Sonographic Ductal Changes and Pertinent Characteristics That Associate with Proliferative Lesions of Breast

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ภาพรูปท่อและคุณลักษณะร่วมที่เกี่ยวข้องโดยการตรวจอัลตราซาวด์ที่สัมพันธ์กับรอยโรคของเต้านมที่มีเซลล์เพิ่มจำนวน

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แองเกรนี อาร์ยู เรงกานิส : ภาพรูปท่อและคุณลักษณะร่วมที่เกี่ยวข้องโดยการตรวจอัลตราซาวด์ที่สัมพันธ์กับรอยโรคของเต้านมที่มีเซลล์เพิ่มจำนวน. (Sonographic Ductal Changes and Pertinent Characteristics That Associate with Proliferative Lesions of Breast) อ.ที่ปรึกษาหลัก : ศ. นพ.พิเชฐ สัมปทานุกุล, อ.ที่ปรึกษาร่วม : ดร.ณุดา จองพิศาล

การดูแลรอยโรคท่อน้ำนมหนาเฉพาะที่พบจากอัลตราซาวด์ยังไม่มีแนวปฏิบัติที่ชัดเจน ส่วนมากของการเจาะดูดด้วยเข็มได้ตัวอย่างที่แทบไม่มีเซลล์ การศึกษานี้มีจุดประสงค์เพื่อหาตัวแปรต้นที่พยากรณ์รอยโรคท่อนมที่มีการเจริญของเซลล์เพื่อสามารถเลี่ยงการเจาะดูดรอยโรคท่อนมหนาที่อาจไม่มีความจำเป็น โดยออกแบบเป็นศึกษาย้อนหลังติดตามกลุ่มผู้ป่วยที่มีรอยโรคท่อน้ำนมหนาเฉพาะที่ไปข้างหน้าหาความสัมพันธ์ของดัชนีต่างๆที่พบร่วมในอัลตราซาวด์กับผลลัพธ์คือท่อนมหนาที่เกิดจากเซลล์เจริญหรือไม่มีเซลล์เจริญในท่อ โดยเกณฑ์คือการวินิจฉัยทางจุลทรรศน์ของชิ้นเนื้อหรือการตรวจเซลล์วิทยาร่วมกับการติดตามต่อเนื่องไม่น้อยกว่าสามปี ผลการรวบรวมข้อมูลในปี พ.ศ.๒๕๕๘ ถึง ๒๕๖๐ ได้ผู้ป่วยหญิงทั้งสิ้น ๑๙๙ คน ของ รพ.จุฬาลงกรณ์ฯ ร้อยละ ๕๖.๓ เป็นผู้ป่วยมาตรวจคัดกรอง(แบบที่ ๑) ร้อยละ ๒๒.๑ เป็นผู้ป่วยที่ตรวจเพราะมีอาการและพบท่อนมหนาร่วม(แบบที่ ๒) และร้อยละ ๒๑.๑ เป็นผู้ป่วยมะเร็งเต้านมที่รักษาหายมาตรวจติดตาม(แบบที่ ๓) สัดส่วนของกลุ่มอายุน้อยกว่า ๕๐ ปีและ ๕๐ ปีขึ้นไป คือ ๕๓:๔๗ ดัชนีที่พบร่วมกับท่อนมหนาพบรอยโรคก้อนในท่อร้อยละ ๖๕.๗ รอยโรคไม่คมชัดที่ผนังท่อร้อยละ ๔๑.๐ ตำแหน่งท่ออยู่ห่างจากหัวนมร้อยละ ๖๙.๐ เส้นเลือดมาเลี้ยงที่ท่อร้อยละ ๓๕.๒ หินปูนในท่อร้อยละ ๓๙.๕ และเส้นผ่านศูนย์กลางท่อเฉลี่ย ๔.๕ มิลลิเมตร (ค่าเบี่ยงเบนมาตรฐาน ๑.๔๓) การวิเคราะห์ผลลัพธ์พบ ภาวะท่อนมชนิดมีเซลล์เจริญมากในท่อจำนวน ๗๑ รอยโรค (๑๘ รอยโรคเป็นมะเร็ง) ร้อยละ ๖๖.๒ เป็นชนิดไม่มีเซลล์มากในท่อ โดยที่ร้อยละ ๕๒.๔ ของการเจาะดูดที่รอยโรคพบตัวอย่างที่แทบไม่มีเซลล์ การวิเคราะห์โดยใช้สถิติแบบถดถอยพบดัชนีเพียงอันเดียวคือการมีเส้นเลือดมาเลี้ยงตรงท่อนมหนามีคุณสมบัติเป็นดัชนีพยากรณ์ โดยมีค่าแต้มต่อ ๒.๒๑ (ค่าความเชื่อมั่นที่ร้อยละ ๙๕ คือ ๑.๑๖, ๔.๑๙) การใส่อายุที่เส้นแบ่ง ๕๐ ปี และรูปแบบคลินิกแบบที่ ๒ และ ๓ เข้าไปในสูตรจำลองไม่พบความสำคัญทางสถิติ โดยสรุปการพบเส้นเลือดมาเลี้ยงที่ท่อน้ำนมหนามีความสำคัญในการพยากรณ์ภาวะเจริญของเซลล์ในท่อนม การพบรอยโรคท่อนมหนาเฉพาะที่เพียงอย่างเดียวโดยไม่มีลักษณะร่วมอื่นอาจใช้การเฝ้าสังเกตได้

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Anggraeni Ayu Rengganis : Sonographic Ductal Changes and Pertinent Characteristics That Associate with Proliferative Lesions of Breast. Advisor: Prof. PICHET SAMPATANUKUL, M.D. Co-advisor: Yuda Chongpison, Ph.D.

Managing for sonographic focally thick duct lesions is not established in practice guidelines. Most cases showed scant cells on fine-needle aspiration (FNA). The study aimed to detect any variables that could predict proliferative lesions of the ducts and avoid unnecessary biopsies. A retrospective cohort design was done to analyze the association between ultrasound (US) variables and the outcome of proliferative or non-proliferative ductal lesions, determined by corresponding histopathology or cytology on consecutive follow-ups for at least three years. The data collection from 2015-2017 at King Chulalongkorn Memorial Hospital showed that 199 female patients with 210 index lesions met the eligibility criteria, 56.3% were the patients on screening (setting#1), 22.1% were examined for symptomatic lesions (setting#2), and 21.6% were treated breast cancer in follow-up (setting#3). The patients' age was categorized into <50 and ≥50 years old with a ratio of 53:47. The presence of the six associated US parameters was as follows; internal nodularity (65.7%), mixed echoic wall (41.0%), location at the periphery (69.0%), vascularity (35.2%), calcification (39.5%), and mean diameter of 4.50 (SD 1.43) mm. Of the final outcome, 71 cases had proliferative ductal lesions (18 of which were malignant). The non-proliferative disease was found in 66.2% of cases (52.4% yielded scanty cells on FNA). The regression model depicted vascularity as the single fixed predictor with an odds of 2.21 (95%CI 1.16, 4.19). The age cutoff at 50 and settings#2, #3 categories did not fit well when added to the model with OR of 1.17 (95%CI 0.62, 2.22), 1.87 (95%CI 0.90, 3.87), 0.55 (95%CI 0.23, 1.30), respectively. In conclusion, feeding vessels are a pertinent parameter to be a predictor of proliferative lesions. Focally thick ducts without associated parameters seem not worrisome, and only observation is merited.

Field of Study:	Health Development	Student's Signature .....
Academic Year:	2020	Advisor's Signature .....
		Co-advisor's Signature .....

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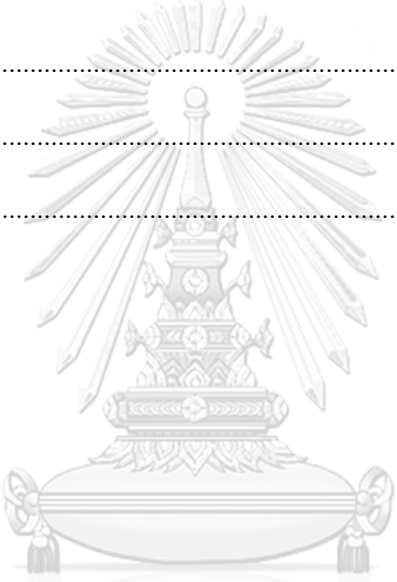

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CHAPTER I

BACKGROUND AND RATIONALE

Ductal change is a tubular-shaped structure lesion found focally in the breast, with more than two millimeters in transposal diameter on breast ultrasonography (1). The ductal change term can be found in the one of the Breast Imaging-Reporting and Data System (BI-RADS) lexicon that has been followed by radiologists in many countries, including Thailand (2, 3). However, the term lacks detailed characteristics since the lesion is not a major finding and only closely observed on an ultrasonogram (4). The change is not by itself belong to any category of BI-RADS (3, 4). However, ductal or tubular lesions are frequently present in routine practices of radiologists and some radiologists are interested in making a correlation to its pathology (4, 5). The radiologist expert team in Queen Sirikit Breast Cancer Centre, King Chulalongkorn Memorial Hospital, has widely used a tool to identify the ductal lesion. The importance of putting ductal changes into the report and mentioning the need for further investigation, particularly when it comes with characteristics such an echoic lesion, calcification, and vascularization has been considered as the suspected lesion which may have proliferative findings. The site uses the term 'focal thickened duct' that equal to the term 'ductal change'.

Focal thickened ducts are defined as a tubular-shaped structure lesions with a larger diameter than 2 mm and appear as discrete or focal lesions (4, 6). The so-called thickened ducts may be found together with accompanying findings such as calcification, internal echogenicity, and vascularity (3). The findings are frequently noted in three separate clinical settings. Setting #1 is a routine check-up without other findings. Most ductal changes are viewed as non-pathologic lesions, but radiologists would likely to report their presence. Setting #2 is a lesion found during work up due to breast problems such as nipple discharges and masses. Most ductal changes would be attributed for pathologic causes in case of nipple discharge and suggested duct extension in case of masses that look like cancer. Setting #3 is a lesion that appears during surveillance for recurrence in treated breast cancer patients. In this situation, the ductal change in ipsilateral breast (conserving breast) is possibly consequence of prior treatment. In any settings, the finding of focal thickened duct does not have standard management guidelines and therefore is based mainly on subjective judgement (4).

The combination of imaging evaluation of the ductal system is necessary, such as a combination of one of these modalities: mammography, galactography, ultrasonography, and magnetic resonance imaging (1, 5). Ultrasound and magnetic resonance guidance are the most used imaging guidance on ductal finding (1). Vacuum-assisted devices help improve the accuracy of sampling on the ductal lesion due to the tiny size of the finding (most of them are smaller

than 1 cm) and located within a duct (1). Thus, since 2008, Queen Sirikit Breast Centre for Breast Cancer and Breast Imaging Unit of the Department of Radiology, King Chulalongkorn Memorial Hospital has equipped an instrument to assist FNA procedure. The machine is composed of a negative pressure generator connecting to the needle via a silicon extension tube. During aspiration, operators can control the negative pressure by footpad, making a smooth handling of the needle and in a precision position. By this equipment, so-called Vacuum Assisted Fine-Needle Aspirator, the radiologists can do FNA on the evaluation of non-palpable lesions that include ductal changes of breast. The possibility of ultrasonographic ductal change varies from benign duct entity to the suspicious duct that is more likely to be malignant. The biopsy of the duct frequently obtains less cellularity or pauci-cellular aspirates rather than high cellularity or substantial cell aspirates. The latter is correlated to the pathology term “proliferative diseases” that embrace ductal hyperplasia, intraductal papilloma, atypical proliferations with DCIS and invasive carcinoma (6, 7). Substantial cellular aspirates are marked with the increasing number in cells, thus suggesting as proliferative lesion. Conversely, pauci-cellular aspirates imply as non-proliferative lesions because of the absence of cellular proliferation found on duct ectasia, fibrous change, and fibrocystic change (6, 7).

The results from FNA biopsy will take into consideration for management, for example patients who have substantial cellular aspirates would be advised for surgical removal (2).

Generally, patients who yield pauci-cellular aspirates or who do not have surgical removal will be followed up in a certain interval with probably re- FNA if indicated (2). Because the term of focal thickened duct or ductal change does not have uniformity in description and many cases of FNA performing (80% in estimation) had pauci-cellular samples, it merits a study for detailed descriptions of what to standardize of the term and for the proper management (1, 4). Hence, the importance of ductal disease is often overlooked and poorly understood. This may lead to delays in diagnosis and patient care (1).

In this study, we have proposed the ductal change study that intends to identify the pertinent characteristics of duct changes lesions found in ultrasound. Besides, this study evaluates the association between pertinent sonographic characteristics as parameter predictors and proliferative diseases of ductal changes lesion.

CHAPTER II
REVIEW OF RELATED LITERATURES

A. Ultrasound pertinent characteristics in breast ductal change lesion

Breast ductal change lesion was frequently a ductal dilatation with echogenicity that found focally or discrete in sonography (1). Ductal lesion can appear as the manifestation of the benign or malignant breast diseases. Due to the broad spectrum of the ductal lesion manifestations, the histopathology was absolutely needed on the diagnosis and treatment (8). Some previous studies, from the literature searching in electronic database and reference citation, have shown the relevance in ultrasound finding and histologic result in breast lesions. Several studies have been conducted in different countries to see the ultrasonographic finding in term of ductal changes correlated with the histologic results.

The ultrasound parameters had been previously studied to find the association between certain breast lesion or breast disease and the outcome. In this study used six ultrasound parameters, viz. internal nodularity, mixed echoic wall, calcification, ductal location, vascularity, and ductal diameter. Some of the ultrasound parameters were aligned with previous study from Kim et al with significant association between malignant and benign duct ectasia. Even though

the target outcome of the disease was different; our study explored the sonographic of intraductal nodule, calcification, location, size, and ductal wall thickening,

In detail, Kim et al studied the differences in ultrasonographic findings between malignant and benign mammary duct ectasia. The evaluation on ultrasonographic findings in terms of involved ductal location, size, margin, intraductal echogenicity, presence of an intraductal nodule, calcification, ductal wall thickening, and echo changes of the surrounding breast parenchyma, was correlated with the pathological features from surgically proven lesion. The result, from the total 54 lesion which divided into 46 benign lesions and 8 malignant lesions, was shown that significantly associates with malignant duct ectasia in term of peripheral ductal location, an ill-defined margin, ductal wall thickening, and hypoechoic change of the surrounding parenchyma with odds ratio (95% CI): 0.05 (0.00-0.49), 0.03 (0.00-0.27), 20 (2.63-192.69), and 13.2 (1.31-159.79), respectively, with p-value <0.05. Those significant features on US highly recommend a prompt biopsy (6).

