The Agreement Between Automated Breast Ultrasound (ABUS) and Digital Breast Tomosynthesis (DBT) in Detecting Architectural Distortions Among Patients Undergoing Breast Imaging.

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

ABUS Automated breast ultrasound

AD Architectural distortion

BIRADS Breast Imaging Reporting and Data System

CI Confidence Interval

CPG Clinical Practice Guideline

DBT Digital Breast Tomosynthesis

HHUS Hand-held ultrasound

PPV Positive Predictive Value

SD Standard Deviation

LIST OF FIGURES

Abstrak

Latar belakang: Kanser payudara merupakan kanser yang terbanyak di kalangan wanita di Malaysia, and seluruh dunia. Ia sangat penting di kesan di peringkat awal bagi mengurangkan kadar kematian dan morbiditi. Perubahan struktur payudara adalah salah satu petanda awal kanser payudara, tetapi ia sukar dikesan pada pesakit yang mempunyai struktur payudara yang padat. Ia adalah petanda yang ketiga penting dalam kanser payudara dimana 44.2% perubahan struktur payudara adalah kanser. Pengimbasan ultrabunyi payudara tiga dimensi boleh menghasilkan imej tiga dimensi dan tidak bergantung kepada pengendali mesin. Imej yang dihasilkan membolehkan tisu payudara dilihat dengan lebih jelas. Memandangkan ia tidak menghasilkan radiasi ion, ia sesuai digunakan untuk wanita muda, serta pesakit yang mempunyai tisu payudara yang padat. Kajian ini dijalankan untuk mengkaji kebolehan pengimbas ultrabunyi payudara tiga dimensi dalam mengesan perubahan dalam struktur payudara, agar dapat mengganti digital tomografi dalam mengesan kanser payudara di kalangan wanita muda, yang mengandung dan yang mempunyai tisu payudara yang padat.

Kaedah: Kajian dilakukan di Hospital Universiti Sains Malaysia, Kubang Kerian. Kelantan. Pesakit yang dikesan mempunyai perubahan struktur payudara di digital tomografi payudara akan dihantar untuk menjalani ujian imbasan ultrabunyi payudara tiga dimensi. Sejumlah 37 perubahan struktur payudara di masukan ke dalam kajian ini, melibatkan 37 pesakit wanita. Imej yang dihasilkan akan dikaji. Persetujuan diantara dua kaedah ini dikira menggunakan ujian Kappa.

Keputusan: Persetujuan sederhana dikesan diantara digital tomografi payudara dan imbasan ultrabunyi payudara tiga dimensi dalam mengesan spikulasi, nilai Kappa 0.525 (p=0.001), dan gangguan struktur sisi, nilai Kappa 0.421 (p=0.008). Persetujuan sedikit dalam mengesan penarikan tisu payudara, nilai Kappa 0.183 (p =0.054).

Kesimpulan: Imbasan ultrabunyi payudara tiga dimensi adalah kaedah yang bagus, menunjukan persetujuan sederhana dengan digital tomografi payudara. Ia boleh digunakan sebagai ujian tambahan dalam mengesan kanser payudara di kalangan wanita muda.

Keyword: Pengimbasan ultrabunyi payudara tiga dimensi, Kanser payudara, Digital tomografi payudara, Perubahan struktur payudara.

Abstract

Background: Breast cancer is the leading cancer affecting women, globally. Early detection is vital to improve the survival rate and reduce morbidity. Architectural distortion is one of the early findings in breast cancer, however it is difficult to visualize especially in a dense breast. It is the third most common presentation of breast cancer, where 44.2% of architectural distortion is often malignant. Automated breast ultrasound (ABUS), enables three-dimensional image giving better visualization of the breast tissues. It is non operator dependent with reproducible images. In view of its non- ionizing feature, it is a better choice for younger patient as well as patients with dense breast. The aim of this study is to explore the ability of detecting architectural distortion as a potential substitute for digital breast tomosynthesis (DBT) in breast cancer screening for the young or pregnant women, and those with dense breasts.

Methods: This is a cross sectional study done in Hospital Unversiti Sains Malaysia, Kubang Kerian, Kelantan. Patients with architectural distortion detected in DBT were subjected to ABUS. The images were reviewed, examined for the presence of architectural distortions. A total of 37 architectural distortions were studied, involving 37 of women. The agreement between mammography and ABUS in detecting architectural distortions were tested using Kappa agreement test.

Results: There is a moderate agreement of straightening of parenchyma edges between DBT and ABUS with kappa value 0.421 (p=0.008), and moderate agreement in spiculation, kappa value 0.525 (p=0.001). Slight agreement in detecting focal retraction, kappa value 0.183 (p =0.054).

Conclusion: ABUS is a good tool in detecting architectural distortion which demonstrated moderate agreement with DBT. It can be considered as an adjunct to DBT as well as, initial screening for young women.

Keyword: ABUS, Breast cancer, DBT, architectural distortion.

CHAPTER 1: BACKGROUND

1.1 Introduction

Breast cancer is the leading cancer among Malaysian women, with it being the second highest mortality among all types of cancer (Registry, 2020). The gold standard for breast cancer screening is mammography, with complementary ultrasound in women with dense breast. It is known that younger patients usually have denser breast. Thus, it is difficult to accurately diagnose these patients, solely using mammography. In this instance, ultrasound is done to help in detecting suspicious breast lesions.

The incidence of breast cancer among younger women who are below 40 years old is increasing (Labrèche et al., 2020), and mammography is not a recommended mode of imaging. Hence, this group of patients depend on ultrasound for lesion detection. Asian women have higher breast density as compared to their western counterpart. This factor also plays a role in the accuracy of detecting breast cancer during screening with mammography where complementary ultrasound is needed.

