

BREAST CANCER SURVIVORS. EARLY DIAGNOSIS – SUCCESSFUL TREATMENT – QUALITY OF LIFE: MULTIDISCIPLINARY APPROACH



T.F. TATARCHUK

MD, professor, corresponding member of NAMS of Ukraine, deputy director for research work, Chief of the Endocrine Gynecology Department, SI "Institute of Pediatrics, Obstetrics and Gynecology, NAMS of Ukraine"

ORCID: 0000-0002-5498-4143

I.I. SMOLANKA

MD, professor, Chief oncosurgeon of the Ministry of Health of Ukraine, head of the Scientific and Research Department of Breast Tumors and its Reconstructive Surgery, National Cancer Institute of the NAMS of Ukraine

O.V. POPKOV

PhD, gynecologist

ORCID: 0000-0001-6306-5117

Contacts:

Tetiana F. Tatarchuk

Institute of Pediatrics, Obstetrics and Gynecology, NAMS of Ukraine, Endocrine Gynecology Department Maiborody str., 8, 04050, Kyiv
tel.: +38 (044) 483 80 87;
+38 (044) 272 10 72
e-mail: ipag.gyn@femina-health.org

INCIDENCE AND EPIDEMIOLOGY

In 2012 according to a clinical data the estimated age-adjusted annual incidence of breast cancer (BC) in 40 European countries was 94.2/100 000 and the mortality 23.1/100 000 (including Ukraine with leading position of BC in female population) [1]. This kind of malignant tumors is still the most commonly diagnosed female cancer.

According to statistics from the International Agency for Research on Cancer (IARC), there are approximately 29 million cancer survivors worldwide as of 2008 [2]. In the United States, there are an estimated 14 million cancer survivors as of 2014, a figure that is expected to increase to approximately 18 million in the next 10 years [3]. Over three million women have a history of BC, which constitutes 41 percent of the population of female cancer survivors [3]. The vast majority of BC survivors are women and most of them will achieve long-term disease-free survival [4]. So it is evident that this aspect of cancer treatment broaches a question in each country and concerns every patient after heavy blow of cancer diagnosis.

Unfortunately, there is a lack of clear evidence for what constitutes best practices in caring for patients with a history of cancer, and this contributes to wide variation in care [5]. Gynecologist is a doctor of first contact with a patient with a case of BC. Unfortunately, particular risk factors for BC, its stage, and treatment protocols, as well as the features of the management of patients who receive treatment, limit the possibility of assistance from gynecological service. Doctors of this service and volunteers could play a major role in helping to restore the health, both physical and psychological.

Diagnosis of BC is widely represented in women with some risk factors such as exposure of endogenous end exogenous estrogens, some genetic predispositions, low parity and others. Consumption of fat, alcohol contributes into the rising incidence of BC last decades. Cases of

BC occur mostly after 50 years (with the quarter of them diagnosed in the interval 35–50 years and less than 5% in women younger 35. Genetic factors demonstrate connection BC with other glandular cancers: thyroid, pancreatic, colorectal ones and also with ovarian cancer. Genetic BRCA1 and BRCA2 polymorphism, family history allows supposing BC in 10% of women in risk group.

BC in males is rare, contributing to ~1% of all cases. The major risk factors include clinical disorders carrying hormonal imbalances (especially gynecomastia and cirrhosis), radiation exposure and, in particular, a positive family history and genetic predisposition [5]. Especially great role radiation played in Ukraine due to Chernobyl atomic station catastrophe in 1986. The radioactive pollution triggers a pale of problems with thyroid gland disorders, lack of immune response and raised the quantity of all kind of cancers. It shows dramatically growth in BC especially in younger female group of population.

The estimated 5-year prevalence of BC in Europe in 2012 was 1 814 572 cases [6]. Prevalence is increasing, as a consequence of increased incidence and due to improvements in treatment outcomes. In most Western countries, the mortality rate has decreased in recent years, especially in younger age groups, because of improved treatment and earlier detection [7, 8]. However, BC is still the leading cause of cancer-related deaths in European women.

Leading group of primarily diagnosed BC person varies from region to region due to the difference of initial state of health and structure of female population, approaches to diagnostics (and access of medical care) and treatment. The most vulnerable group of women is also different through the world. If in the USA women in age interval 50–75 years are at risk, at the same time in Ukraine (and Eastern Europe) young women with firstly diagnosed BC are more regu-

larity diagnosed. Including risk factors and burden of age it is possible to describe portrait of a patient with most common health disturbances.

