DOI: https://doi.org/10.53555/nnmhs.v9i4.1654 Publication URL: https://nnpub.org/index.php/MHS/article/view/1654

DIAGNOSTIC ACCURACY OF CONTRAST-ENHANCED ULTRASOUND TO DIFFERENTIATE BENIGN AND MALIGNANT BREAST LESIONS

Radian Ashar Pambudi*

**Faculty of Medicine, Bandung Islamic University, Indonesia*

Corresponding Author:
radianasharpambudi@gmail.com

Abstract

Cancer of the breast is caused by a cluster of abnormal breast cells that continue to divide and spread throughout the breast. These cells eventually aggregate as a lump in the affected breast. If the cancerous tumor is not treated, the cancer cells may spread to other areas of the body through a process known as metastasis. A metastasis may develop in the lymph nodes located in the axilla or those located above the scapula. In addition, cancer cells have the ability to colonize the bones, lungs, liver, skin, and even the space directly under the skin. Cancer of the breast tissue is a malignancy that can start from either the ductal or lobule epithelium of the breast. Breast cancer is the most common kind of cancer in women. The ability of ultrasonography to identify cystic masses is one of the technology's many strengths. According to BIRADS, the American College of Radiology has also developed a standardized language for the reading and reporting of ultrasounds, which is quite similar to the language used for mammography. Shape of the mass, borders, orientation, kind of posterior acoustic, lesion boundaries, and echo pattern were the characteristics that were described. CEUS is an imaging technology that evaluates breast lesions by analyzing their qualitative qualities as well as their quantitative aspects. The detection of lymphatic channels and sentinel lymph nodes can be done using this method, and it is practical and effective.

Kata kunci: *Benign; Breast; Diagnostic; Contrast-enhanced ultrasound; Malignant*

INTRODUCTION

Cancer is the second largest cause of death due to non-communicable diseases every year (8.8 million people), with an incidence of 14 million cases in 2012, while cardiovascular disease ranks first (17.7 million people).[1,2] According to the American Cancer Society, breast cancer is the most common type of cancer in women and is the second leading cause of death from cancer in women after lung cancer. In 2017 in the United States it is estimated that there will be around 252,710 new cases of invasive breast cancer, 63,410 new cases of carcinoma in situ, and around 40,610 women will die from breast cancer.[3–5]

Intrinsic, extrinsic, and hormonal factors cause breast cancers. Age, sex, ethnicity, and genetics predispose to familial neoplastic illnesses or benign proliferative lesions of the mammary glands. They are independent factors that don't change during a person's life. Extrinsic risk factors, such as lifestyle, food, or long-term medical therapies like oral hormonal contraceptives or hormonal replacement therapy, can modify the neoplastic process. Modifiable factors can help design breast cancer prevention strategies.[6]

Women who have dense breast tissue may benefit from an additional screening with ultrasound because it is a non-invasive, relatively inexpensive, and widely available tool for detecting breast cancer in its early stages.[7,8] The vascular assessment of breast tumors using color and power Doppler modes is still unsatisfactory. This is due to the fact that the assessment is only sensitive to vessels that are larger than 2 millimeters in diameter and that it can only detect flow velocity that is greater than the threshold of the wall filter.[9] Contrast-enhanced ultrasound (CEUS), which stands for contrast-enhanced ultrasonography, is a novel method for assessing the vascularity of tumors and for monitoring the flow of blood through tumors.[10]

The utilization of contrast compounds resulted in a marked improvement of the vascular signals at Doppler US, and the microvascular architecture of breast tumors was able to be delineated in an unmistakable manner.[10,11] Contrast media, enhanced both the specificity (71%) and the positive predictive value (70%) in patients with breast lesions that were categorized as BI-RADS 4 in comparison to B mode ultrasonography (39% and 53%, respectively). Nevertheless, the utilization of CEUS in the diagnostic process of breast cancer has seen rapid development only within the past few years.[12,13]

Previous investigations that were published indicated a wide range of diagnostic performance: the sensitivity was in the range of 67–100%, while the specificity was in the range of 47–100%. There has not been a meta-analysis performed to determine the overall value of CEUS in the diagnosis of breast lesions up until this point. This study was to undertake a meta-analysis to evaluate the diagnostic performance of CEUS in breast neoplasm characterisation. The results of this analysis were to be presented.[12,13] This article showed the diagnostic accuracy of contrast-enhanced ultrasound to differentiate benign and malignant breast lesions.