Digital breast tomosynthesis (DBT) acquires and display three dimensional mammograms. Images are acquired in thin slices by an x-ray source that moves in arc of excursion. The thin slice images are then reconstructed to minimize overlapping tissues (Alabousi et al., 2020). This leads to an increase in sensitivity and specificity in detecting abnormality than using the mammogram; with improved detection of spiculated masses and better in detecting subtle abnormality such as architectural distortion (Partyka et al., 2014).

Architectural distortion is defined as the distortion of the breast parenchyma without a definite mass, features are spiculation from a point, focal retraction and straightening of the parenchyma edges. It can also be associated with a mass. These features are best seen in mammography. Although there are multiple causes of architectural distortion, most of them are benign and is also associated with breast cancer. Architectural distortion is at times the only presentation of breast cancer (Alikhassi et al., 2019). Thus, when architectural distortion is present during screening, radiologist tend to err on the malignancy side. In this instance, radiologists will have difficulty in detecting architectural distortions in patients with dense breast. They are also unable to detect this feature in young women where mammography is not recommended. The positive predictive value of malignancy in architectural distortion is 34.6% (Choudhery et al., 2020).

Hand-held ultrasound (HHUS) is also used as a complimentary to mammography in patients with dense breast, as well as for better lesion characterization. The drawback of HHUS is that it is operator dependent and the images are not reproducible. The field of view for HHUS is small, making it difficult to have a good overview of the breast.

Automated breast ultrasound (ABUS) which was initially developed in the 1960s, is now becoming the alternative for HHUS. The image of the breast can be seen as a whole, with reproducible images (Karst et al., 2019). Unlike HHUS, it is non-operator dependent and less time consuming. With the 3D image produced, better image of the breast tissues is visualized, and the detection of architectural distortion is better as compared to HHUS. 3DUS is now widely used as an adjunct screening for dense breast (Kim et al., 2020).

1.2 Objectives

1.2.1 General Objective

To determine the agreement between automated breast ultrasound (ABUS) and digital breast tomosynthesis (DBT) in detecting architectural distortions.

1.2.2 Specific Objective

1. To determine and compare the proportion of imaging characteristics of architectural distortion in ABUS and DBT.

2. To determine the agreement of architectural distortions characteristics detected by ABUS and DBT.

1.3 Hypothesis

There is a good agreement between automated breast ultrasound and digital breast tomosynthesis in detecting architectural distortion.

1.4 Research Questions

1. What are the characteristics of architectural distortions on automated breast ultrasound and digital breast synthesis?

2. Is there any agreement between automated breast ultrasound and digital breast tomosynthesis in detecting architectural distortion?

CHAPTER 2: LITERATURE REVIEW

2.1 Breast anatomy

The breast is an organ located at the anterior chest wall from the level of third to seventh ribs. It comprises of 15-20 lobes which are arranged in clusters around and behind the nipples. These lobes that are made of multiple lobules which contain the secreting unit and alveoli. The stroma of the breast consists of dense fibrous and adipose tissues. The nipple, which is at the center of the breast, is surrounded by areolar and has small depressions for ducts outlets (Benedetto et al., 2016).

The breast development depends on three interrelated factors, namely age, composition of breast tissues and hormonal environment. The breast also undergoes changes during menstruation, pregnancy, lactation, post-lactation and menopause. During these times, the lobular structures undergo involutions leading to different density of parenchyma, fibrous stroma and fat tissues (Reid et al., 1996).

2.2 Breast architectural distortion and breast cancer

Breast cancer is one of the prevalent cancers in the world (11.7%) and particularly, in Malaysia (Figure 1), with it being one of the leading causes of mortality among women (Asia et al., 2020; Registry, 2020).

Architectural distortion is the distortion of the breast parenchyma without a definite mass, which includes spiculation from a point, focal retraction and straightening of the parenchyma edges. It can also be associated with a mass (Durand et al., 2016). Architectural distortion of the breast is often caused by desmoplastic response leading to the presence of dense collagenous stroma. Desmoplastic reaction of breast malignancy leads to the contraction of surrounding tissues towards the mass; leading to disruption of the normal tissue plane. This resulted in the formation of architectural distortions of the breast (Zheng et al., 2015). The proposed mechanisms for desmoplasia include condensation of pre-existing collagen and synthesis of collagen by myofibroblasts present in the interstitium. Histologically, it is shown that there is varying degree of stromal response, from being predominantly cellular with minimal collagenous tissue to dense collagen stroma with few stromal cells (Walker, 2001).

Architectural distortion is one of the most frequently missed findings in using mammogram. It is subtle and usually found retrospectively in false-negative mammography. The presence of architectural distortion is the earliest manifestation of malignancy. Architectural distortion exhibits high positive predictive value (PPV) for malignancy (10-67% in screening and 60-83% in diagnostic imaging) (Alshafeiy et al., 2018; Gaur et al., 2013).

There are many causes of breast architectural distortion, most of them are benign. They include radial scar, sclerosing adenosis, fibrocystic changes and stromal fibrosis. Malignancy can also cause architectural distortion, where these findings can be seen in infiltrating lobular carcinoma, intraductal carcinoma and infiltrating ductal carcinoma (Boyer and Russ, 2014; Pinochet Tejos et al., 2016). Although most of architectural distortions are benign, it has a high positive predictive value for malignancy, thus radiologists tend to err on the side of malignancy.