In 1999-2007 in Europe the EUROCARE-5 study showed that 5-year related survival for adult ≥ 15 years with BC was 82% in Western and 74% in Eastern Europe and 79% in UK and Ireland. Highest rate of survivors was in Northern Europe except Denmark. Older group of population showed lower rate of survival (86% in age 15–44 years and 72% in age ≥ 75 years. Conclusions pointed out that low rate of survivals in Eastern part of Europe based on advanced stage at diagnosis and/or suboptimum access to adequate care [9]. On average, 65 and 75 year old patients have an anticipating life expectancy of 20 and 12 years respectively [10].

It is important in what stage diagnosis firstly was established (Table 1).

TABLE 1. STAGING OF BC ACCORDING TO AMERICAN JOINT COMMITTEE ON CANCER (AJCC) STAGING MANUAL 7TH EDITION

Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
Stage IIIB	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIC	T4	N2	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

* T1 includes T1mi

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB

Due to data of epidemiologists majority of women are diagnosed with BC at I or II stage. In the PATH's Ukraine Breast Cancer Assistance Project it was shown that level of I stage diagnosis was established from 3.5% (Kherson) and 35% (Kyiv and Odessa). Mortality data from the cancer registry show a mixed picture and varies from 23.2 to 36.2% [11].

Predisposed state of health of female with firstly registered BC is also a point of interest. According to the state of health in European Community cardiovascular disease affected the group of adults 35–65 years right after the group of elders after 65 years. This is the main cause of death in Europe. The second place of causes allows to cancers (in women those are breast and lung cancer). Chronic diseases are widely common and well-managed such as diabetes, chronic kidney disease and dyslipidemia. In Ukraine by data of WHO global health observatory country views in these groups ischemic heart

diseases and cardiovascular pathology are leading causes of death. The level of diabetes is comparable to level of ovarian cancer as a cause of death in female group. High levels of alcohol and tobacco consumption lead to worsen of existing pathology.

As it was pointed below, the diagnosis of BC catches a person usually at I or II stage (Figure).

TREATMENT

In a treatment of BC different methods are used in a combination. Primary surgery and systemic approaches include radiation therapy, hormone therapy and chemotherapy. Important role belongs to a chemotherapy and post-treatment after surgical intervention. With the aging population and increasing incidence of BC with the age it is essential to study feasibility toxicity and efficiency in cancer therapy in this population. National American treatment protocols don't set an upper age limit for the use of chemotherapy, but acknowledge that comorbid medical conditions and life expectancy must be considered when prescribing chemotherapy [12]. Many of comorbid states are well-known and well-controlled and treated [13].

As an alternative way to avoid influence of estrogens on the primal hearth or to improve the results of surgery ovariecto-

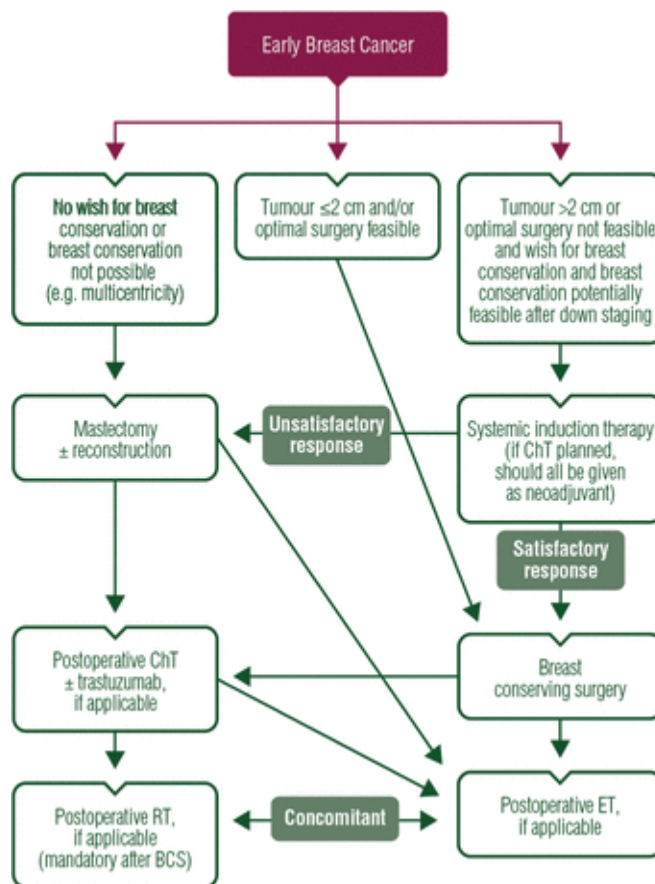


FIGURE. EARLY BC TREATMENT ALGORITHM (EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY CLINICAL PRACTICE GUIDELINES)*

