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THE VALUE OF DIAGNOSTIC METHODS TO DETECT PATHOLOGIC CHANGES IN THE BREAST

LJERKA ELJUGA and ILONA SUŠAC

Eljuga Polyclinic, Zagreb, Croatia

Summary

For diagnosing pathologic changes in the breast, depending on age, clinical examination combined with ultrasound, mammography and cytology are most commonly used. Any positive finding requires a biopsy for a final diagnosis. The biopsy precedes surgical treatment usually performed during the same operative session. To assess the value of some diagnostic methods for detection of pathologic breast changes a retrospective study was carried out on a sample of 78 patients diagnosed and treated at the Eljuga Polyclinic from March 1999 to March 2003. In diagnosing for pathohistologic changes, the aforementioned methods were applied in all of the 78 studied patients (aged 23-77). The patients were assigned to two age groups including patients over 35 (mean age 49) and under 35 yrs of age (mean age 29), respectively. The first group was further divided into 6 subgroups, depending on the correlation between a particular diagnostic method and final pathohistologic finding. The correspondence between pathohistologic finding and all other diagnostic procedures was as follows: clinical examination, US, mammography and cytological analysis showed accuracy in 92.30% (72/78), 96.15% (75/78), 92.53% (62/67, excluding 11 patients <35 yrs not requiring mammography – benign changes), and 84.62 % (64/73, technically failed samples excluded) of the cases, respectively. Ultrasound breast imaging demonstrated superior accuracy over mammography, clinical examination and cytologic puncture. The results lead to the conclusion that in the majority of breast patients, a combination of several diagnostic methods should be used to get an accurate diagnosis.

KEY WORDS: *breast tumors, clinical examination, ultrasound, mammography, cytology*

VRIJEDNOSTI POJEDINIH DIJAGNOSTIČKIH METODA U OTKRIVANJU PATOLOŠKIH PROMJENA U DOJCI

Sažetak

U dijagnosticiranju patoloških promjena u dojci, ovisno o dobi, najčešće se primjenjuju klinički i ultrazvučni pregled, mamografija i citološka analiza. Pozitivan nalaz bilo koje od tih metoda pretrage indicira biopsiju kao konačnu dijagnostičku metodu. Ona prethodi kirurškom liječenju i najčešće se vrši u istom aktu s operacijom. U svrhu procjene vrijednosti pojedinih dijagnostičkih metoda u otkrivanju patoloških promjena u dojci, provedena je retrospektivna studija na uzorku od 78 bolesnica, podvrgnutih dijagnosticiranju i liječenju promjena u dojci u Poliklinici "Eljuga" u razdoblju između ožujka 1999. i ožujka 2003. U svih 78 bolesnica (u dobi između 23 i 77 godina) u postupku dijagnosticiranja patoloških promjena u dojci primjenjivane su sve navedene dijagnostičke metode. Bolesnice su podijeljene u dvije dobne skupine: one starije od 35g. (prosječne dobi od 49 godina) i one mlađe od 35g. (prosječne dobi od 29 godina). Prva skupina bolesnica podijeljena je u daljnjih 6 podskupina, ovisno o korelaciji između pojedinih dijagnostičkih metoda i konačnog patohistološkog nalaza. Podudarnost patohistološkog nalaza i svih drugih dijagnostičkih postupaka bila je sljedeća: klinički pregled pokazao se točnim u 92,30 % (72/78) bolesnica, UZV u 96,15 % (75/78), mamografija u 92,53 % (62/ 67, izuzeto 11 bolesnica <35 god. kojima nije bila potrebna mamografija-benigne promjene), a citološka analiza u 84,62 % bolesnica (64/73, s izuzetkom tehnički neuspjelih uzoraka). Najtočnijom metodom pokazao se UZV pregled dojki, kojeg slijede mamografija, klinički pregled, te citološka punkcija. Rezultati nameću zaključak, da kod većine bolesnica samo kombinacija više dijagnostičkih metoda može dovesti do ispravne dijagnoze.

