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BREAST RADIOLOGY

Intraductal papilloma of the breast: low risk, but handle with care

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Abstract

Introduction This study aims to investigate the management of patients with breast papillomas without atypia diagnosed after ultrasound-guided vacuum-assisted breast biopsy (VABB).

Materials and methods This retrospective, single-centre study analysed 179 patients diagnosed with benign papillomas without atypia between 1999 and 2022. Of these, 32 patients underwent surgery, while the remaining were managed with active surveillance. Diagnostic underestimation was assessed in the surgical group. The association between post-biopsy residual lesions and subsequent surgical management (surgery vs no surgery) with the incidence of recurrence was evaluated.

Results The study cohort had a median age of 49, with 76% of lesions completely removed via VABB. In the surgery group, 9% (95% CI: 2%–25%) had an underestimation, including upgrades to in situ or invasive carcinoma. Among the 126 patients with available follow-up data, 9 (7%) experienced recurrence events on the same side and in the same quadrant. In the multivariable Fine and Gray regression model, patients with post-biopsy residual lesions managed without surgery had a significantly higher recurrence risk than those without residual lesions (HR = 6.76, $p = 0.015$). Among patients with post-biopsy residual lesions who underwent surgery, the risk of recurrence was not significantly different from the reference group (HR = 1.80, $p = 0.56$). Additionally, age at biopsy was identified as an independent risk factor for recurrence (HR = 1.41, $p = 0.001$), whereas lesion diameter showed no significant association (HR = 1.14, $p = 0.49$).

Conclusions Surgical resection may be warranted in cases of papillomas with incomplete removal at VABB, where recurrence risk appears to be higher.

Keywords Papillary neoplasms · Vacuum-assisted breast biopsy (VABB) · Disease-free survival (DFS) · Active surveillance

Introduction

Papillary lesions of the breast (PL) include various pathological types arising from ductal epithelial cells and characterised by abnormal cell proliferation within the mammary ducts, such as intraductal papillomas (IP), papillomas associated with foci of atypia (Atypical Ductal Hyperplasia, ADH / Lobular Neoplasm, LN), papilloma with In Situ Ductal Carcinoma (DCIS), and both capsular and solid intraductal papillary carcinomas [1–4].

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IPs, the most common PL, account for approximately 20% of B3 lesions and are most commonly observed in women aged 30 to 50 years. These lesions are often located in expanded ductal spaces and develop as tufts of bilayered heterogeneous populations of basal (myoepithelial) and luminal (epithelial) cells with a fibrovascular core that arborises into branching papillae and protrudes into the duct lumen [5]. IPs can be further divided into forms with and without atypia [6]. The most common diagnostic radiological IP detection methods are digital mammography (DM) and breast ultrasonography (US), especially in cases involving the breast. DM frequently lacks radiologically suspicious findings (particularly with small IPs); when imaging findings are present, they include solitary or multiple dilated ducts, a circumscribed benign-appearing mass (often subareolar in location), or a cluster of calcifications. On US, IP typically appears as a hypoechoic, well-defined lesion, which may either fill a duct or be partially outlined by fluid, sometimes with a vascular stalk; therefore, a definitive diagnosis requires a US-guided biopsy [7]. Figure 1 illustrates a representative example of the typical mammographic and ultrasound appearance of IP. The management of IPs remains a topic of debate [8]. Determining the most appropriate treatment approach often depends on factors such as the type of biopsy performed (vacuum-assisted breast biopsy or core biopsy, CNB) and whether the lesion is completely or partially excised if VABB is used [9]. In addition, uncertainties persist about the patient's symptomatic status at the time of diagnosis and the concordance between radiological and histopathological findings.