* Cht – chemotherapy; BCS – breast-conserving surgery; ET – endocrine therapy; RT – radiotherapy

my is an alternative way to use luteinizing hormone-releasing hormone analogs (Figure).

The European Registration of Cancer Care (EURECCA) study compared the treatment patterns of 119 125 patients aged 70 and older in Belgium, Ireland, Netherlands, Portugal, Poland and UK, who were diagnosed with non-metastatic (stage I, II or III) BC between 2000 and 2014. The study also compared the number of patients alive five years after BC diagnosis. Investigation demonstrates difference in BC survivors of old patients in dependence of clinical approach and raised new direction of finding optimal way of treatment [14]. In this way, treatment of patient with BC is characterized with different negative effect on them. Primary surgery may include conservative methods or mastectomy (mono- or bilateral).

Effects of surgical treatment are different. Postmastectomy pain syndrome is caused by direct nerve injury (e.g., severance, compression, ischemia, stretching, and retraction) during the BC operation or from subsequent formation of a traumatic neuroma or scar tissue [15]. Different types of sensory disturbances (e.g., tingling, burning, and numbness) can result [16]. BC operations can damage the brachial plexus, intercostobrachial, lateral cutaneous branch of the second intercostal, long thoracic, and medial and lateral pectoral nerves that innervate the breast, chest wall, and ipsilateral extremity [17]. In particular, surgical procedures in the upper outer quadrant of the breast and axilla, where major nerves traverse the operative field, are particularly vulnerable to nerve injury. In addition local radiation treatments and neurotoxic systemic therapy (e.g., taxanes, platinum agents, vinca alkaloids) may also exacerbate postmastectomy pain syndrome [18].

Chemotherapy is recommended in the vast majority of triple-negative, HER2-positive BC and in high-risk luminal HER2-negative tumors (evidence level I, A). The absolute benefit from chemotherapy is more pronounced in ER-negative tumors [19, 20]. In ER-positive tumors, chemotherapy at least partially exerts its effect by induction of ovarian failure [21, 22]. The most frequently used regimens contain anthracyclines and/or taxanes, although in selected patients the CMF therapy (cyclophosphamide, methotrexate, and fluorouracil) may still be used. Four cycles of doxorubicin and cyclophosphamide are considered equal to six cycles of CMF. For most patient use of anthracycline-based therapy followed taxan-trastuzumab therapy is the most preferable. Use of each may lead to short-term or long-term complications negative effects and impacts on health. Trastuzumab causes often neutropenia, fever, variation in systemic arterial pressure, dry eye syndrome, insomnia, anxiety. Paclitaxel mostly cause neutropenia and toxic impact on bone marrow, widely registered vascular reactions and series of gastrointestinal complications. The reversible alopecia is registered in 70–80% of patients.

Cancer patients who are undergoing chemotherapy have an increased risk of developing cardiovascular complications, and the risk is even greater if there is a known history of heart disease. Among the serious clinical cardiac complications that have been reported are: arrhythmias,

myocardial necrosis causing a dilated cardiomyopathy, vasoocclusion or vasospasm resulting in angina or myocardial infarction. A wide range of chemotherapy agents have been associated with cardiotoxicity [23]. The anthracyclines and related compounds (doxorubicin, daunorubicin, idarubicin, epirubicin, and the anthraquinone mitoxantrone) are some of the most frequently implicated agents [24]. Specialists of Abramson Cancer Center of the Pennsylvania University has conducted investigation which main purpose was to review the evidence on the incidence of long-term cardiac or pulmonary toxicity secondary to chemotherapy, radiotherapy, or trastuzumab in symptomatic and asymptomatic cancer survivors. The investigation demonstrates an increased incidence of cardiac and/or pulmonary dysfunction in observed cancer survivors. It is needed to identify high-risk patients, and to determine the optimal screening strategies and subsequent treatment [25]. Some authors pointed out the role of troponin as a predictor of cardiac tissue damage [26].

