



**ORIGINAL RESEARCH** 

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# Ultrasound-Guided Core-Needle Biopsy of Suspicious Breast Lesions

Kincső-Zsófia Lőrincz¹, Zsuzsánna Pap², Simona Lileana Mocan³,⁴, Csanád-Endre Lőrincz⁵, Beáta-Ágota Baróti⁶

- <sup>1</sup> Radiology and Medical Imaging Laboratory, Mureș County Emergency Clinical Hospital, Târgu Mureș, Romania
- <sup>2</sup> Department of Anatomy and Embryology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
- <sup>3</sup> SC Morphomed SRL, Târgu Mureș, Romania
- <sup>4</sup> Department of Pathology, Mureş County Emergency Clinical Hospital, Târgu Mureş, Romania
- <sup>5</sup> Hungarian Department of Biology and Ecology Medical Biology, Babeş-Bolyai University, Cluj Napoca, Romania
- <sup>6</sup> Department of Radiology and Medical Imaging, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Târgu Mureş, Romania

#### **CORRESPONDENCE**

#### Zsuzsánna Pap

Str. Gheorghe Marinescu nr. 38 540139 Târgu Mureş, Romania Tel: +40 265 215 551 E-mail: zsuzsanna.pap@umfst.ro

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Kincsó-Zsófia Lőrincz • Str. Gheorghe Marinescu nr. 50, 540136 Târgu Mureş, Romania. Tel: +4,0 372 653 100. E-mail: bencso@rocketmail.com

Simona Lileana Mocan • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureş, Romania. Tel: +40 265 215 551, E-mail: sImocan70@gmail.com

Csanád-Endre Lőrincz • Str. Mihail Kogălniceanu nr. 1, 400000 Cluj-Napoca, Romania. Tel: +40 264 405 300, E-mail: lendre1992@yahoo.com

Beáta-Ágota Baróti • Str. Gheorghe Marinescu nr. 38, 540139 Târgu Mureş, Romania. Tel: +40 265 215 551, E-mail: beata.baroti@umfst.ro

#### **ABSTRACT**

Background: Breast cancer is the female cancer with the highest mortality. While early detection is a public health priority in Western European countries, a screening program in our country has yet to be implemented. The best diagnostic accuracy is achieved through the use of triple assessment: clinical examination, imaging, and core-needle biopsy where indicated. Prognosis is influenced by clinical, histological, and biological factors, and therapy is most effective when individually tailored. Aim of the study: To analyze the clinical, histological, and immunohistochemical characteristics of the biopsied nodules and summarize our experience from the last three years. Material and Methods: We retrospectively analyzed data from 137 patients who underwent core-needle biopsy between 2017 and 2019. Imaging score was assigned based on ultrasound examination or mammography. Clinical and pathological parameters were recorded, followed by statistical processing of the data. Results: The mean age of the patients was  $58 \pm 14$  years, lesions had a mean size of  $22.83 \pm 14.10$  mm. Most nodules (n = 63, 47.01%) were located in the upper-outer quadrant, and bilateral presence was found in 4 (3.08%) cases. We found a significant positive correlation between lesion size and the patients' age (Spearman r = 0.356; 95% CI 0.186, 0.506; p = 0.000). The malignancy rates within the Breast Imaging Reporting and Data System (BI-RADS) categories were as follows: 0% for "4a", 31.58% for "4b", 71.42% for "4c", and 97.72% for "5". Most malignancies (n = 73, 78.35%) were represented by invasive ductal carcinoma of no special type, 58.43% (n = 52) were grade 2, 89.13% (n = 82) were estrogen receptor positive, and Luminal B-like type was the most common (n = 63, 78.75%). Conclusions: The mean size of tumors was larger than the average size at discovery described in the literature. In our region, age and tumor size are positively correlated. Preoperative histological results may indicate the reliability of the imaging risk stratification system. Most cases can benefit from adjuvant endocrine therapy.

