Difficulties in the diagnosis of intracystic tumors of the female breast

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The objective of the current study was to determine the accuracy of radiological and cytological diagnoses of intracystic and papillary lesions in distinguishing between true papillary benign and malignant lesions.

Seventy cytological reports of intracystic proliferations were selected from our cytopathological database at the Breast Health Corporation, Budapest, Hungary, dating back to the last 7 years. Retrospective analysis of the diagnostic approaches – mammography, ultrasonography, clinical examination and cytology – was performed in selected cases. The results of imaging and cytological examination are routinely reported on a categorical scale ranging from 1 to 5. 44 patients underwent surgical excision: histology showed benign lesions in 21 and malignant lesions in 23 cases. Twelve patients, who did not undergo biopsy and presented a stable disease at follow-ups, were also included in the group of benign lesion. Fifteen patients were not available for follow-up.

Concerning the total investigated cases the mean categorical values of mammography, ultrasonography and cytology were 2.24, 2.78 and 3.05 respectively. The malignant and benign groups significantly differ from each other concerning the mean age of the patients (p=0.0216), the distribution of the coded mammographical results (p= 0.0171) the cytological results (p=0.0001), and average tumor size measured on mammogram images (p=0.0199). The two group does not significantly differ over the distribution of mammographical density patterns (p=0.1075), radiomorphological appearance (p=0.1101), average tumor size measured on ultrasonography (p=0.2665), and patient complaints (p=0.2634). The evaluation of ultrasonography shows borderline significance (Pearson Chi-square test: p=0.0616, M-L Chi-square test: p=0.0404) between the malignant and benign groups.

Differential diagnosis between malignant and benign intracystic and papillary lesions is feasible using common radiological diagnostics. However, more efficient teamwork is needed with the cooperation of a well-trained cytologist and radiologist, who are able to produce precise images of the lesions, and guides the aspiration of the adequate samples for cytology, which is the most valuable examination.

Key words: Breast diagnostics, intracystic carcinoma, papillary lesion, diagnostic error

Cystic breast lesion is one of the most common alteration of female breast, occurs in 7% of women aged between 35 and 50 years, however, only 0.73-1.19% of that are malignant (1). Intracystic and intraductal papillary carcinomas are really rare, constitute merely 0.5% of all breast carcinomas (2,3,4) therefore the rare malignant lesions have to be selected from numerous banal benign growths. Beyond recognition, is it possible to differentiate between malignant and benign masses using the usual examinations of breast diagnostics?

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Materials and Methods

Patients

From 1 January 1997 to 31 December 2004, 10,620 breast cytological samples were obtained from 8,200 patients at the breast diagnostics laboratory of the Breast Health Corporation, out of which 70 samples were diagnosed by the cytopathologist as intracystic epithelial proliferation. In our study, we retrospectively investigated the diagnostic processes of these cases. We distinguished the group considered malignant based upon surgical histology from the group of benign growth proven by histology or long-term follow-up. Surgery was performed in 44 cases: histology revealed benign alter-

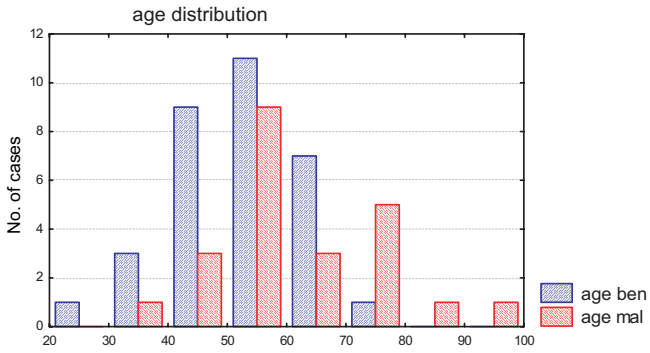


Figure 1. Age distribution among benign and malignant group with intracystic proliferation showes significant difference (p=0.0216)

ations in 21 cases and malignancies in 23 cases, out of which 4 were in situ carcinomas and 19 were diagnosed as invasive breast carcinoma. Although surgery was not carried out in 12 cases, negative results of the repeated follow-up –two years- proved the benign nature of the lesion. After the examination, the follow-up of 15 patients out of the 70 could not be conducted, resulting that all together the comparison of 32 benign and 23 malignant cases was performed.

