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Immunohistochemistry Applied to Breast Cytological Material

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Abstract
Fine-needle aspiration biopsies (FNABs) of the breast are minimally invasive procedures enabling the diagnosis of suspicious breast lesions. Unfortunately, they are often perceived as inferior to core-needle biopsies, namely because they are supposedly unable to differentiate between high-grade ductal carcinoma in situ and invasive carcinoma or provide material for ancillary testing. Several studies have shown, however, that FNAB samples, when handled properly, are indeed capable of providing sufficient and adequate material for ancillary testing, namely immunocytochemistry (ICC). We reviewed the published literature regarding the use of ICC for both diagnostic and theranostic uses in the different types of cytological samples obtained from FNABs of the breast, including smears, liquid-based cytology samples, and cellblocks. We found that p63 and 34βE12 show promise in aiding in the differential diagnosis between in situ and invasive lesions and that most other diagnostic markers may be used as in tissue. Regarding theranostic ICC markers, results vary between publications, but with care, these can successfully be performed in cytological samples. Air-dried smears should be avoided, and cellblocks are overall more versatile than cytology slides, enabling the evaluation of not only hormonal receptors and HER2 by ICC, but also of Ki-67. Particular attention should be paid to fixation and antigen retrieval procedures in all cases. We recommend that laboratories without experience perform short validation runs before adopting these techniques into clinical practice.

Introduction

Fine-needle aspiration biopsies (FNABs) of the breast are still the main method used for the diagnosis of breast lesions in developing countries, and also in certain specialized practices in the Western countries [1–3]. This technique is minimally invasive and can be performed with few, if any, complications [2]. Nevertheless, even though the National Comprehensive Cancer Network guidelines allow for the use of FNABs, they recommend that ideally suspicious breast lesions should be biopsied using a core-needle biopsy (CNB) [4, 5]. This is because CNBs are true tissue biopsies, enabling pathologists to reliably perform immunocytochemistry (ICC) for both diagnostic and theranostic purposes (most commonly estrogen receptors [ER], progesterone receptors [PR],

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HER2, and Ki-67) and oftentimes arrive at a precise etiological diagnosis [2, 6–8]. In particular, they enable the differential diagnosis between high-grade ductal carcinoma in situ (DCIS) and invasive carcinomas, which may be difficult or even impossible in cytology samples, given that there is significant morphological overlap [9–12].

CNBs are not without drawbacks, however. They are more expensive, invasive, and may result in more complications and comorbidities for the patient [13]. Ideally, to make the most of both techniques, CNBs and FNABs would be used in conjunction as part of the well-known "triple-test" (Fig. 1). Published literature has shown that a good diagnostic accuracy is possible using FNABs for the diagnosis of breast lesions [14, 15]. The need for a follow-up CNB may be obliviated in a majority of cases, particularly when applying the Yokohama System for Reporting Breast Fine-Needle Aspiration Biopsy Cytopathology, which defines diagnostic categories with established criteria, risks of malignancy, and guidelines for clinical management [1, 2, 16].

Moreover, and contrary to popular belief, FNAB samples are in fact able to provide sufficient and adequate material for ancillary testing, namely ICC, showing good concordance with both CNBs and resection specimens [17]. This could be particularly useful in the setting of metastatic disease, where biomarker retesting is recommended [4, 17]. In this paper, we review the published literature regarding the use of ICC in breast cytological material for both diagnostic and theranostic purposes, with an emphasis on sample management and highlighting potential pitfalls.

Material and Methods

A review of the literature was performed for publications relating to the use of ICC in breast cytology samples obtained through FNABs using PubMed, Scopus, Google Scholar, and Web of Science databases. We performed different queries using the following terms "cytology," "fine-needle aspiration," "breast," "carcinoma," "metastasis," "theranostics," "diagnosis," immunocytochemistry," "estrogen receptor," "progesterone receptor," "HER2," "Ki-67," and "PD-L1." Certain variations of these terms (plurals and acronyms, for example) were also used. Results were manually screened based on the type of marker (diagnostic vs. theranostic) and then sorted according to their use and type of preparation (smears, cytospins, liquid-based cytology [LBC], and cellblocks). Relevant papers were reviewed. In diagnostic makers, analysis focused on their use and efficacy in this context. For theranostic markers, particular attention was paid to fixation and antigen retrieval methods, as well as the impact of the type of preparation on the quality of the ICC performed.

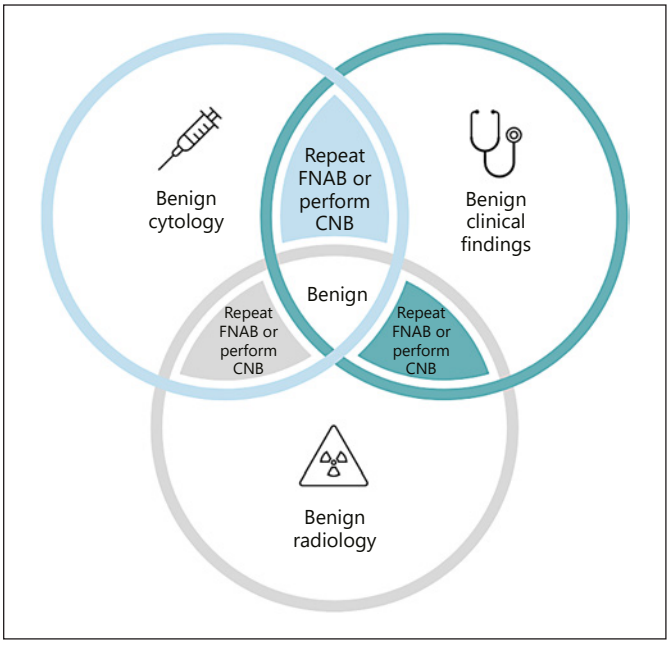

Fig. 1. FNAB of the breast "triple test" – if clinical, radiological, and cytological findings agree, the result is considered benign, and the patient is referred to clinical and imagiological follow-up. If there is any disagreement, a repeat FNAB or CNB is indicated, depending on the particular context.

