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Fine-Needle Aspiration Cytology (FNAC) is a reliable diagnostic tool for small breast lesions (≤ 1.0 cm): a 20-year retrospective study

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Abstract

Background: Breast cancer is a major public health problem worldwide. It is recommended that small breast lesions or those suspicious for malignancy be evaluated via histopathological examination ("core biopsy" or surgical specimens), and lesions that are probably benign and palpable should be examined via fine-needle aspiration cytology (FNAC). This study aimed to assess the accuracy of FNAC for the diagnosis of small breast lesions.

Methods: We reviewed all anatomopathological reports of FNACs collected between January 1, 2000 and December 31, 2019 ($n = 24,721$) in a private community pathology service. Lesions up to 1.0 cm (≤1.0 cm) ($n = 8334$) were included for evaluation and classified according to the recommendation of the International Academy of Cytology Yokohama System for Reporting Breast Fine Needle Aspiration Biopsy Cytopathology in the following categories: (1) insufficient/inadequate; (2) benign; (3) atypical, probably benign; (4) suspicious of malignancy; and (5) malignant. Subsequently, the results of the FNACs were compared to those of the respective histopathological examinations ($n = 785$).

Results: FNAC had a specificity of 99.6%; sensitivity, 97.4%; positive predictive value, 99.6%; negative predictive value, 97.6%; and accuracy, 98.5%.

Conclusions: FNAC is a reliable method for diagnosing small breast lesions (≤1.0 cm).

Keywords: Breast neoplasm, Fine-needle aspiration cytology, Small lesions, Cytology, Accuracy

Background

Breast cancer is the most common malignant neoplasm among women worldwide after non-melanoma skin malignancies (Globocan Observatory W 2019a; Bray et al. 2018). Further, it is the most frequent cause of cancer-related death among women worldwide, with an estimated 2.1 million new cases annually. The survival rate varies by continent, with better rates in developed countries (Globocan Observatory W 2019a; Bray et al. 2018). The implementation of breast cancer screening programs is helpful for early detection of breast lesions that in turn translate to a significant decrease in mortality (Instituto Nacional do Câncer 2018; Urban et al. 2017; Myers et al. 2015; Manfrin et al. 2009). Lesions suspected of malignancy should be subjected to complementary tests as soon as possible for diagnostic confirmation (Instituto Nacional do Câncer 2018; Perry et al. 2008). The most common modalities for initial

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evaluation of breast lesions are fine-needle aspiration cytology (FNAC) and core-needle biopsy (Perry et al. 2008; Kocjan et al. 2008). Compared with core-needle biopsy, FNAC is associated with high rates of insufficiency or inadequate specimens and low accuracy, and thus most clinicians prefer biopsy (Manfrin et al. 2009). In addition, some studies recommend that small breast lesions or those suspicious for malignancy should be evaluated through histopathological examination ("core-needle biopsy" or excision), and FNAC should be indicated for lesions that are probably benign or palpable (Manfrin et al. 2009; Nakano et al. 2015).

However, FNAC is a more simple, low-cost technique with a low risk of complications than that observed with biopsy or excision procedures (Ali and Parwani 2007; DeMay 2012). Core-needle biopsy involves the use of a thick needle to obtain fragments of the lesion, is performed in a specialized service, uses local anesthesia, and requires several fragments for an accurate analysis (Rocha et al. 2013). FNAC when performed in adequate conditions has good accuracy (Ali and Parwani 2007; DeMay 2012). The aspirated specimen can also be processed as a cellblock (Bueno Angela et al. 2013; Journal 2012; Krogerus and Kholová 2018) that can then be used for immunohistochemical analysis of related biomarkers (e.g., estrogen receptor, progesterone receptor, and Her-2). The cellblock specimen can also be used for molecular analysis, providing additional information that can be helpful in the diagnosis and treatment by identifying predictive and prognostic markers (Bueno Angela et al. 2013; Dong et al. 2016; Beca and Schmitt 2019).