KLJUČNE RIJEČI: *tumori dojke, klinički pregled, ultrazvuk, mamografija, citologija*

INTRODUCTION

The prognosis for breast cancer primarily depends on the spread of the disease before starting any therapy, which is a relatively direct function of time. If cancer is detected early when still localized to the breast, without spread to axillary lymph nodes and/or distant organs, the prognosis is more favorable (1). A comprehensive mammography screening program as practiced in many developed countries and its wide range of possibilities result in earlier cancer diagnosis and a significantly reduced relative risk of death from the disease (2). Despite technical improvements, mammography however has its limitations, especially when applied to women with dense breast tissue, implants, severe dysplasia or significantly distorted breast architecture as, for instance, after breast surgery or radiotherapy. Before a decision about definitive therapy is made, the diagnosis often requires confirmation by another method (1). To surmount these limitations, many studies were conducted to evaluate various non-invasive and minimally invasive breast structure imaging techniques and their diagnostic value. Analysis of cytology specimens or breast discharge is the most commonly used method for verification of breast abnormalities (3). In breast lesion diagnosis, fine-needle aspiration is a complementary tool to clinical and mammographic findings and their combination makes the so-called „triple test" allowing for a 100% diagnostic accuracy of palpable breast lesions (4). Initially, in the 1950s and 1960s, ultrasound played only a minor role in the diagnosis of breast disease. Due to low-resolution ultrasound technology, the detection of breast cancer and diagnostic accuracy were by far inferior to mammography as the gold standard. With the technology development in terms of higher resolution, improved software and training of ultrasound operators, ultrasonography becomes an ever more sensitive method for cancer diagnosis. Ultrasonography is of particular value in women with dense breast tissue and in cases of non-palpable breast lesions not visualized on mammograms (5). In the majority of cases, fine-needle aspiration and ultrasound-guided core-biopsy can replace open biopsy with a previous breast lesion marking as applicable to a large proportion of non-palpable lesions of the breast (6). Basic diagnostic procedures (anamnesis, inspection and palpation) are therefore to be supplemented by standard test methods – mammography, ultrasound and fine-needle aspiration cytology. The final diagnosis, however, can only be provided by the histologic test, which is indispensable for accurate classification and treatment of the disease. On the other hand, breast cancer is not easily detected in its early stages. Despite clinical, radiologic or cytologic manifestations, this may sometimes cause diagnostic errors, too.

AIM

The aim of the study was to compare and evaluate the value or accuracy of some diagnostic methods for detection of pathologic changes in the breast, and thereupon determine optimal use of particular diagnostic procedures. At the Eljuga Polyclinic, Zagreb, Croatia, a retrospective study was carried out on a sample of 78 patients undergoing diagnosis and treatment for breast lesions from March 1999 to March 2003. In this process, the most common diagnostic methods used were as follows: clinical examination (CE), ultrasound (US), mammography (M), cytologic diagnostics (C) and biopsy including pathohistologic examination of tissue samples and pathohistologic diagnosis (PHD).

PATIENTS AND METHODS

The study sample included 78 women treated over a four-year period (from March 1999 to March 2003). The patients ranged in age from 23 (the

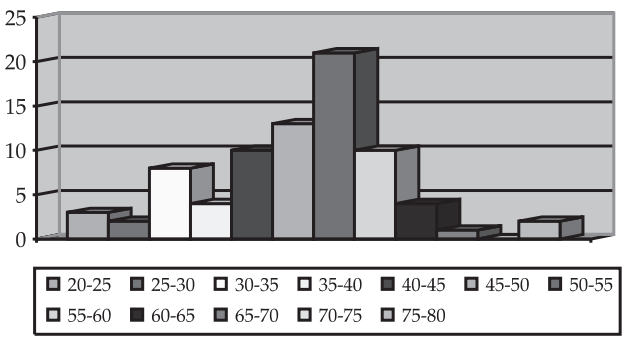

Figure 1. Age distribution of patients

youngest) and 77 (the oldest). The age distribution in five-year intervals is shown in Figure 1.

The patients were assigned to two age groups including patients over 35 and under 35 years of age, respectively. The reason for such a distribution is that patients under 35 did not undergo mammography initially, but only upon a suspicion for a malignant process in the breast raised with other diagnostic procedures. The first group consisted of 65 (65/78) women over 35 years of age, mean age 49. The second group comprised 13 (13/78) women under 35 years of age. The mean age of this group was 29.