Results

Several publications have looked at the potential uses of ICC in the context of breast FNABs for diagnostic purposes. This ancillary technique appears to aid in the diagnosis of hematolymphoid and mesenchymal malignancies, as well as neoplasms metastatic to the breast. ICC has also been shown to be useful in the differential diagnosis between in situ and invasive lesions [17].

For theranostic purposes, clinical guidelines determine that at the time of diagnosis the expression of four markers should be determined through ICC: ER, PR, HER2, and Ki-67 [18]. Recently, PD-L1 was added to this list, in the context of metastatic triple-negative breast cancer [19]. However, although PD-L1 may be performed in cytological samples as demonstrated in lung cancer [20, 21], in the context of breast cancer, PD-L1 expression is evaluated not only in tumor cells but also in tumor-infiltrating lymphocytes, where cytology samples have historically performed poorly [22]. In the following review, we focus only on the better studied markers: ER, PR, Ki-67, and HER2.

Table 1. ICC markers to distinguish benign versus in situ versus invasive lesions in breast cytology

Study	Cases, *N*	ICC markers	Sample type	Antigen retrieval	Main findings
Fischler et al. [23]	45	SMA	Destained, alcohol-fixated PAP smears	Not informed	SMA positive in fibroadenomas and negative in carcinomas
Mosunjac et al. [24]	28	SMA and calponin	Cellblocks	Not informed	Calponin positive in papillomas and negative in papillary carcinomas SMA with more background, stained stroma and was weakly positive in 2 cases of papillary carcinomas
Reis-Filho et al. [25]	23	p63	Destained, alcohol-fixated PAP smears	Heat-based method	p63 positive not only in all cases of DCIS but also in 60% of invasive carcinomas
Reis-Filho et al. [26]	74	p63	Destained, alcohol-fixated PAP smears	Heat-based method	p63 positive in all benign cases, 80% of cases with DCIS and invasive carcinoma, and 56% of pure invasive carcinoma
Harton et al. [27]	46	p63	Cytolyt® and cytospin	Not informed	Using different criteria (cases with fewer than 25% of single cells and fewer than 25% of cell clusters showing p63 positive cells were considered malignant), these authors obtained sensitivity of 80% and specificity of 90% in the differential diagnosis between benign and malignant cases
Aiad et al. [28]	49	p63	Air-dried and alcohol-fixated smears	Heat-based method	Using a cut-off of 25% in cell clusters, below which malignancy was favored, p63 was positive in 75% of benign cases and negative in 89% of malignant cases. Combining morphology with p63 results, a sensitivity of 100% and specificity of 75% was found in the differential diagnosis between benign and malignant cases
Hoshikawa et al. [29]	56	p63 34βE12	Smears and cell transfer slides	No	Using a cut-off of 25% or more for p63 in clusters favored a benign diagnosis. Integrating both markers, the sensitivity was 82% and specificity was 91%. The authors were able to characterize most cases of DCIS: low P63 and low 34βE12
Tanaka et al. [30]	139	p63 CK5/14 CK7/18	Destained, alcohol-fixated PAP smears; and cell transfer slides	Heat-based method	p63 expression in at least one cell and expression of CK5/14 in more than 20% of the cells in a cluster were considered to favor a benign diagnosis. After ICC, the authors improved the sensitivity (from 94.5% to 97.8%) and specificity (from 75% to 91.7%) for the differential diagnosis between benign and malignant cases

SMA, smooth muscle-actin.

Diagnostic Markers

Benign versus in situ versus Invasive Lesions

One of the best recognized criteria to distinguish benign and invasive lesions of the breast is the presence of a myoepithelial cell layer. This is a well-recognized fact in histology and holds true in cytological samples. However, in cytology, myoepithelial cells are more difficult to recognize by morphology alone.

Unlike tissue, in breast FNABs of proliferative epithelial lesions (such as usual ductal hyperplasia), performing a myoepithelial cell marker panel is almost always mandatory. For this purpose, myoepithelial cell markers can be used. These can be cytoplasmic, such as smooth muscle-actin, calponin, and high weight keratins (for example, 34βE12) or nuclear, such as p63. These markers have successfully been used, alone or in combination, for the differential diagnosis between benign, in situ, and invasive lesions, as published in the literature and summarized in Table 1 [23–30].

Cytoplasmic markers may be lost in cytological samples, especially when ICC is performed in smears. Thus, nuclear markers such as p63 should be preferred for the identification of myoepithelial cells. p63, in particular, is one of the easiest markers to evaluate in cytology, not only because it is nuclear but also because it is usually preserved during smearing, processing, and staining. However, as demonstrated in Table 1, this marker is sometimes positive in cases of in situ and invasive carcinoma. Staining in less than 25% of cells in clusters was used as a cut-off in some studies, favoring malignancy. See Figure 2, for example. This proved useful in these publications, providing a reasonable discriminatory power between benign and malignant lesions. Additionally, p63 may be combined with one cytoplasmic marker such as 34βE12

