probably benign breast lesions

*Manuscript*



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## List of abbreviations

ADH	atypical ductal hyperplasia
AI	artificial intelligence
ALH	atypical lobular hyperplasia
BCS	breast conservative surgery
BLES	breast lesion excision system
CAD	computer-aided design
cLCIS	classical lobular cancer in situ
CNB	core needle biopsy
DCIS	ductal cancer in situ
FEA	flat epithelial atypia
FNA	fine needle aspiration
LN	lobular neoplasia
OSE	open surgical excision
VAB	vacuum assisted biopsy
VAE	vacuum assisted excision





# Introduction

In the digital age, the ever-improving quality of diagnostic imaging equipment used in the detection of breast cancer, mammography and ultrasound in particular, has led to the identification of very small cancers (3 mm in size). The specificity for these small lesions remains relatively low, however, especially for those that do not present typical malignant characteristics on diagnostic imaging, prompting the need for more precise diagnostic testing through breast biopsies. The role of AI as a supplement to conventional diagnostic imaging has yet to be defined. Therefore, in the first study of my thesis my team and I investigated the parameters needed to define that role. Large-needle biopsies of breast lesions have traditionally been utilized to improve the diagnostic accuracy of pathology reports. More recently, however, they have been used for the excision of whole breast lesions. In the next three studies, therefore, we investigated various parameters that can affect the results of such excisions, taking into account the patients' perspectives and health costs, in an attempt to improve our understanding of breast lesions of uncertain malignant potential.



# 1 Background

## 1.1 Epidemiology of breast cancer

According to World Health Organization (WHO) and Global Cancer Project (GloboCan), breast cancer is the most common cancer among women, accounting for more than 25% of all cancer diagnoses in this population (1). The mortality rate of breast cancer varies from 6 to 29 per 100,000 individuals worldwide, placing it as the fifth leading cause of death from cancer overall and the most frequent among women (2, 3) (Figs. 1, 2). The number of newly diagnosed breast cancer cases is projected to increase by > 40% by 2040 (3) (Figs. 3, 4).

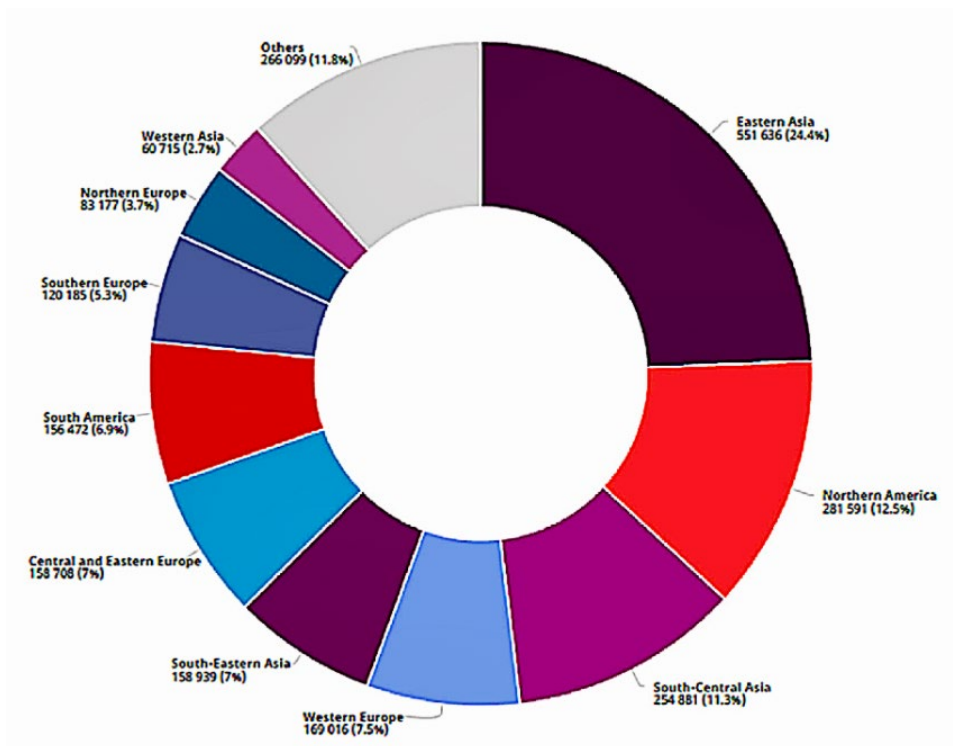


Fig. 1 Worldwide distribution of breast cancer cases by geographic region in 2020 (Datasource: GLOBOCAN 2020)

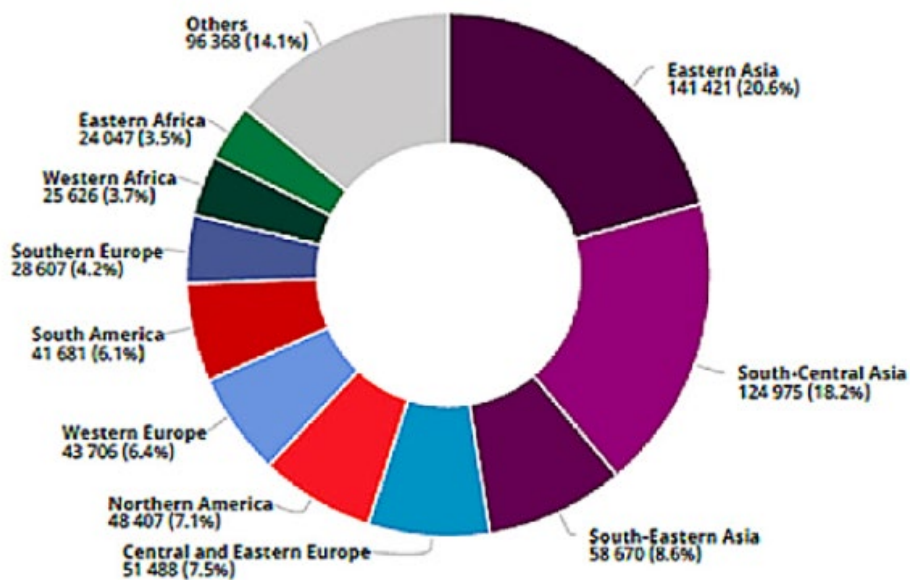


Fig. 2 Worldwide distribution of breast cancer deaths by geographic region in 2020 (Datasource: GLOBOCAN 2020)

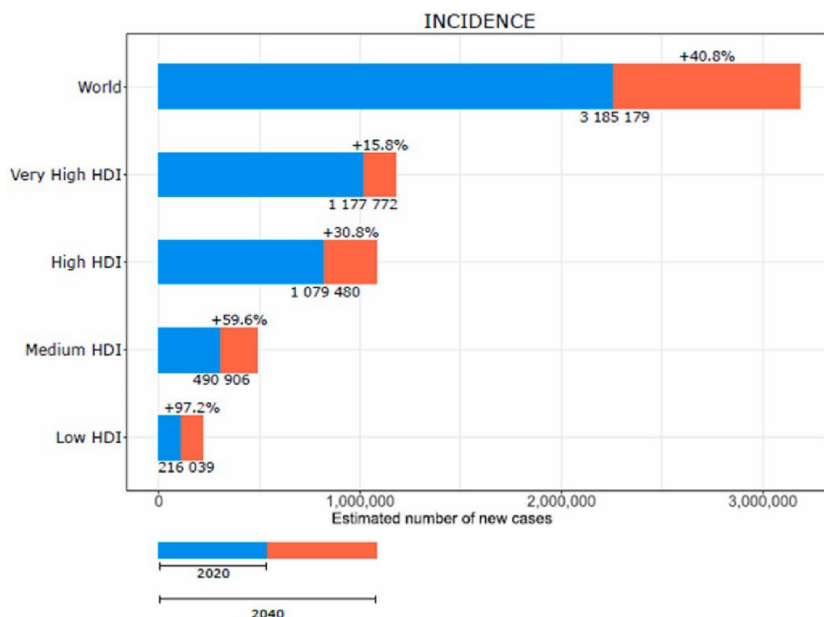


Fig. 3 Estimated distribution of breast cancer cases from 2020 to 2040, by Human Development Index (HDI) (adapted by Arnold et al.)

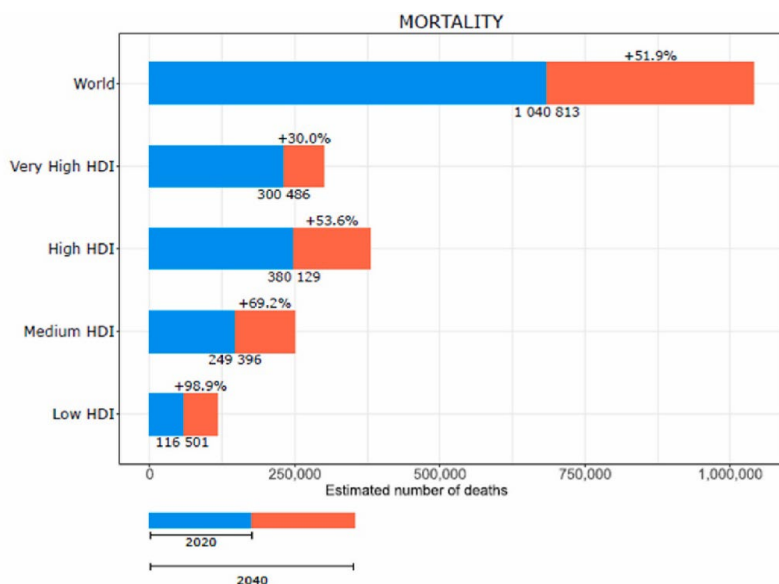


Fig. 4 Estimated distribution of breast cancer deaths from 2020 to 2040, by level of Human Development Index (HDI) (adapted by Arnold et al.)

Tumor size and the number of potentially involved lymph nodes are the strongest predictors of breast cancer outcomes (4, 5). The 5-year overall survival (OS) of breast cancer ranges from 45% for women with tumors > 5 cm in diameter and pathological lymph nodes to > 95% for women with tumors < 2 cm in diameter and no involved lymph nodes (4). The 20-year survival rate for women with tumors < 14 mm in diameter ranges from 86 to 100% (5).

## 1.2 Breast anatomy and physiology

Breasts are exocrine glands, the basic anatomical structures of which include fat, fibrotic/connective tissue for support, glandular tissue composed of lobules and milk ducts as the key functional element, and various neurovascular structures (6) (Fig. 5).