International guidelines [10] recommend a surgical approach for IPs with atypia (especially ADH) and DCIS associated. For IPs without atypia, the influence of the above variables becomes significant in determining the therapeutic approach. The latest international consensus conference suggests "open excision (OE) or therapeutic vacuum-assisted excisional biopsy (VAE) following a diagnosis of IP without atypia based on CNB. If the target lesion is completely removed using VABB, the entire expert panel (100%) recommends radiological follow-up after the diagnostic procedure" [11]. However, scientific evidence is more limited for patients with IPs without atypia who undergo VABB (not VAE) without complete lesion removal, as most available retrospective studies are based on CNB data [12–14].

With this study, we aim to present data from a valuable retrospective case series of US-guided VABB available in our institution, seeking to provide practical guidelines for managing patients diagnosed with IP without atypia following VABB. The purpose is to determine the appropriate indications for recommending surgery in these patients and to assess its impact on the incidence of recurrence (on the same side and in the same quadrant) during follow-up. This retrospective observational study explores the most effective approach to managing an IP diagnosis by VABB. Specifically, in a cohort of patients with atypia-free IPs undergoing US-guided VABB, we set out to compare the cumulative incidence of recurrence (in the same side and quadrant) among three groups: patients with no residual lesion post-biopsy, patients with residual lesions managed without surgery, and patients with residual lesions with subsequent (post-biopsy) surgery. Additionally, we will present and discuss our data on the diagnostic underestimation of VABB findings at the time of surgery.

Materials and methods

This monocentric retrospective study was approved by the Ethics Committees of the European Institute of Oncology (approval number UID 4622; approval date: May 8, 2024).

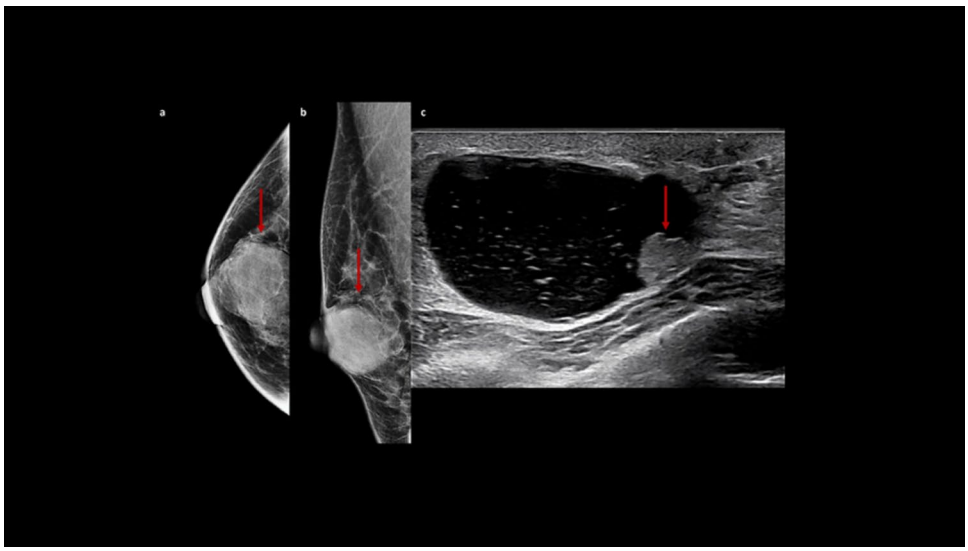

Fig. 1 The craniocaudal **a** and mediolateral oblique, **b** DM views of the right breast show a well-demarcated retroareolar opacity (red arrows), corresponding on US **c** to an anechoic, ectasic ductal structure with corpusculated content and a solid endoluminal overhang (red arrow) suggestive of IP

Due to its retrospective design, individual informed consent was not required. We retrospectively identified all patients who underwent US-guided VABB for a breast lesion at our institution between 1999 and 2022 and who received a histological IP diagnosis. Most of these patients were managed with active surveillance rather than surgical excision.

2.1. Inclusion criteria:

- Histologic diagnosis of pure IP (without atypia)
- US-guided VABB performed at our institution, which led to the above diagnosis (IP).