The first group of 65 patients was further divided into 6 separate categories depending on the correlation between particular diagnostic modalities and final pathohistologic finding. The second group of 13 patients under 35 years of age was integrally shown in respect of the correspondence between clinical diagnostic methods and pathohistologic diagnosis. According to pathohistologic findings, the size of breast lesions ranged from 7.5 mm to 4.5 cm. Considering the results by each method, the changes were characterized as benign, suspicious or malignant. Clinical examination was done first, followed by mammography and/or ultrasound, cytologic analysis and finally, pathohistologic verification. Clinical examination, mammography and ultrasound imaging were done by the oncologist as well as tissue sampling for cytologic examination to be performed by the laboratory specialist (cytologist). Pathohistological analysis was done by the pathologist. Failed cytologic samples were either acellular or contained cells of no diagnostic significance. Benign changes included fibrocystic changes and/or fibroadenoma with atypia and/or proliferation, sclerosing adenosa, *tumor phyllodes* – a benign type. The percentage of correspondence of particular diagnostic modalities and pathohistological diagnosis was calculated and the results expressed in ratio form.

RESULTS

I. Retrospective analysis of diagnostic tests done in *the first group* of patients, those over 35 years of age (N=65; 31 patients aged 50-59), produced the following results:

a) Patients in whom all diagnostic methods gave the same identical result (N=50; 25 patients aged 50-59): (Table 1)

Table 1.

WOMEN OVER 35 YRS OF AGE

Clinical examination	Ultrasound	Mammography	Cytology	Pathohistological diagnosis		Total
carcinoma	carcinoma	carcinoma	carcinoma	carcinoma	23	50
benign changes	benign changes	benign changes	benign changes	benign changes	27	

Table 2.

WOMEN OVER 35 YRS OF AGE

Clinical examination	Ultrasound	Mammography	Cytology	Pathohistological diagnosis		Total
carcinoma	carcinoma	carcinoma	non-malignant	carcinoma	3	7
benign changes	benign changes	benign changes	suspicious changes	benign changes	4	

Table 3.

WOMEN OVER 35 YRS OF AGE (RT-RADIOTEHRAPY; FCC-FIBROCYSTIC CHANGES)

Clinical examination	Ultrasound	Mammography	Cytology	Pathohistological diagnosis		Total
suspicious	suspicious	suspicious	suspicious	fibrosis after RT	1	2
suspicious	suspicious	suspicious	suspicious	FCC with proliferation	1	

Table 4.

WOMEN OVER 35 YRS OF AGE (ILC- INVASIVE LOBULAR CARCINOMA)

Clinical examination	Ultrasound	Mammography	Cytology	Pathohistological diagnosis		Total
non-palpable lesion	carcinoma	normal	failed	ILC	2	4
benign change	benign change	benign change	failed	benign change	2	

Table 5.

WOMEN OVER 35 YRS OF AGE

Clinical examination	Ultrasound	Mammography	Cytology	Pathohistological diagnosis		Total
suspicious	suspicious	suspicious	failed	cicatrix	1	1

Table 6.

WOMEN OVER 35 YRS OF AGE

Clinical examination	Ultrasound	Mammography	Cytology	Pathohistological diagnosis		Total
nonpalpable lesion	carcinoma	carcinoma	carcinoma	carcinoma	1	1

Table 7.

WOMEN UNDER 35 YRS OF AGE

Clinical examination	Ultrasound	Mammography	Cytology	Pathohistological diagnosis		Total
carcinoma	carcinoma	carcinoma	carcinoma	carcinoma	2	3
benign changes	benign changes	not done	benign changes	benign changes	11	

Table 8.

DIAGNOSTIC VARIATION IN ALL THE CASES (+ CARCINOMA; - BENIGN; NON-PALP.-NON-PALPABLE; SUSP.- SUSPICIOUS; ND = NOT DONE IN PATIENTS UNDER 35 YRS OF AGE.; CE-CLINICAL EXAMINATION, US-ULTRASOUND, M-MAMMOGRAPHY, C-CYTOLOGIC ANALYSIS, PHD-PATHOHISTOLOGICAL DIAGNOSIS, ILC- INVASIVE LOBULAR CARCINOMA)

Number (%)	CE 72/78	US 75/78	M 62/67	C 64/73	PHD 78/78
25 (32.05)	+	+	+	+	+
27 (34.62)	_	_	_	_	_
3 (3.85)	+	+	+	_	+
4 (5.13)	_	_	_	susp.	_
2 (2.56)	susp.	susp.	susp.	susp.	_
2 (2.56)	non-palp.	+	_	failed	+ (ILC)
2 (2.56)	_	_	_	failed	_
1 (1.28)	non-palp.	+	+	+	+
1 (1.28)	susp.	susp.	susp.	failed	_
11 (14.1)	_	_	Nr (<35)	_	_

b) Patients in whom cytologic test results were contradictory to the results obtained by other diganostic methods (N=7); all aged 41-51 yrs): (Table 2)

c) Patients in whom the results of all previous tests raised a founded suspicion of malignancy, in contrast to their pathohistologic finding (N=2; 54 and 60 yrs): (Table 3)

d) Patients in whom cytodiagnostics failed for technical reasons (N=4, 46-58 yrs): (Table 4)

e) A case of a non-palpable breast lesion while all other diagnostic tests suggested carcinoma (N=1; 77 yrs): (Table 5)

f) An isolated case showing discrepancy between clinical and pathohistologic test results (N=1; 69 yrs): two years before, the patient underwent breast biopsy. (Table 6)