Endocrine therapy is indicated in all patients with detectable estrogen receptors (ER) expression (defined as $\geq 1\%$ of invasive cancer cells) irrespective of the use of chemotherapy and/or targeted therapy (evidence level I, A). The choice of agent is primarily determined by the patient's menopausal status. Other factors include differences in efficacy and side-effect profiles.

All ER-positive patients need an ovarian suppression. The SOFT trial (Suppression of Ovarian Function Trial) demonstrated no significant overall disease-free survival improvement in patients undergoing ovarian suppression. Treatment effect was most pronounced among those treated with adjuvant chemotherapy. Less clear is the value of combining ovarian suppression and AI, as contradictory results were obtained in the ABCSG-12 and combined SOFT-TEXT trials (evidence level I, C) [27, 28]. Combination of ovarian ablation and tamoxifen in ER-positive patients is at least as effective as CMF type chemotherapy and may be used as an alternative (evidence level II, A) [29, 30]. The optimal duration of ovarian suppression is not known, although it is usually administered for 2–5 years (evidence level V, B).

Use of tamoxifen is associated with an increased risk of endometrial hyperplasia, endometrial cancer and uterine sarcomas [31–33]. Some reports declare that patients who use higher dosage of tamoxifen (40 mg daily) are more prone to develop more biologically aggressive tumors [34]. In one early study of the National Surgical Adjuvant Breast and Bowel Project, the rate of endometrial cancer occurrence among tamoxifen users who were administered 20 mg/d was 1.6 per 1 000 patient years, compared with 0.2 per 1 000 patient years among control patients taking a placebo [33]. In this study, the 5-year disease-free survival rate from BC was 38% higher in the tamoxifen group than in the placebo group, suggesting that the small risk of developing endometrial cancer is outweighed by the significant survival benefit provided by tamoxifen therapy for women with BC [31]. Continuation of tamoxifen therapy for 10 years further reduced the risk of BC recurrence and mortality [35].

For patients with contraindications to tamoxifen, a gonadotropin-releasing hormone (GnRH) agonist in combination with an aromatase inhibitors (AI) should be used. In rare cases where both tamoxifen and AI are not tolerated, a GnRH agonist alone may be considered. The role of GnRH agonists in preventing chemotherapy-related ovarian failure has been recently supported by the efficacy data (less premature ovarian failures and more pregnancies) from the POEMS trial (ER-negative patients) and safety data from TEXT trial (ER-positive patients) (evidence level II, B) [28, 36]. However, due to contradictory results from previous trials, the decision must be taken in a case-by-case manner and after careful discussion with the patient regarding benefits and risks of such an approach postmenopausal patients: AI (both non-steroidal and steroidal) and tamoxifen are valid options. The recently published ATLAS study demonstrated an advantage of 10 years rather than 5 years of tamoxifen. With this in mind, extended adjuvant therapy should be discussed with all patients, except the ones with a very low risk, although the optimal duration and regimen of adjuvant endocrine therapy is currently unknown (evidence level I, C) [35].

At this aspect of treatment is asked for more precise attention. It is fact that use of tamoxifen is associated with an increased risk of thromboembolic complications and endometrial hyperplasia (including endometrial cancer). Caution should be exercised in patients with conditions predisposing to this sequel. Appropriate diagnostic tests should be carried out in those presenting with symptoms that are suggestive of these complications. Patients on tamoxifen should be advised to avoid the use of strong and moderate CYP2D6 inhibitors (although there are no unequivocal data on their detrimental effects). If such drugs cannot be replaced, a switch to alternative treatment, i.e. AI, should be considered (evidence level IV, B) [37, 38]. Patients undergoing ovarian suppression and those taking AI, are at an increased risk of bone loss and should be advised to have adequate calcium and vitamin D3 intake. In addition, periodic assessment of their bone mineral density (by dual energy X-ray absorption scan) should be undertaken (evidence level I, A).