Early diagnosis and small lesion size significantly improve the treatment outcomes and prognosis of patients with breast lesions, especially those with malignant lesions (Instituto Nacional do Câncer 2018).

Methods

This retrospective study aimed to evaluate the accuracy of FNAC as a diagnostic modality for small breast lesions (≤1.0 cm). It was conducted at the Bauru Institute of Pathology (ANATOMED), Bauru-São Paulo, Brazil between January 1, 2000 and December 31, 2019. Several radiologists and five pathologists performed all the examinations. Lesions were identified and measured in three dimensions on ultrasound examination. Then, the pathologist performed the FNAC under ultrasound guidance. All lesions ≤1.0 cm were sampled under ultrasound guidance. FNAC was performed as commonly described in the literature. Briefly, a 25 × 0.6 mm 25-Gauge needle, a common cyto aspirator, and a 10 ml syringe were used (Bueno Angela et al. 2013). The specimen obtained was placed on slides for smears (between 2 and 4 smears stained with hematoxylin-eosin (HE) and May-Gründwald-Giemsa [MGG]), as recommended in the literature, in order to obtain more cytology information (Bueno Angela et al. 2013). The slides for HE staining were fixed in 95% alcohol, whereas those for MGG staining were air-dried. The excess specimen at the needle rinse was processed for cellblock. The cellblock technique involved aspiration of a small amount of 95% alcohol (0.5–1.0 ml) to aid the aggregation of the specimen by coagulation, followed by immediate aspiration of a 10% formaldehyde buffered solution (5–10 ml) for fixation, and usual histological processing in paraffin sections (Bueno Angela et al. 2013). The same pathologist who performed the FNAC examined the slides and made the diagnosis. In doubtful cases, the diagnosis was made in consensus with the opinion of one or more pathologists from the same department.

Data were collected from anatomopathological reports. Lesions measuring ≤1.0 cm on ultrasound at the time of FNAC were included (Fig. 1). Lesions measuring > 1.0 cm or those whose size was not specified were excluded. All reports included in the study were reviewed by two pathologists (JATC and CTS). The results were classified by consensus according to the proposal of the International Academy of Cytology Yokohama System for Reporting Breast Fine Needle Aspiration Biopsy Cytopathology, into five categories: (1) insufficient/inadequate; (2) benign; (3) atypical, probably benign; (4) suspicious of malignancy; and (5) malignant (Field et al. 2019). Subsequently, we searched the related reports on the histopathological diagnosis corresponding to the sampled lesion and the subsequent cytohistological correlation (Fig. 1). The histopathological diagnosis was considered the "gold standard".

Data were processed using Microsoft Office Excel® software to calculate the accuracy, positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity (Wong and Lim 2011), mean age, patient age groups, and mean size of lesions.

Results

Of the 24,471 breast lesions that were subjected to FNAC, 8334 lesions measuring ≤1.0 cm were included in the analysis (Fig. 1). The FNAC of these small lesions were performed for 7920 women (1.1 lesion/patient). The average sizes of the benign and malignant lesions were 7.2 mm (range, 2–10 mm) and 7.3 mm (range, 2–10 mm), respectively. The average patient age was 49.3 years. The age distribution was as follows: ≤30 years, n = 649 (8%); 31–40 years, n = 1402 (18%); 41–50 years, n = 2352 (30%); 51–80 years, n = 3414 (43%); and ≥ 81 years, n = 103 (1%). Of the 8334 lesions, 12 were classified as insufficient (group 1); 7384, benign (group 2); 402, atypical, (group 3); 140, suspicious of malignancy (group 4); and 396, malignant (group 5) (Fig. 1). Of the 8334 sampled lesions, 785 (9.4%) had a corresponding

