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Original Research

Evaluation of Precancerous Breast Lesion Upgrade Rate

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Background: Breast imaging guided core-needle biopsy enable the assessment of suspected precancerous lesions. In some precancerous lesion there is a risk of upgrading to cancer after surgical removal. This study was conducted to determine the upgrading rate of CNB-diagnosed precancerous breast lesions.
Methods: A retrospective study was conducted to examine the data of patients who had undergone core needle biopsy from April 2016 to March 2019 at the Radiology Department of the Breast Clinic of Motamed Cancer Institute and whose pathological reports were indicative of a precancerous lesion such as atypical ductal hyperplasia, sclerosing adenosis, flat epithelial atypia or papillary lesion and had undergone surgery for this lesion. The upgrading rate and its related factors such as the size of the lesion, patient's age, family history of breast cancer and method of core-needle biopsy were analyzed in SPSS software.
Results: A total of 241 patients were recruited with a pathological report of pre-cancerous predisposing lesions. The mean age of the patients was 42.14 years and the highest upgrading rates in the analysis were observed for papillary lesion (19.3%) and atypical ductal hyperplasia, (21.4%), while the upgrading rates were (1.2%) for sclerosing adenosis and (0%) for flat epithelial atypia. Data analysis showed that the lesions' upgrading rate correlated with the lesion's size (P=0.005).
Conclusion: The findings of this study showed that size of the lesions increase the risk of upgrading to cancer, which is much higher in papillary lesion and atypical ductal hyperplasia compared to sclerosing adenosis and flat epithelial atypia. It seems that surgical excision of the entire lesion in patients with larger mass size may decrease the upgrading rate of cancer. Conducting specific studies on each distinct lesion can help yield more conclusive results.

Introduction

About 10% of patients who undergo screening mammography for breast cancer show an indication for additional imaging techniques. In approximately 8-10% of these cases, the findings may lead to breast biopsy. These findings can be reported as the presence of a mass, microcalcification, architectural distortion or focal asymmetry, which are construed as indications for additional imaging. The radiologist may report the existing lesion as suspicious and recommend a biopsy based on the results of these additional imaging techniques. In the case of non-palpable breast lesions, the standard method is Core Needle Biopsy (CNB) guided by either of the imaging techniques including mammography, ultrasound and MRI.

CNB can be either conventional or vacuum-assisted and be guided by ultrasound or mammography (stereotactic). CNB is the standard method for the diagnosis of suspected lesions in the breast and

is less costly compared to surgery and yields results that are consistent with the pathological report obtained by surgical biopsy in 95% of the cases [1-3].

The pathology report of CNB can determine whether there is a need for surgery in the patient. An important point is the conformity of the pathology and radiology findings. If a radiologist reports a lesion suspected of cancer but the pathologic findings indicate a benign lesion, surgery will be necessary for definitive diagnosis. In some cases, the pathology report may suggest a pre-cancerous lesion such as Atypical Ductal Hyperplasia (ADH), Sclerosing Adenosis (SA), Flat Epithelial Atypia (FEA) or Papillary Lesion (PL), which have indications for surgery in order to reduce the risk of future cancer and to get a more precise diagnosis. Post-surgical pathology reports may be similar to the initial pathological report or may be worse and indicate invasive cancer.

Sclerosing Adenosis (SA) is one of the benign lesions that may be identified in CNB pathology reports; despite its high prevalence, this lesion is not well-known. In pathological terms, this proliferative lesion is associated with an increase in convoluted lobules and stromal fibrosis. Several studies have investigated the association of SA with breast cancer and have revealed different results [4]. Also, in some cases, the pathology report following surgery may reveal a more severe condition compared to CNB. ADH is one of these proliferative lesions that develop in the mammary epithelial tissue. The presence of this lesion in the breast increases the risk of invasive cancer in the breast four- or five-fold. Various studies have reported a 7-87% discrepancy between CNB pathology and surgical pathology with respect to the presence of non-invasive or invasive cancer in ADH [5-11]. In other words, the upgrading rate of the lesions in different studies is highly variable. At the same time, due to the high risk of breast cancer development in these lesions, it is reasonable to recommend surgical removal to prevent this risk when

ADH is confirmed by CNB [12-13].

Papillary lesion (PL) is a benign lesion with a lower prevalence in the breast that is seen in the ultrasound as a single lesion or multiple lesions. In some cases, the patient does not have any specific clinical symptoms, while in some patients, blood or serous fluid secreted from the nipple raises suspicion, which can then be confirmed by an ultrasound. In these cases, too, the patient can undergo CNB. Previous studies have reported the upgrading rate of these lesions after surgery as 11% [14].

Flat epithelial atypia (FEA) is a new diagnostic term that is expressed in pathologic reports following CNB and is usually associated with other benign or malignant breast lesions. Due to this association, when this lesion is present in the pathology report following CNB, the site of the lesion is recommended to be removed with surgery, particularly if detected in the mammography despite microcalcification and if, after sampling, calcium deposits are still detected in the control mammogram [15-16]. According to studies, four cases of breast cancer are reported in the post-surgical pathology in every 1,000 patients [17-19].

