

Strategy for Diagnosing Breast Cancer in Indonesia during the COVID-19 Pandemic: Switching to Ultrasound-Guided Percutaneous Core Needle Biopsy

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Abstract

In this era of COVID-19, suspected breast cancer patients experience delay in diagnosis due to the fear of contracting the virus and reduction of non-COVID-19 health services. Furthermore, it may lead to potential increase in the incidence of advanced cancers in the future. Ultrasound-guided (US-guided) percutaneous core needle biopsy (CNB) is a great option for the diagnosis of cancer but it is poorly utilized. This study aimed to prove that the US-guided CNB is accurate when performed in a local setting and a potential solution for diagnosing breast cancer patients in this pandemic. In addition, it was a single health center cross-sectional study, and the participants were all breast cancer patients that had US-guided CNB from 2013-2019. The pathology results from US-guided CNB were compared to specimens from post-CNB surgeries. The data were collected from medical records and the immunohistochemistry (IHC) examinations were carried out for malignancy. There were 163 patients who were included in this study, 86 had malignancies and 77 had benign tumor reported in their CNB results. The US-guided CNB had 100% sensitivity and specificity compared to surgery. With its lower cost, time usage, and patient exposure to the hospital environment, US-guided CNB should replace open surgery biopsy for diagnosing suspicious breast cancers during the pandemic in Indonesia.

Keywords: breast cancer, core needle biopsy, COVID-19, health cost, resources

Introduction

According to the data from the Global Burden of Cancer Study (GLOBOCAN) 2018, breast cancer has the second-highest incidence after lung cancer.¹ Meanwhile, its mortality rate is among the top five, 6.6% from all mortality caused by cancer. Furthermore, being known as one of the most common cancer in Indonesia, its incidence is estimated to about 40.3 per 100,000 women or 48,998 new cases every year. This number is 30.5% from all types of cancer in females or 16.4% from all types of cancer in the general population, which means there are six new cases of breast cancer every hour in the country.²

The current coronavirus disease 2019 outbreak (COVID-19) is affecting the management of cancer patients, including breast cancer. The disease has claimed more than one million life losses worldwide since its outbreak in early 2020. Studies have shown that patients

with cancer were at higher risk of the need for intensive care unit admission and mortality, approximately 1.5–2 times the risk compared to those without cancer.³

A report based on an international survey shows that breast cancer management has changed dramatically.⁴ Most long-term follow-up care of breast cancers was temporarily held and most doctors can only focus on emergencies. In this pandemic situation, international organizations and societies for oncology have published recommendations for the management of breast cancer patients previously diagnosed.⁵ However, in Indonesia, the challenge remains for patients with suspected breast cancer, such as breast lump, but unable to be properly diagnosed due to limitation of hospital services and patients are reluctant to go to a health center for fear of getting infected. With excision biopsy as the main histopathologic diagnostic procedures, breast cancer patients typically must visit the hospital several times,

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which requires lengthy period, exposing them the risk of being prone to COVID-19 infection.

Delaying diagnosis can harm breast cancer patients, which may lead to advanced breast cancer, limiting treatment options and reducing survival rate.⁶ Therefore, it is important to have a quick and accurate procedure for breast cancer diagnosis in this pandemic. An alternative to excision biopsy is ultrasound-guided percutaneous core needle biopsy (US-guided CNB). The CNB, especially US-guided, is recommended for the initial diagnosis and management plan of breast cancer.⁷ Compared to open surgical biopsy, it has similar high accuracy (98–100%), cost-effective (<1 million Indonesian rupiah [IDR] vs. 4–5 million IDR for surgical biopsy), less invasive, minimum side effects (bruising, bleeding or infection <1%), time-saving (only 5–15 minutes), does not need preoperative evaluation and general anesthesia, and can be performed at the outpatient unit.⁸ A panel of experts from the Breast Health Global Initiative (BHGI) also stated that CNB is one of the diagnostic procedures of choice in a limited-resource setting.⁹

Despite these advantages, the US-guided CNB is an uncommon procedure in Indonesia compared to surgical biopsy. Moreover, the National Health Insurance/*Jaminan Kesehatan Nasional* (JKN) only covers this procedure in type A hospitals, which may aggravate the rarity of CNB further. Furthermore, while its use and capability have been established in the international community, there was no previous report on its performance in local settings. Therefore, this study aims to determine the accuracy of the US-guided CNB to differentiate between malignant and benign breast tumors in Indonesia. If the US-guided CNB is proven to be accurate when performed in local settings, perhaps it is time for surgeons in Indonesia to prioritize the US-guided CNB rather than surgical biopsy, especially due to its cost-effectiveness and time-saving characteristics, which may reduce the time that patients spend in hospital, leading to lower risk of infection in this pandemic.

