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Upgrade Rates of DCIS, Intraductal Papilloma, and the Other High-risk Breast Lesions

DCIS, İntraduktal Papillom ve Diğer Yüksek Riskli Meme Lezyonlarında Upgrade Oranları

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ABSTRACT

Background: In benign breast lesions such as intraductal papilloma (IDP), atypical hyperplasia (AH), flat epithelial atypia (FEA) and lobular carcinoma *in situ* (LCIS), there is a 3-20% risk of upgrade to invasive or *in situ* breast cancer following excision. The aim of this study was to determine the upgrade rates for high-risk breast lesions (HRBL), which were diagnosed by core needle biopsy (CNB), to invasive or *in situ* breast carcinoma, and to determine to upgrade rates for ductal carcinoma *in situ* (DCIS) to invasive breast carcinoma in the second group. In addition, we investigated in which patient groups these rates are higher.

Materials and Methods: It was planned to include all female patients who had undergone surgical procedures following the determination of IDP, AH, FEA, LCIS, or DCIS after CNB under ultrasonographic guidance between April 2014 and August 2020. As there were no patients diagnosed with pure LCIS with biopsy, this was not included in the analysis. Patients were excluded from the study if more than 6 months had elapsed between CNB and excision, or if they had a history of breast cancer or radiotherapy. Demographic data, radiological findings and histopathological results were collected retrospectively from the hospital records.

Results: A total of 123 patients with diagnosis following CNB were evaluated. The diagnoses were IDP in 70.7% of patients, AH in 8.9%, FEA in 4.9%, and DCIS in 15.5%. The upgrade rates for invasive breast cancer were 30%, 0%, 16.7%, and 31.6%. The upgrade rates for DCIS were calculated as 3.5% in IDP, 45.5% in AH, and 0% in FEA. Especially, in IDP group upgrade was seen more at older ages, and when there were more than 2 two papilloma ($p<0.05$). The upgrade risk for DCIS after excision was 31.6%.

Conclusion: The upgrade risk for HRBL was found to vary between 5.8% and 45.5%, and the upgrade risk for DCIS after excision was 31.6%. In patients with HBRL; older ages, the presence of a multifocal lesion, a palpable mass, and radiological-histopathological discordance were seen to be risk factors for upgrade.

Keywords: Intraductal papilloma, atypical ductal hyperplasia, proliferative lesions with atypia, upgrade, breast cancer

ÖZ

Amaç: Benign meme lezyonları arasında bulunan intraduktal papillom (IDP), atipik hiperplaziler (AH), flat epitelyal atipi (FEA) ve lobüler karsinoma *in situ* (LCIS) eksizyon sonrası invaziv veya *in situ* meme kanseri için %3-20 arasında değişen upgrade riski taşır. Çalışmada amacımız kalın iğne biyopsisi (CNB) sonrası tanı konan yüksek riskli meme lezyonlarının (HRBL) invaziv veya *in situ* meme kanserine upgrade oranlarını belirlemek ve ikinci bir grup olarak duktal karsinoma *in situ* (DCIS) için invaziv meme kanserine upgrade oranlarını bulmaktı. Ek olarak hangi hastalarda upgrade oranlarının daha yüksek olduğunu araştırdık.

Gereç ve Yöntemler: Nisan 2014-Ağustos 2020 tarihleri arasında ultrasonografi eşliğinde CNB yapıldıktan sonra IDP, AH, FEA, LCIS veya DCIS saptanıp cerrahi işlem uygulanan tüm kadın hastaların dahil edilmesi planlanmıştır. Ancak biyopsi ile pür LCIS tanılı hasta olmadığı için bu hastalar çalışma dışı bırakılmıştır. Ayrıca CNB ile eksizyon arasında 6 aydan uzun süre geçen, meme kanseri veya radyoterapi öyküsü olan hastalar çalışmaya dahil edilmemiştir. Demografik, radyolojik ve histopatolojik veriler retrospektif olarak hasta dosyalarından toplanmıştır.

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ÖZ

Bulgular: CNB sonrası tanı alan 123 hasta çalışmaya dahil edildi. Hastaların %70,7'si IDP, %8,9'u AH, %4,9'u FEA ve %15,5'i DCIS tanılı idi. İnvaziv meme kanseri için upgrade oranları sırası ile %2,3, %0, %16,7 ve %31,6 bulundu. DCIS için upgrade IDP'de %3,5, AH'de %45,5, FEA'da %0 olarak hesaplandı. Özellikle IDP grubunda ileri yaşlarda ve 2'den fazla iki papillom olduğunda upgrade daha fazla görüldü (p<0,05). DCIS'nin eksizyon sonrası upgrade riski %31,58 olarak bulundu.