The female hormones estrogen and progesterone, produced by the ovaries, are critically involved in the development of glandular tissue and also play a role in breast cancer (7). Periodically during the menstrual cycle, but primarily during pregnancy, the glandular tissue reaches functional maturity for milk protein production. Later in life (starting at approximately 40 years of age) the glandular tissue begins to atrophy, resulting in its involution and replacement by connective tissue and fat (6, 8).

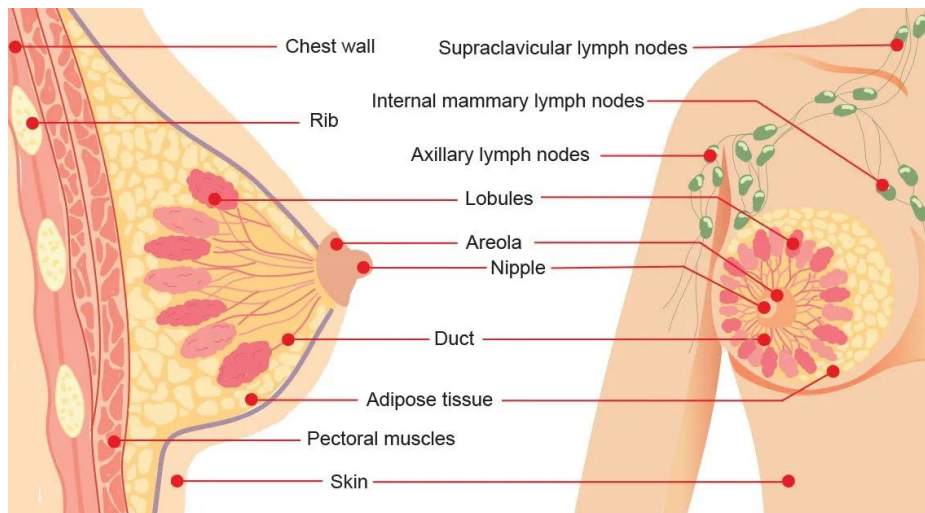


Fig. 5 Anatomy of breast basic structures

The lymphatic system plays an important role in both the tissue-fluid balance and immune cell responses. The lymphatic vessels, which transport lymph, a clear and colorless fluid, are very fragile and almost invisible (9). The vessels must be enhanced to visualize them with the naked eye, making contrast injections essential for lymphatic research (10). Suami et al. (11) showed that there are alternative drainage patterns of breast lymphatics and a more in-depth investigation of the breast lymphatic network and lymphatic molecules is ongoing (12) (Fig. 6).

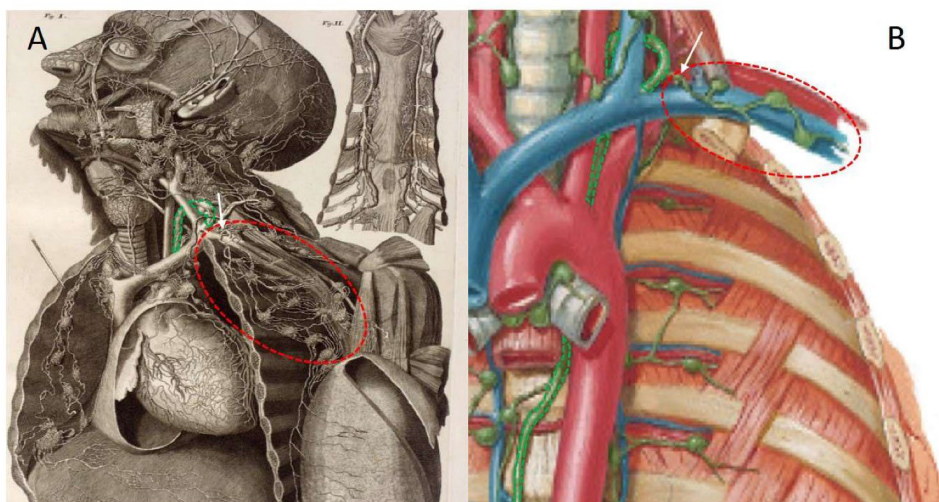


Fig. 6 An anatomical variant in which the subclavian lymphatic trunk ends in the venous angle instead of the thoracic duct. (adapted by Gianfranco et al.)

## 1.3 Breast disease

### 1.3.1 Pathophysiology

A variety of factors, such as radiation exposure (13), hormone imbalance (14), stress (15), and genetics (16) can induce disruptions in physiological development, including the maturation and involution of breast cells, resulting in numerous proliferative or non-proliferative changes. These changes can be defined by their risk of breast cancer development (17, 18) with benign diseases being far more common than malignant diseases (19).

### 1.3.2 Diagnosis

Breast disease can present with a variety of symptoms, including palpable lesions or nipple discharge, which are easily recognized by the patient or otherwise found through diagnostic imaging. Cytology and/or histology are crucial to obtaining a definitive diagnosis and prognosis of the actual findings (20).

Thinner (27G up to 20G; outer diameter, 0.4–0.9 mm) needles are used for a percutaneous procedure called fine needle aspiration (FNA) to obtain tissue samples for cytology. This method aims to obtain a sufficient number of cells from a specific area of interest for diagnostic testing (21). FNA can be performed under imaging guidance if there was an imaging finding, or without imaging guidance for palpable lumps (Fig. 7).

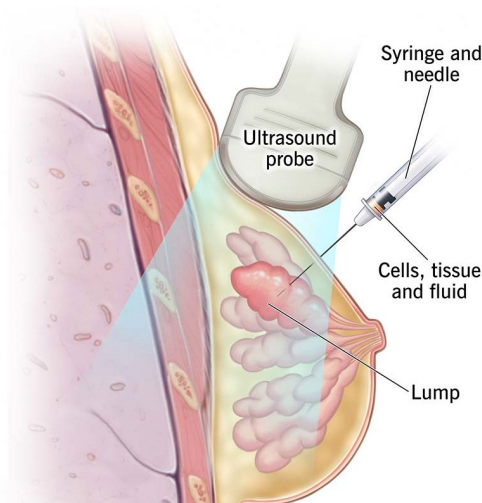


Fig. 7 Fine needle aspiration under ultrasound guidance (adapted by Cleveland Clinic)

Thicker (19G up to 12G; 1–2.8 mm) core-biopsy needles are used for a percutaneous procedure called a core needle biopsy (CNB) to obtain tissue for histology. While FNAs can be performed without imaging guidance (primarily for palpable lesions), CNBs require imaging guidance due to the increased risk of damage to normal tissue (22).

In the last 20 years, needles with larger diameters, up to 7G (outer diameter, 4.6 mm), have been used in cases of inconclusive diagnoses obtained using smaller needles. These larger needles are used in image-guided vacuum-assisted biopsies (VABs), the main advantage of which, in addition to its larger size, is that it can accumulate several samples through a single incision. This allows for the collection of a larger specimen (> 4 g), improving the diagnostic accuracy of the procedure (23, 24). The vacuum draws the tissue into the opening in the front of the needle, and a rotating cutting device collects the sample (Fig. 8).

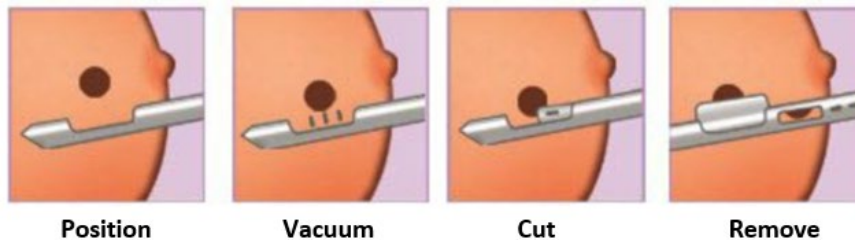


Fig. 8 An example of a vacuum needle. The opening of the needle is positioned underneath the target lesion. The vacuum mechanism is activated and the opening of the needle is positioned closer to the lesion. The cutting mechanism is activated and the portion of the lesion that is closest to the needle's opening is drawn inside the needle and moved into a separate sampling basket. The collection procedure can be repeated as many times as the operator wants, without removing the needle from the breast.

### 1.3.3 Staging on histopathology

Breast lesions with benign histopathology, meaning there is no risk of malignancy in the future, are categorized as B2, according to the European Guidelines for Quality Assurance of Breast Cancer Screening and Diagnosis (25, 26). The most common solid B2 lesion is the fibroadenoma, occurring in 25% of asymptomatic women (27) (Fig. 9). Other B2 lesions include simple cysts, hamartomas, and lipomas.



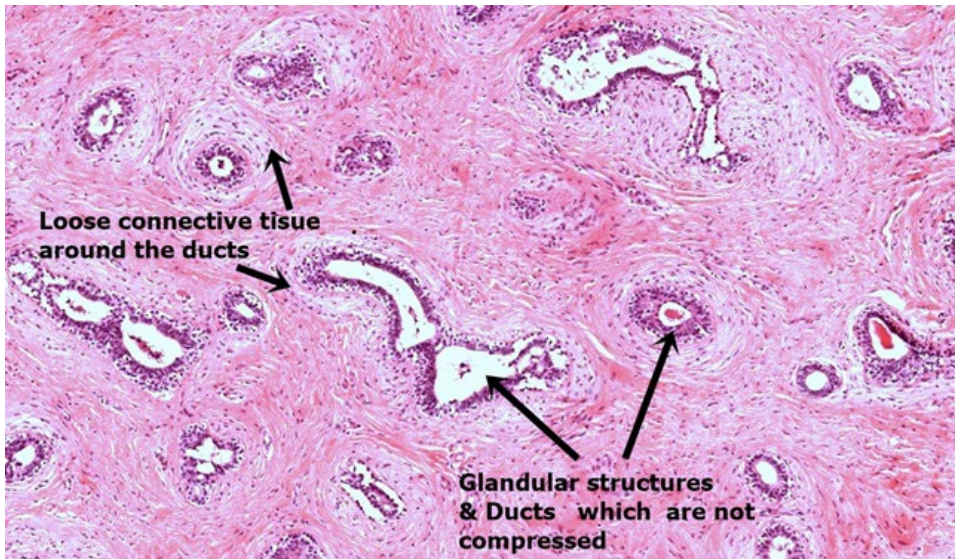


Fig. 9 Microscopy of a fibroadenoma with a pericanalicular pattern (adapted by Vijay Shankar S)

In contrast, lesions suspected of malignancy are categorized as B4, and definitive malignancy as B5 (Fig. 10).