METHODS

Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist was used as the basis for the establishment of the criteria that govern the methodology of this particular systematic review.

Eligibility Criteria

This systematic review was developed to analyze papers on “Diagnostic accuracy”; “contrast-enhanced ultrasound” and “breast lesions". These are the subjects that were mentioned in the evaluated studies. In order for you’re the study to be evaluated, the following requirements must be met: 1) Articles must be fully accessible online; 2) Articles must be written in English; and 3) Articles must have been published between 2015 and the time of this systematic review's preparation. Text submissions of the following kind will not be accepted under any circumstances: 1) Letters to the editor, 2) contributions without a Digital Object Identifier (DOI), and 3) article reviews and comparable submissions.

Search Strategy

The search for studies to be included in the systematic review was carried out from April 28th, 2023 using the PubMed and SagePub databases by inputting the words: “diagnostic accuracy”; “contrast-enhanced ultrasound” and “breast lesions". Where *("diagnosis"[MeSH Terms] OR "diagnosis"[All Fields] OR "diagnostic"[All Fields]) AND accuracy[All Fields] AND contrast-enhanced[All Fields] AND ("ultrasonography, mammary"[MeSH Terms] OR ("ultrasonography"[All Fields] AND "mammary"[All Fields]) OR "mammary ultrasonography"[All Fields] OR ("ultrasound"[All Fields] AND "breast"[All Fields]) OR "ultrasound breast"[All Fields]) AND lesions[All Fields]* is used as search keywords.