Exclusion criteria:

- Histological diagnosis of non-pure IP (e.g. with atypia)
- Use of biopsy methods other than US-guided VABB
- Lack of available follow-up data (relevant only for recurrence analysis)

In our institution, surgical excision is proposed, after multidisciplinary discussion, for patients presenting with one or more of the following risk factors: clinical symptoms (serous or bloody nipple discharge); suspicious enhancement on peribioptic magnetic resonance imaging (if performed); significant residual lesion after VABB; and marked radiologic–pathologic discordance:

Radiologic–pathologic correlation was systematically evaluated during multidisciplinary discussions, considering imaging findings, clinical presentation, and histologic results. In cases of discordance between imaging and pathology, surgical excision was recommended. Most patients under active surveillance underwent complete removal of the lesion by VABB.

A minority group, with low-risk features and without symptoms, was monitored despite residual lesions, based on multidisciplinary consensus and patient preference. A post-biopsy residual lesion was defined as residual tissue of the target lesion still detectable at the biopsy site on immediate post-procedural ultrasound, following vacuum-assisted aspiration, as assessed by the same operator who performed the procedure. In some cases, no residual lesion was observed, indicating complete macroscopic removal. Importantly, all procedures in this study were US-guided diagnostic VABB; no instances of vacuum-assisted excision (VAE) were included. VAE generally refers to a technique intended to achieve complete macroscopic removal of the lesion during the biopsy procedure, often involving the collection of a standardised minimum amount of tissue (e.g. ≥ 4 g) and potentially serving both diagnostic and therapeutic purposes in selected low-risk cases. In our series, complete removal was an occasional finding, not an intended outcome of the procedure. Nevertheless, it occurred frequently, likely due to the small size of most target lesions. For patients undergoing surgery, we assessed the rate of diagnostic underestimation, defined as an upgrade to in situ or invasive carcinoma in the surgical specimen. Follow-up data, when available, were collected for both surgery and non-surgery patients. Recurrence was defined as the appearance of a new lesion in the same quadrant of the ipsilateral breast during follow-up imaging. All recurrence events were detected radiologically, primarily through ultrasound or mammography performed during routine annual surveillance. The cumulative incidence of recurrence was analysed, including residual lesions after biopsy, subsequent surgical management, patient age, and initial lesion diameter. Only ipsilateral recurrences occurring in the same quadrant of the index lesion were considered; those occurring in different quadrants or the contralateral breast were treated as concurrent events.

Statistical analysis

Continuous variables were summarised as medians with ranges, and categorical variables as absolute numbers and percentages.

The primary endpoint was the incidence of recurrence in the same quadrant of the ipsilateral breast. Events in a different quadrant of the same breast or the contralateral breast were treated as competing risks.

Univariable and multivariable Fine and Gray competing risks regression models were used to assess the association of recurrence with the presence of a residual post-biopsy lesion, surgical management (modelled as a time-dependent covariate), patient age at the time of biopsy, and lesion diameter.

All p-values were two-sided, with values ≤ 0.05 considered statistically significant.

Statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Between 1999 and 2022, 223 patients with pure IP were diagnosed at our institute following US-guided VABB. Forty-four patients were excluded due to the detection of atypia, leaving 179 patients eligible for inclusion in the retrospective analysis. The study flow chart is depicted in Fig. 2.

In this cohort, the median age of the patients was 49 years (range 22–79 years), and the median lesion size was 10 mm (range 4–36 mm). In 62% of cases, more than 10 tissue cores were obtained during the VABB procedure. Complete removal of the lesion at biopsy was achieved in 76% of cases (Table 1).