Sonuç: Yüksek riskli meme lezyonlarının upgrade riski %5,75-45,45 arasında değişirken, DCIS'nin eksizyon sonrası upgrade riski %31,58 olarak bulundu. HBRL'li hastalarda; ileri yaş, multifokal lezyon varlığı, ele gelen kitle ve radyolojik-histopatolojik uyumsuzluğun upgrade için risk faktörleri olduğu görüldü.

Anahtar Kelimeler: İntraduktal papillom, atipik duktal hiperplazi, proliferatif atipili lezyonlar, upgrade, meme kanseri

Introduction

In 1985, breast lesions were first grouped as non-proliferative, proliferative without atypia, and proliferative atypical lesions, and the malignancy risks were reported with upgrade rates for each of these lesions (1). Within these, the group with an increased risk of breast cancer and showing an upgrade to invasive cancer or ductal carcinoma *in situ* (DCIS) after excision is accepted as high-risk breast lesions (HRBL). The HRBL group includes intraductal papilloma (IDP), atypical ductal and lobular hyperplasia (ADH-ALH), flat epithelial atypia (FEA), and lobular carcinoma *in situ* (LCIS) (2).

IDPs, which are a specific group within proliferative breast lesions without atypia, have upgrade rates of 5-20%. It has also been reported that this risk increases if a palpable mass is present, if a mass >1 cm is determined on mammography (MG) or ultrasonography (US), or if there are more than 5 papillomas (3).

FEA is a borderline lesion which is a precursor to low-grade invasive and *in situ* cancers, which is grouped in the proliferative atypical breast lesions (4). It is generally diagnosed with core needle biopsy (CNB) applied to microcalcification seen as suspicious on MG. Although the risk is lower in FEA patients when there is compatibility between radiological and histopathological diagnoses, upgrade rates varying from 9.6% to 15% have been reported. ADH or ALH accompanying the lesion increases the upgrade risk (4).

Atypical hyperplasia often emerges as proliferative atypical breast lesions in breast biopsies. The upgrade rates range from 10-20%, and have been reported as <3% in ALH diagnosed incidentally with radiology compatible with the histopathological diagnosis. Treatment with surgical excision following biopsy is recommended for ADH. However, although there are those who recommend surgical excision for ALH, in cases diagnosed incidentally where radiological and histopathological diagnoses are not compatible, follow-up is thought to be sufficient (5,6,7). The risk of the development of ipsilateral or contralateral breast cancer in atypical hyperplasia is 3-4-fold greater than that in the general population (1).

DCIS is a proliferation of ductal epithelial cells in the breast that does not extend beyond the basement membrane and has no evidence of invasion (8). In contrast to all other high-risk lesions, in DCIS, subsequent invasive breast cancer develops in the same breast and same quadrant, and therefore DCIS is accepted as a precursor lesion (8,9). Invasive cancer can be seen after surgical excision in 10-20% of patients with DCIS diagnosed with CNB (10).

The aim of this study was to determine the upgrade rates for HRBL and DCIS diagnosed with CNB in our hospital through evaluation of excisional biopsy results and to demonstrate in which patient group the upgrade risk is higher.

Material and Methods

Case Selection and Study Design

The study included all female patients determined by breast mass or suspicious microcalcification who underwent surgical excision following a diagnosis of IDP, FEA, ADH, ALH, or DCIS as a result of CNB between April 2014 and August 2020. Calcifications that are irregular in size or shape or are tightly clustered together, are called suspicious calcifications. No patient was diagnosed with pure LCIS with biopsy between the defined dates. All the LCIS diagnoses were accompanying invasive cancer, so patients with a diagnosis of LCIS were not included in the study. Other exclusion criteria were i) A period of more than 6 months between CNB and excision, and ii) A history of breast cancer or radiotherapy. Data were retrieved from the medical records and a retrospective review was made of patient age, physical examination, breast US, MG, and magnetic resonance imaging (MRI) findings, and CNB and pathology results.

Imaging Targets and Biopsy Techniques

Breast imaging included US, MG, and MRI methods. Each image was evaluated according to the Breast Imaging

Reporting and DATA System (BIRADS) classification (11). Following the evaluation, CNB was taken from BIRADS 3, 4, and 5 lesions, which were >2 cm, showed growth in follow-up and were developing morphological changes. Biopsy procedures were applied under sterile conditions after local anesthesia with 1% lidocaine underwent the patient. Core biopsies were obtained under USG guidance; at least 6 pieces were collected using a 14-G automatic core-biopsy needle (Geotek Inc., Ankara, Türkiye). After the procedure, the samples were placed into tubes containing 10% formalin and sent for pathological analysis.

