Obstetrics and Gynecology

Review Article

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Upgrade rate of percutaneously diagnosed pure flat epithelial atypia: systematic review and meta-analysis of 1,924 lesions

https://doi.org/10.1515/jom-2021-0206 Received August 22, 2021; accepted December 14, 2021; published online February 14, 2022

Abstract

Context: Management remains controversial due to the risk of upgrade for malignancy from flat epithelial atypia (FEA). Data about the frequency and malignancy upgrade rates are scant. Namely, observational follow-up is advised by many studies in cases of pure FEA on core biopsy and in the absence of an additional surgical excision. For cases of pure FEA, the American College of Surgeons no longer recommends surgical excision but rather recommends observation with clinical and imaging follow-up.

Objectives: The aim of this study is to perform a systematic review and meta-analysis to calculate the pooled upgrade of pure FEA following core needle biopsies.

Methods: A search of MEDLINE and Embase databases were conducted in December 2020. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. A fixed- or random-effects model was utilized. Heterogeneity among studies was estimated by utilizing the I2 statistic and considered high if the I2 was greater than 50%. The random-effects model with the DerSimonian and Laird method was utilized to calculate the pooled upgrade rate and its 95% confidence interval. **Results:** A total of 1924 pure FEA were analyzed among 59 included studies. The overall pooled upgrade rate to malignancy was 8.8%. The pooled upgrade rate for mammography only was 8.9%. The pooled upgrade rate for ultrasound was 14%. The pooled upgrade rate for mammography and

Conclusions: Although the guidelines for the management of pure FEA are variable, our data support that pure FEA diagnosed at core needle biopsy should undergo surgical excision since the upgrade rate >2%.

Keywords: breast; cancer; flat epithelial atypia; high-risk lesion; mammography; ultrasound; upgrade rate.

Ten percent of breast core biopsies represent high-risk lesions [1]. They can be described as borderline lesions that could be a marker of future breast carcinoma. They can correspond to either precursor of breast cancer or an increased risk of oncogenesis [2-6]. Flat epithelial atypia (FEA) has a similar increased risk of subsequent carcinoma as any other benign proliferative changes in the breast. Currently, the high-risk classification includes papillary lesions, radial scar/complex sclerosing lesions, lobular carcinoma in situ (LCIS), atypical hyperplasia (lobular and ductal), and columnar cell lesions (hyperplasia or FEA) [7–10]. FEA is defined by the World Health Organization (WHO) as a "presumably neoplastic intraductal alteration characterized by the replacement of native epithelial cells by a single layer or three to five layers of mildly atypical cells." [10] High-risk lesions are a hot topic in breast imaging; radiologists have to balance the risk of underestimation against the surgical risk to patients.

The management of FEA remains controversial due to the risk that it will upgrade to malignancy. Data demonstrating the frequency of FEA upgrade to malignancy are scant. Namely, observational follow-up is advised by many studies in cases of pure FEA on core biopsy and in the absence of an additional surgical excision. For cases of pure FEA, the American College of Surgeons no longer recommends surgical excision but now recommends clinical observation and follow-up imaging [11]. Surgical excision is recommended, particularly when there is concurrent atypical ductal hyperplasia (ADH) or another high-risk lesion [12]. This approach follows the Second

ultrasound combined was 8.8%. The pooled upgrade rate for MRI-only cases was 27.3%.

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International Consensus Conference on Lesions of Uncertain Malignant Potential, which recommends surveillance if a core needle biopsy (CNB) yields FEA [13]. However, other publications recommend surgical excision when FEA is detected by core biopsy [12, 14, 15].

Thus, the purpose of this systematic review and metaanalysis was to estimate the upgrade rate of percutaneously diagnosed pure FEA in relation to surgical excision.

Methods

Study protocol and quality appraisal

No ethical committee approval was performed for this systematic retrospective review. The study was registered on the Open Science Framework (OSF) Center for Open Science (COS, DOI 10.17605/OSF.IO/ KU82T). No specific funding or support was received for this study. Guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed [16-18].

