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Fibroepithelial lesions: assessing the risk of malignant phyllodes tumors in the breast

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Abstract

Purpose: Phyllodes tumors (PTs) of the breast are rare fibroepithelial tumors (FETs), accounting for approximately 0.5% of all breast tumors. The diagnostic interpretation of borderline fibroepithelial lesions often requires further investigations. *Patients, Materials and Methods*: We used statistical analysis to evaluate the different surgical approaches, risk factors and prognosis during a five-year period, from January 2019 to December 2024, of women who underwent conservative surgeries for benign, borderline tumors and malignant breast tumors. *Results*: We examined a total of 481 breast tumors, with benign, borderline and reserved final diagnosis to paraffin, and discovered 35 FETs, corresponding to phyllodes-type tumors. Studies of enlarged PTs, which are often malignant on final paraffin results, are controversial regarding further postoperative treatment, because they require chemotherapy that is as aggressive as for soft tissue sarcomas, and also hormone therapy that has not shown long-term survival benefit yet. In order to improve the quality of life, survival rate, and disease management, the surgical team needs to be up to date with the latest protocols of management of the disease. *Discussions*: Management of breast tumors includes ultrasound examination, digital or three-dimensional (3D) mammography and magnetic resonance imaging (MRI) evaluation, while surgical management is consistent with core needle biopsy procedures and surgical excision known as tumorectomy, followed in certain cases by an enlarged sectorectomy. *Conclusions*: Aggressive surgery is sometimes necessary to achieve oncological safety margins and prevent subsequent disease recurrence.

Keywords: breast, phyllodes tumors, surgery, fibroepithelial tumor.

Introduction

Fibroepithelial breast lesions are a rare finding, accounting for 10% of the breast tumors and 0.1% of all cancers. The most common types are fibroadenomas and phyllodes tumors (PTs). PTs can be subclassified based on rate of progression, size, ultrasonographic and magnetic resonance imaging (MRI) appearance, and also after biopsy using histological and immunohistochemical markers into benign, malignant, or borderline. Only 10% of PTs are at high risk of malignancy, while the other two types may often require follow-up surgery due to the high risk of local recurrence and surgical excision of the mass with negative surgical margins is performed. The main difference between fibroadenoma and PTs is considered mainly from an anatomopathological point of view by MRI the increased cellularity of the stromal component. The epithelial and stromal components in the fibroadenoma can show intracanalicular and pericanalicular reactive modifications and may present with a multitude of histological aspects.

Genetic modifications are associated with an increased degree of malignancy in these tumors, and recent studies detected more of these discoveries in PTs for MED12 mediator complex subunit 12 protein, telomerase reverse

transcriptase (TERT) promoter. Most borderline and malignant PTs have more than two mutations. Further studies in the pathogenesis of FETs allow proper management and treatment [1].

The diagnostic interpretation of borderline fibroepithelial lesions (FELs) often imposes further investigations such as immunohistochemistry, positron emission tomography (PET)–MRI, long distance evaluation for metastasis, and also carries great anxiety for these patients. The main differential diagnosis in young patients is made with fibroadenoma. Cellular fibroadenoma often requires excision, if a growth in size is noticed in the annual ultrasound (US) evaluation, due to the inability to distinguish it from more aggressive FELs, such as the borderline PTs [1, 2].

PTs are considered to be rare tumors. Women of Asian or Latino descent are considered at risk, and recent studies have shown that women living in the United States may also be at high risk. Like other genetic risk factors, people with Li–Fraumeni syndrome (LFS) – a pathology that associates multiple types of cancer at an early age, are also prone to this disease. A few cases have also been found in men with gynecomastia. The average age of detection is around 40 years. Benign tumors can have a high number of mutations and can develop with different gene alterations. Different forms of fibroadenoma, such as the regular form or the more aggressive cellular form, are differentiated by specific mutations. TERT promoter alterations can help differentiate fibroadenomas from PTs [3, 4]. Appropriate management includes core needle biopsy (CNB), with an accurate diagnosis in 80–95% of cases, and surgical excision is recommended when a complete evaluation of a FEL is required [5–7].

Clinically, the PTs are usually considered benign breast masses, that can grow in size rapidly. The patient notices a breast lump, while on US it appears as a solid mass, with lobulated borders, sometimes with the presence of microcalcifications, with various associations of intramural cysts. The MRI is considered more sensitive in this type of tumor as it has a higher sensitivity in T1 signal and low or equal intensity in T2.