Method

This study was using a single-center cross-sectional design that aims to find out the advantage and accuracy of US-guided CNB. The study was conducted at Metropolitan Medical Centre, Jakarta, Indonesia. The participants were all female breast tumor patients of any age that received US-guided CNB as an initial biopsy method within the period of 2013 to the middle of 2019. The patients that received other initial biopsy methods, such as open biopsy or fine-needle aspiration biopsy, and with incomplete medical records data were excluded. A total sampling method was carried out.

Data were collected from medical records, and the

data were the age of participants, category of tumors based on ultrasound examination, number of specimens obtained, and size of tumors. For patients that received surgery as a treatment, pathology results from surgery were obtained for diagnostic analysis. The discrepancy between the US-guided CNB pathology results and surgical pathology results was noted. For patients with malignant pathology results, data of breast cancer subtypes based on immunohistochemistry (IHC) examination and stage of cancers as described by the American Joint Committee on Cancer (AJCC) were also collected.¹⁰

All cases were biopsied by one operator, a surgical oncologist who has been doing US-guided CNB since 2012, using 14-G automatic spring-loaded core biopsy needle (ACECUT®, ACE-141502 14G x 150 mm, 15 mm-throw, by TSK Laboratory, Japan) with semi-automatic (double) firing. The operator handled the US probe and CNB device by herself, the preferred biopsy technique according to Parker, *et al.*¹¹ A US device with an 11 MHz linear transducer was used.

Based on the ultrasound findings, participants were grouped into the following categories, suspicious benign (absent malignant findings, intense hyperechogenicity, an ellipsoid shape, gentle bi- or trilobulations, and thin and echogenic pseudocapsule), indeterminate (maximum diameter, isoechogenicity or mild hypoechogenicity, enhanced or normal sound transmission, and heterogeneous or homogeneous texture), or suspicious malignant lump (spiculation, angular margins, marked hypoechogenicity, shadowing, calcification, duct extension, branch pattern, and microlobulation). For suspicious benign category, all criteria should be presented.¹²

The sizes of the tumors were grouped into unpalpable (≤ 1.3 cm), palpable small (1.4–2.9 cm), and generally very palpable (≥ 3 cm).¹³ Breast cancer subtype was luminal when the hormone receptor (HR) was positive and human epidermal growth factor receptor 2 (HER2) was negative. The HER2 subtype means HER2 was positive, indifferent to the status of HR. When both HR and HER2 were negative, the subtype was triple-negative breast cancer (TNBC).

IBM SPSS Statistic Version 25 (IBM Corp., New York, USA) was used for statistical analysis. Descriptive data were reported, including mean (for data with normal distribution), median (for data without normal distribution), minimum, and maximum. The data distribution was determined from Shapiro-Wilk analysis, with p-value > 0.05 was categorized as a normal distribution.

A diagnostic analysis was performed to determine the ability of US-guided CNB to identify malignant from benign specimens compared to the subsequent treatment surgery as a gold standard. Sensitivity, specificity, positive predictive value (PPV), and negative predictive

value (NPV) were manually calculated based on a 2x2 table. The ethical approval was obtained from the hospital's ethics committee (No. 239/Kom-Etik/Int/VI/2019).

Results

The data collected showed the number and age distribution of patients, pathology results of the US-guided CNB and their corresponding size. The comparison of pre-biopsy US category and post-biopsy pathology result, number of samples that were obtained when performing US-guided CNB, the accuracy of US-guided CNB compared to surgery, and some discrepancies in cancer grade. Moreover, the stage and subtype of breast cancers in correlation to the size categories of the tumors were also described.

A total of 163 patients were included and all were women. The age of patients was not normally distributed, with a median of 42 (minimum 20 and maximum 83) years old. Out of all, 86 patients had malignancies and 77 patients had benign tumors for their CNB pathology results. The number of patients with unpalpable, palpable small, and generally very palpable size was 39, 86, and 38, respectively (Table 1). In addition, one patient in the small palpable mass group and two in the generally palpable mass group were pregnant. Typically, pregnancy raises awareness to perform surgery under general anesthesia, but for CNB, there was no need for special preparation.

