УДК 618/19-006

PROBLEMS AND PROSPECTS OF DIAGNOSTICS AND TREATMENT OF PRIMARY MULTIPLE BREAST CANCER

V.G.Cherenkov, A.B.Petrov, V.V.Ivanchenko, S.A.Tverezovsky, T.V.Chistyakov, A.S.Aleksandrov, B.B.Frumkin

Yaroslav-the-Wise Novgorod State University, v.g.cherenkov@gmail.com

The experience of modern radiation techniques of diagnosis was assessed in 668 patients with primary multiple tumors and proliferative processes of the breast. 97 patients had bilateral breast cancer, 77 — multiple and 49 — metastatic cancer of second breast. The rest women have been diagnosed different kinds of proliferative diseases and cancer at different stages, even carcinoma in situ by the complex radial and morphological research. The implementation of radiological methods at dispensary check-up allowed improving the quality of the clinical examination of patients with breast cancer and increase of bilateral forms in the Novgorod region over the past 5 years on 2.15%. In 4.3 ± 2.1% of women clinical radiodiagnosis was uninformative or misleading. Necessity of morphological verification of primary multiple tumors of unknown origin has appeared. We developed less invasive way to remove the focal formation by special device with cryoapplicator under ultrasound control, which is promising approach to clarifying diagnosis and at the same time it is the method of medical prevention of invasive forms of breast cancer.

Keywords: mammography, ultrasound, and multiple primary and metachronous polyneoplasia, morphological verification

Оценен опыт современных лучевых методов диагностики 668 пациенток с первично-множественными опухолями и пролиферативными процессами молочной железы. У 97 больных оказался билатеральный РМЖ, у 77 мультицентричный и у 49 метастатический рак второй молочной железы. У остальных женщин установлены разные виды узловых пролиферативных образований и злокачественных новообразований на разных этапах развития, вплоть до carcinoma in situ путем комплексного лучевого и морфологического обследования. Внедрение лучевых методов на этапах диспансерного наблюдения позволило повысить качество диспансеризации больных РМЖ и прирост билатеральных форм в Новгородской области за последние 5 лет на 2,15%. У 4,3±2,1% женщин клинико-лучевая диагностика оказалась неинформативной или ошибочной. Возникает необходимость морфологической верификации первично-множественных образований неясного генеза. Разработанный нами малоинвазивный способ удаления очаговых образований специальным устройством с криоапликатором под контролем УЗИ является перспективным подходом уточняющей диагностики, а вместе с тем, методом медицинской профилактики инвазивных форм РМЖ.

Ключевые слова: маммография, УЗИ, первично-множественные и метахронные полинеоплазии, морфологическая верификация

The end of the 20th century is characterized by «splash» of high frequency of multiple breast cancer (BC), including bilateral one [1-4], which is definitely associated with the introduction of modern visualizing technologies. Massive screening of women, based on the use of mammography (MG), identifies a variety of types of nodular proliferative tumors and cancer at different stages of development including carcinoma in situ, surgically treatable (breast-saving) interference [5].

It should be mentioned that mammography screening, which allows identifying minimal changes characterizing malignant growth, are the only indication for the morphological evaluation of suspicious areas [6] (biopsy under ultrasound control, stereotactic biopsy, partial resection). Such investigations are performed by a clinician at the beginning of outpatient treatment and then at the time of surgery. Precise continuity in work of specialists of different profiles and encoding are necessary. The final diagnosis is made by pathologist, who must be equal member of the team dealing with the problem of breast cancer [7]. Results of treatment of primary multiple breast cancer (PMBC) depend on both the early and accurate diagnosis and adequate selection of surgical interference for each disease. However, literature [8] contains information only about primary multiple malignant tumors developing synchronously or in a year after the first tumor. And what should we do with multiple forms of fibroadenomas and focal disease revealed by new technologies with varying degrees of proliferative processes up to Ca in situ according to pathogenesis and prevention of invasive cancer?

