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The Positive Predictive Value of Vacuum Assisted Biopsy (VAB) in Predicting Final Histological Diagnosis for Breast Lesions of Uncertain Malignancy (B3 Lesions): A Systematic Review & Meta-Analysis

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Abstract

Introduction: High-risk or B3 breast lesions are considered lesions of uncertain malignant potential and comprise between 5-12% of initial biopsy results. We sought to perform a systematic review and meta-analysis of studies published within the last twenty years to determine the pooled Positive Predictive Value (PPV) of VAB in selected B3 lesions.

Methods: The study report is based on the guidelines of PRISMA and Meta-Analysis of Observational Studies in Epidemiology.

Outcomes: The primary outcome of this study was to determine the PPV of VAB in determining final histological diagnosis in B3 breast lesions using pooled estimates. The secondary outcomes were to determine if needle gauge or the re-classification of Lobular Carcinoma in Situ(LCIS) introduced in 2012 influenced pooled estimates.

Results: 78 studies incorporating 6,377 B3 lesions were included in this review, 1214 of which were upgraded to DCIS or invasive malignancy following surgical excision(19%). The pooled PPV of VAB in Atypical Ductal Hyperplasia(ADH) and Lobular Neoplasia(LN) were 0.79(CI 0.76-0.83) and 0.84(CI 0.8-0.88). VAB of Flat Epithelial Atypia(FEA), radial scar and papillary lesions with/without atypia all had a pooled PPV >90% (underestimation rates 7%, 1%, 5% and 3% respectively). Needle gauge size and

the change in LCIS classification did not appear to influence underestimation rates on subgroup analysis.

Conclusion: Results from this meta-analysis suggests it is reasonable to perform VAB as definitive treatment for certain B3 lesions, specifically LN, FEA, radial scar, and papillary lesions when specific criteria are fulfilled. Surgical excision should continue as the mainstay of treatment for ADH.

Keywords: Vacuum assisted biopsy, vacuum assisted excision, breast biopsy, B3 lesion, lesion of uncertain malignancy potential

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Introduction

Breast lesions are divided into five categories according to ascending potential of malignancy [1]. High-risk or B3 breast lesions are considered lesions of uncertain malignancy and comprise between 5 and 12% of all initial biopsy results[2, 3]. The B3 subgroup consists of various separate entities including Atypical Ductal Hyperplasia (ADH), Flat Epithelial Atypia (FEA), classic type Lobular Carcinoma in Situ (LCIS), Atypical Lobular Hyperplasia (ALH), Radial Scar (RS), fibroepithelial lesions and papillomata. Classic type LCIS and ALH are risk factors and non-obligate precursors of invasive carcinoma and are frequently categorised together as Lobular Neoplasia (LN). FEA refers to columnar cell lesions with atypia and share the same morphological features and molecular alterations as ADH and low-grade DCIS[4]. The terms radial scar and complex sclerosing lesion (CSL) refer to the same entity but differ in size with radial scar ≤ 1cm and CSL > 1cm in diameter [5]. Radial scar is a subtype of sclerosing lesion with a central nidus of elastosis and entrapped glands[6]. Papillary lesions refer to benign papillomas, papillomas with atypical hyperplasia/atypia, and papillary carcinomas. The risk of underlying DCIS or invasive carcinoma has been proposed as justification for surgical excision of some of these papillary lesions [7]. In the United Kingdom the term ADH is used to describe histological changes in the excision specimen and Atypical IntraDuctal Epithelial Proliferation (AIDEP) is used in the setting of a diagnostic biopsy[8]**.** The World Health Organisation uses the term ADH in both the core biopsy and excision [9]. Both ADH and AIDEP display the same histological changes, showing an intraductal epithelial proliferation composed of monotonous, evenly spaced cells with small regular nuclei. The morphological appearance of ADH is similar to that of ductal carcinoma in situ (DCIS) but is seen in less than two duct spaces or less than 2mm in diameter. The differing terminology is due to the limited tissue available in core biopsy to accurately fulfil the size extent criteria[10].