Histopathological Assessement

HRBL were defined as IDP, FEA, ADH, and ALH. The histopathological evaluation was defined as follows;

IDP; a lesion formed of branching structures with fibrovascular cores covered by benign epithelial cells (12).

FEA; is by definition flat, i.e. lacks architectural atypia, but has low-grade cytologic atypia (13).

ADH; epithelial proliferation formed from a neoplastic cell population similar in appearance to low-grade DCIS and limited to the breast ductal-lobular system at low volume or dimensions (<2 canals involved or total size ⩽0.2 cm) (14).

ALH; small uniform neoplastic cell proliferation showing loose cohesion similar to LCIS involving <50% of acini in the terminal ductal lobular unit (9).

DCIS; neoplastic proliferation of breast ductal epithelial cells limited to the ductal-lobular system without evidence of invasion from the basal membrane to the stroma (15).

Upgrade was defined as the diagnosis of DCIS or invasive cancer after excision of the lesion initially defined as benign or atypical on CNB. Excisional biopsy was performed on patients with HRBL after CNB and the upgrade rates were determined according to this result.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn. 21 software. The conformity of continuous data to normal distribution was assessed with the Shapiro-Wilk test. Parametric tests were applied to data showing normal distribution and non-parametric tests to data not showing normal distribution. In the comparisons of two independent groups, the Student's t-test or the Mann-Whitney U test were used, and for more than two groups, One-Way ANOVA or the Kruskal Wallis test. In the analysis of categorical data, the chi-square test and the Fisher's Exact test were used. A value of $p<0.05$ was accepted as statistically significant. Thus, the data obtained from clinicopathological and imaging findings were evaluated with the chi-square test. The descriptive features of data such as age and lesion size were evaluated with the One-Way ANOVA and Kruskal-Wallis tests.

Results

Between April 2014 and August 2020, a total of 206 patients were diagnosed with BIRADS 3, 4, or 5 lesions on breast imaging. It was seen that 123 patients were operated on for a diagnosis of HRBL. The CNB results of those patients were 87 IDP, 6 FEA, 11 ADH and 19 DCIS. Imaging of the patients was performed with US, MG, or MRI and all the patients were evaluated according to the BIRADS categories.

When the groups were evaluated ultrasonographically, there was seen to be a regular contoured solid mass in more of the IDP group (36.9%), most of the patients with a normal image (50%) were in the FEA group, and in most patients in the ADH and DCIS groups, there was an appearance of a solid mass (56.4%, 62.5%, respectively). A statistically significant difference was determined between the groups in respect of the US imaging characteristics ($p=0.029$). When we look at the mammographic imaging features, asymmetric density was higher in the patients in the IDP group, while Asymmetric density and microcalcification were more common in the DCIS group ($p>0.05$).

When the distribution according to the BIRADS characteristics was examined, most lesions in all groups were BIRADS 3, followed by BIRADS 4 in the IDP, FEA, and ADP groups, and BIRADS 5 lesions in the DCIS group. A statistically significant difference was determined between the groups in respect of BIRADS distribution ($p<0.001$). There was discordance between radiological and histopathological diagnoses in 62.1% of IDPs, 50% of FEAs, 90.9% of ADHs, and in 68.3% of DCISs. This difference between the groups was statistically significant ($p=0.029$). The demographic, clinicopathological, and imaging findings are shown in Table 1.

There were 87 patients in the IDP group, the mean lesion size was 16.07±10.76 mm, and the mean age was 47.24±12.82 years. A palpable mass was detected in 53 of the patients (60.9%), 33 patients (37.9%) had radiological-histopathological discordance, and 82 patients (94.3%) had a single lesion. The upgrade rate for IDP was found to be 5.8%, upgrade was seen more at older ages, and when there were more than 2 papillomas ($p<0.05$). Although not statistically significant, the presence of a palpable mass was determined in all lesions with upgrade in the IDP group and concordance was lower in the group with upgrade (with upgrade 40%; without upgrade 62.2%). In 2 cases that developed invasive ductal cancer (IDC) in this group, there was seen to be discordance. These results were found to be clinically significant. There was atypia in the biopsy sample of one (1.2%) patient diagnosed with IDP.

