ORIGINAL ARTICLE / Breast imaging

Pure flat epithelial atypia: Is there a place for routine surgery?


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KEYWORDS
Breast cancer; Borderline lesions; Interventional

Abstract
Purpose: To determine whether it is appropriate to routinely undertake surgery if flat epithelial atypia (FEA) or pure flat epithelial atypia (pFEA) is found on large-core biopsy.

Patients and methods: Between 2005 and 2010, 1678 large-core biopsy procedures were carried out, which led to 136 FEA sites being identified, 63 of which across 59 patients were pFEA (four patients had two sites of pFEA each). Forty-eight patients underwent further surgical excision, equating to 52 excised sites of pFEA.

Results: Of the 52 operated sites, there were 20 benign lesions (38%), 26 borderline lesions (56%), and three ductal carcinomas in situ (6%). The rate of histologic underestimation was put at 3.8%. Of the three cases that were underestimated, one was discarded because the definitive histology was not representative of the site from which microcalcifications had initially been taken. The other two cases that were underestimated were found in patients with an increased individual risk of breast cancer.

Conclusion: In patients with no personal or first-degree family history of breast cancer, after complete or subtotal excision under radiology of the radiological lesion, and while excluding images fitting BI-RADS 5, annual monitoring may be offered as an alternative to surgical excision in view of the absence of underestimation found in our study.

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In 2004, breast cancer screening in France was rolled out to women aged between 50 and 74, and this was combined with an increase in mammography monitoring of women outside this age range. This led to a growing number of abnormalities being identified, including microcalcifications, the detection of which was improved further still with the advent of digital mammography. From this resulted an increase in vacuum-assisted biopsies being indicated, as well as new pathological entities being identified such as flat epithelial atypia (FEA).

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According to the 2003 WHO classification, flat epithelial atypia (FEA) is an “intraductal alteration characterized by replacement of the native epithelial cells by a single or three to five layers of mildly atypical cells. The ducts involved are variably distended and often contain intraluminal microcalcifications or secretory material” [1].

The clinical significance of FEA is uncertain. Some authors have put forward the theory that FEA could correspond to a premalignant state of carcinoma in situ or invasive carcinoma, particularly tubular carcinoma, due to cytological, immunohistochemical, and molecular similarities [1–7].

Surgical excision is therefore usually recommended because of the risk of underestimation, which ranges in the literature from 0 to 25% [8–13].

The purpose of our study is to identify our own rate of histologic underestimation and to compare this to data from the literature, in order to appreciate how appropriate it is to automatically proceed to a second surgical intervention.

Patients and methods

This study was carried out between January 2005 and July 2010. We consecutively included 48 female patients with 52 isolated FEA lesions identified on large-core biopsy specimens, who then proceeded to undergo secondary surgery.

Patients

The inclusion criteria were the identification of pure FEA (pFEA) on biopsy specimens and subsequent management by a second surgical procedure.

The exclusion criteria were the existence of lesions associated with FEA (atypical ductal hyperplasia, lobular neoplasia, radial scar, phyllodes tumour, papilloma, ductal carcinoma in situ, and invasive carcinoma) or a second surgical procedure not taking place.

Fibrocystic breast disease and fibroadenomatoid hyperplasia were not considered to be exclusion criteria because of their benign nature.

FEA was identified on 136 of the 1678 large-core biopsy specimens (8.1%) that were taken during the analysis phase.

The following clinical information was recorded in the medical files in order to describe the included population: age, personal or first-degree family history of breast cancer, menopausal status, whether using hormone replacement therapy for menopausal symptoms.

Examination technique

Diagnostic investigations

All of the radiology investigations (mammograms±sonograms) that had been used as the basis for finding large-core biopsy to be indicated were reassessed by a team of two radiologists, one senior approved to carry out the second reading and one junior who defined the lesions by:

- type: microcalcifications/mass/microcalcifications+mass/architectural distortion;
- maximum diameter: < 5 mm/5–10 mm/10–20 mm/ > 20 mm (the largest of the two measurements taken on the anteroposterior and lateral views);
- ACR category according to the BI-RADS classification [14].