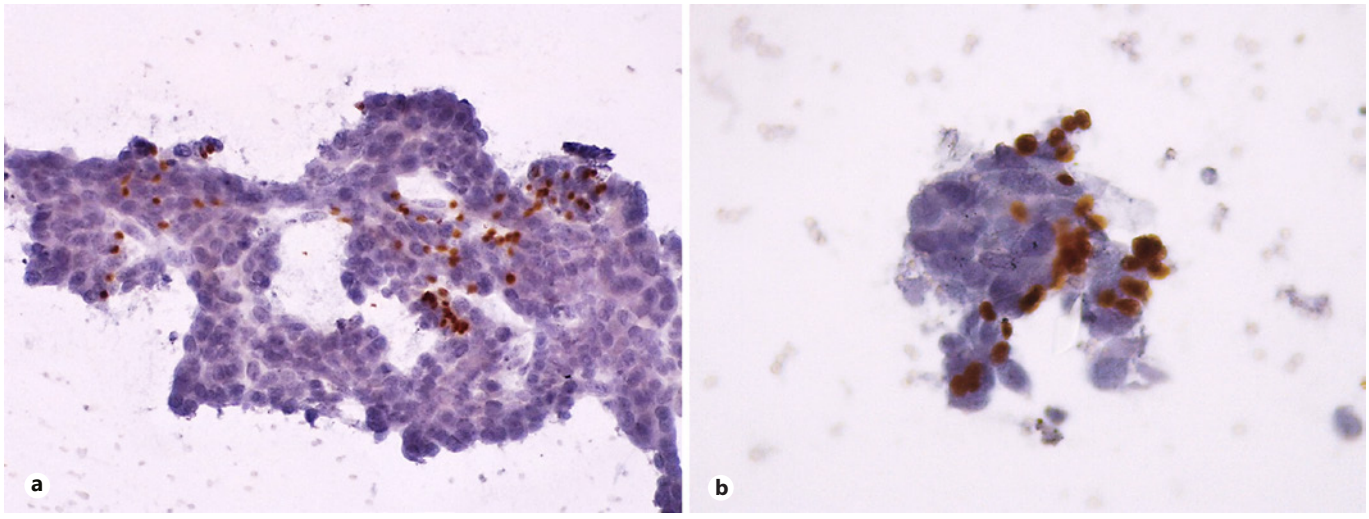

Fig. 2. p63 performed on LBC slides. Nuclear staining can be seen, highlighting myoepithelial cells. We can appreciate a large sheet in (**a**) and a small cluster in (**b**). Both show moderate cytologic atypia and staining in less than 25% of the cells. If this was the predominant pattern of the specimen, it would be adequate to favor a diagnosis of malignancy.

improving its diagnostic utility. This is a good approach: p63 may stain in situ lesions above the threshold of 25%, but DCIS and invasive carcinoma usually lack any staining for 34βE12 in epithelial cells, unlike benign proliferative lesions, which stain in a mosaic pattern [26–30].

This cocktail may also be useful in the differential diagnosis of papillary lesions of the breast, helping exclude a papillary carcinoma if myoepithelial cells are present [26]. This is also true of other rarer tumors of the breast, for example, in the case of salivary gland type tumors where in certain contexts the presence of a layer of myoepithelial cells can help in arriving at the correct diagnosis.

Lobular Carcinomas

A single study looked specifically at lobular carcinomas of the breast diagnosed in FNAB samples. The authors analyzed a series of 46 samples with a histologically confirmed diagnosis. Cytological diagnosis was performed in LBC slides, stained with Papanicolaou or Giemsa. ICC for E-cadherin, ER, PR, and HER2 was performed. E-cadherin was lost in all cases of lobular carcinoma and was considered diagnostically useful in five [31]. Despite the lack of publications on the topic, E-cadherin and P120 are recommended for confirming a diagnosis of lobular carcinoma by the Yokohama system, extrapolating from knowledge acquired in histological samples and based on expert opinion [32].

Mesenchymal Tumors of the Breast

Few publications have looked at the use of ICC in the context of the diagnosis of mesenchymal tumors of the breast. Some of these focus on benign granular cell tumors, showing that S100 positivity in the context of typical morphology can enable a reliable diagnosis and is especially useful in the differential with apocrine lesions [33, 34].

Most other publications focus on breast angiosarcomas. The authors successfully used vascular markers, such as CD31, CD34, and Factor VIII, in the correct morphological setting, enabling a final diagnosis of this tumor type [35–37].

Additionally, in the Yokohama system, authors extrapolate from histology and recommend the use of ICC in all spindle cell lesions of the breast. Namely, ICC for keratins and p63 should be used to exclude metaplastic carcinoma. In the differential between this entity and phyllodes tumor, the authors highlight the usefulness of CD34, Bcl-2, and CD117 as stromal markers. Fibromatoses, which sometimes involve the breast, can be suspected in the adequate morphological and clinical context; according to the authors, this diagnosis may be confirmed using beta-catenin, particularly if the differential is with myofibroblastoma (nuclear vs. cytoplasmatic staining, respectively) [32].

Hematolymphoid Malignancies

Hematolymphoid malignancies, primary or secondary, may involve the breast. In FNAB samples, LCA can be used to determine the lymphoid nature of a given neoplasm. CD3 and CD20 enable a reliable distinction between T- and B-cell populations, respectively, and in the correct morphological context may enable a tentative diagnosis of high- or low-grade lymphoma on their own [38–44]. If Hodgkin lymphoma is on the list of differential diagnoses, CD15 and CD30 may also be of use [44–49]. For other entities, arriving at a definitive diagnosis using FNAB samples and ICC usually requires several more antibodies to be performed than those listed above. Therefore, when possible, material should be collected for cellblock preparation and for flow cytometry analysis [43].

In the context of seromas of the breast, from which anaplastic large-cell lymphomas are known to arise, cellblocks ought to be prioritized over flow cytometry, since they enable nonlymphoid markers and other ancillary tests to be performed. A panel of antibodies should be done in these cases, including CD30 and ALK [50, 51]. Of note, TCR gene rearrangements can be searched for using PCR on cellblock material if sufficient cellularity is available, and the same holds true for immunoglobulin rearrangements, which can be of interest in the diagnosis of anaplastic large-cell lymphomas, but also other T- and B-cell neoplasms. This may be of particular importance if no material is available for flow cytometry [50].