The number of core needle biopsy results yielding a B3 diagnosis is likely to increase as advances in breast imaging techniques increase lesion detection. The management of these high-risk, B3 lesions has evolved overtime and is considered controversial. B3 breast lesions are representative of high-risk breast epithelium and associated with an elevated risk of developing breast cancer[11, 12]. Together ADH and LN confer a greater than fourfold lifetime relative risk of developing breast cancer and a cumulative incidence of breast cancer up to 30% at 25 years of follow-up [11-13]. These lesions not only confer a greater lifetime risk of developing a breast malignancy, but are also indicators of concurrent malignancy that may not be detected due to limited biopsy sampling [14]. Upgrade rate is the term used to describe the finding of malignancy (DCIS or invasive carcinoma)

after excisional biopsy of B3 lesions. Upgrade rates vary considerably between different high-risk breast lesions and depending on the gauge of needle biopsy used during sampling. A recent review of the literature reported the pooled median upgrade rate of ADH to malignancy was 25% (Range 4–54%) [15], whilst the upgrade rate of papillary lesions is much lower ranging from 0% to 6.6% [16, 17]. The gauge of the biopsy needle is also believed to influence upgrade rate with the greater volume of tissue provided by increasing needle diameter unsurprisingly resulting in a lower probability of "missing" a diagnosis of DCIS or invasive cancer. Traditionally, all B3 lesions detected by core biopsy were managed with surgical excision to ensure sufficient tissue was provided to rule out co-existing malignancy[18]. As the final histopathological diagnosis of the vast majority of B3 lesions is benign, there is a trend universally for more conservative management as an alternative to open surgery [19, 20]. Vacuum Assisted Biopsies (VAB) are diagnostic procedures using image-guided vacuum breast biopsy techniques to obtain larger tissue volume than traditional core biopsy. Like VAB, Vacuum Assisted Excision (VAE) is the same procedure but aims to remove the amount of tissue equivalent to a surgical biopsy, equating to about 4g of tissue which can yield a final diagnosis in the majority of cases[10].

The clinical utilisation of VAE in the management of B3 lesions differs across Europe and the UK and this is reflected by conflicting consensus guidelines. The first international guidelines regarding the management of B3 lesions was published in Europe in 2016 and updated in 2019 [20, 21], recommending VAE for most lesions except ADH, spindle cell lesions, papilllomas with atypia and cellular fibroepithelial lesions which should undergo open surgical excision [20] . In the UK, guidelines produced by Pinder et al in 2018 recommend that all B3 lesions should be managed with VAE except for papilloma with atypia, spindle cell lesions and cellular fibroepithelial lesions[10]. The management of ADH is an ongoing source of debate and is the primary difference between the UK and European consensus guidelines. Despite emerging evidence suggesting an acceptable clinical correlation rate between VAE and final histopathological diagnosis, open surgical excision is the default practice for all B3 breast lesions in Ireland [22]. We sought to perform a systematic review and meta-analysis of studies published within the last twenty years to determine the sensitivity of VAB as a diagnostic procedure in selected B3 lesions, specifically ADH, FEA, LN, papillomas, and radial scar/complex sclerosing lesion.

Aim: To conduct a systematic review of prospective and retrospective studies published within the last twenty years to determine the positive predictive value (PPV) of vacuum-assisted biopsy in determining final histological diagnosis in B3 breast lesions.

Objectives:

1. The primary objective was to determine the sensitivity of vacuum assisted biopsy in predicting final histological diagnosis in B3 breast lesions, specifically ADH, FEA, LN, papillary lesions (with/without atypia) and radial scar/complex sclerosing lesions.
2. The secondary objective was to examine whether gauge size influences the positive predictive value of vacuum-assisted biopsy.
3. The third objective was to determine whether the change in classification of LCIS introduced in 2012 influenced pooled estimates by comparing the overall LN cohort to a cohort of studies published within the last five years. Since re-classification, pleomorphic LCIS is considered a separate entity and managed definitely with excision due to its high risk of underlying malignancy[23].

Inclusion Criteria:

Study inclusion criteria were defined according to PICO (ie population, intervention, comparator, outcomes, study design) [24]. To reflect improvements in technology only studies published within the last twenty years were included. To be included in the analyses, studies had to meet the following criteria:

1. Studies included patients with B3 breast lesions reported as subgroups undergoing vacuum-assisted biopsy
2. Studies performed vacuum assisted biopsy assisted under radiological guidance.
3. Timely follow-up surgical excision performed to determine malignancy/DCIS upgrade rate within six months without interval imaging.

