Predictive Factors for Upgrading to Breast Cancer of Atypical Ductal Hyperplasia on Core Needle Biopsy in Thai Population

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Background: *Atypical ductal hyperplasia (ADH) is a proliferative lesion of the breast that expresses some features of carcinoma in situ. This lesion is associated with increased risk of breast cancer. Surgical excision is usually performed in the patients with ADH diagnosed by core biopsy (CNBx) due to discordance of the diagnosis. However, only small portion of the patients had carcinoma in situ or invasive carcinoma.*
Objective: *To identify parameters that can predict the upgrading from ADH on CNBx to malignancy on subsequent surgical excision.*
Material and Method: *Clinicopathological data of the patients with ADH diagnosed by CNBx who were underwent surgical excision at Siriraj Hospital from January 2010 to June 2015 was reviewed. Correlations between clinicopathological parameters and histopathologic results of both CNBx and surgical excision were determined by Chi-square statistics.*
Results: *Total 86 cases were diagnosed as ADH on CNBx then followed by surgical excision. Seventeen (19.8%) patients were subsequently upgraded to malignancy. Thirteen (15.1%) patients had ductal carcinoma in situ (DCIS) and 4 (4.7%) patients had invasive ductal carcinoma. Univariate analysis revealed that palpable mass, irregular margin of the mass and multifocality were associated with upgrading to malignancy. Multivariate analysis showed that palpable mass was the independent predictor of upgrading to malignancy.*
Conclusion: *Presentation with palpable mass was an independent factor for upgrading to malignancy and should be an indication for surgical excision of ADH diagnosed by CNBx.*

Keywords: *Breast cancer, Atypical ductal hyperplasia, Core biopsy*

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Atypical ductal hyperplasia (ADH) is proliferative lesion which associated with 4-5 times increased risk of subsequent development of breast cancer. ADH is histologically defined as either a hyperplastic lesion with some cytological features of low-grade ductal carcinoma in situ (DCIS) that does not fill the entire duct or lack of the overall characteristic architectural growth pattern; or a lesion with classic cytological and architectural features of low-grade DCIS measuring 2 to 3 mm[1,2].

In the presence of inadequate CNBx specimen or missed lesion, misdiagnosis would be occurred. The incidence of upstaging from ADH diagnosed by core needle biopsy (CNBx) to DCIS or invasive carcinoma diagnosed by subsequent surgical excision was varied from 4 to 87%[3-10]. Therefore, subsequent surgical excision is generally recommended when ADH is diagnosed by CNBx. However, not all of ADH had been upgraded to malignancy after excision due to variation of pathology, mammography or CNBx[3,5,7,11]. The predictive factors varied among different studies such as clinical and mammographic findings, CNBx methods, and the diversity of population, that resulted in different prevalence[3,5-9,11,13,14]. Furthermore, there were still in conclusive agreement to omit surgical excision. Some researchers proposed that in low risk patients, excision could be exempted and follow-up with mammography and ultrasonography would be sufficient[3,4,9,12-14]. The objective of this study was to identify predictive factors for the upgrading from ADH diagnosed by CNBx to

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breast cancer (DCIS and/or invasive carcinoma) in Thai breast cancer patients.

Material and Method

The patients were enrolled from the Division of Head Neck and Breast Surgery, Department of Surgery, Siriraj Hospital, Mahidol University from January 2010 to December 2015. The patients who were diagnosed ADH on CNBx and then underwent subsequent surgical excision were recruited. The patients with mammographic data, CNBx or excision from other hospital were excluded.

All patients underwent clinical and radiological examination, including mammography and ultrasonography. Clinical data was obtained from medical records including age at diagnosis, weight, height, previous hormonal use, menopausal status, family history of breast cancer and clinical presentation (breast symptoms such as nipple discharge, pain, itching). The radiological appearance of the lesion was categorized according to the Breast Imaging-Reporting And Data System (BI-RADS) classification. Mammographic characteristics (microcalcification, mass, density, distortion) were reported. All lesions were evaluated for size, shape, margin and location on imaging and presence of microcalcification. All CNBx was performed using 14-gauge needle with ultrasonographic or stereotactic guidance. The number, length, and diameter of CNBx were recorded.

CNBx and surgical specimens were fixed in 10% formaldehyde and embedded in paraffin. Each biopsy specimen was stained with hematoxylin and eosin according to standard protocol. Co-existing associated diagnosis of intraductal papilloma and sclerosing adenosis on CNBx and surgical specimens were recorded.The biopsy slides were diagnosed according to the ADH diagnostic criteria of the World Health Organization guidelines. Any discrepancy finding was discussed before making final diagnosis. Histological diagnoses at surgical excision were classified as benign (non-upgrading) or malignant (upgrading). Any residual ADH or other benign lesion was classified as benign (non-upgrading), whereas DCIS or invasive carcinoma were classified as malignant (upgrading).