A comparison with mammogram images before and after the large-core biopsy procedure allowed us to estimate what percentage had been excised, and this finding was grouped into one of three categories: complete (100%), subtotal (90–99%), or partial (< 90%).

Large-core biopsy sampling

The 52 vacuum-assisted large-core biopsies were carried out by a senior radiologist specialising in breast pathology.

Forty-nine were carried out under stereotactically guidance (Mammotome system: Johnson and Johnson Breast Care/Dedicated table: Mammothet from Siemens) and three were ultrasound-guided (nodule seen on sonogram) (Mammothet Hand Held, Johnson and Johnson Breast Care).

The needle calibre ranged from 11 to 8 gauge (G), depending on breast size.

For each procedure, the needle calibre used and the total number of specimens taken were recorded, as were the number of specimens containing microcalcifications, determined by radiological examination of the biopsy specimens carried out immediately after they had been excised.

When the excision carried out under radiology was complete or subtotal, a metal marker clip was placed in situ in case a second surgical intervention needed to be carried out. We ensured the positioning of the clip was correct by routinely carrying out post-procedure imaging after eight days (anteroposterior and lateral views).

Anatomical pathology

Almost all of the specimens (52/52 or 100% of the large-core biopsy specimens and 46/52 or 88% of the partial mastectomy specimens) were analysed in our centre by three anatomical pathologists experienced in breast disease.

The 136 core biopsy specimens that contained FEA were chosen using the computerised registers of the anatomical pathology laboratory pathology laboratory of our center.

The histology reports of these 136 specimens were reassessed by an anatomical pathologist specialised in breast disease, so that any associated lesion (atypical ductal hyperplasia, lobular neoplasia, radial scar, phyllodes tumour, papilloma, ductal carcinoma in situ, or invasive carcinoma) could be excluded. This led to 63 sites of pure FEA being chosen.

The same anatomical pathologist reassessed the histology reports of the 52 secondary partial mastectomy specimens in order to identify any cases of underestimation.

Checks were made to ensure that each excised specimen contained a metal clip and/or post-biopsy scar tissue changes to confirm that surgery had taken place in the correct location.

The lesions found in the partial mastectomy specimens were classed into three categories:
• benign lesions: benign proliferative breast disease, fibroadenomatoid hyperplasia, epithelial hyperplasia without atypia, or columnar cell change;
• borderline lesions: atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), lobular neoplasia in situ (LNIS), radial scar, or papilloma [15]. If several borderline lesions appeared together, the one with the poorest prognosis was counted. LNIS and ADH were therefore considered over FEA when counting borderline lesions;
• malignant lesions: carcinoma in situ or invasive carcinoma.

Only malignant lesions were taken into consideration when assessing the rate of histologic underestimation.

Results

Of the 1678 vacuum-assisted core biopsy procedures carried out between January 2005 and July 2010, 136 sites of FEA were identified (8.1%), of which 63 were sites of pure FEA (3.8% of the 1678 large-core biopsies) and these were seen in 59 patients (four patients had two sites of pure FEA each). Seven patients (12%) did not undergo further surgical excision because the multidisciplinary team suggested that monitoring was preferred in three situations:
• the atypia was extremely focal and the excision under radiology was complete (four patients);
• there were associated abnormal findings that justified monitoring by mammogram together with breast MRI (two patients);
• history of radiotherapy in the ipsilateral breast (one patient).

Four patients (7%) were lost to follow-up.

The patients who did not undergo surgery were excluded from our study so that we could retain a homogenous series of cases.

In almost 90% of cases, the lesion presented in the form of a site of microcalcifications, which were smaller than 1 cm in size in more than half of all cases (Table 1).

Forty-eight patients (81%) underwent immediate further surgery, and 42 of these interventions took place in our centre. Four patients presented a localisation in two places, which brought the total number of lesions included to 52 cases.