Exclusion Criteria:

Studies were excluded from the analysis if:

1. Published in languages other than English (for English proficiency reasons).
2. Follow up surgical excision to determine upgrade rate was not performed.
3. Only selected high risk lesions or population groups proceeded to excision.

4. Studies only included cellular fibroepithelial lesions due to the need for complete excision to exclude benign or malignant phyllodes tumour.
5. Studies only included mucocele-like lesions as they are very rare.

Methods:

The study report is based on the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [25]. Analysis and results were extracted from previous ethically approved studies therefore patient consent and ethical approval was not required. This study was prospectively registered on PROSPERO on the 15th of November 2021 (ID: CRD42021291511).

Search Methodology

An electronic search was conducted using the Cochrane library, Sciencedirect, PubMed and Embase. All studies from January 2000 to July 2021 were included. We combined search terms and MESH terms in a search strategy developed for PubMed and adapted this strategy for the other databases. The following search terms/MESH terms were used: (Vacuum assisted biopsy (Mesh) OR VAB OR vacuum assisted excision OR VAE OR Mammotome biopsy OR Mammotome truvac OR Mammotome) AND (B3 lesions (Mesh) OR indeterminate OR high-risk OR atypical ductal hyperplasia OR ADH OR lobular neoplasia OR LCIS OR papillary OR papilloma OR intraductal papilloma FEA or flat epithelial atypia OR radial scar OR atypia). All titles were initially screened, and appropriate abstracts were reviewed. Each of the publications' bibliographies and google scholar were manually searched for relevant articles. The last date of search was October 31st, 2021.

Data Extraction

Two reviewers (CC, JB) independently reviewed the available literature according to the above predefined strategy and criteria. Both reviewers performed the primary article screening and relevant studies were inputted to a shared reference management tool file. Each reviewer extracted the following variables: title and study details (year, design, country), study population characteristics (sample size, type of B3 lesion, VAB gauge, image modality, underestimation rate, quality assessment) and entered into data sheets. Underestimation rate referred to the percentage

of patients diagnosed with a B3 lesion on VAB who had a diagnosis of DCIS or invasive cancer on their final histology report. Many histological reports included dual B3 pathology i.e. LN in the presence of ADH. Subtypes were categorised according to the primary diagnosis reported in the study. ADH in the presence of radial scar or radial scar with atypia was not included in radial scar analysis. Lobular neoplasia included non-pleomorphic LCIS and ALH. Complex sclerosing lesions (CSL) were included with radial scar for analysis as both lesions reflect the same underlying pathological entity[5]. Papillary lesions were subdivided into those with and without atypia. When the presence r absence atypia was not explicitly reported in the study, papillary lesions were not included in the analysis.

Risk of Bias

The quality of the studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS II) tool[26]. This consists of four domains including patient selection, index test, reference standards, and flow and timing and are designed to assess risk of bias and applicability for each domain by answering 14 questions as “low,” “high,” and “unclear” (Table 1). The reference standard was open surgical biopsy, and the index test was vacuum assisted excision. Question 11, “were the reference standard results interpreted without knowledge of the results of the index test”, was omitted from the overall assessment score as it was not applicable.

Pooling of Study Data

Data were analysed using STATA version 17.0 (Stata Corp, College Station, TX, USA), using the meta-analysis of proportion commands to determine pooled estimates of effect i.e PPV. Heterogeneity was assessed by I-squared statistics, with >50% being considered significant heterogeneity. A fixed-effects model was preferred to random-effects model when there was no significant heterogeneity and vice versa when there was significant heterogeneity. The study specific PPV’s of determining final histological diagnosis were calculated with 95% confidence intervals and were shown in Forest plots. Descriptive statistical analyses and comparative analyses of the B3 subgroups were performed using STATA version 17.0. Studies were grouped according to VAB gauge and comparison of pooled predictive values was performed. A subgroup analysis of LN studies published within the last five years was performed to calculate pooled estimated PPV.

Results

The initial search in PubMed, MEDLINE, EMBASE, and Cochrane Library resulted in 3527 studies. After removing duplicates and studies published greater than 20 years ago, the titles and abstracts of each of the remaining 966 studies were reviewed for relevance. Forty-five abstracts were not included because the full text was not available in English. Of the remaining 918 studies, full articles were reviewed and 837 were excluded because one of the following reasons.

