Journal of Breast Cancer

JBC

Original Article

Check for updates

Atypical Ductal Hyperplasia of the Breast on Core Needle Biopsy: Risk of Malignant Upgrade on Surgical Excision

Tiffany Sin Hui Bong [1], Jun Kiat Thaddaeus Tan [1], Juliana Teng Swan Ho [2], Puay Hoon Tan [3], Wing Sze Lau [4], Tuan Meng Tan [5], Jill Su Lin Wong [2], Veronique Kiak Mien Tan [1,6,7], Benita Kiat Tee Tan [1,6,7,8], Preetha Madhukumar [1,6,7], Wei Sean Yong [1,6,7], Sue Zann Lim [1,6,7], Chow Yin Wong [6,7], Kong Wee Ong [1,6,7], Yirong Sim [1,6,7]

[1]Department of Breast Surgery, Division of Surgery and Surgical Oncology, National Cancer Centre Singapore, Singapore
[2]Division of Oncologic Imaging, National Cancer Centre Singapore, Singapore
[3]Division of Pathology, Singapore General Hospital, Singapore
[4]Department of Clinical Laboratory, Gleneagles Hospital Hong Kong, Hong Kong
[5]Department of Statistics and Applied Probability, National University of Singapore, Singapore
[6]Department of Breast Surgery, Division of Surgery and Surgical Oncology, Singapore General Hospital, Singapore
[7]SingHealth Duke-NUS Breast Centre, Singapore
[8]Department of General Surgery, Sengkang General Hospital, Singapore

Correspondence to
Yirong Sim
Department of Breast Surgery, Division of Surgery and Surgical Oncology, National Cancer Centre Singapore, 11 Hospital Crescent, 169610 Singapore.
Email: sim.yirong@singhealth.com.sg

ORCID iDs
Tiffany Sin Hui Bong
https://orcid.org/0000-0002-9376-6640
Jun Kiat Thaddaeus Tan
https://orcid.org/0000-0002-6021-5615
Juliana Teng Swan Ho
https://orcid.org/0000-0001-6103-7059
Puay Hoon Tan
https://orcid.org/0000-0002-1052-8605
Wing Sze Lau
https://orcid.org/0000-0002-8915-8474
Tuan Meng Tan
https://orcid.org/0000-0002-8895-2801
Jill Su Lin Wong
https://orcid.org/0000-0002-8115-3425

ABSTRACT

Purpose: This study identified factors predicting malignant upgrade for atypical ductal hyperplasia (ADH) diagnosed on core-needle biopsy (CNB) and developed a nomogram to facilitate evidence-based decision making.
Methods: This retrospective analysis included women diagnosed with ADH at the National Cancer Centre Singapore (NCCS) in 2010–2015. Cox proportional hazards regression was used to identify clinical, radiological, and histological factors associated with malignant upgrade. A nomogram was constructed using variables with the strongest associations in multivariate analysis. Multivariable logistic regression coefficients were used to estimate the predicted probability of upgrade for each factor combination.
Results: Between 2010 and 2015, 238,122 women underwent mammographic screening under the National Breast Cancer Screening Program. Among 29,564 women recalled, 5,971 CNBs were performed. Of these, 2,876 underwent CNBs at NCCS, with 88 patients (90 lesions) diagnosed with ADH and 26 lesions upgraded to breast malignancy on excision biopsy. In univariate analysis, factors associated with malignant upgrade were the presence of a mass on ultrasound ($p = 0.018$) or mammography ($p = 0.026$), microcalcifications ($p = 0.047$), diffuse microcalcification distribution ($p = 0.034$), mammographic parenchymal density ($p = 0.008$). and ≥ 3 separate ADH foci found on biopsy ($p = 0.024$). Mammographic parenchymal density (hazard ratio [HR], 0.04; 95% confidence interval [CI], 0.005–0.35; $p = 0.014$), presence of a mass on ultrasound (HR, 10.50; 95% CI, 9.21–25.2; $p = 0.010$), and number of ADH foci (HR, 1.877; 95% CI, 1.831–1.920; $p = 0.002$) remained significant in multivariate analysis and were included in the nomogram.
Conclusion: Our model provided good discrimination of breast cancer risk prediction

Veronique Kiak Mien Tan [ID]
https://orcid.org/0000-0001-8493-8191
Benita Kiat Tee Tan [ID]
https://orcid.org/0000-0002-8573-4606
Preetha Madhukumar [ID]
https://orcid.org/0000-0001-5070-4442
Wei Sean Yong [ID]
https://orcid.org/0000-0001-5834-2167
Sue Zann Lim [ID]
https://orcid.org/0000-0001-8486-9675
Chow Yin Wong [ID]
https://orcid.org/0000-0002-8449-8437
Kong Wee Ong [ID]
https://orcid.org/0000-0002-4275-2919
Yirong Sim [ID]
https://orcid.org/0000-0001-8758-0455

(C-statistic of 0.81; 95% CI, 0.74–0.88) and selected for a subset of women at low risk (2.1%) of malignant upgrade, who may avoid surgical excision following a CNB diagnosis of ADH.