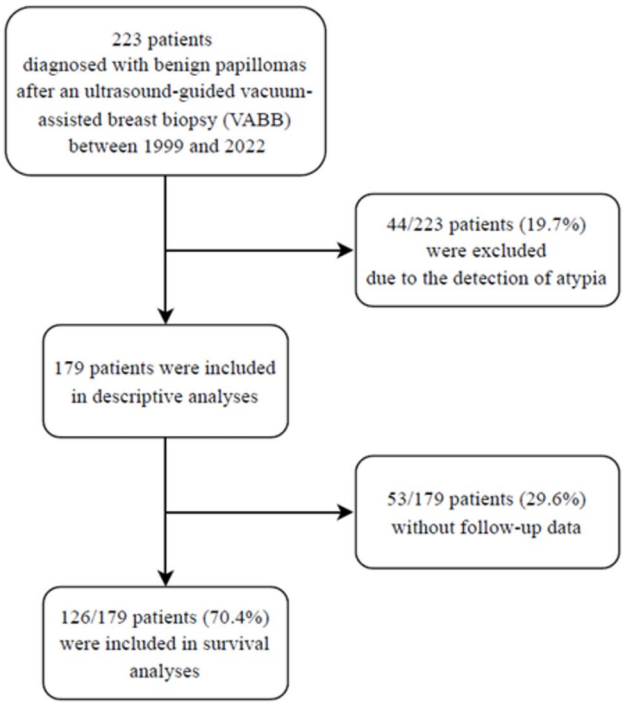

Fig. 2 Flowchart of the study

Table 1 Patients' demographic, tumour and treatment characteristics (N = 179)

Variable	Level	Overall (N = 179)
Year of biopsy, N (%)	1999–2009	57 (31.8)
	2010–2017	63 (35.2)
	2018–2022	59 (33.0)
Age at biopsy, median (min–max)		49 (22–79)
Side, N (%)	Right	89 (49.7)
	Left	90 (50.3)
Number of tissue cores, N (%)	2–4	14 (7.8)
	5–7	32 (17.9)
	8–10	22 (12.3)
	> 10	111 (62.0)
Lesion diameter (mm), median (min–max)		10 (4–36)
Post-biopsy residual lesion, N (%)	No	136 (76.0)
	Yes	43 (24.0)
Clip, N (%)	No	67 (37.4)
	Yes	112 (62.6)
Surgery, N (%)	No	147 (82.1)
	Yes	32 (17.9)

Of the 179 patients, 147 (82.1%) were managed with active surveillance, while 32 (17.9%) underwent surgical excision. Among patients without a residual lesion post-biopsy ($n = 136$), only 14 (10%) proceeded to surgery, compared with 18 of the 43 patients (42%) with a residual lesion ($p < 0.001$).

In the surgically treated group ($n = 32$), histological upgrade was observed in three patients: one case of DCIS and two cases of invasive carcinoma, with an overall underestimation rate of 9% (95% CI: 2–25%). All three patients with histological upgrade had residual lesions after biopsy.

Follow-up data were not available for 53 patients, who were excluded from the survival analysis (Fig. 2). The final cohort for the recurrence analysis included 126 patients: 29 who underwent surgery and 97 who did not. The median follow-up time was 4.0 years (interquartile range [IQR]: 1.9–9.0 years). During follow-up, 9 of 126 patients (7%) developed recurrence in the same quadrant of the ipsilateral breast: 6 in the no residual lesion group, 2 in the residual lesion/no surgery group, and 1 in the residual lesion/surgery group.

In Fine and Gray's multivariable competing-risk regression model, patients with residual lesions post-biopsy managed conservatively (without surgery) had a significantly higher risk of recurrence than those without residual lesions (hazard ratio [HR] = 6.76, $p = 0.015$). No significant difference in the risk of recurrence was observed between patients with residual lesions undergoing surgery and those without residual disease (HR = 1.80, $p = 0.56$). Age at the time of biopsy was independently associated with the risk of recurrence (HR = 1.41, $p = 0.001$), while lesion diameter was not (HR = 1.14, $p = 0.49$) (Table 2).

