Integrated Criteria of Fine-Needle Aspiration Cytology and Radiological Imaging for Verification of Breast Cancer in Nonpalpable Lesions

Pichet Sampatanukul MD, MSc*, Darunee Boonjunwetwat MD**,
Voranuch Thanakit MD*, Patcharajiree Pak-art MD**

** Departments of Pathology, Faculty of Medicine, Chulalongkorn University*
*** Departments of Radiology, Faculty of Medicine, Chulalongkorn University*

Objectives: *To evaluate the accuracy of using radiologic, cytologic and integrated radiologic and cytologic criteria in diagnosis of nonpalpable breast lesions.*
Material and Method: *From January 2003 to May 2004, a prospective study of performing fine-needle aspiration biopsy (FNAB) was carried out at King Chulalongkorn Memorial Hospital on female patients with nonpalpable or vaguely palpable lumps that needed ultrasound localization for the direction and depth.*
Results: *There were 162 lesions from 150 patients, consisting of 29 malignant neoplasms (17.9%) and 133 benign lesions (82.1%). Of the 107 classified as subcentimeter focal lesions (< 1 x 1 cm^2 in size), two of radiological malignancy were false and two others were falsely negative by cytology. While the 23 large/ill-defined lesions (> 1.5 x 1.5 cm^2 in size), one hiding malignant lesion adjacent to a prominent intraduct papilloma was missed. Two others had falsely negative cytologic diagnosis. The integrated criteria achieved accuracy and sensitivity of 97.5% and 93% compared with the cytology, 96.3% and 82.8% and the better scenario of radiology, 95.7% and 82.8% respectively.*
Conclusion: *The integrated criteria provide the most accuracy rate and sensitivity rate for detection of malignancy in nonpalpable breast lesions.*

Keywords: *FNA, Cytology, Breast, Imaging, Nonpalpable, Impalpable*

J Med Assoc Thai 2006; 89 (2): 236-41
Full text. e-Journal: *http://www.medassocthai.org/journal*

The detection of carcinoma in nonpalpable lesions of the breasts by ultrasound-guided fine-needle aspiration biopsy (US-FNAB) has the merit of simplicity, low cost and rare complications; however, it requires skilled medical staff and appropriate diagnostic criteria. According to the authors' prior retrospective study[1], the cytology had a modest sensitivity and an excellent specificity while the ultrasonography elicited a good sensitivity but a suboptimal degree of specificity. When malignant cytologic and imaging criteria were combined, it could achieve 100% accuracy. The authors, therefore, propose that pathologists and radiologists work together and use integrated criteria for management of abnormal imaging lesions that are nonpalpable or vaguely palpable. The present prospective study aimed to evaluate the accuracy of the proposed integrated radiologic and cytologic criteria comparing with separate radiologic and cytologic criteria.

Correspondence to : Sampatanukul P, Departments of Pathology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. Fax 0-2652-4208, E-mail: fmedpst@md2.md.chula.ac.th

Material and Method

The patients and procedure

From January 2003 to May 2004, the patients referred to our diagnostic unit at King Chulalongkorn Memorial Hospital for US-FNAB of nonpalpable/vaguelypalpable breast lesions were included. The aspiration biopsy employed the so-called "indirect technique". The ultrasound was used to mark a point on the skin that was perpendicular to the breast lesion. The distance from the skin to the center of the lesion

was measured. Asking the patient to keep the same position, the author (PS) performed aspiration biopsy using a gauge 22 needle attached to a 10-ml syringe by advancing the needle perpendicularly into the lesion. The usual procedure of aspiration biopsy was operated. Under negative pressure that was created in the syringe, the needle was moved like a screw and jerk inside the lesion. Then negative pressure was released before taking the needle out. Two to three passes were performed to ensure that the needle hit the target. Post-biopsy ultrasound were done to check signals of needling. Cytologic smears were prepared as wet-fixation and stained according to Papanicolaou staining protocol.