Keywords: Breast; Carcinoma in Situ; Carcinoma, Intraductal, Noninfiltrating; Nomograms; Prognosis

INTRODUCTION

Percutaneous core needle biopsy (CNB) is widely performed for the diagnosis of radiologically suspicious breast lesions. Found in up to 15% of CNB specimens [1,2], atypical ductal hyperplasia (ADH) of the breast is considered a high-risk lesion that is biologically related to low nuclear grade ductal carcinoma *in situ* (DCIS). It is also associated with an increased risk of developing breast cancer, with a relative risk of 4 and a cumulative incidence of breast cancer approaching 30% at 25 years of follow-up [3]. ADH may also coexist with DCIS and invasive breast cancer. This risk is further augmented by up to ten-fold in patients with a family history of breast cancer [4].

The distinction between low nuclear grade DCIS and ADH can be challenging, with frequent inter-observer variation between pathologists. Often regarded as a borderline epithelial lesion [5], the pathological diagnosis of ADH has been refined with histological criteria of cytoarchitectural atypia affecting less than two separate duct spaces [6] or with a size or extent of no more than 2 mm in maximum dimension [7]. However, owing to the possibility of sampling error with CNBs and the risks of size underestimation and missing a co-existing breast malignancy, an excision biopsy is still recommended to be performed after the diagnosis of ADH on CNB [8].

The risk of upgrade from ADH on CNB to *in situ* carcinoma or invasive carcinoma ranges from 19% to 87% [1,2,9]. However, in many instances, no upgrade lesions have been identified. Therefore, strategies to reliably identify patients with ADH at low risk of upgrade are of great interest to select women who can be safely observed. Several groups, including Nguyen et al. [10] from the MD Anderson Cancer Centre and Peña et al. [11] from the Mayo Clinic, have attempted to triage patients with ADH lesions found on CNB according to the risk of upgrade to an associated carcinoma. However, the study populations in these reports were Caucasian. Asian women have smaller breasts with denser breast parenchyma and may have different features that portend malignancy. Our national screening program, BreastScreen Singapore (BSS), initiated in 2002, now has 17 years of records. We examined the upgrade rate of ADH on excision biopsy within BSS; evaluated the clinical, radiological, and histological factors predicting an upgrade to DCIS or invasive cancer; and developed a nomogram to strengthen risk-benefit-based decision making.

METHODS

Patients

The study was performed with the approval of the SingHealth Centralized Institutional Review Board (reference number: 2017/2120), which provided a waiver of consent. The study was conducted in accordance with the principles of the 1964 Declaration of Helsinki. A retrospective analysis of a prospectively maintained database of the national BSS program

was performed. Consecutive patients who were recalled for imaging abnormalities and had ADH diagnosed on CNB in the National Cancer Centre Singapore, a single assessment center, between 2010 and 2015 were included. Histologic upgrade was defined as a lesion diagnosed as ADH on CNB that subsequently revealed malignancy (DCIS and/or invasive carcinoma) on follow-up surgical excision.

Radiologic evaluation

All mammograms were read by at least two specialist breast radiologists. All CNBs were performed with either 11- or 14-gauge Trucut or vacuum-assisted breast biopsies (VABBs). All patients with ADH diagnosed with Trucut or VABB were identified and included in the study. Breast density was classified according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) system into four categories: almost entirely fat, scattered fibroglandular tissue, heterogeneously dense, and extremely dense. Microcalcification distribution was classified as diffuse, regional, clustered, linear, or segmental. Diffuse calcifications were scattered randomly throughout the breast. Regional distributions corresponded to calcifications scattered over large volumes (> 2 cc of breast tissue) without a ductal distribution. Clustered calcifications contained at least five microcalcifications in a small tissue volume (< 1 cc). The linear distribution described calcifications arrayed in a line, suggesting ductal extension. Segmental distribution referred to calcification in the ducts and branches of a segment or lobe.

Statistical analysis

The associations between clinical, radiological, and histological factors were assessed using Fisher's exact tests. To identify independent clinical, radiological, and histological factors associated with an upgrade to malignancy, multivariate analysis using the Cox regression model was used. In developing a multivariate model, we followed the recommendation of ≥ 10 events per variable to avoid overfitting and optimize generalizability to other settings [12]. Multivariable logistic regression coefficients were used to estimate the predicted probability of upgrade for each factor combination, with combinations with the lowest predicted probabilities (≤ 5%) showing a low risk of upgrade. All tests were two-sided, and statistical significance was set at $p < 0.05$. Analyses were conducted using SPSS for Windows, version 14.0 (SPSS Inc., Chicago, IL, USA).

In creating a multivariate model to identify a group with a low risk of upgrade, several potentially important variables were identified. A simple model that included the three variables with the strongest association in the multivariate analysis was chosen.

Secondary approaches to model choice, including stepwise variable selection and a model including all univariately significant variables, were explored. However, these models were rejected due to concerns regarding multicollinearity of the predictor variables, overfitting, and increased complexity for clinical use without substantial performance improvement. Therefore, we selected the original three-variable model as the final model (**Figure 1**).