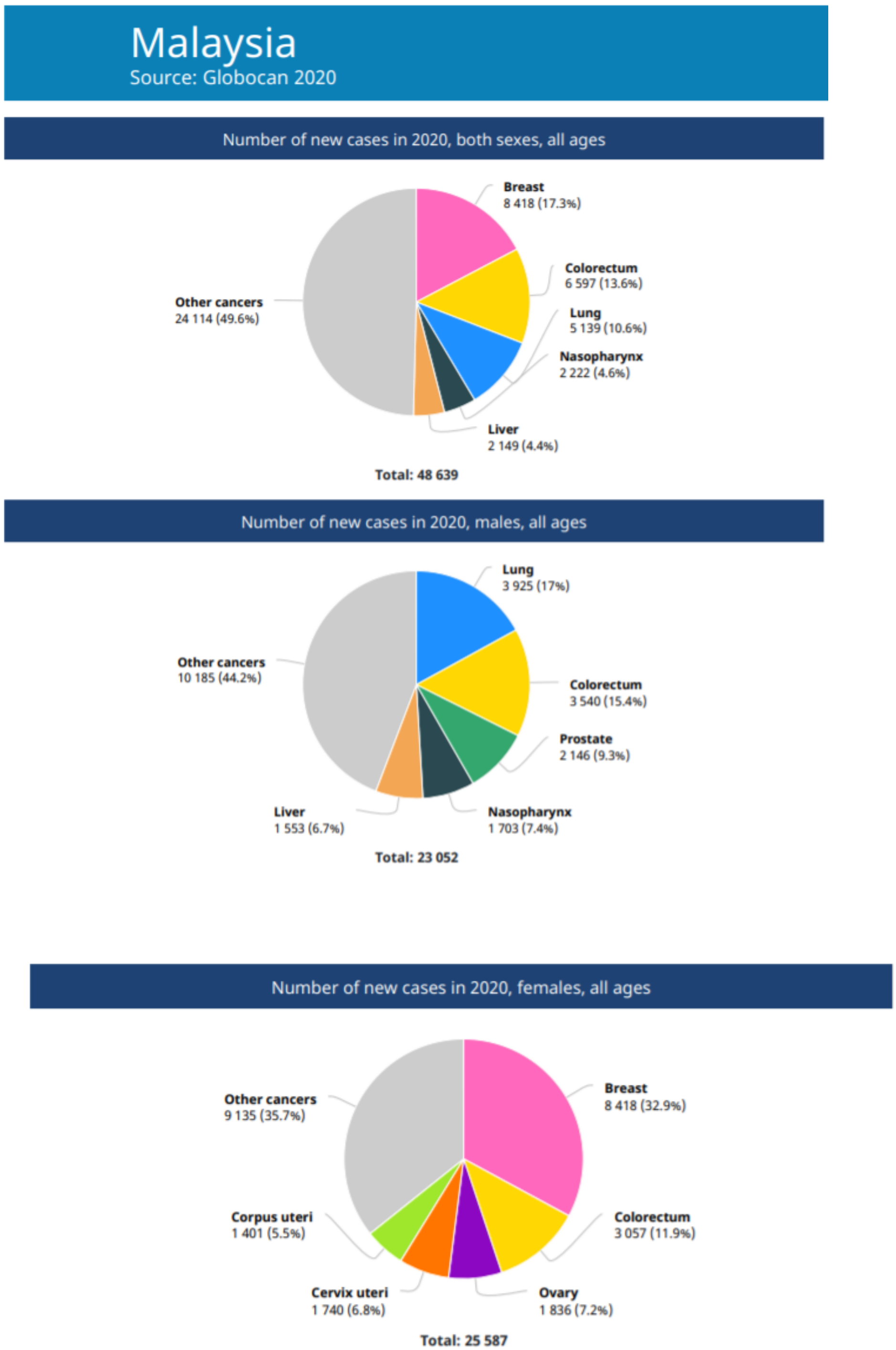


Figure 1: Cancer statistics in Malaysia

There are multiple risk factors associated with breast cancer, and they are divided into modifiable and non-modifiable risk factors. The modifiable risk factors include nulliparity, lack of breastfeeding, hormonal factors such as the use of oral contraceptive pills, lifestyle, and radiation exposure. The non-modifiable risk factors for breast cancer are age, gender, family history of breast cancer, early menarche, late menopause, history of neoplastic disease of the breast and breast density.

According to the 2019 Malaysian Clinical Practice Guidelines (CPG) for the management of breast cancer (third edition), triple assessment is used in the assessment and diagnosis of breast cancer. Triple assessment consists of clinical assessment, imaging (ultrasound and/mammography and pathological assessment (histology or cytology). It is recommended that a combination of ultrasound and DBT is used in the assessment for breast cancer.

There are multiple meta-analysis studies on the use of DBT, which yielded higher sensitivity and specificity. An example (Hodgson et al., 2016), concluded that DBT has higher invasive cancer detection rates (90.77% sensitivity and 96.49% specificity). Adjunct ultrasound increases the sensitivity of cancer detection as demonstrated by Kolb et al., 2002 that 42% more non-palpable, mammographically occult breast cancers were detected.

2.3 Automated breast ultrasound

The concept of automated breast ultrasound first started in the 1970s. It is developed to overcome the downside of handheld ultrasound. It acquires a series of consecutive B-mode images and reconstructs 3D data sets of the entire breast volume (Figure 2). Thus, it can project an image the breast as a whole in a single set of images. The data sets will be sent to a separate workstation for analysis. With this, automated breast ultrasound is able to eliminate the operator dependency of handheld ultrasound and the images available are reproducible (Karst et al., 2019; Wojcinski et al., 2011).

This machine uses a wide linear array transducer (5-14MHz) with a specific lotion to prevent air bubbles and ensure adequate contact with the breast. Three to five views will be obtained, depending on the breast size, which includes antero-posterior, lateral, medial, superior and inferior views. The nipple will be the reference point for all the views. This is to allow correct orientation and post-processing reconstructions (Rella et al., 2018). Total scanning time will be about 10 minutes.

The multi-planar 3D reconstructed images improve lesion detection and with the availability of coronal view, retraction phenomenon can be observed. Retraction phenomenon is a stellate pattern of hypoechoic tissue surrounding a lesion (Van Zelst et al., 2015). Presence of retraction phenomenon has higher diagnostic value in differentiating benign from malignant lesion where it shows 80-89% sensitivity and 96-100% specificity. This retraction phenomenon is not able to be produced using handheld ultrasound (Kim et al., 2020).