PREVENTION

Due to the changed treatment regime and earlier diagnosis and effective treatments in order to prevent recurrence the number, as was mentioned above, the number of BC survivors has improved within the last decades due to earlier diagnosis and effective treatments in order to prevent recurrence [39]. By 2024, over 18 million cancer survivors will be alive in the United States alone [43]. It is necessary to touch all aspects of treatment, when the main protocol is completed. It is always helpful if practitioner is not only professional but supportive. Patient should know that right treatment can reduce the risk of recurrence on 25%. Unlike other countries, in Ukraine, a small number of support groups for patients and communities help patients face the diagnosis correctly, and continue to live on. At the first stage it is necessary to involve family members in helping first aid. Given the risk factors, according to the recommendations of American Cancer Society, it is use-

ful to reduce or refuse alcohol consumption, avoid smoking or reduce number of cigarettes. Fat consumption is also has to be reduced. High body mass index is associated with postmenopausal BC and it is recommended to decrease body mass index to appropriate level.

One of the plenty of recommendation is given below at Table 2.

It is necessary to dwell separately on the methods of weight loss. Keep in mind that patients are in a difficult psychological condition, experiencing anxiety, anger, confusion, and often depression. It is necessary to look more precise on the methods of weight loss. Keep in mind that patients are in a difficult psychological condition, experiencing anxiety, anger, confusion, and often depression. To insist on the immediate weight loss (to reduce risk) is not necessary. Especially worth taking into account the dietary recommendations that some fat burning drugs such as bitter orange and green coffee extracts can cause heart palpitations, anxiety, and arrhythmia. Intake of antioxidants should be recommended after primary therapy.

In follow up guidelines, routine physical examination with a careful taking history has been the most valuable means of detecting BC recurrence. The European Society for Medical Oncology (ESMO) recommends regular visits every 3 to 4 month in the first 2 years, every 6 month from years 3 to 5 and annually thereafter. "In contrast", the American Society of Clinical Oncology (ASCO) recommendation for physical examinations is every 3 to 6 month for the first 3 years, every 6 to 12 month for years 4 and 5 and annually thereafter [40]. Based on the evidence, mammographic surveillance remains the principal examination in detecting curable recurrences and improving survival. ESMO suggests ipsilateral (after breast-conservation surgery) and contralateral mammography every 1 or 2 years and ASCO recommends a post-treatment mammogram 1 year after the initial mammogram and at least 6 months after completion of radiation therapy. According to ESMO, in the follow-up of patients on endocrine therapy, routine blood tests are usually indicated due to the potential side-effects of these drugs namely in the lipid profile. Furthermore, for patients on tamoxifen, an annual gynecological examination (by a gynecologist experienced) is recommended [41].

Several approaches have been explored for screening asymptomatic women using tamoxifen for abnormal endometrial proliferation or endometrial cancer. Correlation is poor between ultrasonographic measurements of endometrial thickness and abnormal pathology in asymptomatic tamoxifen users because of tamoxifen-induced subepithelial stromal hypertrophy [42]. In asymptomatic women using tamoxifen, screening for endometrial cancer with routine transvaginal ultrasonography, endometrial biopsy, or both has not been shown to be effective [43–45]. Although asymptomatic postmenopausal tamoxifen-treated women should not have routine testing to diagnose endometrial pathology, sonohysterography has improved the accuracy of ultrasonography in excluding or detecting anatomic changes, when necessary [46]. There is an increased risk of endometrial polyp formation secondary to tamoxifen use for both premenopausal and postmenopausal women [47].

TABLE 2. DIET, NUTRITION AND PHYSICAL ACTIVITY AND BC SURVIVAL*

	Timing of exposure assessment	BEFORE DIAGNOSIS				LESS THAN 12 MONTHS AFTER DIAGNOSIS				12 MONTHS OR MORE AFTER DIAGNOSIS			
		DECREASES RISK		INCREASES RISK		DECREASES RISK		INCREASES RISK		DECREASES RISK		INCREASES RISK	
		Exposure	Outcome	Exposure	Outcome	Exposure	Outcome	Exposure	Outcome	Exposure	Outcome	Exposure	Outcome
STRONG EVIDENCE*	Convincing												
	Probable												
LIMITED EVIDENCE	Limited-suggestive	Physical activity	All mortality BC mortality	Body fatness	All mortality BC mortality ² 2nd BC			Body fatness	All mortality BC mortality ² 2nd BC	Physical activity	All mortality	Body fatness	All mortality
		Foods containing fibre	All mortality	Total fat	All mortality					Foods containing fibre	All mortality		
				Saturated fatty acids	All mortality					Foods containing soy	All mortality		
	Limited-no conclusion ¹	Fruits, vegetables, foods containing folate, foods containing soy, carbohydrate, glycaemic index, glycaemic load, protein, dietary supplements, alcoholic drinks, dietary patterns, underweight, body fatness (premenopause), adult attained height, energy intake				Foods containing fibre, carbohydrate, protein, total fat, saturated fatty acids, alcoholic drinks, physical activity, underweight, body fatness (premenopause), adult attained height, energy intake				Fruits, vegetables, foods containing fibre, foods containing folate, foods containing soy, carbohydrate, glycaemic index, glycaemic load, protein, total fat, saturated fatty acids, alcoholic drinks, dietary patterns, physical activity, body fatness, underweight, height, energy intake			
STRONG EVIDENCE	Substantial effect on risk unlikely												