Among 16 patients with malignant unpalpable breast lesions (as shown in Table 1), 13 (81.25%) initially had suspicious malignant pre-biopsy characteristics, while the

rest (18.75%) had indeterminate pre-biopsy characteristics. From 23 patients with benign unpalpable breast lesions, initial pre-biopsy characteristics of malignant, indeterminate, and benign were detected in 2 (8.7%), 20 (87%), and 1 (4.3%) patients, respectively. The largest dimension of all unpalpable tumors was 1.37 cm while the smallest was 0.56 cm. In this group, 2 (8.7%) patients with benign pathology results and 6 (37.5%) patients with malignant pathology results showed no visible mass but architectural distortion lesions on US examination.

The number of samples obtained from biopsies played an important role in obtaining accurate pathology results. Furthermore, the minimum number of samples obtained was three, while seven was recorded as the highest number of samples. The mean number of samples was four (Table 2).

Out of 163 patients that received US-guided CNB, 75 patients also underwent surgeries in our institution, 53 patients and 22 patients had congruent US-guided CNB and surgeries pathology results for malignant and benign tumors, respectively. Based on these results, in the terms of determining if the tumor was benign or malignant, the

Table 1. Size of Tumors with Their Pathology Results after Ultrasound-guided Core Needle Biopsy

Category	Pathology Result	
	Benign	Malignant
Unpalpable (n = 39)	23	16
Palpable small (n = 86)	45	41
Generally very palpable (n = 38)	9	29

Table 2. Pre-Biopsy Radiological Diagnosis and Post-Biopsy Pathology Results

Pre-Biopsy	Post-Biopsy	Number of Patient	Number of CNB Sample Taken		Mean Number of Sample
			Minimum	Maximum	
Benign	Benign	5	4	5	4.2
Indeterminate	Benign	63	3	7	4.2
Indeterminate	Malignant	16	4	7	4.4
Malignant	Malignant	70	3	6	4.28
Malignant	Benign	9	3	5	3.5
Mean number of samples in average					4.116

Note: CNB: Core Needle Biopsy

Table 3. Core Needle Biopsy and Surgery Pathology Discrepancy Comparison in Three Patients

Core Biopsy Specimen Pathology Result	Surgery Specimens Pathology Result
Invasive Ca* NST† grade 1	Invasive Ca* NST† grade 2
Invasive Ca* NST† grade 2	Invasive Ca* NST† grade 3
Invasive Ca* metaplastic grade 3	Invasive Ca* metaplastic grade 2

Notes: *Ca: Cancer; †NST: No Special Type

Table 4. Breast Cancer Subtypes and Stages Grouped by Pre-Biopsy Size

Subtype	Stage ^a	Size		
		Unpalpable	Palpable Small	Generally Very Palpable
Luminal	0	1	0	0
	I	4	5	0
	II	3	10	4
	III	1	3	6
HER2 [†]	IV	0	3	4
	0	1	0	0
	I	2	3	0
	II	1	11	6
TNBC [‡]	III	1	0	2
	IV	0	2	1
	0	0	0	0
	I	0	0	0
DCIS [*]	II	0	2	1
	III	0	0	4
	IV	0	2	0
	0	2	0	1

Notes: *DCIS: Ductal Carcinoma In Situ, †HER2: Human Epidermal Growth Factor Receptor 2, ‡TNBC: Triple-Negative Breast Cancer
^aStage was categorized based on the Tumor (T), Node (N), and Metastasis (M) of tumors as described in the 8th cancer staging manual of the American Joint Committee on Cancer (AJCC).¹⁰

sensitivity, specificity, PPV, and NPV of US-guided CNB compared to surgeries were 100%. There were cancer grade differences between specimens obtained from US-guided CNB compared to surgeries in 3 out of 53 patients (Table 3). However, these differences did not affect treatment.

Because one of the important purposes of performing US-guided CNB is to treat breast cancer patients, based on recent studies, patients were classified based on tumor’s size, stage, and subtype as shown in Table 4. Patients with benign pathology results in whom the tumor had not been removed were followed up while they presented to the day clinic for a routine examination. None of the patients showed signs of malignancy for the lumps that had been biopsied. Furthermore, there was no adverse case of continuous bleeding, severe pain, infection, or pneumothorax.

Discussion

This study showed that the US-guided CNB was able to differentiate malignant from benign breast tumors compared to standard operations with perfect sensitivity and specificity (both 100%). The result of this study was similar to the previous studies of larger international studies.^{8,14–16} For example, a meta-analysis showed that US-guided CNB had a sensitivity of 87% (95% CI = 84–88%) and a specificity of 98% (95% CI = 96–99%).¹⁴ The reason for perfect sensitivity and specificity was perhaps due to a less varied setting (single-center study with all procedures performed by one surgical oncologist).

There were three patients with discrepancies in pathology grade of the cancers, but it did not have any implication on the management of the cancers.