Of the 48 patients included in our study, the mean age was 51-years-old (36–73 years old); 11 patients (23%) had a first-degree relative with a history of breast cancer, and six of these (12%) had developed under the age of 60; six (12%) had a personal history of breast cancer (ipsilateral or contralateral) and two (4%) had a history of borderline lesions of atypical ductal hyperplasia; in total, 17 patients (35%) had a personal history or a first-degree relative with a history of breast cancer. Twenty-five patients (52%) were post-menopausal, and six (12%) of these were taking hormone replacement therapy.

| Table 1 | Main morphologic features of the large-core biopsy specimen and the methods used to take specimens for the 52 pure flat epithelial atypia (FEA) lesions. |
|---|---|---|
| Imaging | Site of isolated microcalcifications | 45 (86%) |
| Primary lesion | Mass + microcalcifications | 2 (4%) |
| | Mass only | 1 (2%) |
| | Architectural distortion + microcalcifications | 1 (2%) |
| | Hypoechoic nodule | 3 (6%) |
| Maximum diameter | < 5 mm | 6 (12%) |
| | 5–10 mm | 21 (40%) |
| | 10–20 mm | 16 (31%) |
| | > 20 mm | 9 (17%) |
| BI-RADS classification | BI-RADS 3 | 9 (17%) |
| | BI-RADS 4 | 37 (71%) |
| | BI-RADS 5 | 6 (12%) |
| Large-core biopsy | Stereotactic | 49 (94%) |
| Guidance modality | Ultrasound | 3 (6%) |
| Needle calibre | 11 gauge | 34 (65%) |
| | 8 gauge | 18 (35%) |
| Mean number of specimens | 15 (5–45) | |
| Mean number of specimens | 6 (0–17) or 38% of the total number of specimens | |
| with microcalcifications | Percentage excised under radiology | 100% Complete excision 19 (37%) |
| | 90–99% Subtotal excision 19 (37%) |
| | < 90% Partial excision 14 (26%) | |
The main morphologic features of the 52 pure FEA lesions are summarised in Table 1, together with information about the large-core biopsy method.

Histologic examination of the surgical biopsy specimens identified 20 benign lesions, 29 borderline lesions, and three malignant lesions, equating to a histologic underestimation rate of 5.8% (Table 2). The most commonly identified borderline lesion was pure FEA (13/29 or 45% of cases). Scar tissue from the large-core biopsy was formally identified on all except one of the surgical biopsy specimens in the three cases of underestimation (case 2).

The three malignant lesions identified were ductal carcinomas in situ: two were grade 2 and one was grade 3. There was no proven case of invasive carcinoma.

The first case of underestimation (2007) concerned a 55-year-old female who had a first-degree relative with a history of breast cancer before the age of 60, and a personal history of breast cancer in 2006 (ductal carcinoma in situ) that had been treated with partial mastectomy and radiotherapy. During her annual monitoring, a site of polymorphic linear-clustered microcalcifications (ACR 5) with a maximum size of between 10 and 20 mm was found, and this warranted a vacuum-assisted large-core biopsy (20 specimens taken, ten of which contained microcalcifications) that amounted to a subtotal excision under radiology. In view of her personal and family history of cancer, and the finding of a site of microcalcifications classed as ACR5 in the operated breast corresponding to FEA together with a site of ADH being diagnosed in the contralateral breast at the same time, the patient expressed a wish to undergo a prophylactic bilateral mastectomy. This treatment decision was approved in the multidisciplinary meeting. This means that it was a total mastectomy specimen in which sites of grade 3 DCIS were identified, away from the scar tissue of the large-core biopsy. The definitive histologic diagnosis (grade 3 DCIS) did not formally correlate with the site from which the microcalcifications had initially been taken. This case cannot therefore be considered to be an underestimation of the large-core biopsy, but rather an associated lesion away from the site.