II. In *the second group* of patients including those under 35 yrs of age, the analysis of performed diagnostic tests showed the following results (N=13, 8 aged 30-35 yrs): (Table 7)

Table 8 shows diagnostic variations observed in all the cases.

The collective data (Table 9) show the correspondence between clinical examination, US, mammography and cytopuncture results ex-

Table 9.

COLLECTIVE TABLE

Diagnostic variations	Correspondence with PHD (%)	Share of total
CLINICAL EXAMINATION	92.30%	72/78
ULTRASOUND	96.15%	75/78
MAMMOGRAPHY	92.53%	62/67 (- 11 not done)
CYTOLOGY	84.62%	64/73 (- 5 failed)

pressed as percentage in all study patients, with pathohistologic diagnosis remaining the most accurate method. Clinical examination, ultrasound, mammography (excluding patients with benign changes, aged under 35, who did not undergo mammography) and cytology showed to be accurate in 92.30 % (72/78), 96.15 % (75/78), 92.53 % (62/67) and 84.62 % (66/73) patients, respectively (technically failed tests excluded).

DISCUSSION

The principle diagnostic procedures used for detecting pathologic changes in the breast include anamnesis, inspection and palpation, supplemented with standard tests (mammography, ultrasound and cytologic examination of the puncture specimen or breast discharge).

Anamnesis should comply with the leading symptoms. Previous examination and diagnostic tests, or any previous breast surgery, are also required. In our study, 17 patients (21.8%) detected breast change by self-examination. Seven of them (8.9%) were diagnosed with cancer. Six of them were over 45, and one was 41 years of age. Suspicion was raised upon clinical examination, and all lesions were larger than 1.5 cm. Only a few studies worldwide show the predictive value of particular diagnostic modalities for detecting breast cancer in women under 45 yrs of age, especially of breast self-examination. According to one American study conducted in the 1990s, even 71% of women under 45 detected breast cancer by self-examination. Only 29% of breast cancer were identified by routine mammography and clinical breast examination (20% and 9%, respectively), and unlike those self-detected, the above cancer cases were at an earlier stage of the disease. Such results are not a surprise as the value of mammography for breast cancer increases with age, and that of clinical examination with the tumor size (7). Even today, palpation is a useful diagnostic tool that may disclose the tumor process in the breast, especially valuable in countries with increasing breast cancer incidence where screening mammography is not widely practiced so the disease is identified mostly at its high stage. Tumor enlargement increases the possibility of such detection, where the experience of the examining physician also plays an important role. The sensitivity of clinical examination for detecting palpable changes in the breast ranges from 53.2% to 57.14%, and in the majority of cases, the disease is thus identified at its advanced stage. Moreover, clinical breast examination alone, even in experienced hands, does not demonstrate a high accuracy in discriminating benign from malignant lesions (8). In detection of early breast cancer (less than 1 cm or negative lymph nodes), clinical breast examination has not shown a great efficacy. The rate of breast cancer detection increases by only 2-6% when clinical examination is combined with mammography compared to mammography as the sole diagnostic method (9). The sensitivity of clinical examination increases with larger tumor size (from 17% for tumors <0.5cm to 58% for tumors >2.1 cm), and decreases with higher body weight (from 48% to 23%). Considering hormone replacement therapy (HRT) users, the sensitivity of clinical breast examination decreases from 52% in HRT non-users to 33% in HRT users. Clinical breast examination has its highest sensitivity in the 50-59 age group compared to younger and older groups where it has shown to be much less sensitive. Especially younger and obese women receive less benefit from clinical breast examination (10). The largest number of lesions in this study was detected by clinical breast examination in the age group of 50-59 years. In 31/33 women of this age group, the lesion was palpable and larger than 1 cm. In two cases, non-palpable lesion was diagnosed as invasive lobular carcinoma in patients aged 52 and 46 years with dense glandular tissue. The 52-year-old patient was a HRT user. In a 77-year-old patient with a non-palpable lesion, 7.5 mm cancer was confirmed. In the majority of women under 35 yrs of age (11/13), benign changes larger than 1.5 cm were