The image reporting

The records were on the agreement of two radiologists. The breast imaging reporting and data system (BI-RADS™), version1993 was used[2]. The categories were as follows.

BI-RADS1 meant normal or no lesion. BI-RADS2 defined lesions that were not doubtful for malignancy. BI-RADS3 or indeterminate was for lesions that were likely benign but follow-up imaging to see the stability of the lesions was needed. BI-RADS4 was defined as suspicious and BI-RADS5 was for highly suspicious malignant lesions.

The cytology reporting

The cytologic diagnosis was categorized at the time of review by two pathologists according to the Cytologic Category Code system[3]. Code 1 meant no cell or scanty cells on the smear. Code 2 was defined as presence of substantial number of benign cells on the smear. Code 3 was for atypical cells that were inconclusive. Code 4 represented suspicious cells of malignancy and Code 5 was malignancy.

The proposed integrated criteria

The integrated criteria were as follows. Positive test included Cytologic Code 5 in any BI-RADS categories and BI-RADS 5 without cytologically inflammatory feature. Negative test meant the others, which also included the scanty cellularity (Cytologic Code 1).

Final diagnosis criteria

All patients were followed up by ultrasound for a 6-month interval for at least 1 year except for those who had operations. The final diagnoses were based on surgical pathology and/or follow-up with triple assessment (clinical, imaging and cytologic findings).

Results

There were 150 patients with 162 lesions. The

Table 1. Frequencies of BI-RADS and Cytologic Code categories according to subgroups

SUBGROUP	Number of lesions	BI-RADS			Cyto Code				
		B3	B4	B5	C1	C2	C3	C4	C5
Focal	107	62 (62/0)	35 (34/1)	10 (2/8)	61 (59/2)	38 (38/0)	0	1 (1/0)	7 (0/7)
Small	32	15 (13/0)	10 (9/0)	7 (0/7)	15 (15/0)	10 (10/0)	0	1 (0/1)	6 (0/6)
Large + Ill-defined	23	3 (2/1)	11 (8/3)	9 (0/9)	7 (7/0)	5 (3/2)	1 (0/1)	0	10 (0/10)

Note: B3, B4, B5 = BI-RADS 3, 4, 5 respectively; C1, C2, C3, C4, C5 = Cytologic Codes 1, 2, 3, 4, 5 respectively; The figures in parenthesis (x / y) represent (benign / malignant)

Table 2. Comparison of characters and diagnostic performance among the three subgroups

SUBGROUP	Depth (cm) median	Area (cm^2) mean	PPV B5	PPV B4	PPV B3	%FNC1,C2	%C1 rate
Focal	1.2	0.48	80	2.9	0.0	3.0	61.2
Small	1.3	1.42	100	0.0	0.0	0.0	60.0
Large + Ill-defined	1.8	3.68	100	27.3	33.3	16.7	70.0

Note: PPV = Positive predictive value, FN = False negative, %C1 rate = Percentage of scant cellularity smears in benign cases, B5, B4, B3, C1, C2 = BI-RADS 5, 4, 3 and Cytologic Codes 1, 2, respectively