Ideally, however, samples should be submitted fresh also for flow cytometry, as this technique usually proves very useful in the diagnosis of hematolymphoid malignancies [19, 51–56]. Illustratively, a classical publication from 1998, including cytological samples from several organs, shows that using this technique may allow a definitive diagnosis to be reached in 81% of lymphoma cases. This also seems to hold true in the breast. In a small series of 15 lymphomas diagnosed in FNABs from this organ, Levine et al. [56] were able to achieve a partial classification in all cases, and a full classification according to the World Health Organization in 42% and 91% of primary and secondary breast lymphomas, respectively.

Malignancies Metastatic to the Breast

Several publications, mostly case reports but also small case series, have demonstrated the successful use of ICC markers in the identification and characterization of malignancies metastatic to the breast. Sample types vary, including smears, LBC slides, and cellblocks. Antigen retrieval is usually not commented on [45, 46, 57–72].

Pan-keratins are useful to confirm or exclude the epithelial nature of a given neoplasm. CEA and EMA may also be helpful for this purpose. If an epithelial nature is confirmed, CK7 and 20 can then be used to narrow down the list of possible organs. These may be used in conjunction with more specific markers, such as transcription factors, to specifically identify a primary location. Of particular importance in the breast are TTF-1, positive in carcinomas from the lung, and WT-1 for carcinomas originating in the ovaries. CD10 may be useful in renal neoplasms, and Synaptophysin, Chromogranin, and CD56 can help in confirming neuroendocrine differentiation, for example, in the setting of metastatic carcinoids or small-cell carcinomas [45, 46, 59, 61, 62, 64, 65, 70, 72].

Of note, Calcitonin may be used to confirm a diagnosis of metastatic medullary carcinoma of the thyroid, and in men, PSA and PSAP may point to an origin in the prostate. In the latter case, care must be taken; however, as there are rare cases of primary breast carcinomas positive for these markers [57, 62, 69, 73].

Malignant melanomas may be identified by their typical morphology or the presence of melanin pigment. In case these are insufficient, however, S100, HMB-45, and Melan-A have all been successfully used to confirm histogenesis in a variety of publications [45, 59–61, 67, 74–76].

Soft-tissue malignancies may also be suspected on morphology and characterized by ICC. Desmin, Vimentin, and Myoglobin should stain rhabdomyosarcomas and leiomyosarcomas are usually positive for smooth muscle-actin. Metastatic angiosarcoma will show positivity for vascular markers, such as CD31 [45, 46, 62, 63, 66, 68, 77].

Theranostic Markers

ER, PR, HER2, and Ki-67, performed at the time of breast cancer diagnosis, enable an approximation of the molecular subtype of a given carcinoma, allow for selection of adequate therapy and provide prognostic information [4, 78]. ER and PR are hormonal receptors, both with several isoforms. Those of clinical importance in breast cancer are intranuclear are thought to render a breast carcinoma susceptible to the trophic stimuli of estrogen and progesterone. In accordance, an expression of ER and PR in more than 1% of neoplastic nuclei is associated with response to tamoxifen and other antiestrogenic therapy. ER is the most important of the pair, also providing prognostic information [79, 80].

HER2 is a tyrosine kinase and a member of the epidermal growth factor receptor family. Located in the cytoplasmatic membrane, this protein lacks a known ligand, and in physiological conditions dimerizes with other members of its family. In up to 30% of breast cancers, ERBB2, the gene that encodes HER2, may be amplified. This results in the formation of HER2 homodimers, which self-activate in a ligand-independent fashion resulting in autophosphorylation of the tyrosine kinase domain and consequent downstream activation of several cascades promoting cell growth and inhibiting apoptosis [81].

Ki-67 is a nuclear protein associated with cell proliferation. When the proliferative index is high, as determined by ICC, breast cancer patients may derive greater benefit from adjuvant therapy [82].

Several studies have looked at the determination of these markers in FNABs of the breast and how they perform. Methodologies vary between publications and the greatest differences in performance are seen between sample types (smears, LBC, cytospins, and cellblocks). Thus, publications have been divided according to the specimen type. Before proceeding, it is worth mentioning that in terms of discordant cases, for HER2, studies report on both false positives and false negatives in cytological samples, whereas for ER and PR disagreement was mostly due to false negatives, although in a few series a higher intensity of staining was reported on. A summary of our findings can be found in Table 2.

Smears

Smears may be prepared in several fashions, with an impact on ICC performance. Schmitt et al. [83] first demonstrated the importance of antigen retrieval in breast FNAB samples in 1995, studying a series of 31 cases of breast FNABs with matched tissue samples. Ethanol-fixated smears were prepared for ER ICC and antigen retrieval was done using a microwave heat-based method and a citrate buffer. With tissue as the gold standard, the authors reported on a sensitivity of 95.4% and a specificity of 100% [83].

This was replicated by Gong et al. [84] in a unique experimental study. The authors performed a comparative analysis of ER ICC in matched smears fixated through four different methods: (1) a sequence 10% formalin-methanol-acetone at −20°C (Abbott method); (2) air-drying for 3 min, followed by the Abbott method; (3) 10% formalin at room temperature; (4) Carnoy's fixative (a solution of ethanol, chloroform, acetic acid, and ferric chloride) followed by Papanicolaou staining. Antigen retrieval was performed using a heat-based method, but this step was initially omitted in smears 3 and 4. After antigen retrieval, the authors found a concordance with tissue for the determination of ER of: 91.5% in method 1; 84.4% in method 2; and 93% in methods 3 and 4. Of note, without antigen retrieval, the concordance for the latter two methods was of 34% and 71.4%, respectively. Antigen retrieval did not result in an increase in false positives [84].

In fact, heat-based antigen retrieval seems to work across a variety of fixation methods, not just for ER, but also for PR and HER2. Follow-up studies reported on sensitivities of 75%–95% for ER, 90% for PR, and 88%–100% for HER2, and specificities of 100%, 100%, and 98–100%, respectively [85–87]. Interestingly, publications that do not use or mention antigen retrieval have also shown good results [88–94].