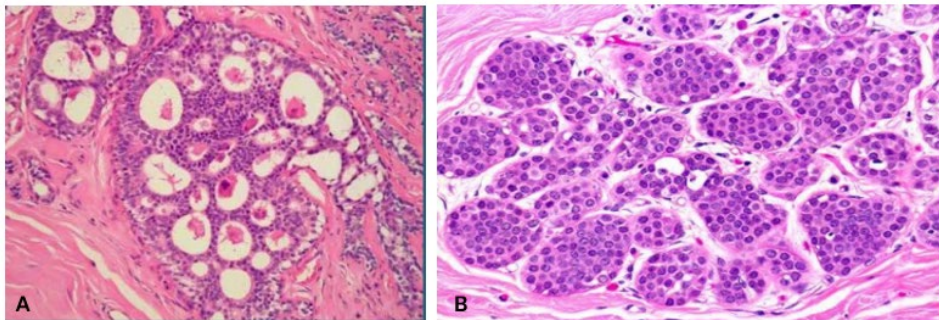


Fig. 10 Microscopy of (A) cribriform ductal carcinoma in situ (DCIS) and (B) invasive lobular carcinoma

B1 represents normal tissue or otherwise non-diagnostic material.

Additionally, some lesions with an uncertain potential for malignancy cannot be categorically assigned to any of the aforementioned groups. These lesions are thus categorized as B3 and their significance lies in the inconsistent opinions in the literature regarding their management. The upgrade rate of B3 lesions to malignancy is varying extremely and is dependent on the primary mode of diagnosis (FNA, CNB, or VAB), the different settings of the published studies, and the relatively low level of reproducibility between pathologists (28). Moreover, in

this era of studies aiming to reduce overtreatment, especially in regard to low-risk carcinoma in situ (including the UK LORIS, EORTC LORD, and US COMET trials) (29–31), there is an interest in determining alternate treatment courses, whereas an upgraded lesion risk represents a risk for the development of ductal carcinoma in situ (DCIS) or invasive carcinoma.

Lesions representative of this group include:

#### *Atypical ductal hyperplasia (ADH)*

The variation in the upgrade rate to breast cancer after surgical excision for these lesions is high, with a spectrum between 5% and 50% in international literature (32). The cumulative risk for ipsilateral malignancy (in situ or invasive), 25 years after biopsy diagnosis of ADH, is up to 30% (33) with a higher risk the first 5 years (34).

#### *Flat epithelial atypia (FEA)*

Pure FEA on histology is associated with a low upgrade risk, with a pooled upgrade rate for breast cancer after surgery is calculated up to 5% (35).

#### *Lobular neoplasia (LN)*

This term encompasses both atypical lobular hyperplasia (ALH) and classical lobular cancer in situ (cLCIS). To date, no concordance has been observed in the upgrade rates of malignancies following either of these diagnoses; however, on average, it is 12% for ALH and 22% for cLCIS (36–38).

#### *Phyllodes tumour*

Phyllodes tumors can be classified as benign, borderline, or malignant; however, histologically separating fibroadenomas (B2) can be difficult (39). Additional parameters such as lesion growth rate and size > 3 cm have been proposed to guide the final diagnosis and management (40).

#### *Intraductal papilloma with/or without atypia*

The presence of atypia defines the upgrade rate to breast cancer, which increases to 27–36% while the absence of atypia has an upgrade rate < 10% (41–43). The risk for invasive cancer is threefold for multiple papillomas (papillomatosis) (44).

### *Radial scar or complex sclerosing lesion*

Radial scars without atypia on histological biopsy have an upgrade rate of 1% (45), while the presence of atypia can indicate a spectrum of upgrade to breast cancer from 2–28%, depending on the needle size used during biopsy (46, 47).

### *Miscellaneous*

This group encompasses several rare stromal spindle and myofibroblastic proliferations for which international literature, to date, has been unable to provide sufficient data for the risk of malignancy.

### *Mucocele-like lesions*

Excluding mucinous carcinoma, the upgrade rate of free mucus pools within the breast tissue to breast cancer is < 2% (48).

The prevalence of B3 category diagnoses ranges from 5 to 10% (49–51) with papillomas being the most frequent diagnosis (52–55). All of the lesions in this category represent a clinical dilemma for treatment planning, as the only means of excluding malignancy is to refer the patient for open surgical excision (OSE) of the whole lesion, which is considered to be the “gold standard” for obtaining a conclusive diagnosis (56). Needle biopsy, however, allows for proper pre-operative planning and decreases the re-excision rate, as OSE often leads to reoperation to establish clear margins in cases of a cancer diagnosis (57). The utilization of VAB for lesions in the B3 category has become increasingly necessary, leading to fewer surgical interventions and unnecessary follow-ups (58). Furthermore, histological underestimation becomes substantially lower when a vacuum is utilized during CNB procedures (59, 60).

### *Breast cancer molecular staging and immunochemistry*

After a breast cancer diagnosis (B5) is established, tumor heterogeneity should be considered by evaluating the phenotype of the lesion (61, 62), which is both prognostic and predictive of specific therapies to be addressed. Three broad phenotypes have been identified in clinical practice: estrogen receptor (ER) and progesterone receptor (PR)–positive, human epidermal growth factor receptor 2 (HER2)–positive, and triple–negative breast cancers (63).

In addition to the aforementioned phenotypes, specific gene expression patterns have also been investigated by evaluating thousands of genes in separate experiments (64). Four categories have been proposed for breast cancer

subtypes: luminal A, luminal B, HER2-positive, and triple-negative, with luminal A having the best prognosis and triple-negative the worst.

#### 1.3.4 Comparison of FNA, CNB and VAB

FNA has a relatively high sensitivity (65) for detecting breast cancer, although this varies among different studies (66). In general, however, it is comparable to CNB (67, 68). The major difference between FNA and CNB is that FNA has shown a lower diagnostic accuracy for distinguishing some B3 lesions as well as low-grade in situ carcinomas (66, 69) (Fig.11).

In contrast, VAB has the highest pooled positive predictive value for determining the final histological diagnosis, at > 90% (32, 70).

Features	CNB	FNAC
Sensitivity	High	Lower/equivalent to CNB
Specificity	High	Lower/equivalent to CNB
Positive predictive value	High	Equivalent to CNB
Negative predictive value	Higher especially in gray zone lesions	High but variable
False positivity	Low	Low
False negativity	Variable; at times higher than FNAC	Variable
Inadequacy	Variable	Variable (difficult to obtain a good sample in fibrocollagenous lesion)
Necessity for anesthesia	Required	Not required
Necessity for radiology guidance	Required always	May be required in nonpalpable lesions
Turn-around time	Relatively more	Relatively less
Cost	Higher	Low
Complications	Low	Very low
Therapeutic aspiration	Not possible	Can be possible
Immunohistochemistry for steroid receptors, growth factor receptor and proliferative index	Reliable	Possible but some people question its reliability
Tumor grading	Performed and reliable	Performed and less reliable
Detection of <i>in-situ</i> component	Possible	Not possible
Lymphovascular emboli	Possible	Not possible
Perineural invasion	Possible	Not possible
Diagnostic difficulty in papillary lesions including subtyping	Low to moderate	High
Diagnostic difficulty in preneoplastic lesions	Low	High
Diagnostic difficulty in radial scar/complex sclerosing lesions	Moderate	High
Diagnostic difficulty in fibroadenoma and benign phyllodes tumor	Low to moderate	Low to moderate

FNAC: Fine-needle aspiration cytology, CNB: Core needle biopsy

Fig. 11 Comparison of FNA (FNAC) and CNB. (adapted by Suvradeep et al.)

## 1.4 Breast Imaging

### 1.4.1 Methods

#### *1.4.1.1 Mammography*

Mammography and sonography are the most commonly used modalities for diagnostic imaging. Mammography is currently the most important and widely used radiographic modality worldwide (71). The image created by mammographic equipment is formed using an X-ray tube on one side of the breast and a detector on the other. Mammography uses low energy X-ray (approximately 20 keV) to enhance the contrast between potential tumors and fatty tissue (72). It is used for both the clinical management of patients with symptoms such as lumps and for screening purposes (73). Its main advantage is its high spatial resolution (74), which allows the detection of microcalcifications (MCCs) a term used to describe calcium deposits in the breast with a diameter  $< 1$  mm, which may represent a very early stage and be the only sign of breast cancer (75). Because of the unique ability of mammography to detect MCCs over the last 20 years, as a special technique for biopsy of MCCs under mammographic guidance has been developed, known as stereotactic breast biopsy (76). VAB technique was first introduced as an adaptment to stereotactic breast biopsy in the late 1990s (76, 77).

Mammography screening has led to a substantial reduction in breast cancer mortality (78) largely because it helps detect tumors  $< 15$  mm in diameter (5, 79); however, cancer detection during screening is a monotonous and exhaustive process. Only approximately 4 out of every 1,000 mammography examinations contain a malignant tumor (80), often occupying only 1% of the image. The sensitivity and specificity of mammography varies between 63%–87% and 89%–97%, respectively, and is largely dependent on the density of breast tissue (81, 82) (Fig.12). The recall rates varies between 2% and 11% depending on the country and the screening setting (80, 83), resulting in an incidence of B3 lesions that varies from 3% to 17% (49). Recalled patients, even when the results are benign, cause increased clinical and radiographic breast examinations as well as increased anxiety for patients during future examinations (84). Restriction of the recall rates, and appropriate management of B3 lesions with concrete information regarding the results, are essential for the continuous development of the screening programs.

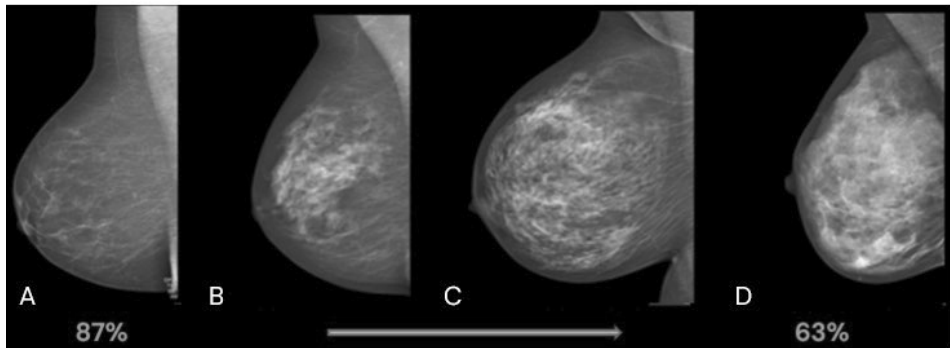


Fig. 12 Breast density on mammography and its relation to cancer detection sensitivity. (A) Almost entirely fatty breast; (B) Scattered areas of fibroglandular density; (C) Heterogeneously dense; (D) Extremely dense

### *Tomosynthesis*

Tomosynthesis is a relatively new add-on technique for mammographic image acquisition. Its three-dimensional (3D) view of the breast provides perspectives from different angles, slightly increasing radiation exposure. With this relatively new technique, however, detection rates increase, whereas false positive rates decrease (85).