The present study was designed in view of the differences of opinion about upgrading rates after surgery and the need for more extensive interventions. The results can guide the surgeon’s decision for surgical procedures and the rate of tissue removal and, at the same time, help present preventive therapies for patients who are prone to breast cancer.

Materials and Methods

This cohort study was conducted on candidates of CNB guided by one of the imaging techniques due to a suspicious lesion observed in the ultrasound or mammogram who had then undergone surgery within a maximum of one month at the Breast Clinic of Motamed Cancer Institute, Culture and Research. Data on the imaging reports, post-CNB pathology and post-surgical pathology were collected and compared. Upgrading rate in different studies had been reported between 7 – 87

percent [5-11]. So upgrading rate, α error and absolute precision of current study were considered equal to 0.47, 0.05 and 0.07, respectively and 198 samples was the sample size were estimated 198 patients.

Breast Clinic of Motamed Cancer Institute is a multidisciplinary center in Tehran. Referred patients are examined by surgeons and different diagnostic and treatment modalities are achieved according to its updated guideline [12].

Of the 2582 patients who had undergone CNB guided by one of the imaging techniques from April 2017 to March 2020 at the Radiology Department of the Breast Clinic of Motamed Cancer Institute, 241 whose pathologic reports indicated one of the listed pre-cancerous lesions and had their lesion surgically removed by a surgeon and whose medical files were complete were recruited.

Definition of upgrading

A change in any of the pre-cancerous lesions diagnosed as Atypical Ductal Hyperplasia (ADH), Sclerosing Adenosis (SA), Flat Epithelial Atypia (FEA) or Papillary Lesion (PL) to in-situ or invasive carcinoma in the post-surgical pathology is considered an instance of upgrade. Since the transformation of any of the noted pre-cancerous lesions to ADH is considered an upgrade and deems breast cancer preventive measures necessary, the upgrade of FEA, SA and PL detected in the surgery as ADH was also considered a general instance of upgrade. This study was conducted to examine the relationship between demographic and clinical variables, including the patient's age, family history of breast cancer, size of the mass, biopsy method, pathology according to CNB, pathology according to the surgery and the upgrading rate of the lesion. The study was accepted in scientific committee of Breast Cancer Research Center and received the ethics committee approval (code No. IR.ACECR. IBCRC. REC.1394.47).

Statistical analysis

The absolute and relative frequency of demographic and clinical characteristics and upgrading rates were reported by descriptive statistical tests. The relationship of upgrading rate with other variables was analyzed by Pearson Chi-Square and Fisher's Exact Tests.

Results

The mean age of the patients was 42.14 (±9.8) years. Table 1 presents the frequency of each of the variables. The most frequent pre-cancerous lesion in the CNB (49.4%) was PL, 23 (19.3%) of which were diagnosed as cancer in the surgical pathology.

Variable	Number	Percentage
Age (year)		
<30	29	12
30-50	180	74.7
>50	32	13.3
Family history of breast cancer		
Positive	43	17.8
Negative	198	82.2
Size of the lesion (cm)		
=<2	226	93.8
>2-5	15	6.2
Biopsy method		
CNB***	208	86.3

Vacuum-assisted CNB	25	10.4
Stereotactic CNB	8	3.3
Biopsy pathology		
ADH	28	11.6
SA	83	34.4
FEA	11	4.6
PL	119	49.4
Surgical pathology**		
ADH	17	7.1
SA	67	27.8
FEA	7	2.9
PL	84	34.9
Carcinoma	19	7.9
Other benign lesions *	47	19.5

Table 1. The Absolute and Relative Frequency of the Demographic and Clinical Variables in the Subjects (n=241).

* Other benign lesions, Fibroadenoma, Fibrocystic changes, Phyllodes tumor; **Atypical Ductal Hyperplasia (ADH), Sclerosing Adenosis (SA), Flat Epithelial Atypia (FEA), Papillary Lesion (PL); ***Core Needle Biopsy (CNB)

According to the findings of Table 2, the upgrading rate of the lesions was also different of lesions. The highest upgrading rate were noticed in ADH (21.4%) and PL (19.3%) and the lowest rates (1% and 0%) in SA and FEA, respectively (p-value = 0.033).

Upgrading			Biopsy Pathology*		
	ADH	SA	FEA	PL	Total
Negative	22	82	11	96	211
	78.60%	98.80%	100%	80.70%	87.60%
Positive	6	1	0	23	30
	21.40%	1.20%	0%	19.30%	12.40%
Total	28	83	11	119	241
	100%	100%	100%	100%	100%

Table 2. The Upgrading Rate in Each of the Pre-cancerous Lesions.

*Atypical Ductal Hyperplasia (ADH), Sclerosing Adenosis (SA), Flat Epithelial Atypia (FEA), Papillary Lesion (PL)

The second part of the data analysis examined the relationship of each study variable with the upgrading rate using Pearson Chi-Square and Fisher's Exact Test (Table 3).