Two outliers deserve special mention, however, finding sensitivities between 33 and 49% for ER, 25 and 28.8% for PR and 46% for HER2, and specificities between 75 and 84.5% for ER, 33 and 90.6% for PR, and 86.6% for HER2. Several methods for fixation and antigen retrieval were used in these studies. Air-drying of slides prior to fixation was done in one of them. It is unclear what was determinant for these results [95, 96].

Liquid-Based Cytology

LBC can be performed using several different methodologies from different vendors. Most systems include a proprietary fixative. A large proportion of publications using this technology for ICC in breast FNABs focused on the use of the ThinPrep® system and either CytoLyt® or PreserveCyt® as fixatives, both of which are methanol based.

In most publications, a heat-based method for antigen retrieval was used. A concordance of 98%–98% is reported for ER, of 90.9%–96% for PR, and of 78%–100% for HER2 [97–101]. For HER2 specifically, one study documents a high sensitivity (89%–100%), but a low specificity (72–83%) when compared to tissue, suggesting that positive HER2 results should be validated through another method, such as fluorescent in situ hybridization [97].

Slightly lower values were reported using the Liquiprep™ system combined with antigen retrieval done using proteolytic enzyme digestion, a heat-mediated method, or a mixture of both. In this particular series of 45 cases, the authors report on a concordance with a tissue of 84% for ER, 91% for PR, and 76% for HER2 [102]. Two other studies, one with no antigen retrieval and another

Table 2. Summary of the literature regarding the use of theranostic markers in breast cytology samples

Study	Cases, *N*	Matched tissue?	ICC markers	Sample type	Antigen retrieval	Main findings
Smears						
Schmitt et al. [83]	31	Yes	ER	Alcohol-fixated smears	Heat-based method and a citrate buffer	Sensitivity of 95.4%; specificity of 100%
Gong et al. [84]	47	Yes	ER	Experimental study, three smears from each case: Abbott method, air-dried smears, and destained, alcohol-fixated PAP smears	Yes	**Abbott method** Concordance of 91.5% **Air-drying + Abbott method** Concordance of 84.4% **Formaldehyde** Concordance of 34% **without antigen retrieval** Concordance of 84.4% **with antigen retrieval** **Destained, alcohol-fixated PAP smears** Concordance of 71.4% **without antigen retrieval** Concordance of 93% **with antigen retrieval**
Durgapal et al. [85]	100	Yes	HER2	Alcohol-fixated smears	Heat-based method	Concordance of 99% **with tissue** and of 100% **with FISH**
Ferguson et al. [86]	46	Yes	ER, PR, HER2	Alcohol-fixated smears	Heat-based method and a citrate buffer	**ER:** Sensitivity of 95% **PR:** Sensitivity of 90% **HER2:** Sensitivity of 88% **Specificity of 100% for all markers**
Acs et al. [87]	110	Yes	ER and HER2	Destained, alcohol-fixated PAP smears; post-fixation in acetone	Heat-based method for ER; none for HER2	**ER:** Sensitivity of 75%, specificity of 100% **HER2:** Sensitivity of 54%, specificity of 95.4%
Radhika and Prayaga [95]	100	Yes	ER and PR	Destained, alcohol-fixated PAP smears; post-fixation in acetone	Heat-based method and a Tris-HCl buffer	**ER:** Sensitivity of 33%, specificity of 75% **PR:** Sensitivity of 25%, specificity of 33%
Toi et al. [96]	252	Yes	ER, PR, HER2	Air-dried smears stored at 4°C; cellblocks	Heat-based method and a citrate buffer	**ER:** concordance of 69.6% **PR:** concordance of 71.5% **HER2:** concordance of 70%
Stålhammar et al. [88]	346	Yes	ER, PR, Ki-67	Air-dried smears fixated in a 4% formaldehyde solution	No	**ER:** concordance of 89.5%–91% **PR:** concordance of 88.7%–92.5% **Ki-67:** concordance of 67.2%–70.2%
Robertson et al. [89]	301	Yes	ER and Ki-67	Air-dried smears fixated in a 4% formaldehyde solution	No	**ER:** concordance of 96.5% **Ki-67:** concordance of 66.4% **Estimation of the molecular subtype:** concordance of 64.9% **Survival analysis:** Correlation between Ki-67 observed on tissue but not on cytology
McKee et al. [90]	62 (ER and PR) and 36 (HER2)	Yes	ER, PR, HER2	Alcohol-fixated smears	No	**ER:** Concordance of 94%, sensitivity of 93.4%, specificity of 93.7%, and PPV of 97.8% **PR:** Concordance of 71%, sensitivity of 57%, specificity of 100%, and PPV of 100% **HER2:** Concordance of 77%, sensitivity of 76.4%, specificity of 98.8%, and PPV of 92.8%
Moriki et al. [91]	110	Yes	ER, PR, HER2	Destained, alcohol-fixated PAP smears	No	**ER:** Concordance of 98% **PR:** Concordance of 95% **HER2:** Concordance of 100%
Corkill et al. [92]	36	Yes	HER2	Destained, alcohol-fixated PAP smears	Not informed	3 false positives and no false negatives; differences attributed to alcohol fixation and variable fixation times
Billgren et al. [93]	732	No	Ki-67	Air-dried smears	Not informed	**Multivariate survival analysis** Ki-67 was a significant and independent predictor of disease-free survival (median follow-up of 5.7 years)

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Table 2 (continued)