Imaging

In each case the complex examination of the breast included mammography, physical examination, ultrasonography and cytology.

Mammography:

Mammography was performed with Contour Plus Mammograph (Trex Medical USA).The FUJI AD-Mammo-Fine film- screen cassette system was used with FUJI AD-M films . Films were processed in a Mammoray-Compact E.O.S. daylight machine using extended cycle processing. Each breast was examined in two standard views,(cranio-caudal, mediolateral oblique), and additional views (spot magnifications) were taken when it was necessary for better visualization. Mammographic findings were categorized on the basis of a 5 –point rating scale describing the degree of suspicion for malignancy according to the Tabár system (5) and ACR/BI-RADS (Breast Imaging Reporting and Data System of the American College of Radiology) assessment scoring system (6). In cases of intracystic lesions, mammography showed a single, well-defined and lobulated mass occasionally with blurred contour. Microcalcifications were uncommon.

Ultrasonography

The US examinations were performed by using a Diasus-2000 ultrasound system with 7.5-10 MHz and 10-22 MHz high resolution linear array and Hitachi 4 real-time ultrasound machine equipped with a 7.5 MHz linear transducer. Gray- scale US evaluation of breasts and axilla regions were performed. Intracystic lesion is a well defined complex solid/cystic mass with frequently posterior enhancement on sonogram. Inhomogenous, hypoechoic intraluminar mass, and irregularly thickened wall were considered as signs of malignancy. Lesions identified by US were scored on a level of suspicion scale from 1to5. US was performed with the knowledge of the clinical and mammographic findings.

Cytology

Fine needle aspirations were performed with US-guidance in all cases. Smears, on-site fixed wet and stained with hematoxylin and eosin, were examined.

Image interpretation and diagnostic workup

The results of all examinations were coded in the same manner from 1 to 5 like the mammography. 1 means normal tissue, 2 indicates benign alteration, 3 stands for borderline undefined alteration, 4 is suspected malignant and 5 is malignant lesions. This coding provided the possibility of the comparative evaluation of different diagnostic methods and their statistical analysis. Mammography was abbreviated as R, physical examination as K, ultrasonography as U and cytology as C.

Statistical analysis:

Our statistical analysis was conducted to demonstrate whether the evaluation of malignant and benign groups gives significantly different results when various diagnostic methods are used.

The following tests were carried out: Mann-Whitney test, Chi-square test, Mann-Whitney U test, Pearson Chi-square test, M-L Chi-square test.

Results

Detailed preoperative diagnostic data of all patients where cytological evaluation proved intracystic epithelial proliferations are shown in Table 1. Concerning the total investigated population the diagnostic evaluation of all method resulted in border-line degree, the mean category score-values of mammography was 2,24, ultrasonography was 2.78 and cytology was 3.05 respectively. Based on the final histopathological

Table 1. Diagnostic characterization of all cases of intracystic epithelial proliferations diagnosed by cytology.