Descriptive statistics were used to present characteristics of the patients. The data was analyzed using Chi-square or Fisher exact test for categorical parameters and Student t-tests for continuous parameters. The *p*-values of <0.05 were considered statistically significant. Binary logistic regression was performed for multivariate analyses. Statistical analyses were performed using SPSS Version 16.0 (IBM Corporation, Armonk, New York, USA).

Results

Total 86 patients were diagnosed ADH on CNBx then underwent surgical excision at our institution. Of the 86 patients, 17 (19.8%) were subsequently upgraded to malignancy after surgical excision. Amongst the malignant cases, the histological results revealed that 13 (15.1%) patients had DCIS and 4 (4.7%) patients had invasive carcinoma. Demographic data of the patients was summarized in Table 1.

The average age at diagnosis was 49.8 years, ranging from 37 to 71 years. Seventy-seven patients (89.5%) had no history of hormonal usage and 79.1% had no family history of breast cancer. Most of the patients (91.9%) were examined in a breast cancer screening context. Some of the patients (18.6%) had multifoci lesion (more than one suspicious lesions in different quadrant of the breast). Most of the lesions (70.9%) were in upper outer quadrant while other quadrants accounted for approximately 9 to 10%. All imaging results were in BIRADS category 4. Only 5.8% of the patients were classified in BIRADS 4C. Most of CNBx (79.1%) was performed by stereotactic guidance due to presence of microcalcification without visualized mass by ultrasonography. ADH was diagnosed alone in 82.6% of cases and co-diagnosed with intraductal papillary lesion, sclerosing adenosis in 9.3% and 8.1% of cases, respectively.

Univariate analysis revealed that presence of palpable breast mass, irregular margin mass detected by ultrasonography, multifoci lesion, and BIRADS category 4C were associated with upgrading to malignancy in subsequent surgical excision. Seven patients who were presented with breast symptoms. Two of them had no upgrading (28.5%) and 5 of them had upgrading (71.4%). The patients without symptom and presented with screening detected lesion were non-upgrading in 67 cases (84.8%) and upgrading in 12 cases (15.2%). The shape and margin of detectable mass from ultrasonography were related to upgrading. Irregular margin were found in 14 cases, of which, 7 cases were upgraded (50%). Multifoci lesion was also associated with upgrading. It accounted for 37.5% of upgrading (6 cases). Five patients were categorized in BIRADS 4C and 4 of them were upgraded (80%). Multivariate analysis showed that only palpable mass was the independent predictor of upgrading to malignancy (Table 2).

Table 1. Demographic data and characteristics of the patients

Characteristics	Frequency (%)
Age	
≤50	48 (55.8)
>50	38 (44.2)
BMI	
≤23	54 (62.8)
>23	32 (37.2)
Previous hormonal use	
No	77 (89.5)
Yes	9 (10.5)
Menopause	
No	52 (60.5)
Yes	34 (39.5)
Family history of breast cancer	
No	68 (79.1)
Yes	18 (20.9)
Presentation	
Screening detected	79 (91.9)
Mass, symptoms	7 (8.1)
Multifoci lesion	
No	70 (81.4)
Yes	16 (18.6)
Location	
Upper outer	61 (70.9)
Upper inner	8 (9.3)
Lower outer	9 (10.5)
Lower inner	8 (9.3)
BIRADS	
4A	36 (41.9)
4B	45 (52.3)
4C	5 (5.8)
CNBx modality	
Stereotactic guided	68 (79.1)
Ultrasound guided	18 (11.9)
Co-diagnosis in CNBx	
No	71 (82.6)
Intraductal papillary lesion	8 (9.3)
Sclerosing adenosis	7 (8.1)

Discussion

The authors identified four predictive factors for upgrading to malignancy of ADH, including presentation with breast mass, irregular margin mass in ultrasonographic findings, multifoci lesions, and BIRADS 4C. Presentation with palpable breast mass was the independent factor that associated with upgrading to malignancy on subsequent surgical excision.

The rate of upgrading to malignancy in this study was within the reported range[3,5,6,8,9,11]. Several factors were reported to be associated with upgrading to malignancy of ADH on subsequent surgical excision[3-5,7,9-11,15-19].

In the current study, all of the patients were classified into BIRADS 4 category. The patients in BIRADS 3 and 5 category were not included due to the rate of malignancy of BIRADS 3 in our institution was 0.4%, so there was no indication to perform CNBx in the women who were classified into BIRADS 3 and all of CNBx results from the patients in BIRADS 5 category were malignancy. However, some studies included the patients in BIRADS 3 and 5 category into the analysis[8,9]. This might be due to the inconsistency of radiologist and pathologist among different institutes. Similar study in Thailand by Wiratkapun et al in 2005 revealed that the rate of upgrading to malignancy was 20.5%, comparable to the current study. The authors also demonstrated that the lesion classified as BIRADS 5 was the only factor that indicate the upgrading[20]. Difference in imaging technique and resolution according to different period of the studies might contribute to the discrepancy.