The goal of the study — to study the features of diagnosis and surgical treatment options of breast polyneoplasia.

Materials and methods

The work is based on the results of clinical, radial and morphological examination of breast performed in 668 women with polyneoplasia. All patients with polyneoplasia were divided into 6 groups according to the nature of tumor-growth and localization and into 12 subgroups with taking into account the terms of appearance (synchronous or metachronous).

In 174 (26.0%) patients with diagnosed primary multiple breast cancer (PMBC) including 97 patients with bilateral and 77 — multiple cancer. Database of Population Cancer Registry of Novgorod Regional Clinical Oncology Center contains data on 146 patients with bilateral breast cancer. However, in 49 cases of these a detailed analysis showed the presence of diffuse form of cancer, peritumoral invasion, locally advanced process of cancer emboli in blood vessels, distant metastases caused by metastatic dissemination to contralateral breast.

To identify features of manifestation and the comparative evaluation of diagnostic methods we analyzed data of 120 patients with breast cancer (control group) without multiple growth and focal changes in the second breast for 10 years.

In 454 of 682 women synchronous or metachronous focal formation has been detected by using digital mammography after more than one year, including benign tumors with some degree of proliferation. All patients with primary multiple tumors have been fully examined, including the use of non-invasive and invasive technologies, techniques for target biopsy (fine needle aspiration and trepanobiopsy) and labeling non-palpable tumors to perform minimally invasive surgical interference. Immunohistochemical and DNA cytometric tests were performed to identify the pathomorphological diagnosis of cancer.

Results and discussion

In 97 patients with bilateral forms of breast cancer seemed to be independent being in 2010 — 4.05% (against 1.9% in 2005) to the total number of observed group of patients with breast cancer. 29 patients (29.9%) had both tumors synchronously and 68 women (70.1%) metachronously (Table 1). Percentage increase of bilateral forms to the total number of observed breast cancer patients over the past 5 years was 2.15% generaly due to metachronous cancers. We refer cases of cancer diagnosed during a year

Table 1

Comparison of efficacy of clinical and radial diagnostics of polyneoplasia depending on the nature and terms of its identification

№	Types of polyneoplasia	Quantity	Including		Investigation	
			Terms of identification	Quantity	Helped to establish diagnosis	Was uninformative and misleading
1	Bilateral breast cancer	97	synchronous	29	28	1 (3,4%)
			metachronous	68	66	2 (2,9%)
2	Multiple breast cancer	77	synchronous	65	62	3(4,6%)
			metachronous	12	11	1 (8,3%)
3	With metastatic dissemination to the second breast	49	synchronous	31	29	2 (6,45%)
			metachronous	18	17	1 (5,5%)
4	Breast cancer with focal fibroadenomatosis or adenosis of the second breast	124	synchronous	92	89	3 (3,2%)
			metachronous	32	31	1(1,9%)
5	Multiple fibroadenomatosis or adenosis	203	synchronous	156	153	3 (0,6%)
			metachronous	47	45	2 (4,2%)
6	Bilateral focal fibroadenomatosis or adenosis	118	synchronous	84	83	1(1,2%)
			metachronous	34	32	2(5,8%)
	Total	668	synchronous	457	444	13 (2,8%)
			metachronous	211	202	9(4,3%)