Table 1. Demographic, clinicopathologic and imaging findings in the patients

Characteristic	Lesions								Total		
	IDP		FEA		ADH		DCIS				
	Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		p[1]
Age (year)	47.24±12.82		43.5±8.48		57.36±9.36		50±13.18		12.7±8.48		0.058
Lesion size (mm)	16.07±10.76		14.17±10.15		18.51±14.26		25.55±24.68		17.66±14.3		0.764[a]
	n	%	n	%	n	%	n	%	n	%	p[2]
Ultrasonography (n=120)											
Irregular contour solid mass	26	31.0	2	33.3	3	27.3	6	31.6	37	30.8	**0.029***
Regular contour solid mass	31	36.9	0	0.0	3	27.3	4	21.1	38	31.7	
Irregular contour cystic mass	15	17.9	1	16.7	2	18.2	1	5.3	19	15.8	
Regular contour cystic mass	3	3.6	0	0.0	1	9.1	1	5.3	5	4.2	
Ductal ectasia	5	6.0	0	0.0	0	0.0	0	0.0	5	4.2	
Normal imaging	4	4.8	3	50.0	2	18.2	7	36.8	16	13.3	
Mammography (n=94)											
Asymmetric density	19	29.7	2	40.0	1	12.5	1	5.9	23	24.5	0.124
Asymmetric density and mass	18	28.1	1	20.0	3	37.5	5	29.4	27	28.7	
Asymmetric density microcal and mass	5	7.8	0	0.0	1	12.5	1	5.9	7	7.4	
Asymmetric density microcalcification	7	10.9	1	20.0	3	37.5	8	47.1	19	20.2	
Normal imaging	15	23.4	1	20.0	0	0.0	2	11.8	18	19.1	
MRI (n=55)											
Mass	21	70.0	0	0.0	3	50.0	5	31.3	29	52.7	0.095
No mass	9	30.0	3	100.0	3	50.0	11	68.8	26	47.3	
BIRADS (n=123)											
3	32	36.8	2	33.3	4	36.4	2	10.5	40	32.5	**<0.001***
4	53	60.9	3	50.0	6	54.5	10	52.6	72	58.5	
5	2	2.3	1	16.7	1	9.1	7	36.8	11	8.9	
Palpable mass											
Present	53	60.9	5	83.3	7	63.6	12	63.2	77	62.6	0.75
Absent	34	39.1	1	16.7	4	36.4	7	36.8	46	37.4	
Concordance											
Present	33	37.9	3	50.0	1	9.1	2	10.5	39	31.7	**0.029***
Absent (discordance)	54	62.1	3	50.0	10	90.9	17	89.5	84	68.3	

p[1]: One-Way ANOVA ([a]Kruskal-Wallis test), p[2]: Chi-square test, *: Statistically significant (p<0.05), IDP: Intraductal papilloma, FEA: Flat epihtelial atypia, ADH: Atypical ductal hyperplasia, DCIS: Ductal carcinoma *in situ*, BIRADS: Breast imaging reporting and DATA system, Concordance: Mention of imaging-histologic concordance, SD: Standard deviation

There were a total of 6 patients in the FEA group. The mean age of the patients was 43.5±8.48 years, and the mean lesion size was 14.17±10.15 mm. While two patients (40%) had multifocal lesions, 5 patients (83.3%) had palpable masses. In the FEA group, there was one lesion with upgrade (16.7%), and there was radiological-histopathological concordance in this lesion, which was also multifocal and there was a palpable mass.

The ADH group comprised 11 patients. The mean age of the patients was 57.36±9.36 years, and the mean lesion size was 18.51±14.26 mm. Two patients (18.2%) had multifocal lesions, seven patients (63.6%) had palpable masses, and 2 patients (18.2%) had radiological-histopathological discordance. The upgrade rate for ADH was found to be 45.5% and all the patients showed upgrade to IDC. Palpable mass was detected in 3 of 5 (60%) patients who were upgraded. Evaluations were made in this group (p>0.05).

Nineteen patients included in the study were diagnosed with DCIS. The mean lesion size in these patients was 25.55±24.68 mm, and the age was 50±13.18 years. In this

group, 12 (63.2%) of the patients had palpable masses, 2 patients (10.5%) had radiological-histopathological discordance and 7 (36.8%) had multifocality. In the examination of DCIS, a palpable mass was determined in 83.3% of the lesions with upgrade and in 53.9% of the lesions without upgrade. The upgrade rate for DCIS was found to be 31.6%. In patients with DCIS, the mean age of the patients in the upgraded group was lower. Although the findings were clinically significant, they were not statistically significant. The findings are shown in Table 2.

