K.S. Loskutova, M.P. Kirillina, A.S. Innokentyeva, T.N. Zharnikova

Male Breast Cancer in the Republic Sakha (Yakutia)

ABSTRACT

Data of pathomorphological and immunohistochemical research of breast cancer at male population of Yakutia are presented in this article. At all male patients BC is revealed in the setting of gynecomastia before metastases in lymph nodes, presented in a structure of infiltrative ductal BC with an immunophenotype of luminal A subtype.

Keywords: male breast cancer, pathomorphology, immunohistochemistry, Yakutia.

INTRODUCTION

The male breast cancer (BC) is the rare disease diagnosed approximately in 1% of all cases of BC. In 2008 in Russia on 52469 new cases of a breast cancer about 500 diseases at men are revealed [2].

BC rarity at men, insufficient acquaintance of doctors to early symptoms of an illness, small awareness of the man's population on possibility of development of a tumor in a mammary gland result in low vigilance of doctors, lack of complex inspection at a gynecomastia and, as a result, to identification of BC at men in later stages in comparison with women [6,8]. Men get sick, on average, for ten years after women, is the most frequent in the 6-7th decades of life though this pathology meets aged from 9 till 90 and more years [8]. Thanks to an anatomic structure of a mammary gland, at men the minimum manifestations of an illness can be revealed even at a usual palpation, however early stages of a cancer are diagnosed only for 34% of patients. Approximately in 20% of supervision the diagnosis of a breast cancer at men at primary address isn't established. In 46,8% of supervision at primary address local distribution of process, from them in 40% of cases - with metastatic defeat more than 3 lymph nodes is noted [4,8]. Most often the tumor is localized in the central departments of gland, more than 2 cm in size, is frequent with existence of metastases in axillary lymph nodes (at 50% of patients). Therefore the increase and consolidation of axillary knots can be the first symptoms of a disease. In 21% of cases patients for the first time address to the doctor apropos is long not healing ulcer in a mammary gland [6]. At 1/3 patients the tumor rather quickly sprouts skin, is connected with people around to fabrics, with the advent of symptoms of "umbilikation", "platform", "a lemon crust", etc. Approximately the areola fold thickening (Krause's symptom), a symptom of "retraction of a nipple" is found in a half of patients at the time of the address. In rare instances

(approximately at every 7th patient) fixing of a tumor to a big pectoral muscle meets [3]. Allocations from a nipple (from serous to bloody) meet rather seldom.

Risk factors of BC at men can be divided into two groups: 1) existence of androgenic insufficiency, for example at a cryptorchidism, a secondary testicular atrophy, at violation of an exchange of androgens and estrogen at chronic hepatopathy, such as cirrhosis, and also at the liver failure caused by chronic intoxication (medicamentous, professional, etc.); 2) excess estrogen stimulation at long reception of preparations of the estrogen (at adenomas, a prostate cancer, at hyperfunction of bark of adrenal glands with obesity, an arterial hypertension and diabetes, etc.) [5]. In particular, explain these frequencies of bilateral changes in chest glands. The synchronous cancer is noted at 2% of patients and more than at a half of them during 1 year — 20 years before detection of a malignant tumor existed the centers of consolidations in chest glands. There are data on such risk factors as racial accessory [15], the ionizing radiation and genetic predisposition to this disease. In pathogenesis of a cancer of chest gland at men many note a role of repeated injuries.

It is considered that at men develops in 30 — 70% of cases of BC against a gynecomastia, in particular its nodal form, thus the risk of transition of a nodal form to BC makes 9,3-12,2% [4]. At 26,3% with the focal gynecomastia forms elements of intraductal proliferation of an epithelium, in 7,9% - atypical ductal proliferation of an epithelium in a varying degree came to light [7]. Are available sported about existence of BRCA1 and BRCA2 at BC at men [9,15]. 7-27% of sick BC of men in the anamnesis had an instruction on existence of a malignant tumor of a mammary gland for direct relatives of the first and second generation.