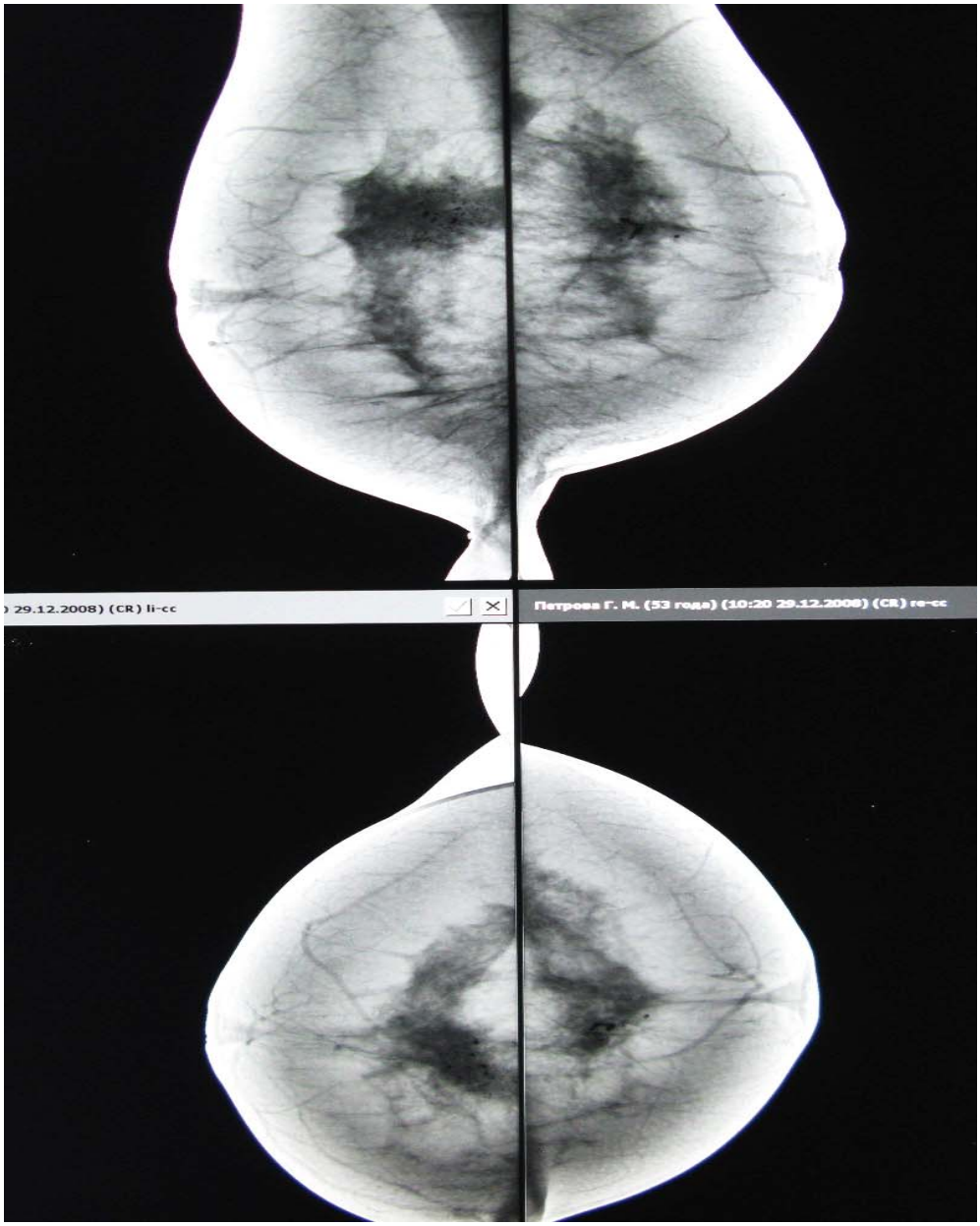

Figure 1. Mammograms of patient P., 47 years old. Synchronous breast cancer T2NoMo (on the background of the relatively «mirror» shadows with radiant and scalloped outline and multiple calcifications in the right and left breast)

after discovery of the first tumor to synchronous tumors as well as Rozhkov N.I. and others. (2010).