The diagnosis is made after anatomopathological confirmation, the previous biopsy being rarely done with CNB or surgery that consists in breast tumorectomy with safety margins. Also, an appropriate management includes CNB, with an accurate diagnosis in 80–95% of cases, and surgical excision is recommended when a complete evaluation of a FEL is required [5–7].

According to the "Protocol for the Examination of Resection Specimens from Patients with Phyllodes Tumor of the Breast" in March 2022, the following elements are suggestive histological features for PTs, as it is shown in the Table 1 [8].

Table 1 – ***Histological features of phyllodes tumors (adapted from Tse et al. [8])***

Histological feature	Benign	Borderline	Malignant
Stromal cellularity	Mild	Moderate	Marked
Stromal atypia	Mild or none	Mild or moderate	Marked
Stromal overgrowth	Absent	Absent or very focal	Present
Mitotic rate	≤4 mitoses/10 HPFs or <2.5 mitoses/mm^2	5–9 mitoses/10 HPFs or 2.5–5 mitoses/mm^2	≥10 mitoses/10 HPFs or ≥5 mitoses/mm^2
Tumor border	Circumscribed	Usually circumscribed but may be focally infiltrative	Focally or extensively infiltrative (permeative)
Malignant heterologous stromal elements	Absent	Absent	Sometimes present

HPFs: High-power fields.

Aim

The aim of this article was to demonstrate that the diagnostic interpretation of borderline FELs require further investigation, such as PET–MRI for distant evaluation of metastases.

Patients, Materials and Methods

We performed a statistical analysis of 35 female patients from a total of 481 female patients with breast tumors (from January 2019 to December 2024), who presented after the detection by self-palpation of a mass generally involving the external superior quadrant of the breast.

The statistical analysis was comprised in Excel and three main parameters were analyzed (patient's characteristics, macroscopical aspects and microscopical elements). All the patients were given an Informed Consent and agreed to be included in the study. Ethical approval for this study was obtained from the Institutional Ethics Committee of Cuza Vodă Clinical Hospital of Obstetrics and Gynecology, Iaşi, Romania (Approval No. 8769/9 January 2019).

As a minimum requirement for pathological specimens, the localization of the lesion, findings from the physical examination, radiomorphology of the lesion, the radiologist's opinion on the lesion, the method of sampling, either by CNB or tumorectomy, were all mentioned in the operative protocol, and the relevant data in the medical history such as history of malignancy of other organs, number of pregnancy and lactation period at the time of sampling were also noted.

For fine-needle aspiration (FNA), we recommend the use of European (UK) terminology or the more recent *International Academy of Cytology* (Yokohama, Japan) terminology. For CNB, the B1–B5 category classification is a requirement (Table 2) [9].

Table 2 – ***Cytological diagnostic categories (adapted from Ellis et al. [9])***

European (UK) diagnosis	International Academy of Cytology (Yokohama)
C1: Inadequate (quantitatively and/or qualitatively)	Inadequate (2.4–4.58%)
C2: Benign lesion	Benign (1.2–2.3%)
C3: Atypical, probably benign	Atypical (probably benign) (13–15.7%)
C4: Suspicious of malignancy	Suspicious (of malignancy) (87.6–97.1%)
C5: Malignant (both *in situ* and invasive)	Malignant (99–100%)

For large lesions found to be suspicious on radiological examinations, and for lesions detected exclusively in the form of microcalcifications, intraoperative frozen section examination was not performed because it does not help to clarify the diagnosis and may render the tissues unsuitable for making the eventual diagnosis. Frozen sections must not be prepared from lesions of 10 mm or less, since failure to obtain a sufficient quantity and quality of tissue from the lesion for embedding could impact the final diagnosis and also the ability to assess prognostic and predictive factors for smaller tumors. If there is a definitive preoperative diagnosis, there is no need for intraoperative examination to confirm this diagnosis. The indications for frozen section examination have become significantly limited. In exceptional cases, if attempts to obtain a preoperative diagnosis have failed, a multidisciplinary decision can examine frozen sections; this may also be justified if there are insufficient or uncertain preoperative findings. The aim of intraoperative examination may also be the assessment of surgical resection margins or the distance between the tumor and the tumor-free margin. These examinations can be performed as imprints (cytology), frozen sections and macroscopic measurements.

All women reported that the tumor had increased in size over the course of the year, becoming more solid and easier to detect. Breast US revealed images with a mean echographic diameter of 6.5 cm, with solid, hypoechoic aspects in 65% of cases. Studies show that dimensions greater than 3 cm are predictive of malignant forms of PTs. Mammography showed a non-spiculated soft tissue mass, containing calcifications, approximately 6 cm in diameter in 20% of cases in which this examination was performed during the preoperative steps.