Two other studies only focus on intraductal mass from the breast imaging, which was correlated with the malignancy on the breast. The study in 2015 by Sheikh et al showed that the ultrasound and mammographic findings in term of intraductal mass have association with malignancy. Total 251 intraductal breast masses from 198 patients were assess from both

ultrasound and mammogram. Ultrasound assessed about the mass, distance from the nipple, pattern of duct filling by the mass, involving the branch ducts, and presence of abnormal axillary lymph nodes. The result showed that 46 malignant masses were significantly correlated with ultrasound in term greater size than the benign mass, greater distance from the nipple, filling the duct completely, extended outside the duct, and involved branch duct (9). Compared to previous study which focused on the intraductal mass lesion, our study also studied the ductal location and the size of the lesion. The previous study showed a significant association between location and lesion's size.

Another study from Kim et al in 2013, had focused on the intraductal mass in breast ultrasound as the predictors of malignancy. The retrospective study on 147 women who had 163 intraductal masses with more than 24 months of follow up. Among 8% of the total masses were diagnosed as malignant breast disease. The result showed that malignancy was significantly associated with symptoms, personal history of breast cancer, larger size of mass, complete filling the duct, and involving the branch duct, with p-value <0.05 (10).

The study from Park et al in 2017 investigated about non-mass lesion (NML) on clinical and radiological finding and correlated with malignancy. The retrospective study which was conducted in 2011-2014 found 119 women with 121 NMLs with available histopathologic or

sonographic follow-up (over 2 years) data. The studied variables in this study were clinical variables (patient's age, symptoms, and mammographic density), ultrasound findings (distribution and associated features, e.g., calcification, architectural distortion, and ductal changes), and histopathologic data. Results of the 121 NMLs showed that 88 (72.7%) were benign and 33 (27.3%) were malignant. Malignancy was significantly associated with palpability (p-value < 0.001). Mammographic findings (frequent calcifications combined with asymmetry) and sonographic distribution (linear-segmental) and associated features (associated calcifications (p-value = 0.019) or architectural distortions (p-value = 0.015)) on ultrasound were significantly different between benign and malignant lesions (p-value < 0.001, p-value = 0.004, and p-value = 0.001, respectively) (11).

The ultrasound parameters derived based on the literature and clinical experience in daily basis. The six ultrasound parameters were chosen because they are the most distinct variables in ultrasound to evaluate the thick duct lesions.

Table 1. The sonographic characteristics and outcome among previous studies

Author	Year	Imaging modality	Imaging parameter	Outcome	Results
Kim,	2010	US	ductal location, size,	malignant and	54 lesion which

K.W., et al			margin, intraductal echogenicity, presence of an intraductal nodule, calcification, ductal wall thickening, and echo changes of the surrounding breast parenchyma	benign mammary duct ectasia	divided into 46 benign lesions and 8 malignant lesions, was significantly associated with malignant duct ectasia
El Sheikh, H., et al.,	2015	US and mammographic	Ultrasound assessed about the mass, distance from the nipple, pattern of duct filling by the mass, involving the branch ducts, and presence of abnormal axillary lymph nodes	intraductal mass to be associated with malignancy	46 malignant masses were significantly correlated with ultrasound
Kim,	2013	US	symptoms, personal	intraductal	Among 8% of the

W.H., et al			history of breast cancer, larger size of mass, complete filling the duct, and involving the branch duct	mass as the predictors of malignancy	total malignant masses breast showed that malignancy was significantly associated with US parameter
Park, J.W., et al	2017	US	distribution and associated features (calcification, architectural distortion, and ductal changes)	non-mass lesion (NML) on clinical and radiological finding and correlated with malignancy	Breast NMLs on ultrasound showed high risk of malignancy

B. Clinical risk factor in in breast ductal change lesion

Setting became important to study in ductal change lesion since the lesion was hardly find in women without symptoms. However, the study from Guo et al found that malignant

intraductal masses were more often associated with symptoms and a personal history of cancer. The study also stated that very limited knowledge on uncommon lesions finding in asymptomatic women, however about 2.8% of malignancy was constituted by (12). The sign and symptoms which commonly appeared in women were palpable lumps and nipple discharge (1). However, the incidentally detected symptoms in asymptomatic women need careful imaging surveillance (12). In this study setting divided into three setting corresponded to the daily practice findings, includes screening, women with symptoms, and women with previous cancer history.

Patients' age correlated with the incidence of breast cancer. In the study from Bae et al omen under 50 years old had a significantly increased frequency of additional cancer detection by pre-operating MRI, compared with women more than 50 years old with OR 3.3; 95% CI 1.2-9.2; p-value = 0.02). In the same study, age at diagnosis was an independent risk factor associated with higher frequency of additional cancer detection by MRI with younger women (< 50 years) had 3.2-fold higher frequency of cancer detection (13) .

Breast malignancy in women consistently found in left breast than in the right breast (14). At least 5% difference in cancer incidence found in left breast than in right breast (14, 15). This predisposition highly associated with genetic factors rather than breast size (14). The

occurrence pattern of breast malignancy especially in early lesion provide the development of detection and diagnosis.

CHAPTER III

RESEARCH DESIGN AND METHODOLOGY

3.1 Research Questions

1. What are the association between cyto-histology finding and the ultrasound characteristics as parameter predictors of the ductal change lesion?

2. Does the predictive model have good performances for predicting proliferative lesion in ductal change lesion found in ultrasound?

3.2 Research Objectives

1. To identify the pertinent characteristics as parameter predictor (internal nodularity, mixed echoic wall, calcification, peripheral location, vascularity, and ductal diameter) for focally thick duct lesion found in ultrasound

2. To determine the pertinent characteristics of breast sonographic duct changes lesion that correlate with proliferative lesions

3. To develop the prediction model for focally thick duct lesion found in ultrasound

3.3 Research Hypothesis

1. The ultrasound characteristics of duct changes have associations with proliferative lesion

2. The predictive model has good performances for predicting proliferative lesion

3.4 Conceptual Framework

The scope of the study based on ultrasound characteristic and cyto-histologic finding:

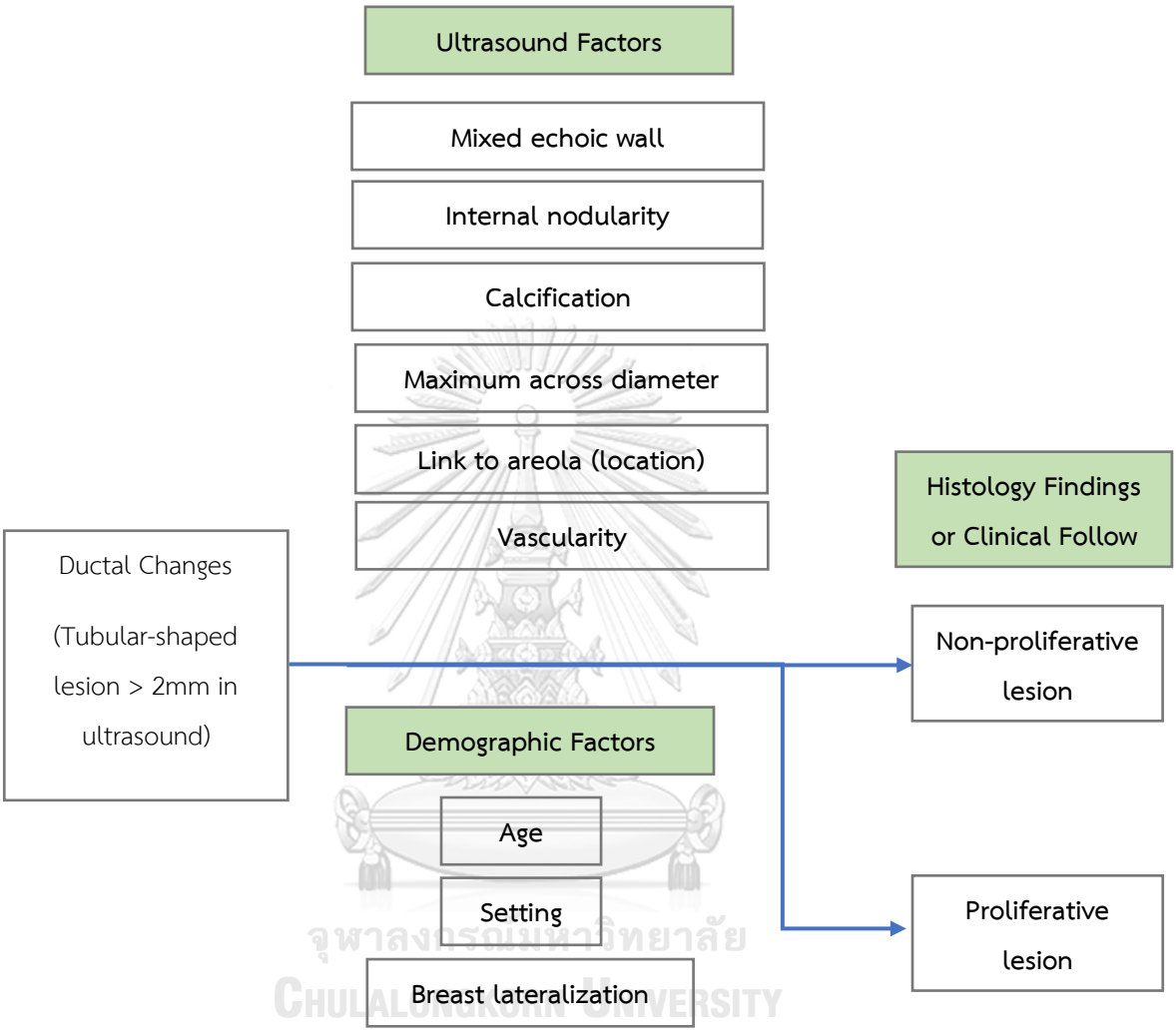


Figure 1. Conceptual framework

3.5 Keywords

Ductal lesion, proliferative, ultrasound, breast cancer, vacuum-assisted fine needle aspiration

3.6 Operational Definitions

A. Identification of focally thick duct lesion in ultrasound

- Focally thick duct lesion identifies as a single or branched tubular-shape structure represent as ductal system in the breast, which is focally found in ultrasound examination (Fig. 2)
- Criteria:

1. Ultrasound images contains two planes of ductal views with different configuration and found duct features with at least one plane have duct features (Fig. 3)
2. Sonographic images supported any ductal features finding as association to focally thick duct lesion
3. The suspected thick duct lesion which has any attributes that does not go along with ductal configuration in term of shape and size in duct criteria should be excluded, for example diameter of the suspected lesion larger than 5 mm without any explanation of any accumulation of duct, suspected

fatty lobule, nodule with marked lobulated margin, and diffuse prominent ducts

4. focally thick duct was found in area of the breast without any suspicion

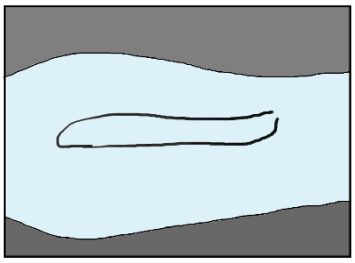


Figure 2. Ductal change has tubular-shaped structure, represent focally thick duct lesion

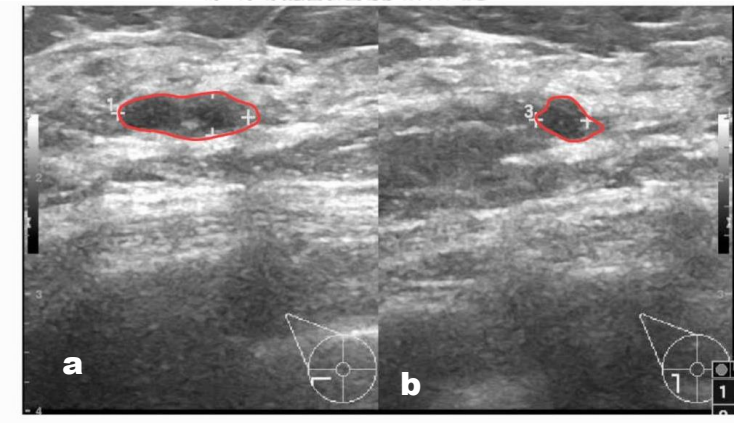


Figure 3. Two different planes of ultrasound examination (a, b). The procedure of detection on focally thick duct using ultrasound needs two different planes to confirm the configuration of tubular structure. Radial and anti-radial views to diagnose the entity.

B. Description of focally thick duct lesion in ultrasound

Focally thick duct assessed along with some parameter, there are following parameters (4, 6):

a. Internal nodularity showed mild dilatation of the duct which contain echogenicity as internal debris, solid mass, or ductal lining cell projection (9, 12), with anechoic lumen of the duct and assessed using two different sonographic planes.

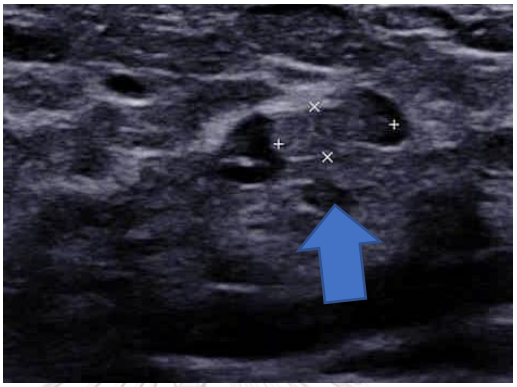


Figure 4. Internal nodularity in focally thick duct lesion

b. Mixed echoic wall, represent as thickened wall sign, showed the complexity or bunch of ducts or in the affected area. It assessed by comparing ductal wall with by fibro-adipose tissue by ultrasound (16) and ductal lumen.