The group of synchronous forms of breast cancer contained 29 (29.9 ± 8.2% cases of bilateral breast cancer) patients; the analysis of diagnosis of synchronous breast cancer showed that only 14 (48.2 ± 7.8%) patients had malignant tumor which was found in both breasts by physical examination. 28 (96.6 ± 7.5%) patients with synchronous tumors are suspected after digital mammography and are stated after ultrasound with biopsy. One patient (3.4 ± 2.1%) had non-palpable tumor which was diagnosed after 9 months of control dynamic examination in the second breast. Women under the age of 49 years (62.4%, n = 18) prevailed in this group, aged 50-59 years — 27.5% (n = 8) and over 60 years only 10.3 % (n = 3). Genetic factors play important role in emergence of synchronous cancer [9]. In D.Anderson's opinion (1974) synchronous breast cancer occurred before menopause is strongly hereditary. According to our materials breast cancer or ovarian cancer were found out in 34.8% of blood relatives.

Research of mammogram with synchronous breast cancer showed that it had symmetrical 'shadows' by location and size in 17.2% of the cases (n = 5), others did not differ from the X-ray pictures with unilateral cancer. Tumor nodes often had irregular round shape with scalloped asymmetrical lines and located in the upper-outer or on the boundary of outer quadrants. Their sizes ranged from 0.5 to 6 cm including 9 women (31%) with non-palpable (6 in one breast and 4 in both) tumors, often against a background of adipose involution. It was found out with the help of target biopsy and cytology that palpable tumors contained cancer cells in all cases. Analysis of histological structure of the tumors showed that 20 (68.9%) patients had similar constitution (infiltrative ductal — 14 (48.2%), lobular — 6 (20.7%)), while 31.1 % had different types of cancer.

Table 2

Comparison of breast cancer according to age at the moment of identification of the «first» tumor and terms of the «second» one

Age when «tumor» registered	Synchronous	Metachronous	Including terms of identification of the «first» tumor			
			Up to five years	5-9 years	10-20 years	20 and more
Up to 39 years	4	20	5	7	6	2
40-49 years	14	31	8	14	8	1
50-59 years	8	12	4	6	1	1
60 лет and more	3	5	3	1	1	—
Total	29	68	20 (29,4%)	28(41,2%)	16(23,5%)	4 (5,9%)

Metachronous breast cancer. 68 (70.1%) patients with breast cancer were under medical observation in which the second breast cancer was diagnosed within the first 5 years in 29.4% (n = 20) cases and in terms of 5 to 9 years in 41.2% (n = 28) patients (Table 2). In 23.5% of patients cancer of the second breast has evolved over 10-20 years after the first operation. Proportion of developing breast cancer after 20 years of regular medical check-up was 5.9% of the total number of metachronous forms which testify the growth of risk of second tumor regardless of how long ago the first tumor was cured.

In 2 women (2.9%) nonpalpable breast cancer was not detected by oncologist due to limited investigation by ultrasound in municipal hospital. Breast cancer in II and III stage were established in 1.5 and 3 years after the first operation respectively.

As seen from Table 2, the synchronous tumors are more common in people under 50 years old (62,1%) and the development of the first tumor in metachronous cancer also occurs mainly in persons younger than 50 years (75%) with a median of appearance terms 6.7 years.

As seen from Figure 1, 18 patients (26.4%) who are at the dispensary have breast cancer of the remaining breast in 0-1 stages, 61.8% of women in II stage, while 11,8% — in III stage, which shows the necessity of the obligate mammographic examination of the remaining breast in women aged 40-60 years at least 1-2 times a year.

Metachronous cancer manifested as one or (14.7 ± 3.2%) as multiple tumor nodules with vague, asymmetric radiant loop, often against a background of involutive processes of glandular tissue in 10 women. 11 women (16.2%) with this type of cancer that appeared in 5-8 years after treatment the first tumor had thickened skin and slight swelling of the tissue that in our opinion is directly related to the changes after radiotherapy in the parasternal area and possible development of cancer in the medial quadrants. In any case metachronous cancer microscopic calcified foci were not found.