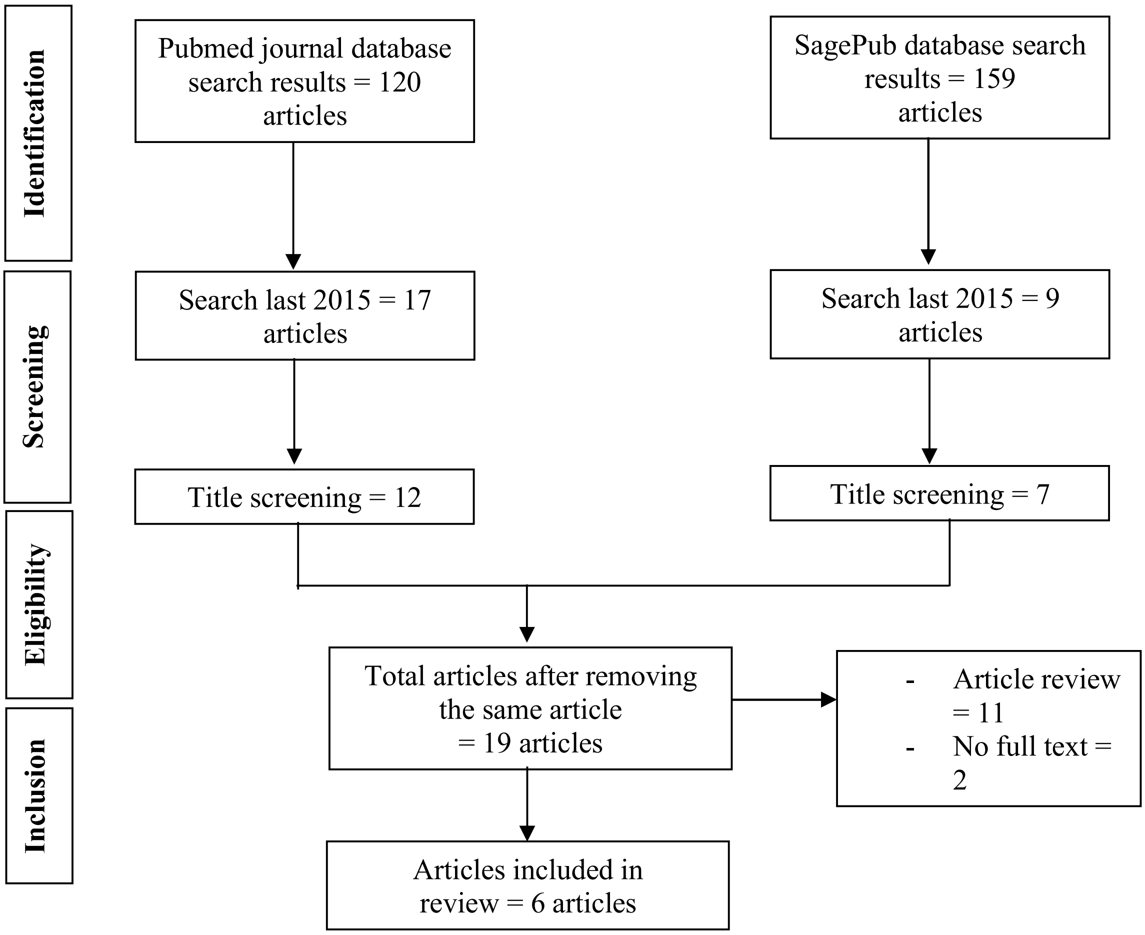

Figure 1. Article search flowchart

Data retrieval

The author of the study altered the criteria for what should be included in the study and what should not be included in the study after completing a literature search and reading the titles and abstracts of previously published studies. In the process of compiling the systematic review, consideration was given only to those research projects that were successful in fulfilling each and every one of the conditions. It is possible to gather information about each individual study in the form of a title, author, publication date, origin of study location, research study design, and research variables. This data is presented to you in a certain format for your review and consideration.

Quality Assessment and Data Synthesis

To determine which studies might be eligible for consideration, the authors conducted their own independent reviews of a selection of the studies found in the articles' titles and abstracts. Following this, the full texts of the studies that qualify for inclusion in the systematic review will be read in order to determine which studies can be used as final inclusions for the purpose of the review.

RESULT

Zhao, et al (2015)[14] showed the enhancement pattern parameters of Group 1 (<20 mm) tumors with those of Group 2 (>20 mm) tumors revealed statistically significant differences ($p < 0.001$). The differences between the two groups in enhancement degree, enhancement order, presence of penetrating vessels, and enhancement area expansion were not statistically significant ($p < 0.001$). Thus, small breast tumors exhibit homogeneous enhancement patterns, whereas larger tumors exhibit heterogeneous enhancement patterns.

Zhang, et al (2020)[15] conducted a study with 125 patients. They showed the sensitivity and specificity analysis, the Youden indexes for time to peak, wash-out time, and rising slope were 14.43, 149.76, and 10.55, while the corresponding sensitivities were 89.7, 85.6, and 72. Changes in the Youden index may provide imaging information for distinguishing malignant from benign breast lesions in the clinic as a tool for assessing authenticity. Notably, all three parameters had high sensitivities for diagnosing malignant breast lesions, suggesting that these three parameters may reflect angiogenesis within breast masses.

Luo, et al (2016)[16] showed CEUS-based BI-RADS review put 116/235 (49.36%) lesions into category 3, 20 (8.51%), 13 (5.53%), and 12 (5.11%) lesions into categories 4A, 4B, and 4C, respectively, and 74 (31.49%) lesions into category 5. When choosing CEUS-based BI-RADS group 4A as a good cut-off, the sensitivity and specificity for diagnosing a malignant disease were 85.4% and 87.8%, respectively. When CEUS-based BI-RADS 4A was used as the biopsy threshold, the cancer-to-biopsy yield was 73.11 percent, while it was only 40.85 percent when BI-RADS 4A was not used. The biopsy rate was only 42.13 percent, but it was 100 percent when BI-RADS 4A was not used. Overall, only 4.68 percent of cancers that spread were wrongly identified.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Zhao, 2015[14]	China	Retrospective study	133 suspicious malignant breast	Thus, tiny breast tumors have homogenous enhancement patterns, while larger tumours have heterogeneous enhancement patterns. Prognosis may be improved by correlating CEUS characteristics of different-sized breast tumors with prognostic variables.
Zhang, 2020[17]	China	Cross sectional study	125 female subjects	In the end, this study showed that the time-intensity curves (TIC) factors from contrast-enhanced ultrasound of breast lesions have a good chance of helping doctors tell the difference between malignant and harmless lesions. Time to peak, time to wash out, and rising slope may all help find malignant breast lesions, which could help with early treatment and the patient's outlook.
Luo, 2016[16]	China	Cross sectional study	235 solid breast lesions classified	Based on the findings of this pilot investigation, it appears that evaluating BI-RADS 4 breast lesions using CEUS resulted in lower biopsy rates and higher cancer-to-biopsy yields.
Park, 2019[18]	Republic of Korea	Cross sectional study	Ninety-eight breast masses	Microflow assessment using SMI and CEUS is valuable in distinguishing malignant from benign solid breast masses, with equivalent diagnostic performance. Furthermore, the additional use of SMI or CEUS on B-mode US can reduce unnecessary biopsy of benign masses without the loss of sensitivity.
Xiao, 2016[19]	China	Retrospective study	132 patients (with 132 breast lesions)	Monochrome superb microvascular imaging (mSMI) has the potential to improve blood flow detection while also depicting the microvascular architecture of breast lesions. There was not a significant difference between the diagnostic performance of mSMI and that of microvascular imaging (MVI). superb microvascular imaging has the potential to be useful in the diagnostic process for breast lesions.
He, 2023[20]	China	Retrospective study	26 patients	In comparison to the use of CEUS and shear wave elastography (SWE) on their own, combining the two procedures results in a higher diagnostic value when attempting to differentiate benign from malignant breast lesions.