As an additional note, the US-guided CNB of the breast did not need a long learning curve. The data also included patients that received US-guided CNB when the surgical oncologist only had one year of experience with the procedure (patients in 2013). While there was no previous study on the learning curve of US-guided CNB for breast tumors, a report showed that US-guided vacuum-assisted breast biopsy (VABB), an almost similar procedure to US-guided CNB, can give a clue about the learning curve of such procedure. In the study, operators tended to gradually get faster after the first procedure until optimal skill was achieved at the twentieth procedure.¹⁷ The mean number of specimens obtained with CNB from each lesion was 4 and a minimum of 3. There was no standard or consensus on the minimum number of specimens that were needed to obtain an accurate result, but the US-guided CNB with a 14G core needle may need at least two specimens from each lesion.¹⁸

In addition to the accuracy of US-guided CNB, this study also showed that there were 57 (45.6%) patients with breast tumor size <3 cm that had malignant results (Table 1). This was an important finding because of the current practice in Indonesia, most surgeons only perform CNB without US guidance for breast tumor with size ≥3 cm.¹³ For comparison, latest guidelines from the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) did

not restrict CNB indication based on size.^{19,20} These guidelines recommended US-guided CNB as the procedure of choice for breast tumor biopsy. If this study had only performed CNB on patients with tumor size ≥ 3 cm, nearly half of the patients with small or unpalpable breast mass might have mis- or delayed diagnosis, resulting in decreased survival rate due to advancement of cancer stage.

The use of US guidance while performing CNB should be recommended for all tumor sizes. Non-image-guided CNB was no longer recommended in the international community due to the significantly lower sensitivity and specificity when compared to the US-guided or stereotactic-guided one.^{19,20} Recently, the latest guideline by the Indonesian Society of Surgical Oncology recommends the US-guided CNB as a standard biopsy method for all suspicious breast lesions that can be detected by the US. However, the guideline also includes a contradicting algorithm that suggests an incisional or excisional biopsy with a frozen section as the initial biopsy approach for a breast lesion without further explanation on when such a non-standard method may be used. This inconsistency can potentially cause confusion among surgeons.¹³

Among the patients with tumor size of <3 cm, there were 16 (41%) patients with unpalpable size tumor that showed post-biopsy malignant pathology results. Considering the tumor size of this group, without US-guided CNB, a definitive diagnosis could not be carried out. Therefore, those cases could eventuate as delayed diagnosis. Such circumstances were a prime example of US-guided CNB's importance. Furthermore, out of the 16 patients, six had architectural distortion, which is defined as a distortion of the normal architecture of the breast with no visible definite mass.²¹ Originally, architectural distortion cases should be biopsied with VABB.^{21,22} However, at the time of the study, VABB was not available in Indonesia, therefore the US-guided CNB was used as an alternative. In this study, six of eight patients that had architectural distortion breast lesions turned out to be having breast cancers. These cases showed another strong point of US-guided CNB.

In contrast, there were 68 (54.4%) patients experiencing benign unpalpable or small size tumors (Table 1). Based on the authors' experience (as there was no published data), Indonesian surgeons typically preferred open surgery biopsy intending to remove the tumor in "one swoop". If such practice had been applied, approximately half of the patients would have received unnecessary surgery along with all of its potential complications.

Every discrepancy between clinical, radiological, and pathology results was investigated carefully. There were two patients with clinically and radiologically suspicious malignant unpalpable tumors. Both had benign pathology results, mastitis with usual ductal hyperplasia (UDH)

from US-guided CNB. Due to the incongruity between clinical-radiological and pathology results, further excisions were offered to the patients. Eventually, the same benign pathology results were reported from excisions, corresponding to the results of the US-guided CNB.

In this study, other than indeterminate and suspicious malignant pre-biopsy characteristics, US-guided CNB was also performed for other indications. There were five patients with benign pre-biopsy characteristics (as shown in Table 2) but underwent US-guided CNB due to large tumor size, therefore necessitate reconstructive surgery. Since reconstructive surgery is a complex procedure, definitive diagnosis confirmation with US-guided CNB was deemed necessary to avoid inappropriate procedures.

In correlation to breast cancer treatment based on stage and subtype, there were 21 patients with HER2 subtype and 7 patients with TNBC subtype breast cancers that were in stage II and III (Table 4). Among these, there were 13 out of 21 HER2 patients and 2 out of 7 TNBC ones whose tumors were unpalpable or small. St. Gallen expert panel consensus in 2019 agreed that stage II and III HER2 and TNBC subtype breast cancer should be treated with neoadjuvant systemic therapy (NAT) to allow surgical de-escalation, prevent unneeded full axillary dissection in selected patients, learn in vivo response of systemic therapy to predict patients' survival, and recognize worse recurrence risk.²³ On the contrary, patients with such cases can receive direct excision as a form of prior therapy without NAT if doctors did not perform US-guided CNB.