1. Follow up surgical excision was not performed

2. The radiological abnormality was not accurately targetted

3. Only selected high risk patients were selected for surgery

A citation search yielded two studies not identified in the initial search. Finally, 78 studies met the purpose and inclusion criteria of this study. PRISMA flow diagram Figure 1.

Characteristics of Included Studies

The characteristics of the included 78 studies[4, 8, 16, 27-101] are outlined in Table 1. All studies were prospective or retrospective cohort studies, there were no randomised control trials. Overall, there were 6,377 B3 lesions included in the study, 1214 of which were upgraded to DCIS or invasive malignancy following surgical excision (19%). Studies from sixteen different countries spanning four continents were included. Forty-five studies were published in the last ten years, the other 33 studies were published more than ten years ago. The median patient age, as reported in 57 studies, was 54. Twenty-six studies included multiple B3 subtypes and analysed them individually. Thirty-five studies examined vacuum-assisted biopsies with ADH while four studies focused on LN. RS and FEA were examined in three studies each and upgrade rates for papillary lesions were reported in seven studies. Total number of B3 lesions excised differed significantly between studies and ranged from 1644 to 4 lesions. Twenty studies included less than twenty B3 lesions (25.3%) whilst fourteen studies (16.4%) included a sample size of over 100. The majority of studies used stereotactic guidance to obtain VAB (54.9%). MRI was used in 12 studies (15%) making it the second most common modality followed by Ultrasound (US) and Digital Breast Tomosynthesis (DBT). The gauge of VAB needles used in the studies ranged from 7Gauge (1.2%) to 13Gauge (1.2%) with the majority of studies using size 11Gauge vacuum devices (N = 34, 43.4%). Use of multiple needle gauges was reported in nineteen studies (24%) and five studies (6.2%) did not report what gauge was used for

VAB. Pooled positive predictive values and underestimation rates for each B3 subtype are outlined in table 2.

Risk of Bias Analysis

Although studies were only included where it was stated that cases were identified retrospectively from a pathology database, or prospectively as they were identified, it was impossible to fully exclude the presence of a case selection bias. The QUADAS II tool was used to assess the quality of the studies. Fifty-four studies (69.2%) were deemed to have low risk of bias and in 24 studies (30.8%) it was unclear the degree of bias due to missing data.

Atypical Ductal Hyperplasia

Sixty studies, with a total of 3878 ADH lesions were included in the pooled analysis. Rovera et al included patients with LN in their analyses of 21 patients with ADH[100]. The total upgrade rate to malignancy was 22%. The pooled positive predictive value of VAB in determining the final histological diagnosis was 0.79 or 79% (CI 0.76-0.83) using a random effects model as there was significant heterogeneity between the studies (I^2 = 81.26%). Figure 2.

Lobular Neoplasia

Twenty-four studies comprised of both ALH and LCIS pathology had a pooled PPV estimate of 0.84 (CI 0.8-0.88, I^2 = 50.33%). Of the total 1089 LN lesions biopsied with VAB, 210 (19%) were upgraded to malignancy following surgical excision. To determine whether the change in classification of LCIS introduced in 2012 influenced pooled estimates a subgroup analysis of six studies published within the last five years was performed. There was no difference in pooled estimates between the two cohorts. Figure 3 & 4.

FEA

Thirteen studies included 615 FEA lesions obtained with VAB and the overall upgrade rate to malignancy was 9% (N=58). The pooled positive predictive value of VAB in the setting of FEA was 0.93 (CI 0.90-0.95) with some heterogeneity between the studies (I^2 = 45%). Supplementary Figure 1.

Radial Scar

Radial scar and complex sclerosing lesions were categorised together and a total of sixteen studies, incorporating 211 lesions were suitable for estimate analysis. The overall upgrade rate to malignancy from VAB was 4% (N=9). The pooled diagnostic positive predictive value was 0.99 (CI 0.96-1.01) with no heterogeneity between the studies (I^2 = 0.00%). Supplementary Figure 2.