Both the US and the mammography confirm the masses, usually larger than 4 cm in diameter, similar to the findings from the patients we have monitored. All our patients underwent oncology board consultation, with the recommendation of CNB, followed by surgical excision with safety margins.

The CNB revealed fibroepithelial aspects with characteristics of a PTs in all cases, and surgery was scheduled for the following two months in the majority of patients. As a particularity, one of the patients was 33 weeks pregnant and the surgery was performed simultaneously with the Caesarean section. In the majority of cases, a tumorectomy followed by an extended sectorectomy was performed, and the tumor was sent to an extemporaneous examination, that revealed suspicious features for malignity, such as marked stromal hypercellularity and pleomorphism, stromal overgrowth, increased mitotic activity, infiltrative borders. Malignant PTs were described in 11 cases.

Results

We examined in all 35 female patients' characteristics and macro and microscopic findings, as it is shown in the Table 3. Typically, the macroscopic section described a well contoured, usually round and firm mass. The cutting sections revealed a pinkish-gray color with a fleshy and mucoid aspect and curved clefts with a "leaf-like" appearance (Figure 1, A–C). Small areas of hemorrhage and necrosis were also present in 31% of cases.

Table 3 – ***Tumoral characteristics and patient general information***

Patient characteristics	Macroscopic aspects	Microscopic aspects
Age (27–59) [years]	Tumor size (6.5 cm) 26 (74%) patients	Multinucleated giant cells 26 (74%) patients
Investigations performed previous of hospitalization 26 (74%) patients	Firm mass, well-contoured 35 (100%) patients	Fusiform cells with nuclear atypia 27 (77%) patients
Self-diagnosis (80%)	Pinkish-gray, mucoid macroscopical aspect of the tumor 35 (100%) patients	Myxoid stroma, rich capillary vascularization 30 (86%) patients
Desire for surgery 25 (71%) patients	Curved clefts 26 (74%) patients	"Leaf"-like aspect 20 (57%) patients
Pregnancy occurring in one case, previously pregnant 20 (57%) patients	Hemorrhage and necrosis 11 (31%) patients	Focal infiltrative aspects 11 (31%) patients

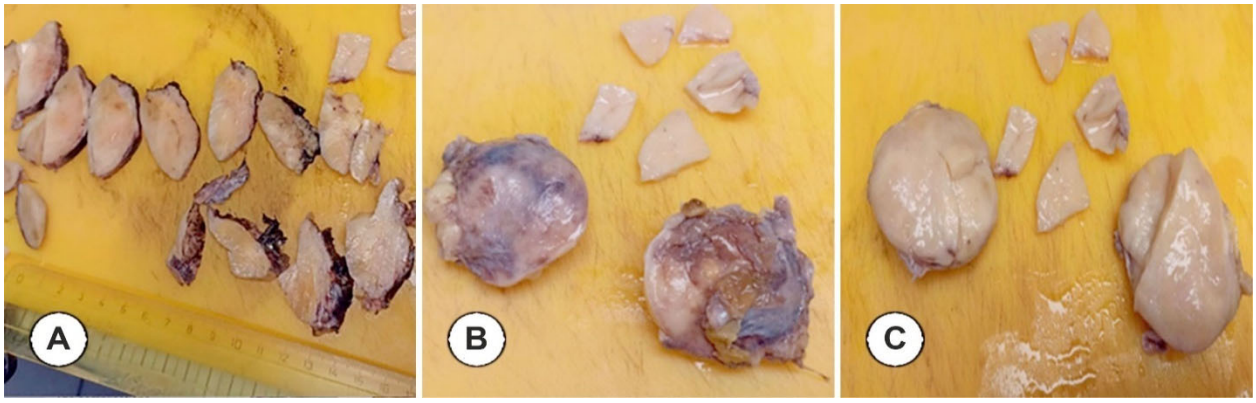

Figure 1 – ***(A–C) Macroscopic aspects of breast tumor section, cut sections in the cases larger than 5 cm size (26 patients).***

Microscopic examination showed an intracanalicular growing pattern with "leaf-like" projections, marked as nuclear pleomorphism and "chicken wire"-like aspects in 90% of the tumors examined, corresponding to fibro-epithelial aspects.