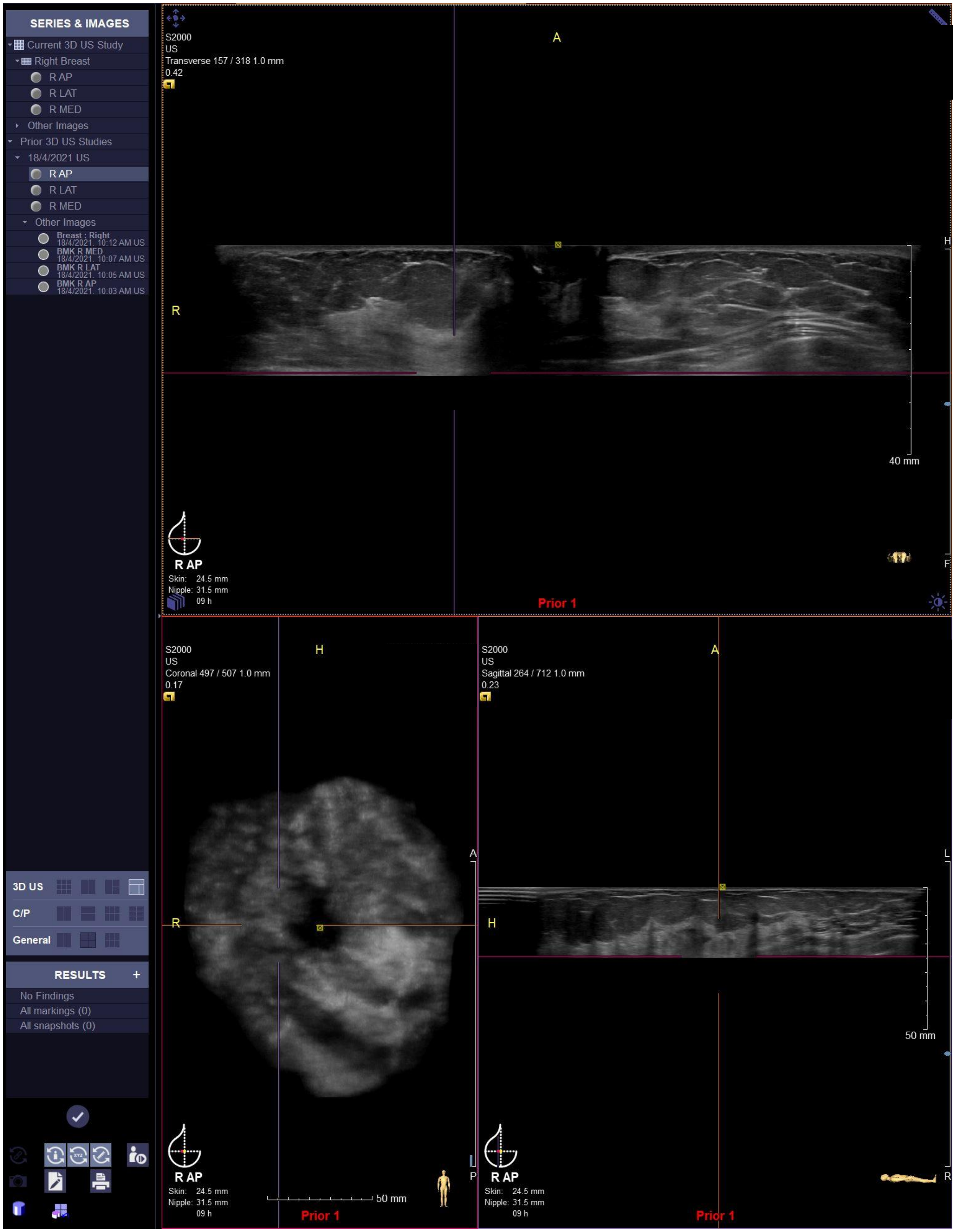
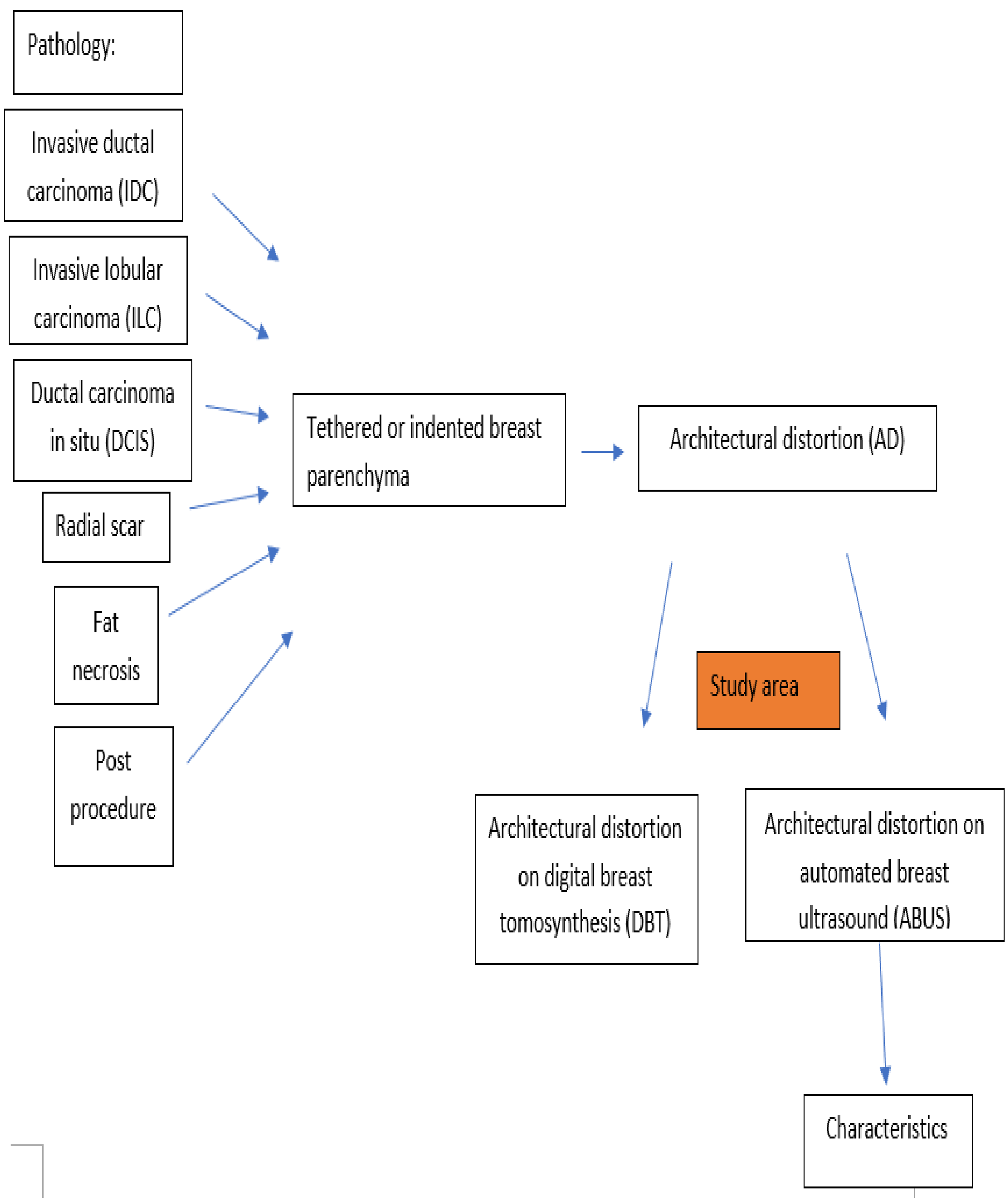