* Breast cancer survivors report 2014. Continues update project.

All mortality - all cause mortality; BC mortality - breast cancer mortality; 2nd BC - second primary breast cancer.

STRONG: Evidence strong enough to support a judgement of a convincing or probable causal relationship and generally justify making recommendations.

LIMITED: Evidence that is too limited to justify making specific recommendations.

¹ Includes various exposure-outcome combinations where evidence was available but too limited to draw conclusions. For more details of the outcomes related to the exposures listed here, see the full Breast Cancer Survivors SLR

² Postmenopause only

The American college of obstetricians and gynecologists (ACOG) Committee opinion made in 2014 these recommendations for the patients who use tamoxifen therapy:

- ☞ Tamoxifen use may be extended to 10 years based on new data demonstrating additional benefit.
- ☞ Women taking tamoxifen should be informed about the risks of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas. They should be encouraged to promptly report any abnormal vaginal symptoms, including bloody discharge, spotting, staining, or leucorrhoea.
- ☞ Any abnormal vaginal bleeding, bloody vaginal discharge, staining, or spotting should be investigated.
- ☞ Postmenopausal women taking tamoxifen should be closely monitored for symptoms of endometrial hyperplasia or cancer.
- ☞ Premenopausal women treated with tamoxifen have no known increased risk of uterine cancer and as such require no additional monitoring beyond routine gynecologic care.
- ☞ Unless the patient has been identified to be at high risk of endometrial cancer, routine endometrial surveillance has not proved to be effective in increasing the early detection of endometrial cancer in women using tamoxifen. Such surveillance may lead to more invasive and costly diagnostic procedures and, therefore, is not recommended.
- ☞ Emerging evidence suggests the presence of high-risk and low-risk groups for development of atypical hyperplasia with tamoxifen treatment in postmenopausal women based on the

presence or absence of benign endometrial polyps before therapy. Thus, there may be a role for pretreatment screening of postmenopausal women with transvaginal ultrasonography, and sonohysterography when needed, or office hysteroscopy before initiation of tamoxifen therapy.

- ☞ If atypical endometrial hyperplasia develops, appropriate gynecologic management should be instituted, and the use of tamoxifen should be reassessed. If continued use of tamoxifen therapy is advised and the risks are accepted by the patient, hysterectomy should be considered in women with atypical endometrial hyperplasia. Tamoxifen use may be reinstated following hysterectomy for endometrial carcinoma in consultation with the physician responsible for the woman's breast care.

Finally, for patients on AI, regular bone density evaluation is advised. According to ASCO, in asymptomatic patients, other laboratory or imaging tests (e.g., blood counts, chemistry tests, chest X-rays, bone scans, magnetic resonance imaging, liver ultrasound exams, computed tomography or any tumor markers) are not recommended for routine BC follow-up.

Last but not least, the follow up should not only focus in cancer surveillance but also in late-treatment complications such as psychosocial issues [48]. As more research is completed with large cohorts that permit subgroup analyses and with longitudinal follow-up [50], there is an increasing recognition that psychological issues are primary concerns for cancer sur-

vivors post treatment, although the magnitude of difference between survivors and healthy controls is not clear [50–54]. For example, cohort studies show that compared with subjects with no histories of cancer, cancer survivors report higher rates of anxiety consistently; while some show higher rates of depression, and this has not been consistently demonstrated [55–57]. In addition, survivors who have clinical depression have a twofold risk of all-cause mortality [58]. Unfortunately, data suggest that we are not meeting these needs in cancer survivors as well as we should. For example, in a survey of hematopoietic cell transplantation survivors, 50% of those who reported feeling distressed said they had not received any treatment for their emotional needs [59]. This section reviews psychosocial issues in cancer survivors, which increasingly are recognized as extending beyond anxiety and depression. Although the term “cancer survivor” may refer to anyone alive after a cancer diagnosis, in this section, we address psychosocial issues in disease-free survivors who have completed treatment. Psychological symptoms may worsen if a woman is in a reproductive period and has no possibility to have a child due to disease. This kind of patients may have needed fertility preservation technologies [60]. Fertility preservation requires individualization. The optimal approach depends upon the type of gonadotoxic treatment (radiation versus