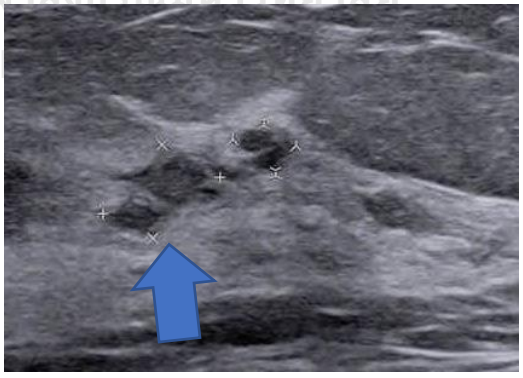


Figure 5. Mixed echoic wall in focally thick duct lesion

c. Calcification shows presence the accumulation of calcium salts in a body of lumen of the duct. In some cases, real-time ultrasound is difficult to evaluate calcification, thus need mammogram as additional tool.

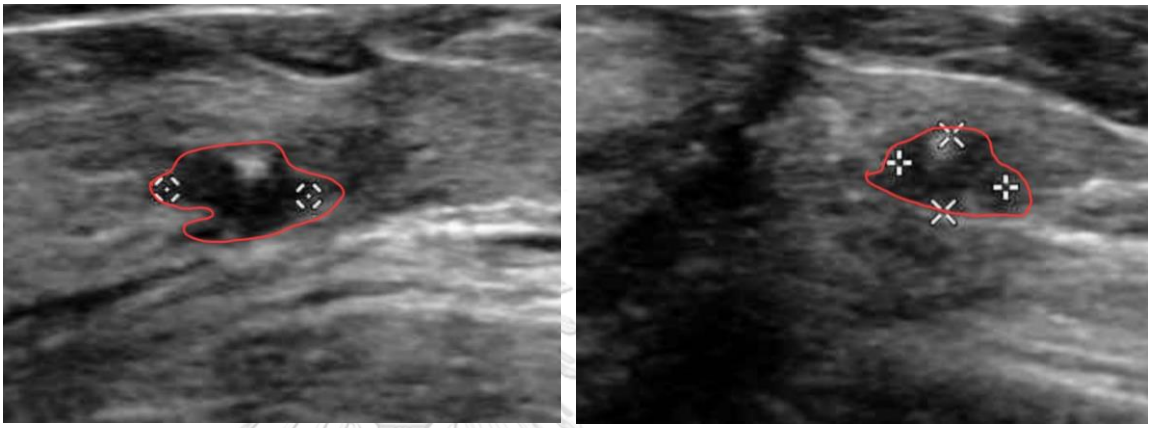


Figure 6 Calcification inside thick duct lumen

d. Vascularity shows presence or absence of the color doppler flow that represents the feeding vessel in ultrasound. Additional color doppler image is warranted to show the vascularization activity around the focally thick duct.

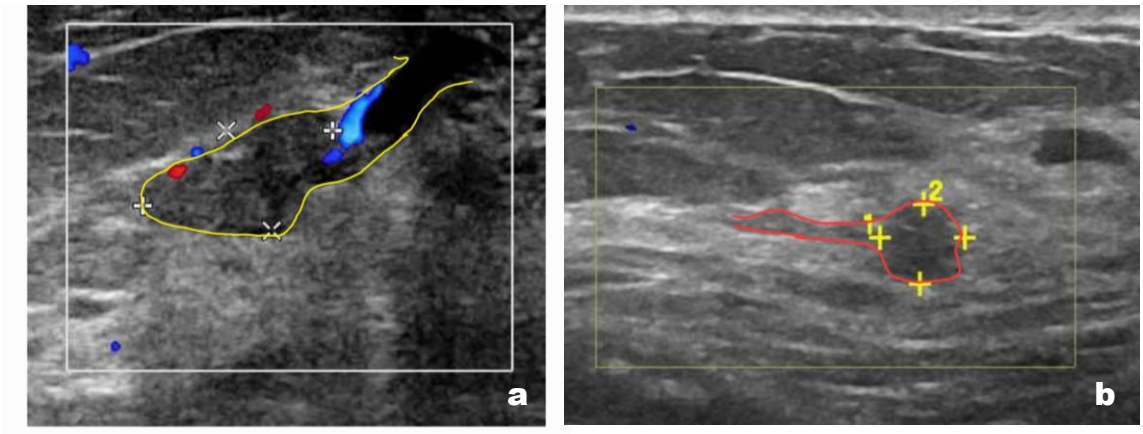


Figure 7. Thick duct lesion with hypervascularity (a) and without hypervascularity (b)

e. Location of the duct that is evaluated by the region where the lesion lies, which is divided into central location defined as the subareolar and periductal areas, and peripheral defined as the upper outer quadrant, upper inner quadrant, lower outer quadrant, lower inner quadrant, and mid area. Location of the duct assessed by any linkage to areolar area within duct lies which represent any connection with areolar or not.

f. Maximum across diameter is defined as maximum width of duct. For single duct, the diameter measurement used the maximum diameter of the duct. Whereas for bunch of ducts, the diameter measurement was done on the one biggest duct.

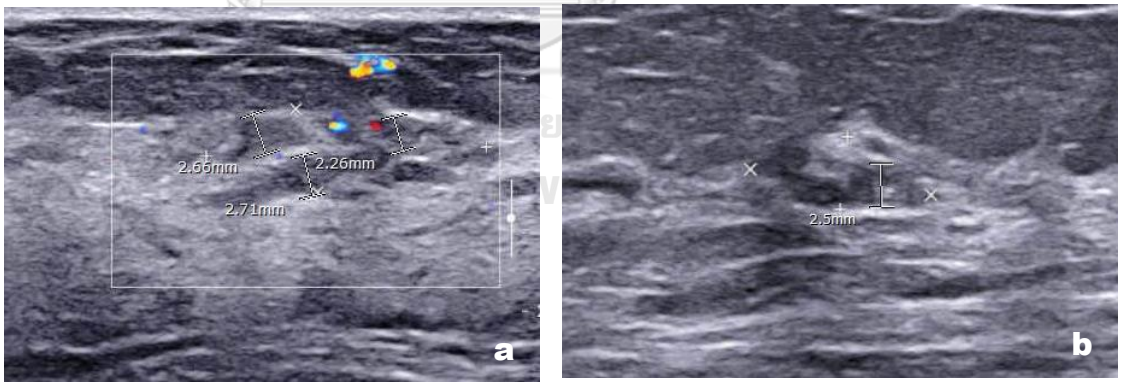


Figure 8. Thick duct in bunch of ducts, measure the biggest duct diameter (a). Thick duct lesion, measure the greatest diameter in single duct (b).

1. Clinical setting defines as the clinical status when the FNA procedure had done to the index duct of the breast, which divided into three settings:

- Setting #1 is routine check-up/ clinical (without any symptom).
- Setting #2 is patient presented with suspicious mass or nipple discharge.
- Setting #3 is treated breast cancer patient on surveillance.

2. FNA abbreviates for fine-needle aspiration, is a biopsy technique using needle of gauge 22 or 23, and the biopsy yields sample that is prepared as cytology smear for cytologic diagnosis (17). In this study, the cytologic diagnosis will be surrogate outcome. The cytology result is either suggesting of proliferative or suggesting non-proliferative lesions. Distinctive term that used in cytology result is substantial cellular aspirate which suggest proliferative lesions and pauci-cellular aspirates which suggest non proliferative lesions.
3. Proliferative lesions are breast diseases that have cellular proliferations/ increasing in number of cells. Proliferative lesion defines as histology verifying proliferative lesion or malignancy (6, 17, 18).
4. Non-proliferative lesions, in this study, are changes in the breast that do not have cellular proliferation. The lesions involved some breast disease or self-recovered and non-changed in three-years period of follow up (6, 17, 18). Non proliferative lesion defines as cytology suggests non-proliferative lesion and clinical /imaging showed no progression over follow up 3-year period; or histology verifying non-proliferative lesion.

3.7 Research Design and Research Methodology

a. Research Design

Retrospective Cohort Study

b. Population and Sample

- **Population**

Patients who undergone fine needle aspiration biopsy guided by ultrasound at King Chulalongkorn Memorial Hospital from January 1, 2015, until December 31, 2017.

- **Inclusion and Exclusion Criteria**

1. Inclusion criteria

    a. Women, age > 17 years old.

    b. Had records of cytology reporting from FNA of breast lesion done under direct ultrasound guidance at focal thickened duct in the years 2015 - 2017.

    c. Had corresponding ultrasonogram that available at the time of study.

    d. Had medical records, pertinent surgical pathology and/or follow up data for at least three years since the first-time date of FNA procedure of study.

e. Had cyto-histology result from the cytology examination from US-FNAB or histology examination from surgical specimen.

2. Exclusion criteria

a. Ultrasonograms were not meet the criteria of thickened duct lesion.

b. Final pathology results did not explain the index focal thickened duct lesion.

c. The follow up data of ultrasound did not complete (less than three years follow up) for the non-surgical patients.

c. Sample Size Calculation

Data collection was be done to build a regression model as a predictive tool on proliferative lesion as the final outcomes. According to the rule of thumb, potential associated factors are identified using recommended method, 10 events per predictor variable (19). In this study, there are 9 factors, hence, number of events needed is 9 x 10 = 90 events.

Previous epidemiological study of Silvera and Rohan showed that the prevalence of benign proliferative epithelial disorders was 15-64% (20). Another sonography study that took concern in intraductal mass showed 62.21% prevalence of

the lesions (10). Assumed 10% rate of missing data, thus the sample size needed is this study is (90/0.64) / (1-.01) = 157.

d. Outcome Measurement

Proliferative lesions define as cellular proliferations or increasing in number of cells in breast biopsy resulting in physiologic or pathologic breast diagnosis (6, 17, 18). The proliferations can be benign proliferative epithelial (ductal epithelial hyperplasia) and atypical proliferative (papillary neoplasm, ductal carcinoma in situ, invasive ductal carcinoma) (6, 17, 18). Breast biopsy involved some methods such as fine needle biopsy, core needle biopsy, vacuum assisted biopsy, while in this study focused on the vacuum assisted biopsy guided by ultrasound. In this study, proliferative lesion defined using two methods. Firstly, the histology verifying proliferative lesion or malignancy using specimen from the surgical procedure. Secondly, the proliferative lesion in cytology finding in biopsy then followed up to be stable lesion in the end of observation time would be concluded as proliferative lesion.

Non-proliferative lesions, in this study, were changes in the breast that do not have cellular proliferation. The lesions encompassed duct ectasia, fibrous change, fibrocystic change, scar, self-recovered and non-changed in three-years period of follow

up (6, 17, 18). Non proliferative lesion defined as cytology suggests non-proliferative lesion from the cytology, histology, and follow study. Non-proliferative outcome suggested from the cytology result from biopsied lesion and clinical/imaging showed no progression (regression) over follow up 3-year period; or histology verifying non-proliferative lesion.

The surrogate outcome from cytology results used to assist the final outcome. In this study, cytology outcome was divided into four groups, viz. high, moderate, low, and scant cellularity. The high and moderate cellularity assigned as proliferative lesion in the end of follow up period, whereas the low and scant cellularity assigned as non-proliferative lesions. For the patients who had surgery in the end of follow up period, the histology result counted as the final outcome.

Table 2. The characteristics of potential focally thick duct predictors and outcome

Candidate predictors	Range	Types of Data	Descriptions
Age	17-90	continuous	Age at data collected. In the analysis patient age was described as <50 and ≥ 50 years old

Setting	1,2,3	categorical	1 = routine check-up, 2 = patients with suspect cancer or nipple discharge, 3 = treated cancer patients
Breast lateralization	1,2	categorical	1 = right, 2 = left
Internal nodularity	0,1	categorical	1 = present, 0 = absent
Mixed echoic wall	0,1	categorical	1 = present, 0 = absent
Calcification	0,1	categorical	1 = present, 0 = absent
Vascularity	0,1	categorical	1 = present, 0 = absent
Lies in peripheral location	0,1	categorical	1 = present, 0 = absent
Maximum across diameter	2-12	continuous	the width of single duct or the width of the greater duct for bunch of ducts in mm
Histology result	0,1	categorical	1= proliferative lesion, 0 = non proliferative disease

3.8 Data collection

- **Research Protocol**

1. Protocol registration

The study has been reviewed and approved by Institutional Research Ethical Board Committee, IRB No. 666/63 and COA No. 1473/2020. Besides, the permission be sought from the director of King Chulalongkorn Memorial Hospital and Chulalongkorn Research Hospital Unit to use hospital data to be processed. Any information revealing the subjects' identities is avoided.

2. Recruitment

Patients, who met with the eligibility criteria, enrolled to the study retrospectively by reviewing online medical record chart of fine needle aspiration biopsy guided by ultrasound result and cyto-histologic result of King Chulalongkorn Memorial Hospital from January 1, 2015, to December 31, 2017.

Patient breasts were registered. The patient who had one index lesion in one breast, the clinical and imaging data analyzed on that breast. If there were more than one lesion in the breast, the one that was the most distinct would be the chosen index lesion. If a patient had index lesions in both breasts, only one lesion included into the analysis with random selection.

3. Data collection and management

- Firstly, Pathology Assistant handled the patients' list from the online hospital record (breast cytology archival in years 2015, 2016, 2017) according to research period to the principal investigator (PI).

- The PI screened patients who met with eligibility criteria, then collect data for baseline characteristics of patients' breast and ultrasound imaging results. The imaging data compiling under supervision of the radiologist expert. Data recorded were included age, date of examination, and history of breast cancer. Result from the FNA guided ultrasound collected for the index thick duct including internal nodularity, mixed echoic wall, ductal location, calcification, maximum across diameter, and any vascularity. Besides, result from cytology and histologic finding reviewed by pathologist and authorized for the follow up on online medical record. Case record form used to record all of patients' data and any identification of the patients (name, ID number, etc.) were not appeared. Panel review was conducted to minimize the risk of bias due to subjectivity in imaging results, likewise the patients were anonymous to protect the right and maintain patients' confidentiality.

- Data collection was done by the research team and data management handled by the PI. The research team consist of the PI and qualified physicians of Queen

Sirikit Centre for Breast Cancer (QSC), King Chulalongkorn Memorial Hospital, as well as the staff assistant of the Pathology Department.

- Consensus protocol:

  The ultrasound characteristics data was collected based on the panel review to fill out the case record form of the ductal characteristics. On the panel review, the final decision of sonographic ductal change according to the operational definition was made.

- The researcher used keywords “breast” and certain period to search the patients. All the patients’ records were reviewed against the eligibility criteria thus avoid selection bias. Only eligible patients were included in the study then were reviewed for the clinical and sonographic parameters. After the consensus, the cytology and histology results were done blindly. The decision was done by the expert in each field.