The total upgrade rate for HRBL was 10.6%. The IDC upgrade rate for DCIS was found to be 31.6%. For IDP, the DCIS upgrade rate was 3.5% and the IDC upgrade rate was 2.3%. For FEA, the IDC upgrade rate was calculated as 16.7% and for ADH, the DCIS upgrade rate was 45.5%. The upgrade rates for HRBL and DCIS are shown in Table 3. Pathological samples of the patients who developed an upgrade are shown in Figures 1 and 2.

Table 2. Characteristics of groups with upgrade and no upgrade in high-risk breast lesions and DCIS

Intraductal papilloma							
	Total (n=87)		**Upgrade (n=5)**		**No upgrade (n=82)**		
Characteristic	**Mean ± SD**		**Mean ± SD**		**Mean ± SD**		**p[1]**
Age (year)	47.24±12.82		60.2±7.29		46.45±12.68		0.019*
Lesion size (mm)	16.07±10.76		20.4±20.83		15.81±10.01		0.985[a]
	n	**%**	**n**	**%**	**n**	**%**	**p[2]**
Palpable mass							
Present	53	60.92	5	100	48	58.54	0.065[a]
Absent	34	39.08	0	0	34	51.46	
Concordance							
Present	54	62.07	2	40	51	62.2	1.00[a]
Absent (discordance)	33	37.93	3	60	31	37.8	
Number of lesion							
Single	82	94.25	2	40	80	97.56	<0.001*
2-5	3	03.44	2	40	1	1.22	
>5	2	02.29	1	20	1	1.22	
Flat epithelial atypia							
	Total (n=6)		**Upgrade (n=1)**		**No upgrade (n=5)**		
Characteristic	**Mean ± SD**		**Mean ± SD**		**Mean ± SD**		**p[1]**
Age (year)	43.5±8.48		41		44±9.38		NC
Lesion size (mm)	14.17±10.15		5		16±10.17		NC
	n	**%**	**n**	**%**	**n**	**%**	**p[2]**
Palpable mass							
Present	5	83.33	1	100	4	80	1.00[a]
Absent	1	16.66	0	0	1	20	
Concordance							
Present	3	50	1	100	2	40	1.00[a]
Absent (discordance)	3	50	0	0	3	60	
Multifocal							
Present	2	40	1	100	1	20	0.333[a]
Absent	4	60	0	0	4	80	
Atypical ductal hyperplasia							
	Total (n=11)		**Upgrade (n=5)**		**No upgrade (n=6)**		
Characteristic	**Mean ± SD**		**Mean ± SD**		**Mean ± SD**		**p[1]**

Table 2. continued

Age (year)	57.36±9.36		57.2±10.06		57.5±9.71		0.961
Lesion size (mm)	18.51±14.26		26.6±16.89		11.77±7.65		0.177[a]
	n	**%**	**n**	**%**	**n**	**%**	**p[2]**
Palpable mass							
Present	7	63.64	3	60	4	66.67	1.00[a]
Absent	4	36.36	2	40	2	33.33	
Concordance							
Present	9	81.82	4	80	5	83.33	1.00[a]
Absent (discordance)	2	18.18	1	20	1	16.67	
Multifocal							
Present	2	18.18	2	40	0	0	0.182[a]
Absent	9	81.82	3	60	6	100	
Ductal carcinoma *in situ*							
	Total (n=19)		**Upgrade (n=6)**		**No upgrade (n=13)**		
Characteristic	**Mean ± SD**		**Mean ± SD**		**Mean ± SD**		**p[1]**
Age (year)	50±13.18		46.83±15.56		51.46±12.34		0.493
Lesion size (mm)	25.55±24.68		20.42±15.98		27.92±28.07		0.701[a]
	n	**%**	**n**	**%**	**n**	**%**	**p[2]**
Palpable mass							
Present	12	63.16	5	83.33	7	53.85	0.333[a]
Absent	7	36.84	1	16.67	6	46.15	
Concordance							
Present	17	89.47	6	100	11	84.62	1.00[a]
Absent (discordance)	2	10.53	0		2	15.38	
Multifocal							
Present	7	36.84	3	50	4	30.77	0.617[a]
Absent	12	63.16	3	50	9	69.23	

p[1]: Student's t test ([a]Mann-Whitney U test), p[2]: Chi-square test ([a]Fisher's Exact test) NC: Not calculated, SD: Standard deviation, *: Statistically significant (p<0.05)

Discussion

Knowing the risk of upgrade in breast lesions is very important in decision-making for follow-up or excision. With the developments in imaging methods over time, there has started to be more detailed evaluation of lesions, and in parallel with this, decisions have become clearer in determining the lesions from which biopsy will be taken and those for which subsequent excision is planned.