### *Contrast-enhanced mammography*

Contrast-enhanced mammography is based on the principal of the increased blood circulation within tumors. In this procedure, an iodine-based dye is injected through the venous system, and subsequent 2D mammography is performed to delineate eventual tumors. The proposed indications for this method include high-risk screening, preoperative evaluation, and neoadjuvant therapy (86) (Fig.13).

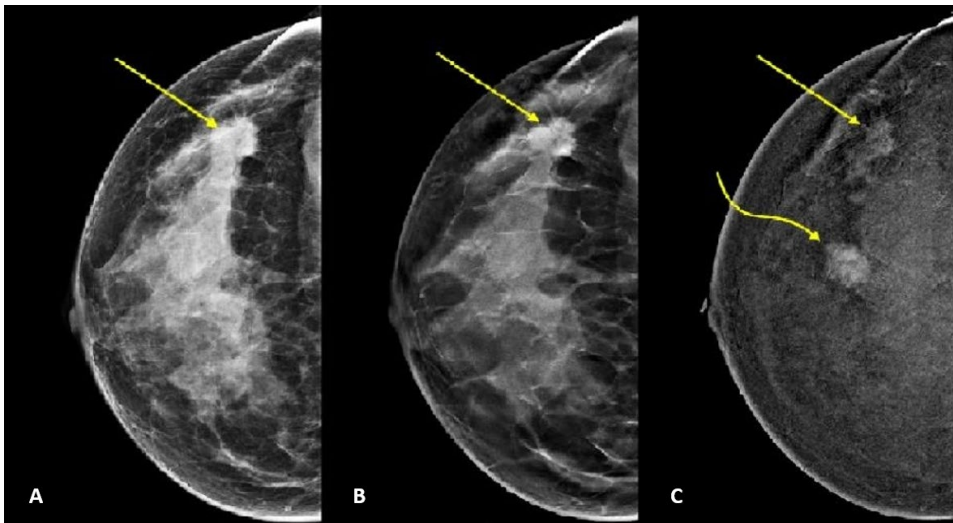


Fig. 13 Preoperative evaluation of a breast cancer patient. (A) A conventional 2D mammogram, showing a suspicious lesion on the lateral part of the right breast (yellow arrow); (B) 3D tomosynthesis showing the same suspicious lesion (slice 35/85) but with better detail, revealing the malignant characteristics and prompting further work-up (yellow arrow); and (C) 2D contrast-enhanced mammogram from the same patient confirming the contrast uptake of the lesion in the lateral part of the breast (straight yellow arrow) and revealing another lesion closer to the nipple (curved arrow) that was not noted on the previous two techniques.

#### *Artificial intelligence (AI)*

The digitalization of mammography and the evolution of AI have led to the development and application of computer-aided detection (CAD) both 2D (87) and 3D (88) mammographic examinations. AI-CAD can be highly accurate for the interpretation of mammograms, and some systems are now comparable to the average breast radiologist in detecting breast cancer with screening mammography (89, 90). Prospective studies have shown improved results when radiologists supplement the interpretation of mammographic images with an AI algorithm (90–92), and the future appears promising for improvements in AI-CAD performance (93). Taplin et al. (94) hypothesized that benign breast biopsies might influence subsequent mammography screening performance, even in the absence of concrete results. It would be interesting, therefore, to see if AI-CAD algorithms are influenced by such procedures, or if the integration of such information with other clinical information and the personalization of the algorithms can help improve screening accuracy, thereby reducing the workload of radiologists.



#### 1.4.1.2 Ultrasound

Sonography uses high-frequency sound waves that cannot be heard by the human ear to create images. These waves pass through the breast tissue, creating images without radiation. Ultrasound is the modality of choice for a more in-depth examination of imaging findings or breast symptoms, as well as for searching for pathological lymph nodes in areas that are not included in mammographic images, primarily in the axilla.

For solid tumors, the ultrasound is the most accurate method for determining tumor size (95); however, the main advantage of this method is that it allows dynamic examination of the area of interest, making it the method of choice for needle guidance during invasive procedures (96).

In recent years, optoacoustic techniques, which are the latest advances in ultrasound technology, have been introduced to increase the correlation between ultrasound imaging and histopathological biomarkers (Fig. 14) (97, 98). Other ancillary ultrasound technologies include strain- or shear-wave elastography and contrast-enhanced ultrasound.

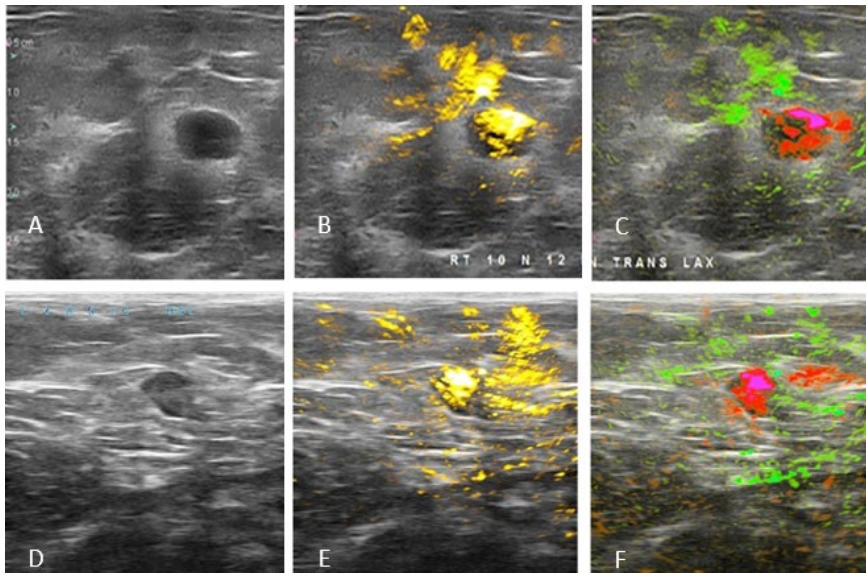


Fig. 14 Optoacoustic technique in two different masses (A-C and D-F) where the functional imaging upgrades the lesions from BI-RADS 3 (gray-scale, traditional ultrasound) to BI-RADS 5). (adapted by Oraevsky et al.)

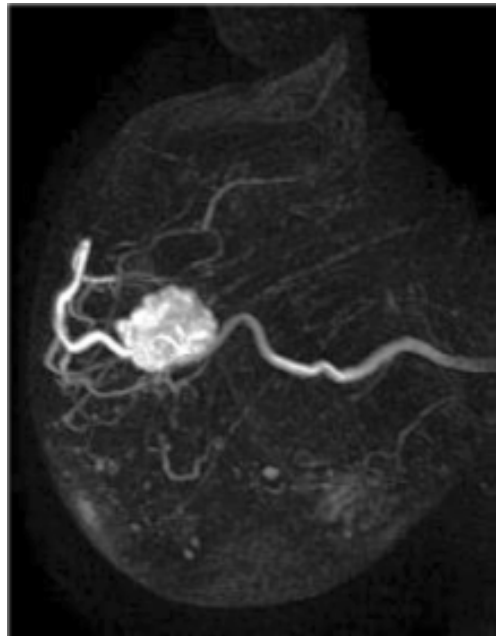


#### *1.4.1.3 MRI*

MRI uses strong magnetic fields and radio waves to create images of the breast. Unlike mammography, MRI does not involve the use of ionizing radiation. These examinations are performed with the patient lying on their stomach and entering the MRI machine, which is typically a long tunnel.

Breast MRI is a notable imaging technique that is being used more frequently and helps better understand the physiology of breast cancer, primarily due to the use of intravenous contrast agents (99). The main advantage of this modality is its high accuracy in detecting abnormalities, with a negative predictive value up to 99% (100) (Fig.15).

Fig. 15. Maximum intensity projection magnetic resonance imaging view where the feeder vessels are clearly delineated 2 minutes post-contrast injection



#### *1.4.1.4 PET*

Positron emission tomography (PET) is the latest imaging modality in the current diagnostic arsenal. PET is a noninvasive nuclear medicine imaging technique used to visualize the metabolism of the breast by exploiting positron-emitting isotopes, known as radiotracers, such as oxygen, carbon, nitrogen, and fluorine (101), the most frequently used of which is F-18 fluorodeoxyglucose (18F-FDG). The intracellular uptake of 18-FDG by tumors, as well as its use in various metabolic pathways, cause the emission of photons that create the resulting image (102).

The relevant body structures can be anatomically correlated by combining PET with computed tomography (CT) or MRI, which is primarily performed for staging and monitoring the response to therapy (103, 104) (Fig.16).

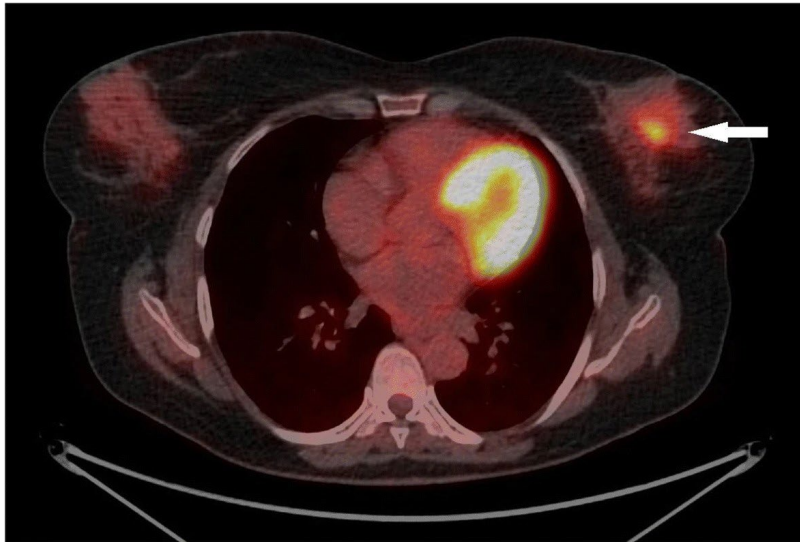


Fig. 16. Axial F-18 fluorodeoxyglucose positron emission/computed tomography image of a patient with breast cancer, showing the primary tumor in the left breast (adapted by Iakovou et al.)