Park, et al (2019)[18] study showed malignant masses were associated with a higher vascular index (15.1 ± 7.3 vs. 5.9 ± 5.6), complex vessel morphology (82.9% vs. 42.1%), central vascularity (95.1% vs. 59.6%), penetrating vessels (80.5% vs. 31.6%) on SMI (all, $p < 0.001$), as well as higher peak intensity (37.1 ± 25.7 vs. 17.0 ± 15.8, $p < 0.001$), slope (10.6 ± 11.2 vs. 3.9 ± 4.2, $p = 0.001$), area (1035.7 ± 726.9 vs. 458.2 ± 410.2, $p < 0.001$), hyperenhancement (95.1% vs. 70.2%, $p = 0.005$), centripetal enhancement (70.7% vs. 45.6%, $p = 0.023$), penetrating vessels (65.9% vs. 22.8%, $p < 0.001$), and perfusion defects (31.7% vs. 3.5%, $p < 0.001$) on CEUS ($p \leq 0.023$).

The areas under the receiver operating characteristic curve (AUCs) of SMI and CEUS were 0.853 and 0.841, respectively ($p = 0.803$). In 19 masses measuring < 10 mm, central vascularity on SMI was associated with malignancy (100% vs. 38.5%, $p = 0.018$). Considering all benign SMI parameters on the BI-RADS assessment, unnecessary biopsies could be avoided in 12 category 4A masses with improved AUCs (0.500 vs. 0.605, $p < 0.001$). US vascular parameters associated with malignancy showed higher MVD ($p \leq 0.016$). MVD was higher in malignant masses than in benign masses, and malignant masses negative for estrogen receptor or positive for Ki67 had higher MVD ($p < 0.05$).

Xiao, et al (2016)[19] showed mSMI was more sensitive in detecting blood flow signals in breast lesions than colour Doppler flow imaging (CDFI) ($p < 0.001$) and cSMI ($p < 0.001$). Differences of vessels inside breast lesions and morphologic features of vessels between benign and malignant lesions were statistically significant on mSMI ($p < 0.001$). Using root hair-like and crab claw-like patterns as the criteria for malignant lesions, the sensitivity, specificity and accuracy for differentiation based on the microvascular architecture patterns were 77.6, 90.5 and 84.8% for mSMI and 89.6, 87.8 and 88.6% for MVI. Areas under curve of mSMI and MVI were not significantly different (p = 0.129).

He, et al (2023)[20] The ages of the patients ranged anywhere from 23 years old to 76 years old, with a mean age of 42.5 years. The total number of breast lesions contained 19 benign lesions and 7 cancerous lesions. Emean + Imean and Emax + Emean + Imean of shell at 1.0 mm both had the highest area under the curve (AUC) of 0.86 (95% confidence interval [CI] = 0.67-0.96), with the sensitivity and specificity of 71.43% and 89.47%, respectively, for breast lesions, and SWE synchronized with CEUS can effectively improve the diagnostic performance of breast lesions.