**Keywords:** breast cancer, screening, imaging, biopsy, immunohistochemistry

#### INTRODUCTION

Breast cancer accounts for a quarter of all female cancers and is among the leading causes of cancer deaths. In Romania, its general mortality is lower than in Western European countries, with an age-standardized incidence of 54.5 cases per 100,000 and a 15.5 mortality rate in 2018.

While national mortality has decreased in the younger population over the last two decades, it is still rising in the 65+ age group, suggesting that information about the necessity of screening has not reached the target population.<sup>2</sup> On the other hand, screening carries the risk of overdiagnosis, followed by overtreatment, and can lead to a 20% increase in mastectomies and more use of radiotherapy, according to a Danish study.<sup>3</sup> Cancer experts from several countries advise making early detection a public health priority and taking action to decrease the number of false positive diagnoses, which could be facilitated by the use of core-needle biopsy in the evaluation process.<sup>4,5</sup>

In multidisciplinary breast clinics, lumps undergo a triple assessment consisting of clinical examination, imaging, and preoperative biopsy, where needed.6 While the Breast Imaging Reporting and Data System (BI-RADS) developed by the American College of Radiology approximates the risk of malignancy in breast lumps, ultrasound-guided core-needle biopsy provides gold-standard histological results, with a sensitivity of 97-99%.7 Therapy is most effective when individually tailored; as a result, in addition to histological classification, it is of great importance to establish hormone-receptor status and the molecular subtype of each tumor. The urge to request the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status of all invasive breast cancers is included in the United Kingdom National Health Service guidelines for the diagnosis and management of early and locally advanced breast cancer.8 The traits that characterize the different subtypes are pathological grade and proliferation, response to chemotherapy, and response to endocrine therapy.9 In addition, Ki-67 protein status is possibly a prognostic and predictive factor for adjuvant chemotherapy. 10-12

In the effort to diagnose breast cancer in its early stages, we have been performing core-needle biopsies as part of the triple assessment used in multidisciplinary breast clinics. The aim of this study is to analyze the clinical, imaging, histological, and immunohistochemical characteristics of the biopsied nodules and summarize our experience from the last three years.

#### MATERIAL AND METHODS

We retrospectively analyzed the case records of 137 patients with breast lesions who underwent triple assessment consisting of clinical examination, imaging, and core-needle biopsy between January 2017 and December 2019. During the selection of the cases, we divided the patients into two groups. The first one was formed of 130 female patients, of all ages, with no personal medical history of breast malignancies. The second group of 7 patients was formed of special cases which corresponded to one of the following criteria: male; previous treatment for breast cancer; metastasis found in the breast, with the primary tumor located in other organs. Bilateral breast nodules were catalogued as two separate cases. Clinical information included the patients' sex, age, and relevant personal and family medical history. During ultrasound examination, the location and size of the lump, morphologic features, imaging characteristics, and presence of suspicious lymph nodes were noted. The risk of breast cancer was determined by mammography and ultrasound in the majority of cases; for patients younger than 35 only ultrasonography was used. Cancer risk was estimated using the BI-RADS risk stratification tool: 0 – incomplete; 1 –negative; 2 – benign; 3 – probably benign; 4 - suspicious for malignancy, where 4a represents a probability of 2-9%, 4b 10-49%, 4c 50-94%; 5 - highly suspicious of malignancy, with a probability of over 95%. The core-needle biopsy was performed with ultrasound guidance, under local anesthesia with 1% lidocaine using a Bard Magnum biopsy gun with a 14-gauge needle. Histopathological examination of the bioptic material delivered information about the histological type and grade of malignancy of the tumor. We used the protocol of the College of American Pathologists (CAP) for the examination of biopsy specimens from patients with invasive carcinoma of the breast to report every malignant specimen; we also included current WHO classification of breast tumors and the Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system). 13-16 A surrogate molecular breast cancer classification was used based on immunohistochemical assessment of biomarkers (ER, PR, HER2, and Ki-67) and in situ hybridization confirmation, adopted by the 13th St. Gallen International Breast Cancer Conference (2013).<sup>17-19</sup> The five categories were: Luminal A-like (ER positive, PR positive, HER2 negative, Ki-67 low), Luminal B-like (HER2-negative) (ER positive, HER2 negative, and at least one of the following: Ki-67 high, or PR negative or low), Luminal B-like (HER2-positive) (ER positive, HER2 overexpressed or amplified, PR any), HER2-positive (nonluminal) (HER2 overexpressed or amplified, ER negative, PR negative), and Triple-negative (ER negative, PR negative, HER2 negative). Cut-off values were set according to the guideline of the American Society of Clinical Oncology/College of American Pathologists for immunohistochemical testing.<sup>20</sup>