Study	Cases, *N*	Matched tissue?	ICC markers	Sample type	Antigen retrieval	Main findings
Angelidou et al. [96]	70	No	ER, PR, Ki-67	Alcohol-fixated smears	Not informed	**Multivariate analysis** Correlation between **Ki-67** and lymph node metastasis; no correlation for **ER and PR**
LBC						
Bédard et al. [97]	63	Yes	HER2	ThinPrep® LBC slides; samples fixated in CytoLyt®	Dako epitope retrieval solution	Sensitivity: 89%–100% Specificity: 72%–83%
Sartelet et al. [98]	103	Yes	HER2	ThinPrep® LBC slides; samples fixated in CytoLyt®	Heat-based method and a citrate buffer	Good concordance **with tissue** with slightly increased indeterminate (2+) cases; sensitivity of 100% (2+ and 3+ as positives) **compared with FISH**
Nishimura et al. [99]	82	Yes	ER and PR	ThinPrep® LBC slides; samples fixated in Preserve-Cyt ®	Heat-based method	**ER:** concordance of 98% **PR:** concordance of 95%
Pegolo et al. [100]	116	Yes	ER, PR, HER2	ThinPrep® LBC slides; samples fixated in Preserve-Cyt ®	Heat-based method and a citrate buffer	**ER:** concordance of 98% **PR:** concordance of 90.9% **HER2:** concordance of 100%
Domanski et al. [101]	267	Yes	ER and PR	ThinPrep® LBC slides; samples fixated in CytoLyt®	Heat-based method and a citrate buffer	**ER:** concordance of 98% **PR:** concordance of 96%
Tripathy et al. [102]	45	Yes	ER, PR, HER2	Liquiprep™ LBC slides	Heat-based, proteolytic enzyme digestion or both	**ER:** concordance of 84% **PR:** concordance of 91% **HER2:** concordance of 76%
Komatsu et al. [103]	9	Yes	ER, PR, HER2	ThinPrep® LBC slides; samples fixated in ethanol	No	No discordant cases; higher staining intensity in LBC slides
Konofaos et al. [104]	119	Yes	HER2, p53, Ki-67	ThinPrep® LBC slides; samples fixated in CytoLyt®	Not informed	Strong association for all three markers
Cytospin						
Marinšek et al. [105]	-	No	ER and PR	Cytospin slides prepared from samples fixated in methanol	Heat-based method	**An experimental study with two "runs"** Round 2 following standardized procedures Marked improvement between runs
Srebotnik Kirbiš et al. [106]	52	Yes	ER	Cytospin slides prepared from samples in a cell culture medium, fixated in ethanol and stained with papanicolaou or in methanol, unstained	Yes, only for ethanol-fixated slides	Concordance of: 100% for **methanol-fixated cytospins** 94% agreement for **ethanol-fixated, papanicolaou-stained cytospin slides** 92% for **ethanol-fixated, papanicolaou-stained smears**
Nizzoli et al. [107]	66	Yes	HER2	Cytospin smears; samples preserved in a formaldehyde solution and stored up to a month at –20°C in a glycerol-sucrose storage medium	No	Concordance of 84%
Makris et al. [108]	147	Yes	ER, PR, p53, Ki-67, Bcl-2	Cytospin slides, air-dried and preserved at –80°C	Not informed	**ER:** concordance of 91.5% **PR:** concordance of 75.5% **p53:** concordance of 75% Good agreement found for **Ki-67**
Railo et al. [109]	98	Yes	ER, PR, Ki-67	Cytospin prepared from samples in RPMI, fixated using the Abbot method (ER and PR), and air-dried (Ki-67)	Not informed	No difference between specimens for **ER** and **PR** **Ki-67** from cytological samples better approximated results from surgical specimens compared to CNBs
Kapila et al. [110]	12	No; comparison with ISH	HER2	Cytospin slides prepared from samples fixated in ethanol	Not informed	From 7 cases negative for HER2 by ICC, 3 were also negative by FISH and 5 were negative by CISH; 3 of the 5 cases positive or equivocal for HER2 amplification by ICC also showed gene amplification by FISH and CISH
Cellblocks						

Table 2 (continued)

Study	Cases, *N*	Matched tissue?	ICC markers	Sample type	Antigen retrieval	Main findings
Dong et al. [15]	275	Yes	ER, PR, HER2	Cellblocks; fixation in formaldehyde	Not informed	**ER:** concordance of 98.2% **PR:** concordance of 83.1% **HER2:** concordance of 93.5%
Domanski et al. [101]	25	Yes	ER and PR	Cellblocks; fixation in formaldehyde	Heat-based method and a citrate buffer	**ER:** concordance of 92% **PR:** concordance of 96%
Pinder et al. [111]	34	Yes	ER, Ki-67 HER2	Cellblocks; fixation in formaldehyde	Heat-based method	Correlation: Near perfect for **ER** and good for **Ki-67** Concordance of 78% for **HER2**
Briffod et al. [112]	38	Yes	ER, PR, HER2, and Ki-67	Cellblocks; fixation in formaldehyde	Heat-based method	**ER:** concordance of 96% **PR:** concordance of 82% **HER2:** concordance of 84% **Ki-67:** concordance of 85%
Kumar et al. [113]	50	Yes	ER, PR, HER2	Cellblocks; fixation in formaldehyde	Not informed	**ER:** concordance of 90% **PR:** concordance of 94% **HER2:** concordance of 90%
Bansal et al. [114]	50	Yes	ER, PR, HER2	Cellblocks; fixation in formaldehyde	Heat-based method	**ER and PR:** concordance of 92% **HER2:** concordance of 93.75%
Vohra et al. [115]	134	Yes	ER, PR, HER2	Cellblocks; fixation in formaldehyde	Not informed	**ER:** concordance of 96.2% **PR:** concordance of 77.5% **HER2:** concordance of 98%
Puccetti et al. [116]	93	Yes	ER, PR, HER2	Cellblocks; fixation in formaldehyde	Not informed	**ER:** concordance of 98% **PR:** concordance of 84% **HER2:** concordance of 96% **Ki-67:** concordance of 90%
Hanley et al. [117]	41	Yes	ER, PR, HER2	Cellblocks; fixation initially in a solution of ethanol and then in formaldehyde	Heat-based method and a citrate buffer	**ER:** concordance of 82% **PR:** concordance of 43.7% **HER2:** concordance of 87.5%
Williams et al. [118]	34	Yes	ER, PR, HER2	Cellblocks; fixation initially in a solution of ethanol and then in formaldehyde	Heat-based methods	Agreement: Good for **ER and PR,** moderate for **HER2** Several false positives in **HER2**, which the authors attribute to ethanol fixation
Mardanpour et al. [119]	45	Yes	ER, PR, HER2, Ki-67, and p53	Cellblocks; fixation in formaldehyde	Heat-based method	**ER:** concordance of 80% **PR:** concordance of 93% **HER2:** concordance of 76% **Ki-67:** concordance of 87% **P53:** concordance of 96%
Alwahaibi et al. [120]	48	Yes	ER, PR, HER2	Cellblocks; fixation in a solution of ethanol, acetic acid, and formaldehyde	PT link from Dako	**ER:** Sensitivity of 67.7% **PR:** Sensitivity of 50% **HER2:** Sensitivity of 58.3%
Bueno Angela et al. [121]	62	Yes	ER, PR, HER2	Cellblocks; fixation in a solution of ethanol and formaldehyde	Not informed	**ER:** Sensitivity of 92.7%, specificity of 85.7% **PR:** Sensitivity of 92.7%, specificity of 94.7% **HER2:** Sensitivity of 70.0%, specificity of 100.0%
Kimambo et al. [122]	65	Yes	ER	Cellblocks; fixation in formaldehyde	Heat-based method	Concordance of 90.3%
Brandão et al. [3]	210	Yes	ER, PR, HER2, and Ki-67	Cellblocks	Not informed	**ER:** concordance of 88.2% **PR:** concordance of 80.4% **HER2:** concordance of 83.7% **Ki-67:** concordance of 76.1%