Search strategy and study eligibility criteria

We conducted research of studies in MEDLINE and Embase through December 2020. All of the studies reporting the correlation of FEA with definite pathology were searched. Correlation with the outcome of pure FEA after definite pathology was performed. A malignant finding was defined as invasive mammary carcinoma or ductal carcinoma in situ (DCIS). All of the remaining findings were considered to be nonmalignant.

The search string was as follows: "(('flat epithelial atypia'/exp OR 'flat epithelial atypia' OR 'FEA'/exp) AND ('biopsy'/exp OR 'biopsy') AND ('intraductal carcinoma'/exp OR 'DCIS' OR 'breast intraductal carcinoma' OR 'carcinoma, intraductal, noninfiltrating' OR 'ductal carcinoma in situ' OR 'intraductal carcinoma' OR 'breast carcinoma'/ exp OR 'breast carcinoma' OR 'carcinoma, infiltrating duct' OR 'carcinoma, mammary' OR 'invasive ductal carcinoma' OR 'mamma carcinoma' OR 'mammary carcinoma')) AND 'article'/it."

Only manuscripts written in English were considered for the analysis. Publications were selected based on the title and abstract by one independent reader (R.F., with 10 years of experience in breast imaging). Once selection was performed, all the studies were read thoroughly by the two authors (C.M.K., with over 20 years of experience in breast imaging). The details regarding the number of pure FEA lesions with correlation with outcome were analyzed, as well as the number of nonmalignant vs. malignancies. The full text was assessed by two readers who performed the first selection.

Data extraction

The two independent readers performed the data extraction. When the two readers did not agree, the manuscript was rejected. When possible, the following data were recorded: (1) year of publication; (2) study design; and (3) number of patients and lesions.

Primary point

The primary and unique outcome was the correlation between the FEA findings and the definite outcome after surgery.

Statistical analysis

This meta-analysis study was conducted utilizing STATA 15 software to seek the relationship between the variables. Heterogeneity among the studies was estimated by utilizing the I2 statistic and was considered high if I2 was greater than 50%. The random-effects model with the DerSimonian and Laird method was utilized to calculate the pooled upgrade rate and its 95% confidence interval (CI).

Results

Literature search and characteristics of the analyzed studies

Figure 1 demonstrates the literature search flowchart. Among 307 retrieved publications, 248 were excluded because they did not meet the inclusion criteria. Thus, 59 (19%) of them met the inclusion criteria and comprised our study cohort.

The articles comprising our study cohort were published from 2007 to 2020 [19-77]. A total of 1,924 pure FEA cases were identified. No details regarding the demographic data or imaging appearance were analyzed because few studies reported them. Forest plots of the overall upgrade rate to breast cancer are detailed in Figure 2.

Percutaneous biopsies

Imaging guidance for CNB was reported in all 59 studies. In 39% (23/59) of the studies, all lesions were biopsied under stereotactic guidance. In 2% (1/59) of the studies, the lesions were biopsied under ultrasound-guidance only. In 5% (3/59) of the studies, the lesions were biopsied with MRI-guidance only. Thirty-six percent (21/59) of the studies reported lesions being biopsied utilizing stereotactic or ultrasound-guidance, whereas in 19% (11/59) of the studies, the lesions were biopsied with any of the imaging modalities: stereotactic, ultrasound-, or MRI-guidance.

The parameter of CNB size could not be assessed in this study because all the studies were not reporting the biopsy needle size.

Overall upgrade rate

Among the 1,924 pure FEA lesions, 255 (13%) were upgraded to malignancy on surgical excision (Table 1 and Figure 2).