Because of small number of supervision BC morphology at men is studied absolutely insufficiently, there are no large-scale researches on the analysis of dependence of the forecast of a disease on degree of a histologic malignant index of BC at men. There are ambiguous and inconsistent data on existence for men of lobular and noninvasive forms of a pro-current cancer [8,12].

In literature a number of features of the hormonal status of BC at men is noted: existence of higher level of receptors of an estrogen men, than at women, lack of growth have a receptor - positive tumors with age. Clinically significant levels of receptors of an estrogen are present at a tumor approximately at 75% of patients, and at 43% of patients – receptors of progesterone [4].

MATERIALS AND METHODS

As a material of this research macro - and microscopic preparations of mammary glands of 5 men with BC were used. Histologic processing of the material was carried out by the

standard techniques. Immunohistochemical (IGH) research was conducted with reinstatement of anti-genes under pressure in the Epitop Retrieval Solution pH 6,0 solution with use of monoclonal antibodies of Novocastra (Great Britain), "HercepTest" (Dako A/c, Glostrup, Denmark), Diagnostic Biosystem according to instructions of manufacturing firms. Antigen positive cells and cellular structures were identified on their brown coloring at the light-optical level.

RESULTS AND DISCUSSION

During 2009-13 BC was diagnosed at 5 men. Thus, despite such a small quantity, we note a tendency to growth of the BC incidence rate at men. So, if 1 case was diagnosed in 2009, in 2010-11 – any, in 2012 and 2013 – on 2 cases. Men were aged from 50 till 64 years, from them 4 (80%) – at the age of 50-54 years (54,6±3,76). It is a decade earlier, than is noted by other researchers (in 6-7 decades of life). 4 (80%) BC are revealed at representatives of a indigenous nationality (yakuts). All men had no excess body weight, didn't abuse alcohol.

In total BC had a histologic structure of an infiltrative ductal cancer, with existence out of a tumor of changes, characteristic for a gynecomastia. At 4 (80%) the sizes of a tumor were 2,0 cm and less, with localization in an around the nipple zone. At 1 man at the age of 64 years the big size of a tumor – 6,5 cm is noted.

One of the microscopic criteria characterizing biological behavior of a carcinoma of a mammary gland is their histologic malignant degree. In our research in 4 cases (80%) GI malignant degree, in 1 case (20%) – GII degree is established. Thus, at 80% of patients the favorable factor of 5-year survival is established. In a number of researches direct link with the forecast of a disease is established: the tumor malignant degree is higher, the survival period is shorter. Patients with a tumor of the I malignant degree survive 5 years and more after operation in 75% of supervision, more than 10 years — in 45%; at tumors II and III malignant degrees — in 53 and 27% and in 31 and 18% of supervision respectively [4].

In the regional lymph nodes metastases aren't found in all men (100%). It corresponds to results of a number of researches in which distinct direct dependence between histologic degree of a malignant of BC at men and identification frequency the regional metastases is established [1]. And existence of metastases in lymph nodes has the most significant predictive value [13].

All studied BC had infiltrative growth. At IGH with anti-genes to a muscular aktin of SMA total absence of a layer the mioepithelial cells is revealed, at their existence out of a zone of tumoral growth, by places with a gynecomastia picture. Studying E-kadkherin - protein the epithelial intercellular adhesive contacts, the transmembran glycoprotein providing homotypic

adhesion in the epithelial fabrics is of interest. This gene is responsible for safety of cellular communications in the epithelial tissues of adults, and also acts as a supressor of a fabric invasion. There are data that decrease in quantity E-kadkherin in a number of carcinomas, is an adverse predictive factor and happens mainly at the transkriptsion level [11]. In our research in 3 of 5 BC (60%) lack of expression E-kadkherin is revealed. Also there was no reaction with a bazal keratin of CK5/6. Thus, 100% of the studied tumors expression a pan-cytokeratin of PCK and granular an epithelial membrane anti-gene of EMA (figure 1).