FISH, fluorescent in situ hybridization; PPV, positive predictive value.

where it is not mentioned, did not show significant differences between cytology and tissue samples [103, 104].

Cytospin

Two studies focusing on cytospin slides are of particular relevance. Marinšek et al. [105] performed a very informative and experimental multicentric study involving ten laboratories in ten different countries. The study was organized in two phases. In the first one, a single reference laboratory sent out cytospin slides prepared from breast carcinoma samples obtained by FNAB. Participants performed ICC for ER and PR according to in-house protocols, returning them for evaluation at the reference laboratory. At this stage, only 2 laboratories showed a "good result." Four laboratories failed to get any staining at all. In a second run, specific instructions were provided, both for fixation, using methanol, and antigen retrieval, using a heat-based method coupled with a Tris/EDTA buffer. Slides were again sent out and participant laboratories once again performed ICC for ER and PR. In this phase, 7 laboratories showed a "good result." After analyzing the data from both runs, the authors conclude that antigen retrieval provides a clear advantage in obtaining good ICC results in FNAB samples. They recommend that guidelines for hormonal receptor determination should be written up and that external quality controls should be performed on cytological samples [105].

Kirbiš et al. [106] build on these findings in an interesting, comparative study, focusing on ER ICC. The authors performed several experiments, some relying on breast cancer cell lines. They also tested their methods in cytospins prepared from 52 FNABs of the breast, with matched tissue samples. FNAB material was collected to a cell culture medium. Cytospin slides and smears were fixated in ethanol, and stained with Papanicolaou; from the same sample, additional cytospin slides were prepared and fixated in cold methanol. Antigen retrieval was used only in ethanol-fixated slides. The authors found a 100% concordance for methanol-fixated cytospins, a 94% concordance for ethanol fixated, Papanicolaou-stained cytospin slides, and a slightly lower value of 92% in smears prepared in the same fashion [106]. The remaining publications either do not mention or do not use antigen retrieval, but report overall good results [107–109], except for a small series of 9 cases [110].

Cellblocks

Cellblocks are often thought of as the best approximation of histology using cytological samples and may be preferred by some for ICC studies. Given the fact that samples are embedded in paraffin, usually, antigen retrieval procedures are the same as those used for histology. However, methods of sample fixation vary, with an impact on ICC.

Most studies used samples fixated in formaldehyde. Antigen retrieval is not always commented on, but heat-based methods are more common. In these publications, concordance values reported vary between 90% and 98.2% for ER, 77.5% and 96% for PR, 78% and 98% for HER2, and 85% and 96% for Ki-67 [15, 101, 111–116]. When alcohol is also used as a fixative in conjunction with formaldehyde, slightly worse results are reported [117–121].

Two other studies deserve special mention, given their focus on the feasibility of performing ICC in cellblocks in a low-resource setting. Kimambo et al. [122] performed ICC for ER in 65 cellblocks prepared from FNAB samples of the breast from Tanzania. ICC for ER was performed in Tanzania and in a reference center in the USA. A concordance of 93.8% was found between institutions. Matched tissue specimens were available in 62 cases. Concordance between cellblocks and tissue was 90.3% [122]. Building on these results, a series of 210 patients from Mozambique with a comparison between ICC performed on cellblocks and tissue was published. ICC was done at a single reference center in Mozambique. A concordance between sample types of 88.2% was found for ER, 80.4% for PR, 83.7% for HER2, and 76.1% for Ki-67. Additionally, out of a total of 109 cellblocks performed, 15 were sent out for quality control at a reference center in Portugal. A concordance between centers in these specimens of 93.3% was found for both ER and PR, of 80% for HER2, and of 50% for Ki-67 [3].

Metastatic Breast Cancer

ICC may be performed in FNAB samples from patients with metastatic breast cancer for two purposes: diagnostic and theranostic. Both are intertwined, given the recommendation for biomarker retesting on metastases.

To confirm the origin of breast primaries, the pattern of expression of CK7 and 20 (positive and negative, respectively, in breast epithelial tumors) may point in the right direction [123–125]. Hormonal receptors, particularly ER, may also be of diagnostic use. These markers are not entirely specific or sensitive, however. Other neoplasms can express ER, and a significant percentage of breast cancers are either negative for this receptor at diagnosis or become negative on disease progression [124, 126–128].