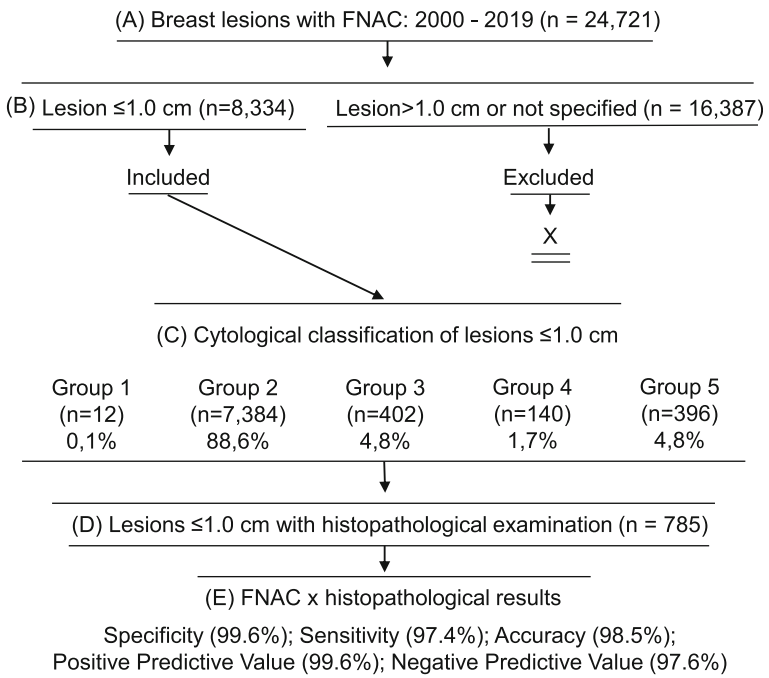

Fig. 1 Flowchart of the study design. **a** Retrospective assessment of breast lesions subjected to FNAC between January 1, 2000 and December 31, 2019. **b** Lesions ≤1.0 cm were included in the study, and those measuring > 1.0 cm were excluded. **c** Review of FNAC reports and classification of the lesions into one of five categories: group 1, insufficient or inadequate; group 2, benign; group 3, atypical; group 4, suspicious of malignancy; and group 5, malignant. **d** Review of histopathological reports to identify a surgical specimen corresponding to the sampled lesion and cytohistological correlation. **e** Results obtained from the cytohistological correlation between benign and malignant lesions. Abbreviations: FNAC, fine-needle aspiration cytology

histopathological examination (core-needle biopsy or surgical procedures such as lesion excision or quadrantectomy/mastectomy) (Fig. 1).

None of the lesions in group 1 had a corresponding histopathological diagnosis. Three lesions were subjected to a second FNAC analysis and were classified as benign (two fatty necrosis and one benign lesion without cytological atypia). In group 2, 250 lesions had a corresponding histopathological examination, with 244 confirmed as benign and 6 as malignant, resulting in a negative predictive value (NPV) of 97.6%. In group 3, 214 lesions had a histopathological exam that confirmed 170 as benign (79.4%) and 44 as malignant (20.6%). In group 4, 27 (28.4%) were confirmed as benign and 68 (71.6%) as malignant. In group 5, 225 lesions were confirmed as malignant and only one was confirmed as benign (as fatty necrosis), resulting in a positive predictive value (PPV) of 99.6%. The sensitivity was 97.4%; specificity, 99.6%; and accuracy, 98.5% (Fig. 1 and Table 1).

Table 1 lists the main diagnoses obtained in each group using the FNA and surgical specimen. The risk of malignancy for each group was: 0 (group 1), 2.4% (group 2), 20.6% (group 3), 71.6% (group 4), and 99.6% (group 5). The lesions considered malignant in groups 2, 3, and 4 accounted for a substantial percentage of neoplasms in situ. The main benign lesions or those with low potential for malignancy that were diagnosed in each group are listed in Table 1.

Discussion

FNAC and core-needle biopsy are the two most common modalities for the initial evaluation of breast lesions, but the accuracy of FNAC has been controversial. This study found that FNAC is a reliable diagnostic method for small breast lesions (≤1.0 cm), with a specificity of 99.6%; sensitivity, 97.4%; PPV, 99.6%; NPV, 97.6%; and accuracy, 98.5%.