RESULTS

Demographics

From January 1, 2010, to December 31, 2015, 238,122 women underwent mammographic screening under BSS. A total of 5,971 breast CNB were performed for suspicious lesions
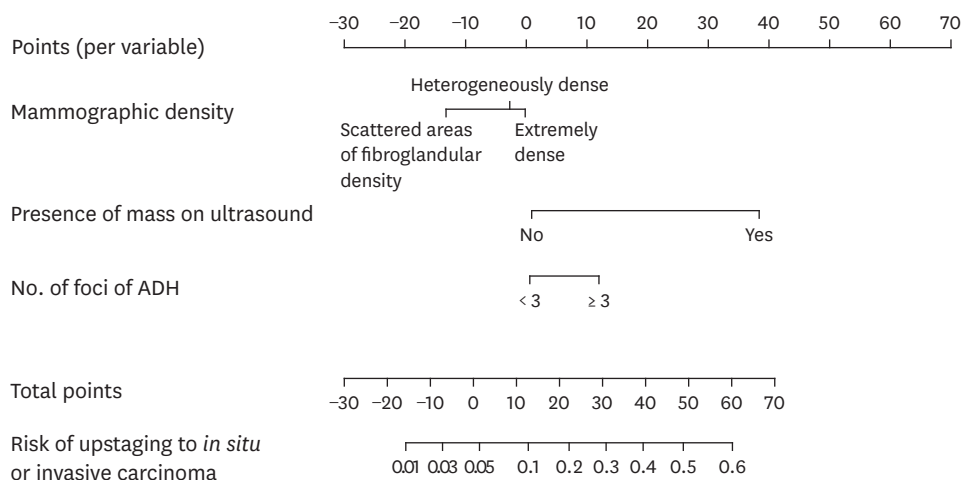
Figure 1. Nomogram predicting the risk of upstaging to *in situ* or invasive carcinoma in ADH diagnosed by core needle biopsy. An example is shown to demonstrate the use of this nomogram. The topmost 'point' scale is applicable to the three variables: mammographic density (scattered areas = −12.5, heterogeneously dense = −2.5, and extremely dense = 0 points), presence of a mass on ultrasound (no = 0, yes = 37.5 points), and number of ADH foci (< 3 = 0; ≥ 3 = 12.5 points). For instance, patients with mammographic density showing scattered areas of fibroglandular density will be assigned a score of −12.5 points. In addition, the scores for "no mass on ultrasound" and "less than 3 ADH foci, are 0 and 0 respectively. In this case, the total points are 0+0+ (−12.5) = −12.5, with the corresponding risk of upstage to *in situ* or invasive carcinomas of 0.01–0.03.
ADH = atypical ductal hyperplasia.

detected through radiographic imaging. Two thousand eight hundred seventy-six of these CNB were performed at the BSS clinic at the National Cancer Centre Singapore. Of these, 88 patients with 90 ADH lesions were diagnosed.

The mean age of these 88 patients was 62.2 years of age. Other demographic and baseline characteristics are presented in **Table 1**.

Radiological characteristics

Breast density was classified according to the American College of Radiology BI-RADS into four categories: almost entirely fat (n = 0), scattered fibroglandular tissue (n = 10), heterogeneously dense (n = 58), and extremely dense (n = 22).

In this study, 51% of patients (n = 45) underwent both mammography and ultrasound screening, while the rest underwent mammography screening only. Overall, 93% of

Table 1. Demographic characteristics of the 88 patients diagnosed with atypical ductal hyperplasia on core biopsy

Demographics	Not upstaged (n = 64)	Upstaged (n = 26)	*p*-value
Age (yr)	62.9 ± 13.2	61.3 ± 15.7	0.875
Menopausal status			0.707
Premenopausal	37 (58)	14 (54)	
Postmenopausal	27 (42)	12 (46)	
Race			0.504
Chinese	51 (80)	19 (73)	
Malay	6 (9.4)	4 (15)	
Indian	4 (6.3)	2 (7.7)	
Others	3 (4.7)	1 (3.8)	
BMI (kg/m²)	23.6 ± 4.8	24.3 ± 5.2	0.624

Continuous and continuous data are presented as means ± SD and counts (percentage), respectively.
BMI = body mass index.

Table 2. Univariate analysis of the radiological and histopathological factors predicting an upgrade to DCIS or invasive carcinoma on excision biopsy