Figure 2: ABUS image: Image of the normal breast as viewed in the syngo®. Ultrasound Breast Analysis (sUSBA)

2.4 Conceptual Framework



2.5 Study Rationale

The aim of this study is to explore the ability of ABUS in detecting architectural distortion in comparison with DBT. If so, ABUS can be considered to be a potential substitute for mammogram in view of it being non ionizing imaging. It will be valuable for younger patients and those who are pregnant. ABUS can be helpful in the screening of women with dense breast as well.

CHAPTER 3: METHODOLOGY

3.1 Study Design

This is a cross sectional study conducted in Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan. Data were collected from February 2022 until August 2022.

3.2 Study Population

i. Reference population - Patients who underwent breast imaging.

ii. Source population - Patients who underwent breast imaging in Radiology Department Hospital Universiti Sains Malaysia.

iii. Target population - Patients who had architectural distortions for DBT.

3.3 Sample Size Calculation

1. For objective number 1, the sample size was calculated using Sample Size Calculator: Single Mean by Wan Ariffin. Based on the study entitled, Malignant Outcome of Architectural Distortions on Tomosynthesis: A Systemic Review and Meta-analysis, the percentage of architectural distortion detected on tomosynthesis was 34.6% (95% CI: 24.5%-46.3%) (Choudhery et al., 2020). The estimated sample size was calculated using the Kappa (2 raters) estimation. The calculated sample size is 207 lesions.

2. For objective number 2, the sample size was calculated using Sample Size Calculator: Single Mean by Wan Ariffin. There was no study done to determine the characteristics of architectural distortions on 3D breast ultrasound, thus estimations are made based on previous

study by Samreen et al,2020, which included 2D ultrasound correlate in architectural distortions detected on tomosynthesis. The percentage of ultrasound that correlates to architectural distortion is 92% (Samreen et al., 2020). The estimated sample size calculated using 1 proportion estimation. is 155.

Drop-out cases was estimated at 10%. The highest sample size was taken as the sample size of this study. Therefore, the sample size of this study is 207 lesions.

3.4 Sampling Method

There was no sampling method applied. Patients with architectural distortions on DBT who fulfilled the inclusion and exclusion criteria were enrolled in this study.

3.5 Inclusion Criteria

1. Patients with architectural distortion on DBT in one or both breasts.

2. Patients with history of wide local excision.

3.6 Exclusion Criteria

1. Inflammatory conditions of the breast.

2. Fungating lesion on the breast.

3. Skin disorders over the breast e.g.: neurofibromatosis, multiple skin tags.

3.7 Research Tool

1. Acuson 2000 Automated Breast Volume Scanner Ultrasound System (ACUSON S2000 AVBS Product Version 1.0, 2009-2013 Siemen Medical Solution USA).

2. Mammomat Revelation (Product version VC20 2020 Siemens Medical Solutions USA)

3. syngo®.Ultrasound Breast Analysis (sUSBA) Product version 3.0, software version VA40, 2012-2019 Siemens Medical Solutions USA

4. syngo.Breast Care (Product version VB20 2020 Siemens Medical Solutions USA).

3.8 Operational Definition

1. Architectural distortion is the distortion of the breast which includes spiculation from a point, focal retraction and straightening of the parenchyma edges.