Thus, for this purpose, four other markers should be considered: GCDFP-15, Mammaglobin, SOX-10, and GATA-3. The latter seems to be the most sensitive and specific. In cellblocks, current literature shows values of sensitivity, specificity, positive predictive value, and NPV of, respectively, 82.7%–89.3%, 88.9%–98.6%, 95.7%–96.2%, and 63.5%. GCDFP-15 and Mammaglobin show lower sensitivities and positivity rates [123, 124, 129–131]. GATA-3 may also stain carcinomas from other sites, such as urothelial carcinomas, however [132], and its positivity is strongly correlated with the expression of ER, with some studies reporting particularly low sensitivities in triple-negative breast cancer [124, 132, 133]. In this context, SOX-10 might be a useful adjuvant marker staining most cases of breast carcinoma negative for GATA-3 [133].

In terms of theranostic uses, several studies compared results of markers performed in the primary tumor and in FNAB samples obtained from metastases. Most did ICC in cellblocks and fixated samples in formaldehyde. Reported values of concordance vary between 78.5% and 91% for ER, 47% and 87% for PR, and 71% and 96.9% for HER2 [107, 134–137]. Other publications, with different methodologies, also reported on good results for determining these markers in cellblocks from FNABs, even in the setting of bone metastases [138–142].

Discussion

Many papers have been published on the topic of ICC in breast FNAB samples in the last few decades, with varying results. We have extensively reviewed the published literature on the subject, looking at possible diagnostic uses of ICC in breast FNABs and on the performance of theranostic markers in different cytological sample types, including smears, LBC, cytospins, and cellblocks. We gathered relevant information from these publications, particularly in regard to the size of the series, study design, concordance between cytological samples and tissue, reported sensitivity and specificity, fixation methods, and antigen retrieval.

In terms of diagnostic uses, it is interesting to note that although the differential diagnosis between high-grade DCIS and invasive carcinoma is often thought to be impossible in FNAB samples, some publications have shown promising results using p63 and 34βE12. p63 seems particularly useful when a cut-off of 25% is used for cells in clusters. 34βE12 shows a mosaic pattern in ductal hyperplasia and a lack of staining in DCIS and invasive carcinoma, which may be appreciated in cytological samples. Although these results need to be validated in further, larger series, they show promise in this difficult differential diagnosis for FNABs, when correctly incorporated with morphological findings.

The judicious use of these myoepithelial markers may also be very important for the correct evaluation of the theranostic markers we have discussed. This is because DCIS may show higher rates of positivity for ER, PR, and HER2 versus invasive carcinoma, leading to possible mistreatment if these markers are mistakenly performed in an FNA specimen of DCIS. If both DCIS and invasive clusters are present, telling them apart may also be troublesome. Thus, from personal experience, we recommend that theranostic marker evaluation should only be done in cytological material if the cytopathologist is confident of the diagnosis of malignancy, correlating with clinical and imagiological findings (triple test), and only if there is not a significant component of concomitant high-grade DCIS, which can be excluded using the markers above and as described. This is particularly true for HER2, and also applies to testing using in situ hybridization techniques.

Going back to the studies on other diagnostic uses of ICC in the setting of breast FNABs, these are sporadic and include several case reports. However, they lead us to consider that with proper experience and technique, most markers may be used in breast FNAB samples similarly to how they are used in histology, with good results, as suggested by the Yokohama system.

In terms of theranostic markers, after literature review, varying results were found across specimen types. Smears showed the potential for poorer results when compared to the other sample types. LBCs and cellblocks showed overall good results and were quite consistent. Care must be taken; however, air-drying may diminish ICC performance in smears, and the same is true for alcohol fixation in cellblocks.

ER, PR, and HER2 seemed to show overlapping performance, with a lower floor for PR and HER2. On the other hand, the evaluation of Ki-67 consistently showed lower values of concordance across publications, particularly in smears. Cellblocks seem to be the method of choice for the evaluation of Ki-67, with good results also reported in cytospins.

There is no consensus on the importance of proper antigen retrieval. The publications from Radhika and Prayaga [95] and Toi et al. [96] attributed the poor results observed in their publications to the methods of fixation and antigen retrieval used. However, other studies showed

Table 3. Theranostic immunohistochemistry in breast cancer and different cytology sample types

Marker	Sample type		
	smears	LBC	cellblocks
ER PR	Yes – using antigen retrieval with a heat-mediated method		
HER2	Yes – using antigen retrieval with a heat-mediated method Higher number of uncertain (2+) results expected; ethanol fixation may increase false positives		Yes – use a solution of formaldehyde as a fixative; perform antigen retrieval as in tissue
Ki-67	Results vary; may have no correlation with prognosis	Not reported	

LBC, liquid-based cytology.

good results on smears even without antigen retrieval, in samples fixated in formaldehyde, ethanol, and methanol.

Regardless, most publications across sample types report on the successful use of antigen retrieval through a heat-based method, similar to the one first proposed in 1995 by Schmitt et al. [83]. It is our recommendation that a similar method should be used, regardless of sample type or fixative used, particularly since antigen retrieval does not seem to increase false positives. A summary of these findings can be found in Table 3.

In conclusion, both diagnostic and theranostic markers may be performed in all types of cytological material. Air-dried smears should be avoided, particularly for theranostic purposes, and in smears, ethanol-based fixation seems to provide the best results but should be avoided in cellblocks. LBC slides are mostly adequate for ICC, particularly when methanol fixatives are used. Cellblocks show the most consistent results and seem to enable a reliable evaluation of Ki-67. Although some evidence is contradictory, antigen retrieval procedures should be performed in all cases, ideally using a heat-based method. We recommend that laboratories without experience perform short validation runs, perhaps using scrapes obtained from breast surgical specimens and using their preferred cytological sample type. These scrapes may also be used as tests for ICC, if fixated and prepared in the same fashion as actual diagnostic samples.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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