Variable	Upgrade to DCIS or IBC		OR (95% CI)	p-value
	No (n = 64)	Yes (n = 26)		
Radiological variables				
Imaging modality			1.80 (0.81–4.58)	0.224
Mammogram alone	35 (54.7)	10 (38.5)		
Mammogram + US	29 (45.3)	16 (61.5)		
Mass present on US	7 (10.9)	14 (51.9)	5.81 (1.33–25.32)	0.018*
Size of mass on US (mm)	12.5 ± 4.3	14.1 ± 5.1	1.25 (0.89–1.56)	0.231
Mass lesion on MMG	1 (1.6)	4 (14.8)	4.96 (1.68–8.76)	0.026*
Size of mass on MMG (mm)	15.1 ± 7.6	16.7 ± 8.9	1.09 (0.71–1.36)	0.462
Residual lesion post-CNB on MMG	20 (31.3)	34 (54.8)	2.35 (0.87–6.37)	0.092
Microcalcification present	61 (95.3)	21 (80.8)	2.23 (1.23–3.67)	0.047*
Microcalcification				
Morphology			0.55 (0.37–1.23)	0.078
None	3 (4.7)	5 (19.2)		
Amorphous	19 (29.7)	4 (15.4)		
Coarse heterogenous	26 (40.6)	11 (42.3)		
Fine pleiomorphic	11 (17.2)	4 (15.1)		
Linear	5 (7.8)	2 (7.7)		
Distribution			0.16 (0.04–0.74)	0.034*
None	3 (4.7)	5 (19.2)		
Diffuse	2 (3.1)	3 (11.5)		
Regional	9 (14.1)	1 (3.9)		
Clustered	25 (39.1)	9 (34.6)		
Linear	9 (14.1)	1 (3.9)		
Segmental	16 (25.0)	7 (26.9)		
Breast composition				0.008*
Extremely dense	4 (6.3)	10 (38.4)		
Heterogenously dense	20 (31.3)	12 (38.5)	0.31 (0.07–1.24)	
Scattered areas of fibroglandular density	40 (62.5)	4 (15.4)	0.06 (0.04–0.15)	
Histopathological variables				
CNB technique				0.031*
Trucut	4 (6.3)	5 (19)		
Trucut and VABB	7 (11)	2 (7.7)	0.40 (0.09–0.78)	
VABB	53 (83)	19 (73)	0.48 (0.15–0.85)	
No. of tissue cores obtained	5 (1–17)	5 (1–10)	0.89 (0.80–0.94)	0.045*
No. of separate foci of ADH found on CNB	1.1 ± 0.3	1.8 ± 0.5	1.52 (1.08–1.98)	0.024*
Presence of microcalcification in biopsy	37 (58)	12 (46)	1.34 (1.03–1.65)	0.120
ADH architectural pattern			1.23 (0.80–1.72)	0.803
Cribriform	37 (58)	19 (73)		
Micropapillary	22 (34)	4 (15)		
Tufting	5 (7.8)	2 (7.5)		
Solid	0 (0)	1 (3.8)		

Continuous and categorical data are presented as means ± SD, median (interquartile range), and counts (percentage), respectively.
DCIS = ductal carcinoma in situ; IBC = invasive breast carcinoma; OR = odds ratio; CI = confidence interval; US = ultrasound; MMG = mammogram; CNB = core needle biopsy; VABB = vacuum-assisted breast biopsy; ADH = atypical ductal hyperplasia.
*Indicate significant variables ($p < 0.05$).

mammographic lesions were classified radiographically as BI-RADS category 4. The most common abnormality noted on mammography was microcalcifications in 91% (n = 82) participants, followed by the presence of a mass in 5.6% (n = 5) and distortion in 3.3% (n = 3). The microcalcification distributions are shown in **Table 2**.

Of the five lesions presenting as masses on mammography, four had non-circumscribed margins, all of which were upgraded on excision biopsy. The margin details were obscured (one lesion), microlobulated (one lesion), and spiculated (two lesions). The mean diameter of the lesions measured at mammography was 16.7 ± 8.9 mm for malignant lesions and 15.1 ±

7.6 mm for nonmalignant lesions ($p = 0.462$). 36 out of 90 (40.0%) did not have any residual lesions seen on mammography post CNB.

Forty-five patients (51%) underwent ultrasound evaluation, 23 of whom had abnormal findings. Sonographically, most lesions appeared as hypoechoic masses (n = 21) with oval (n = 11) or irregular shapes (n = 10). The margins were indistinct (n = 9), circumscribed (n = 3), spiculated (n = 3), microlobulated (n = 4), or angular (n = 2). The mean diameters of the lesions measured at sonography were 10.5 ± 7.3 mm (range, 3–45 mm), and 14.1 ± 5.1 and 12.5 ± 4.3 mm for malignant and nonmalignant lesions, respectively ($p = 0.231$). Ultrasound was more sensitive than mammography for detecting mass lesions. The other two abnormal sonographies revealed punctate calcifications.

Univariate analysis identified the following radiological features to be associated with an upgrade to malignancy (**Table 2**): the presence of a mass on either ultrasound or mammography ($p = 0.018$ and $p = 0.026$, respectively), mammographic presence of microcalcifications ($p = 0.047$), diffuse microcalcification distribution on mammography ($p = 0.034$), and parenchymal density on mammography ($p = 0.008$). Mammographic parenchymal density ($p = 0.001$) and the presence of a mass on ultrasound ($p = 0.010$) remained significant in multivariate analysis (**Table 3**).

Comparison of biopsy techniques

There were 88 patients with 90 ADH lesions diagnosed through CNB, and two patients had bilateral ADH. 71 lesions were biopsied using VABB, 10 by Trucut, and 9 by both Trucut and VABB. In this last group of patients, both biopsy modalities were utilized to biopsy breast nodules and microcalcifications, and both yielded ADH.

Core needle samples were obtained using 11-gauge VABB (80%, n = 72), 14-gauge Trucut (10%, n = 9), or both (10%, n = 9). The median number of samples obtained was 12 (range, 7–25) with the 11-gauge vacuum-assisted CNB and 6 (range, 3–18) for the 14-gauge Trucut core biopsies. The subsequent upgrade rate of ADH samples to malignancy was 28.9% (26 out of 90) to 26.0% (19 out of 72) for VABB, 55.5% (5 out of 9) for Trucut, and 22.2% (2 out of 9) for specimens taken by both VABB and Trucut.