3.9 Data Transformation

Data collection process:

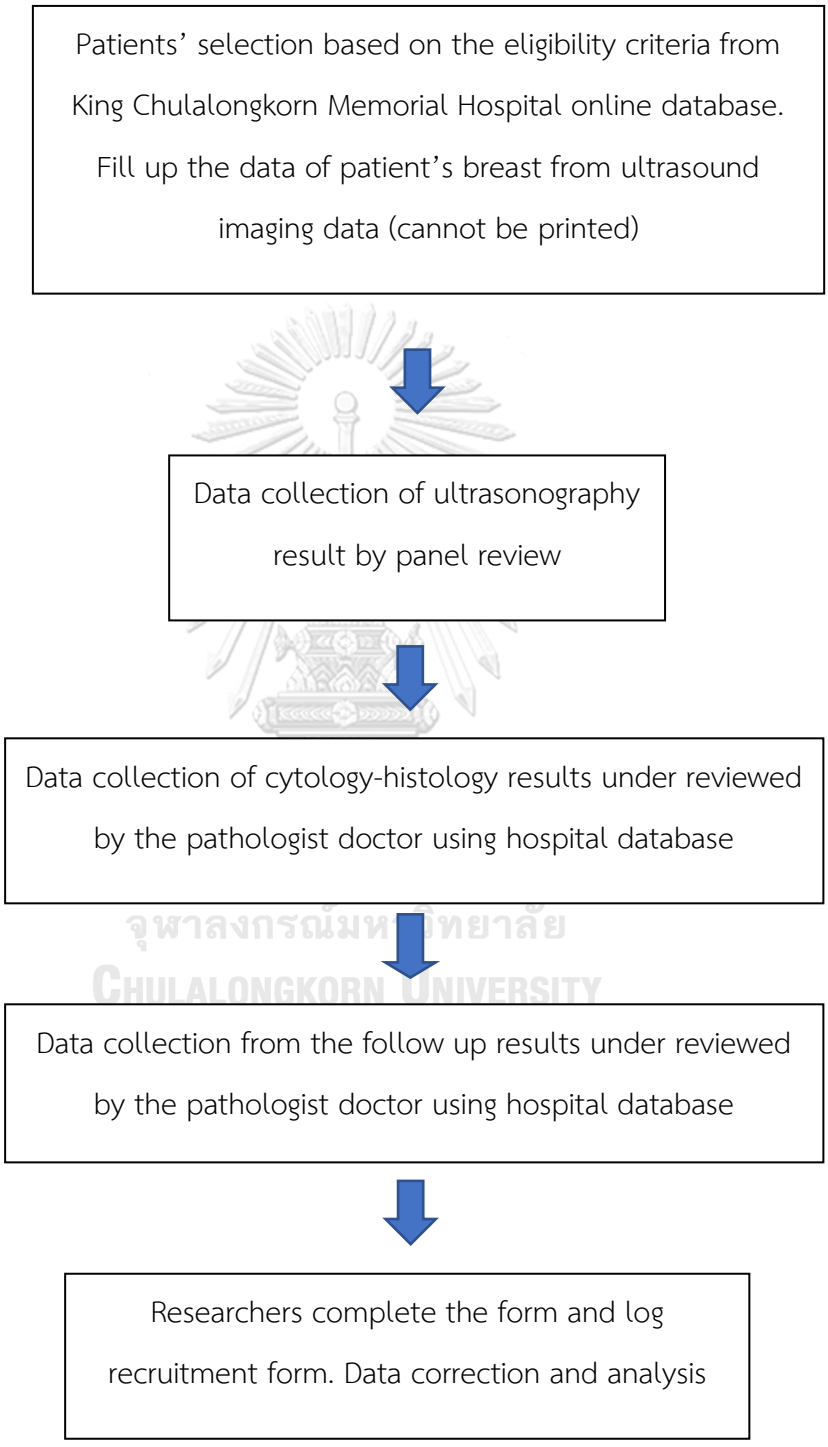


Figure 9. Flow Chart in Data Collection Process

Data recording flow chart

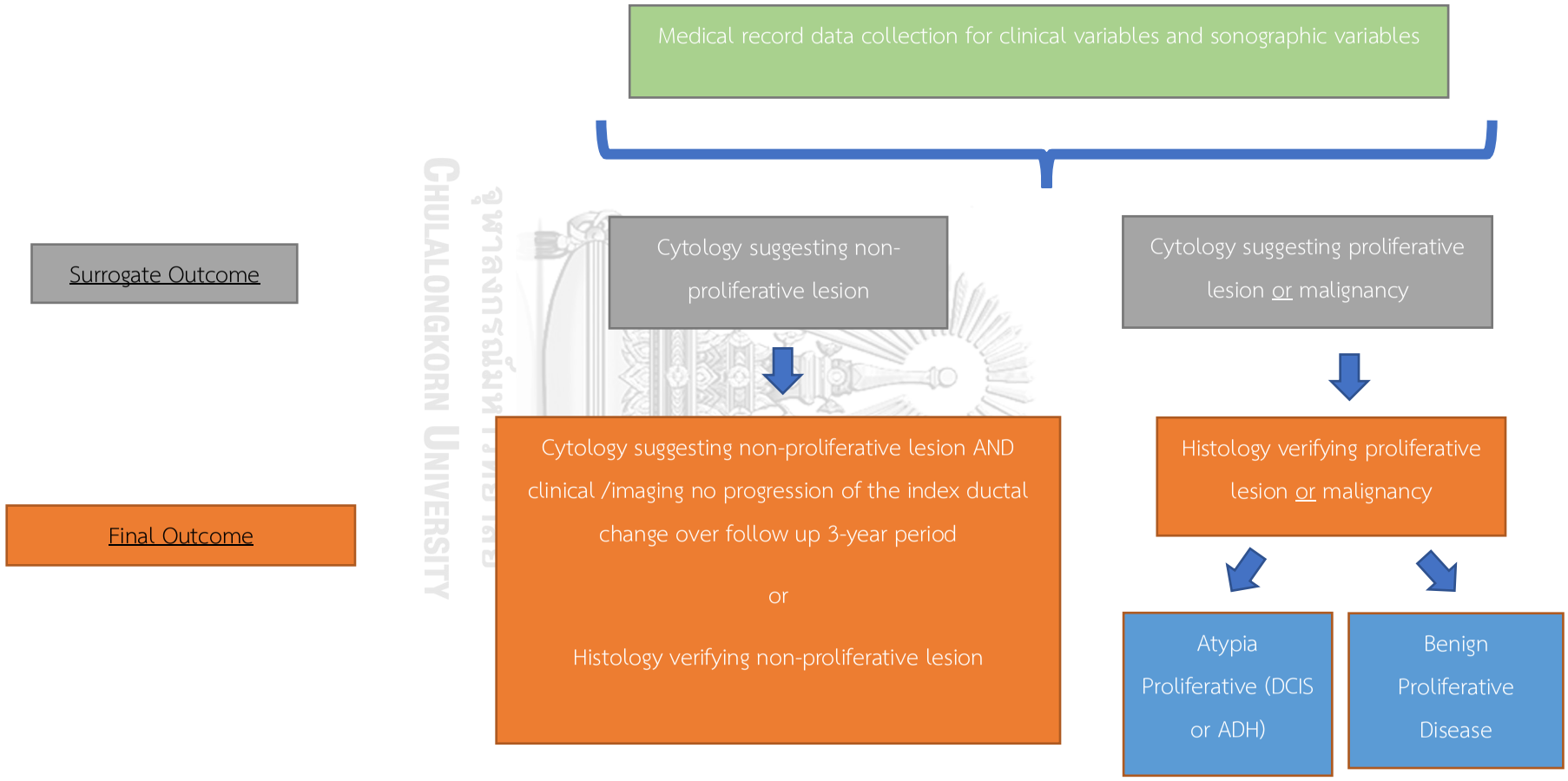


Figure 10. Data recording flow chart

3.10 Data Analysis

Demographic and baseline variables were presented using descriptive statistics to summarize the histologic and breast ultrasound characteristics, as well as patients' characteristics, as follows:

- Measurement data expressed as the mean ± Standard Deviation (SD) for continuous variables.
- Measurement data employed as the frequencies (n) and percentages (%) for categorical variables.

Regarding the study objective, univariable analyses for comparisons in proportions was conducted along the p-value. The Chi square test and independent t-test were used to determine factors associated with proliferative lesions.

The predictive model using binomial logistic regression was generated to determined factor associated with the final outcomes. Nine independent variables were included into the regression model. To develop and validate a model for proliferative lesions, all subjects were analysed:

- Univariable analysis used to start the model development, to determine factors associated with the proliferative lesions, such as independent t-test and Chi-square test which produce crude odds ratio (OR) and 95% CI. Variables with univariable p-

value < 0.2 or variables of interest were entered into the multiple logistic regression model.

- A rigid parsimonious regression model generated by only included independent variables with p-value < 0.05 which kept in the final model. A risk score ($z = b_0 + b_1x_1 + b_2x_2 + ... + b_px_{p)}$ was developed based on regression coefficient (b) from the final logistic regression model. Adjusted OR and 95% CI were reported as the result.
- Multicollinearity among independent variables in the model was evaluated using variance inflation factor (VIF).
- Goodness of fit test for the final model was assessed using Hosmer-Lemeshow chi-square test which test the agreement between predicted probabilities based on the model and actual observed probabilities.
- All data analysis was conducted using Stata version 15.1 (StataCorp, College Station, Texas, USA, serial number 301506268458 licensed to MDCU).

3.11 Ethical Consideration

All procedures performed in studies involving human participants in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The approved

proposal for ethics approval from the Ethics Committee from Faculty of Medicine, Chulalongkorn University has been waived. This research fulfilled the ethical consideration as follows:

1. Respect for persons – Data collected without name or surname of the patients to ensure the data will be kept safely and de-identified before analysis. Hospital ID number used for tracking the laboratory and ultrasound result and would not appear in any documentation.
2. Beneficence – Result of the study presented in general, not as individual data. The study will be benefit for the physician and patients for the diagnosis and treatment care plan.
3. Justice – eligibility criteria are appropriate for representing the target patients.

Letter asking for permission to use Hospital data to the director of King Chulalongkorn Memorial Hospital and Chulalongkorn Research Hospital Unit had been processed.

3.12 Limitation

The study design was retrospective descriptive study which use secondary data as the source of data collection. Some ultrasound images were difficult to evaluate since ultrasound examination was an operator-depended and real-time procedure.

3.13 Expected Benefits and Application

The result of the study showed relationship between ductal lesion in breast ultrasound and proliferative disease from the cyto-histology result in women, this can used by:

1. The radiologists can make specific assessment about the ductal changes in breast ultrasound more precisely.
2. The specific assessment can be used to formulate more efficient and effective communication tools to the referring physician clearly and consistently.
3. The result of the study can assist the radiologists to make final assessment and specific management recommendation. It may avoid further unnecessary procedure of US-FNA in patients having probability of breast abnormality, thus can be lessen the burden of patients.

3.14 Obstacles and Strategies to Solve the Problem

Since the vacuum-assisted fine needle aspiration biopsy guided by ultrasound is an operator-depended procedure and real-time procedure, the result might be subjective. Thus, it needs complete recording in ultrasound assessment including different plane of the probe to minimize it.

CHAPTER IV
RESULTS OF THE STUDY

A. Demographic Data

A total of 1,789 patients were enrolled in this study between period of three years, from January 2015 until December 2017. The study was carried out at The Queen Sirikit Breast Cancer Centre, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. In details, there were 539 patients in 2015; 541 patients in 2016; and 709 patients in 2017. During the review process of 1,789 recruits, 1,315 patients were excluded due to uncomplete data and different target lesion on FNAB such as mass, cyst, nodule, and other lesions (seroma, lymph node, focal shadow, etc). The results of ultrasound disclosed a positive thickened duct lesion among 390 patients were shown in figure 10 and 11.

All patients were subjected to do breast ultrasonography and undergone ultrasound guided fine needle aspiration biopsy. About 390 patients of the FNA biopsy guided ultrasound had cytology result from the procedure. After comprehensive review for the ultrasound examination follow up test until three years and any histology report from the previous surgery, there were 210 index lesion who assessed for the pathology examination for proliferative lesion from 199 patients.