average age was 49 years old (range, 22-80 years). The lesions were classified into 3 categories according to the lesion sizes (Table 1). Subgroup of focal or sub-centimeter lesions, 107 lesions, was defined as a lesion size less than 1 x 1 cm^2 (the area < 1 cm^2). Subgroup of small mass lesions, 32 lesions, had a lesion size in the range from 1 x 1 cm^2 to 1.5 x 1.5 cm^2 (the area ranged from 1 cm^2 to 2.25 cm^2). The subgroup of large/ill-defined masses included large mass lesions and ill-defined lesions that comprised an area larger than 1.5 x 1.5 cm^2 (the area > 2.25 cm^2) had 23 lesions. The focal lesion subgroup was comprised of 2 falsely positive diagnoses of BI-RADS5 and 2 cases of falsely negative diagnosis by cytology. The two falsely positive cases were revealed in the wide-excision specimens, atypical ductal hyperplasia and sclerosing adenosis. Both cases of cytologically false negative belonged to Cytologic Code 1 category. The small mass lesion subgroup had no false positive or false negative in either radiology or cytology. All of the seven malignant tumors were classified as BI-RADS 5 whereas six of them were Cytologic Code 5 and one was Cytologic Code 4. The subgroup of large mass/ill-defined lesions consisted of one case with falsely negative radiology and cytology due to the hiding carcinoma adjacent to an intraductal papilloma. The US-FNAB had targeted the papilloma. In addition, two missed carcinoma cases by US-FNAB existed. These two cases showed Cytologic Code 2. The average depths and areas of the three subgroups as well as positive predictive values of BI-RADS 3, 4 and 5 are illustrated in Table 2. The percentage of falsely negative lesions by cytology was calculated for the focal, small and large/ill-defined subgroups at 3%, 0% and 16.7% respectively. Scanty cellularity smears or Cytologic Code-1 smears were present in 60%, 61% and 70% of the benign lesions of the three subgroups respectively. The Cytologic Code-1 appeared in BI-RADS 3, 4 and 5 in 60% (48 out of 80), 62.5% (35 out of 56) and 3.8% (1 out of 26) respectively (Table 3).

The final diagnoses were based on surgical biopsy and radical operation in 72 out of 162 lesions (45.5%) and clinical and imaging follow-up for more than one year in 90 out of 162 lesions (55.5%). Table 4 reveals two options of calculation for the diagnostic performance of radiologic criterion. Option One, which counted BI-RADS 4 and 5 as malignant, disclosed the sensitivity of 96.5% and the accuracy of 66%. Option Two that counted only BI-RADS 5 as malignant exhibited the sensitivity of 82.8% and the accuracy of 95.7%. Table 5 illustrates the calculation of diagnostic

Table 3. Correlation of BI-RADS and Cyto Code

BI-RADS	Cyto Code					Total
	C1	C2	C3	C4	C5	
3	48	32	0	0	0	80
4	35	18	0	0	3	56
5	1	2	1	2	20	26
Total	84	52	1	2	23	162

Table 4. Diagnostic performance according to radiological criteria

Option One: Both BI-RADS 4 and 5 are malignant

	Malignant	Benign	Total
BI-RADS 4 + 5	28	54	82
BI-RADS 3	1	79	80
	29	133	162

Sensitivity = 96.5%
Specificity = 59.4%
Accuracy = 66.0%

Option Two: Only BI-RADS 5 is malignant

	Malignant	Benign	Total
BI-RADS5	24	2	26
BI-RADS3 + 4	5	131	136
	29	133	162

Sensitivity = 82.8%
Specificity = 98.5%
Accuracy = 95.7%

Table 5. Diagnostic performance according to cytological criteria

	Malignant	Benign	Total
C4 + 5	24	1	25
C1 + 2 + 3	5	132	137
	29	133	162

Sensitivity = 82.8%
Specificity = 99.2%
Accuracy = 96.3%

Table 6. Diagnostic performance according to integrated criteria

	Malignant	Benign	Total
C5 and/orB5 wo inflam	27	2	29
The others	2	131	133
	29	133	162

Sensitivity = 93.1%
Specificity = 98.5%
Accuracy = 97.5%

Note: C5 = Cytological Code 5, B5 wo inflam = BI-RADS 5 without cytologic inflammation feature

performance based on cytological criterion. Cytologic Codes 4 and 5 were grouped as malignant while the others were benign. The sensitivity and accuracy for cytology criterion were 82.8% and 96.3% respectively. Table 6 demonstrates the calculation of diagnostic performance using integrated criteria. The sensitivity and accuracy were 93% and 97.5% respectively.