Variable	Upgrading Frequency (Percentage)		P-Value
	Yes	No	
Age (year)			0.088 **
<50	21 (10.8)	174 (89.2)	
≥50	9 (19.6)	37 (80.4)	
Family history of breast cancer			0.546**
Positive	5 (11.6)	38 (88.4)	

Negative	25 (12.6)	173 (87.4)	
Size of the lesion (cm)			<0.005**
=<2	24 (10.6)	202 (89.4)	
>2-5	6 (40)	9 (60)	
Biopsy method			0.550*
CNB	27 (13.0)	181 (87)	
Vacuum-Assisted/Stereotactic	3 (12.0)	30 (88)	

Table 3. The Relationship between Upgrading and Demographic and Clinical Variables.

*Pearson Chi-Square Test, **Fisher's Exact Test

The findings of this table show that the upgrading rate was higher in patients with a lesion larger than 2 cm compared to those with a lesion smaller than or equal to 2 cm. The results of this analysis showed a significant relationship between size of the lesion and upgrading rate at the significance level of 5% (P = 0.005).

Also, according to the findings of the study, the upgrading rate was higher in patients over age 50 compared to patients younger than 50 (P=0.088).

As for family history of breast cancer, as shown in Table 3, the upgrading rate was higher in patients with a positive family history compared to those with a negative family history; however, this correlation was not significant (P=0.546).

As for CNB method, the upgrading rate was higher in the conventional CNB method compared to vacuum-assisted and stereotactic CNB; however, this correlation was not significant at the significance level of 0.05 (P=0.55).

Discussion

Benign breast conditions include a wide range of histopathologic lesions. Of the many benign types of these lesions, only a small number are clinically considered pre-cancerous or predisposing lesions of breast cancer.

A history of benign lesion biopsy in a patient’s breast, especially if the result of the pathology has shown a proliferative lesion, suggests an increased risk of breast cancer in the future.

The present study was conducted to determine the upgrading rate of pre-cancerous lesions and the factors affecting it and examined 241 women who had undergone CNB guided by mammography or ultrasound followed by a surgery at the Radiology Clinic of the Breast Clinic of the Academic Center for Education, Culture, and Research. The results show that the upgrading rate was the highest for Pl (19.3%) and ADH (21.4%) and the lowest (1%) for SA and (0%) for FEA, which is somewhat similar to the results obtained by Chae and Mooney, who reported the upgrading rate for ADH as 22.2% and 18%, respectively [13, 20]. According to a study by Dyrstad suggesting a 3.93-fold increase in the risk of breast cancer in proliferative lesions, preventive therapeutic measures can only be recommended to these patients if the upgrading rate obtained in this study for ADH and PL are taken into consideration [21]. Obviously, the presence of other risk factors of breast cancer in the patient, such as a high density of mammary tissue in the mammography, necessitates the use of additional diagnostic methods and ultimately surgery for the removal of the suspicious lesion in order to reduce the risk of cancer [22-24]. Particularly in cases where there is a discrepancy between the results of imaging and CNB, the physician should candidate the patient for the surgical removal of the lesion [25].

In cases where CNB indicates a papillary lesion in the breast, the probability of CNB errors in detecting papillary cancer in these lesions should be taken into account as well [26-27]. In papillary lesions, especially if combined with atypia, or if conventional CNB has been administered, it is advisable to remove the lesion by surgery. Some studies have shown evidence of cancerous lesions along with these lesions and advised to remove these lesions with proper margins [28-31].

In the present study, the upgrading rate for papillary lesions was 19.3%, which is less than that reported in previous studies (0 to 29%), which might be due to the smaller sample size from each of the pre-cancerous lesions in this study [32]. The biopsy method also affects the upgrading rate. This study found a lower upgrading rate in the patients undergone vacuum-assisted CNB compared to those undergone conventional CNB (12% vs. 13%), which could be related to the volume of extracted tissue as per the explanations. Seely et al. suggested that, in cases where the lesion is small and not associated with atypia and when vacuum-assisted biopsy is used, the surgery decision may be disclaimed and the patient might be put under periodical monitoring [33].

In the case of SA and FEA, the upgrading rate was 1.2% & 0% in this study, which, given the wide range of upgrading rates obtained for these lesions in different studies (0-35%), means a difference of opinion about whether to remove these lesions or put the patient under regular monitoring observe. The different upgrading rates of these lesions in the present study might be due to the small sample size in each of the pre-cancerous lesions compared to the other studies, which have examined only one type of lesion. In some cases, however, these lesions are associated with other pre-cancerous lesions that may not be detected in conventional CNB. In these instances, the patient's age, positive family history of breast cancer or size of the lesion may be important factors in the surgeon's choice of treatment. Since vacuum-assisted CNB yielded more precise results, it helps offer the patient better recommendations.

In conclusion, Overall, the results of this study showed that, in patients with large lesions and a pathology report of ADH or PL, the probability of upgrading is higher and the patient must undergo surgery to remove the lesion. In the case of SA or FEA, a proper decision needs to be made according to each patient's particular circumstances for reducing the risk of future cancer. Unnecessary surgeries may be preventable by periodic follow-ups in some low- risk cases. However, we acknowledge that the number of cases in our study for each pre-cancerous lesion was not large enough. Further studies with larger sample sizes are necessary for obtaining more accurate results.

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