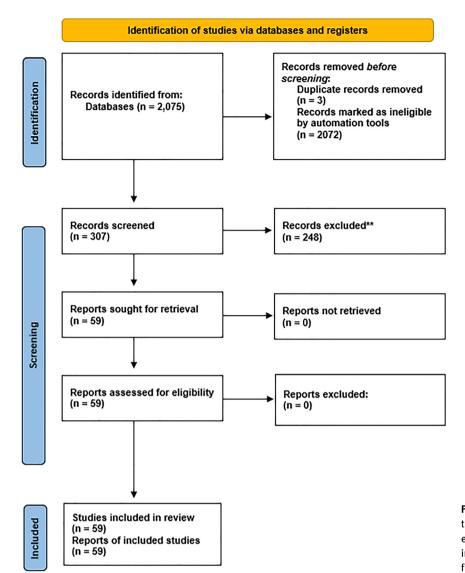


Figure 1: Flow diagram of study selection. Of the 307 initially retrieved articles, 248 were excluded because they did not meet the inclusion criteria, thus 59 were included the final analysis.

The pooled upgrade rate for lesions detected only on mammography was 9%, the pooled upgrade rate for lesions detected only on sonography was 14%, and the pooled upgrade rate for a lesion seen both mammographically and sonographically was 9%. The pooled upgrade rate for MRI-only-detected lesions was 27%.

Upgrade details

Over the 59 studies, there were 36 studies that detailed the findings among upgrades. They corresponded to 1,660 lesions, of which 193 (12%) were upgraded. Among these 193 upgrades, there were:

- 75 invasive ductal carcinomas no special type (75/ 193, 39%)
- 59 DCIS (59/193, 31%)

- 57 invasive lobular carcinomas (57/193, 30%)
- 2 invasive tubular carcinomas (2/193, 1.0%)

Risk of publication bias

The derived model showed from the forest plot seen above shows that the error analysis had a substantial impact on writing progress. Despite the results, the calculated statistical period for certain experiments crossed the no-effect axis. Because the CIs did not converge, these figures seem to be significantly heterogeneous; thus, both the fixedeffect models and their predictions, which indicate that the analysis could be significantly realistic for the data set and which proved the existence of heterogeneity (p<0.0001), confirm this. Additionally, the mean I2 test,

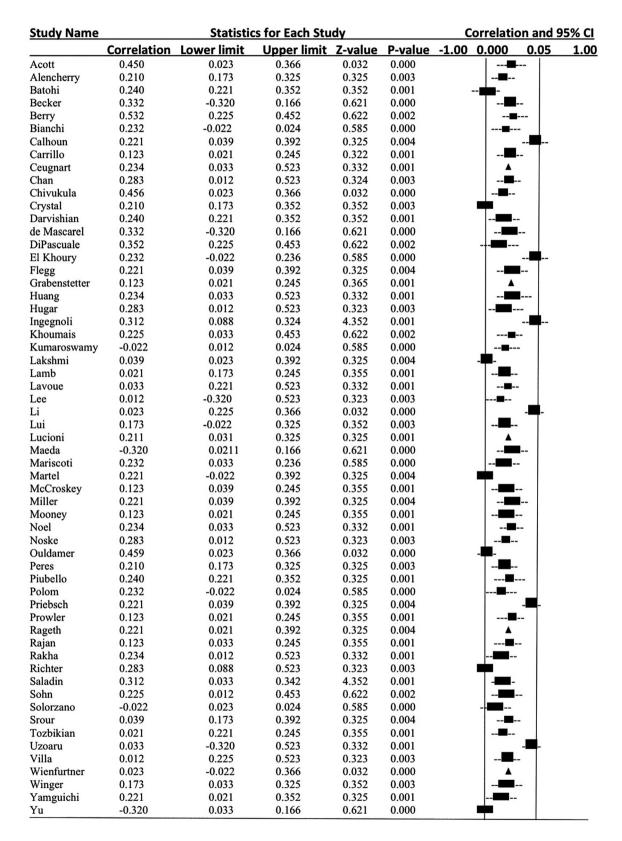


Figure 2: Forest plots of the overall upgrade rate to breast cancer.

Table 1: Findings and recommendation of included studies.