Statistical analysis was performed using Microsoft Excel Professional Plus 2010 (version 14.0.7116.5000) and Graph Pad Prism (version 8.4.0.671). Numerical data were expressed as mean ± standard deviation. Categorical data were expressed as frequency and percentage. Associations between age and other prognostic factors were evaluated by Chi square tests. P values smaller than 0.05 were considered statistically significant.

The study was conducted in accordance with the principles stipulated in the Declaration of Helsinki. Informed consent was waived by the ethics committee of the institution, as the study was retrospective.

#### **RESULTS**

The study population consisted of 137 patients with breast lumps who underwent core-needle biopsy, 136 (99.27%) of which were females. The mean age of the patients was  $58 \pm 14$  years. Malignant tumors were found in 97 (80.17%) cases, and 24 (19.83%) cases were benign. In 17.05% (n = 15) of breast cancer cases, family history was positive for breast cancer, and two of these patients were younger than the recommended screening age for normal risk of breast cancer.

Upon presentation, the lesions had an overall mean size of  $22.83 \pm 14.10$  mm, malignant lesions being slightly larger ( $23.46 \pm 10.75$  mm) (Table 1). Nodules were most frequently located in the upper-outer quadrant (UOQ) (n = 63, 47.01%), and bilateral presence was found in 4 cases (Table 1). Tumor frequency for each site and BI-RADS scores are listed in Table 1, along with size and age distributions. We found a significant positive correlation between lesion size and the patient's age (Spearman r = 0.356; 95% CI 0.186, 0.506; p = 0.00), suggesting an increase in tumor size with the advancement of age (Figure 1).

The malignancy rates within the BI-RADS categories were as follows: 0% for "4a", 31.58% for "4b", 71.42% for "4c" and 97.72% for "5".

Tumor histological types for each category are listed in Table 2.

The occurrence of benign/malignant tumor types was significantly different (p <0.0001) in patients aged 40 or younger, mostly diagnosed with benign nodules (n = 8, 88.89%), compared to older patients whose nodules were mostly malignant (n = 92, 85.19%). Malignancy rates based

on age categories are presented in Figure 2. The cancerfree biopsies were mostly fibroadenomas (n = 15, 62.5%), normal breast tissue being found in 4 cases (16.67%). Most malignancies (n = 73, 78.35%) were represented by invasive ductal carcinoma (IDC) of no special type, followed by lobular (n = 9, 9.28%), mucinous (n = 5, 5.15%), papillary (n = 4, 4.12%), tubular (n = 1, 1.03%), cribriform (n = 1, 1.03%), and neuroendocrine (n = 1, 1.03%) types. No cases of carcinoma with medullary pattern were found. The histological type of the tumors showed a correlation of statistical significance with the patient's age, as IDC was the most frequently diagnosed type in all age categories, except the last one (81 and older), where the mucinous type was the most common (p = 0.044). The rates of tumor types found in each age category are presented in Figure 3. The distribution of malignancy grades across age groups is