chemotherapy), time available, patient age, the specific disease, whether the patient has a partner, costs, and long-term issues (storage and use of frozen gametes or embryos). ASCO and the American Society of Reproductive Medicine (ASRM) have published similar recommendations [61–64].

CONCLUSION

BC survivors faced with significant psychological and physical difficulties after the diagnosis. Difficulty coping with access to diagnosis: fear, anxiety about the future, the various aspects of psychological avoidance themselves play the role of the background, which is unfolding battle for the right to live. The results of the subsequent surgery therapy create a number of negative effects, which themselves make this path even more arduous. It is necessary to emphasize the difference in the groups: young women with newly diagnosed BC when there is still the opportunity to realize their reproductive potential. Prolonged estrogen receptor antagonist therapy worsens the course of menopausal disorders in a group perimenopause.

Increasing the number of survivors in all countries, the aging of the female population, the formation of youth groups with a diagnosis of BC creates a separate area of supervision in these patients.

REFERENCES/ЛІТЕРАТУРА

- National Cancer Registry. Ukraine. NCI (2011).
- GLOBOCAN 2008 Update. Available from: [http://www.iarc.fr/en/media-centre/iarcnews/2011/globocan2008-prev.php], last accessed Feb 15, 2016.
- De Santis, C.E., Lin, C.C., Mariotto, A.B., et al. “Cancer treatment and survivorship statistics, 2014.” *CA Cancer J Clin* 64 (2014): 252.
- Jemal, A., Siegel, R., Xu, J., Ward, E. “Cancer statistics, 2010.” *CA Cancer J Clin* 60 (2010): 277.
- Cheung, W.Y., Neville, B.A., Cameron, D.B., et al. “Comparisons of patient and physician expectations for cancer survivorship care.” *J Clin Oncol* 27 (2009): 2489.
- Ottini, L., Palli, D., Rizzo, S., et al. “Male breast cancer.” *Crit Rev Oncol Hematol* 73 (2010): 141–55.
- Autier, P., Boniol, M., La Vecchia, C., et al. “Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of WHO mortality database.” *BMJ* 341 (2010): 3620.
- Allemani, C., Weir, H.K., Carreira, H., et al. “Global surveillance of cancer survival 1995–2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2).” *Lancet* 385 (2015): 977–1010.
- Sant, M., Chirlaque Lopez, M., Agresti, R., et al.; EUROCARE-5 Working Group. “Survival of women with cancers of breast and genital organs in Europe 1999–2007: results of the EUROCARE-5 study.” *Eur J Cancer* (2015). Available from: [http://www.ncbi.nlm.nih.gov/pubmed/26421822], last accessed Feb 16, 2016.
- Minino, A.M., Murphy, S.L. “Death in the United States, 2010.” *NCHS Data Brief* 1–8 (2012).
- Tsu, V. “Evaluation of Key Components of PATH’s Ukraine Breast Cancer Assistance Project: Ten Years After.” Available from: [http://sites.path.org/rh/files/2012/06/PATH_Breast_cancer_eval_report_Ukraine_2011.pdf], last accessed Feb 16, 2016.
- McDermott, A.M., Toelle, T.R., Rowbotham, D.J., et al. “The burden of neuropathic pain: results from a cross-sectional survey.” *Eur J Pain* 10 (2006): 127–35.
- McDonald, M., Hertz, R.P., Unger, A.N., et al. “Prevalence, awareness, and management of hypertension, dyslipidemia, and diabetes among United States adults aged 65 and older.” *J Gerontol A Biol Sci Med Sci* 64 (2009): 256–63.
- Materials of European Cancer Congress – 2015. “Treatment patterns for older patients with non-metastatic breast cancer in four European countries – preliminary data from a EURECCA international comparison.” Available from: [http://oncologypro.esmo.org/Meeting-Resources/European-Cancer-Congress-2015/Treatment-patterns-for-older-patients-with-non-metastatic-breast-cancer-in-four-European-countries-preliminary-data-from-a-EURECCA-international-comparison], last accessed Feb 16, 2016.
- Miguel, R., Kuhn, A.M., Shons, A.R., et al. “The effect of sentinel node selective axillary lymphadenectomy on the incidence of postmastectomy pain syndrome.” *Cancer Control* 8 (2001): 427.
- Meijuan, Y., Zhiyou, P., Yuwen, T., et al. “A retrospective study of postmastectomy pain syndrome: incidence, characteristics, risk factors, and influence on quality of life.” *Scientific World Journal* (2013). DOI: 10.1155/2013/159732
- Wallace, M.S., Wallace, A.M., Lee, J., Dobke, M.K. “Pain after breast surgery: a survey of 282 women.” *Pain* 66 (1996): 195.
- Poleshuck, E.L., Katz, J., Andrus, C.H., et al. “Risk factors for chronic pain following breast cancer surgery: a prospective study.” *J Pain* 7 (2006): 626.
- Berry, D.A., Cirrincione, C., Henderson, I.C., et al. “Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer.” *JAMA* 295 (2006): 1658–67.
- Clarke, M., Coates, A.S., Darby, S.C., et al. “Adjuvant chemotherapy in oestrogen receptor-poor breast cancer: patient-level meta-analysis of randomised trials.” *Lancet* 371 (2008): 29–40.
- Colleoni, M., Gelber, S., et al. “Tamoxifen after adjuvant chemotherapy for premenopausal women with lymph node-positive breast cancer: International Breast Cancer Study Group trial 13–93.” *J Clin Oncol* 24 (2006): 1332–41.
- Swain, S.M., Jeong, J.H., Wolmark, N. “Amenorrhea from breast cancer therapy—not a matter of dose.” *N Engl J Med* 363 (2010): 2268–70.
- Floyd, J.D., Nguyen, D.T., Lobins, R.L., et al. “Cardiotoxicity of cancer therapy.” *J Clin Oncol* 23 (2005): 7685.
- Singal, P.K., Iliskovic, N. “Doxorubicin-induced cardiomyopathy.” *N Engl J Med* 339 (1998): 900.
- Carver, J.R., Shapiro, C.L., et al.; ASCO Cancer Survivorship Expert Panel. “American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects.” *J Clin Oncol* 25.25 (2007): 3991.
- Auner, H.W., Tinchon, C., Linkesch, W., Tiran, A., et al. “Prolonged monitoring of troponin T for the detection of anthracycline cardiotoxicity in adults with hematological malignancies.” *Ann Hematol* 82.4 (2003): 218.