#### 1.4.2 Staging on imaging

Changes of the standard anatomical structures on imaging are classified based on their malignant potential, classified using the Breast Imaging Reporting and Data System (BI-RADS) (105). This classification system uses a scale from 1 to 5, with 1 representing normal tissue and 5 representing malignant lesions. The probability of malignancy are as follows: BI-RADS 2, 0%; BI-RADS 3, 0.5–2%; BI-RADS 4, 2–95%; and BI-RADS 5, 97%. Because of the wide range for BI-RADS 4 lesions, subcategories have been introduced – BI-RADS 4A, 2–10%; BI-RADS 4B, 10–50%; and BI-RADS 4C, 50–95%.

This system proposes specific morphological characteristics for every conventional breast imaging modality (mammography, ultrasound, and MRI), with ultrasound remaining the most accurate (106).

The recommended pathway for lesions categorized as BI-RADS 3 is a 6-month follow-up for up to 2 years, whereas for those categorized as BI-RADS 4A, a biopsy should be performed.

After a breast cancer diagnosis, anatomical staging is recommended (107), and should be performed according to the latest edition of the primary tumor, lymph node, and metastasis (TNM) classification system published by the American Joint Committee of Cancer (AJCC) (62).

## 1.5 Management of breast disease

The conventional management of primary breast cancer, which previous included a mastectomy, has been replaced by other techniques that aim to preserve as much disease-free breast tissue as possible while ensuring that the margins of the excised area of the tumor are free from tumor cells (108). Techniques involving breast-conserving surgery (BCS) are primarily recommended for patients with early stage breast cancer (107, 109). There is a de-escalation trend in surgical treatment (110), which reduces functional and aesthetic morbidity by being less aggressive while simultaneously achieving the same, or even superior, results to those of mastectomy (111, 112). Many approaches have been developed to combine histopathological and imaging features to achieve more concrete decision-making in the treatment planning process (113–117).

For noncancerous imaging or clinical findings, traditional management with OSE prior to a potential BCS follows a similar de-escalation trend, with a shift to image-guided biopsies (52, 118), with the future pointing towards excision or even ablation techniques (119). Some of the latest examples of these techniques are the breast lesion excision system (BLES™; Medtronic Inc., Dublin, Ireland) and cryoablation (ProSense™; Icecure Medical Ltd, Caesaria, Israel).

AI, in the form of machine and deep learning, may play an important role in the future of clinical decision-making. Documenting quantitative image features (radiomics) that represent every lesion category and combining them with histopathological signs are thought to help build specific therapeutic algorithms(120–123) (Fig. 17).

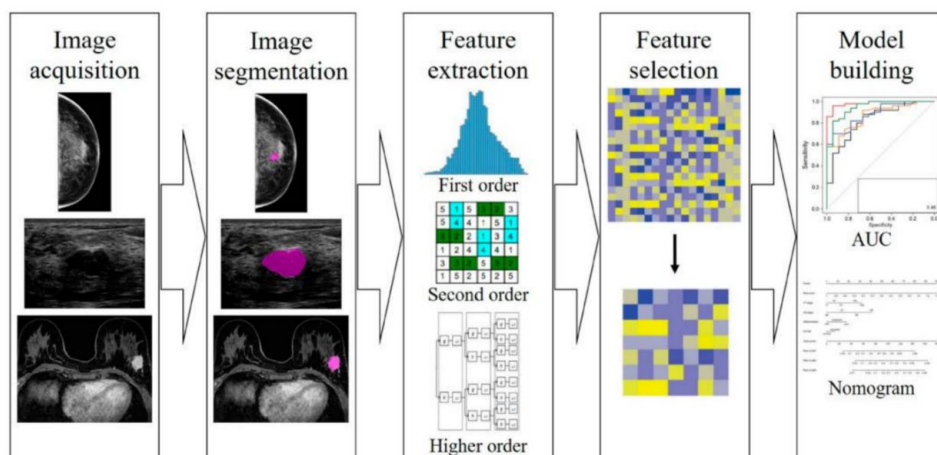


Fig. 17 Different steps in radiomics workflow for breast imaging (adapted by Pesapane et al.) \*AUC, area under the curve

### 1.5.1 BLES

A BLES is a percutaneous excisional device which is used for the histological diagnosis of breast cancer (124, 125). This technique uses radiofrequency and a tissue capture basket to excise breast lesions for laboratory testing through a single insertion point. BLES has been tested for the excision of small cancerous lesions under mammographic guidance, with an excision rate up to 65%(126) and with ultrasound guidance, with an excision rate up to 46% (127). Its role seems to be limited, however, to the excision of selected benign breast lesions, with its biggest disadvantage being the increased risk of damaging sensitive surrounding tissues (such as the skin) or causing thermal damage to the lesion itself, making it difficult to assess radicality (128) (Fig. 18).

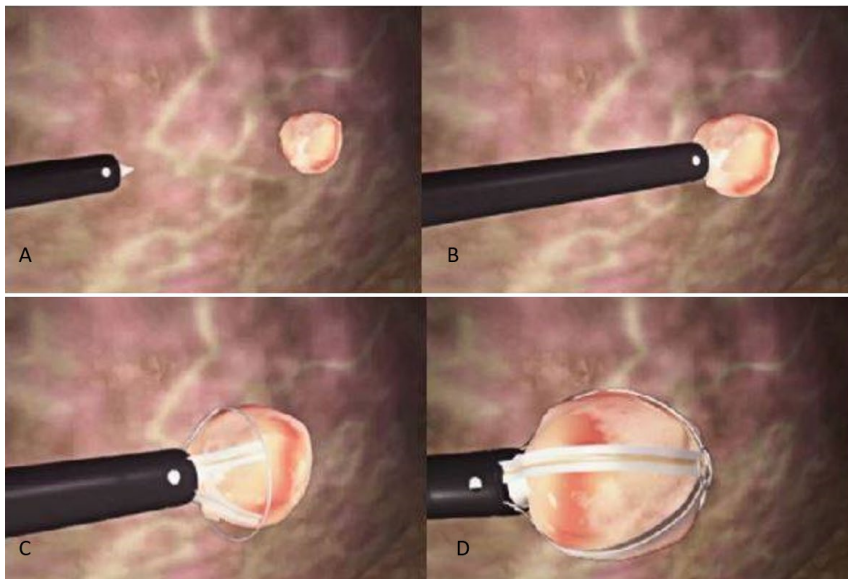


Fig. 18 Figure showing the steps for excising a target lesion with a breast lesion excision system (BLES). (A) The lesion is identified and the intact BLES needle is positioned towards the center of the target; (B) the tip of the needle is positioned in front of the lesion; (C) the electrode basket that envelops the target tissue is deployed; and (D) the needle with the imbedded lesion is removed from the breast.

### 1.5.2 Cryoablation

Cryoablation is a transcutaneous, image-guided ablation technique that applies very low temperatures (approximately  $-170^{\circ}\text{C}$ ) to an area of the breast with the goal of destroying the tumor cells, resulting in *in situ* treatment of the area in question. This procedure is performed under local anesthesia and has been evaluated in both benign and malignant lesions (129, 130). The major disadvantage of cryoablation is its widespread damage to the tissue sample, barring histopathological characterization (131). The main role of cryoablation seems to be limited to reducing the size of the mass in cases where surgery is contraindicated; however, there are signs that it can boost the response of distant lesions to immunotherapy (132). Two ongoing clinical trials, ICE3 (Cryoablation of Low Risk Small Breast Cancer) and FROST (Freezing instead of Removal Of Small Tumors), aim to evaluate the efficacy of cryoablation without surgery in early-stage hormone receptor-positive and HER2-negative breast cancer diagnosed in women 50 years of age or older, as well as its impact on 5-year local and/or distant recurrence (133, 134) (Fig. 19).

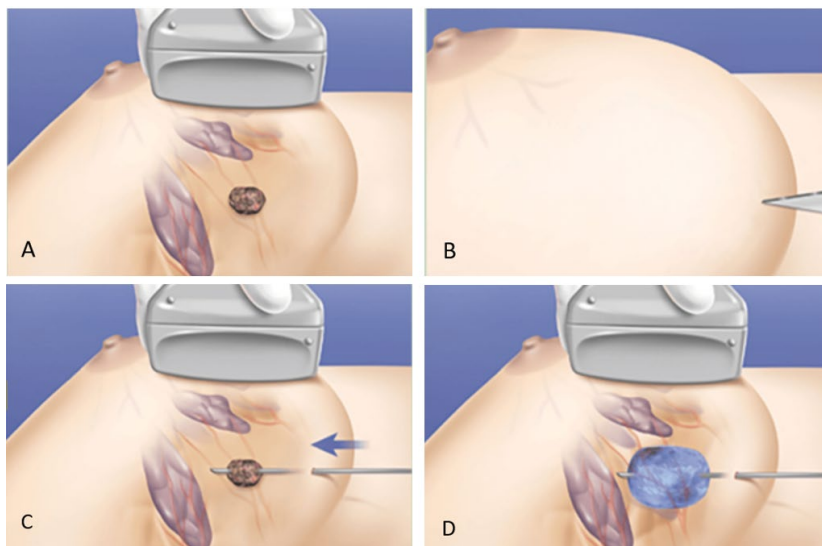


Fig. 19 Cryoablation procedure. (A) Ultrasound imaging is used to locate the lesion; (B) after the administration of a local anesthetic, a small incision is made in the appropriate location; (C) the cryoprobe is positioned in the center of the lesion; and (D) the freezing-cycle is activated and ball of ice forms around the tumor, destroying the tissue.

### 1.5.3 Vacuum assisted excision (VAE)

Among the available minimally invasive approaches, one method stands out, especially after the 1<sup>st</sup> and 2<sup>nd</sup> International Consensus Conferences on B3 Lesions held in Zurich, Switzerland, in January 2016 and March 2018, respectively. These conferences were organized by the International Breast Ultrasound School (IBUS), where therapeutic VAE was proposed as the method of choice for excising a number of B3 lesions, as opposed to OSE (52, 53). The 3<sup>rd</sup> International Consensus Conference (2023) (55), followed by the first publication of the European Guidelines (2024) (32), confirmed the use of VAE for the management of B3 lesions.

Therapeutic VAB or VAE, is essentially the same technique as VAB, with the main difference being that the goal is to completely remove the lesion from the breast. Needles up to 7G can collect up to 400 mg of tissue in one sample. As these samples can be obtained 10–20 times, it is possible to remove breast lesions > 3 cm in diameter (4 g) (24) (Fig. 20).