	1	%	2	%	3	%	4	%	5	%	No exam	%
R	10	(14.2)	22	(32.5)	23	(32.9)	8	(11.4)	3	(4.3)	4	(5.7)
U	3	(4.3)	22	(32.5)	34	(48.6)	7	(10.0)	3	(4.3)	1	(1.4)
C	0	(0)	20	(28.5)	33	(47.1)	10	(14.2)	7	(10.0)	0	(0)
Total	13	(6.1)	64	(30.6)	90	(43.0)	25	(11.9)	13	(6.2)	5	(2.3)

Table 2. Complaints of patients in benign and malignant group proved any significant difference (p=0.2634)

	With complaints	Without complaints
Benign	59%	41%
Malignant	74%	26%

Table 3. Mean mammographical and sonographical sizes of abnormalities in benign and malignant group

RTG	ben.size (mm)	mal.size (mm)	**UH**	ben.size (mm)	mal.size (mm)
Mean	11.7	18.6	Mean	13.8	16.3
S.D.	9.4	9.4	S.D.	7.6	8.5

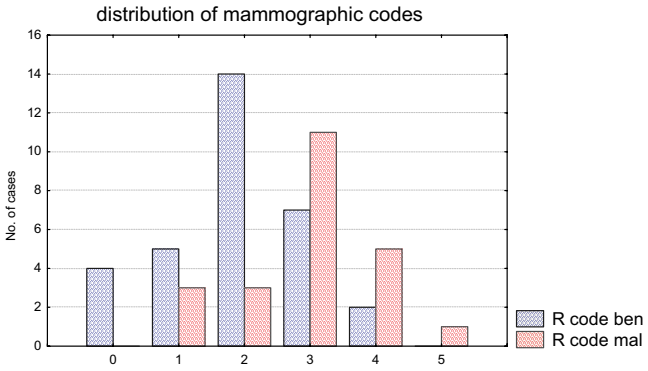


Figure 2. Distribution of mammographic codes of benign and malignant groups showes significantly differences (p= 0.01774 Pearson Chi-square test, p= 0.00712 M-L Chi-square test).

diagnosis, or long-term follow-up malignant and benign group were compared in many ways: on the ground of age, complaints and all diagnostic methods.

The average age of patients in the benign and malignant groups was 53 and 63 years and differs significantly respectively (Fig .1) .

Complaints included palpable mass, or nipple discharge had 65% of all patients, 35% of the 70 cases were screened without any complaints. No significant difference was found between the malignant and benign groups in respect to either the quality or the quantity of complaints (Table 2).

Accordingly mammography, as the first modality we examined not only the distribution of mammographic scores, but breast types, radiomorphological appearances, and the size of the abnormalities too.

Fig. 2. demonstrates the distributions of mammographic reports, that differ significantly in the benign and malignant groups, and Fig. 3. illustrates one of the typical lesions.