Based on those results, there are two implications. First, a US-guided CNB performed at a local hospital by a local surgical oncologist is not inferior to a US-guided CNB that is performed in developed countries. Furthermore, the training for US-guided CNB is probably minimum because it does not need a long learning curve. Therefore, it is feasible to be performed in Indonesia.

The second implication is the possible benefit of the US-guided CNB in the COVID-19 pandemic era. Due to this, the incidence of advanced breast cancer may rise because patients become more reluctant to go to the hospitals, and with the limited capability of health providers to provide adequate services.²⁴ The US-guided CNB has the advantage as a time-saving and cost-effective procedure and is associated with fewer complications compared to surgical biopsy.^{25,26} The current data from JKN in 2015–2020 showed that the unit cost of breast biopsy was approximately four million IDR, while the US-guided CNB can be performed with cost only one-fourth to one-third of it.²⁷

Another major advantage of the US-guided CNB is that it can be performed at an outpatient unit.^{28,29} The patients may directly go home after the biopsy in such a way that the risk of exposure to COVID-19 can be low-

ered. This advantage is important because there were at least about 60,000–80,000 small breast procedures every year in Indonesia and almost all were performed in an inpatient unit. This means that for cases suitable for US-guided CNB instead of open surgery biopsy, there will be spared resources for more urgent cases.²⁷

Preoperative biopsy also offers a significant benefit as pathological findings can help surgeons classify urgent cases (e.g., malignant tumors, giant fibroadenomas, and phyllodes tumors) and non-urgent cases. Patients with non-urgent cases can delay their surgery until the national health system recovered after this pandemic, which will help to de-escalate hospital burdens during this period. There is also a future notable use of US-guided CNB with the global development of gene assay in the treatment of breast cancer. The biomolecular and genetic characteristics from samples taken by preoperative CNB have a role to direct more appropriate therapy for breast cancer patients and therefore can boost the survival of the patients.³⁰ Understanding this insight, clinicians in Indonesia should be familiar with the US-guided CNB.

The strength of this study was the total sampling of breast tumor patients over seven years with both benign and malignant results. Meanwhile, the limitation of this study was the involvement of only one surgical oncologist. Therefore, the sensitivity and specificity of US-guided may be slightly different from the studies with multiple operators because the accuracy of US-guided CNB is influenced by the learning curve of the operator.

Conclusion

This study showed that US-guided CNB is a reliable breast biopsy procedure that can potentially be performed in local hospitals by local clinicians in Indonesia. Instead of an open biopsy surgery, the US-guided CNB, which has the advantages as a time-saving method that does not require inpatient observation should be implemented as the procedure of choice for breast tumor biopsy, following the international guidelines. Further multicenter studies involving multiple clinicians may be needed to confirm the accuracy of the US-guided CNB in Indonesia.

Abbreviations

US: Ultrasound; CNB: Core Needle Biopsy; IHC: Immunohistochemistry; GLOBOCAN: Global Burden of Cancer Study; COVID-19: Coronavirus Disease 2019; IDR: Indonesian Rupiah; BHGI: Breast Health Global Initiative; JKN: *Jaminan Kesehatan Nasional* (National Health Insurance); AJCC: American Joint Committee on Cancer; HR: Hormone Receptor; HER2: Human Epidermal Growth Factor Receptor 2; TNBC: Triple-Negative Breast Cancer; PPV: Positive Predictive Value; NPV: Negative Predictive Value; VABB: Vacuum-Assisted Breast Biopsy; ESMO: European Society for Medical Oncology; NCCN: National Comprehensive Cancer Network; UDH: Usual Ductal

Hyperplasia; NAT: Neoadjuvant Systemic Therapy.

Ethics Approval and Consent to Participate

Ethical approval was obtained from the local hospital (No. 239/Kom-Etik/Int/VI/2019).

Competing Interest

The authors declare that there are no significant competing financial, professional, or personal interests that was likely to have affected the performance or presentation of the work described in this manuscript.

Availability of Data and Materials

Data was available from the corresponding author on request.

Authors' Contribution

FBS proposed, planned, carried out, and supervised the study and report, AB and SSP guided, supervised, and finalized the writing of the report, JCR carried out the research and collected medical record data, EK carried out pathologic examinations and provided pathologic data, NT carried out radiologic examinations and provided radiologic data, PWY wrote the report. All authors read and approved the final manuscript.

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