Discussion

The word "nonpalpable" or "impalpable" is not defined by lesion size. Any masses in superficial location can be palpated and small masses in deep areas are hardly palpable. A lump, which is not really small, sometimes can be vaguely felt if it is situated deep. Some ill-defined palpable lesions are tissue reactions, not masses. In the literature, a study from three different centers in the Netherlands showed the mean and standard deviation of lesion sizes that were measured by ultrasound from 1.09 ± 0.53 cm, 1.30 ± 1.03 cm to 1.63 ± 1.27 cm[4]. The lesion size appeared in a study from Kentucky University varied from 0.6 to 3 cm[5]. The present study has divided the size of the lesions according to the ultrasound into three subgroups using 1 cm^2 and 2.25 cm^2 as cutoff. This subgroup classification can demonstrate the trend of larger lesions that are non-palpable or vaguely palpable being seated deeper than smaller lesions. The mean distance from the skin to the center of the large/ill-defined masses is 1.8 cm compared with 1.2 cm and 1.3 cm of the focal subcentimeter lesions and small masses respectively. On this regard, the authors define nonpalpable breast lesions herein are lesions that need imaging guidance to direct the needles on doing fine-needle aspiration biopsy.

The technique of guidance and biopsy used in the present study is a freehand technique. The authors prefer the perpendicular direction to the skin to avoid the inaccurate angle adjustment and to perform the shortest distance of needling. It is called "indirect" method because it is not performed with a needle guide attached to the transducer that can guarantee that the needle is inserted within the scan plane[6]. After the biopsy, post-biopsy signals can be checked. This "indirect" method is simply and less time consuming comparing with the "direct" method. Both methods are used in our current practice.

The imaging interpretation is important for the management of nonpalpable breast lesions. BI-RADS 1 and 2 do not require intervention. BI-RADS 3 usually recommended a 6-month interval follow-up[2]. Nevertheless, an alternative way is to perform US-FNAB. There are less than 2% of BI-RADS 3 to be malignant [2]. In the present study, all but one case was benign. The missed-call case, falls in the large mass subgroup, is caused by the hiding tumor that is located adjacent to the intraduct papilloma that has drawn the attention. The positive predictive value for BI-RADS 3 is compromised in the large lesion subgroup that is 33.3% compared with 0% in the subcentimeter focal and small mass subgroups. The BI-RADS 4, though it is called suspicious for malignancy, has a positive predictive value for subcentimeter focal lesions, small lesions and large/ill-defined lesions in only 2.9%, 0% and 27.3% respectively. The authors' findings support the recent version of ACR BI-RADS to further classify BI-RADS 4 into subcategories of 4a, 4b and 4c [7]. This can help to make BI-RADS 4c more predictive of malignancy. The authors have used two scenarios for the assessment of accuracy for radiologic criteria. The "only BI-RADS 5 is malignant" option gives much better accuracy. The BI-RADS 5 is a strong predictor of malignancy and is true in the authors' work. Its positive prediction is 100% for the small and large/ill-defined subgroups. However, its prediction is 80% in the subcentimeter focal lesions due to sclerosing adenosis in one case and atypical ductal hyperplasia in another case. Therefore, lesion sizes have influences on the prediction of BI-RADS.

In general, cell yields from benign lesions, particularly small benign conditions, are scanty. The number is usually less than 6 clusters of epithelium and is classified as Cytologic Code 1 (C1). In this study, C1 rate is 60-70% for benign lesions among the three subgroups. Cytology by itself is considered inadequate in a large number of cases which will make US-FNAB inappropriate for evaluation of nonpalpable lesions[8]. But in this concept of integrated criteria, the

scanty cellularity will be interpreted in conjunction with radiological imaging. Therefore, it is not judged as inadequate in this sense. It is mandatory to determine if the needle tip is placed within the lesion during the aspiration biopsy. The authors' new device is now underway[9]. The sensitivity of cytology has shown much improvement in this study compared with the previous one[1]. The present figure, 82.8%, is within the range of published studies that is between 82% and 100%[10]. This may be contributory to more experience of the medical team.