The mean age of the patients in this study was 49,3 (group 3), for both benign and malignant lesions, similarly to the incidence rate peaks reported of 40 to 60-year-olds. (Bray et al. 2018; Journal 2012; Instituto Nacional do Câncer 2019; Globocan 2018; Globocan Observatory W 2019b). Similarly, most patients in this study, regardless of whether they had benign or malignant lesions, were aged between 41 and 50 years (mean age: 49.3 years). Most breast lesions detected by palpation or imaging examinations are benign or have a low potential for malignancy and have a higher incidence between the fourth and fifth decades of life (Orr and Kelley 2016). Benign lesions are usually followed up by clinical or radiological examination and, in most cases, there is no indication for a surgical approach, except in certain

Table 1 Number of cases in each group and the main FNAC and histopathological diagnoses

FNAC (*n* = 8334)	Histopathological (*n* = 785)
Group 1: Insufficient (*n* = 12/8334; 0.1%)	**Group 1 (*n* = 0; 0,0%)**
Group 2: Benign (*n* = 7384/8334; 88.6%) Cyst (*n* = 3477; 47.0%) PBDWA (*n* = 1400; 19.0%) Fibroadenoma (*n* = 1227; 16.6%) Others (*n* = 1286; 17.4%)	**Group 2: 250** **Benign (*n* = 244/250; 97.6%)** Fibroadenoma (*n* = 72) FBD (*n* = 69) Cyst (*n* = 52) Others (*n* = 51) **Malignant (*n* = 6/250; 2.4%)** IBC (*n* = 2) Tumor phyllodes, ILC, DCIS (*n* = 4)
Group 3: Atypical, probably benign (*n* = 402/8334; 4.8%)	**Group 3: 214** **Benign (*n* = 170/214; 79.4%)** FBD (*n* = 83) P (*n* = 47) Fibroadenoma (*n* = 29) Others (*n* = 11) **Malignant (*n* = 44/214; 20.6%)** DCIS (*n* = 19) IBC (*n* = 17) Others (*n* = 8)
Group 4:: Suspicious, probable in situ or invasive carcinoma (*n* = 140/8334; 1.7%)	**Group 4: 95** **Benign (*n* = 27/95; 28.4%)** FBD (*n* = 16) Fibroadenoma (*n* = 7) P (*n* = 4) **Malignant (*n* = 68/95; 71.6%)** IBC (*n* = 41) DCIS (*n* = 11) ILC (*n* = 8) Others (*n* = 8)
Group 5: Malignant (*n* = 396/8334; 4.8%)	**Group 5: 226** **Benign (*n* = 1/226; 0.4%)** Fatty necrosis (*n* = 1) **Malignant (*n* = 225/226; 99.6%)** IBC (*n* = 186) ILC (*n* = 23) Others (*n* = 34)

Abbreviations: *FBD* fibrocystic breast disease, *IBC* invasive breast carcinoma, *NOS* not otherwise specified, *DCIS* ductal carcinoma in situ, *ILC* invasive lobular carcinoma, *LCI* lobular carcinoma in situ, *P* papilloma, *PBDWA* proliferative breast disease without atypia, *FNAC* fine-needle aspiration cytology

conditions (e.g., frequent recurrence of cystic lesions or a major change in its shape and size) (Field et al. 2019; Orr and Kelley 2016). In the present study, the majority of the lesions were benign on FNAC, and most of the patients with such lesions were only followed up clinically. Only 250 of the 7384 patients with benign lesions underwent surgery or biopsy (Fig. 1 and Table 1).

The combination of correlated imaging examinations and cytopathological characteristics improves the FNAC. This combination of clinical assessment-imaging-cytology improves the PPV of FNAC to almost 100% compared to the results obtained using biopsy or surgical specimens (Dong et al. 2016; Field et al. 2019; Irwig et al. 2002; Field et al. 2017; Tse and Tan 2010; Anderson 2016). Some authors suggest FNAC as the first-line modality for assessing breast lesions, except in cases with only microcalcifications. Ultrasound-guided FNAC is recommended in cases of non-palpable lesions (Kocjan 2006). When the combination of three assessments is used, treatment can be based solely on the result of FNAC, without the need for a complementary histopathological study (Kocjan et al. 2008). The high PPV, NPV, sensitivity, specificity, and accuracy of FNAC in the current study indicates that it can also be used as a reliable first-line diagnostic modality for small breast lesions (≤1.0 cm) (Fig. 1 and Table 1).