Study	Year	Number for analysis	Upgrade	No upgrade	Recommendation
Acott	2016	46	1	45	Case-by-case discussion
Alencherry	2018	72	2	70	Case-by-case discussion
Batohi	2019	88	20	68	Case-by-case discussion
Becker	2013	239	10	229	Surgery
Berry	2016	27	3	24	Case-by-case discussion
Bianchi	2012	190	18	172	Surgery
Calhoun	2014	73	5	68	Case-by-case discussion
Carrillo	2019	52	2	50	Surgery
Ceugnart	2013	52	3	49	Case-by-case discussion
Chan	2017	68	0	68	Follow-up
Chivukula	2009	35	5	30	Surgery
Crystal	2010	2	1	1	Surgery
Darvishian	2009	12	2	10	Surgery
de Mascarel	2011	24	0	24	Case-by-case discussion
DiPascuale	2019	75	12	63	Follow up
El Khoury	2017	41	4	37	Case-by-case discussion
Flegg	2010	5	2	3	Surgery
Grabenstetter	2019	34	2	32	Case-by-case discussion
Huang	2020	8	3	5	Surgery
Hugar	2018	94	0	94	Follow-up
Ingegnoli	2009	15	3	12	Surgery
Khoumais	2012	94	10	84	Surgery
Kumaroswamy	2015	5	2	3	Surgery
Lakshmi	2007	12	3	9	Surgery
Lamb	2017	200	5	195	Follow-up
Lavoue	2010	60	8	52	Surgery
Lee	2010	7	1	6	Follow-up
Li	2020	2	0	2	Case-by-case discussion
Liu	2019	- 89	0	89	Follow-up
Lucioni	2020	18	2	16	Follow-up
Maeda	2014	22	6	16	Surgery
Mariscoti	2020	158	10	148	Case-by-case discussion
Martel	2007	5	0	5	Follow-up
McCroskey	2018	43	0	43	Follow-up
Miller	2020	33	2	31	Follow-up
Mooney	2016	55	6	49	Case-by-case discussion
Noel	2009	20	0	20	Case-by-case discussion
Noske	2010	30	2	28	Case-by-case discussion
Ouldamer	2018	20	3	17	Case-by-case discussion
Peres	2011	95	9	86	Surgery
Piubello	2009	20	0	20	Case-by-case discussion
Polom	2011	20	2	18	Case-by-case discussion
Preibsch	2011	5	2	3	Surgery
Prowler	2014	24	0	24	Follow-up
	2014	221	40	181	Follow-up
Rageth		37		30	Case-by-case discussion
Rajan	2011		7		
Rakha Richter	2011	24	5	19	Case-by-case discussion
Saladin	2018	69	15 15	58	Surgery
	2015	82	15	67	Surgery
Sohn	2011	24	2	22	Surgery
Solorzano	2011	27	4	23	Surgery
Srour	2019	34	1	33	Follow-up
Tozbikian 	2019	57	3	54	Case-by-case discussion
Uzoaru	2012	95	3	92	Follow-up
Villa	2013	125	5	120	Follow-up
Weinfurtner	2015	4	0	4	Case-by-case discussion

Table 1: (continued)

Study	Year	Number for analysis	Upgrade	No upgrade	Recommendation
Winer	2019	12	3	9	Surgery
Yamguchi	2012	8	1	7	Surgery
Yu	2015	20	1	19	Case-by-case discussion

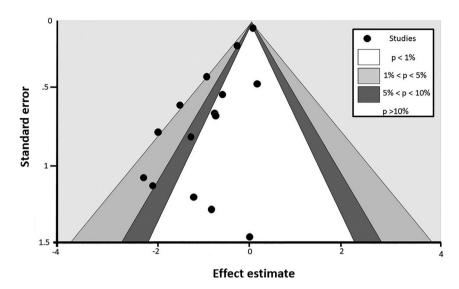


Figure 3: Contour-enhanced funnel plot to assess publication bias.

which calculated the quantity of heterogeneity through experiments, indicated the existence of an estimated 97% high heterogeneity.

The funnel plot (Figure 3) described here can therefore be viewed as asymmetric, suggesting that smaller studies appear to yield findings illustrating the analysis. The contour-enhanced plot separated the effects between bias in publication and other sources of asymmetry. The plot shows, however, that smaller findings were found not only in the areas of statistical significance provided by the shaded areas but also in the areas of nonsignificance shown by the nonshaded areas. The level of asymmetry could therefore have been caused by several variables and not solely by publication bias.