HER2/neu is the most important independent factor of the forecast at BC, including at men. According to Bloom et al. [16] HER2 hyperexpression at IGH research was revealed only in 1 case from 58 supervision (1,7%). According to the European institute of Oncology (European Institute of Oncology, IEO), the frequency of an expression of a gene of Her2/neu makes 15% [12]. In our research the hyper expression of HER2 is established in 1 case from 5 supervision (20%) (figure 2). .

All BC investigated by us were receptor - positive. The average total point of the assessment of positive cells and intensity of IGH-reaction rated 5,6 (ER estrogen receptors) (figure 3) and 6,6 (PGR progesterone receptors) (figure 4). Thus we revealed the growing tendency of receptor - positive tumor cells at older ages, as ER (diagram 1), and PGR (diagram 2).

The criterion of an indicator of proliferative activity of Ki-67 has already been applied at breast cancer of women, however its role in the forecast of male cancer hasn't precisely been found out yet and demands further studying. In total BC in our research had very low proliferative activity (the Ki-67 index less than 14%), and also low indicators of existence of a mutant gene-supressor p53.

CONCLUSIONS:

1. BC at men, despite increase in frequency of occurrence is rare tumor.

2. Under the timely complex inspection of doctors, BC at men can be revealed in early stages before metastases of lymph nodes.

3. The infiltrative pro-current cancer is the BC main histologic form at men, in the presence of gynecomastia as a background process.

4. 80% of cancer of mammary gland have low histologic malignant degree G1.

5. According to molecular and genetic classification BC immunophenotype at men corresponds luminal A (80%) and B (20%) subtypes of BC that allows to use the complex

treatment with inclusion of hormonal therapy with anti-estrogen, and also aromatase inhibitors at 80% of patients.

6. In studying of this disease at men it is necessary to consider challenges demanding further studying and accumulation of supervision, large-scale researches for studying of risk factors, predictive importance of biological markers, ethnic and genetic features.

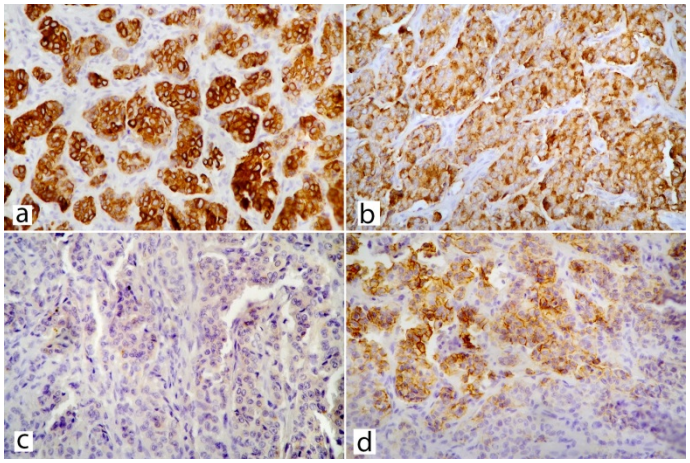

Figure1. The patient Zh., 54. Infiltrative ductal cancer, malignance degree G2: a - bright membranous and cytoplasmatic expression (PanCK, clone 5D3 fnd LP34); b - moderated granular cytoplasmatic expression of epithelial-membranous antigen (EMA, clone GP1.4 Ber-EP4); c - absence of expression of basal keratin (Cytokeratin 5/6, clone D5/16B4); d - loss E-cadherin by tumor cells: groups of tumor cells with remained membranous antigen expression in a zone of "thawing" membranes with transition in fields of total absence of expression (E-cadherin, clone NCH-38) (x200).