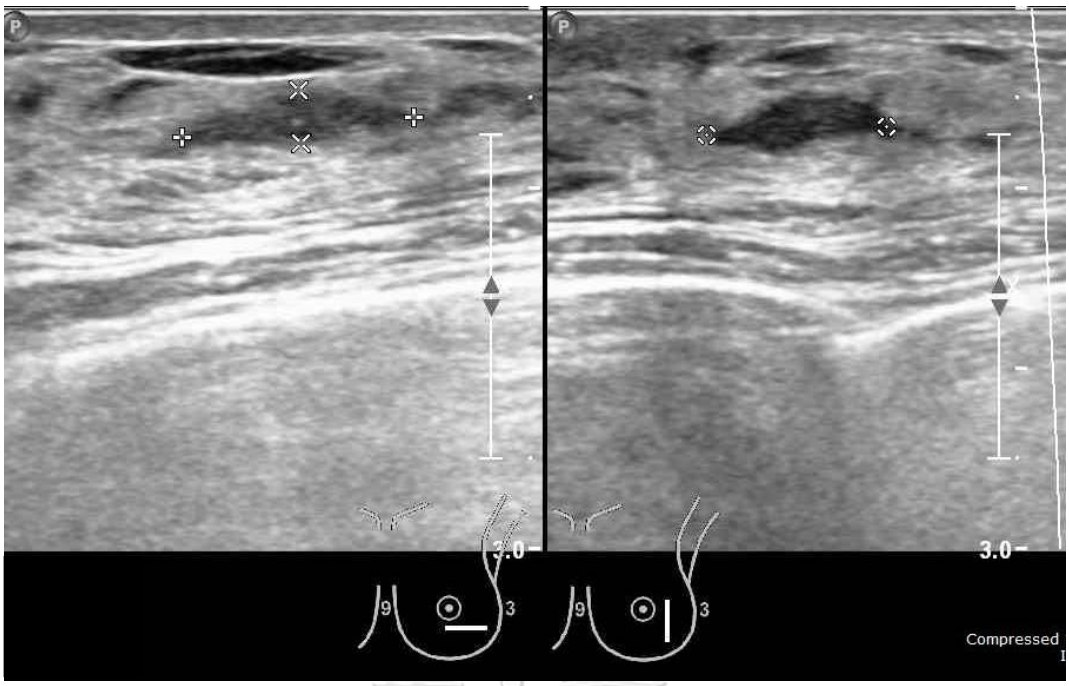


Figure 11. Ultrasonography of lower outer quadrant of the left breast. Simple tubular shape of the focal thickened duct lesion shown on the two planes

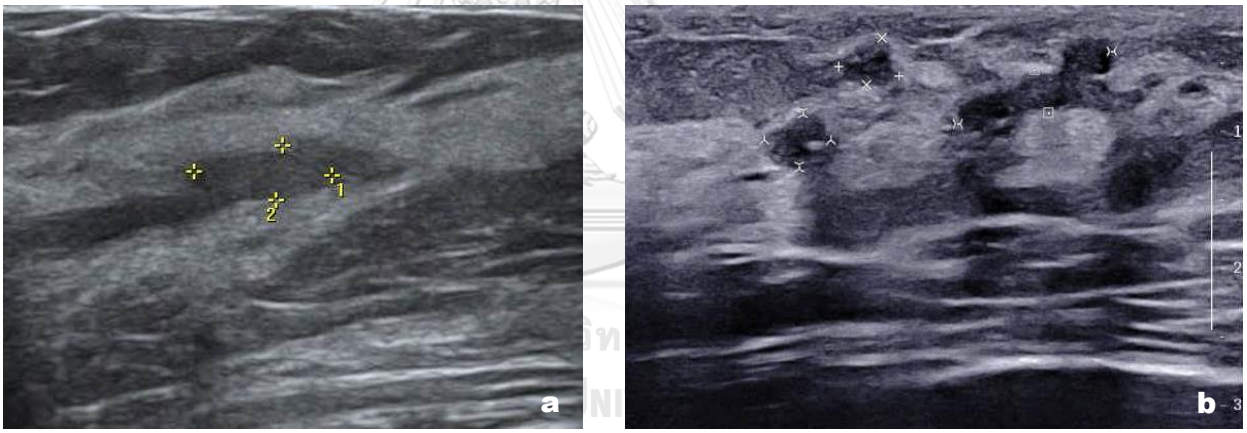


Figure 12. Ultrasonography of right breast. Intraductal nodule with focal thickened duct lesion found on the region lower outer quadrant (a) and branched ductal lesion with calcification and saccular end (b)

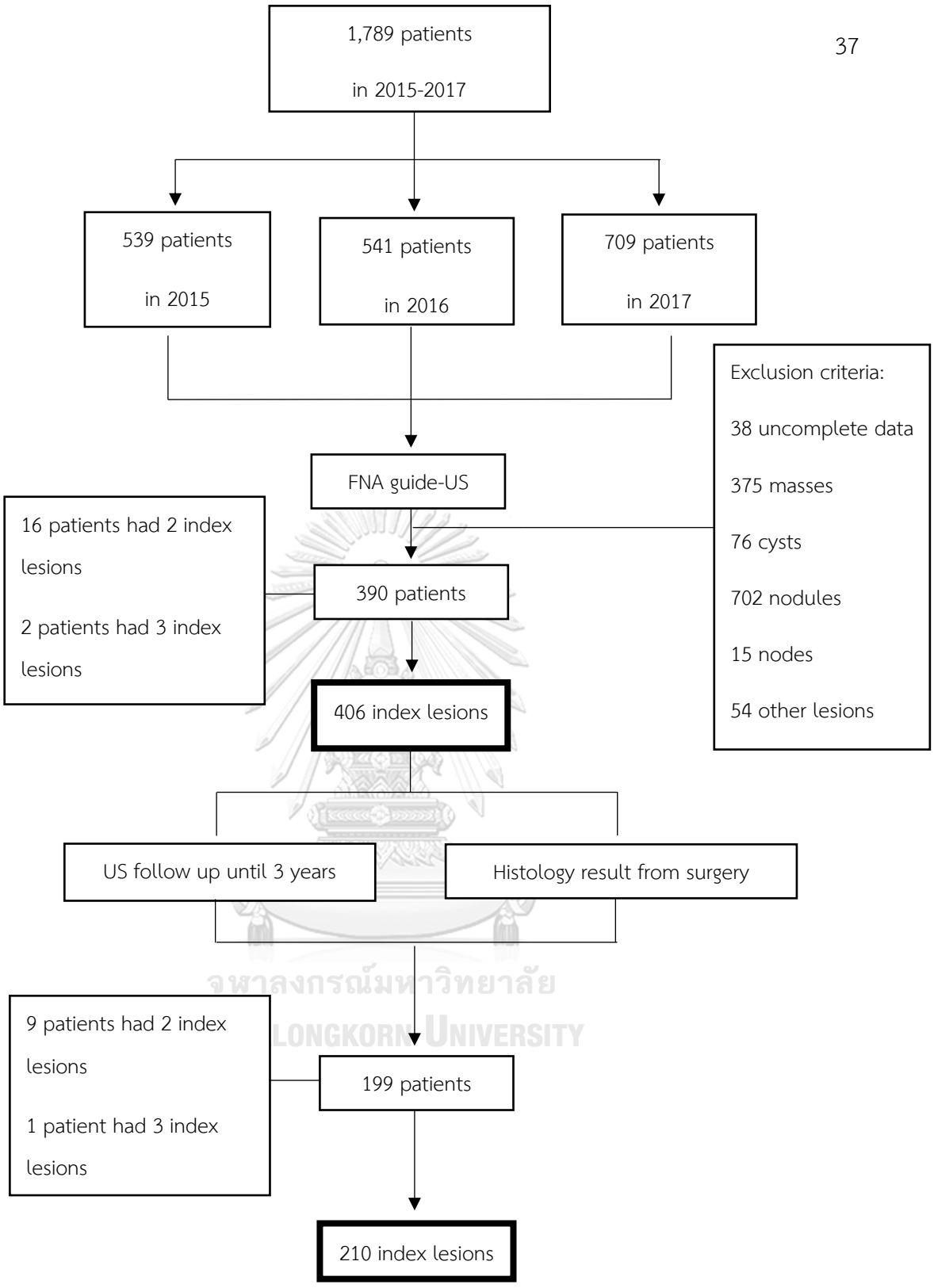


Figure 13. Study flow chart

Clinical baseline data among 199 patients from this study shown in table 3. Of 199 patients were females and the age ranged from 21 to 84 years old, with median age 49 years old. The mean age for the subjects was 50.46 with 10.86 standard deviation. Most of the patients came to the centre for screening or routine check-up without any symptoms, estimated 56.3%. About 44 (22.1%) of the patients were come for diagnosis or follow up of the former suspicious mass, lesion, or nipple discharge and 21.6% patients were treated breast cancer or patients on treatment who come for surveillance. Most of the patients came to the center because of the palpable mass as the symptom about 14.1%, while about 5.5% came due to nipple dischange.

Table 3. Clinical baseline characteristics of 199 patients

Baseline Data	**Mean ± SD or number (%)**
	Total (n=199)
Age (year)	
Mean ± SD	50.46 ± 10.86
Median (Q1, Q3)	49.0 (21, 84)
≥ 50	93 (46.7%)
< 50	106 (53.3%)
Setting	
#1	112 (56.3%)
#2	44 (22.1%)
#3	43 (21.6%)

Symptoms	
Palpable mass	28 (14.1%)
Nipple discharge	11 (5.5%)
Both of palpability and nipple discharge	2 (1.0%)
Nipple ulcer	1 (0.5%)
Mastalgia	2 (1.0%)
None (screening)	112 (56.3%)
Previous breast cancer	43 (21.6%)

Baseline data among 210 index lesions from this study shown in table 4. Lesions were almost equally laid in both breasts, around 109 (51.9%) lesions were found in left breast, whereas 101 (48.1%) lesions in the right breast. The fine needle aspiration biopsy guided ultrasound mostly done in central region of the breast, especially in subareolar or peri-areolar area and upper outer quadrant of the breast around 26.2% and 24.8%, respectively. The least area of the lesions to be found were lower mid area, mid inner area, and lower inner quadrant, about 3.3%, 3.3%, and 2.9%, respectively. Most of the patients was diagnosed on BIRADS system score 4. More than half of the patients were BIRADS 4A about 156 patients, then BIRADS 4B were 10 patients (21.0%).

Table 4. Clinical baseline characteristics of 210 index lesions

Baseline Data	**Mean ± SD or number (%)** **Total (n=210)**
Breast lateralization	
Right	101 (48.1%)
Left	109 (51.9%)
Lesion's region	
Central area	55 (26.2%)
Lower inner quadrant	6 (2.9%)
Lower mid area	7 (3.3%)
Lower outer quadrant	22 (10.5%)
Mid inner area	7 (3.3%)
Mid outer area	17 (8.1%)
Upper inner quadrant	15 (7.1%)
Upper mid area	29 (13.8%)
Upper outer quadrant	52 (24.8%)
Surgery	
Excision or mastectomy	76 (36.2%)
Follow up study for stable lesion	134 (63.8%)
BIRADS	
2	2 (0.5%)
3	8 (3.8%)
4A	166 (79.1%)

4B	10 (21.0%)
4C	7 (3.3%)
5	7 (3.3%)

Table 5 described baseline ultrasound data from 210 index lesions. The ductal lesion was classified into six parameters. Internal nodularity present in two third of all index lesions, around 65.7%. Mixed echoic wall found in 86 patients (41.0%). The data showed that 83 (39.5%) of the patients had internal calcification. Minority of the duct showed feeding vascularization about 74 (35.2%) from the ductal index lesions. Majority of the index lesions laid on the peripheral side of the breast, about 145 (69.0%) and only 65 (31.0%) in the central area. The caliber of the ductal diameter was divided into four groups, 2-3.99 mm with 82 patients (39.0%), 4-5.99 mm with 96 patients (45.7%), 6-7.99 mm with 26 patients (12.4%), and more than 8 mm with 6 patients (2.9%), respectively. The mean of the diameter was 4.50 with 1.43 SD.

Table 5. Baseline ultrasound characteristics of 210 lesions

Baseline Data	**Mean ± SD or number (%)**
	Total (n=210)
Internal nodularity	
Absent	72 (34.3%)
Present	138 (65.7%)

Mixed echoic wall	
Absent	124 (59.0%)
Present	86 (41.0%)
Calcification	
Absent	127 (60.5%)
Present	83 (39.5%)
Vascularization	
No	136 (64.8%)
Yes	74 (35.2%)
Location	
Peripheral	145 (69.0%)
Central	65 (31.0%)
Width	4.50 ± 1.43

The histology findings from 210 index lesions described in table 6. The cytohistological parameters were defined into two categories, 71 (33.8%) proliferative lesions and 139 (66.2%) non proliferative lesions. Proliferative lesion comprised of malignant proliferative lesion 8.6% and benign proliferative lesion 25.2%. There were four types of surrogate outcome resulted by cytology examination from FNA biopsy which majority was scant cellularity, about 110 lesion (52.4%).

Table 6. Baseline histology parameters of 210 index lesions

Baseline Data	Mean ± SD or number (%) Total (n=210)
Final outcome	
Non proliferative lesion	139 (66.2%)
Proliferative lesion	71 (33.8%)
Malignant proliferative lesion	18 (8.6%)
Benign proliferative lesion	53 (25.2%)
Surrogate outcome	
Scant cellularity	110 (52.4%)
Low cellularity	41 (19.5%)
Moderate cellularity	30 (14.3%)
High cellularity	29 (13.8%)

B. Factors associated with proliferative lesions

Table 7 displayed result from a Chi Square Test on each ultrasound characteristic to show any correlations with the proliferative lesion. The ductal lesion vascularization was the only ultrasound parameters which had correlation with the cytohistological result with 0.004 (p-value). Whereas the rest of the radiological characteristics such as internal nodularity, mixed echoic wall, calcification, peripheral location of the duct, and diameter of the duct did not have any

correlation with the cytohistological result, with p-value 0.895; 0.480; 0.759; 0.255; and 0.309, respectively.

Table 7. Association between US parameters and cytohistological result on 199 index lesions

Ultrasound characteristics	**Number of proliferative lesions**	**Number of non- proliferative lesions**	**p- value**
Internal nodularity			
No	24	45	0.895
Yes	44	86	
Calcification			
No	40	80	0.759
Yes	28	51	
Mixed echoic wall			
No	38	80	0.480
Yes	30	51	
Vascularization			
No	36	96	**0.004**
Yes	32	35	
Lies in peripheral area			
No	24	36	0.255
Yes	44	95	
Width of duct	4.42 ± 1.41 (4.18-4.67)	4.64 ± 1.44 (4.29-4.99)	0.309*

*Unpaired t test for continuous diameter variable only

C. Development and validation of the model for proliferative lesion

The dataset was analyzed into three parts: univariate analysis, multiple multivariate analysis, and. proliferative lesion risk equation generating. The dataset was contained 199 index lesion which used six ultrasound parameters and three demographic parameters to identify which factors related to proliferative lesion.

1. Univariate Analysis

The dataset was obtained to develop proliferative lesion model. Nine potential prognostic variables, including internal nodularity, mixed echoic wall, calcification, vascularization, width of the duct, peripheral location, age, breast lateralization, and clinical setting was analyzed in univariate analysis. Based upon a univariable analysis, three factors were found to be statistically significant, viz. vascularization, age, and setting with p-value <0.001, 0.15, and 0.04, respectively (table 8).