A comparison of the baseline characteristics of patients excluded from the recurrence analysis due to missing follow-up data ($n = 53$) with those included ($n = 126$) was conducted. The results of this comparison are presented below and in supplementary Table xxx1.

Overall, no statistically significant differences were found between the two groups in terms of age at biopsy, number of tissue cores, lesion diameter, presence of post-biopsy residual lesion, or clip placement. A significant difference was found for surgery (66% of patients without surgery vs. 91% of patients with surgery had FU data, $p = 0.005$), and for post-biopsy residual lesion with/without surgery (FU data was NOT missing for 73% of patients without post-biopsy residual vs. 40% of patients with post-biopsy residual and surgery vs. 94% of patients with post-biopsy residual and with surgery, $p < 0.001$).

Discussion

PLs account for approximately 20% of B3 breast lesions [15], and their management remains a subject of ongoing clinical debate in healthcare [16–19]. In clinical practice, IPs are commonly diagnosed by US, appearing as well-defined, hypoechoic intraductal lesions, often with a

Table 2 Association between post-biopsy residual lesion with/without surgery, age and lesion diameter with the cumulative incidence of recurrence

Variable	Level	N	Person-Years	Event [a]	Competing event [b]	Univariable analysis			Multivariable analysis		
						HR	95% CI	*P*-value	HR	95% CI	*P*-value
Post-biopsy residual lesion±surgery [c]	No post-biopsy residual	99	600	6	11	Ref	-	–	Ref	–	–
	Post-biopsy residual without surgery	10	49	2	1	3.96	0.81–19.3	0.088	6.76	1.45–31.5	0.015
	Post-biopsy residual with surgery	17	115	1	0	0.97	0.12–7.89	0.98	1.80	0.25–13.2	0.56
Age at biopsy	+ 5 years					1.33	1.02–1.73	0.036	1.41	1.14–1.73	0.001
Lesion diameter	+ 5 mm					1.00	0.57–1.75	0.99	1.14	0.79–1.66	0.49

a. Same side and quadrant

b. Same side and different quadrant or different side

c. Time-dependent variable

vascular pole on a colour Doppler technique [20], making them easily accessible for a US-guided biopsy approach [21, 22]. A typical example of a vacuum-assisted biopsy procedure for a papilloma is shown in Fig. 3.

Although the management of IP with atypia is well established today, requiring surgical excision according to current guidelines, the optimal approach for pure IPs remains less clearly defined [11, 23]. A key consideration in managing these lesions is the biopsy technique used. Most of the published literature focused on cases diagnosed by CNB, a method that does not allow complete macroscopic excision of the lesion, unlike VABB [24, 25]. This distinction is critical as it affects diagnostic accuracy and subsequent therapeutic decisions [26–28]. Indeed, although pure IPs are generally considered low-risk lesions, CNB-based diagnoses carry a recognised underestimation risk. Therefore, surgical excision is often recommended to rule out occult atypia or malignancy [11, 29].

In recent years, the use of US-guided VABB has become increasingly popular in breast units [25, 30, 31]. This technique enables the acquisition of a larger volume of tissue, thereby improving diagnostic reliability and significantly reducing underestimation rates [32, 33]. In selected cases, particularly for small benign nodules, VABB can also serve a therapeutic purpose by achieving complete removal of the lesion [34, 35]. However, management strategies after VABB remain controversial, especially when the lesion is not completely excised during the biopsy procedure [36, 37].