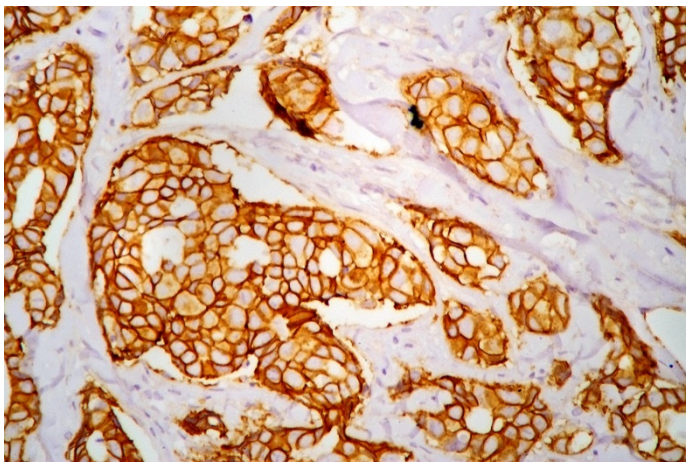

Figure 2. The patient S., 52. Hyperexpression of oncoprotein Her/2-neu (+3) in tumor cells of infiltrative ductal cancer (x200)

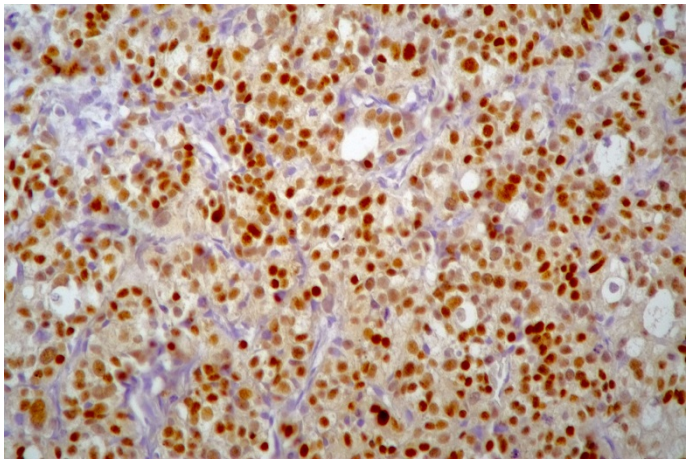

Figure 3. The patient Ya., 64. Estrogen-positive infiltrative ductal mammary gland cancer (ER, clone1D5): a share of stained cells in scores =5 (from 2/3 to 100 % of cages), intensity of expression in scores =2 (strong nuclear stain), total score =7 (X200).

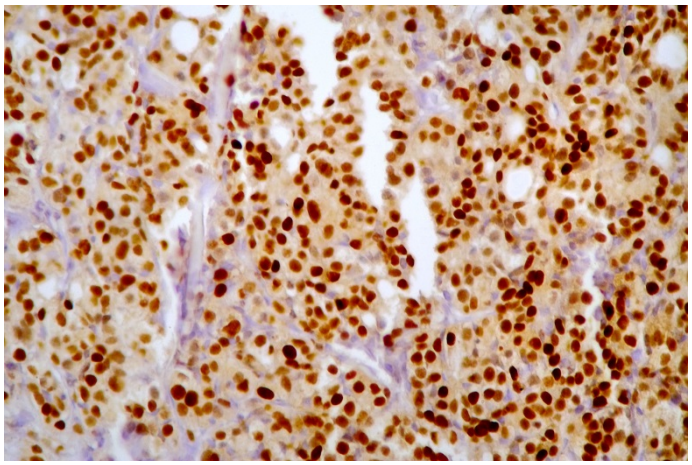

Figure 4. The patient B., 64. Progesterone-positive infiltrative ductal mammary gland cancer (PGR, clone PgR636): a share of stained cells in scores =5 (from 2/3 to 100 % of cages), intensity of expression in scores =2 (strong nuclear stain), total score =8 (X200).