Performing of biopsy revealed in 66 (97 ± 2.8%) patients tumor cells, multiple tumors were established in 2 women only by histological examination of operational material.

Multiple (multifocal) breast cancer is characterized by the presence of multiple tumor nodules in the breast. Multiple cancer occurs in one or both breast (the latter described as synchronous and metachronous forms of breast cancer). In total we have established multiple forms of breast cancer in 77 cases by pathohistological research. This form of breast cancer was recorded almost the same frequency as aged 40-49 years (32.4 ± 6,5%) and after 60 years (33.7 ± 7.2%). According to histological structure invasive ductal carcinoma prevailed (n = 51-66.2%). Invasive lobular carcinoma was in 24.6 ± 5.4% (n = 19) which is significantly higher than in the control group (18.9 ± 5.7%). The same histological constitution was in 71.4 ± 6.3% of patients with breast cancer and multiple breast cancer was in 28.6 ± 5.3% of cases.

Physical examination of breast revealed only one tumor in 42 (54.5%) patients, 2 in 11 (14.2%) ones and few nodes in 2 patients which is associated with a small

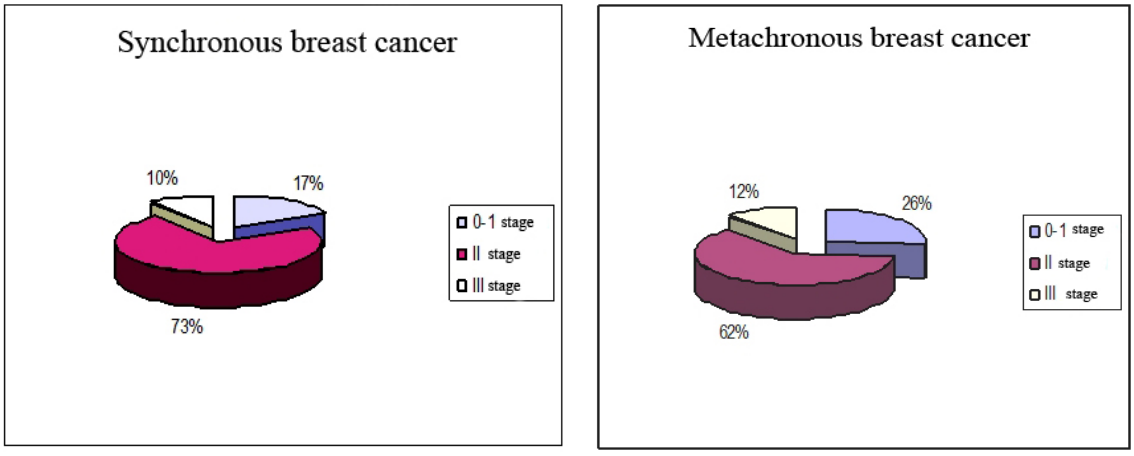

Figure 2. Comparison of synchronous and metachronous breast cancer forms depending on the stage of disease

size of nodes. Mammography showed only 1 or 2 tumor in 8 (10.3%) patients due to the presence of diffuse mastopathy and cancer tissue density for their X-ray imaging. Additional nodes with a characteristic pattern of malignant growth have been identified in 4 of 8 patients during sonography. 42 (54.6 ± 7.6%) women have tumor nodes in several quadrants and only 35 (45.4 ± 7.6%) — in one. The latter according to many authors may be consequence of intraorganic metastasis. Thus, due to the consistent use of digital mammography and ultrasound number of tumor nodes coincided with the histological findings of the study in 73 observations (94.8 ± 4.1%).

For 5.2 ± 3.2% of patients radial diagnostics were not informative.

The importance of identification of this form and localization of cancer is related to the choice of adequate level of operations and the necessity to reject breast-saving operations when nodes located in different quadrants.