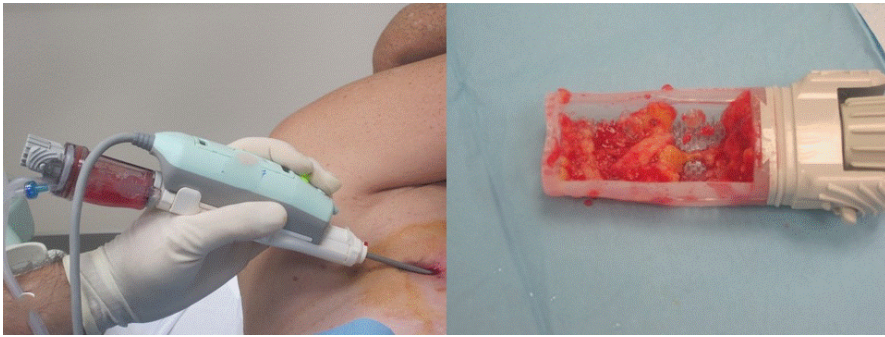


Fig. 20 Vacuum assisted needle biopsy (right) with its basket, filled with tissue (left)

VAE is performed under local anesthesia with the patient fully conscious. The incision site has a maximum length of 5–7 mm, which does not require stitching upon completion of the procedure. The multimodal application of the vacuum instrument adds flexibility to this method. VAE can be performed under mammographic guidance for small areas of microcalcification ( $< 10$  mm) (135, 136), although its therapeutic role in the excision of malignant calcifications is debated (137, 138). VAE is most frequently performed under ultrasound guidance, where the possibility of real-time evaluation offers excellent environmental control, with a complete excision in 72–99% of cases (139–142). At the same time, the ongoing development of ultrasound technology allows for the unique possibility of analyzing the specific characteristics of the target lesions, thus giving birth to pattern identification and prognostic model development, even for lesions  $< 5$  mm (113, 114, 123). VAE can also be performed under MRI guidance (143–145); however, the main challenge with this method is that it can be technically demanding in patients with very small or very large breasts, or for lesions that are localized in the deep prepectoral or far lateral parts of the breast. The main disadvantage of using MRI guidance is the risk of undersampling heterogeneous or small lesions that require the retrieval of larger tissue samples during the procedure, and likely an annual follow-up MRI (146, 147).

No major complications associated with VAE have been described in the literature, regardless of the guidance method used, although the most frequent adverse event is post-procedural pain, followed by hematoma. Bleeding and infection are rare events, as are skin injuries (142, 148). Patients seem to accept the procedure quite well and  $> 95\%$  would recommend the procedure to others (139, 142, 148–153). More data from studies that include larger patient numbers are required to determine the optimal conditions for these procedures.

### *VAB/VAE and breast cancer*

There are several ongoing trials (154, 155) and already performed studies (156) investigating the role of VAE in the excision of malignant tumors with promising results. The focus of those studies is the removal of early breast cancers, defined as mass < 2 cm in diameter, with the exception of the aggressive phenotypes of triple-negative and HER2-positive (157), as these cancers have an excellent prognosis (158, 159) and can be safely excised using minimally invasive techniques.

VAB has also been proposed as a potentially reliable method for assessing pathological complete response in patients receiving neoadjuvant cancer therapy (160, 161). The ultimate goal is to select patients who show a remarkable response after neoadjuvant therapy to completely omit surgery (162, 163).



## 2 Research aims

### Overall aim

To acquire a deeper understanding of invasive diagnostic methods – how they influence imaging modalities, including AI, and how they can be used as therapeutic tools.

### Specific aims

#### Study 1

To investigate the effects of previous benign biopsies on AI cancer detection programs during mammography screening, and compare this effect with radiologist assessments.

#### Study 2

To investigate how vacuum-assisted biopsy (VAB) technique can be optimized for excision (VAE) of probable benign breast disease in minimally invasive image-guided breast procedures.

#### Study 3

To evaluate VAE needle size and the method used in relation to the patient's experience, as well as elaborate on the economic and health benefits of the procedure.

#### Study 4

To examine the possible underestimation during the subsequent biopsy procedures and identify the high-risk lesions and those that are more appropriate for VAE.



## 3 Materials and methods

### 3.1 Study 1

#### 3.1.1 Study population

The study population for this retrospective study was derived from the Cohort of Screen-Aged Women (CSAW) (164), and a specific case-control sub-set was separately defined to include all women from Karolinska University Hospital, Stockholm, who were diagnosed with breast cancer ( $n = 1,303$ ) and 10,000 randomly selected healthy controls.

#### 3.1.2 Equipment

Screening and diagnostic mammograms were performed using equipment from GE Healthcare, Hologic, and Siemens.

The AI-CAD system used was Insight MMG (version 1.1.4.3; Lunit Inc.), which was selected for this study owing to its superior results in a retrospective analysis published in 2020 (90).

#### 3.1.3 Assessment

The study population was divided into three groups based on biopsy status: cancer, benign biopsy, and normal. The cancer group included patients with biopsy-verified breast cancer at or within 12 months of screening; the benign biopsy group was defined as those with benign biopsy findings without any history of breast cancer; and the normal group did not have breast cancer or prior benign biopsy findings.

The following screening decision data were collected: flagging of abnormal screening by one or both radiologists and the final post-consensus recall decision. Screening decisions and clinical outcome data has been collected by linking them to regional cancer center registries.

For the AI assessment, the generated prediction score for tumor presence was a decimal number between 0.00 and 1.00, with 1.00 representing the highest level of suspicion. The program assessed two images of each breast, and the highest score among the four images was selected to represent each patient's examination. The cutoff point (0.40; AI abnormality threshold), defined in a prior study (90) determined whether an examination was considered as flagged by an AI-CAD system.

## 3.2 Study 2-4

### 3.2.1 Study population

#### Study 2

This single-center, single-blind, randomized trial included 208 patients, who had either an ultrasound-visible lesion or microcalcifications that were visible only on mammography. Ultrasound-visible lesions should correspond to BI-RADS 2 to 4A (165) with a biopsy performed corresponding to B2 or B3 (25, 26) lesions. The lesions did not exceed 30 mm in diameter.

Microcalcifications should correspond to BI-RADS 3 and BI-RADS 4a imaging findings with a size of <15 mm. A previous biopsy corresponding to the B3 lesion was accepted; however, the absence of a previous biopsy was also eligible for inclusion in the study.

Each lesion was randomized to the VAE procedure using either a 7G (3.8 mm) or 10G (2.7 mm) needle.

#### Study 3

For this study, we included the same study population as in Study 1; however, a number of patients were excluded at various follow-up time points if they did not complete the questionnaire or for other reasons (Fig. 21).

#### Study 4

For this study, we excluded all lesions that had been excised during the first study without prior biopsy (cytology or histology).

## Flow Diagram

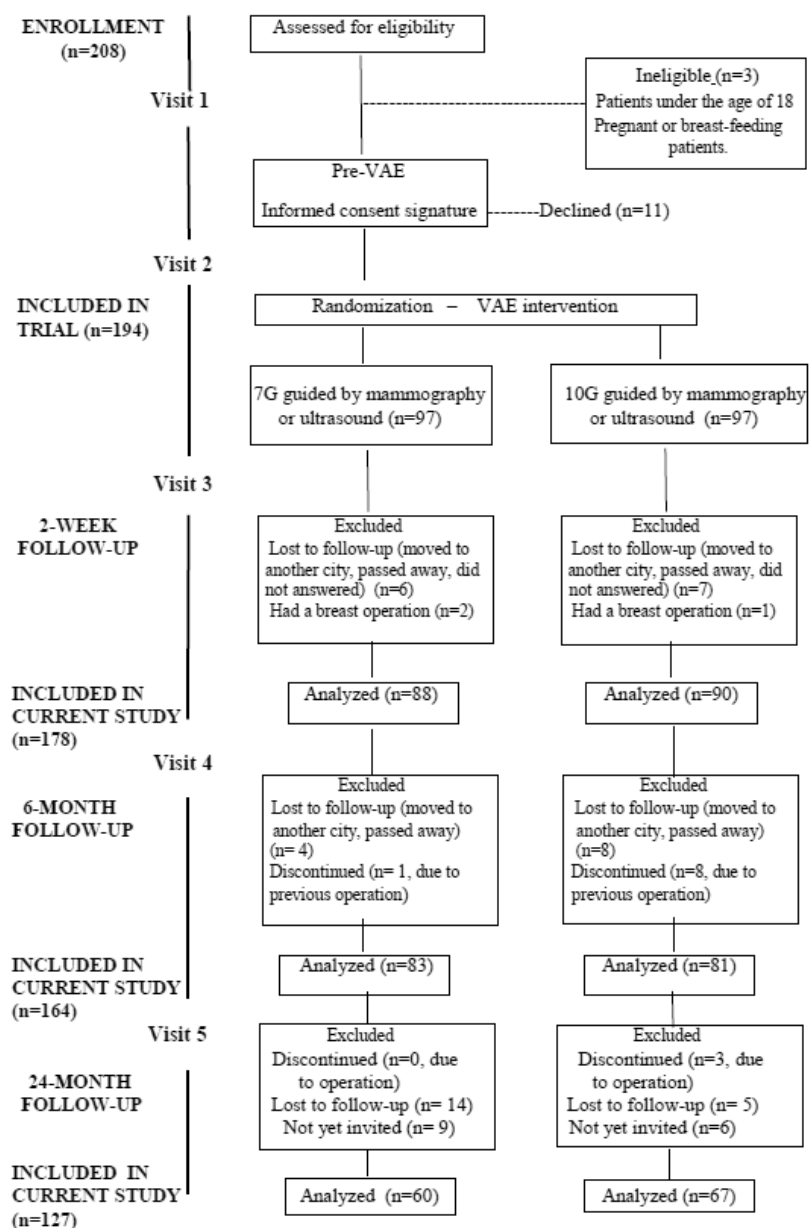


Fig. 21. Flow diagram for Study 3 \*VAE, vacuum assisted excision

### 3.2.2 Equipment

The EnCor EnSpire™ Breast Biopsy system was used for the excision procedures. A Philips Epiq Elite ultrasound machine was used for ultrasound-guided VAE, while all stereotactically-guided excisions were performed by using the Hologic Selenia® Dimensions® tomosynthesis machine.

At the end of the procedure, a Seno Ultra-Breast Tissue Marker was placed in the resected area for follow-up assessment.

### 3.2.3 Assessment

#### Study 2

The radicality assessment was first obtained by visual assessment by the radiologist who performed the VAE procedure and subsequently crosschecked the results after the 6- and 24-month follow-ups.