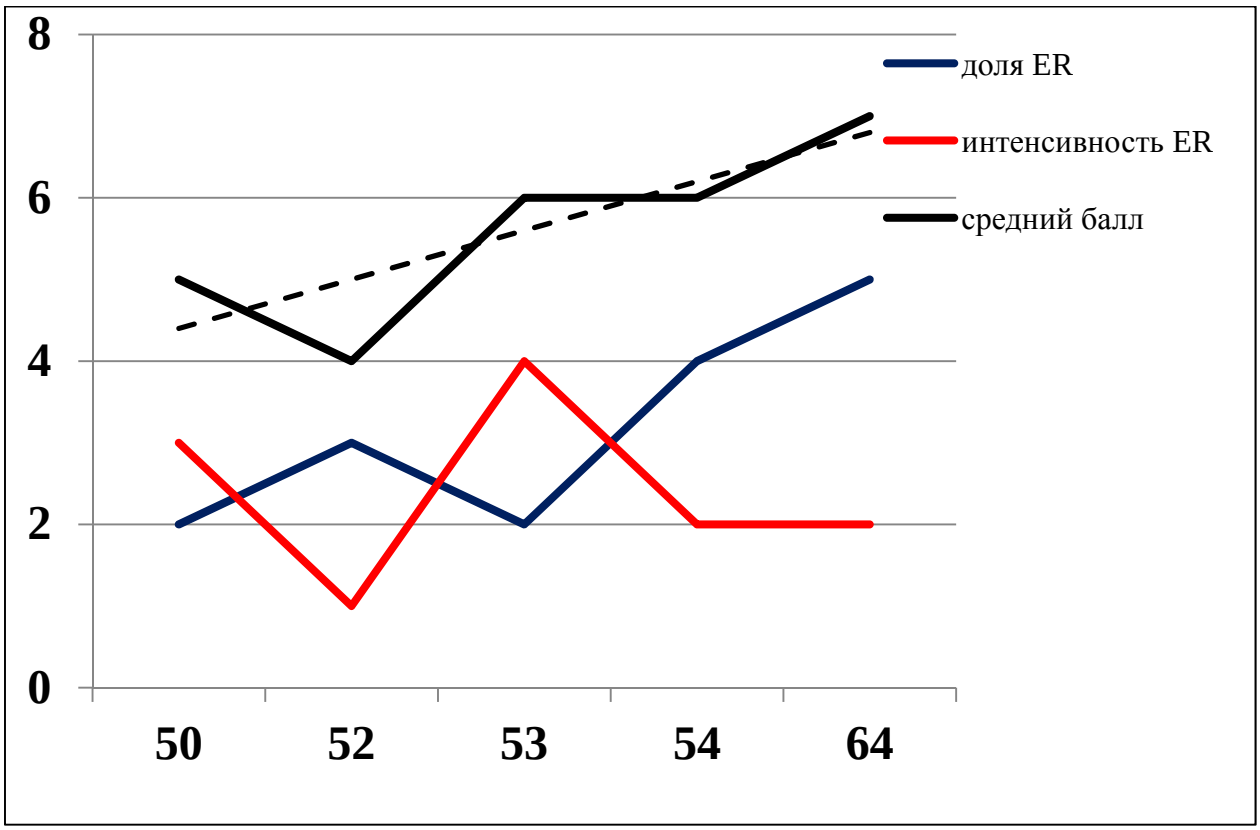

Diagram 1. The level of expression ER with aging in male breast cancer.