Table 8. Univariate analysis of factors associated with proliferative lesion (n=199)

Predictors	Crude OR	95% CI	p- value
Internal nodularity	0.95	0.51, 1.77	0.89
Calcification	1.09	0.60, 1.99	0.75
Mixed echoic wall	1.23	0.68, 2.24	0.48
Vascularization	2.43	1.30, 4.57	**<0.001**

Peripheral location	0.69	0.36, 1.30	0.25
Width of duct	1.11	0.90, 1.36	0.30
Setting			
#1	1		
#2	2.02	0.98, 4.17	**0.05**
#3	0.53	0.23, 1.24	**0.14**
Age			
≥ 50	1		
< 50	1.54	0.84, 2.80	**0.15**
Breast lateralization			
Right	1		
Left	0.82	0.45, 1.48	0.51

The magnitude of confounding was assessed using the method favoured by biostatisticians. A factor that makes the difference between crude and adjusted odds ratio of more than 10% would be considered as confounder. Vascularization appeared as fixed variable among all predictors. All parameters did not show any difference more than 10%. However, age and setting showed the highest difference in odds ratio compared to the rest of variables.

$$\text{Magnitude of confounding} = \frac{ORcrude - OR\ adjusted}{ORadjusted}$$

Table 9. Crude odds ratio, adjusted odd ratio and change of odds ratio for proliferative lesion by predictors

Predictors	Crude OR (95%CI)	Adj. OR (95%CI)	Adj. OR of vascularization (95%CI)	Change of OR (%)
Vascularization	2.43 (1.31, 4.50)	-	2.43 (1.31, 4.50)	-
Mixed echoic wall	1.23 (0.68, 2.24)	1.16 (0.63, 2.13)	2.41 (1.30, 4.45)	0.82%
Calcification	1.09 (0.60, 1.99)	1.05 (0.57, 1.93)	2.43 (1.31, 4.49)	0%
Width of duct	1.11 (0.90, 1.36)	1.08 (0.88, 1.33)	2.39 (1.29, 4.42)	1.67%
Internal nodularity	0.95 (0.51, 1.77)	1.01 (0.54, 1.90)	2.44 (1.31, 4.51)	-0.40%
Peripheral location	0.69 (0.36, 1.30)	0.75 (0.39, 1.44)	2.37 (1.28, 4.40)	2.53%
Setting	-	-	2.29 (1.22, 4.28)	6.11%
#2	2.02 (0.98, 4.17)	1.89 (0.91, 3.91)	-	-
#3	0.53 (0.23, 1.24)	0.54 (0.23, 1.27)	-	-
Age group	0.76 (0.41, 1.42)	1.30 (0.70, 2.41)	2.30 (1.22, 4.31)	5.65%
Breast lateralization	0.82 (1.31, 4.50)	0.82 (0.45, 1.50)	2.43 (1.31, 4.50)	0%

In multivariate analysis, peripheral location and type of setting are excluded due to greater AIC (p-value > 0.05). As the result, only one parameter is selected in the final model. Vascularization shows as the fixed predictor in all models.

Table 10. Multivariate logistic regression for model 1, 2, and 3

Predictors	Model 1			Model 2			Model 3		
	b	Adj. OR (95%CI)	p-value	b	Adj. OR (95%CI)	p- value	b	Adj. OR (95%CI)	p- value
Internal nodularity	-	-	-	-	-	-	-	-	-
Mixed echoic wall	-	-	-	-	-	-	-	-	-
Calcification	-	-	-						
Width of duct	-	-	-	-	-	-	-	-	-
Vascularization	0.89	2.43 (1.31, 4.50)	0.004	0.83	2.30 (1.22, 4.31)	0.009	0.79	2.21 (1.16, 4.19)	0.015
Peripheral location	-	-	-	-	-	-	-	-	-
Setting									
#2	-	-	-	-	-	-	0.62	1.87 (0.90, 3.87)	0.08
#3	-	-	-	-	-	-	-0.58	0.55 (0.23, 1.30)	0.18
Age group	-	-	-	0.26	1.30 (0.70, 2.41)	0.40	0.16	1.17 (0.62, 2.22)	0.61
Breast lateralization	-	-	-	-	-	-	-	-	-
Constant	-0.98		<0.001	-1.10		<0.001	-1.07		<0.001
Pseudo R^2	0.43%		0.03	0.12%		0.03	6.01%		<0.001
Pearson test			<0.001			0.20			0.11
Hosmer-Lemeshow test			<0.001			0.45			0.74

All models showed vascularization as the strongest predictor and adjusted to two other predictors, which is peripheral age and setting. In model 3, the focally thick duct lesion had higher risk to be proliferative lesion with adjusted OR of 2.10 compared to without feeding vascularization (95% CI: 1.16, 4.19). If patient came from setting 2 and had age less than 50-year-old would have higher risk to be proliferative lesion with adjusted OR of 1.87 (95% CI: 0.90, 3.87) and 1.17 (95% CI: 0.62, 2.22), respectively. However, the focally thick duct lesion decreased the risk of proliferative lesion with adjusted OR of 0.55 in setting 3 (95% CI: 0.23, 1.30). The prediction model is fit the data quite well with p-value from Hosmer-Lemeshow test was 0.74 and Pearson test of goodness of fit was 0.11 (Table 10). However, the variables age and setting might be confounding factors (Table 9).

Z = -1.07 + 0.79*vascularization + 0.16*age <50-year-old + 0.62 (if setting 2) – 0.58 (if setting 3)

Setting	Z
#1	-1.07 + 0.79*vascularization + 0.16*age <50-year-old
#2	-1.07 + 0.79*vascularization + 0.16*age <50-year-old + 0.62
#3	-1.07 + 0.79*vascularization + 0.16*age <50-year-old - 0.58

The discrimination ability of final logistic regression was evaluated using ROC curve. ROC curve was applied to define the effect of cut point for predicted probability of proliferative lesion on sensitivity and specificity which showed area under ROC curve (c-statistics) of 0.601 for model 1 (Figure 14), 0.625 for model 2 (Figure 15), and 0.671 for model 3 (Figure 16). Figure 17 showed the comparison of all models in ROC curve with p-value 0.028. The graph showed ROC area 0.601 (95%CI 0.53, 0.67) for model 1, ROC area 0.625 (95%CI 0.54, 0.70) for model 2, and ROC area 0.671 (95%CI 0.59, 0.74) for model 3.

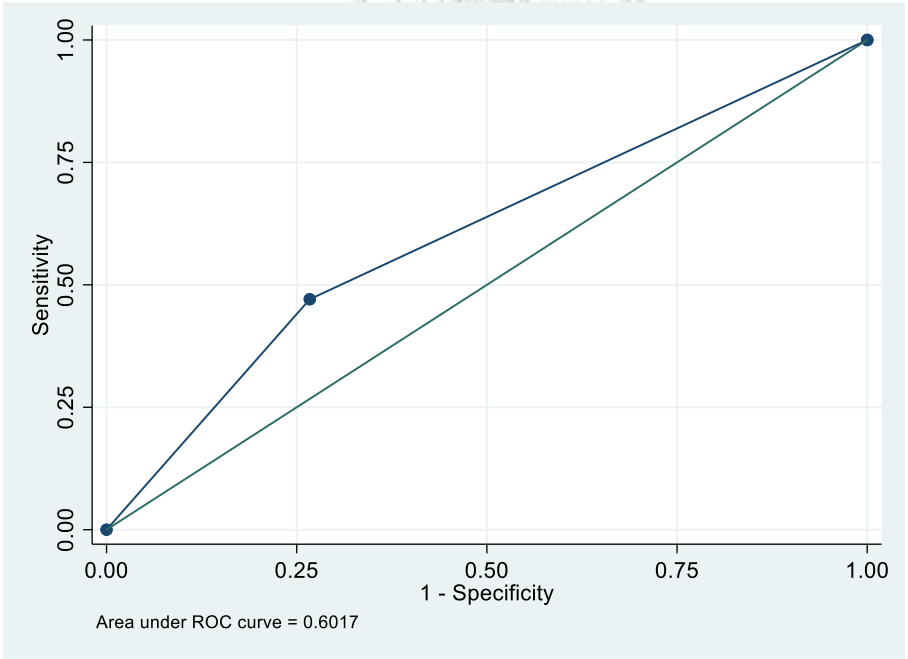


Figure 14. ROC curve for model 1 probability of proliferative lesion among 199 index lesions

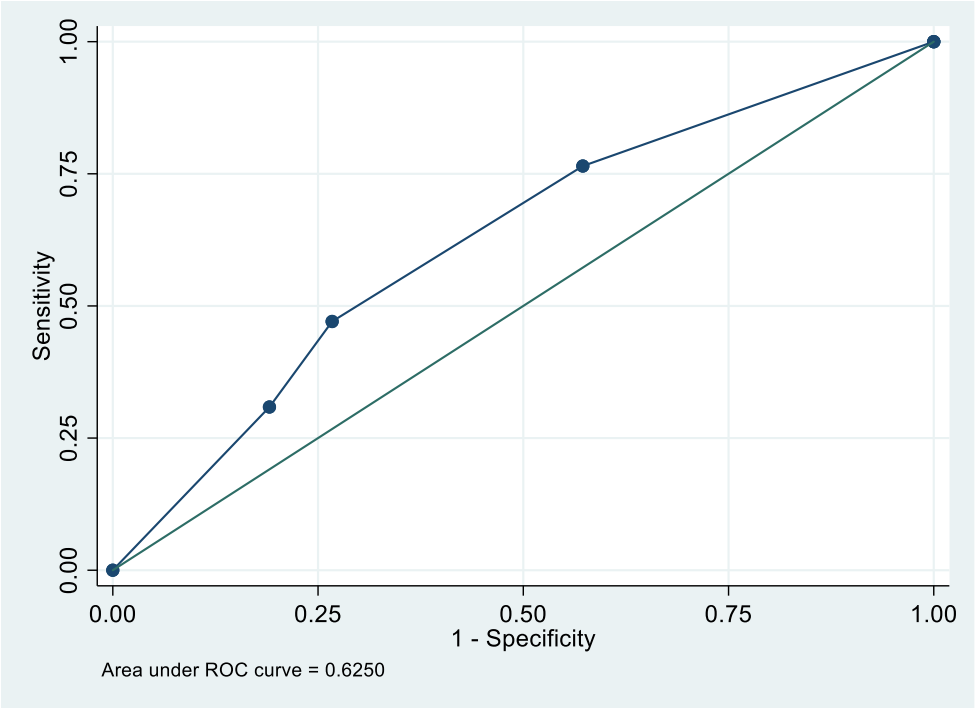


Figure 15. ROC curve for model 2 probability of proliferative lesion among 199 index lesions

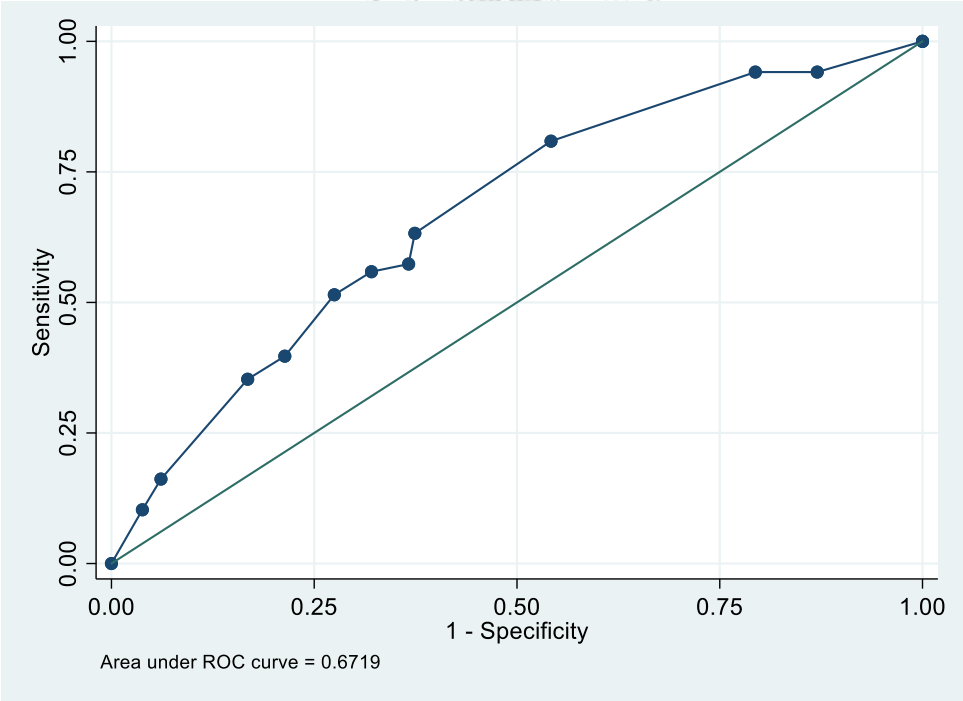


Figure 16. ROC curve for model 3 probability of proliferative lesion among 199 index lesions

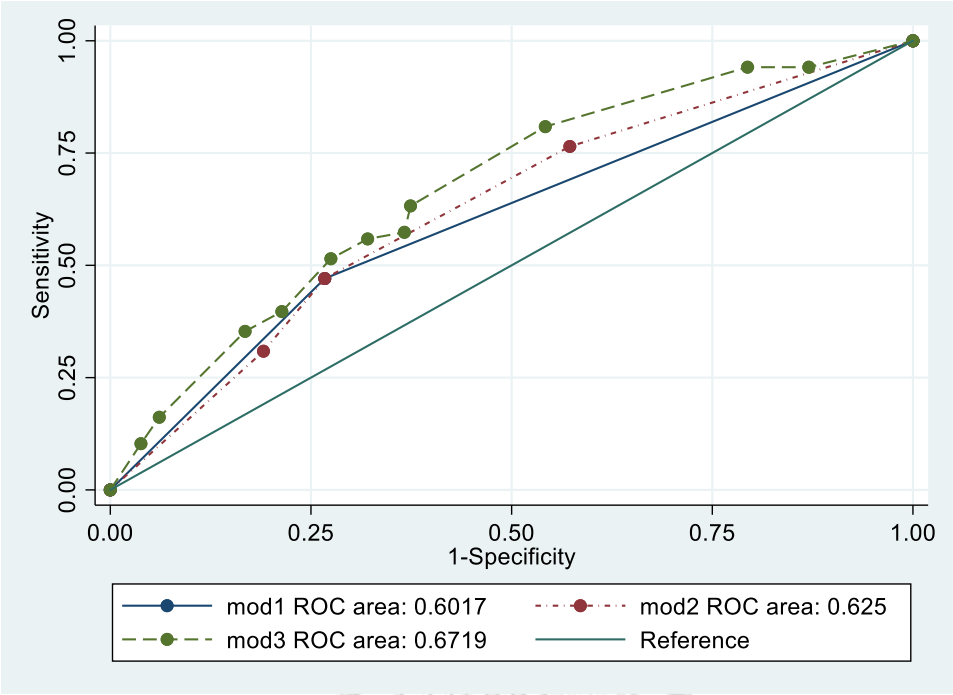


Figure 17. ROC curve for three models' probability of proliferative lesion among 199 index lesions

Table 11 showed sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for diagnosis utility of the probability of proliferative lesion model with vascularization. Model 1 showed sensitivity of 45.9% and specificity of 72.8%, respectively.