The diagnostic accuracy of FNAC for breast lesions has varied among previous studies. A literature review by Mitra et al. showed that the sensitivity of FNAC for diagnosing breast cancer ranged from 77 to 97%, and they considered the experience of the cytopathologist, the presence of the cytopathologist at the moment of the FNAC, and a larger lesion size as influencing factors of accuracy (Mitra and Dey 2015).

In general, the accuracy varies between 86.1 and 95.7% (Dong et al. 2016; Yamaguchi et al. 2012). In contrast, other authors reported favorable accuracy of FNAC, suggesting that FNAC should be preferred over core-needle

biopsy for small lesions considering that biopsy procedures can completely remove the lesion, leading to difficulties in assessing surgical margins (Tse and Tan 2010). Yamaguchi et al. also reported that if FNAC findings are used in conjunction with clinical and radiological data, the diagnostic accuracy can reach almost 100% (Yamaguchi et al. 2012). Another strategy for improving the accuracy of FNAC is implementation of the appropriate technique; this allows for obtaining specimens representative of the lesion and the use of different staining to obtain more cytological information, as one gives some nuclear or cytoplasmic details that can improve the analyses.

Proper slide preparation, adequate technical quality control, analysis by an experienced cytopathologist, discussion of doubtful cases with other cytopathologists, and correlating with radiologic findings will help improve the reliability of FNAC (Perry et al. 2008; Mitra and Dey 2016; Yamaguchi et al. 2012; Smith et al. 2012). The values obtained in the present study (accuracy, 98.5%; NPV, 97.6%; PPV, 99.6%; sensitivity, 97.4%; specificity, 99.6%) show that FNAC is reliable for evaluating small breast lesions regardless of their status (benign or malignant), and the results were highly consistent with those obtained via histopathological examination (Fig. 1). It is important to note that FNAC in the present study was performed under the following conditions: (1) all lesions ≤1.0 cm were sampled under ultrasound guidance; (2) the lesions were identified by radiologists, and the puncture performed by a pathologist; (3) at least two different smears were performed (MGG and HE); (4) the specimen obtained was sufficient for smearing and cellblock analysis, adding important information for the analysis; (5) the pathologist who performed the FNAC was the main personnel responsible for evaluating the smears and the cellblock specimen, and (6) the doubtful cases were evaluated by one or more cytopathologists, allowing for a consensus diagnosis. With these conditions, adequate specimens for examination and for accurate analyses (Fig. 2) were obtained. In our experience, the use of complementary stains (MGG and HE) and cellblocks provides additional important information that improves the accuracy of the diagnosis by FNA. Usually, the cellblocks have enough material to perform immunohistochemistry for different prognostic and predictive markers, as well as for molecular techniques. In these cases, the FNAC can provide all the information necessary for proper management or treatment, without the need for any surgical procedure to obtain additional material. There is an increasing emphasis on the accurate classification of malignancy using smaller specimens. Currently, tumor-specific subtyping with prognostic and predictive biomarker testing has become a significant component of cytopathology (VanderLaan 2016). In this context, the material obtained by FNA to conduct these studies using ancillary or molecular techniques showed results equivalent to those obtained by core biopsy, which may renew the interest of FNA as a first-line diagnostic modality for the diagnosis of different types of neoplasms (VanderLaan 2016).