The second case of underestimation (2007) concerned a 48-year-old female who presented an ipsilateral synchronous breast cancer (tubulolobular adenocarcinoma). The initial assessment of this subclinical image showed, around 3 cm away from the opacity that corresponded to the tubulolobular adenocarcinoma, a site of microcalcifications classed as ACR3, with a maximum diameter of less than 5 mm, and this warranted a vacuum-assisted core biopsy (18 specimens taken, of which six contained microcalcifications), amounting to complete excision under radiology. After the multidisciplinary meeting, it was decided that a double tumourectomy was indicated, the first to remove the subclinical ACR6 mass (confirming the histologic diagnosis of tubulolobular adenocarcinoma), and the second to remove the site from which the core biopsy specimens had been taken. On excision of this second area, FEA lesions surrounding sites of grade 2 DCIS only millimetres in size were identified. However, the usual finding of large-core biopsy scar tissue was not seen, probably because of significant electrocoagulation hindering interpretation. In spite of this, ultrasound-guided preoperative identification of both sites using methylene blue (the ACR6 mass on the one hand, and the metal marker clip on the other) ensured that the surgery was guided towards the correct location.

The third case of underestimation (2006) concerned a 48-year-old female who had a first-degree relative with a history of breast cancer developed before the age of 60. The finding of a site of polymorphic microcalcifications classed as ACR5, with a maximum diameter of 35 mm, warranted a vacuum-assisted large-core biopsy (13 specimens taken, seven of which contained microcalcifications), and the size of this site meant that only a partial excision under radiology was possible. Anatomical pathology examination of the excision specimen from the secondary partial mastectomy identified a site of grade 2 DCIS. The main clinical and morphologic features, information about the biopsy method, and the definitive histology of these three cases of underestimation are summarised in Table 3.

If we exclude the case in which the histology of the surgically excised specimen did not correlate to the histology of the large-core biopsy specimen (case 1), the histologic underestimation rate of pure FEA lesions diagnosed by vacuum-assisted large-core biopsy is 3.8% (2/52).

### Discussion

Flat epithelial atypia (FEA) is an entity defined by anatomical pathology that was described in 2003 in the WHO classification of breast disease. It forms part of the disease

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Histology of the excision specimens of the 52 pure flat epithelial atypia lesions diagnosed on large-core biopsy specimens.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Definitive histology</td>
</tr>
<tr>
<td></td>
<td>Benign lesions</td>
</tr>
<tr>
<td>Number</td>
<td>20 (38%)</td>
</tr>
<tr>
<td>(n = 52)</td>
<td>FEA: flat epithelial atypia; LNIS: lobular neoplasia in situ; ADH: atypical ductal hyperplasia; DCIS: ductal carcinoma in situ.</td>
</tr>
<tr>
<td>Borderline lesions</td>
<td></td>
</tr>
<tr>
<td>29 (56%)</td>
<td>FEA: 13</td>
</tr>
<tr>
<td>Malignant lesions</td>
<td></td>
</tr>
<tr>
<td>3 (6%)</td>
<td>DCIS: 3</td>
</tr>
<tr>
<td>Invasive carcinoma: 0</td>
<td></td>
</tr>
</tbody>
</table>

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spectrum of "columnar cell lesions", a group to which various different terminologies have been applied since the 1940s. For Jara-Lazaro et al. [16], some of these terms suggest a benign process, such as "blunt duct adenosis" [17], "pretubular hyperplasia" [18], "columnar alteration of lobules" [19], "columnar alteration with prominent apical snouts and secretions (CAPSS)" [20], and "enlarged lobular units with columnar alteration" (ELUCA) [21]. By contrast, other terms are suggestive of malignancy, including "ductal intraepithelial neoplasia 1—flat type" [9], "clinging carcinoma—monomorphic type" [22] and "clinging in situ duct carcinoma—flat type" [23]. The variability of terms used illustrates the polymorphic nature of FEA lesions.