Univariate analysis revealed that the use of the Trucut biopsy method ($p = 0.031$) and the number of tissue cores obtained ($p = 0.045$) were associated with upgrading (**Table 2**). These two variables were correlated, and both were not significant in the multivariate analysis.

Histopathological characteristics

The architectural patterns of ADH in the CNB specimens included cribriform (56 cases, 63%), micropapillary (26 cases, 29%), tufting (7 cases, 7.7%), and solid (1 case, 1.1%). The

Table 3. Multivariate analysis of factors predicting an upgrade to ductal carcinoma *in situ* or invasive carcinoma on excision biopsy

Variable	Multivariate analysis		
	Hazard ratio	95% CI	*p*-value
Mammographic density			0.014
Heterogeneously dense	0.32	0.010–0.89	
Scattered areas of fibroglandular density	0.04	0.005–0.35	
Presence of mass on ultrasound	10.50	9.21–25.2	0.010
No. of foci of ADH	1.877	1.831–1.920	0.002

CI = confidence interval; ADH = atypical ductal hyperplasia.

tufting appearance referred to monotonous epithelial protrusions that did not form distinct micropapillary structures. One focus of ADH was defined as a cytoarchitecturally atypical epithelial proliferation that was distinct and separate, either existing in different cores or located at least 5 mm apart on the same core. The median number of ADH foci was 1 (mean ± SD, 1.2 ± 0.3), with a median ADH foci size of 1 mm (mean ± SD, 1.6 ± 0.1 mm). The extent of ADH was limited to one or two foci in 70 cases (78%), confined to three foci in 11 cases (12%), and involved four or more foci in nine cases (9.9%). The sensitivity and specificity of ≥ 3 ADH foci on CNB in predicting upgrade on excision biopsy were 0.78 and 0.89 respectively, as opposed to 0.51 and 0.60, respectively for < 3 foci lesions on CNB.

Twenty-six of the 90 (29%) ADH lesions were subsequently upgraded to a breast malignancy on excision biopsy; 25 (28%) were DCIS and one (1.1%) was invasive ductal carcinoma. Of the twenty-five DCIS lesions, 19 were cribriform, four were micropapillary, two were tufting, and one was solid histologic type. The histological diagnosis of invasive ductal carcinoma was mucinous carcinoma of nuclear grade 1.

Regarding the remaining 64 lesions, excision biopsy revealed other forms of benign breast pathology in 35 lesions (39%), including fibrocystic change, apocrine metaplasia, sclerosing adenosis, usual ductal hyperplasia, fibroadenoma, intraductal papilloma, and radial scar. Five patients (5.5%) had coexisting atypical lobular hyperplasia. Only 24 lesions (26%) remained pure ADH (**Table 4**).

In univariate analysis (**Table 2**), the histopathological factors associated with an upgrade to malignancy included the number of separate ADH foci found on CNB ($p = 0.024$). In multivariate analysis, the number of separate ADH foci (hazard ratio, 1.877; 95% confidence interval [CI], 1.831–1.920; $p = 0.002$) remained significant for predicting the upgrade of CNB-diagnosed ADH to malignancy (**Table 3**).

Definition of low risk

The predicted probability of upgrade for each factor combination was estimated, and the lowest risk categories were identified. A predicted probability ≤ 5% [13] was used to maximize the predictive accuracy of this model, resulting in sensitivity, specificity, and positive and negative predictive values of 91.9%, 79.0%, 80.1%, and 92.9%, respectively. Low upgrade risk was defined as women who fulfilled the following criteria: 1) two or fewer ADH

Table 4. Summary of histopathological diagnoses on excision biopsy

Excision biopsy results	Values
Benign	64 (71)
Non-proliferative lesions and proliferative lesions without atypia	35 (39)
Fibrocystic change	9 (10)
Apocrine metaplasia	7 (7.8)
Sclerosing adenosis	6 (6.7)
Usual ductal hyperplasia	5 (5.6)
Intraductal papilloma	4 (4.4)
Radial scar	2 (2.2)
Fibroadenoma	2 (2.2)
Atypical ductal hyperplasia	24 (27)
Atypical lobular hyperplasia	5 (5.5)
Malignant	26 (29)
Ductal carcinoma *in situ*	25 (28)
Invasive carcinoma	1 (1.1)

Continuous and continuous data are presented as counts (percentage), respectively.

foci on biopsy, 2) mammographic density with scattered areas of fibroglandular density, and 3) absence of a mass on ultrasound. Patients with low risk represented 16% of the entire study set, which had an upgrade risk of 2.1% (95% CI, 1.1%–3.4%). In contrast, the remainder of the sample that did not meet this definition of low risk had an estimated upgrade rate of 29.0% (95% CI, 26.9%–34.2%). Based on the selected independent risk factors, we developed a nomogram using a multivariable logistic model to predict the probability of an upgrade to *in situ* or invasive carcinoma (**Fig. 1**). The sensitivity, specificity, positive predictive value, and negative predictive value of the nomogram in predicting upgrade were 91.9%, 79.0%, 80.1%, and 92.9%, respectively. Despite the lack of an external validation sample in this study, 10-fold cross-validation analyses showed continued good performance, with a cross-validation C-statistic of 0.81.