2. Breast Imaging Reporting and Data System (BIRADS) breast density:

a. BIRADS A – almost entirely fatty breast

b. BIRADS B – scattered fibroglandular tissue density

c. BIRADS C – heterogeneously dense breast

d. BIRADS D – extremely dense breast

3. Features of architectural distortions on mammogram (Fallis, 2013):

a. Straightening of the parenchyma edges

b. Focal retraction or distortion

c. Thin line or spiculation radiating from a point source

4. Features of architectural distortions on ultrasound (Figure 4-6) (Fallis, 2013)

a. Straightening or disruption of the Cooper ligament

b. Retraction phenomenon

c. Spiculation

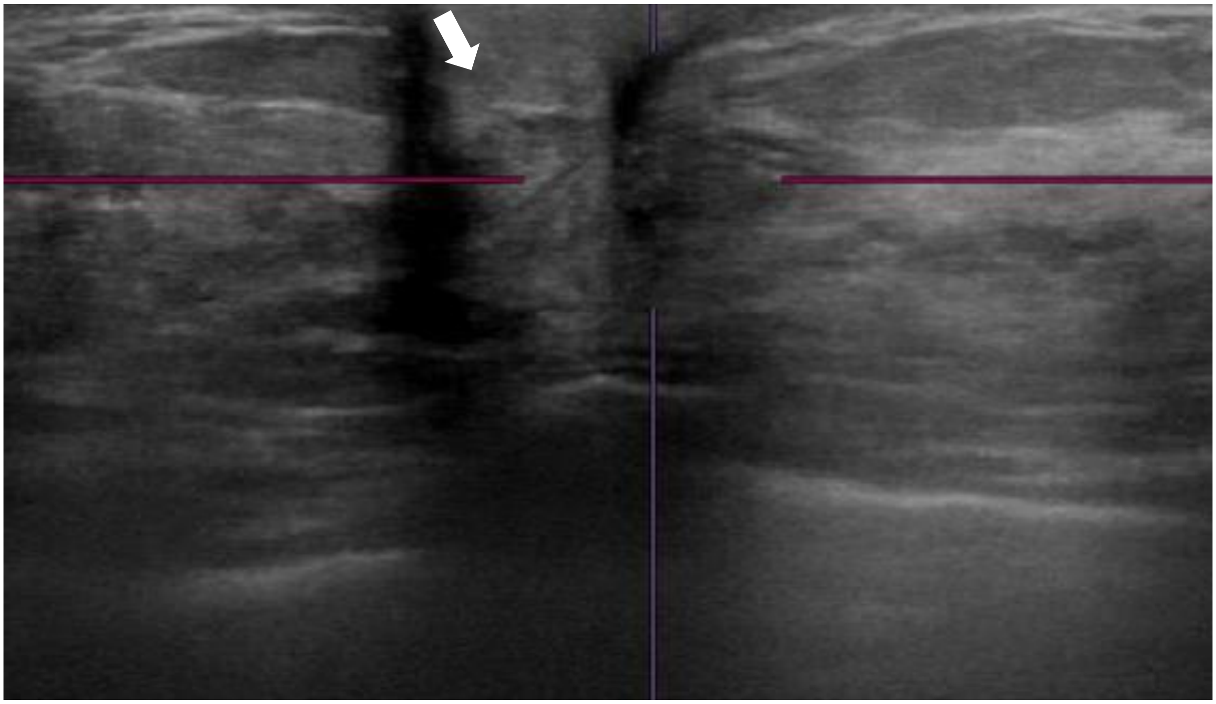


Figure 4: Ultrasound of the breast showing disruption of Cooper ligament (white arrow)