FEA is characterised by the presence of cellular changes and it differs from ADH and DCIS due to an absence of architectural atypia [1]. Some authors have put forward the theory that FEA could be a premalignant state of carcinoma in situ or invasive carcinoma, especially invasive tubular carcinoma, because of cytological, immunohistochemical, and molecular similarities [1—7]. However, there is no consensus and one recent work has just shown in a population of 77 patients with cancer who had been diagnosed with FEA on a previous biopsy that the features of these neoplasms were similar to those seen in sporadic cases [24]. The risk of cancer during long-term monitoring was estimated by Boulos et al. [25] to be 1.47% for cases of FEA compared to a rate of 3.5% in ADH. There is no current consensus on how to manage FEA, probably due to the range of synonyms that existed before the WHO established a collective term, and because there is minimal published data. It is for this reason that the treatment algorithm defined for ADH (which advises routine secondary surgical excision [2—29]) has been applied to cases of FEA in our centre. The purpose of this study is to assess whether this procedure is appropriate.

Pure FEA lesions were identified on 3.8% of the large-core biopsies carried out over the 6 years of the study. This rate is relatively close to that identified by some other authors (3.6% for Martel [9], 3.7% for Piubello [11]), but it exceeds the 1.5% described in the multicentre French study carried out by Lavoué et al. [12]. In the latter study, this difference is attributed to the extremely strict criteria used to diagnose pure FEA. By contrast, our figure is below the 4.9% found in the Saint-Cloud team’s study, which covered the largest number of cases.

There is a high rate of further surgery in our study (81%), higher than that seen in most of the other studies previously published (32% for Noel et al. [4], 68% for David et al. [30], 70% for Noske et al. [10]) and similar to that of Ingegnoli et al.’s study [13] (83%) which did, however, cover a smaller number of pFEA sites (18, 15 of which were operated). Lavoué et al.’s study [12] included only patients who had undergone surgery (60 cases). This high rate of further surgery is an indicator of the quality of our study, with a low rate of patients lost to follow-up (7%) and very good compliance on the part of both patients and surgeons to the predefined protocol.

In our study, the rate of histologic underestimation of pure FEA lesions diagnosed by vacuum-assisted large-core biopsy was put at 3.8% (2/52). This underestimation rate was relatively low compared to the data from the literature, where it ranges from 0% to 25% [4, 8—13], and even more so since our study concerned a population of patients attending a cancer specialist centre. Indeed, 31% of the patients included in our study had a personal history or first-degree relative with a history of breast cancer, which is not representative of the general population. In a recently published meta-analysis [31], the rate of underestimation for flat epithelial atypia lesions was calculated at 17% (10—27% with a confidence interval of 95%) for 389 cases that

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**Table 3** Main clinical and morphologic features, method of taking the large-core biopsy, and definitive histology in the three cases of underestimation.

<table>
<thead>
<tr>
<th></th>
<th>Case No. 1</th>
<th>Case No. 2</th>
<th>Case No. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>55-years-old</td>
<td>48-years-old</td>
<td>48-years-old</td>
</tr>
<tr>
<td>Age</td>
<td>Yes &lt; 60-years-old</td>
<td>No</td>
<td>Yes &lt; 60-years-old</td>
</tr>
<tr>
<td>Family history</td>
<td>DCIS</td>
<td>Invasive carcinoma</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Personal history</td>
<td>Ipsilateral</td>
<td>Ipsilateral</td>
<td>Synchronous</td>
</tr>
<tr>
<td>Imaging</td>
<td>Site of microcalcifications</td>
<td>Site of microcalcifications</td>
<td>Site of microcalcifications</td>
</tr>
<tr>
<td>Primary lesion</td>
<td>10—20 mm</td>
<td>&lt; 5 mm</td>
<td>&gt; 20 mm</td>
</tr>
<tr>
<td>Maximum diameter</td>
<td>BI-RADS 5</td>
<td>BI-RADS 3</td>
<td>BI-RADS 5</td>
</tr>
<tr>
<td>BI-RADS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-core biopsy</td>
<td>11 G</td>
<td>11 G</td>
<td>8 G</td>
</tr>
<tr>
<td>Needle calibre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of specimens</td>
<td>20</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Number of specimens with microcalcifications</td>
<td>10</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Radiological excision</td>
<td>Subtotal</td>
<td>Complete</td>
<td>Partial</td>
</tr>
<tr>
<td>Histology</td>
<td>DCIS grade 3</td>
<td>DCIS grade 2</td>
<td>DCIS grade 2</td>
</tr>
<tr>
<td>Definitive histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy representative of surgical excision?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
underwent surgery in 668 biopsied patients. However, in this study, the majority of the percutaneously obtained specimens had been taken by standard core-needle biopsy, and in the majority of cases the lesions that they were associated with were described (lobular neoplasia and/or atypical ductal hyperplasia). A summary of the rates of underestimation is brought together in Table 4.