Our results support the following approach: for patients with a US-guided VABB diagnosis of pure IP and complete excision of the lesion, active surveillance appears to be a safe strategy, as recommended by the current guidelines of the Third International Consensus Conference on B3 lesions [11]. In these cases, post-biopsy contrastographic evaluation, such as MRI or contrast-enhanced mammography, may be valuable tools to confirm the absence of a residual lesion, as also suggested by the existing data [38, 39]. Conversely, in patients with evidence of a residual lesion post-VABB, our data suggest that surgical excision may help reduce the risk of recurrence. This is confirmed by the significantly higher hazard ratio (HR = 6.76, $p = 0.015$) for recurrence observed in patients with conservatively managed residual lesions. In addition, multivariable analysis identified age at biopsy as an independent predictor of recurrence (HR = 1.41, $p = 0.001$), while lesion diameter showed no significant association (HR = 1.14, $p = 0.49$). This is likely because the lesions selected for US-guided VABB are typically small, as defined by established patient selection criteria [25]. In our case series, only 10 of 179 lesions exceeded 20 mm in size. Therefore, apparent complete macroscopic excision becomes a more relevant factor, enabling the pathologist to thoroughly evaluate the entire lesion.

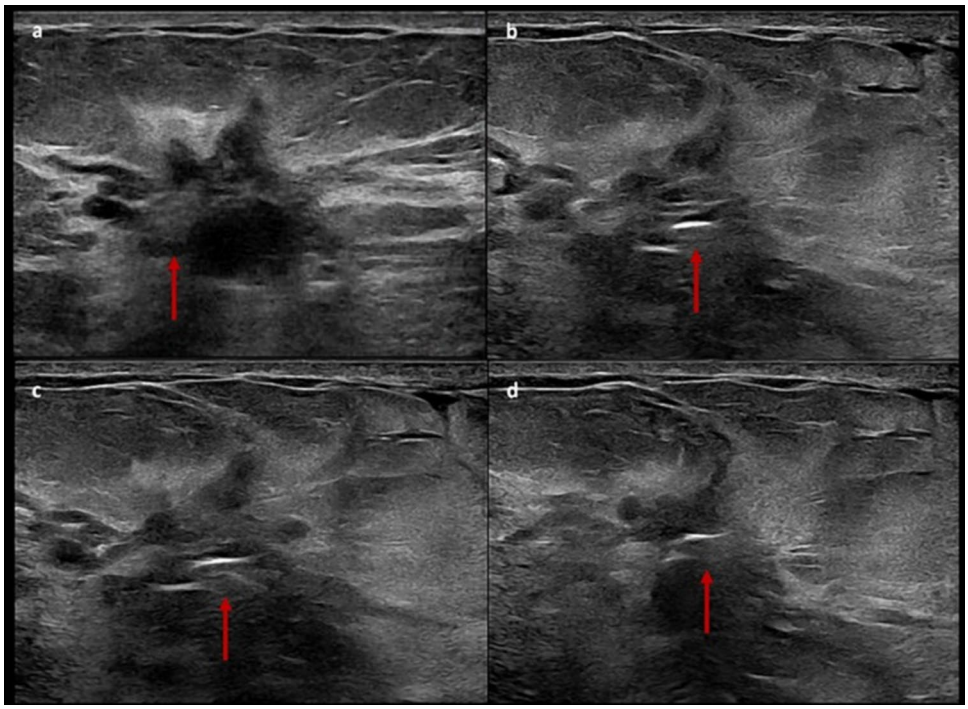

Fig. 3 US-guided VABB of IP (red arrow, a). Note the progressive and complete excision of the lesion using an 8-gauge needle (red arrows b, c, d)

Our findings are consistent with routine clinical practice: in cases of incomplete removal—especially when symptoms, suspicious imaging, or radiologic–pathologic discordance are present—surgical excision is typically recommended following multidisciplinary discussion [40, 41]. In our cohort, the overall rate of diagnostic underestimation in surgically treated patients was 9% (95% CI: 2–25%) [42, 43]. In the literature, the underestimation rates reported for pure IP vary widely, from 1 to 12% [44]. For example, Seely et al. [31] reported an understatement rate of 5%, while Maccoll et al. [14] reported an approximately 12% rate, and the most recent international consensus cites rates of up to 2% [11]. This variability likely reflects the heterogeneity of patient populations and risk profiles [45, 46]. In our study, patients selected for surgery often presented with higher-risk features (symptoms, residual lesions, ambiguous enhancement), which explains the observed 9% upgrade rate [47]. These patients may present a substantially higher risk of underestimation than those without such risk factors.