Papillary lesion with atypia

Papillary lesions or papillomata were classified according to the presence or absence of atypia. Seven studies reported on VAB of papillomata with atypia with an overall 10% upgrade rate to malignancy (N= 15). The pooled PPV was 0.95 (CI 0.91-0.99) using a fixed effects model. I^2 = 33.5%. Figure Supplementary Figure 3.

Papillary lesion without atypia

Sixteen studies consisting of 434 lesions, were reported as papillomata without atypia using VAB. After surgical excision, 25 (5.7%) were upgrade to malignancy. The pooled PPV was lower than VAB reporting papillomata with atypia [(PPV 0.999 (CI-0.97- 1.01) versus 0.95 (CI 0.91-0.99)]. There was no heterogeneity between the studies (I^2 = 0.00%). Supplementary Figure 4.

VAB Gauge

Subgroup analysis was performed to determine whether needle gauge size would influence the PPV of final histological diagnosis of ADH. Studies were divided into two cohorts according to VAB gauge. Forty-two studies included gauge 10-13G (mean PPV 0.79) and 15 studies used size 7–9-gauge VAB (mean PPV 0.74). There was no significant difference between the mean PPV values of the studies

that used a larger gauge compared to the studies that used a smaller gauge (P = 0.1707). The pooled PPV estimates of VAB performed with a smaller gauge needle (7-9G) and larger gauge needle (10-13G) were similar (0.82 (CI 0.78-0.85), 0.82 (CI 0.78-0.86). There was significant heterogeneity observed between the studies in the smaller gauge needle cohort (I^2= 82%) which was not evident in the larger gauge needle cohort (I^2 = 26%). Supplementary Figure 5 and 6.

Discussion

This systematic review and meta-analysis of VAB of lesions of uncertain malignant potential (B3 lesions) shows that there are considerable differences in the upgrade rate according to B3 subtype. The PPV of VAB for predicting final histological diagnosis of ADH and LN were 79 and 84% respectively. This was considerably lower than the pooled PPV observed in the FEA subtype (93%). The highest estimated pooled PPVs were in radial scar, papillary lesions without atypia and papillary lesions with atypia (99%, 97% and 95% respectively). Overall, the upgrade rate to malignancy was 22% in patients with ADH on VAB and 19% in patients with LN excised on VAB. The finding that ADH confers the greatest risk of upgrade to malignancy was also corroborated by a recent meta-analysis of core biopsy reports [102]. The rate of underestimation with ADH was 28% (CI 24-31) compared to 22% in our subgroup.

Management recommendations for lesions of uncertain malignant potential vary considerably internationally depending on B3 subtype and national guidelines. In the United Kingdom, the National Health Service Breast Screening Programme(NHSBSP) introduced new guidelines in 2016 stating that certain B3 lesions diagnosed on core biopsy (ADH, LN, Radial scar, FEA, mucocoele-like lesion with/without epithelial atypia) should undergo excision with VAE[103]. Provided 4 grams of tissue was obtained and there was no evidence of malignancy on VAE, these patients would be suitable for annual mammographic surveillance. On the other hand, papillary lesions with atypia, cellular fibroepithelial lesions and spindle cell lesions were deemed inappropriate for VAE by the NHSBSP, and surgical excision of these lesions was recommended. To reflect this change in practice a new radiology quality performance indicator was introduced by the NHSBSP stating that <25% of eligible B3 lesions should have a surgical diagnostic biopsy[104]. A recent audit of national data from the English Screening Programme reported that the overall upgrade rate of B3 lesions (including LN, AIDEP and FEA) was significantly higher in the presence of atypia versus no atypia (29.1% versus 13.3%)[73]. When considered independently in both VAE and surgical groups, ADH or AIDEP had the highest upgrade rate at 30%[73].