Ko et al identified palpable lesion as one of independent predictors of malignancy[9]. The authors also proposed scoring system to predict malignancy in the patients with ADH diagnosed by ultrasound-guided CNBx. The score was based on five factors, composed of age, palpable lesion, microcalcification on mammography, size by imaging and focal ADH. However, this scoring system was developed in ultrasound-guided CNBx setting and in limited number of patients. A study by Khoury et al identified similar factors including age, microcalcification in ADH, presence of mass on imaging, number of foci, and size of the lesion which correlated with upgrading[8]. The authors also developed a nomogram to predict the likelihood for upgrading. However, there was no data to predict the risk of subsequent breast cancer if ADH is left without surgical excision.

Deshaies et al identified six factors including mammography for ipsilateral symptoms, mammographic lesions other than microcalcifications alone, severe ADH, co-diagnosis of papilloma, use of 14-gauge needle, and ADH diagnosis performed by pathologists with low volume. The authors also suggested that ipsilateral breast symptoms (nipple discharge, pain, and itching) may be an indication of more serious disease[6]. In some studies, the size of CNBx device was related to upgrading as described by factors affecting the accuracy of CNBx. A review by Jackman et al suggested a more modest underestimation rate of 10 to 38% for an

Table 2. Characteristics of the patients according to upgrading status

Characteristics	Non-upgrading	Upgrading	*p*-value
Age			
≤50	41 (85.4)	7 (14.5)	0.175
>50	28 (73.7)	10 (26.3)	
BMI			
≤23	45 (83.3)	9 (16.7)	0.348
>23	24 (75.0)	8 (25.0)	
Previous hormonal use			
No	62 (80.5)	15 (19.5)	0.845
Yes	7 (77.8)	2 (22.2)	
Menopause			
No	44 (84.6)	8 (15.4)	0.207
Yes	25 (73.5)	9 (26.5)	
Presentation			
Screening detected	67 (84.8)	12 (15.2)	0.002
Mass, Symptoms	2 (28.5)	5 (71.4)	
Imaging findings			
Round/oval mass(US)	20 (83.3)	4 (16.7)	0.029
Irregular margin mass (US)	7 (50.0)	7 (50.0)	
Calcification detected by MMG without visualized mass by US	27 (71.0)	11 (29.0)	
Multifoci lesion			
No	59 (84.3)	11 (15.7)	0.048
Yes	10 (62.5)	6 (37.5)	
Location			
Upper outer	50 (75.7)	11 (24.3)	0.519
Upper inner	5 (62.5)	3 (27.5)	
Lower outer	8 (88.9)	1 (11.1)	
Lower inner	6 (75.0)	2 (25.0)	
BIRADS			
4A	31 (86.1)	5 (13.9)	0.002
4B	37 (82.2)	8 (17.8)	
4C	1 (20.0)	4 (80.0)	
CNBx modality			
Stereotactic guided	54 (79.4)	14 (20.6)	0.851
Ultrasound guided	14 (82.4)	3 (17.6)	
Co-diagnosis in CNBx			
No	59 (83.1)	12 (16.9)	0.317
Intraductal papillary lesion	5 (62.5)	3 (37.5)	
Sclerosingadenosis	5 (71.4)	2 (28.6)	

11-gauge needle, compared with 11 to 58% for a 14-gauge needle[16]. Mesurolle et al reported that ADH diagnosed by ultrasound-guided 14-gauge needle had a high underestimation rate, in consistent with the study by Deshaies et al[6,21]. However, in the current study, every patient was diagnosed ADH using 14-gauge needle and there was no vacuum assisted biopsy was included in the study.

The rate of upgrading to malignancy of ADH was rather high and 11.5% of the women with ADH developed breast carcinoma on follow-up[22]. Thus, whether or not the patients were underwent surgical excision, long-term follow-up should be performed. In addition, chemoprevention can reduce ten-year breast cancer risk from 21.3 to 7.5% in the women with atypical breast lesions[23].

The evidences from the current study indicated that surgical excision should be performed in the patients who were presented with palpable breast mass with suspicious findings on ultrasonography and

diagnosed ADH by CNBx. Limitations of this study were small number of the patients and lack of follow-up data to evaluate subsequent carcinoma.