TABLE 1. Clinical and imaging data

		n	%
Laterality	Left	61	44.53
	Right	72	52.55
	Bilateral	4	2.92
Location	UOQ	63	47.01
	LOQ	6	4.48
	UIQ	18	13.43
	LIQ	7	5.22
	CC	18	13.43
	U	10	7.46
	L	7	5.22
	1	0	0
	0	5	3.73
Size	<10 mm	18	14.52
	10.1–20 mm	50	40.32
	20.1–30 mm	32	25.81
	31–40 mm	12	9.68
	41–50 mm	10	8.06
	>50 mm	2	1.61
Age (years)	<20	2	1.50
	20-30	2	1.50
	31-40	6	4.51
	41-50	32	24.06
	51-60	22	16.54
	61-70	37	27.82
	71-80	24	18.05
	>80	4	3.01
BI-RADS	4a	7	5.79
	4b	19	15.70
	4c	7	5.79
	5	88	72.73

UOQ, upper-outer quadrant; LOQ, lower-outer quadrant; UIQ, upper-inner quadrant; LIQ, lower-inner quadrant; CC, central; U, limit of upper quadrants; L, limit of lower quadrants; I, limit of inner quadrants; O, limit of outer quadrants

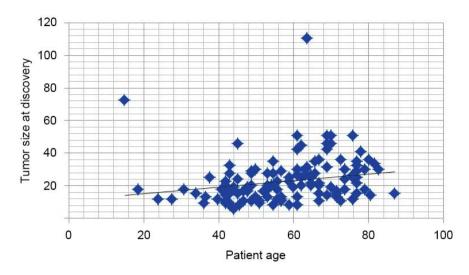


FIGURE 1. Patient age and tumor size correlation

presented in Figure 4. Grade 2 tumors were the most common (n = 52, 58.43%), especially in the 61-70 and 41-50 age groups. Grade 1 tumors were observed in patients aged 41 and older, becoming more and more frequent until the age of 70. Grade 3 tumors were present in patients aged between 41 and 80, most of them occurring in the 61-70 age group. There was no statistically significant correlation between age and grade of malignancy (p >0.05).

The immunohistochemistry assays concluded that 89.13% (n = 82) of lesions were ER-positive with all specimens above 10% staining, 67.03% (n = 61) were PR positive, and 80.43% (n = 74) expressed high Ki-67 levels. HER-2 positivity was 26.09% (n = 24). Luminal B-like (HER2-negative) type was the most common (n = 45, 56.25%), followed by Luminal B-like (HER2-positive) (n = 18, 22.5%), Luminal A-like (n = 8, 10%), and HER2-positive (n = 6, 7.5%). Triple-negative tumors (TNBC) were the least common, accounting for 3.75% (n = 3) of

TABLE 2. Tumor histological type by BI-RADS categories

	BIRADS 4a (n)	BIRADS 4b (n)	BIRADS 4c (n)	BIRADS 5 (n)
Benign				
FA	4	10	1	0
Other	3	3	1	2
Malignant				
IDC	0	5	3	68
Lobular	0	0	0	9
Papillary	0	0	2	2
Mucinous	0	0	0	5
Other	0	1	0	2

FA, fibroadenoma; IDC, invasive ductal carcinoma

all cases. Luminal B-like (HER2-positive) tumors were more frequent in patients under 50 years, Luminal B-like (HER2-negative) tumors being dominant above this age. The largest triple-negative tumor rate was observed in the 80+ age category. There was no statistically significant correlation between age and tumor molecular type (p >0.05).

A number of 7 cases were not included in the calculations above. One male patient underwent biopsy for a BI-RADS 4c lesion, which proved to be gynecomastia with normal breast tissue. Two female patients, already surgically treated for breast cancer, were found with suspicious lesions. Histopathological examination found no sign of recurrence, the ultrasonographic appearance being due to scar tissue. There were two cases of recurrence, one intramammary lymph node metastasis involving IDC of no special type, and one case of metastatic melanoma.