DISCUSSION

To our knowledge, this is the first study in Southeast Asia to incorporate radiological and histological characteristics to develop a predictive model for malignant upgrade of ADH diagnosed on CNB; although predictive tools have been proposed, they have been validated in different populations [10,14]. Our results showed a ≤ 2.1% risk of a malignant upgrade in patients with risk scores of ≤ –10. This is equivalent to the risk of a BIRADS 3 lesion that can be conservatively managed with short-interval radiological surveillance. With further validation in a larger cohort, this nomogram has the potential for use as an adjunct to aid surgeons and patients to make an informed decision regarding open excision biopsy following a diagnosis of ADH on CNB.

The upgrade rate in our study was 28.9%, lower than the previously reported rates of 7%–87% [1,2,9]. This could be a result of improved breast imaging modalities and a more stringent review of our screening mammograms by multiple dedicated breast radiologists. All lesions after biopsy were also discussed at multidisciplinary meetings with radiologists, pathologists, and surgeons.

Our BSS participation rate increased from 10% in 2005 to 39.6% in 2020. Performance indicators, except for recall rates, specificity, and interval cancer rate (for the first screen), generally improved over time and were comparable to those for organized breast screening programs in other developed countries [15].

The strongest predictive factors of upgrade to malignancy in the present study were the presence of a mass on sonography, mammographic parenchymal density, and number of ADH foci. Multivariate modeling was used to identify a subgroup of women with ADH on core biopsy with low risks of harboring concomitant malignancy, in whom surgical excision might be avoided. Approximately 16% of our study population met the low-risk criteria, defined as 1) absence of a mass on ultrasound, 2) mammographic parenchymal density of scattered areas of fibroglandular density, and 3) two or fewer foci of ADH on core biopsy. The malignant upgrade rate in this subset of patients was 2.1%.

Similar to previous reports, our results also showed a higher upgrade rate in patients with higher mammographic parenchymal density [16]. The mammographic percent density, computed as the proportion of the parenchymal area occupied by radiologically dense breast tissue, is related to screening sensitivity and specificity and is one of the strongest established

risk factors for the development of DCIS [9] and invasive breast cancer [7]. Mammographic density is a function of genetic factors [2], is higher in nulliparous women, and is inversely associated with age and body mass index (BMI) [7]. Asian women have a lower average BMI than their Western counterparts and more frequently have dense breasts on mammography [17-20]. The increased mammographic parenchymal density could account for the higher upgrade rates of CNB-diagnosed ADH [21,22] as well as the younger peak age of breast cancer (10 years younger) [23] in Asia compared to Western countries. This could also explain why ultrasound was more sensitive than mammography for mass detection in this study.

Microcalcification with or without a mass is the most common finding on screening mammograms for both ADH (58% and 88%) and DCIS (68% and 98%) [24]. Ninety percent of non-palpable DCIS and 20% of non-palpable infiltrating carcinomas were identified by their microcalcifications [25]. Several studies have identified microcalcification morphology and distribution (e.g., clustered, segmental, or linear branching calcifications) on imaging as predictive of upgrade [26]. We demonstrated that patients with diffuse calcifications were more likely to have a core biopsy diagnosis upgraded on subsequent excision biopsy. Inherent in diffuse calcifications is the increased difficulty of adequate representative sampling compared to clustered calcification. Hence, in patients with diffuse calcifications on mammogram, sufficient and representative samples should be taken for core biopsies to increase the adequacy of biopsy sampling. Likewise, for patients with ADH and diffuse calcifications, with higher risks of false-negative findings, surgical excision should be considered if sampling adequacy is of concern.

Although the breast screening program was designed for clinically asymptomatic women, 5.6% (5/90) of the screening mammograms revealed a mass, 60% (n = 3) of which were clinically palpable. Among the five mammograms harboring a mass lesion, four lesions were upgraded to *in situ* or invasive carcinoma on excision biopsy. Most women diagnosed with ADH on CNB were asymptomatic, with anomalous findings identified only with mammographic screening. This finding highlights the complementary roles of breast self-examination and mammographic screening [14].

In our study, the presence of a mass on either mammogram or ultrasound was associated with an increased risk of upgrading to DCIS or invasive cancer, with the presence of a mass on ultrasound being an independent predictor of upgrade to *in situ* or invasive malignancy, consistent with previous studies [27,28]. The presence of a mass on imaging likely represents a more aggressive lesion with a higher potential for local invasiveness, breaking through the basement membrane of the breast ducts and infiltration of adjacent tissues. As ADH is a microscopic lesion, it is rare for pure ADH to present as a mass, and therefore one should have a high suspicion of a false sampling, should a biopsy of a breast mass yield only ADH.

The histological criteria independently associated with cancer upgrade in our study were the number of ADH foci on core biopsy. Similar to previous studies [29,30], we also demonstrated that ADH involving three or more foci in CNB was an independent predictor of upgrade on excision. Some studies have reported that the micropapillary histologic subtype predicted the presence of DCIS [28,29]. However, we did not observe the architectural pattern of ADH related to upgrade risk ($p = 0.80$).