IDP, FEA, ADH, ALH, and LCIS are high-risk lesions in respect of upgrade after excision. It has been reported that an upgrade to invasive cancer can be seen in up to 20% of DCIS (16,17).

In studies in literature, MacColl et al. (18) reported the upgrade risk for IDP as 12% (8.3% DCIS and 3.3% invasive breast cancer. According to that study, the risk is greater in the group with high BIRADS, in the older ages group, in lesions that contain calcifications and in lesions >5 mm in size (18).

Qui et al. (19) determined an upgrade rate of 11.1% for IDP and reported that in all the cases with upgrade to invasive cancer, there was accompanying atypia in the biopsy and no upgrade in benign papilloma.

Han et al. (20) found the upgrade risk to be 0.8% for IDP without atypia and stated that conservative follow-up may be sufficient in solitary lesions that are thought to be benign with CNB and which do not show clinically suspicious characteristics, and in patients without concurrent contralateral breast cancer.

Table 3. High risk breast lesions upgrade rate

Tru-cut biopsy	Excision						Total upgrade rate (DCIS+invasive Ca)	
	No upgrade			Invasive Ca				
	n		%	n		%	n	%
DCIS (n=19)	13		68.42	6		31.58	6	31.58
	No upgrade		DCIS		Invasive Ca			
	n	%	n	%	n	%	n	%
IDP (n=82)								
Atypia	1	1.15	0		0		0	0
No atypia	81	93.1	3	3.45	2	2.3	1	5.75
Total	**82**	**94.25**	**3**	**3.45**	**2**	**2.3**	**7**	**5.75**
FEA (n=6)								
Atypia	1	16.67	0	0	0	0	0	0
No atypia	4	66.67	0	-	1	16.67	1	16.67
Total	**5**	**83.33**	**0**	**0**	**1**	**16.67**	**1**	**16.67**
ADH (n=11)	6	54.54	5	45.45	0	0	-	45.45
All patient (IDP, FEA, ADH) (n=104)	93	89.42	8	7.69	3	2.88	11	10.58

IDP: Intraductal papilloma, FEA: Flat epithelial atypia, ADH: Atypical ductal hyperplasia, DCIS: Ductal carcinoma *in situ*