Additionally, a new method was proposed for determining radicality using separate sample containers in three different steps. During the first step, the first sample container contained all of the tissues obtained from the target lesion. In the second step, the performer obtained additional tissue from the lesion cavity, with a minimum of four samples, and performed a circle of 360 grades. This procedure was repeated in the third step.

The procedure time from the administration of local anesthesia until the end of the excision procedure and marker placement was documented by the nurse in the examination room. The nurse would even document the “total doctor time,” defined as the time from the radiologist’s entrance into the examination room to perform the excision until leaving the room following the completion of the procedure.

#### Study 3

The patients were provided a questionnaire at the end of the VAE procedure, which was a modified version of a previously published survey (153, 166) and is shown in (Fig. 22). The questionnaire was answered within 2 weeks of the procedure and in a simpler form 24 months after the primary VAE. A nurse addressed additional questions through telephone calls on days 7 and 17 post-VAE to document probable short-term complications. At 6 and 24 months post-

VAE, a physical examination was performed together with follow-up imaging. Visual assessment of the scar and any patient-reported long-term complications were documented.

For cost analysis, we documented the total costs for VAE, including the cost of complications, re-excisions, maintenance equipment, and staff, and compared them with the total costs for OSE. We used a model originally developed by the National Health Service of England for documentation and analysis (167).

#### Study 4

In this study, we documented the pathology and/or cytology report from the first biopsy and compared it with any subsequent histopathology reports until the completion of treatment with VAE and eventually OSE. For lesions that were excised in more than one round, the histological analysis from every consequent container (round) was compared.

CNB and VAE diagnoses were documented using category B (26), while FNA was documented using category C (168).

We also documented information regarding eventual re-excision or recurrence after follow-up of the patients for at least 2 years.

### **Vacuum-assisted removal of benign breast lump questionnaire**

1. Did you experience any pain during the procedure? Please encircle one

1      2      3      4      5      6      7      8      9      10

(1=No pain at all)

(10=Worst pain imaginable)

2. Did you experience any pain a week after the procedure? Please encircle one

1      2      3      4      5      6      7      8      9      10

(1=No pain at all)

(10=Worst pain imaginable)

3. Did you take analgesia ("pain killers") after this procedure?    Y    N

4. Can you feel any lumps at the site of the procedure?    Y    N

5. Would you recommend this procedure to other people?    Y    N

6. If you had another benign breast lump would choose this procedure again?    Y    N

7. Following this procedure did you have any bruising?    Y    N

If yes was it    mild    moderate    severe

8. Did you have an infection needing antibiotics?    Y    N

9. Did you require a further breast procedure?    Y    N

10. Have you been satisfied with the cosmetic result?    Y    N

Please encircle one      Very much    Quite a bit    A little    Not at all

If you have any further comments regarding the procedure please add below:

Fig. 22. Modified version of the questionnaire used by Thurley et al.



### 3.3 Statistical Calculations

All statistical analyses were performed using the computer software Stata, version 15.1. *P*-values were calculated for all studies with a prespecified level of significance of 0.05.

#### Study 1

Statistical analysis was performed for each patient, but not for each lesion. Owing to the skewed distribution of AI scores, the medians from each group were chosen, and the Wilcoxon rank-sum test and quantile regression analysis were performed.

The Wilcoxon rank-sum test was performed to determine whether there was a significant difference in the effectiveness of AI-CAD compared to the radiologist assessments.

#### Study 2-4

For these studies, calculations were performed to increase statistical power. The available literature is inconsistent regarding the definitions and reference values of procedural time for VAE (169–171). Therefore, an internal audit was performed before the trial began, and the mean procedural time for the 10G needle was 8 min (standard deviation [SD]: 2 min). For the experimental arm (7G), we decided to accept a maximum increase of 25% in the procedural time (2 min), with a mean procedural time of 10 min. We decided to contain a type 2 error of 0.1 (90% power) and provisionally accepted an increase in power to 95% if the recruitment rate allowed for it. This resulted in total sample sizes of 170 and 210 patients, respectively. Calculations were performed using GPower statistical software v.3.1. and Rstudio (SampleSize4ClinicalTrials package v1).

Descriptive statistics for mammographic and sonographic lesions were calculated by lesion type for relevant continuous and categorical parameters. The mean, standard error, median, minimum, and maximum values were used to characterize the distribution of the continuous parameters. Counts and percentages were used to summarize the distribution of the categorical parameters. Logistic regression analysis was performed to determine predictors of excision completeness. The total VAE procedure and total doctor times were summarized and stratified according to the method of excision guidance and

other variables. Linear regression analysis was performed to determine the predictors of time. In the case of bivariate analysis between categorical and quantitative variables, Student's t-test was applied according to normality conditions.

### 3.4 Ethical considerations

All the four studies included in this thesis were approved by the Swedish Ethical Committee. Study I, dnr 2016/2600-31; Study II-IV, dnr 2019/04096. The requirement for informed consent was waived for Study I due to its retrospective nature. For studies 2-4, all participants provided written informed consent.

In Study I, AI was implemented in the screening praxis. The high attendance of women in screening initiatives combination with the vast number of images to be diagnosed, especially if tomosynthesis is integrated into the screening setting, makes the workload of radiologists unacceptably high. The socioeconomic impact of work-ups during unnecessary recalls will increase in the future, causing possible overdiagnosis that threatens the screening program.

In the digital era, AI is a tool with great potential to improve and support such programs.

For studies 2-4, we investigated the VAE as an alternative to the OSE. With the continuous increase in indeterminate breast lesion diagnoses, it is imperative to identify new methods that would reduce the socioeconomic impact and simultaneously offer the same confidence to patients and physicians as OSE. VAE has been widely accepted as an alternative method from both patients and physicians' perspectives. Caution should be exercised in the existing VAE indications that are continuously evolving and changing to avoid unnecessary risks and expenditures.



## 4 Results

### 4.1 Study 1

For the final assessment, 10,889 were women included in the analysis.

Of these, 917, 234, and 7,371 patients were included in the cancer, benign biopsy, and normal groups, respectively.

We found a significant difference ( $P < 0.001$ ) among the cancer, benign, and normal mammography groups.

The abnormal assessments are shown in Table 1.

**Table 1.** Recall rate and abnormal assessments by artificial intelligence. Data are presented in percentages and fractions.

	<b>Radiologist 1</b>	<b>Radiologist 2</b>	<b>Consensus</b>	<b>AI-% above cut-off point</b>
<b>Total</b>	10% (831/8307)	10% (827/8307)	9.2% (767/8307)	11% (880/8307)
<b>Normal and benign biopsy</b>	3.6% (274/7583)	3.1% (234/7583)	2% (154/7583)	3.8% (290/7583)
<b>Normal</b>	2.8% (203/7371)	2.2% (162/7371)	1% (73/7371)	3.6% (265/7371)
<b>Benign biopsy</b>	33% (71/212)	34% (72/212)	38% (81/212)	12% (25/212)
<b>- Biopsy before     Mx</b>	8.5% (5/59)	6.8% (4/59)	6.8% (4/59)	8.5% (5/59)
<b>- Biopsy after     Mx</b>	49% (66/135)	50% (68/135)	57% (77/135)	15% (20/135)
<b>Cancer</b>	77% (557/724)	82% (593/724)	85% (613/724)	81% (590/724)
<b>With benign     biopsy</b>	75% (12/16)	88% (14/16)	88% (14/16)	81% (13/16)
<b>Without     benign biopsy</b>	77% (545/708)	82% (579/708)	85% (599/708)	82% (577/708)

Mx: mammography.

## 4.2 Study 2

Of the 164 patients who attended the 6-month follow-up, no remaining lesions were found in 90 and 81.5% ( $P = 0.109$ ) patients for the 7G and 10G needle sizes, respectively.

The mean procedure time was 7.7 min and 8.5 min for the 7G and 10G needle size, respectively ( $P = 0.126$ ).

Lesion size was the only parameter that was significantly associated with both excision completeness and procedure time (Tables 2 and 3).

**Table 2.** Parameters associated with procedure time (min) – Multivariate analysis (excluding the microcalcifications)

Multivariate Linear Regression (n = 158)			
	Beta	95% CI	P
Needle size: 10G vs 7G	0.08	(-0.93 to 1.07)	0.878
Age, per 5 years	-0.10	(-0.27 to 0.63)	0.226
<b>Lesion size</b>	0.27	(0.18 to 0.36)	<b>&lt; 0.001</b>
Initial biopsy: Normal tissue vs Other	-1.31	(-3.08 to 0.45)	0.143
Mass vs Microcalcifications	NOT	INCLUDED	
<b>Radiologist: More vs Less experienced</b>	<b>-1.78</b>	<b>(-3.39 to -0.17)</b>	<b>0.030</b>

CI, Confidence interval; Bold text indicate the significant parameters

**Table 3.** Multivariate analysis of parameters affecting completeness of excision at 6-month follow-up. (adapted from Zouzos et al.)

Multivariate Logistic Regression (n = 164)			
	Beta	(95% CI)	P
Number of containers	-0.527	(-1.24 to 0.19)	0.151
<b>Lesion size, per mm</b>	0.301	(0.18 to 0.42)	<b>0.001</b>
Needle size: 10G vs 7G	0.915	(-0.20 to 2.03)	0.109
<b>Mass vs microcalcifications</b>	3.277	(1.63 to 4.92)	<b>0.001</b>

CI, Confidence interval; Bold text indicate the significant parameters

### 4.3 Study 3

Of the 208 patients included in this study, 178 completed the questionnaires.

Ninety-five patients (53%) experienced pain levels of 1/10 and 2/10 during the procedure and 99 patients (56%) reported the same pain levels 2 weeks after the procedure. Twenty-four patients (13%) reported pain levels equal or higher than 6/10 during the procedure, and 17 (10%) 2 weeks after the procedure.

Pain in relation to needle size is presented in (Table 4) with no significant difference found during the procedure ( $P = 0.713$ ) or two weeks after the procedure ( $P = 0.291$ ).

**Table 4.** Pain in relation to needle size (n = 178)

Group	n	Mean	SE	SD	95% CI
1	87	2.87	0.20	1.87	2.47 to 3.27
2	91	2.97	0.21	2.01	2.55 to 3.39
Difference		-0.10	0.29		-0.67 to 0.47

SE, standard error; SD, standard deviation; CI, confidence interval; Group 1, treated with a 7G needle; Group 2, treated with a 10G needle

The documented short-term complications were hematoma (40%) (71/178), excessive bleeding lasting more than 10 minutes (3%) (6/178), and infection (1%) (1/178). No long-term complications were documented during the 6- or 24-month follow-up period.