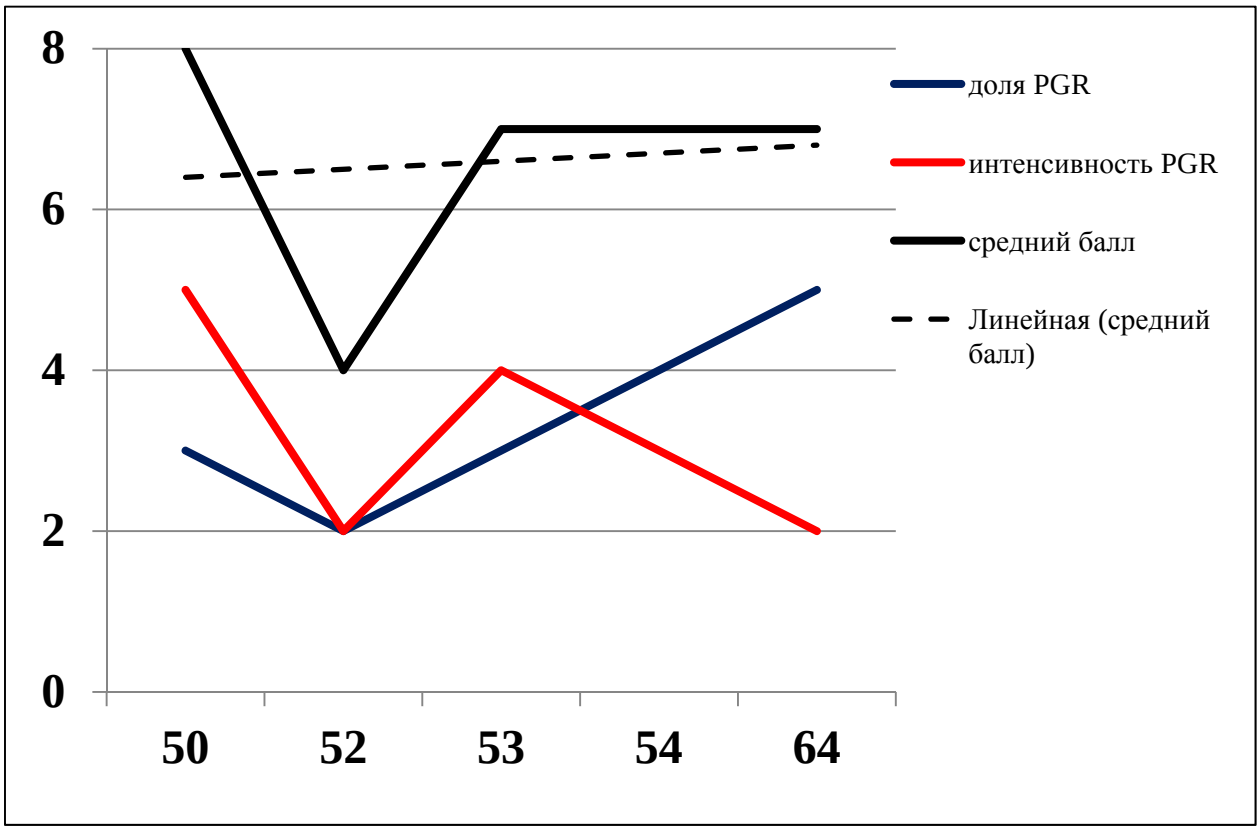

Diagram 2. The level of expression PGR with aging in male breast cancer.

References:

1. Akimov O. C. Morfologicheskaya I klinicheskaya kharakteristika raka molochnoi jelezy u mujchin [Morphological and clinical characteristics of breast cancer in men]: abstr. dis.... cand. med. sciences.- SPb. - 1992. – P. 23.
2. Davydov M. I. Zabolevaemost' zlokachestvennymi obrazovaniyami naselenia Rossii I stran SNG v 2008 g. [Incidence of malignant tumors in the population of Russia and SIC countries in 2008] / M. I. Davydov, E. M. Axel // Bulletin of the Russian oncological scientific center named after N. N. Blokhin RAMS. 2010. - № 2(21). (Mgr.1). – P. 55-56.
3. Klinicheskaia mammologia; Prakticheskoe rukovodstvo [Clinical mammography: Practical guide] / M. I. Davydov, B. N. Lyagina.- M: ABC press. - 2010.- P. 110-111.
4. Letyagin B. N. Opukholi molochnykh jelez u mujchin [Breast tumors at men] / V.P. Letyagin // Mammology. -2006, №.2.- P. 13 - 16.

Letyagin V. P. Opukholi molochnykh jelez u mujchin [Breast Cancer in men] / V.P. Letyagin // Bulletin of the Russian oncological scientific center named after N. N. Blokhin. - 2000. - №4 (11). - P. 58-62.

Makarenko N. P. Rak molochnykh jelez u mujchin [Breast cancer in men] / N. P. Makarenko // Russian medical journal. 1998. So 6. № 10. P. 648-650.