Microscopic examination showed in 80% of cases a breast tumor with marked, excessive mesenchymal proliferation, consisting of frequent multinucleated giant cells and fusiform cells, with atypia and nuclear hyper-chromasia and pleomorphic lipoblasts; tumor cells showed moderate mitotic activity; relatively prominent myxoid stroma with rich capillary vascularization, often with a "chicken-wire" appearance, was observed; tumors did not show aspects of tumor necrosis or suspicious hemorrhagic

areas or images of angioinvasion; in the periphery, rare, compressed ducts were identified, and in one of the sections, there were epithelial structures with a "leaf-like" appearance and cellular stroma with atypia were seen (Figure 2, A and B; Figures 3 and 4; Figure 5, A and B).

Several (55%) tumors showed focal infiltrative aspects in the surrounding breast tissue and safety margins were reconsidered surgically.

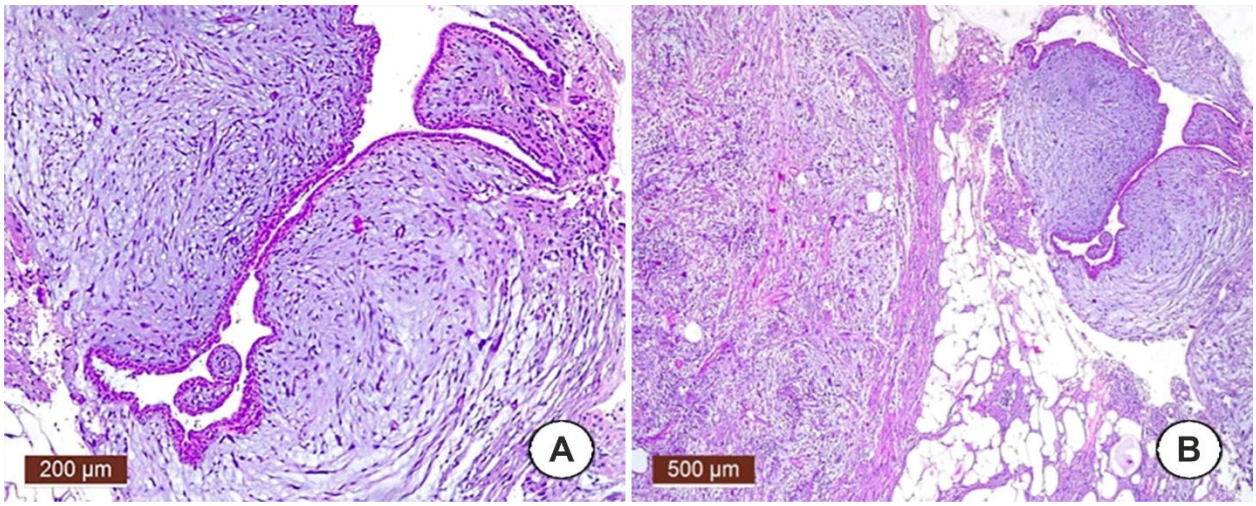

Figure 2 – ***(A and B) Cellular epithelial "leaf"-like aspect. Hematoxylin–Eosin (HE) staining, ×40.***