There has been growing interest in the standardised vacuum-assisted excisional biopsy (VAE) technique for small lesions, aiming to collect at least 4 g of tissue and achieve complete lesion removal both for diagnostic and therapeutic purposes [48, 49]. VAE is increasingly being explored as a minimally invasive alternative to surgery for selected low-risk B3 lesions, including IPs, particularly in specialised breast centers. By allowing for more extensive sampling and potential lesion removal, it may help reduce underestimation rates and, in carefully selected cases, limit the need for surgical excision.

Conclusions

Our results support a risk-adapted approach to managing atypia-free Ips diagnosed by US-guided VABB. When the lesion is completely excised at biopsy and there are no additional clinical or radiological risk factors, active surveillance appears to be a safe and appropriate strategy, in line with recent international recommendations. On the contrary, a post-biopsy residual lesion significantly increases the risk of ipsilateral recurrence in the same quadrant if not treated surgically. In these cases, surgical excision may be advisable, particularly in the presence of additional risk factors such as patient age, clinical symptoms, or discordance between imaging and pathology. The observed diagnostic underestimation rate of 9% in the surgically treated subgroup further supports the need for a tailored multidisciplinary decision-making process. VAE may represent a valid therapeutic alternative in selected low-risk cases, potentially reducing the need for surgery. Overall, our data contribute to refining the clinical management of B3 papillary lesions, promoting a personalised approach based on the status of the residual lesion and the individual risk of the patient. Although not formally assessed in this study, the potential cost-effectiveness of a conservative, risk-adapted approach—particularly when surgical excision can be avoided—may have relevant implications for both healthcare resource utilisation and patient quality of life. Future studies should also explore patient preferences and the psychological effects of different management strategies.

Several limitations must be considered in this study. The retrospective design inherently involves risks of selection bias and missing data. Many patients were lost to follow-up, limiting the robustness of the survival and recurrence analyses. The comparison groups (surgery vs. no surgery; residual vs. non-residual lesions) were not completely matched or randomised, potentially introducing confounding variables. Furthermore, no formal interobserver agreement analysis was conducted for the assessment of post-biopsy residual lesions, which may introduce variability in classification. The monocentric nature of the study may also limit the generalisability of the findings to other clinical settings with different protocols and expertise. Moreover, a potential selection bias should be considered, as patients without a post-biopsy residual lesion had less frequent follow-up (73% vs. 94% with residual lesion and surgery), possibly due to being deemed lower risk. This imbalance may have led to an underestimation of recurrence in the "no residual lesion" group and to a lower observed hazard ratio for the comparison with the "residual with surgery" group. Finally, the small number of recurrence events (same side and quadrant, $n=9$) limits the statistical power of our multivariable analyses and results in wide confidence intervals, which may affect the robustness and precision of the estimated associations.

Despite these limitations, the study benefits from a large cohort of US-guided VABB from a single institution, providing meaningful information on real-world clinical practice and supporting the development of more personalised management strategies for atypia-free IPs.

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Data availability The data presented in this study (raw data) are available upon request from the corresponding author. Due to privacy considerations and GDPR compliance, the data are not publicly available.

Declarations

Conflict of interest Filippo Pesapane and Serena Carriero are editors of this journal. All other authors declare no conflicts of interest.

Ethical approval and consent to participate The ethics committee of the European Institute of Oncology (IEO), IRCCS Milan, Italy, approved this retrospective study and waived the requirement for specific informed consent (approval number UID 4622; approval date: May 8, 2024).

Consent for publication Ethics committee approval for the retrospective study was granted after verification of the institutional consent proposed to patients at our institution (general consent to scientific research).

All data were anonymized. Figures do not contain sensitive data and cannot be traced back to individual patients.

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