Our two cases of underestimation arose in patients with a raised personal risk of breast cancer: one with an ipsilateral synchronous cancer and the other with a history of a first-degree relative with breast cancer before the age of 60. There was no case of underestimation found in any patient who did not have this kind of history. The existence of a personal history or a first-degree relative with a history of breast cancer could therefore constitute a risk factor for histologic underestimation of FEA lesions diagnosed on large-core biopsy. This clinical criterion was not identified as a significant risk factor by David et al. [30].

With regard to the method for taking the large-core biopsy specimen, the calibre of the needle used and the percentage excised under radiology do not allow us to make a judgement about histologic underestimation. In both our experience and in the literature, there was no significant difference in the rate of underestimation whether an 11 G or 8 G needle was used for a large-core biopsy [30]. However, underestimation is higher when core-needle biopsies are used (14 G–18 G needles) as illustrated by the Kunju study [8], which covered only pure FEA, and this conclusion was borne out by the recent meta-analysis into FEA in which there was 17% underestimation with core-needle biopsies as against 12% with large-core biopsies [31].

The features defining a site of microcalcifications according to the BI-RADS classification do not seem to add any further distinction in terms of histologic underestimation, confirming recent data on the lack of specificity in mammogram images [32]. The most commonly seen feature is microcalcifications (60%) that are amorphous (65%) and very often in clusters (70%). Masses are found more rarely, and they are often irregular in shape with microlobulation [32]. The BI-RADS classification also demonstrated poor specificity in our study since four sites of microcalcification classified as BI-RADS 5, one of which had a maximum diameter of over 20 mm, turned out to be histologically-proven pure FEA lesions. Equally, one of the cases of underestimation was identified for a site classified as BI-RADS 3 that was found in a specimen taken in the assessment of an ipsilateral synchronous cancer. Clearly, the average reproducibility of the BI-RADS classification, especially for microcalcifications, could be one explanatory factor. However, David et al. [30] suggested that the size of the site of calcifications (>20 mm) could be a risk factor for histologic underestimation, especially when it was impossible to achieve full excision of the lesion. This criterion is found in the Peres et al. study [33] since the rate of underestimation is twice as high in cases of incomplete excision under radiology (21 versus 10%), although it does not reach a threshold of significance. On the contrary, this criterion is not held to be statistically significant by David et al. [30].

In our study, the extent of excision under radiology (complete, subtotal, or partial) does not seem to be a criterion for drawing any distinctions, since out of the 14 cases of partial excision under radiology (<90%), only a single case of underestimation was found (case 3). Nor did complete excision under radiology mean there was no risk of underestimation, as one of our case studies shows (case 2). The subjective nature of making an assessment of the degree of excision when it is incomplete makes it difficult to draw a comparison between different studies. In the same way, the way in which this parameter is assessed can give rise to discrepancies (assessment made on imaging to establish the target or on repeat imaging with or without enlargements). Both anteroposterior and lateral images that are