Conclusion

Palpable mass, irregular margin of the mass and multifocality were predictive factors for upgrading from ADH on CNBx to malignancy on subsequent surgical excision. Presentation with palpable mass was an only independent factor for upgrading to malignancy. In the patients who presented with breast symptoms and diagnosed as ADH on CNBx, subsequent excision should be performed to exclude upgrading to malignancy.

What is already known on this topic?

ADH diagnosed by CNBx could be upgraded to malignancy. Surgical excision is usually performed after ADH was diagnosed by CNBx. However, only small proportion of the patients would be upgraded.

What this study adds?

Surgical excision should be performed in the patients with palpable breast mass and CNBx revealed ADH.

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Potential conflict of interest

None.

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ปัจจัยทำนายการเป็นมะเร็งเต้านมในผู้ป่วยที่ได้รับการวินิจฉัยการเจริญเพิ่มขึ้นของเซลล์ท่อน้ำนมผิดปกติโดยวิธีการใช้เข็มเจาะชิ้นเนื้อ

ณิชา จิระมงคล, ดุลยพัฒน์ สงวนรักษา, นรเศรษฐ์ สมานไทย, พรชัย โอเจริญรัตน์

ภูมิหลัง: *การเจริญเพิ่มขึ้นของเซลล์ท่อน้ำนมผิดปกติเป็นรอยโรคที่มีลักษณะของมะเร็งเต้านมระยะไม่ลุกลาม แต่ยังไม่ครบเกณฑ์การวินิจฉัยว่าเป็นมะเร็งระยะไม่ลุกลาม รอยโรคนี้เพิ่มความเสี่ยงในการเป็นมะเร็งเต้านม ผู้ป่วยมักได้รับการผ่าตัดรอยโรคออกเพื่อทำการตรวจทางพยาธิวิทยา เนื่องจากมีความขัดแย้งกันของการวินิจฉัยโรค โดยการตรวจทางคลินิก ภาพวินิจฉัยและการตรวจทางพยาธิวิทยา อย่างไรก็ตามมีผู้ป่วยเพียงส่วนน้อยที่ได้รับ การวินิจฉัยเป็นมะเร็งเต้านมจากการผ่าตัดรอยโรคไปตรวจ*

วัตถุประสงค์: *เพื่อหาปัจจัยที่สามารถทำนายการตรวจพบมะเร็งจากการผ่าตัดรอยโรคในผู้ป่วยที่ได้รับการวินิจฉัย เซลล์บุท่อน้ำนมเจริญผิดปกติโดยการใช้เข็มเจาะชิ้นเนื้อ*

วัสดุและวิธีการ: *ข้อมูลทางคลินิกและพยาธิวิทยาของผู้ป่วยที่ได้รับการวินิจฉัยการเจริญเพิ่มขึ้นของเซลล์ท่อน้ำนมผิดปกติโดยการใช้เข็มเจาะชิ้นเนื้อและได้รับการผ่าตัดรอยโรคเพื่อตรวจทางพยาธิวิทยาได้รับการรวบรวมและทบทวนตั้งแต่ เดือนมกราคม พ.ศ. 2553 ถึง เดือนมกราคม พ.ศ. 2558 การหาความสัมพันธ์ระหว่างข้อมูลทางคลินิกและพยาธิวิทยา กับการวินิจฉัยทำโดยใช้วิธีการทางสถิติ (Chi-square)*

ผลการศึกษา: *มีผู้ป่วยทั้งหมด 86 ราย 17 ราย (19.8%) พบว่าเป็นมะเร็งโดย 13 ราย (15.1%) เป็นมะเร็งระยะไม่ลุกลามและ 4 ราย (4.7%) เป็นมะเร็งระยะลุกลาม การมีก้อนเต้านมที่คลำได้ การเห็นลักษณะของก้อนที่มีขอบไม่เรียบ จากการตรวจด้วยคลื่นความถี่สูง และการมีรอยโรคหลายตำแหน่ง มีความสัมพันธ์กับการเป็นมะเร็ง โดยพบว่าการมีก้อนที่คลำได้เป็นปัจจัยอิสระไม่ขึ้นกับปัจจัยอื่นสามารถใช้เป็นตัวทำนายการวินิจฉัยเป็นมะเร็งโดยการผ่าตัดรอยโรคเพื่อตรวจทางพยาธิวิทยา*

สรุป: *การมีก้อนเต้านมที่คลำได้ในผู้ที่ได้รับการวินิจฉัยการเจริญเพิ่มขึ้นของเซลล์ท่อน้ำนมผิดปกติโดยการใช้เข็มเจาะ ตรวจชิ้นเนื้อเป็นปัจจัยที่สามารถทำนายการเป็นมะเร็งเมื่อผ่าตัดรอยโรคมาตรวจ และควรใช้เป็นข้อบ่งชี้ในการผ่าตัด*