Another important factor in the use of FNAC for evaluating breast lesions is the accuracy of the method to define the nature of the lesions (benign versus malignant) and to avoid doubtful reports that may require new procedures to confirm the diagnosis. The uncertainty of the diagnosis after FNAC may be attributable to the cytological characteristics of the lesion (high cellularity, nuclear pleomorphism, presence of non-cohesive epithelial cells, presence of mitosis and changes in the nucleus/cytoplasm ratio) or problems related to the technique and processing of the specimen obtained (Nakano et al. 2015; Mitra and Dey 2015). Benign lesions or those with low malignant potential that are difficult to diagnose via FNAB are mainly fibroadenomas, fibrocystic breast disease, radial scars, papillomas with epithelial hyperplasia, proliferative epithelial lesions with or without atypia, gynecomastia, lactation changes, fatty necrosis, and phyllodes tumors. For malignant lesions, classic lobular carcinoma, tubular carcinoma, mucinous carcinoma, lobular carcinoma in situ, ductal carcinoma in situ (DCIS), nuclear grade 1, and well-differentiated breast carcinoma (not otherwise specified) are the most challenging to diagnose via FNAC (Perry et al. 2008; Nakano et al. 2015; Mitra and Dey 2015; Berner and Sauer 2011). Similar data were obtained in the present study. In previous studies, most specimens classified as groups 1, 3, and 4 could be classified as groups 2 or 5 if FNACs were carried out under appropriate conditions. This would avoid increased costs related to the need for further procedures to confirm the diagnosis and also shorten the interval between diagnosis and treatment initiation, which is particularly crucial in treating patients with malignant lesions. Some guidelines suggest that cases classified in categories 3 and 4 should not exceed more than 20% of the total cases (Perry et al. 2008; Mitra and Dey 2015). In the present study, 0.1% (12/8334) of cases in group 1, 4.8% (402/8334) in group 3, and 1.7% (140/8334) in group 4, corresponding to 6.6% (554/8334). The low levels of insufficient specimens (group 1) and undefined diagnoses (groups 3 and 4) are probably due to appropriate conditions in which FNAC was performed, allowing an accurate diagnosis in most cases.

It is important to note that among the lesions in group 3 (atypia, probably benign), 79.4% were confirmed to be benign on histopathological analysis, with only 20.6% considered malignant. Furthermore, almost half of these cases were diagnosed as DCIS (Table 1). For group 4 (atypia, probably malignant), 71.6% were histopathologically confirmed to be malignant (Table 1).