Metastatic cancer in the second breast is interesting from the standpoint of differential clinical and radial diagnosis which has been performed in 49 patients initially due to multiple cancer. The age of patients was generally over 60 years old (61.2%), 50-59 years — 20.4% and up to 49 years — 18.4%. Metastases in the remaining breast were identified by palpation only in 6 (12.2 ± 4.8%) patients, in the rest cases by ultrasound and mammography. Tumor nodes were determined in the form of one or more formations with relatively smooth contours in most cases within 1-2 cm. When enlarged lymph nodes diffuse swelling of the tissue and thickening of the skin were registered. Metastatic formation located at the chest wall and tissue edema was not identified by ultrasonography in 2 (6.45%) cases during primary visit to doctor and in 1 (5.5%) case during visit in 1.5 years. However the diagnosis of the metastatic cancer was based on complex set of factors including the results of thin needle biopsy, evaluation of stage and growth forms of the primary tumor.

Breast cancer with focal fibroadenomatosis or sclerosing adenosis of the second breast was found in 124 patients: 92 were found simultaneously and 32 — in 2-5 years after surgery. Age of women with this combined pathology is mainly reproductive (n = 87 – 70.2%). Differential diagnosis based on palpation was difficult and it was carried out between cyst, nodular fibroadenomatosis and bilateral metastatic cancer. Node with clear boundaries, often with a rim of clarification (as sign of pressing tissue due to expansive growth) is typical for fibroadenoma (FA) on mammogram. Color Doppler ultrasound helps to differential diagnosis of fibrocystic mastopathy by evaluating the tissue density and character of vascularization. In 5.1% of women complex diagnosis was uninformative or misleading.

Multiple as bilateral fibroadenomatosis or sclerosing adenosis pose even greater difficulty for differential diagnosis. Age of the patients is mostly reproductive and perimenopausal (respectively 55.1% and 28.6%). 9 patients (10.7 ± 4.1%) with bilateral synchronous fibroadenomatosis and sclerosing adenosis had a «mirror» shadows on mammographic picture. Target puncture, performed under ultrasound, including use of pistol-needle carried out in 25.5% recealed in all cases glandular cells with varying degrees of proliferation. However, it is impossible to evaluate the malignancy FA as sclerosing adenosis based on the mammography and ultrasound, even with punctate cytology without histological examination. In this situation the trepanobiopsy or stereotactic biopsy is necessary [8].

Proliferative processes of cellular elements of II-III degree in the middle of the menstrual cycle are indication for the surgical removal because it is impossible to predict when it would happen real malignancy [11-13]. In this regard surgical removal of tumor foci in women with primary multiple focal formations (which increases cancer risk) is intended as medical prevention and detection of early cancers (stages 0-1 being synchronous and metachronous neoplasms in respectively 17 ± 3,4% and 26,4 ± 4,3%). We performed 19 breast-saving operations in terms of combined and complex treatment. Patients treated for early forms of cancer, survived the 4-year disease-free period and now are under observation.

Traditional method of surgery treatment of benign nodules and focal formations of unknown origin is partial resection or lumpectomy with urgent histological research. To avoid sectoral resections company SenoRx proposed vacuum device for breast biopsy. After the insertion of trocar into the tissue under ultrasound control vacuum is created and suction of fragmented tissue for biopsy specimens is performed [14]. However, this method leads to a violation of the principles of ablation. Material during strong negative pressure vacuum pollutes the whole expensive system of single use. For the purpose of ablation and complete removal of tumor forations we developed a «method of minimally invasive removal of breast tumors and device for its implementation» (invention patent number 2394521 dated July 20, 2010). After the skin incision of 2 cm and rarefaction of wound edges cryotube is supplied to the pathological focus under ultrasound control. Temperature of –120 C° is created turning formation into «ice ball» with its complete fixation to the tip of the tube. Cryotube with lesions is drawn into special cylinder with the help of handle and cut from the surrounding tissue by coagulation. Method was tested in 15 patients with nodal mastopathy and fibroadenoma including 2 cases with syndrome of microscopic calcified foci and 2 other cases with palpable tumors of unknown origin. The result showed that application of the proposed method is promising and allow removing the pathological focus entirely in one piece. Ultrasound clearly defined boundaries of the frozen tissue. The average time of minimally invasive removal of focus (from skin incision to stiching) was 12 ± 3.0 min, while similar removal of nodules with the use of the apparatus SenoRx takes 1 hour. Our method is less traumatic, reliably fixes the pathological focus, tightens and cuts it at the same time. For its implementation expensive disposable equipment is not required.