Table 11. Diagnostic value of final logistic regression model for model 1

ROC area 95% CI	0.594 (0.525, 0.662)
Sensitivity (%) 95% CI	45.9% (34.3, 57.9)
Specificity (%) 95% CI	72.8% (64.5, 80.1)
LR + (%) 95% CI	1.69% (1.17, 2.44)

LR - (%) 95% CI	0.743% (0.588, 0.93)
PPV (%) 95% CI	47.9% (35.9, 60.1)
NPV (%) 95% CI	71.2% (62.9, 78.6)

CHAPTER V
DISCUSSION

A. Focally thick duct as ductal change lesion of the breast

The ductal change lesion is observed on the tubular entity on sonographic examination if only its transposal diameter more than two mm (1). The lesion is focally found on one area of the breast, then called focally thick duct lesion. Thus, focally thick duct lesion is a tubular-shape structure lesion found focally in the breast represent ductal system, with more than two mm in transposal diameter. This statement was parallel with the study by Ferris James et all stated that duct had tubular structure which normally collapsed and not visible with 1-2 mm in diameter (1). The number was set as cut off value to its minimum detection on high-resolution ultrasound. In expectation, the detection of malignant or pre-malignant lesion can be escalated in the tiny lesion.

Ductal change would present as focal area of dilatation due to obstruction in milk duct or peri-ductal inflammation (1). The imaging modality remained as the gold standard for evaluating the ductal system was ductography (1). However, ultrasound imaging appeared as new standard reference because of better resolution and availability (12). Ultrasound could be fruitful for assisted the diagnostic in biopsy procedure (17). MRI also used to evaluate ductal lesion. MRI

can be advantageous since it could show the ductal extend from the nipple until terminal duct if any abnormality appeared as the enhancement even without contrast injection. However, compared to the MRI examination on breast that has high sensitivity but low specificity, ultrasound result showed more prominent on the evaluation on breast ductal changes (21).

The ductal change lesion typically found in patient who present with palpable mass and/or clear or bloody nipple discharge (1, 12). Women with focal asymmetry in routine screening in mammogram were likely to be ductal lesion in follow up ultrasound examination (12). Surveillance study after breast cancer treatment was warranted to discover of ductal lesion. Biopsy was recommended for lesion detected on diagnostic studies that revealed as benign papilloma, ductal carcinoma *in situ* or invasive ductal carcinoma (Figure 16 and 17) (12, 22).

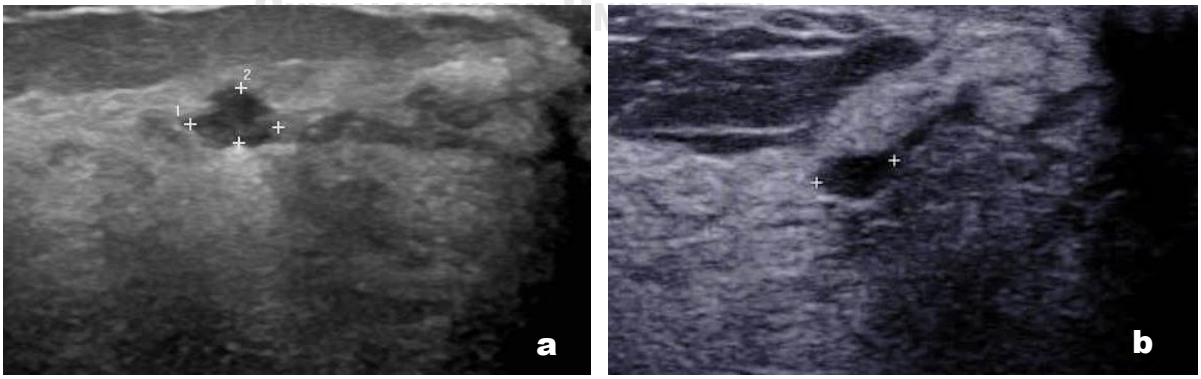


Figure 18. Focally thick duct lesion found from setting 1 (a) shown proliferative cytology examination. However, the lesion is proved as papillary lesion that not harmful and stable in ultrasound follow up (b).

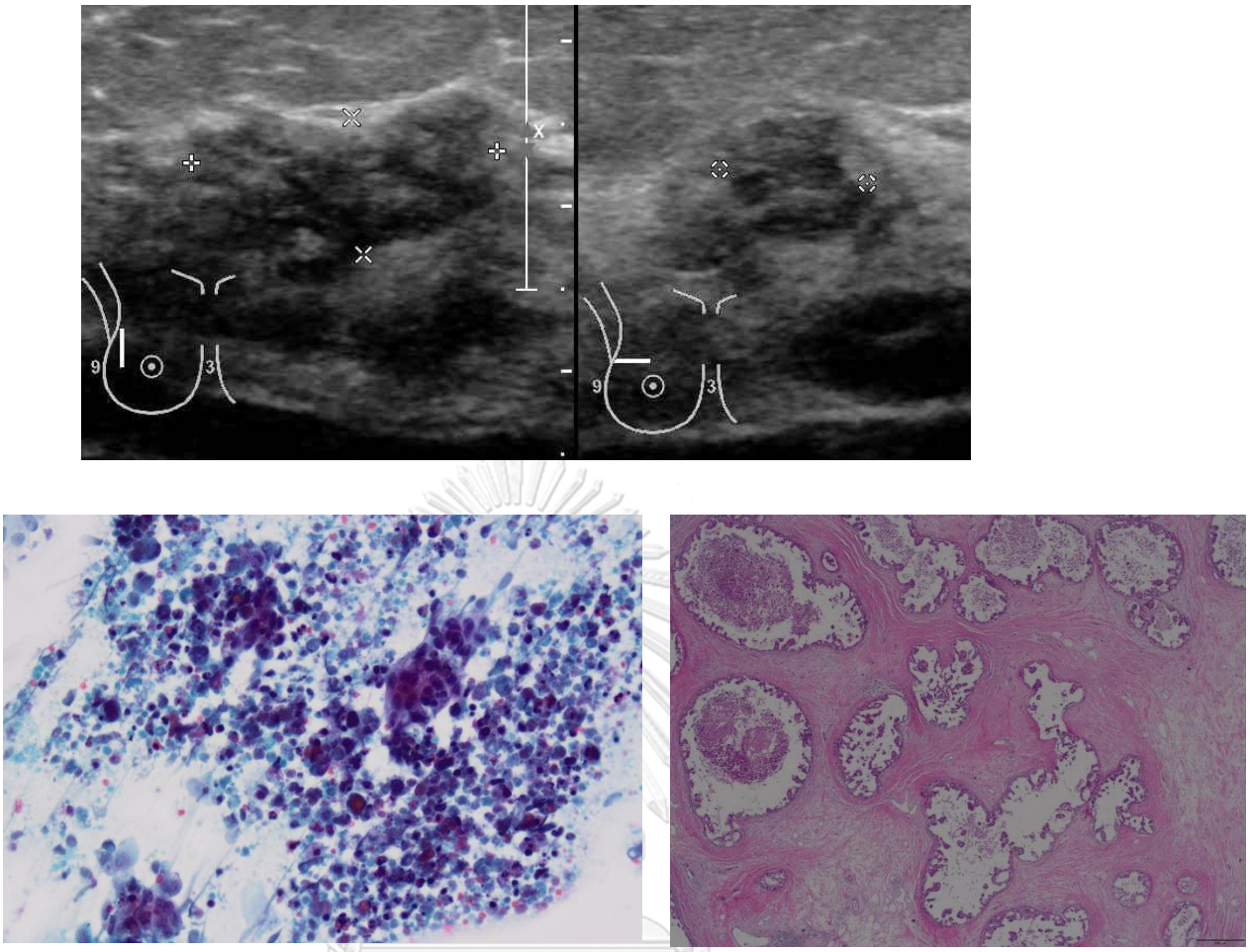


Figure 19. The focally thick duct lesion revealed as DCIS. The cytology showed high cellularity and histology showed ductal malignancy.

Vacuum assisted fine needle biopsy guided by ultrasound (FNAB) was commonly used in our institution (23). The procedure could reach out the sub-centimeter lesion and diagnosed the breast malignancy earlier (22). Even though most of the cytology showed scant cellularity, proliferative result considerate as meaningful outcome to diagnosis breast disease. The pathology showed that non mass finding abnormality in ultrasound was more likely become DCIS or

invasive ductal carcinoma (24). The FNAB is the part of the triple assessment which is the gold standard for evaluating the patients with palpable breast lesion, that consisted of clinical examination, imaging, and cyto-histological biopsy (25, 26). In detail, clinical assessment comprises patients' history including (age) and physical examination; radiological imaging such as ultrasound and mammography; and pathological analysis such as fine needle and core needle biopsy (27). This procedure was done to assess any symptomatic problem arising in breast, such as palpable lump, nipple discharge, or mastalgia (1). The biopsy assisted the evaluation on palpable breast lump to diagnose into benign or malignant lesion (28, 29). Since the symptoms could be manifested as broad range of breast disease such as fat necrosis, fibroadenoma, or abscess. Moreover, it might be emerged as invasive carcinoma (28).

B. Ultrasound parameters as proliferative lesion predictors

Ductal change lesion on the breast was poorly understood on breast imaging study (1, 11). This entity in ultrasound can be found as single focal lesion or multiple lesions, thus the lesion can be identified as a single or branched tubular-shape structure. The ductal change lesion should be focal in the change, means only certain area of the breast that affected not diffuse. Even though its focal, the change can be occurred in multiple ducts either single tubular duct or branching duct. Diffuse breast duct change might be due to hormonal change or ageing. Tubular-

structured lesion in ultrasound represent one pathologic condition in one duct or could be in one segment.

Thick duct lesion is a unique entity which has some characteristics in ultrasound. First, internal nodularity showed as a mild dilatation of the duct which contain echogenicity as internal debris, solid mass, or ductal lining cell projection (9, 12), with anechoic lumen of the duct and assessed using two different sonographic planes. The special character was found the crescent sign that indicates lesion inside the duct (intraductal nodule). This can be explained by the mechanism of nodule growth in one side of the tubal lumen, made remaining space into more anechoic or hypoechoic in ultrasound.

Secondly, mixed echoic wall, represent as thickened wall sign, showed the complexity or bunch of ducts or in the affected area. The comparison of echogenicity in ductal wall with by fibro-adipose tissue by ultrasound and its lumen was made to assess this parameter (16). Most of the case revealed to be group of dilated ducts. The ductal thick wall might represent some proliferation or inflammation process in that area.

Third, location will tell which ductal part involved into changes, which is very important to see the ductal distribution where it can be more suspicious peripherally (30). Location of the duct that is evaluated by the region where the lesion lies, to assess any linkage to areolar area

which represent any connection with areolar area. Since major duct lies on retro areolar or subareolar area, whereas terminal duct includes TDLU lies more peripherally which most of DCIS case initiated here. In the other word, ductal change lesion in terminal duct more worrisome since many breast malignancies start from this area. Need to be carefully examined about the surrounding area of the duct, since hyperechoic in surrounding area will tell any cell infiltration or fibrosis in fibro-stromal area.

Fourth, calcification shows presence the accumulation of calcium in the lumen of the duct. Sometimes real-time ultrasound is difficult to evaluate calcification, thus need mammogram as adjunctive modality. Mammogram is established as the reference tool to evaluate the calcification on the breast (31, 32). Mammogram will capture any focal asymmetry or microcalcification in the ductal lesion, but this tool cannot visualize duct clearly. If mammogram found calcification, then positive for the calcification finding on the lesion. However, if mammogram did not find any calcification, then became doubtful for the calcification finding.

Fifth, vascularity of the duct was assessed to evaluate any feeding vessel in ultrasound. Using colour doppler image, the vascularization activity around the focally thick duct can be easily found. Lastly, the maximum across diameter is defined as maximum width of ductal

change lesion. The suspected thick duct lesion has typical size that fit to its configuration. Thus, on its evaluation need to be carefully evaluated the shape and size of the ductal change lesion. In some case, the diameter of the suspected lesion might be larger than 5 mm without any explanation of any accumulation of duct, suspected fatty lobule, nodule with marked lobulated margin, and diffuse prominent ducts, thus these cases should not be examined as focally thick duct lesion.

The presence of the six associated ultrasound parameters in the focally thick duct lesions, could be seen as internal nodularity (65.7%), mixed echoic wall (41.0%), location at the periphery (69.0%), vascularity (35.2%), calcification (39.5%), and mean diameter of 4.50 (SD 1.43) mm. Among the six parameters, vascularization showed significant association with the proliferative lesion as histology outcome, p-value 0.004. Nevertheless, the rest of the parameters cannot be ignored during routine practice since their existence have clinical value and clinically significant. The operational definition for some ultrasound variables needs more concerned to be clear and can be established. This is impacted on the increasing the p-value on the association analysis. Furthermore, it can affect the inter-rater reliability because of the vague of the ductal change lesion definition in practice by one clinician to the others. In the future, need further study to define the ductal change lesion more clearly.

C. Proliferative lesion model prediction development and performance

In our study, we created a proliferative lesion prediction equation in model 3 comprised of three predictors as ultrasound characteristics and demographic parameters. This is the first study to evaluate a ductal change lesion of the breast in Thai women population for prediction of some sonogram pertinent characteristics.

Since sonographic focally thick duct lesions is not established in practice guidelines, knowledge of the lesions is scarce, making it lack detailed characteristics (1). Most of the ductal change lesions were pauci-cellular samples which does not have uniformity in description, lead to some potential drawbacks in the routine practice. An identification and detection of sonogram variables that could predict proliferative lesions of the ducts is needed.

According to categorized predictors in model 3, the predictive performance of model 2 is vascularization parameter as fixed predictor. We used Hosmer-Lemeshow chi-square test to calibrate all models with significant results in model 3. The model had good discrimination that these showings indicated that the model had accurate predictions for patients. Confirmed results showed in probabilities by ROC curve (Figure 17) that revealed model 3 had higher AUC ROC as 0.671 (95%CI 0.59, 0.74) compared with two other methods. However, the variables age and setting might be found to be confounding factors in this prediction model (Table 9).

