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28622 – VACUUM-ASSISTED BIOPSY AS A DIAGNOSIS OF LOW-RISK DUCTAL CARCINOMA IN SITU (DCIS) WITH PROGRESSION POTENTIAL AND SUBSEQUENT ACTIVE SURVEILLANCE

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Introduction: The treatment of breast cancer has evolved from radicalization and broad application — such as radical mastectomy for all cases — to personalized and de-escalation approaches, targeted therapies, and conservative surgery. Likewise, the diagnosis of breast cancer has progressed from diagnostic surgery and incisional biopsies to minimally invasive percutaneous procedures, fine-needle aspiration biopsy (FNAB), and core biopsies. Accurate histological diagnosis is a prerequisite for proper therapeutic planning, aiming to achieve optimal disease control with minimal aesthetic and functional sequelae. While in the past, cytological diagnosis of malignancy (FNAB) was sufficient to initiate treatment, today it is imperative to obtain an accurate histological and immunohistochemical diagnosis. In the era of personalization, precise percutaneous diagnosis of malignancies requiring immediate surgical, systemic, and radiotherapy treatment is imperative. Previously, the differential diagnosis of ductal carcinoma *in situ* (DCIS) of the breast and invasive carcinomas (IC) was a priority. Currently, with the possibility of de-escalation of various therapeutic modalities, a higher level of sophistication is needed. Regarding DCIS and the future possibility of active surveillance for selected cases, it would be especially important to differentiate them into low-risk of progression (DCIS-LR) and high-risk of progression (DCIS-HR). **Methodology:** 1.1. Patient eligibility and study design: The study was approved by the Ethics Committee of Santa Casa de Belo Horizonte under number 25761019.8.0000.5138, and all procedures were conducted in accordance with national guidelines. Written informed consent was obtained from all patients for participation. The dataset used and/or analyzed during this study will be available within a reasonable timeframe upon request to the corresponding author. A total of 1,061 vacuum-assisted biopsies for suspected malignant breast lesions (BI-RADS 4, BI-RADS 5, or lesions with uncertain malignant potential on previous core needle biopsy [B3 lesions]) performed at a dedicated breast diagnostic center in Brazil from 04/13/2017 to 11/28/2020 were analyzed. Patients with benign histology on vacuum biopsy, those with confirmed malignancy who did not undergo primary surgery, or when final surgical pathology was unavailable, were excluded. This resulted in 116 cancers (IC and DCIS) with complete biopsy and surgical data that were included in the analysis. Baseline demographic data were recorded. The imaging data collected included: findings (mass with or without calcifications), image-guided method for VAB (ultrasound/stereotactic), and maximum radiological tumor size (MT). 1.2. Vacuum procedures: All patients underwent diagnostic vacuum-assisted biopsy. Assisted vacuum procedures were categorized as simple vacuum-assisted biopsy (VAB) versus extended (EVAB), when the lesion was completely excised or more than 12 fragments were collected with a 7G needle, or 18 fragments with a 10G needle. The biopsy device (EnCor Enspire™ Breast Biopsy System – BD or Mammotome Revolve™ Dual Vacuum Assisted Breast Biopsy System) and needle gauge used were at the discretion of the operating physician. 1.3. VAB/EVAB pathology: The raw specimens were separated from the clots, measured, weighed, and stained. All fragments were included and sectioned at every four microns. The cases ranged, on average, from one to five paraffin blocks. Tests varied from hematoxylin-eosin (H&E) analysis of the slides, with or without immunohistochemistry (IHC), at the discretion of the pathologist, followed by fluorescence *in situ* hybridization (FISH) and genetic analyses (e.g., Oncotype DX), if indicated. All tissue samples underwent histopathological examination. The maximum pathological tumor size after VAB was defined as the measurement of the largest tumor dimension on the slide of the most involved sample. The histopathological diagnosis of VAB (invasive disease ± DCIS), presence of DCIS with comedonecrosis, biomarker status (ER/PR/HER2/Ki67), tumor morphological type, nuclear grade, and histologic grades were evaluated and recorded. In cases of multicentric tumors or bilateral breast cancers, only the tumor measurements and outcomes of the lesions submitted to VAB were included. In one patient,