The high upgrade rate associated with ADH on core and VAB is echoed in both this study and the literature [14, 56, 76] and is the reason why European guidelines have been reluctant to adopt VAB in the setting of ADH[21]. In 2016, the panel of the first International Consensus Conference on B3 lesions stated that every B3 lesion should be discussed at a multidisciplinary meeting (MDM)[21]. As the decision between surveillance and surgical excision is largely based on balancing the risks of surgery against missed diagnosis of DCIS or invasive carcinoma the rate of acceptable underestimation has been questioned. A panel of experts agreed that underestimation rates should be below 5% for invasive cancer and below 10% for DCIS[20]. For this reason, the European consensus recommended VAE for most B3 lesions except for ADH, spindle cell lesions, papillary lesions with atypia and cellular fibroepithelial lesions which should undergo open surgical excision[20]. Regardless of the initial biopsy results, many clinicians would agree that open surgical excision should be considered in the presence of solid lesions, incomplete removal on imaging, associated microcalcifications and for lesions >2.5cm in diameter[58, 61, 105]. Internationally, the National Comprehensive Cancer Network (NCCN) recommends surgical excision when ADH is identified on core biopsy however the American Society of Breast Surgeons (ASBrS) Consensus Guidelines suggest that a select subset of patients with ADH completely removed on biopsy and without other adverse features may be suitable for close surveillance and avoid surgery [106, 107]. NCCN guidelines further recommend surgical excision of other specific lesions that require additional tissue to confirm histopathological diagnosis including mucin-producing lesions, potential phyllodes tumours, papillary lesions, radial scars, or other diagnoses of concern to the pathologist[107]. Both the ASBrS and NCCN support surgical excision of pleomorphic LCIS diagnosed on core needle biopsy (CNB). However, neither organisation continues to advocate routine excision of classic LCIS and ALH and instead suggest surveillance as an option when radiologic and pathologic diagnoses are concordant and no other high-risk lesion requiring excision is present [107] [106]. Whilst a more conservative approach to the management of B3 lesions is emerging from data in the United States, the utilisation of VAE as an alternative to surgical excision does not appear to feature in the current guidelines. The estimated upgrade rate of malignancy in the setting of ADH after VAB was 22% in the present review, considerably higher than the 10% acceptable rate recommended by the European consensus group [20]. Based on these results, it does not appear that omission of surgical excision after identification of ADH on VAB should be recommended.

Regarding the management of LN, the European guidelines recommend both complete removal of the radiological lesion via VAB and surveillance or open surgical excision as safe management options[20]. This review estimated the positive predictive value of VAB in predicting final LN histological diagnosis as 84% suggesting a pooled upgrade rate of 16%, similar to the rate reported

by Forester et al in their recent review (17%)[102]. Re-classification of LCIS was introduced in 2012 which has a significant impact on the interpretation of historical data. Prior to 2012, florid and pleomorphic LCIS(PLCIS) which are often associated with upstaging to invasive lobular carcinomas on excision were categorised under the LN subgroup. Since this classification, pleomorphic LCIS is considered a separate entity and managed definitely with excision due to its high risk of underlying malignancy[23]. A study by Mahoney et al reported a 19% malignancy upgrade rate in 2006 when reviewing VAB with LN [59]. Conversely, after re-classification Meroni et al compared the underestimation rate of LCIS and PLCIS separately in 2014 and reported the VAB underestimation rate when compared to surgical excision was 7.1 % for ALH, 12 % for LCIS and 50 % for PLCIS[77]. In this review, a subgroup analysis was performed to compare pooled PPV of the LN studies published within the last five years to the overall twenty-four studies included in the meta-analyses. The pooled PPV estimates for both cohorts were 84% suggesting that the change in nomenclature has not had a significant influence on reported upgrade rates..The other B3 entities included in this meta-analysis, FEA, radial scar and papilloma's with/without atypia all appeared to have a pooled underestimation rate of less than 10% implying that VAB is acceptable without subsequent surgical excision. Despite being deemed unsuitable for VAB in the NHSBSP and European guidelines, papillomata with atypia had a 95% pooled PPV of predicting final histological diagnosis in this meta-analysis.

Underestimates of malignancy in biopsied B3 lesions range up to 35% and are associated primarily with increasing size of the lesion and the presence of atypia rather than the nature of the mammographic abnormality (e.g., calcification vs. mass or architectural distortion)[108]. There may also be certain ultrasound features associated with an increased risk of underlying malignancy in B3 lesions such as an irregular shape (P = 0.000), uncircumscribed margin (P = 0.000), increased vascularity (P = 0.002) or suspicious calcifications (P = 0.000)[109]. Li et al also reported that age greater than 50 years was a significant risk factors of malignant potential for B3 lesions [109]. Several studies have attempted to establish an accurate criterion to identify radiological and patient specific B3 features with the highest upgrade rate at surgical excision. Khoury et al developed a nomogram using histological variables, such as number of involved cores, the size of the largest focus, histological pattern, and demographic data such as age, previous history of breast cancer, menopausal status and lesion type to predict ADH lesions with a higher potential of upgrade to malignancy[110]. Increasing number of involved cores and number of foci correlated with a higher upgrade rate on surgical excision [110] however the validity of this nomogram has not been proven in prospective studies. The influence of needle diameter on malignancy upgrade rates in B3 lesions remains inconclusive. NHSBSP guidelines suggest a minimum of 4grams of breast tissue should be obtained via VAB for accurate