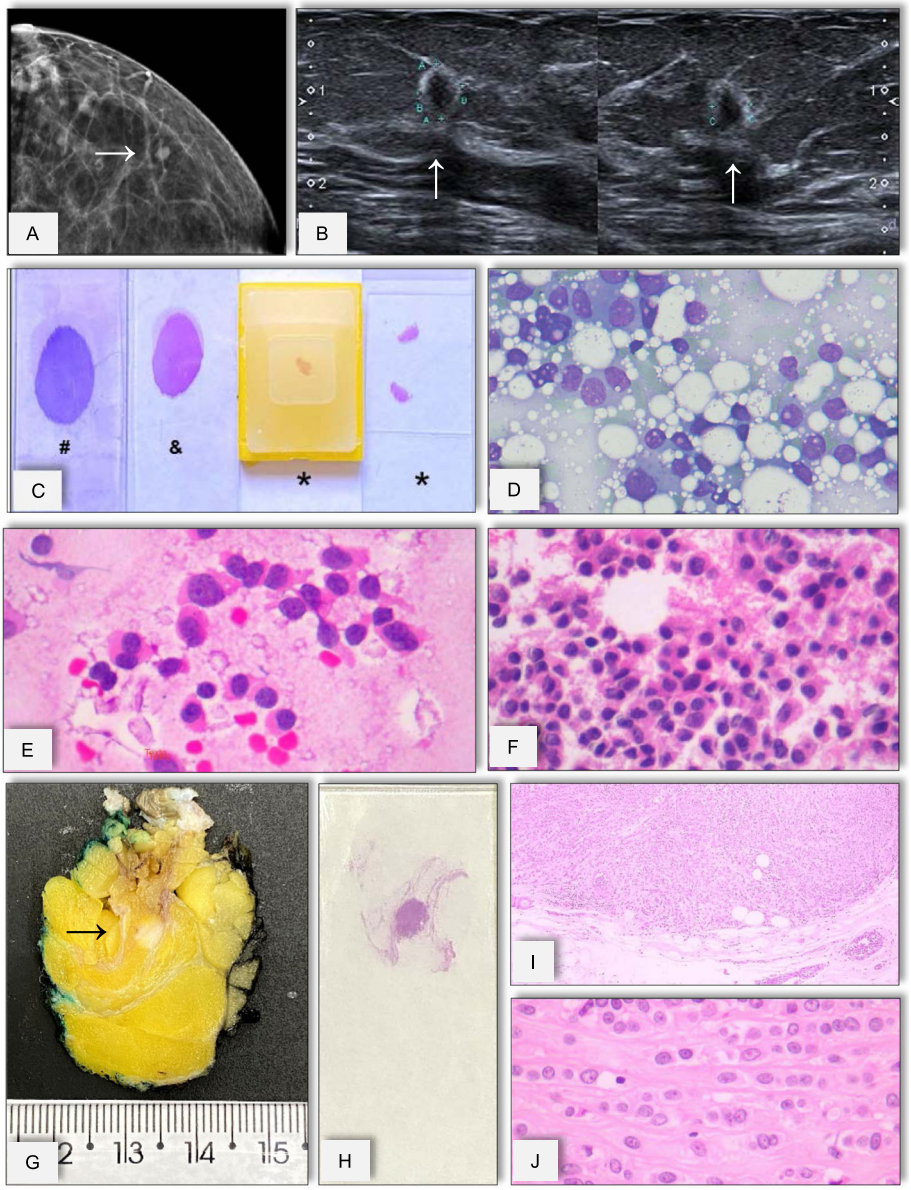

Fig. 2 Example of a ≤ 1.0 cm lesion diagnosed via FNAC and confirmed via histopathological examination. Mammographic examination (**a**) and ultrasound examination (**b**) demonstrate a suspected irregular lesion for malignancy. The FNAC specimen was stained with MGG (#) and HE (&) and also prepared for cellblock (*) (**c**). On MGG (**d**) and HE (**e**) staining, the specimen show characteristics of a well-differentiated carcinoma, consisting of loose cells or forming small clusters with low cohesiveness. Histological sections of the cellblock show atypical epithelial cells similar to smears (**f**). Macroscopic examination of a quadrantectomy shows a 0.5 cm lesion surrounded by adipose tissue (⟶) (**g**). Histological sections stained using HE confirm the diagnosis of classic lobular carcinoma (**h**, **i** and **j**). Abbreviations: FNAC: fine-needle aspiration cytology; MGG: May-Gründwald-Giemsa; HE: hematoxylin-eosin

Collectively, these results show that even in doubtful cases (groups 3 and 4), FNAC has good agreement with histopathological examination, offering important information for establishing an accurate diagnosis.

Some limitations may be present in a retrospective study such as the current one. The number of cases in groups 3, 4, and 5 was significantly lower than that in group 2. This may have introduced some selection bias; however, even though there was a proportionally smaller number in groups 3, 4, and 5, the number of cases was relatively large for all groups, which can minimize any undesirable effects in the analyses.

Conclusion

The results of this study show that FNAC is a reliable method for the diagnosis of small breast lesions (≤1.0

cm) as evidenced by the high accuracy, sensitivity, specificity, PPV, and NPV. FNAC findings correspond to those obtained via histopathological evaluation.

Abbreviations

FNAC: Fine-needle aspiration cytology; DCIS: Ductal carcinoma in situ

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Authors' contributions

JC reviewed the data, conducted the statistical analysis, and drafted and critically reviewed the manuscript. MM evaluated and critically reviewed the project. CC conducted the radiological evaluation and critical review. FS evaluated and critically reviewed the project. CS conceived and design the study, reviewed the data, and drafted and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee of the State University of São Paulo "Júlio de Mesquita Filho" (UNESP), and the letter of discharge was authorized ("Universidade Estadual Paulista Júlio de Mesquita Filho" - CAE: 28211619.1.0000.5411 and according to the substantiated opinion number 3,822,926 in Platform Brazil).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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