The rationale of integrated criteria is that the breast imaging and cytology is not perfect by oneself. The breast imaging has some limitation on the specificity particularly when the lesions are inflammatory or small. The cytology has the two major drawbacks that are insufficiency rate and the need of experienced cytopathologists. The spring-loaded, core-needle biopsy gun has dominated the usage of fine-needle aspiration in several centers in the United States[11], however, it is higher cost and the inability to be available nationwide makes it unsuitable here. The concept of pathologist and radiologist working together and the integrated criteria will make the FNA cytology reliably to use and achieve its optimal management for nonpalpable lesions like the practice in Sweden[12]. In the present study, with the combined breast imaging and cytology, the authors can save 55.5% of 162 lesions from surgical excision. Of the 72 lesions that received surgery, 29 lesions (40.3%) were proved malignant. The authors anticipate that with the improvement of the novel device and experience, the management scheme can be adopted by other institutions. Among the 3 subgroups of non-palpable lesions, the subcentimeter focal lesions are the most challenging. Due to the small size, the lobulated contour is not fully appreciated and that can be the source of worrying on imaging. According to the recent breast imaging survey, we have approximately 500 cases of subcentimeter focal lesions per year[13]. With the authors implementing this working scheme, such a large number of cases will be manageable.

Acknowledgement

This work was supported by a grant from the National Research Council of Thailand.

References

1. Sampatanukul P, Boonjunwetwat D, Pak-art P. Role of combined fine needle aspiration and ultrasonography in the diagnosis of impalpable lesions of the breast. J Med Assoc Thai 2003; 86(Suppl 2): S284-90.
2. American College of Radiology. Breast imaging reporting and data system (BI-RADS). Reston, VA: American College of Radiology; 1993.
3. The uniform approach to breast fine needle aspiration biopsy. A synopsis. Acta Cytol 1996; 40: 1120-6.
4. Pijnappel RM, van den Donk M, Holland R, Mali WP, Peterse JL, Hendriks JH, et al. Diagnostic accuracy for different strategies of image-guided breast intervention in cases of nonpalpable breast lesions. Br J Cancer 2004; 90: 595-600.
5. Liao J, Davey DD, Warren G, Davis J, Moore AR, Samayoa LM. Ultrasound-guided fine-needle aspiration biopsy remains a valid approach in the evaluation of nonpalpable breast lesions. Diagn Cytopathol 2004; 30: 325-31.
6. Fornage BD. Ultrasound-guided percutaneous needle biopsy of nonpalpable breast masses. In: Singletary SE, Robb GL, editors. Advanced therapy of breast disease. Hamilton: B.C.Decker; 2000: 99-111.
7. American College of Radiology (ACR). Breast imaging reporting and data system (BI-RADS™). 3rd ed. Reston, VA: American College of Radiology; 1998.
8. Pisano ED, Fajardo LL, Tsimikas J, Sneige N, Frable WJ, Gatsonis CA, et al. Rate of insufficient samples for fine-needle aspiration for nonpalpable breast lesions in a multicenter clinical trail: The Radiologic Diagnostic Oncology Group 5 Study. The RDOG5 investigators. Cancer 1998; 82: 679-88.
9. Sampatanukul P, Tansatit T, Boonjunwetwat D, Pak-art P. Chula Aspirator: a newly invented instrument to facilitate FNA biopsy of nonpalpable breast lesions. Poster Presentation No.1. The 2nd Asian Breast Diseases Association Teaching Course 2004. http://www.abda2004.com
10. Masood S. Fine needle aspiration biopsy of nonpalpable breast lesions. In: Schmidt W, ed. Cytopathology annual 1993. Baltimore: Williams & Wilkins, 1994: 33-63.
11. Venta LA. Image-guided biopsy of nonpalpable breast lesions. In: Harris JR, Lippman ME, Morrow M, Osborne CK eds. Diseases of the breast 3rd edition. Philadelphia: Lippincott Williams & Wilkins 2004: 199-219.
12. Azavedo E, Svane G, Auer G. Stereotactic fine needle biopsy in 2594 mammogrphically detected nonpalpable lesions. Lancet 1989; 1(8646): 1033-6.
13. Pak-art P, Bunjunwetwat D, Vajragupta L, Amorn-

rattanapaijit W, Vajarapongse K, Sampatanukul P, et al. Abnormal findings in breast imaging: a hospital-based survey in 4264 Thai women. J Med Assoc Thai 2004; 87(Suppl 2): S179-84.