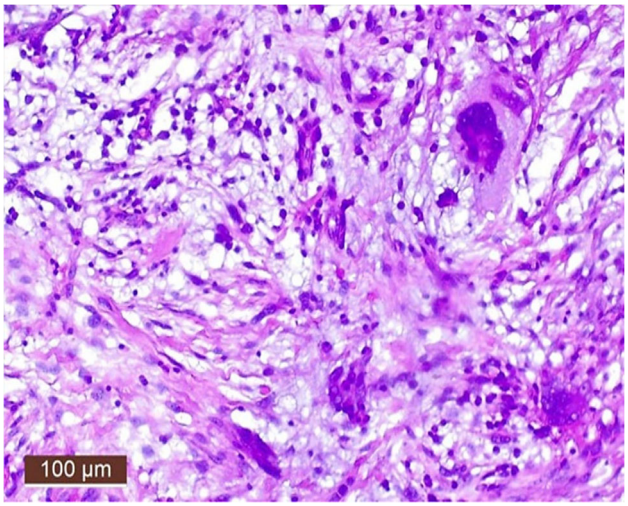

Figure 3 – ***Marked nuclear pleomorphism. HE staining, ×40.***

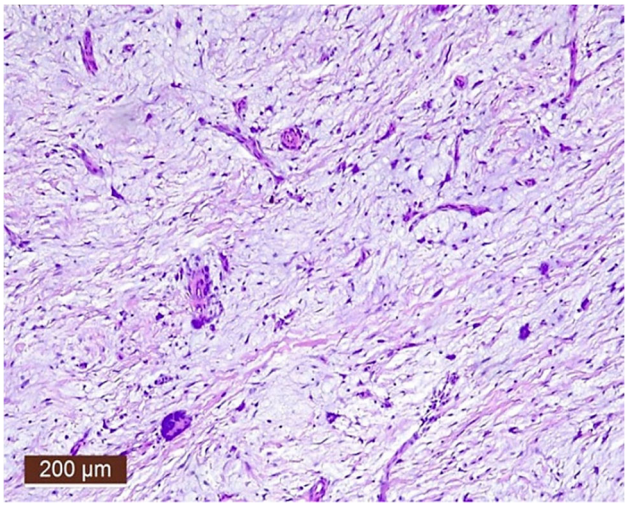

Figure 4 – ***Fibromyxoid stroma and "chicken wire" vessels. HE staining, ×40.***

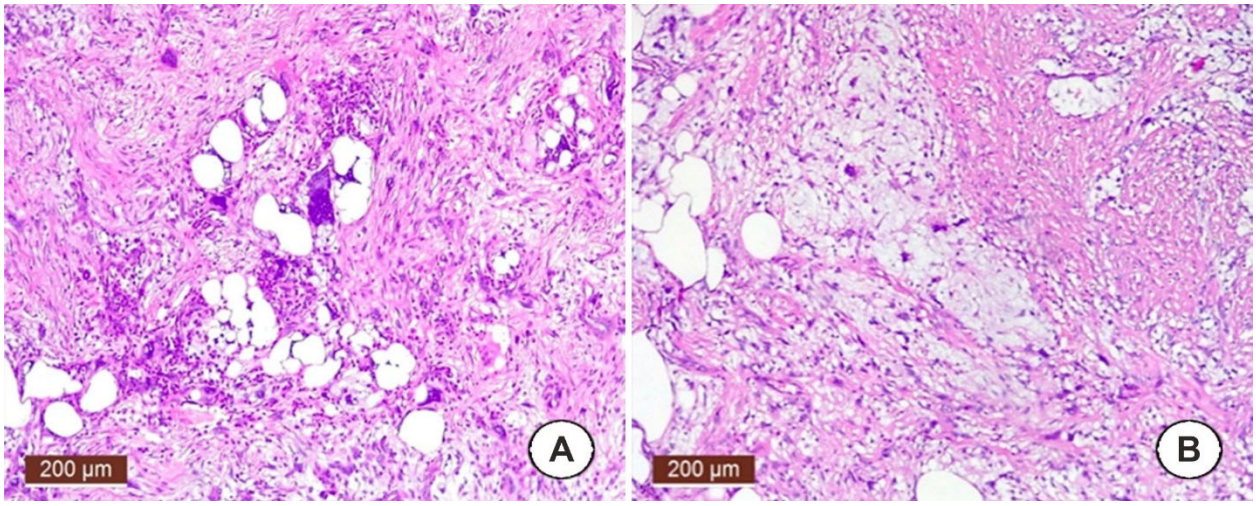

Figure 5 – ***(A and B) Marked nuclear pleomorphism and lipoblasts. HE staining, ×40.***

Discussions

During the evaluation of 35 female patients in our Clinic, diagnosed by self-palpation with a mass predominantly located in the external superior quadrant of the breast, we discovered that PTs had a mean diameter exceeding 3 cm, with an average size of 5 cm. Pathological anatomy revealed firm, well-contoured masses, with mucoid pinkish gray aspect, curved clefts, areas of hemorrhage, and necrosis. Microscopy revealed multinucleated cells, fusiform cells, nuclear atypia, myxoid stroma, "leaf-like" aspects, and focal infiltrative aspects in 31% of cases.

PTs of the breast are rare FETs, representing around 0.5% of all types of tumors and are mostly benign, with a small number of borderline tumors and in rare cases, around 15% of the tumors are malignant [10–14]. They have a high chance of recurrence and a large breast sectorectomy is recommended to avoid recurrence. Metastatic disease may occur in up to 25% of the malignant phyllodes and when it does, it is considered to have a very poor outcome, as these tumors do not respond to standard oncological treatment. The studies citing survival rates are only found for up to three years after the metastatic disease is confirmed, regardless of the treatment approach [15]. Treatment for metastatic disease includes chemotherapy, similar to what is used for aggressive tumors such as soft tissue sarcomas [16].