diagnosed. Physician's experience, tumor size and patient's age (mostly postmenopausal women with a marked degree of involutive changes) may elucidate such a high detection rate of breast lesions of no less than 92.3 %. After anamnesis and physical examination, further tests were made to either confirm or exclude the diagnosis. The advantage of breast ultrasonography over other diagnostic modalities is reflected in its enviable precision and absolute safety. However, the use of ultrasound in screening of asymptomatic population would be inadequate for the duration of the test and its incapability of identifying microcalcifications, which may be an indication of intraductal carcinoma *in situ* and early invasive cancer (11). On the other hand, there are also studies showing that high-resolution ultrasonography may be useful in the detection of microcalcifications associated with non-palpable breast lesions and early breast cancer, especially in young women who are at high risk of developing breast cancer and in whom mammography is not usually performed (12). In young women, breast ultrasonography yields better results than mammography as dense breast parenchyma in young women may impede mammographic interpretation. Over 90% of cancers in women under 40 yrs of age are detected by ultrasonography (13). Some studies show that the sensitivity of ultrasonography reaches even 100%, and that ultrasound examination is capable of detecting breast cancer of a 60% lesser diameter than that on mammography, and that such cancer can be visualized on ultrasonography even a few years before it becomes visible with mammography (14). The highest value of ultrasonography is demonstrated in its capability of distinguishing breast cysts and discriminating cystic and fibrocystic changes from solid tumors. In addition, its high-frequency probes are capable of discirminating complicated, septated or mixed cystic-solid lesions in the breast, and combined with fine-needle aspiration biopsy and core-biopsy, open biopsy can be avoided in about 80% of the cases and the number of unnecessary mammography reduced in young women (15). According to some studies, complementary ultrasound imaging and color Doppler (the latter to a smaller extent) increases the specificity of mammography, from 51.5% to 66.4% at a prevalence of 31.3% malignancy in all age groups (women under or over 50 years of age) and regardless of the tumor size (smaller or larger than 1 cm), especially in women with a non-palpable breast abnormality (16). In women with a palpable abnormality in the breast, the sensitivity and predictive value for a combined sonographic and mammographic assessment can be up to 100% with the specificity of 80%, which means a lower rate of false-negative findings on mammography (17). Some earlier studies showed the 92% sensitivity and specificity of combined sonographic and mammographic assessment, or 97.7% in women with symptomatic disease (18). The high accuracy of mammography combined with ultrasound imaging, of 92.23% or 96.15% as shown in our patients, too, can also be partly explained by a high percentage of clinically recognized lesions in the breast. Both methods, however, showed as unreliable in 3 cases. The first was a case of a patient with massive changes of scar tissue from quadrantectomy performed two years before, which clinically, sonographically and mammographically looked markedly suspicious, but the cytology specimen obtained by puncture biopsy did not show to be diagnostically valid. The second patient received radiotherapy following conservative surgery for carcinoma of the breast. The suspicion of recurrence was based upon the clinical finding of blood discharge from the irradiated breast, and the cytology, ultrasonography and mammography results were also markedly suspicious for malignancy. Pathohistologic analysis, however, showed it was a case of heavy fibrosis in a portion of postsurgical scar tissue. The third was a case of fibrocystic changes including proliferation and fibrosis. In accordance with literature citations, the validity of ultrasound as a complement to mammography has also been demonstrated in this study. Two cases of invasive lobular carcinoma were not observable on mammography, or the mammograms were negative. The patients were of 46 and 52 years of age (the latter was a HRT user). As ultrasound imaging of the breasts in our patients also showed to be the most accurate in correlation with pathohistologic results, it is important that we point out that also postmenopausal women with dense glandular tissue (potentially as a result of HRT use) require ultrasound breast imaging as a

complement to mammography. Figures 2 and 3 show a patient aged 52, with a mammogram without suspicious abnormalities, and a 14 mm cancer (CLI) detected on ultrasonography.