Conclusions

1. The growth of bilateral forms with respect to the total number of observed breast cancer patients in the Novgorod region over the past 5 years has increased by 2.15% (mainly due to metachronous cancers) and is asso-

ciated primarily with the introduction of modern radiation techniques on the stages of medical check-up.

2. Proportion of patients identified in the early stage (stage 0-1) can serve as a criterion for the quality of dispensary observation of patients with breast cancer 26 ± 4.6%. However, cancer of the second breast in women who are at the dispensary and detected in III stage of disease still remains high (12 ± 5.6%).

3. Performing MG screening identifies new problem of morphological verification of multiple and bilateral forms of fibroadenomatosis, sclerosing adenosis and other primary-multiple tumors of unknown origin. We developed less invasive way to remove the focus under ultrasound control it is promising approach to clarifying diagnosis and at the same time it is method of prevention of invasive forms of breast cancer.

1. Selezneva T.D. Diagnosis of the second synchronous tumors in patients with breast cancer. Book of abstracts. USRP, 2008. P.5-7.
2. Massao T., Hiroyoshi A., Katsunobu K. et al. Bilateral breast cancer. Acta Med Nagasak, 1991; 36; 1-4:136-40.
3. Safroni L. Aspecte etiopatogenetice ale cancerului primar-multiplu al organellor hormonodependente la femei. Teza de doctor habilitat in medicina. Chisinau, 2007.
4. Veloso V., Maia N., Gomes D et al. Bilateral breast cancer. Eur J Surg Oncol, 1992, 11 (Suppl): 27.
5. Semiglazov V.F., Semiglazov V.V., Kletsel A.E. Non-invasive and invasive breast tumors. St. Petersburg, 2006. 349 p.
6. Rozhkov N.I., Frolov I.M. Clinical and radiological evaluation of primary multiple forms of breast cancer // Tumors of the female reproductive system. 2010. №2. P.21-25.
7. Yermilova V.D. Role of Modern Pathology in the characterization of breast cancer // Practical Oncology - operable breast cancer, 2002. V.3. №1. P.15-20.
8. Selcuk V.Y. Primary multiple synchronous malignant neoplasms of the reproductive system in women // Rus. oncol. journal, 2001. (3): P.18-21.
9. Filyushkin I.Y., Ivanov V.M., Buydenok Y.M. Synchronous breast cancer: clinical features, diagnosis, treatment, prognosis / Tumors of the female reproductive system. 2007. №4. P.14-16.
10. Anderson D.E. Genetic study of Breast cancer: identification of highrisk group. Cancer.1974, 34, 1090-7.
11. Prilepskaya V.N., Shvetsova O.B. Benign breast diseases: principles of therapy // Gynecology. 2000; 2 (6): 201-4.
12. Prokopenko S.P. Interventional Radiology in the diagnosis and treatment of benign breast disease. Questions of Oncology, 2000. 46 (6): 693-8.
13. Serebryakova S.I., Trufanov G.E., Fokin V.A., Yukhno E.A. Magnetic resonance semiotics of fibroadenomas of the breast / Tumors of the female reproductive system, 2010. №2. P.4-9.
14. Rozhkova N.I. Highly efficient energy saving technologies in diagnostic mammology (the 5th anniversary of the Russian Association of mammalogists) / Tumors of the female reproductive system. 2008. №1. P.12-17.