5. Novitskaya T. A. Ginekomastia: kliniko-morfologicheskie i molekulyarno-biologicheskie osobennosti [Gynecomastia: clinical-morphological and molecular biological features] / T. A. Novitskaya, I.N. Chuprov, E.E. Topuzov, R.L. Aristov // Oncology. - 2012.- №4 (23). - P. 39-41.
6. Problema raka molochnoi jelezy u mujchin [The problem of breast cancer in men] / A.V. Bykov, I. K. Collars, J. C. Vishnevskaya [et al.] // Siberian Oncology journal. - 2011.- №4 (46). - P. 64-68.
7. CYP17 promoter polymorphism and breast cancer risk among males and females in relation to BRCA2 status/ K. Gudmundsdottir, S. Thoracius, J.G. Jonasson [et al.] // Br. J. Cancer. – 2003.-V.88. – P. 933-936.
8. BRCA2 germline mutations in male breast cancer cases and breast cancer families. / F.J. Couch, L.M. Farid, M.L. DeShano [et al.] // Nat. Genet. – 1996. – V.13(1). – P. 123-5.
9. Epithelial-mesenchymal transitions in development and disease /J.P. Thierry, H. Acloque, R.Y. Huang, M.A. Nieto // Cell. - 2009. - V.5(139). – P. 871–90.
10. Multidisciplinary meeting on male breast cancer: summary and research recommendations. / L.A. Korde, J.A. Zujewsri, L. Kamin [et al.] //J. Clin. Oncol.- 2010. – V.28 (12). – P. 2114-22.
11. Paget's disease arising near a male areola without an underlying carcinoma / T.Takeuchi, M. Komatsuzaki, Y. Minesaki [et al.]//J. Dermatol. – 1999. – V.26(4). – P. 248-52.
12. Recognizing features that are dissimilar in male and female breast cancer: Expression of p21Waf1 and p27Kip1 using an immunohistochemical assay / G. Curigliano, M. Colleoni, G. Renne [et al.] // Ann. Oncol. - 2002. - V.13. - P. 895-902.
13. Similar prevalence of founder BRCA 1 and BRCA 2 mutations among Ashkenazi and non-Ashkenazi men with breast cancer: Evidence from 261 cases in Israel, 1976–1999/ G. Chodick, J.P. Struewing, E. Ron [et al.] // Eur. J. Med. Genet. - 2008. - V.51. - P.141–147.

14. Status of HER-2 in male and female breast carcinoma/ K.J. Bloom, H. Govil, P. Gattuso [et al.] // Am. J. Surg. – 2001/ - V.182. – P. 389-392.

Authors:

ЛОСКУТОВА Кюнняй Саввична – к.м.н. гл. внештат. патологоанатом МЗ РС(Я), зав.ПАО ГБУ РС (Я) «РБ №1-НЦМ», зав. лаб. ФГБНУ «ЯНЦ КМП», lockutovaks@mail.ru; **КИРИЛЛИНА Мария Петровна** – к.б.н., зав. учеб.-науч. лаб. Клиники МИ ФГАОУ ВПО СВФУ им. М.К. Аммосова, kirillinamp@ mail.ru; **ИННОКЕНТЬЕВА Александра Степановна** – зав. отделением биопсий РБ№1-НЦМ; **ЖАРНИКОВА Татьяна Николаевна** – к.м.н., зав. отд. ГБУ РС (Я) «ЯРОД», н.с. ФГБНУ «ЯНЦ КМП», zharnikova_tn@mail.ru.

LOSKUTOVA Kunnjay Savvichna - cand. med. sciences, chief non-staff pathologist of MH RS (Ya), head of the pathologic department SBI RS (Ya) «RH №1-NCm», head of the laboratory FSBSI «YSC CMP», lockutovaks@mail.ru <mailto:lockutovaks@mail.ru>;
KIRILLINA Maria Petrovna – cand. boil. sciences,head of lab. Clinics of MI FSAEI HPE NEFU of M.K.Ammosov, kirillinamp@ mail.ru;
INNOKENTIEVA Alexandra Stepanovna – head of the department of biopsy RH№1-NCM;
JARNIKOVA Tatyana Nikolaevna – cand. med. sciences, head of the department SBI RS (Ya) «YROD», research ass. FSBSC “YSC CMP”, zharnikova_tn@mail.ru.