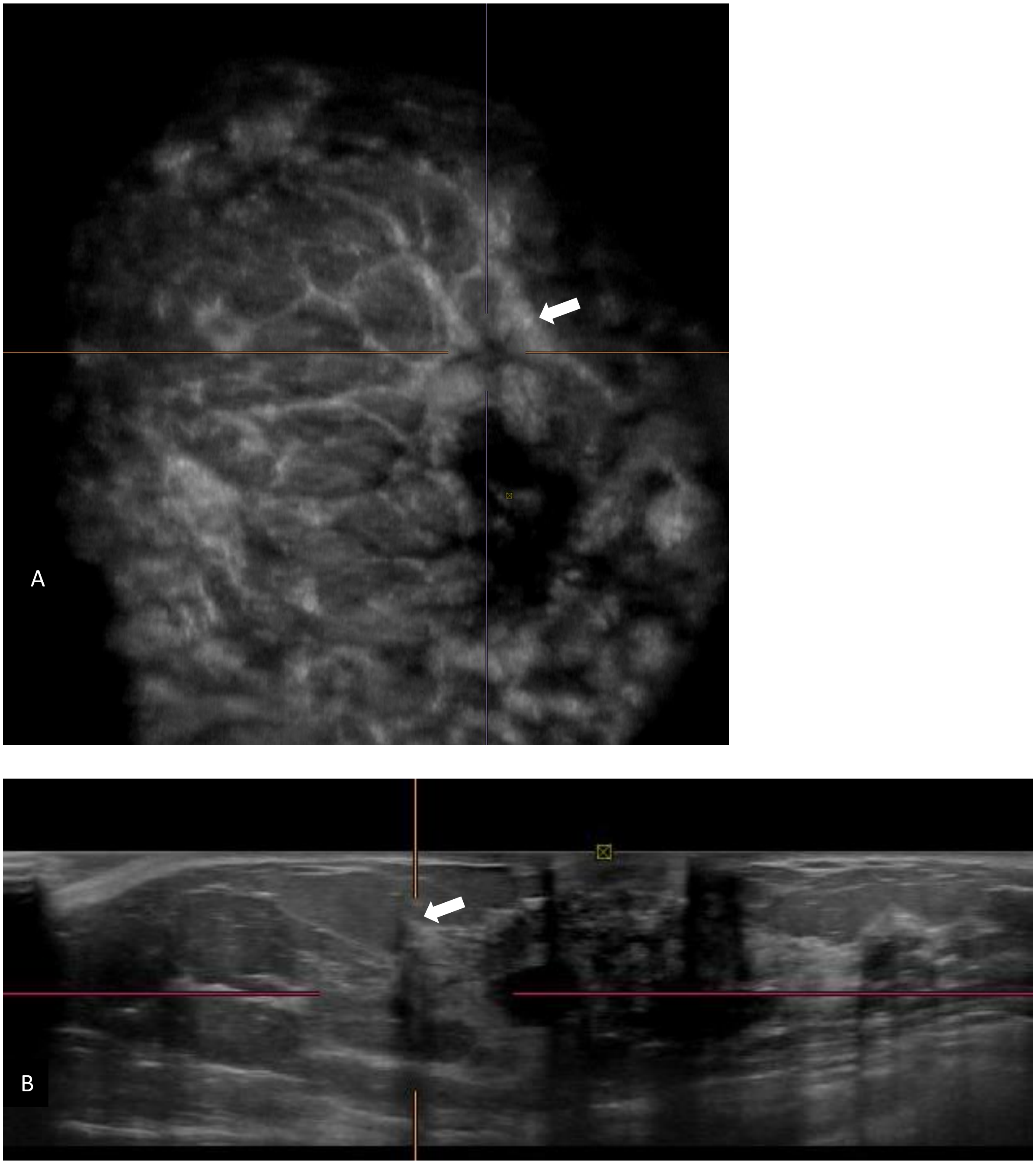


Figure 5: ABUS image in coronal view (A) and sagittal (B) view showing retraction phenomenon (white arrow).

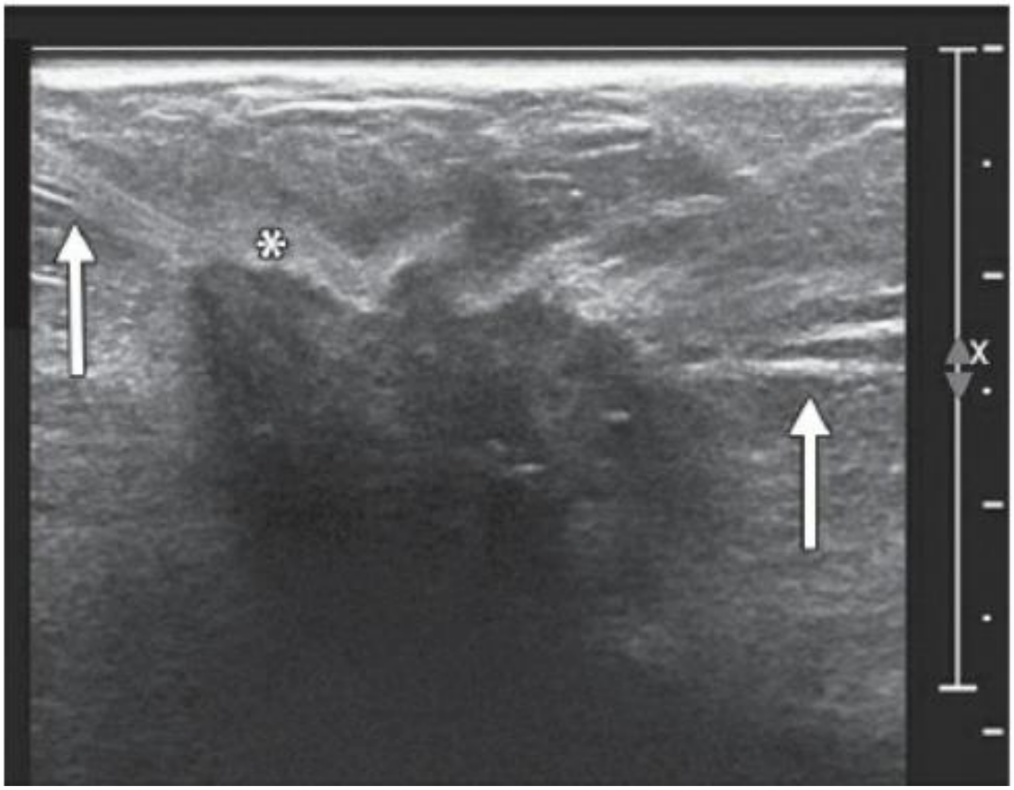


Figure 6: Ultrasound of the breast showing spiculation (*).

3.9 Data Collection

This was a cross sectional study, whereby the previously available images from 1st December 2020 until 31 August 2022 will be included, as well as new prospective candidate were recruited in this study.

The patients who come for breast imaging appointments and fit the inclusion criteria were included in this study. Informed consent from patients were obtained by the primary investigator/radiographer in charge. Subjects were assigned with serial numbers so as to maintain their anonymity. Demographic data such as age, parity and family history of malignancy were also recorded. This data collection time took five to ten minutes.

The patients followed the normal flow of breast imaging. The DBT images will be reviewed for presence of architectural distortions. ABUS was performed when there is a presence of architectural distortion on DBT.

DBT examination in HUSM is performed using the Mammomat Revelation machine (Siemens Healthineers), which included the mediolateral oblique and craniocaudal views. This examination was done in a private imaging suite. The patient stood facing the machine with the ipsilateral hand rested on the machine. Images were obtained using 50-degree wide angle tomosynthesis in the views mentioned, and post processing was then performed to produce 2D and 3D images. The images were sent to syngo.Breast Care viewer for reviewing.

Previous images of DBT carried out during this study period were reviewed to look for the presence of architectural distortion on DBT. Selected patients were called, informed and explained about the study. These patients underwent 3D ultrasound imaging after informed consent were obtained, as per in the above explanation.

The patients were then sent to 3D breast ultrasound room. In our center, the 3D ultrasound machine used is, ABVS ACUSON S2000 (Siemens Medical Solutions, USA). It consisted of the ABVS module with flexible arms, scanner (transducer, scan box, and screen-membrane for contact) with high frequency linear probe and a touch screen monitor.