<table>
<thead>
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<th>Table 4</th>
<th>Rate of underestimation of flat epithelial atypia (FEA) diagnosed by vacuum-assisted large-core biopsy in recent studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>Surgical excision</td>
</tr>
<tr>
<td></td>
<td>Pure FEA operated</td>
</tr>
<tr>
<td>David et al., 2006 [30]</td>
<td>n = 40</td>
</tr>
<tr>
<td>Noske et al., 2010 [10]</td>
<td>n = 30</td>
</tr>
<tr>
<td>Piubello et al., 2009 [11]</td>
<td>n = 20</td>
</tr>
<tr>
<td>Noël et al., 2006 [4]</td>
<td>n = 20</td>
</tr>
<tr>
<td>Ingegnoli et al., 2010 [13]</td>
<td>n = 15</td>
</tr>
<tr>
<td>Lavoué et al., 2011 [12]</td>
<td>n = 60</td>
</tr>
<tr>
<td>Peres et al. 2012 [33]</td>
<td>n = 95</td>
</tr>
<tr>
<td>Our study, 2012</td>
<td>n = 52</td>
</tr>
<tr>
<td>Others: 5 (10)</td>
<td>1 non-significant case</td>
</tr>
</tbody>
</table>

strictly post-biopsy need to be compared routinely with the
pre-biopsy imaging in order to assess whether the excision
is complete or not as well as clip positioning. The extent
of excision under radiology (complete, subtotal or partial)
remains one of the major criteria for validating the quality
of the technique of a large-core biopsy procedure and for
assessing the correlation between radiology and histology.
It is therefore essential to propose further surgery where
there is partial excision, especially if the image is classed
as BI-RADS 5. In our study, in two out of the three cases
of underestimation there were microcalcifications classified
as BI-RADS 5.

The study that found the closest rate of histologic under-
estimation to ours was that of Noske et al. (6.6%) [10], but
this study covered a lower number of sites of pure FEA (30
any cases of carcinoma in situ and/or invasive carcinoma
after immediate further surgical excision of residual micro-
calcifications in a relatively small series of 20 sites of pure
FEA.

By contrast, Ingegnoli et al. [13], Lavoué et al. [12] and
Peres et al. [33] recently reaffirmed the need for further
surgical excision due to high rates of histologic underesti-
mation of 20%, 13%, and 10% respectively. It is interesting
to compare our work with the last two studies because
they took place in other institutions of the CFLCC net-
work of specialist cancer centres in France. Lavoué carried
out a multicentre study involving five centres and includ-
ing 60 sites of pure FEA: all specimens taken by large-core
biopsy were re-evaluated retrospectively by two anatomical
pathologists who were unaware of the definitive histologic
diagnosis. Peres et al. [33] brought together all cases of FEA,
whether associated with lesions or otherwise (230 cases),
for a centralised assessment by experienced pathologists
at the Saint-Cloud CFLCC centre. The population included
in these studies was comparable to ours in terms of age
and menopausal status. However, a higher proportion of
our patients presented a family history (23% vs. 18% for
Lavoué and 14% for Peres) or personal history (12% com-
pared to 3% for Lavoué) of breast cancer. The very different
rates of underestimation (3.8%, 13%, and 10% respectively)
could in part be explained by the average reproducibility
of anatomical pathology criteria in spite of the assessment
being made by pathologists who were specialised in breast
disease. Additionally, depending on their respective expe-
rience and possibly on local consensus, some teams must
prefer to point to a diagnosis of ductal carcinoma in situ
when the large-core biopsy specimen produces ambiguous
results, while other teams will put forward a diagnosis of
FEA, and this inevitably leads to different rates of underes-
timation.