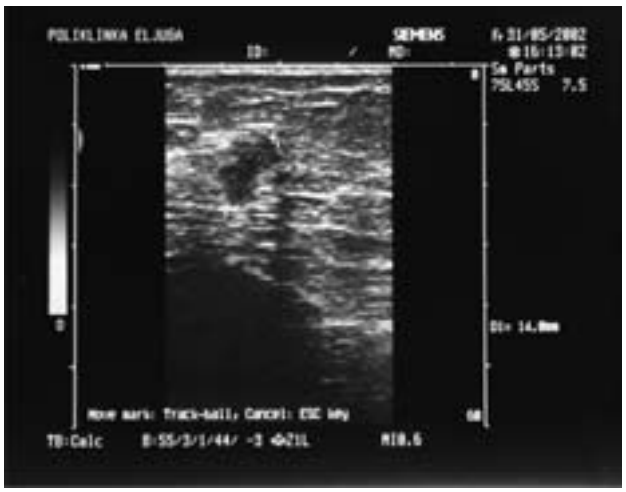

Figure 2. Ultrasound finding of CLI in a 52-year-old HRT user

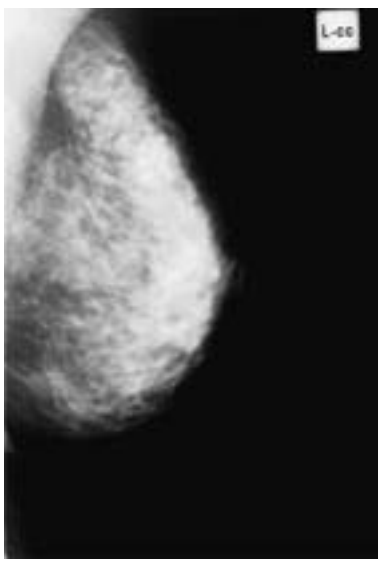

Figure 3. Mammogram of the same patient without clearly suspicious changes

Despite controversies in recent years, the majority of experts agree on the evident usefulness of mammography as a screening modality for women aged 50 and more years, and it is, therefore, still considered "the gold standard" in early breast cancer detection in this age group. In women under 50 years of age, the picture is, however, much less clear (19). The effect of the implementation of the Dutch screening program throughout the period 1990-1997 was an increase in incidence in the early 90ies, especially in the age group of 50-69 years, primarily of T1 carcinoma and DCIS, along with a significant decrease in the incidence rate of advanced breast cancer of 12.1%, compared to 1989. The increased incidence of localized breast cancer was accompanied with a similar fall in mortality about two years after. This has yet been another proof that screening mammography not only contributes to the fall in moratality, but also to the decrease in advanced breast cancer rate (20). In the countries adopting regular mammography screenings, an ever increasing number of nonpalpable lesions requiring further diagnostic work-up has been reported. According to some studies, ultrasound-guided biopsy of non-palpable breast lesions showed a high specificity and sensitivity (88%). Using this method, even up to 93% of invasive carcinomas can be correctly identified as invasive carcinoma (21). The diagnostic accuracy of fine-needle aspiration cytology varies for different centers, depending on the skill and experience of the medical staff performing cytopuncture, and processing and analyzing sample preparations. Many studies, however, show that experience reduces the number of false-positive and false-negative results. One of the major problems is the number of false-positives, which according to some studies may be zero, or according to others, it may exceed 10%. Some authors therefore point out the importance of the combination with other modalities – mammography and clinical examination (22). In our study, 5/78 (6.4%) cytopunctures were unsuccessful in obtaining diagnostically valuable material. From 73 successful punctures, 4 (5.48%) gave false-positive and 3 (4.1%) false-negative results. In two of the failed cases, invasive lobular cancers were verified only with ultrasonography.

CONCLUSION

The sequence of diagnostic procedures performed at the Eljuga Polyclinic in Zagreb, Croatia complies with the above diagnostic principles. According to our experience, ultrasound breast imaging has shown to be the most accurate diag-

nostic modality, followed by mammography, clinical examination and cytologic diagnostics. The physician's experience in performing diagnostic tests and procedures, and interpretation of the results plays a crucial role. Besides mammography, postmenopausal women with dense glandular tissue (potentially resulting from HRT use) should therefore also be recommended for an ultrasound examination of the breast. Although for the small number of patients included in this study, the data reported herein are, to some extent, in contrast to large-sample statistics, the results lead to the conclusion that in the majority of breast patients, only a combination of several diagnostic modalities could produce an accurate diagnosis. Thereby, the possibility of predicting malignant breast changes is reduced to a large extent. Finally, the identification of benign changes in the breast results in a reduced number of unnecessary surgical breast biopsies, particularly in younger female population.

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Author's address: Ljerka Eljuga, M.D., Eljuga Polyclinic, Bukovačka cesta 121, 10 000 Zagreb, Croatia