In the model 3, the age showed that women under 50-years old had 1.17-fold to have proliferative lesion compared to the older women. The previous study found higher odds ratio in younger age to the breast malignancy, accounted as 3.2-fold (13). The vascularization depicted the feeding vessel around the lesion. The formation of blood vessels was used for the grow of ductal proliferation or angiogenesis of breast carcinoma (33). Even though some ultrasound parameters did not appear as significant variables, such as ductal size, ductal location, any calcification, internal nodule, and mixed echoic wall, they remained important sonographic parameter in the practice (10, 11). The larger diameter, appearance of calcification, internal nodule, mixed echoic thick wall, and peripheral location showed a positive association towards breast disease (9-11).

We compared the predictive model with the previous study by Park et al. The study showed prediction analysis between malignant and benign lesion on non-mass lesion. The study showed odds ratio of ultrasound and mammogram parameters on non-mass lesion including ductal changes lesions. The results showed significant association between calcification on mammogram and distribution, calcification, architectural distortion and duct ectasia found on ultrasound (11). Some ultrasound parameters overlapped with our study, however, the scope of the lesion in the previous study was broader, not only captured the ductal change lesions.

The final model shows high accessibility of health care setting since the vascularization predictor can be easily obtained by colour doppler ultrasound. The vascularization depicted as the strongest predictor. In the clinical practice, we can see the usage of vascularization through diagnostic utility with sensitivity of 45.9% (95% CI: 34.3, 57.9), specificity of 72.8% (95%CI: 64.5, 80.1), positive predictive value of 47.9% (95%CI: 35.9, 60.1), and negative predictive value of 71.2% (95% CI: 62.9, 78.6).

The proliferative lesion prediction model comprised of malignant and benign proliferative lesion, that can be used in routine practice. The feeding vessels showed as pertinent parameter to predict of proliferative lesions in focally thick duct lesion. The final prediction model which contained ultrasound parameters is suitable for recognizing the sub-centimetre lesion and assist the judgement on the decision making. Focally thick ducts without associated parameters could be observed with certain interval period using ultrasound since the lesion did not give alarm to be suspected lesion.

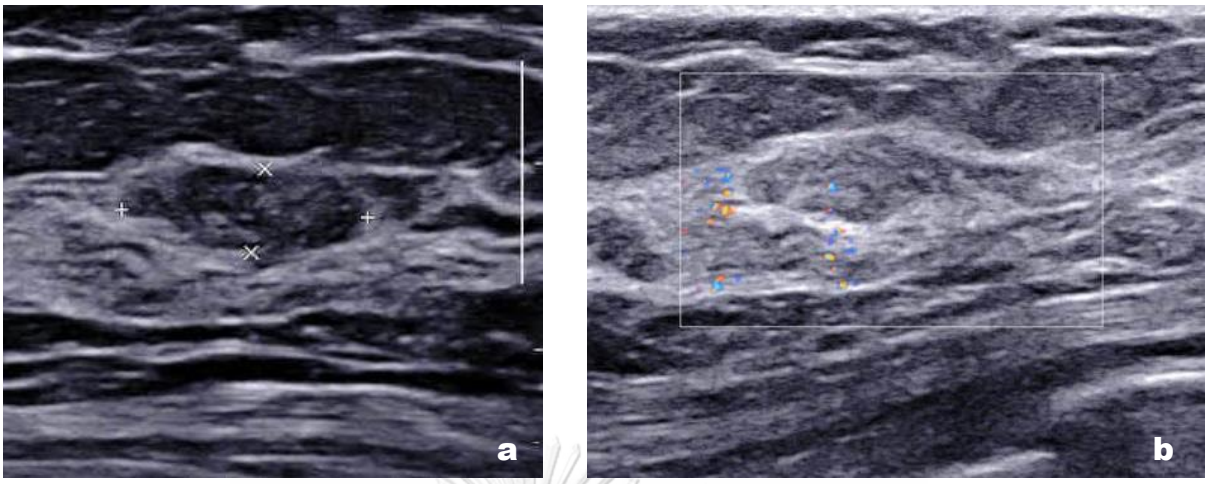
D. Focally thick duct lesion in clinical practice routine

Various imaging modalities are available on breast ductal abnormalities evaluation. Galactography, known as ductogram, remains the gold standard for ductal evaluation. The method uses contrast agent that can help visualized any defect on duct that appeared as filling defect (1). Ultrasound arises as the new of emerging ductal diagnostic tool. Using high resolution

of sonography can help to detect any duct dilatation and or duct thickened. This tool can also assist the diagnostic and therapeutic procedure using fine or core needle biopsy.

The procedure of detection on focally thick duct using ultrasound needs two different planes to confirm the configuration of tubular structure. Radial and anti-radial views help to diagnose the entity. Radial view will give location and ductal extension from subareolar to peripheral, and anti-radial view shows the echoic content and ductal margin (1). Additional colour doppler image is warranted to show the vascularization activity around the focally thick duct.

The detection suspicious focally thick duct can make significant change in patients' diagnosis since most of them was non proliferative lesion (66.2%), especially scant cellularity in cytology (52.4%). However, 8.2% was malignant proliferative lesion, which the proportion is outnumbered the probability of breast cancer according to BIRADS 3. Hence, about 33.8% of the patients carefully need ultrasound examination for focal thick duct lesion identification, follow up, and/or biopsy procedure. Early detection for focally thick duct utilized the benefit of ultrasound to detect sub-centimetre lesion in breast ducts using vacuum assisted biopsy guided by ultrasound, because it can diagnosed the breast malignancy earlier and leaved non suspicious ductal lesion to be followed up (17, 22).



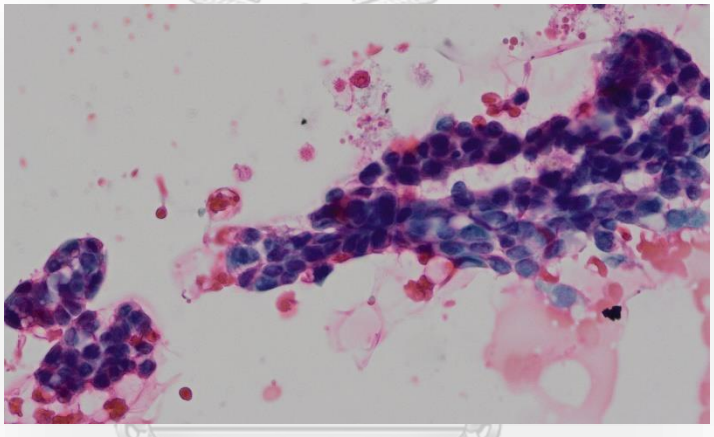
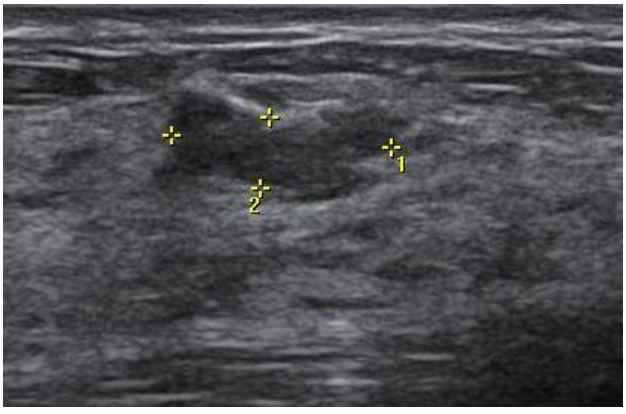


Figure 20. The focally thick duct lesion as a benign proliferative lesion (a) that stable until 3 years follow up by ultrasound (b). Previously, the cytology described as proliferative with moderate cellularity and non-atypia cell.



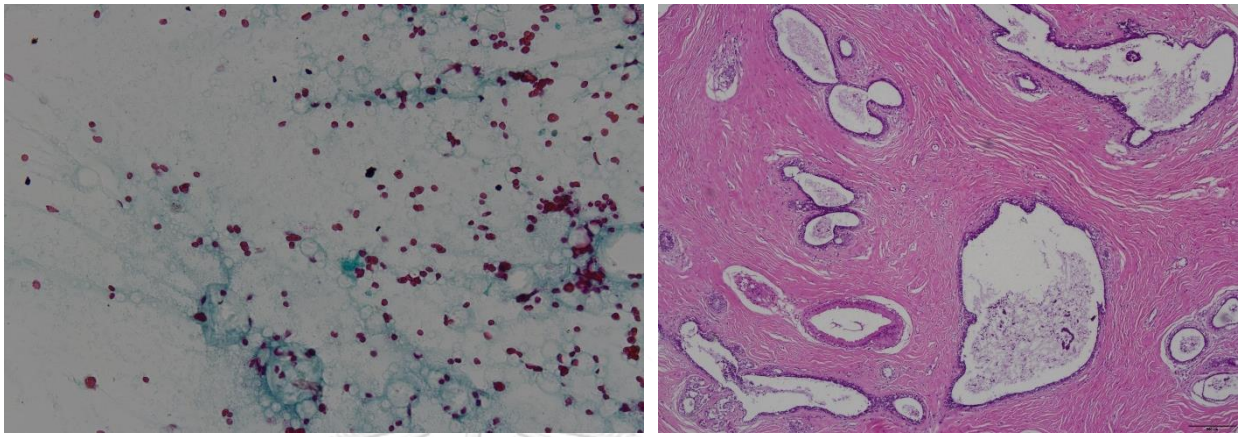


Figure 21. The focally thick duct lesion revealed as non-proliferative duct dilatation. Previously, the cytology described as scant cellularity with adipose tissue.

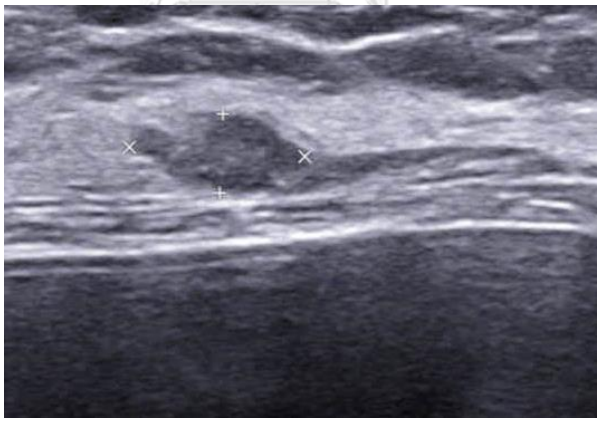


Figure 22. The focally thick duct lesion revealed as invasive carcinoma, then surgery. Previously, the cytology described as proliferative and atypia cell, which showed early diagnosis on this lesion from screening.

Management of focally thick duct lesions found on ultrasound can be challenging (12). Of the final outcome, 71 cases had proliferative ductal lesions with 18 of which were malignant.

It is important to identify the lesion at screening and follow up study. Due to the consideration of high-risk on malignancy, surgical procedure was often advised (12, 34). However, follow up care on imaging and clinical was beneficial to reduce the burden on patient due to unnecessary surgical procedure. The non-proliferative disease was found in 66.2% of cases (52.4% yielded scanty cells on FNA). In addition, ultrasound follow up of the certain lesions was warranted because certain number is scant cellularity that unmerited biopsy.

E. Strength and limitations

Our study has several limitations: first, this is a retrospective study which did not show real time ultrasound procedure. As a result of the limited images from retrospective study, some ultrasound parameters cannot be evaluated, and the case was excluded. Second, as we did not conduct external validation, our prediction models might not be generalizable to all patients. Despite these limitations, our study has several strengths. First, there are limited number of studies on ductal change lesions and our study is the first to assess focally thick duct lesion specifically in Thai patients. Second, the identification of ultrasound parameter that simple and easily to found during routine practice since ultrasound is an efficient and cost-effective tool to assess any breast abnormality. Third, the predictors in proliferative lesion which provide less bias in routine clinical practice.

CHAPTER V
CONLUSION AND RECOMMENDATIONS

CONLUSION

Breast ductal change was present as tubular-shape structure with focal abnormality in ultrasound. Vacuum-assisted biopsy guided by ultrasound can improve the accuracy of sampling, because the ductal change is a sub-centimeter lesion that smaller than 1 cm and located within a duct. Among the six ultrasound parameters, vascularization showed significant association with the proliferative lesion as histology outcome.

Proliferative lesion prediction model is developed in this study. The fixed predictor which is vascularization shown to be most significant predictor in the model. More than half of the lesion resulted in scant cellularity with non-proliferative outcome. According to analysis of the parameters, follow up of the certain lesions is needed because certain number of lesion were scant cellularity that unwarranted biopsy. In the prediction model, the absence of vascularity was entailed follow up study rather than biopsy. The proliferative lesion prediction model is expected to help assist the radiologist to early detect for focally thick duct lesion and avoid unnecessary biopsy procedure for the patients.

RECOMMENDATIONS

Further study needs to conduct in prospective study and external validation should be done. This study started from the practical daily work from the basis of experience, so it needs more in specific definition of predictor for the future project. Besides, inter-rater reliability analysis can be performed in multi-centre study. More sonographic characteristics should be explored as predictor candidate, such as types of calcifications and periductal area with specific and clear-cut definition.

Appendices

Case Record Form

No. Form : Code ID:

Date : ☐☐/☐☐/20☐☐ (date/month/year)

Patient's Characteristics

1. Date of FNAB guided by US : ☐☐/☐☐/20☐☐ (date/month/year)
2. Age : _____ years old
3. Clinical settings : Setting #1 ☐1
   Setting #2 ☐2
   Setting #3 ☐3

Histology Finding

4. Diagnosis :
5. Surgery : Yes ☐1

Years: .....

No ☐2

6. Classification of surrogate outcome:

Cytology suggesting proliferative lesion or malignancy ☐1

Cytology suggesting non-proliferative lesion ☐2

7. Classification of final outcomes:

Histology verifying proliferative lesion or malignancy ☐1

Histology verifying non-proliferative lesion ☐2

Cytology suggesting non-proliferative lesion AND ☐3

no progression over follow-up

Ultrasound Finding

1. Internal nodularity : Present ☐1

Absent ☐2

2. Location : Central ☐1

Peripheral ☐2

3. Mixed echoic wall : Present ☐1

Absent ☐2

4. Calcification : Present ☐1

Absent ☐2

5. Maximum across diameter: ..... mm

2-3.99 mm ☐1

4-5.99 mm ☐2

6-7.99 mm ☐3

>8 mm ☐4

6. Vascularity : Present ☐1

Absent ☐2

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AWARD RECEIVED	Silver Medal Winner of Indonesian National Scientific Week in Research, Indonesia (2014) The research's title is optimization of synthetic leather design with lead filler as radiation-protecting apron for health care provider in radiology unit