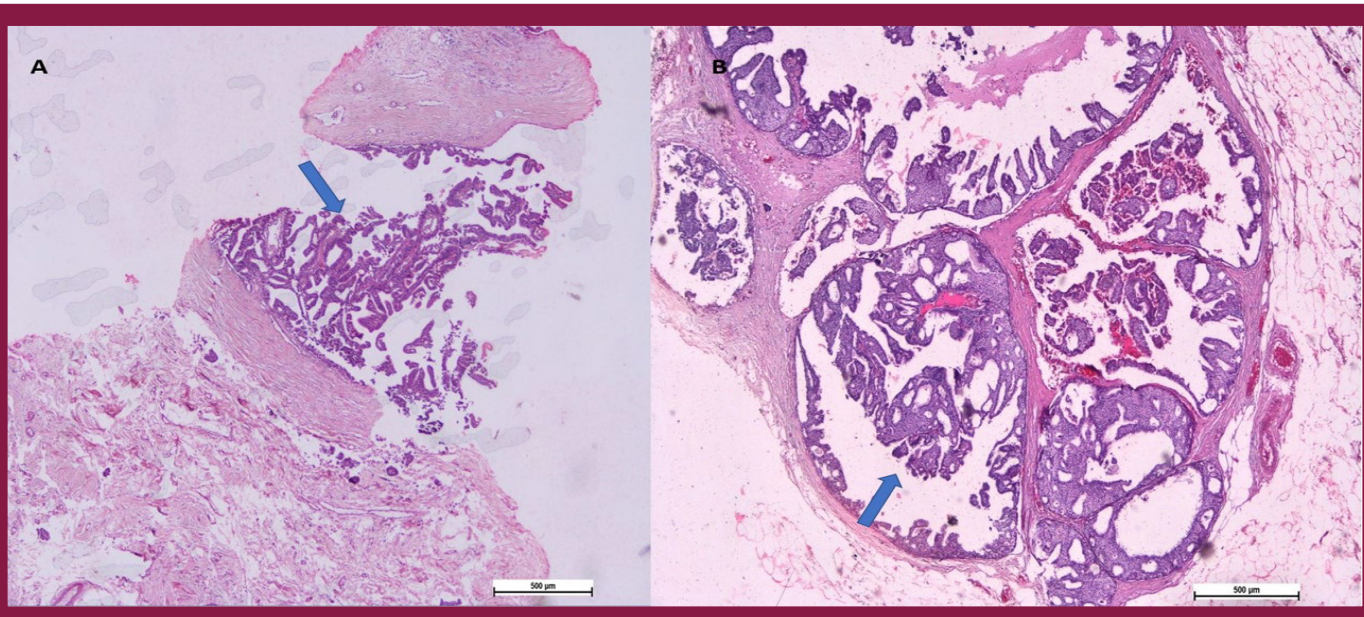

Figure 1. Case 1; a 56-year-old female patient with upgrade. A- Intraductal papilloma diagnosed on core needle biopsy (blue arrow), (H&E, x40) B- Was an upgraded to papillary ductal carcinoma *in situ* on partial mastectomy (blue arrow), (H&E, x40)

In the current study, the upgrade rate for IDP was found to be 5.8%, which was consistent with the literature. There was upgrade to DCIS in 3.5% of patients and to IDC in 2.3%. This risk was greater at older ages, when there were more than 2 papilloma, when a palpable mass was present, and when there was radiological-histopathological discordance.

There is no clear consensus about performing surgical excision after biopsy for FEA. In an analysis of 32 studies, Rudin et al. (21) reported upgrade rates varying between 0% and 42% and calculated the mean value to be 11.1%. Furthermore, detailed evaluation was made of 16 high-quality studies and the upgrade rate was determined to

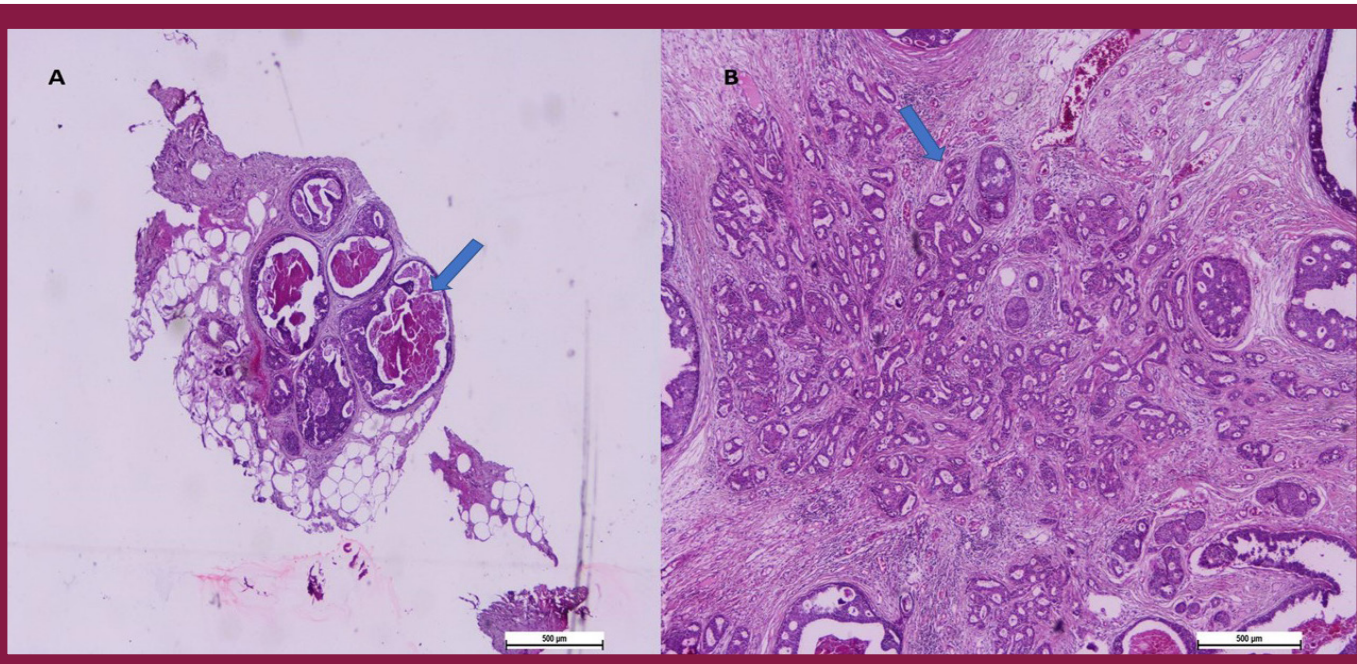

Figure 2. Case 2; 41-year-old female patient with upgrade. A- Ductal carcinoma *in situ* diagnosed on core needle biopsy (blue arrow), (H&E, x40) B- Was an upgraded to invasive ductal carcinoma on partial mastectomy (blue arrow), (H&E, x40)

be 7.5%. In the same study, the upgrade rate to ADH was found to be 18.6% and in conclusion, surgical excision was recommended for FEA (21). Lamb et al. (22) reported the DCIS upgrade risk for FEA as 2.4% and showed that there was ADH, ALH, and LCIS upgrade in 29.8% of patients.