DISCUSSION

Breast cancer is a group of abnormal cells in the breast that continue to grow in multiples. Eventually these cells form a lump in the breast. If the cancerous lump is not treated, the cancer cells can metastasize to other parts of the body. Metastases can occur in the axillary lymph nodes or above the scapula. In addition, cancer cells can nest in the bones, lungs, liver, skin and under the skin. Breast cancer is a malignancy of breast tissue which can originate from the ductal or lobule epithelium.[21,22]

Triple diagnostics in breast cancer is an effort made to help determine the malignancy of breast cancer when there are doubtful circumstances. Triple diagnostics carried out include physical examination, imaging examination, and cytological examination. If with this effort the diagnosis cannot be established, it is necessary to diagnose tissue pathology. The following conditions are indications for triple diagnostics: all solid tumors >35 years of age; all tumors questionable as benign at any age; and nipple discharge in the form of blood accompanied or without a tumor.[23,24]

Mammography and ultrasound are the two imaging modalities that are most important for diagnosing breast tumors. Contrast-enhanced magnetic resonance imaging (MRI) is utilized in situations in which ultrasound and mammography are unable to adequately diagnose breast cancer, in order to screen for hereditary breast cancer, and to map the size of the tumor both before to and during the administration of neoadjuvant treatment. The use of contrast-enhanced ultrasonography, also known as CEUS, has been suggested for use as an alternate imaging strategy because to the fact that the technology provides morphological in addition to functional information. In the evaluation, quantitative criteria drawn from the examination may be taken into account.[25]

One of the advantages of ultrasound is in detecting cystic masses. Similar to mammography, the American College of Radiology has also developed a standardized language for ultrasound reading and reporting according to BIRADS. The characteristics described were: shape of the mass, margins, orientation, type of posterior acoustic, lesion boundaries, and echo pattern.[23,24] It is common knowledge that microvasculature and microcirculation are distinctively different in benign and malignant breast cancers (references are required for this statement).[16]

This information can be provided via CEUS, which will enable us to better optimize the BI-RADS that have been assigned. Although we originally reviewed all lesions prior to CEUS and excluded those lesions reclassified as BI-RADS 3, there were still 116/235 (49.4%) lesions reclassified as BI-RADS 3 following CEUS in our study. This was despite the fact that we omitted those lesions that were reclassified as BI-RADS 3.[16]

Ultrasound images of lumps that must be suspected of being malignant include: uneven surface; taller than wider; hyperechoic edge; heterogeneous internal echo; vascularization increased, irregular and into the tumor at an angle of 90 degrees. The use of ultrasound in addition to mammography increases its accuracy to 7.4%. However, ultrasound is not recommended to be used as a screening modality because based on research it turns out that ultrasound has failed to show its efficacy.[24,26]

Using qualitative morphological features, Xiao et al.[19] compared the diagnostic efficacy of CEUS and SMI and found no difference between the two microflow imaging modalities (p = 0.129). Both qualitative and quantitative imaging parameters, which were more variable and specific, were utilized in the current investigation. In addition, we found that SMI and CEUS have comparable capabilities for distinguishing benign from malignant breast tumors. Considering that SMI is a convenient and noninvasive technique that does not require post-processing or contrast injection, we propose that SMI is a valuable alternative to CEUS for vascular imaging.

CONCLUSION

CEUS is an imaging technology that evaluates breast lesions by analyzing their qualitative qualities as well as their quantitative aspects. The detection of lymphatic channels and sentinel lymph nodes can be done using this method, and it is practical and effective.

REFERENCES

[1]. GLOBOCAN (IARC). Breast Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012. IARC World Health Organization. 2012.

[2]. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin.