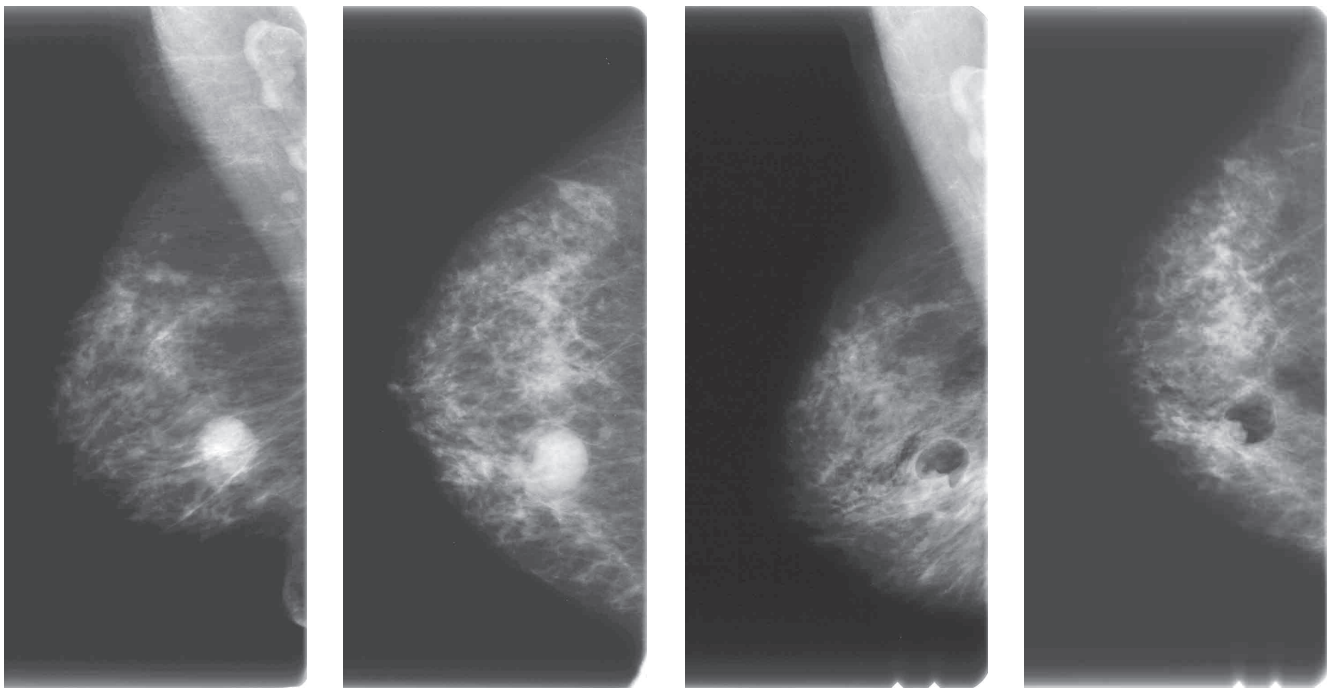


Figure 3. Mammogram of a typical intracystic lesion and its pneumocystograpy (two standard view) of a circumscribed ,homogenous mass with sharply contour Pneumocystography of the lesion (the lumen of the lesion was fullfilled with air)

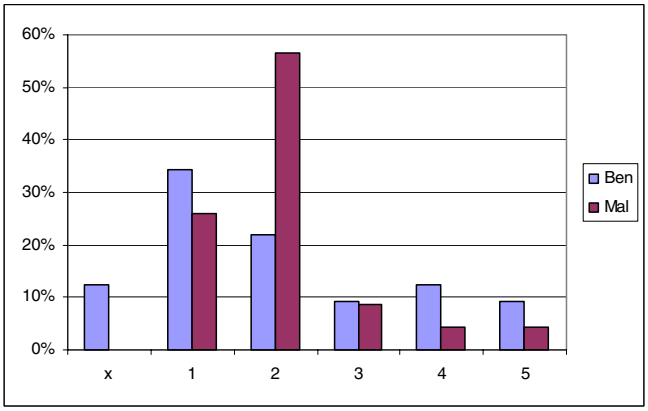


Figure 4. Distribution of breast types of benign and malignant group proved no significant difference (p= 0.10749 Person Chi-square test, p=0.6081 M-L Chi-square test).

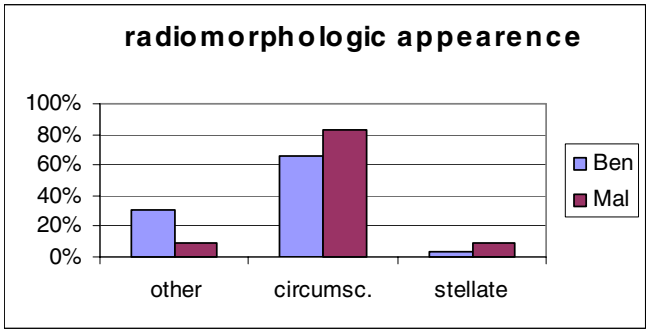


Figure 5. Distribution of radiomorphologic appearance of abnormalities between benign and malignant group gives no significant difference (p= 0.11014 Pearson Chi-square test, p=0.0915 M L Chi-square test).