In a similar study, the upgrade rate was reported to be 12%, but the radiological follow-up was recommended as a reasonable option in patients where microcalcifications with characteristics of pure FEA could be completely removed with vacuum-assisted biopsy (23).

In the current study, the upgrade rate for FEA was found to be 16.7%, but there were very few patients diagnosed with FEA in the HRBL group organized in this study.

In the studies in literature related to upgrade rates in ADH, in a meta-analysis by Schiaffino et al. (24) in which 14 studies of the excision of all lesions after biopsy were evaluated, the upgrade rate for IDC was found to be 14% and surgical excision was recommended for patients determined with ADH.

Sutton et al found a similar upgrade rate of 16% for ADH. Of these patients, 81% were upgrade to DCIS and 19% to IDC (25).

Co et al. (26) reported an upgrade rate of 25% and stated that the risk was higher in patients with a mass and suspicious appearance on mammography.

In a study evaluating high-risk lesions, Mooney et al. (27) reported upgrade rates of 18% for patients with ADH and 9% for those with ALH.

Zhao et al. (28) are among the researchers who have found the upgrade risk to be low for ALH, reporting upgrade to DCIS or IDC for only 3.1% of patients. In another study, Cangiarella et al. (29) reported an upgrade rate of 6%.

In the current study, the upgrade rate for ADH was found to be 45.5% and all the patients showed upgrade to IDC. That there was a palpable mass (at least 1 cm) in all the patients with upgrade was found to be worthy of attention.

DCIS is not only high risk but also a precancerous lesion. In a study by Hogue et al. (30), approximately 29.1% of the patients were seen to have upgraded after excision. Lamb et al. (31) found the upgrade risk for DCIS to be 21.8% and reported that the risk increased in those with a family history. Allen et al. (10) determined an upgrade risk of 19.6%.

In the current study, there was seen to be 31.6% upgrade in patients diagnosed with DCIS. These patients were younger than those without upgrade and most had a palpable mass.

Study Limitations

The main limitation of this study was the sample size despite having included all the patients determined with a suspicious mass in the breast and then applied with biopsy. The low number of patients, especially in the FEA and ADH groups, may not have been sufficient to reflect all the results. However, the possibility of encountering upgrade lesion in the excision results of patients diagnosed with HRBL in needle biopsy should be considered.

Take Home Messages

• ADH, ALH, FEA and IDP all indicated an increased risk of *in situ* or invasive breast cancer.

• DCIS indicated an increased risk of invasive breast cancer.

• HRBLs should be evaluated for each patient, along with patient-specific risk factors and imaging findings.

• In patients with HBRL; older ages, the presence of a multifocal lesion, palpable mass, and radiological-histopathological discordance were seen to be risk factors for upgrade.

• Upgrade rates increased especially in IDPs at older ages and in the presence of more than two lesions, and excision should be recommended.

Conclusion

The results of this study showed a general upgrade risk of 10.6% in HRBL, calculated as 5.8% for IDP, 16.7% for FEA, and 45.5% for ADH. This risk was seen to be 31.6% for DCIS. When the patient results were evaluated, older ages, the presence of a multifocal lesion, a palpable mass, and radiological-histopathological discordance were seen to be risk factors for upgrade, especially in the IDP group. A young age and the presence of a palpable mass increase upgrade in DCIS, and in the FEA and ADH groups, the presence of a palpable mass increases the risk.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval for this study was granted from University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital Ethics Committee for Clinical Studies in May 2021 (reg: 266).

Informed Consent: Informed consent was not required due to the retrospective use of de-identified administrative data.

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Authorship Contributions

Surgical and Medical Practices: E.Y., S.B., A.M.E., Concept: E.Y., S.B., N.U., Design: E.Y., Data Collection or Processing: E.Y., M.Ö., A.K., Analysis or Interpretation: E.Y., Literature Search: E.Y., M.Ö., A.K., Writing: E.Y.

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