หลักเกณฑ์ร่วมของเซลล์วิทยาของการเจาะดูดและเงาภาพรังสีวิทยาเพื่อยืนยันการวินิจฉัยมะเร็งเต้านมในรอยโรคที่คลำไม่ได้

พิเชฐ สัมปทานุกุล, ดรุณี บุญยืนเวทวัฒน์, วรนุช ธนากิจ, พัชราจิรี ภาคอรรถ

วัตถุประสงค์: *เพื่อศึกษาความถูกต้องของการแปลผลทางรังสีวิทยา เซลล์วิทยา และการวินิจฉัยร่วมโดยทั้งสองวิธีในการวินิจฉัยรอยโรคเต้านมที่คลำไม่ได้*

วัสดุและวิธีการ: *ระยะเวลาตั้งแต่ มกราคม พ.ศ. 2546 ถึง พฤษภาคม พ.ศ. 2547 ผู้วิจัยได้ศึกษาการเจาะดูดรอยโรคด้วยเข็มขนาดเล็กสำหรับตรวจก้อนที่คลำไม่ได้หรือคลำไม่ชัดเจนในผู้ป่วยสตรี ซึ่งการเจาะดูดจำเป็นต้องใช้คลื่นความถี่สูงช่วยบอกทิศทางและตำแหน่งในการแทงของเข็ม ที่โรงพยาบาลจุฬาลงกรณ์ โดยใช้รูปแบบการวิจัยแบบศึกษาไปข้างหน้า*

ผลการศึกษา: *มีรอยโรคที่ทำการศึกษาทั้งสิ้น 162 รอยโรคจากผู้ป่วย 150 คน ประกอบด้วยรอยโรคมะเร็ง 29 ราย (ร้อยละ 17.9) รอยโรคไม่ใช่มะเร็งจำนวน 133 รอยโรค (ร้อยละ 82.1) กลุ่มรอยโรคขนาดพื้นที่เล็กกว่า 1 ตารางเซนติเมตร มีจำนวน 107 รอยโรค มีผลบวกลวงของลักษณะทางรังสีวิทยา 2 ราย และผลลบลวงในการเจาะดูดไม่ได้เซลล์มะเร็ง 2 ราย ขณะที่ กลุ่มรอยโรคขนาดพื้นที่มากกว่า 2.25 ตารางเซนติเมตร และรอยโรคที่มีขอบเขตคลุมเครือวัดพื้นที่ไม่ได้ มีจำนวน 23 รอยโรค พบมะเร็งแฝงอยู่บริเวณใกล้เคียงกับก้อน intraduct papilloma ทำให้พลาด 1 ราย และผลลบลวงโดยเซลล์วิทยาอีก 2 ราย การใช้หลักเกณฑ์ร่วม ให้ความถูกต้องและความไวของการทดสอบที่ร้อยละ 97.5 และ 93, เปรียบเทียบกับการวินิจฉัยโดยหลักเกณฑ์เซลล์วิทยา ที่ร้อยละ 96.3 และ 82.8, และโดยหลักเกณฑ์รังสีวิทยาที่ให้ผลจำเพาะสูง ที่ร้อยละ95.7 และ 82.8 ตามลำดับ*

สรุป: *การใช้หลักเกณฑ์ร่วม เพื่อยืนยันการวินิจฉัยมะเร็งเต้านมในรอยโรคที่คลำไม่ได้ ให้ร้อยละของความถูกต้องและความไวของการทดสอบดีที่สุด*