According to the classification by Tabar (7), no significant difference in breast parenchyma types is revealed between the benign and malignant groups (Fig.4) frequencies of certain breast parenchyma types in the investigated population are the same as in healthy women. From the point of view of radiomorphology, lesions mostly appear as circumscribed, occasionally as star-shaped growths, the distributions of their appearances do'nt differ significantly in the benign and malignant groups (Fig.5) .

Although sonography can distinguish between solid and cystic well (Fig.6), applying two statistical tests, the comparison of the ultrasonographic occurrences of benign and malignant lesions provides different results, with borderline significances only (Fig.7).

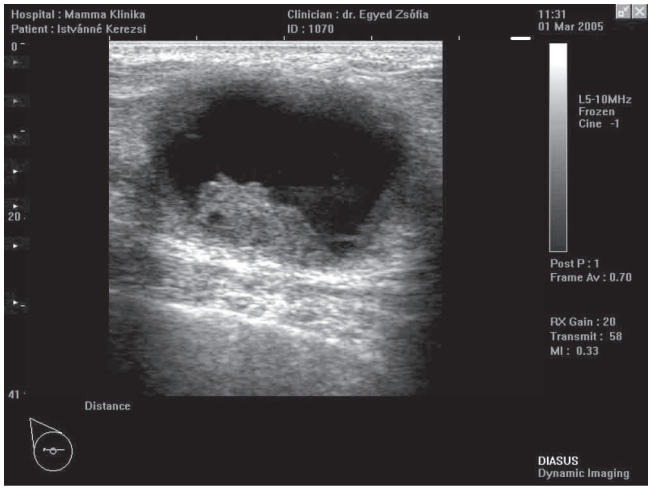
Concerning the size of lesions on ultrasound images, the two groups did not differ from each other significantly (Fig.8), but the size distribution on mammography showes significant distinction between the two groups (Fig.9). At the time of diagnosis malignant lesions are larger, Table 3 showes the average sizes of the two methods.

Cytological examination was the most valuable method to differentiate between benign and malignant cases through its strongest significance (Fig.10).

Discussion

Pathology

Due to the pathomorphology and clinical characteristics (asymptomatic 10-year survival is 91%) (8), intracystic papillary breast carcinoma is considered as a subtype of the non-comedo in situ carcinoma (9). The name "intracystic" implies that the lesion originates from the cyst wall (10). Nev-



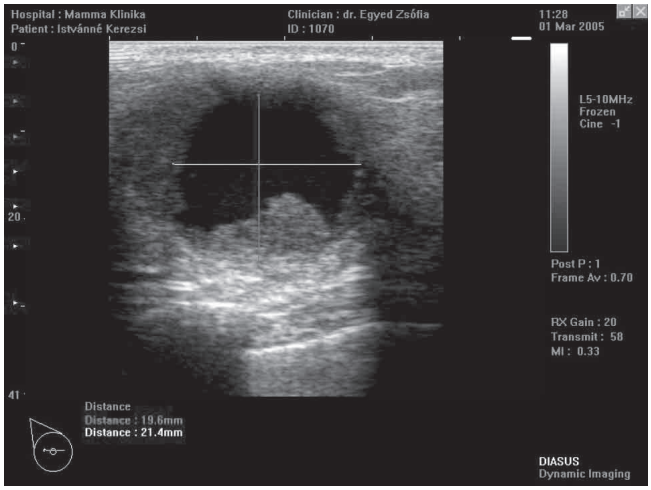


Figure 6. Sonogramm of an intracystic breast lesion: the irregular intraluminar mass suspect for malignancy