Although there is no universal agreement on the number of cores necessary for an accurate histological diagnosis, most studies have shown that increasing the number of core biopsies

can decrease the risk of malignancy underestimation [24]. Similarly, our results showed decreased upgrade rates with larger samples via larger needle gauge size and the use of a vacuum device. However, these did not reach significance in the multivariate analysis. This lack of independent correlation may be related to the size of the mammographic or pathologic lesions biopsied. Higher rates of underestimation would also be expected for less adequate sampling, which would be more likely to occur in cases with larger target lesions. As shown in the present study, even with the use of vacuum assistance with an 11-gauge needle and complete removal of the mammographic lesion, there remained a 20% risk of a malignant upgrade with the diagnosis of ADH.

While previous studies investigated if the absence of residual microcalcifications after biopsy would obviate the need for surgical excision, the consensus is mixed [10,30,31]. In our study, the presence of residual calcifications associated with ADH lesions was a strong predictor of upgrade on subsequent excision, with a sensitivity of 0.96 in our patient population. In the absence of residual calcifications post-biopsy, 20% (n = 7) of CNB-diagnosed ADH were upgraded to *in situ* or invasive cancer after surgical biopsy.

Among women with a low risk of upgrade, short-term radiologic follow-up should be adequate to detect progression. This is supported by the fact that all but one of the upgraded lesions *was in situ* disease. The only case upgraded to invasive carcinoma was a case of mucinous carcinoma in which CNB revealed a mucocele-like lesion with ADH. Mucinous carcinoma usually has a favorable prognosis, with low recurrence and metastatic rates. This was also reported by Menen et al. [32], which observed 125 women at low risk for ADH (using Nguyen et al.'s criteria [10]) without surgical excision. With a median follow-up of 3 years (and chemoprevention use reported in 23% of women), only seven cases of breast cancers occurred (5.6%). The index site and ipsilateral cancer rates were comparable to those in the group that underwent excision, while contralateral breast cancers occurred only in the surgical group.

This study has several limitations. The retrospective, single-institution design included only 90 cases, with a selection bias of only patients who underwent surgery. Although all had screening mammograms and only 45 had a complementary breast ultrasound, slightly less than half of them (n = 21) had a mass on ultrasound. It will be useful to validate these nomogram findings in a prospective cohort study with larger numbers and with standardized mammogram and ultrasound breast imaging for each patient. Moreover, interobserver variability in radiologic and pathologic features was possible. However, these limitations were minimized by including at least two specialist radiologists and pathologists from a high-volume tertiary center, who reviewed the radiological images and histological slides. In addition, after biopsy, all cases (core and surgical specimens) were also discussed at a multidisciplinary meeting with independent radiologists, pathologists, and surgeons.

In conclusion, we retrospectively examined the upgrade rate of core biopsy-diagnosed ADH on excision biopsy among women in Singapore. The strongest predictive factors for an upgrade to malignancy were the presence of a mass on sonography, mammographic parenchymal density, and the number of ADH foci. We also developed a nomogram to help identify women at low risk (< 5%) of a malignant upgrade, who may be candidates for avoiding open excision surgery, following a core-needle biopsy diagnosis of ADH.

REFERENCES

1. Harvey JM, Sterrett GF, Frost FA. Atypical ductal hyperplasia and atypia of uncertain significance in core biopsies from mammographically detected lesions: correlation with excision diagnosis. Pathology 2002;34:410-6.
   PUBMED | **CROSSREF**

2. Jackman RJ, Birdwell RL, Ikeda DM. Atypical ductal hyperplasia: can some lesions be defined as probably benign after stereotactic 11-gauge vacuum-assisted biopsy, eliminating the recommendation for surgical excision? Radiology 2002;224:548-54.
   PUBMED | **CROSSREF**

3. Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K. Atypical hyperplasia of the breast--risk assessment and management options. N Engl J Med 2015;372:78-89.
   PUBMED | **CROSSREF**

4. Page DL, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast. A long-term follow-up study. Cancer 1985;55:2698-708.
   PUBMED | **CROSSREF**

5. Page DL, Dupont WD. Anatomic indicators (histologic and cytologic) of increased breast cancer risk. Breast Cancer Res Treat 1993;28:157-66.
   PUBMED | **CROSSREF**

6. Page DL, Rogers LW. Combined histologic and cytologic criteria for the diagnosis of mammary atypical ductal hyperplasia. Hum Pathol 1992;23:1095-7.
   PUBMED | **CROSSREF**

7. Tavassoli FA. Intraduct hyperplasias, ordinary and atypical. In: Tavassoli FA, editor. Pathology of the Breast. Norwalk: Appleton and Lange; 1992. p.155-91.

8. National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis. National Comprehensive Cancer Network v3.2018:BSCR-8. Plymouth Meeting: National Comprehensive Cancer Network; 2018.

9. Dahlstrom JE, Sutton S, Jain S. Histological precision of stereotactic core biopsy in diagnosis of malignant and premalignant breast lesions. Histopathology 1996;28:537-41.
   PUBMED | **CROSSREF**

10. Nguyen CV, Albarracin CT, Whitman GJ, Lopez A, Sneige N. Atypical ductal hyperplasia in directional vacuum-assisted biopsy of breast microcalcifications: considerations for surgical excision. Ann Surg Oncol 2011;18:752-61.
    PUBMED | **CROSSREF**

11. Peña A, Shah SS, Fazzio RT, Hoskin TL, Brahmbhatt RD, Hieken TJ, et al. Multivariate model to identify women at low risk of cancer upgrade after a core needle biopsy diagnosis of atypical ductal hyperplasia. Breast Cancer Res Treat 2017;164:295-304.
    PUBMED | **CROSSREF**

12. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373-9.
    PUBMED | **CROSSREF**

13. Harrell FE. Overview of maximum likelihood estimation. In: Harrell FE, editor. Regression Modeling Strategies Springer Series in Statistics. New York: Springer; 2001.

14. Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. BMJ 2014;348:g366.
    PUBMED | **CROSSREF**

15. Robin A, Wilson M. European group for breast cancer screening: breast cancer screening in Europe — current status. Eur J Cancer, Suppl 2006;4:4-5.
    CROSSREF

16. Gill JK, Maskarinec G, Pagano I, Kolonel LN. The association of mammographic density with ductal carcinoma in situ of the breast: the Multiethnic Cohort. Breast Cancer Res 2006;8:R30.
    PUBMED | **CROSSREF**

17. Habel LA, Capra AM, Oestreicher N, Greendale GA, Cauley JA, Bromberger J, et al. Mammographic density in a multiethnic cohort. Menopause 2007;14:891-9.
    PUBMED | **CROSSREF**

18. del Carmen MG, Hughes KS, Halpern E, Rafferty E, Kopans D, Parisky YR, et al. Racial differences in mammographic breast density. Cancer 2003;98:590-6.
    PUBMED | **CROSSREF**

19. El-Bastawissi AY, White E, Mandelson MT, Taplin S. Variation in mammographic breast density by race. Ann Epidemiol 2001;11:257-63.
   PUBMED | CROSSREF

20. Tan SM, Evans AJ, Lam TP, Cheung KL. How relevant is breast cancer screening in the Asia/Pacific region? Breast 2007;16:113-9.
   PUBMED | CROSSREF

21. Eby PR, Ochsner JE, DeMartini WB, Allison KH, Peacock S, Lehman CD. Frequency and upgrade rates of atypical ductal hyperplasia diagnosed at stereotactic vacuum-assisted breast biopsy: 9-versus 11-gauge. AJR Am J Roentgenol 2009;192:229-34.
   PUBMED | CROSSREF

22. Chae BJ, Lee A, Song BJ, Jung SS. Predictive factors for breast cancer in patients diagnosed atypical ductal hyperplasia at core needle biopsy. World J Surg Oncol 2009;7:77.
   PUBMED | CROSSREF

23. Pathy NB, Yip CH, Taib NA, Hartman M, Saxena N, Iau P, et al. Breast cancer in a multi-ethnic Asian setting: results from the Singapore-Malaysia hospital-based breast cancer registry. Breast 2011;20 Suppl 2:S75-80.
   PUBMED | CROSSREF

24. Stomper PC, Cholewinski SP, Penetrante RB, Harlos JP, Tsangaris TN. Atypical hyperplasia: frequency and mammographic and pathologic relationships in excisional biopsies guided with mammography and clinical examination. Radiology 1993;189:667-71.
   PUBMED | CROSSREF

25. Feig SA. Mammographic evaluation of calcifications. In: Kopans DB, Mendelson EB, editors. Syllabus: A Categorical Course in Breast Imaging. Oak Brook: Radiological Society of North America Publications; 1995. p.93-105.

26. Boyd NF, Stone J, Martin LJ, Jong R, Fishell E, Yaffe M, et al. The association of breast mitogens with mammographic densities. Br J Cancer 2002;87:876-82.
   PUBMED | CROSSREF

27. Schulz S, Sinn P, Golatta M, Rauch G, Junkermann H, Schuetz F, et al. Prediction of underestimated invasiveness in patients with ductal carcinoma in situ of the breast on percutaneous biopsy as rationale for recommending concurrent sentinel lymph node biopsy. Breast 2013;22:537-42.
   PUBMED | CROSSREF

28. Yeh IT, Dimitrov D, Otto P, Miller AR, Kahlenberg MS, Cruz A. Pathologic review of atypical hyperplasia identified by image-guided breast needle core biopsy. Correlation with excision specimen. Arch Pathol Lab Med 2003;127:49-54.
   PUBMED | CROSSREF

29. Ely KA, Carter BA, Jensen RA, Simpson JF, Page DL. Core biopsy of the breast with atypical ductal hyperplasia: a probabilistic approach to reporting. Am J Surg Pathol 2001;25:1017-21.
   PUBMED | CROSSREF

30. Sneige N, Lim SC, Whitman GJ, Krishnamurthy S, Sahin AA, Smith TL, et al. Atypical ductal hyperplasia diagnosis by directional vacuum-assisted stereotactic biopsy of breast microcalcifications. Considerations for surgical excision. Am J Clin Pathol 2003;119:248-53.
   PUBMED | CROSSREF

31. Bonnett M, Wallis T, Rossmann M, Pernick NL, Bouwman D, Carolin KA, et al. Histopathologic analysis of atypical lesions in image-guided core breast biopsies. Mod Pathol 2003;16:154-60.
   PUBMED | CROSSREF

32. Menen RS, Ganesan N, Bevers T, Ying J, Coyne R, Lane D, et al. Long-term safety of observation in selected women following core biopsy diagnosis of atypical ductal hyperplasia. Ann Surg Oncol 2017;24:70-6.
   PUBMED | CROSSREF