Regarding general satisfaction, 97% (173/178) of the patients would recommend the procedure to others and 96% (171/178) would choose the same method again if a new lesion occurred.

Finally, after our healthcare cost analysis, we documented a 60% (325,000 EUR) reduction in hospital expenditures by implementing VAE instead of the standard-of-care use of OSE in these 208 patients ( $P < 0.0001$ ).

#### 4.4 Study 4

One hundred sixty-nine lesions were followed up from their first diagnosis with FNA until the final treatment. Seventy-one patients were diagnosed based on the FNA findings (Table 5), whereas 126 patients were diagnosed based on the core biopsy findings (Table 6).

**Table 5.** Comparison between FNA and VAE (n = 71)

	n, (%)	Upgraded	Downgraded	Unchanged
Normal tissue	10 (14%)	8 (80%)	–	2 (20%)
Fibroadenosis	11 (15%)	2 (18%)	–	9 (82%)
Papillary formations	40 (56%)	5 (13%)	5 (13%)	30 (74%)
Atypia	10 (14%)	2 (20%)	5 (50%)	3 (30%)

FNA, fine needle aspiration; VAE, vacuum-assisted excision

**Table 6.** Comparison between CNB and VAE (n = 126)

	n, (%)	Upgraded	Downgraded	Unchanged
B1	8 (6%)	5 (62%)	–	3 (38%)
B2	37 (29%)	5 (13%)	1 (3%)	31 (84%)
B3				
Papillomas	51(40%)	4 (13%)	4 (13%)	43 (84%)
Radial scar/complex lesion	6 (5%)	1 (17%)	3 (50%)	2 (33%)
ADH	12 (9%)	2 (17%)	6 (50%)	4 (33%)
Low grade LN	5 (4%)	1 (20%)	–	4 (80%)
FEA	4 (3%)	–	3 (75%)	1 (25%)
Myofibroblastoma	1 (1%)	–	–	1 (100%)
B5 (DCIS I)	2 (2%)	1 (50%)	1 (50%)	–

CNB, core needle biopsy; VAE, vacuum-assisted excision; ADH, atypical ductal hyperplasia; LN, lobular neoplasia; FEA, flat epithelial atypia; DCIS I, ductal cancer in situ grade 1

Among the 11 patients diagnosed with cancer by VAE and/or consequent surgery, the highest upgrade rate was observed when ADH was diagnosed on core biopsy (3/12, 25%), followed by ADH diagnosed during VAE (1/5, 20%), ALH on core biopsy (1/5, 20%), atypia on cytology (2/10, 20%), papillary formation on cytology (3/40, 8%), and papilloma without atypia on core biopsy (2/50, 4%).







## 5 Discussion

### 5.1 Study 1

As expected, there was a significant difference between the normal and benign biopsy groups, with increased AI-CAD flagging on screening mammography for women in the benign biopsy group. Further investigation regarding the probability that AI is affected by alterations on mammography because the biopsy was excluded, since we found a similar increase in the recall rate for the radiologists. It is important to note that the radiologists had access to the outcomes of prior biopsies, whereas the AI did not.

Another observation was that AI-CAD flagging was substantially lower than that by radiologists in women in the benign biopsy group who underwent biopsy after screening mammography. In such cases, applying the AI-CAD system for screening would have resulted in a much lower false-positive recall rate and unnecessary biopsies. Further studies on this matter would be of significance, as radiologists may be affected by the symptoms that women register during screening mammography. The AI-CAD system had no access to this information.

In this study, the AI-CAD system did not flag a specific area of the breast but the whole breast. We did not differentiate between the type of biopsy performed (FNA or CNB) and the size of the needle used. This analysis may have provided more information regarding the reasons for AI-CAD flagging in the benign biopsy group. Furthermore, we did not consider the different biopsied benign lesions or their sizes.

The concordance of AI-CAD flagging with radiologists in patients with cancer confirms the reliability of the system; however, further development and research are needed to improve the AI-CAD flagging rate in the healthy population.

### 5.2 Study 2

In this study, we used VAE to remove lesions of uncertain malignant potential using two different needle sizes, 7G and 10G. We found no significant difference between the two needle sizes with regard to excision completeness or procedure time, but procedures with a 7G needle size showed 8% better excision completeness results and were performed 40 s quicker. These differences were not statistically significant; however, their magnitude could be further

accentuated in a larger study population. Other studies that compared 8G and 11G needle size have shown preferable results for larger needles (172, 173).

Caution should be exercised during the analysis of short-interval post-procedure images, where scar tissue can cause misinterpretation (Fig. 23). Freeman et al. (174) recommended routine surveillance first, 36 months after VAE procedure of B3 lesions.

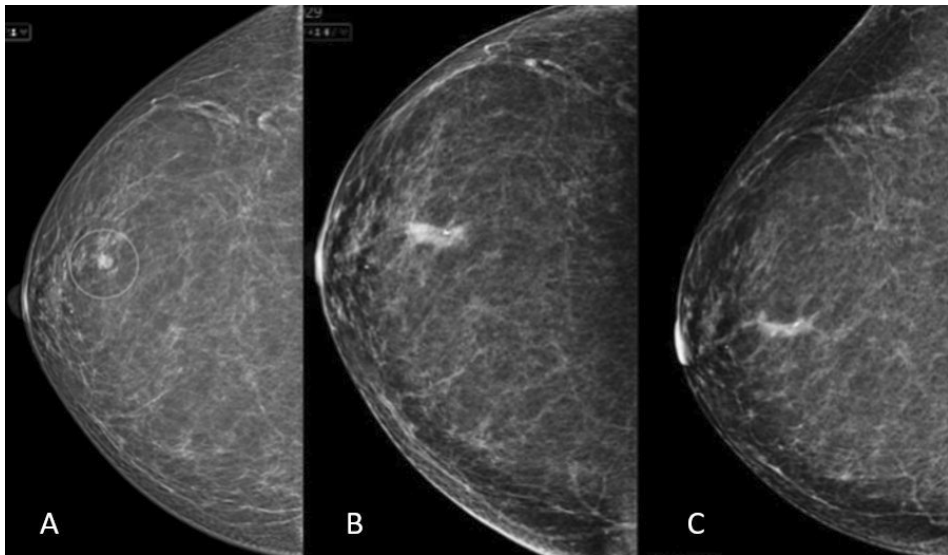


Fig. 23. (A) Mammography of a 5-mm papilloma; mammography of the same breast 6- (B) and 24- months (C) after VAE, showing scar tissue

This is the first randomized trial to compare a 7G needle size with a 10G one during VAE. The study was performed at a single center, mostly by one operator, adding a potential limitation to the external validity of the outcomes.

### 5.3 Study 3

This study investigated the relationship between needle size and patient experience. Pain, during and two weeks after the procedure, did not differ significantly when we used a 7G or 10G needle, remaining at acceptable levels with a number of patients documenting pain, some days after the procedure, radiating towards the ipsilateral shoulder and diminishing over time.

The major complication to be addressed after a VAE is bleeding, which can occur during the procedure, causing an abrupt termination of the excision procedure, or

hours after the end of the procedure, causing stress to the patients. Placing adrenaline in combination with local anesthesia and avoiding blood vessels during ultrasound-guided VAE are important for reducing the incidence of bleeding. Even here, no difference in the incidence of bleeding was observed between the 7G and 10G needle.

The economic advantage of VAE in comparison to OSE is clear, and although our study assessed the economic burden in Sweden only, several other studies (175–180) have confirmed the decisive reduction in hospital expenditures after the implementation of the VAE, which generalizes our results.

#### 5.4 Study 4

In this study, we compared FNA and CNB using VAE. Furthermore, we stratified the lesion types to identify the lesions that had the highest upgrade rates within the different B and C categories.

In concordance with other studies (66, 69, 181–185), we found that FNA diagnoses had a 24% upgrade rate, which eventually led to unnecessary re-biopsies and probably even therapies. In contrast, CNB diagnoses have a general upgrade rate of 15%, which is an improvement over FNA.

The highest interlesional upgrade rate was noted in groups C1 and B1, probably because of sampling and diagnostic issues (186). The highest upgrade rate to malignancy was documented in ADH (22%) included one case in where an existing ADH lesion was excised with VAE and later upgraded to DCIS grade II after subsequent surgery.

A limitation of this study is that we had to include a small number of individual lesion types that did not allow further analysis.

Regarding the results of our study, caution should be exercised regarding C1 and B2 diagnoses and their correlation with imaging findings. Thus, CNB is preferable to FNA as the primary diagnostic method.



## 6 Conclusions

AI is an important add-on to mammography. Excision of benign breast lesions can be successfully performed using VAE.

In Study I, we found a similar sensitivity in detecting breast cancer by both radiologists in a screening setting. The same sensitivity was applied to women with a history of benign breast biopsy before mammography in the same setting. Lower recall rates would have been possible in all the other healthy women in this study; however, further analysis through prospective studies is important.

In Study II, we found no overall difference in excision completeness or time of the procedure during VAE when comparing the 7G and 10G needle sizes. Lesion size played a significant role in both outcomes, whereas excision of microcalcifications had the highest rate of re-excision.

In Study III, we confirmed that VAE is a well-accepted method for patients with lesions of uncertain malignancy, with noticeably reduced hospital costs compared with OSE.

In Study IV, we found that CNB is a preferable choice for primary diagnosis compared to FNA but not ideal. B3 lesions should be excised with special consideration for ADH.

## 7 Points of perspective

Breast cancer screening programs have proven very successful, but there is a need to improve screening settings. The implementation of AI-CAD systems in mammography in combination with radiologists has been shown to be reliable. By integrating AI, a patient's clinical information and history, including previous imaging findings, will further help understand and develop AI-CAD systems for patient personalization.

Further studies that excise and follow rare B3 lesions are imperative to better understand and select lesions that can be safely removed with VAE. Already experienced physicians in ultrasound-guided biopsies can with a short learning curve start using VAE instead of OSE for the excision of B3 lesions. AI machine learning can be used to predict the risk of malignancy by combining imaging and histopathological characteristics to provide personalized pathways.

We also welcome the results from international studies that investigated additional implementations of VAE, such as for early breast cancer and for patients with complete response after neoadjuvant therapy, contributing to ongoing research on minimally invasive therapy.



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## 9 Declaration about the use of generative AI

I have not used any AI assisted tools for writing the "kappa"/comprehensive summary of the thesis.

I take full responsibility for the content of the "kappa"/comprehensive summary of the thesis.



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