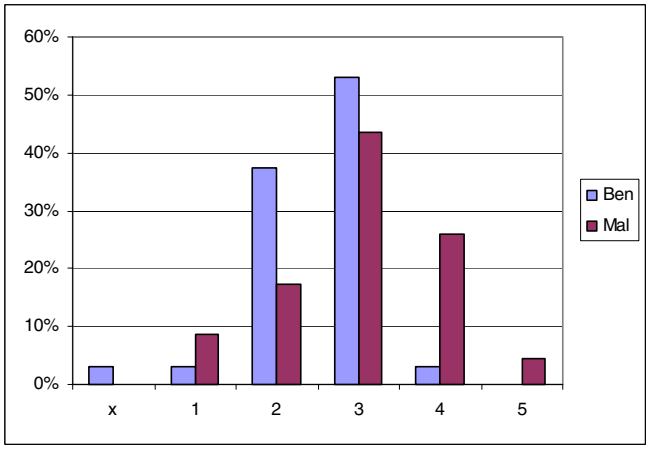


Figure 7. Distribution of sonographic code in benign and malignant groups: borderline significances (p=0.06159 Pearson Chi-square test, p=0.0404 M L Chi-square test).

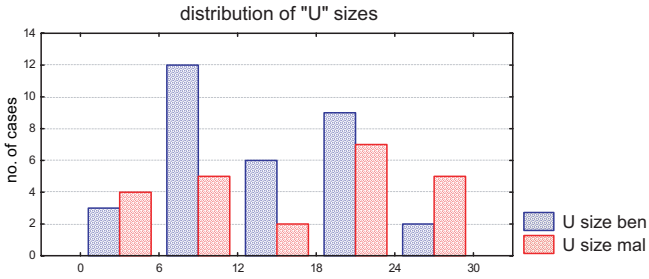


Figure 8. Distribution of sonographic sizes in benign and malignant groups: do'nt differ from each other significantly (p=0.2665 Mann Whitney test).

ertheless, it may also grow from the wall of a central and wider duct, and then through increased secretion to its surroundings coupled with the cystic dilatation of the duct, it can have a similar appearance. The proliferation does not spread over the basal membrane of the wall of the cyst or the duct, therefore intracystic papillary carcinoma and intraductal papillary carcinoma are very similar entities.

In an extensive overwiev of in situ carcinomas -167 cases- 80% were ductal type alone or in combination with lobular carcinoma in situ or intracystic carcinoma or Paget's disease, and only two cases were pure intracystic carcinomas (11).

According to a Greek study based on a 12-year surgical database, only 1.19% out of 1510 cases of breast carcinoma showed cystic forms: 0.66% was diagnosed as intracystic papillary carcinoma (IPC), 0.48% was proven to be intraductal carcinoma with cystic degeneration and a very limited number of mucinous carcinoma was also revealed (12).

Differential diagnosis is critical since the appearances of invasive and in situ carcinomas are very similar. In our study, the incidence of intracystic epithelial proliferation is the same as in the literature; out of the investigated 10,620 cytological findings we found intracystic epithelial proliferation in 0.659% of the cases.

Age

At the time of diagnosis, patients with malignant intracystic breast tumor are 10 years older than patients with other types of breast cancer (13). Malignant intracystic breast tumor is usually recognized above 60 years of age (14), and according to an Italian survey the average age of these patients is 75 years (15). Women, who do not receive hormone replacement therapy and at postmenopause have cystic lesion with slow growth rate, should be examined because these abnormalities are suspicious of malignancy (8,12).

Our experience is in accordance with these findings; in our study the average age in the malignant group is 63 years, 10 years higher than in the benign group (p= 0,0216).

Diagnostics

The diagnostic spectrum of the complex intracystic lesions of the breast is broad. On mammography cysts in the form of

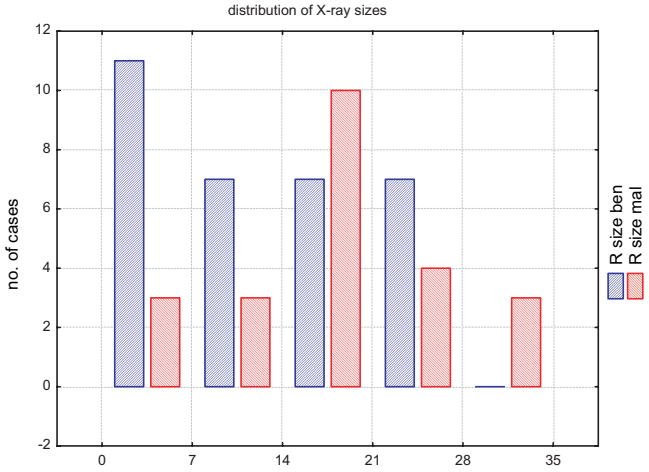


Figure 9. Distribution of abnormality's X-ray size in benign and malignant group: The difference is significant (p= 0.0199)