diagnostic purposes [21]. Similarly, Darling et al reported that increased sample weights result in significantly decreased rates of upgrade[111]. With an increasing repertoire of vacuum assisted devices and needle gauges, several studies have compared different needle gauges in terms of upgrade rate. Lourenco et al and Eby et al did not find any correlation between vacuum assisted biopsy gauge and underestimation rate [41, 57]. These studies corroborate with the findings reported in this meta-analysis as there was no significant difference between the mean PPV values of the studies that used a larger gauge compared to the studies that used a smaller gauge (P = 0.1707). These results suggest that needle gauge does not appear to correlate with malignancy upgrade rate in B3 lesions and should not influence clinical decision making.

Strengths and Limitations

To the best of our knowledge this is the first systematic review to consider PPV of VAB in key subgroups of B3 lesions and to calculate the risk of malignancy for individual groups. The inclusive nature of the review allowed assessment of a large number of B3 lesions (6,377 in total). Inclusion of studies published within the last twenty years provides a breadth of data whilst reflecting modern clinical practice.

One of the main limitations of this study was the absence of randomised controlled trials to determine whether VAB or surgical excision ultimately impact survival outcomes. The studies included in this meta-analysis were cohort studies and therefore subject to selection bias. One of the studies included in the ADH analysis also included patients with LN which may have influenced the results, although this study only contributed 1.4% weight to the pooled estimate[100]. Although study selection attempted to remove any lesion selection bias by excluding studies that explicitly reported a period of follow-up prior to surgical excision biopsy, it cannot be determined whether some studies proceeded straight to excision biopsy for more suspicious lesions. Similarly, many of the studies did not report on the size of the lesion and therefore could not be included in this analysis. This is a significant limitation as underestimation rates correlate with increasing lesion size[108]. European consensus guidelines provide benchmarks for acceptable VAB underestimation rates for DCIS and invasive carcinoma. It was not possible to provide subgroup analysis to determine the underestimation rate for DCIS and invasive cancer individually as many studies only reported overall upgrade rate which is a limitation of this study.

Another considerable limitation of this study is the intra-observer variability that exists between pathologists when reporting on B3 breast lesions. Unfortunately, rates of agreement between

pathologists and institutions were not routinely reported and could not be controlled for during meta-analysis but may go some way to explaining variation in upgrade rates between studies. Moreover, dual B3 pathology is often reported in CNB and VAB specimens. Subtype categorisation was performed by authors based on the primary pathological component. It is possible that the presence of background co-existing histological changes may influence overall risk but adjusting for this was not possible.

Conclusion

In conclusion, this study presents pooled estimates of the positive predictive value of VAB in predicting final histological diagnosis in subgroups of B3 lesions. The management of B3 breast lesion varies considerably internationally and is reflected in the contrasting consensus guidelines. Pooled estimates from this meta-analysis suggests that it is reasonable to perform VAE as definitive management for certain B3 lesions, specifically FEA, radial scar, and papillary lesions with/without atypia when specific criteria are fulfilled. Pooled estimated lobular neoplasia underestimation rates were 16% in this meta-analysis. UK, European and American guidelines all concur that VAB of LN and follow-up radiological surveillance is acceptable management. Close surveillance with annual mammography and accurate targeting of the radiological abnormality should be performed to reduce the malignancy risk post VAB of LN. The underestimation rate (21%) for ADH remains too high to safely recommend VAE, therefore surgical excision should continue as the mainstay of treatment. There is a subset of patients who may be suitable for close surveillance after VAB however this should be decided on a limited case by case basis. Regardless of the initial biopsy results, open surgical excision should be considered if a solid lesion is present, >2.5cm in size, not entirely removed on imaging and associated micro calcifications.

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