## **DISCUSSIONS**

In the European Union (EU), the breast is the most common site of cancer among women, whereas male breast cancer represents approximately 1% of all breast cancer cases. <sup>21,22</sup> Recommendations of the European Commission (EC), last updated in 2020, include biannual mammography screening for women aged between 45 and 69 years. <sup>23</sup>

Over the last two decades, the median tumor size has been decreasing, reaching 11–15 mm with the use of radiological screening methods, but remains between 19–21 mm when discovered by self-detection or clinical examination. The mean age of patients in our study (58  $\pm$  14 years) fits the target age group for screening; however, the mean size at discovery was above average (23.46 vs. 11–15 mm/19–21 mm). The 2017 EC Eurostat report regarding

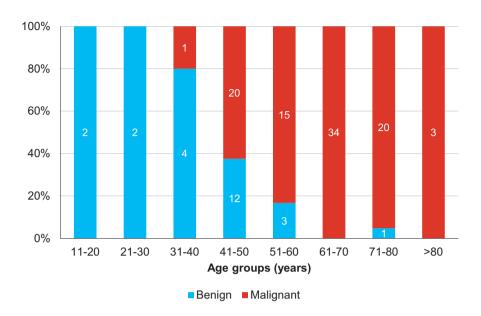


FIGURE 2. Rate of benign and malignant lesions within age groups

breast cancer screening places Romania last among EU member states with 0.2% participation in 2015.<sup>26</sup> According to data collected in 2016, participation reached 6%.<sup>21</sup> By contrast, in Western member states, participation is above 75%.<sup>26</sup> This discrepancy in screening participation rates and median tumor size suggest that either self-detection or clinical examination applied to the majority of our cases. Multiple studies have concluded that tumor size at discovery is correlated with lymph node status and the presence of metastases, and it is an independent predictor for mortality.<sup>27–31</sup> In a cohort study of 819,647 women, published in 2018, for tumors from 9 to 20 mm, mortal-

ity increased from 7.0 to 22.3%.<sup>32</sup> We found a statistically significant positive correlation between lesion size and the patients' age. Although slower growing tumors are diagnosed in elderly women, this category of patients is often less informed than the younger population and is reluctant to seek medical help. Studies from other geographical regions have reached opposite conclusions, suggesting that size decreases with advancement of age or have not found any significant correlation.<sup>33–35</sup>

General screening recommendations apply to women aged 45 to 69 with normal risk for breast cancer, but in many cases individual risk factor identification is neces-

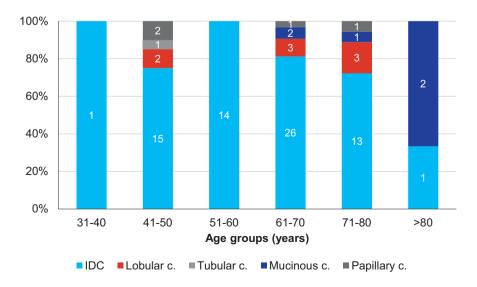


FIGURE 3. Tumor histological types within age groups

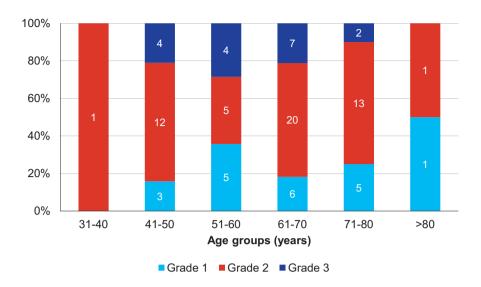


FIGURE 4. Tumor malignancy grades within age groups

sary to provide personalized suggestions such as screening from a younger age. Patients whose first- or second-degree relatives have been diagnosed with breast cancer have a twofold risk or higher, according to a systematic review.<sup>36</sup> Similarly to other results,<sup>37</sup> among our patients with malignant tumors, 15 (17.05%) had a positive family history, two of whom were under the age of 45.