Mesenchymal breast tumors are rare. Few epithelial tumors also have mesenchymal components, such as the markers p53, E-cadherin, and β-catenin, which should be performed to obtain a correct diagnosis. Breast FELs are characterized by epithelial and stromal proliferations, with fibroadenomas and PTs being the primary differential diagnoses. Diagnosing these lesions can be challenging, particularly in distinguishing cellular fibroadenomas from benign PTs, accurately grading PTs, and managing surgically negative margins in more aggressive forms. Recent molecular advances have enhanced the understanding of the pathogenesis of these lesions and improved their management, enabling more effective treatment for patients. A six-month follow-up is recommended because most recurrences occur in the first two years after surgery, close to the surgical margins. Benign types have a survival rate of more than 95%, while malignant types have a five-year survival rate of 65%.

Patients of young age should be screened for LFS especially if another first-degree relative has been diagnosed with this kind of illness. Other comorbidities include pregnancy-related estrogen elevation, local trauma, causing epithelial and fibroblast overgrowth, middle age of 40 years.

The differential diagnosis of PTs and fibroadenomas is important for proper treatment and also for the breast surgeons to properly perform the tumorectomy or sectorectomy as we discovered in the series of cases. Therefore, it is important for surgeons to consider performing a second look surgery in certain high-risk patients, even in the absence of negative margins, if a grade 3 PTs is present in the anatomopathological result. Both tumors have the same original cell provenance, and even though both US image may be similar, further evaluation by MRI is sometimes required to establish the correct differentiation [17–19].

In a recent study, some key diagnoses were found regarding tumoral description in 80% of the patients with increased stromal cellularity, stromal overgrowth in 76.6% of the cases, increased stromal mitoses in 67.8% of the cases, stromal atypia in 61.5% of the cases, stromal fronding in 59.0% of women, periductal stromal condensation in 58.0% of the cases, irregular tumor borders in 46.3% of the cases and lesional heterogeneity were the less frequent, in 33.7% of the cases. The most important parameters for grading purposes were considered to be the mitotic activity, the stromal overgrowth, stromal atypia, the increased stromal cellularity and negative tumor margin [19, 20].

Physiopathology recognizes that these changes occur in the connective tissue of the breast, known as the stroma, in the Cooper's ligaments, and in the adipocytes, which are outside of the main targeted zones, usually for breast cancer: lobules and ducts. Therefore, there is a high need to look around the whole breast while screening during routine breast US.

Sonoelastography of breast lesions is an imaging technique that can assess the hardness of soft tissue, by showing the behavior of the breast tissue when subjected to mechanical stress, such as when the US probe is pressed against the skin [21]. Promising results with US associated excisional biopsy have been shown for tumors less than 3 cm in diameter. A tumor diameter of 3 cm or more appears to be associated with a higher likelihood of malignancy, therefore annual breast cancer screening should be more widely promoted in underserved areas. Increased economic efficiency in health care does not only mean finding ways to mechanically reduce hospital costs, as the primary goal aim is to improve medical care by using the existing human, financial, material and time resources more effectively. Consequently, a parametric evaluation of treatment techniques and patient satisfaction is imperative, and a medico-economic evaluation is complete only under these circumstances [22].

Recurrence is rare in benign tumors, but depending on the tumor size, stromal growth, nuclear atypia and pleomorphism, the risk of local recurrence ranges between 0 and 60%. Common sites of distant metastasis are lungs and bones. The risk of local recurrence is considered to be as high as 15% in cases with positive margins, and aggressive grade 3 tumors should be considered for enlarged sectorectomy.

Conclusions

Our study showed that in the pathology of FETs, the determining factor is the rapid growth period in size, as well as the tumor diameter over 5 cm. Partial recurrence can occur in cases of incomplete excision and malignancy is possible in these cases. An accurate preoperative diagnosis of PTs allows for improved surgical planning. The management of malignant PTs requires a multidisciplinary team consisting of a radiologist, a surgical oncologist, an oncologist, and a pathologist. CNB is a commonly used diagnostic tool for investigating breast lesions. Surgical management is the cornerstone of treatment, as local recurrence in PTs has been associated with inadequate local excision. The role of adjuvant radiotherapy and chemotherapy remains uncertain, as does the use of hormone therapy. As shown in our study, it is imperative that the diagnostic interpretation of

borderline FELs require further investigations for metastases. Also, an appropriate management includes CNB, and a surgical excision, with safety margins, is recommended.

Conflict of interests

The authors declare that they have no conflict of interests.

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