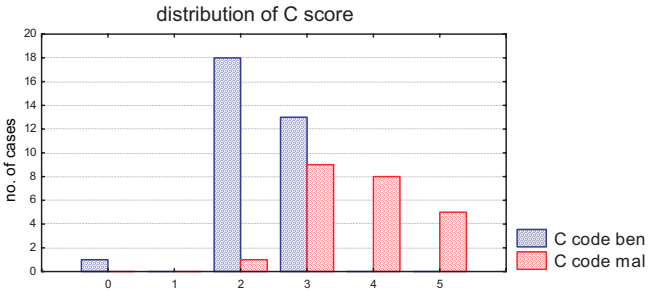


Figure 10. Distribution of the cytological evaluation:The two groups significantly differ over the distribution of „C" codes (p= 0.0001 Pearson Chi-square test, p<0.0001 M L Chi-square test).

nodular lesions are diagnosed in 95% of the cases. However, if cysts have atypical appearance, further examinations are needed to distinguish between benign and malignant forms. Pneumocystography used to be a useful tool earlier (16), but it has been almost entirely replaced by the widespread application of real-time ultrasound imaging (17). At present even by means of color-Doppler ultrasonography, MRI, PET and tumor markers and reliable differentiation is still elusive, so in these cases cytological or histological examinations always has to be carried out (18,19). Fiberoptic ductgraphy is able to get a direct image of the intraductal papilloma, and if a duct leads there, the intracystic tumor can also be visualised (20). In our study, analyzing the findings of the 70 cases – which had benign (46%), malignant (33%) or undefined (21%) histological results – on mammography, physical examination, ultrasonography and cytology with respect to coding by dignity, all the examinations gave values between the benign and the undefined categories. These results correspond with data in the literature.

On mammography, intracystic tumors can mostly be detected if they are circumscribed, 50% of them are well-circumscribed and the other 50% is lobulated with blurred contours and rarely with microcalcification. Star-shaped lesions are almost never seen (18).

Among malignant intracystic abnormalities, Soo et al. separate the intraductal in situ form, which manifest as cluster-type microcalcification, and the intracystic in situ form, which is circumscribed. However, due to the small number of cases (16 cases) generalization is problematic (21).

Even though our own experience also supports that the nodular form occurs most frequently, in a small proportion spiculated forms were detected as well, but there is no difference in the radiomorphologic distribution between the benign and malignant groups. As opposed to that, the evaluation of abnormalities by dignity represents a significant difference: in the group with malignant histological findings signs suspected of malignancy are noted more often than in the benign group, while in the latter one benign characteristics were more often described. In accordance with literature data (22), in our study the size of malignant lesions on mammographical images was also significantly larger than that of benign forms (p=0,0199).

We also investigated whether intracystic lesions accumulate in any of the density categories. Our results suggest that in patients with intracystic tumor belonging to either the benign or the malignant group, breast types classified by Tabar (8), density and parenchyma patterns demonstrate similar distributions compared to healthy individuals.