The examination was performed in a private imaging suite to ensure the privacy of patients. The patient laid in a supine position with the arm positioned above the head so as to flatten the breast. The pod was then placed onto the breast to acquire the appropriate view. The views taken were anteroposterior, medial, lateral. Additional views were superior and inferior, depending on the patients' cup size. The estimated time of performing ABUS on each patient was approximately 30 minutes. Images were then sent to syngo®.Ultrasound Breast Analysis (sUSBA) for reviewing.

The demographic data (age, family history of malignancy) and presence of mass on palpation were documented in a data sheet with patients' identification; labelled with serial numbers to ensure confidentiality. The demographic data were stored in a password-protected computer, in which only the principal investigator had access to.

The principal investigator then reviewed all the images and determine the presence of architectural distortion. The breast density and associated mass on DBT/ABUS was also recorded.

The total estimated time taken for each participant was approximately 40 minutes to one hour.

Data validation was done by a radiologist for at least 10% of the total sample.

3.10 Statistical Analysis

Data were entered and analyzed using SPSS version 26. Descriptive statistics was used to summarize the socio-demographic characteristics of subjects. Numerical data were presented as mean (standard deviation, SD) based on their normality distribution. The characteristics of architectural distortion on ABUS, which were Cooper ligament disruption, retraction phenomenon and spiculation, were presented as frequency (percentage). Kappa agreement test was used to determine the agreement for straightening of parenchymal edges, focal retraction, or distortion, and spiculation from a point source between ABUS and DBT. This analysis was presented in at two-by-two table for each of the characteristics.

3.11 Confidentiality and Privacy

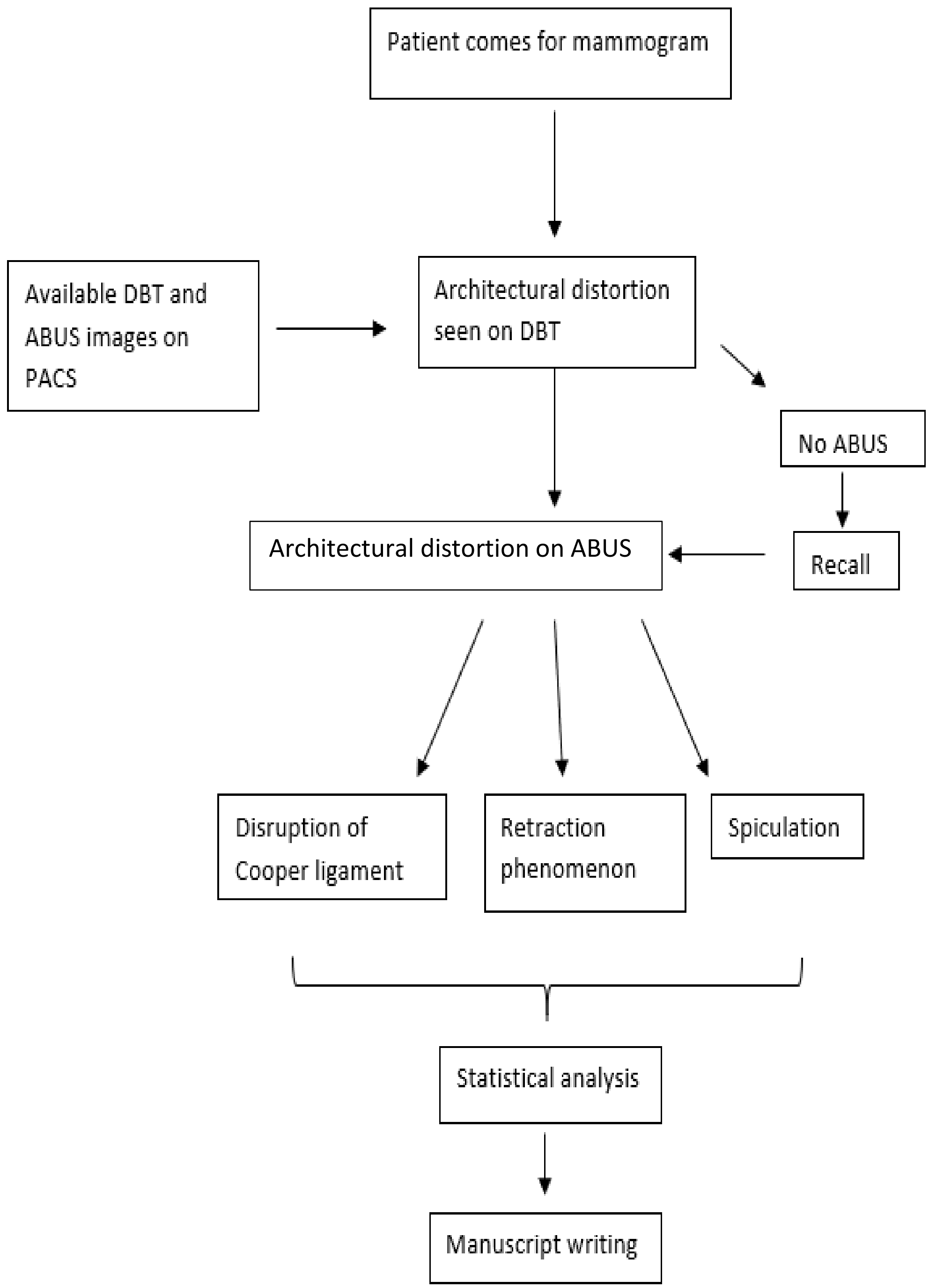
The subjects were identified using a unique serial number. No identifiable data was shared publicly. Only research team members are able to access the data. The data was presented as a grouped data and will not identify the responders, individually.

Upon completion of the study, all data were stored in CDs, and the database on the computer was erased. The data were retained by the researchers for knowledge purposes only. Neither the name nor any identifying information was used in any publication or presentation resulting from this study.

3.12 Ethical Consideration

The study was approved by Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/21120774).

3.13 Study Flowchart



CHAPTER 4: MANUSCRIPT