Tumors are located most frequently in the UOQ across multiple populations, which is also our case (47.01%). Although tumor location is not an independent prognostic factor, central tumors are more difficult to evaluate mammographically, and as a result, they may be discovered in more advanced stages.<sup>38</sup> Other studies have discovered an increasing trend in mortality with increasing distance from the axilla, regardless of axillary lymph node invasion, concluding that survival is significantly better for UOQ tumours.<sup>39,40</sup>

Screening mammography can be very useful for detecting cancer in early stages; however, it has a major downside: overdiagnosis. Supplemental ultrasound breast screening can be used when breast density is high, but its specificity is low compared to mammography.<sup>41</sup> Overdiagnosis is defined as the discovery of breast lesions that would never cause symptoms or harms in the absence of screening.<sup>42</sup> These represent 0–54% of all cases, according to a systematic review.<sup>43</sup> Consequential overtreatment can be limited by adding the third step to the diagnostic process, represented by histopathological evaluation and proposing all suspicious lesions (BI-RADS 4 and 5 categories) for core-needle biopsy. In our study, malignancy rates, confirmed by histopathological examinations, were in the estimated range for each category, except BI-RADS 4a (0% vs. estimated 2–10%).

Most tumors (n = 73, 78.35%) were represented by IDC of no special type, with the highest frequency in all age categories, with the exception of patients over 80 years, who were mostly diagnosed with the mucinous type. This supports data from international literature, where the rate of IDC is estimated to 40–75%, and mucinous carcinoma is associated to elderly patients.<sup>44</sup> Preoperative histopathological examination is not only useful for avoiding unnecessary treatment of benign tumors, but also for improving surgical results, including margin negativity, in malignant tumors.<sup>45</sup>

Once the need for treatment is confirmed, evaluation of prognostic factors is a key part of defining a personalized therapeutic strategy. Practitioners rely on the Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) for malignancy stratification and decision making regarding treatment.<sup>46</sup> The Nottingham combined histologic grade evaluates the amount of tubule formation, the extent of nuclear pleomorphism, and the mitotic count. Tumor grade proportion is variable in the literature, but grade 2 tumors are the most frequent in the majority of studies.<sup>447–51</sup> In our study, grade 2 tumors were observed in more than half of the cases.

Besides tumor grade, the molecular subtype of the tumor strongly influences survival.<sup>52–54</sup> Breast cancer is heterogeneous at the molecular level, with different patterns of gene expression leading to differences in behavior and prognosis. Due to time and cost constrains, a surrogate molecular breast cancer classification is used, based on immunohistochemical assessment of biomarkers (ER, PR, HER2, and ki-67).<sup>18</sup> Approximately 75% of breast cancers express estrogen and progesterone receptors, which indi-

cates responsiveness to hormonal therapy. In our study, 89.13% of lesions were ER-positive and 67.03% PR-positive. 46 Estrogen expression rate is based on the percentage of cells staining by immunohistochemistry, but in the clinical practice the response of low positive (1–10% staining) ER cancers is uncertain. The 2020 guideline of the American Society of Clinical Oncology (ASCO)/CAP recommends reporting these cases in a new category, ER low positive.<sup>55</sup> In order to predict the benefit of hormonal therapy, the Allred score combines both the percentage and intensity of staining.<sup>20</sup> Luminal B-like subtype was dominant in this study, which means that most of our patients will need additional chemotherapy, compared to luminal A, where hormonal therapy is sufficient in most cases.<sup>46</sup> The least favorable cases, HER2-positive and TNBC, were found predominantly in the older age groups; however, we have found no significant association between age and molecular subtype. Some studies have reached the same conclusion; at the same time, it is widely recognized in the literature that younger women present with more aggressive tumors. 51,56

## **CONCLUSIONS**

Most of the newly diagnosed breast cancers in our region are localized in the upper-outer quadrant, the 61–70 age group being most affected. At the time of discovery, these tumors are larger than the average size at discovery described in the literature, and they also show a positive correlation with age. The introduction of triple assessment to our routine was successful; however, it cannot compensate the lack of screening participation. Preoperative histological results suggest the BI-RADS risk stratification system's reliability and appropriate use. Most tumors express both ER and PR, and these patients can benefit from adjuvant endocrine therapy.

# **CONFLICT OF INTEREST**

Nothing to declare.

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