Complaints and physical examination

Most of the reviews are considering palpable resistance as the patient's main complaint (13, 23, 24,), sometimes extreme in size (25). Some data in the literature state that 77% of malignant intracystic tumors are palpable (22), in our study about half of the cases that were cytologically suspected of intracystic epithelial proliferations were palpable. The technic of surgical biopsy depends on palpability,of the lesion and in our series was performed with guide-wire. But by opinion of surgeons from Slovenia ROLL proved to be superior to guide-wire localization of non-palpable breast lesions. (23). In 13% of the cases nipple discharge or the combination of the two symptoms occurred. 35% of the patients were asymptomatic and came for screening. The distribution of complaints (palpable mass and/or nipple discharge) doesn't differ significantly in the benign and malignant groups. Among the malignant cases the incidence of asymptomatic tumors was slightly lower (28%) than among the benign ones (39%). This implies that complaints are non-specific, they are not distinctive of either benign or malignant lesions, and since 35% of patients are asymptomatic, mammographic screening plays a crucial role concerning this disease. Physical examination provides the least help in differentiating between benign and malignant cases.

Ultrasonography

On one hand, ultrasonography alone has close to 100% sensitivity in the detection of cystic abnormalities, on the other hand, its specificity is merely 73%, but can be raised to 96.7% by additional cytology (17). Ultrasound signs suspicious of malignancy are irregular contour and heterogeneous cyst content, which appear in 96% of malignant tumors. Increased septation of cysts could also raise awareness of a malignant mass (26). The analysis of a large database proved that 57% and 43% of complex lesions comprising cystic and solid components were benign and malignant respectively (27). Adenomyoepitelioma, a rare tumor of the breast can show similar appearance (28).On ultrasonography, benign and malignant complex cysts contain cystic and solid areas in different proportions (29), especially with application of high-resolution technics using 10-13 Mhz probes (30).

Real-time ultrasonography can be supplemented with color Doppler method if it is needed (15). If the majority of solid components are not removed by puncturing the cyst, and are still palpable, or if the cyst refills, ultrasound follow-up is required (31).

According to our experience it is notable that ultrasonography, which is able effectively differentiate between solid and cystic masses, can assess the benign or malignant nature of intracystic breast tumors only with borderline significance.

Cytology

Cytology is an indispensable examination in the diagnosis of complex cysts (9). Although Dutch authors reported 36% of false negativity (32), and several other reports verified low sensitivity (4, 33,34), cytological findings of the sanguinolent content of the cyst and samples from the intracystic solid component, where precise guidance is almost exclusively provided by ultrasonography, are unequivocal (8, 35,36). Benign processes as fibrocystic changes and fibroadenoma may closely simulate papillary lesion on cytology. FNAC complemented by using immunocytochemical staining increases the reliability of diagnosis. It could be a helpful procedure of establishing more exactly the biology of these lesions and

essential factor in clinical follow-up(37). However the majority can be classified accurately into benign and atypical or malignant categories by FNAB (38). Nipple aspirate fluid is not a sensitive test for detecting invasive carcinoma, but atypical cytology in nipple aspirate fluid is often associated with papillary lesions in the underlying breast parenchyma (39). While the diagnostic value of core needle biopsy and histology are almost the same, English authors reported that after Core-biopsy had been undertaken, tumor cells may be identified in the needle track at the histological assessment of the surgical sample, therefore the abnormality is not an in situ lesion any more (40).

Our own experience justifies that in the preoperative assessment of intracystic papillary breast lesions, the most remarkably significant difference between the benign and malignant groups is achieved by cytological examination.

Conclusion

Although the diagnostic spectrum of the complex cystic abnormalities of the breast is broad, and these procedures are applied in daily clinical practice, the preoperative differential diagnosis of these rare pathologies –concerning their benign or malignant nature – is frequently impossible. By means of imaging techniques, physical examination and cytology, our diagnosis is most often borderline and undefined. However, the combination of imaging and cytology can provide differentiation in a significantly larger number of cases. Therefore teamwork, led by a radiologist and a cytologist, and their mutual agreement on the diagnosis is crucial. The most possibly precise, cytologically verified preoperative diagnosis should be aimed to avoid futile operations and delayed interventions.

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