In view of our results, with the low rate of histologic
underestimation identified and cases of underestimation
being highlighted only in patients with an increased indi-
cidual risk of breast cancer, we suggest abstaining from surgery
when patients are diagnosed with pure FEA based on large-
core biopsy if the following criteria are met: no personal
history (current or previous) or first-degree relative with a
history of breast cancer, imaging classed as BI-RADS 3 or 4,
and complete or subtotal excision under radiology of the
radiological lesion. This definition avoids the subjectivity
inherent to the process of estimating the percentage of the
lesion excised under radiology. This proposal is almost iden-
tical to that made very recently by De Mascarel et al. based
on a large-scale series conducted at a large specialist cancer
centre in Bordeaux [34].

The underestimation rates of pFEA reported in the liter-
are are restated in Table 4.

As discussed by Kunju et al. [8], the solution may
lie in the discovery of biomarkers that are able to pre-
dict which sites of FEA are likely to be associated with
a carcinoma, as this would guide the management of
patients either towards further surgical excision or close
monitoring.

In addition, if there were clinical and/or radiological
criteria that were associated with a significantly increased
risk of histologic underestimation, then these could be
useful tools for making treatment decisions.

The main source of bias in our study could arise from not
automatically undertaking a second reading of the large-
core biopsy specimen or the partial mastectomy specimen
slides, or from not having a "blind" second reading of the
slides as Lavoué et al. did [12]. Yet diagnosing and
identifying FEA constitutes a challenge for the anatomical
pathologist and there is significant inter- and intra-observer
variability [35,36]. Almost all of our specimens (52/52 or
100% of the large-core biopsy specimens and 46/52 or 88% of
the partial mastectomy specimens) were analysed in our
centre by three anatomical pathologists who are experi-
enced in breast disease. In view of the very low rate of
underestimation in our study, we can conclude that there
is relatively high reproducibility in the histologic diagnoses
made by our team.

It should be noted that distinguishing the borderline
lesions associated with FEA (Table 4) had only a minimal
impact on the subsequent management of these patients,
because the fact of their being identified led to annual moni-
toring either being initiated or continued, irrespective of the
exact nature of the lesion. This parameter could be taken
into consideration in the future if work was carried out that
amended the frames of reference, in particular the indica-
tions for further surgery after large-core biopsy. Indeed, a
recent study [25] showed that discovering an FEA only very
slightly increased the risk of developing breast cancer at a
later date. Furthermore, the few neoplasms that are dis-
covered later are luminal A type, which means they are
low-grade in terms of progression. Based on these kind of
arguments, we could move away from the established annual
monitoring and propose follow-up every 2 years while incor-
porating patients in the relevant age range back into the
organised screening system.

The other weak points in our study consist of the absence
of further surgical excision in 11 patients (in seven of these
patients, annual monitoring was indicated, while the other
four were lost to follow-up) and a failure to identify the
large-core biopsy scar tissue on the partial mastectomy
specimen in one of our two cases of proven underestima-
tion. However, the biopsy scar tissue was identified on all
of the other partial mastectomy specimens, and this con-
stitutes a major quality criterion in terms of proving that
the post-biopsy surgical excision was adequate. This means
that we did not have to include routine long-term follow-
up in our study in order to screen for possible surgical false
negatives.
Conclusion

In our study, the rate of histologic underestimation of pure FEA lesions identified on vacuum-assisted large-core biopsies is estimated at 3.8% after further surgical excision. Our two cases of underestimation were found in patients with an increased personal risk of breast cancer. These observations lead us to propose initiating monitoring as an alternative to further surgical excision in patients who have no personal or first-degree family history of breast cancer when there has been complete or subtotal excision under radiology of the site of microcalcifications, except for when images are classed as BI-RADS 5.

The intervals between monitoring would remain yearly although some recent studies seem to show that the risk of developing cancer is low, often occurring much later, with slow-growing disease. Further studies will be needed to validate this proposed management approach and also to decide on how often monitoring should take place. Personalising monitoring in terms of individual, family, radiological and histologic factors while genomics progresses will be one of the challenges in the years to come. The differences in underestimation rates reported in the literature demonstrate how important it is for each centre to analyse its own databases and to work in multidisciplinary teams.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