The previously mentioned estimates, despite the study having limited meta-analysis, indicate that the number of experiments utilized was adequate to assert the estimation of the addressed effect. In other words, to utilize a large number of experiments to find an overall meaningful impact, the plot provided evidence of the asymmetry of testing.

Discussion

High-risk lesions represent a unique spectrum of breast pathologies that are commonly seen in clinical practice. However, these lesions can be challenging for both radiologists and breast surgeons. The management of breast lesions has always been balanced by two opposite antagonist risks: underdiagnosis and undertreatment vs. overdiagnosis and overtreatment. Data regarding the rates of FEA upgrades are scant and sometimes contradictory. The question of excision or close surveillance can be a source of debate between clinicians and patients. In the literature, it has been reported that surgical excision may not be traditionally performed for breast lesions when the risk of upgrade is lower than 2% [78].

Several previous publications have analyzed the radiology and pathologic correlations of pure FEA diagnosed on CNB, focusing on the malignancy upgrade in the surgical specimen [19–77, 79]. The reported upgrade rates are variable, ranging from 0 to 30% [33]. However, our publication is the largest meta-analysis assessing the upgrade rate of pure FEA diagnosed on CNB with that undergoing surgical excision. In our study, we found a pooled upgrade rate of 9%. Our results are similar to those of other published data [79]. A recent meta-analysis estimated a pooled upgrade rate of 5% [79]. The difference between that study and ours is that study also included imaging follow-up whereas ours only analyzed the surgical excision results.

Compared to other studies [79], our study also included FEA findings under modalities other than mammography only. Our study also included ultrasound- and MRI-detected

lesions. We determined a rate of 9% and 27% pooled upgrade rate for ultrasound and MRI, respectively. Our results also demonstrated that there is a higher likelihood of upgrade for a MRI finding of FEA, which supports the study by Acott and Mancino [19]. This study included 48 pure FEA and recommended surgical excision in a scenario of MRI-guided biopsy yielding pure FEA [19]. Their reported upgrade rate was 25% (4/16). However, other publications have reported that there was no need for surgical excision in cases of MRI-guided biopsy showing pure FEA [12, 80, 81]. Among 16 cases of pure FEA, no cases of upgrade with a CI of 0-21% were reported [12].

Our study has some limitations. All studies in this analysis were retrospective, which can introduce a bias with a variability in design and patient selection. Also, our study did not assess the risk factors for FEA upgrade. The significant reported risk factors are a personal history of breast cancer, calcifications in a segmental distribution, mass lesion, removal of less than 24% of calcifications, calcifications that span greater than 2 cm, and papilloma diagnosis [20]. Similarly, Ouldamer et al. [57] showed there were three factors significantly predictive of underestimation or occurrence of cancer for pure FEA when the radiologic lesions are calcifications: age ≥57 years, radiologic size >10 mm, and number of FEA foci ≥4 on MRI. Another parameter that was not assessed in our study was the size of and type of the CNB device utilized [11]. Jackman et al. [13] reported a difference of the false negative rate of the 11-gauge biopsy vs. the 14-gauge vacuum biopsy with a respective of 0.5% vs. 4%. However, Alencherry et al. [20] showed that there was no significant difference in the number of core samples between upgraded and nonupgraded patients among any of the biopsy modalities (stereotactic, ultrasound, and MRI-guided biopsy modalities). There was also no significant difference between 9-gauge and 12-gauge needles for the stereotactic biopsies (p=1.0) [20, 79]. Additionally, the limitations could have been lessened by having stricter criteria in study selection for analysis.

Conclusions

As with managing other high-risk lesions, the management of pure FEA will continue to evolve. Nevertheless, our data support that pure FEA diagnosed at CNB should undergo surgical excision because the upgrade rate >2%.

Research funding: None reported.

Author contributions: Both authors provided substantial contributions to conception and design, acquisition of data,

or analysis and interpretation of data; both authors drafted the article or revised it critically for important intellectual content; both authors gave final approval of the version of the article to be published; and both authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests: None reported.

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