2016;66(2):115–32.
[3]. Parada H, Sun X, Tse CK, et al. Lifestyle Patterns and Survival Following Breast Cancer in the Carolina Breast Cancer Study. Epidemiology. 2019;30(1):83–92.
[4]. Narod SA. Personalised medicine and population health: breast and ovarian cancer. Hum Genet. 2018;137(10):769–78.
[5]. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020 : GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. Vol. 71. 2021.
[6]. Kaminska M, Ciszewski T, Szatan KL, et al. Breast cancer risk factors. Prz Menopauzalny. 2015;14(3):196–202.
[7]. Corsetti V, Houssami N, Ferrari A, Ghirardi M, Bellarosa S, Angelini O, et al. Breast screening with ultrasound in women with mammography-negative dense breasts: evidence on incremental cancer detection and false positives, and associated cost. Eur J Cancer. 2008;44(4):539–44.
[8]. Thigpen D, Kappler A, Brem R. The Role of Ultrasound in Screening Dense Breasts-A Review of the Literature and Practical Solutions for Implementation. Diagnostics (Basel, Switzerland). 2018 Mar;8(1).
[9]. Lee SH, Chang JM, Kim WH, Bae MS, Cho N, Yi A, et al. Differentiation of benign from malignant solid breast masses: comparison of two-dimensional and three-dimensional shear-wave elastography. Eur Radiol. 2013;23:1015–26.
[10]. Wilson SR, Greenbaum LD, Goldberg BB. Contrast-enhanced ultrasound: what is the evidence and what are the obstacles? Am J Roentgenol. 2009;193(1):55–60.
[11]. Furlow B. Contrast-enhanced ultrasound. Radiol Technol. 2009;80(6):547S-561S.
[12]. Ricci P, Cantisani V, Ballesio L, Pagliara E, Sallusti E, Drudi FM, et al. Benign and malignant breast lesions: efficacy of real time contrast-enhanced ultrasound vs. magnetic resonance imaging. Ultraschall der Medizin-European J Ultrasound. 2007;28(01):57–62.
[13]. Forsberg F, Goldberg BB, Merritt CRB, Parker L, Maitino AJ, Palazzo JJ, et al. Diagnosing Breast Lesions With Contrast-Enhanced 3-Dimensional Power Doppler Imaging. J ultrasound Med. 2004;23(2):173–82.
[14]. Zhao L-X, Liu H, Wei Q, Xu G, Wu J, Xu H-X, et al. Contrast-Enhanced Ultrasonography Features of Breast Malignancies with Different Sizes: Correlation with Prognostic Factors. Corsi C, editor. Biomed Res Int [Internet]. 2015;2015:613831. Available from: https://doi.org/10.1155/2015/613831
[15]. Zhang Z, Wang R-K, Duan B, Cheng Z-G, Wang E, Guo Q-L, et al. Effects of a Preoperative Carbohydrate-Rich Drink Before Ambulatory Surgery: A Randomized Controlled, Double-Blinded Study. Med Sci Monit Int Med J Exp Clin Res. 2020 Aug;26:e922837.
[16]. Luo J, Chen J-D, Chen Q, Yue L-X, Zhou G, Lan C, et al. Contrast-enhanced ultrasound improved performance of breast imaging reporting and data system evaluation of critical breast lesions. World J Radiol. 2016;8(6):610.
[17]. Zhang Y, Zhang B, Fan X, Mao D. Clinical value and application of contrast-enhanced ultrasound in the differential diagnosis of malignant and benign breast lesions. Exp Ther Med [Internet]. 2020;20(3):2063–9. Available from: https://doi.org/10.3892/etm.2020.8895
[18]. Park AY, Kwon M, Woo OH, Cho KR, Park EK, Cha SH, et al. A prospective study on the value of ultrasound microflow assessment to distinguish malignant from benign solid breast masses: association between ultrasound parameters and histologic microvessel densities. Korean J Radiol. 2019;20(5):759–72.
[19]. Xiao X-Y, Chen X, Guan X-F, Wu H, Qin W, Luo B-M. Superb microvascular imaging in diagnosis of breast lesions: a comparative study with contrast-enhanced ultrasonographic microvascular imaging. Br J Radiol. 2016 Oct;89(1066):20160546.
[20]. He H, Wu X, Jiang M, Xu Z, Zhang X, Pan J, et al. Diagnostic accuracy of contrast-enhanced ultrasound synchronized with shear wave elastography in the differential diagnosis of benign and malignant breast lesions: a diagnostic test. Gland Surg. 2023 Jan;12(1):54–66.
[21]. De Vita Vt, Leeman S, Rosenberg SA. Principles and Practice of Oncology. Philadelphia: Lippincott Williams & Wilkins; 2004.
[22]. Horn L; Araujo L; Nana P; et al. Principles and Practice of Oncology. New York: McGraw-Hill Education; 2015.
[23]. Purwanto H, Handojo D, Hayono SJ, et al. Panduan Penatalaksanaan Kanker Payudara. Jakarta: Peraboi; 2014.
[24]. Peraboi. Panduan Penatalaksanaan Kanker. Jakarta: Peraboi; 2020.
[25]. Kristiansen MU, Martiniussen MA, Larsen ASF. Contrast-enhanced ultrasound of breast tumors: an initial experience. Acta Radiol Open [Internet]. 2022 Apr 1;11(4):20584601221097456. Available from: https://doi.org/10.1177/20584601221097458
[26]. Ahmadi N, Negahban S, Aledavood A, Daneshbod K, Daneshbod Y. Malignant adenomyoepithelioma of the breast: a review. Breast J. 2015;21(3):291–6.