two multicentric nodules were subjected to two different procedures, so this case was treated as two separate lesions. 1.4. Surgical pathology: All cases underwent surgical excision following VAB, and radiography of the surgical specimen was performed to confirm the presence of the marker placed during VAB. Macroscopically, the specimens were measured, weighed, and stained. All surgically excised tissue was included for analysis and sectioned every four microns. H&E analysis was performed on the slides, with or without IHC, at the discretion of the pathologist, followed by FISH and genetic analyses (e.g., Oncotype DX), if indicated. The evaluated parameters included: the maximum size of residual tumor in the surgical specimen, the pathological diagnosis (invasive disease±DCIS), presence of DCIS with comedonecrosis, biomarker status (ER/PR/ HER2/Ki67), tumor morphological type, nuclear grade, and histological grade. Sentinel lymph node biopsy (SLNB) was performed according to the practice of the originating facility. Surgical excision after VAB was defined as complete resection (CR) if no residual tumor was present at the time of surgery, minimal residual disease (MRD) if residual tumor was ≤3 mm, gross residual disease (GRD) if residual tumor >3 mm, and "upgrade" from DCIS to invasive cancer if the pathology revealed invasive disease following initial VAB. Needle gauges from 7G to 10G were used. A 7G needle (4.57 mm diameter) provides a fragment weighing about 0.363 g. The 3 mm cutoff for MRD was based on the smallest fragment weighing 0.221 g, provided by a 10G needle (3.5 mm diameter). Thus, residual disease of 3 mm could be easily resected with one or two additional fragments. 1.5. Adjuvant treatment: All patients received adjuvant systemic therapy and radiotherapy according to the Brazilian Guideline for the Diagnosis and Treatment of Breast Cancer issued by the Ministry of Health. 1.6. Diagnostic Test: For the evaluation of the diagnostic test, the pathological results of VAB/EVAB were analyzed separately and together in relation to the surgical pathology, which was considered the gold standard. The pathological diagnoses were grouped into malignancies requiring immediate surgical treatment or with the potential for active surveillance in the future. Lesions indicated for immediate surgical treatment were considered positive and included invasive carcinomas (IC) and high-risk DCIS (DCIS-HR). Lesions with potential for future active surveillance were considered negative and included low- and intermediate-grade DCIS (DCIS-LG and DCIS-IG). DCIS-HR was defined as any high-grade ductal carcinoma ***in situ*** with comedonecrosis. DCIS-LG/IG evolving lesions were defined as low- or intermediate-grade ductal carcinoma in situ without comedonecrosis. 1.7. Statistical analysis: 1.7.1. Descriptive analysis: An initial exploratory analysis was conducted using the Shapiro-Wilk test to determine the normality of the continuous data distribution. For continuous variables, measures of central tendency (mean and median) and dispersion (standard deviation) were calculated. For categorical variables, frequencies and percentages for each category were determined. Considering that most continuous variables exhibited non-parametric distributions, results were presented as medians, minimums, maximums, and interquartile ranges (P25 and P75). Fisher's exact test was used for comparisons between the frequencies observed in each categorical variable. 1.7.2. Evaluation of the diagnostic test: 2x2 contingency tables, containing the results of EVAB/VAB versus surgery (gold standard), were analyzed to assess the association between the results. Sensitivity (S), specificity (E), positive predictive value (PPV), negative predictive value (NPV), and overall accuracy were calculated for each comparison. Fisher's exact test was used for comparisons between the frequencies obtained in each analysis. For the evaluation of the diagnostic test, the ability of VAB/EVAB to diagnose DCIS-HR/IC versus DCIS-LG/IG was compared. Statistical analyses were performed using GraphPad Prism® (GraphPad Software, version 8.0, La Jolla, California, USA, www.graphpad.com) for Windows, the GraphPad QuickCalcs software for detecting potential outlier values, and Stata® (version 14.0, Stata Corporation, College Station, TX, USA). **Conclusion:** Vacuum-assisted procedures (VAB/EVAB), whether alone or combined with clinical, imaging, or immunohistochemical criteria (COMET trial), are not an effective diagnostic method to exclude the presence of high-risk DCIS for progression or residual IC at surgery based on a low-risk DCIS result on biopsy. Active surveillance in a broad context would significantly reduce overtreatment of women with breast cancer by only a small margin (6%), at the expense of potentially undertreating a very low number (1.7%) of patients. However, the oncological safety of active surveillance for patients with low-risk DCIS for progression can only be determined through randomized controlled trials that evaluate this approach, with or without hormonal therapy, to elucidate the natural history of the disease as well as the clinical consequences of underdiagnosed high-risk invasive carcinoma and DCIS for progression.