27. Gnant, M., Mlineritsch, B., Schippinger, W., et al. "Endocrine therapy plus zoledronic acid in premenopausal breast cancer." *N Engl J Med* 360 (2009): 679–91.
28. Pagani, O., Regan, M.M., Walley, B.A., et al. "Adjuvant exemestane with ovarian suppression in premenopausal breast cancer." *N Engl J Med* 371 (2014): 107–18.
29. Cuzick, J., Ambroisine, L., et al. "Use of luteinizing-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials." *Lancet* 369 (2007): 1711–23.
30. Jonat, W., Kaufmann, M., Sauerbrei, W., et al. "Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the Zoladex Early Breast Cancer Research Association study." *J Clin Oncol* 20 (2002): 4628–35.
31. Sismondi, P., Biglia, N., Volpi, E., Giai, M., de Grandis, T. "Tamoxifen and endometrial cancer." *Ann NY Acad Sci* 734 (1994): 310–21.
32. Bissett, D., Davis, J.A., George, W.D. "Gynaecological monitoring during tamoxifen therapy." *Lancet* 344 (1994): 1244.
33. Fisher, B., Costantino, J.P., Redmond, C.K., et al. "Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14." *J Natl Cancer Inst* 86 (1994): 527–37.
34. Magriples, U., Naftolin, F., Schwartz, P.E., Carcangiu, M.L. "High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients." *J Clin Oncol* 11 (1993): 485–90.
35. Davies, C., Pan, H., Godwin, J., Gray, R., et al. "Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial." *Lancet* 381 (2013): 804–16.
36. Moore, H.C., Unger, J.M., Phillips, K.A., et al. "Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy." *N Engl J Med* 372 (2015): 923–32.
37. Regan, M.M., Leyland-Jones, B., Bouzyk, M., et al. "CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the breast international group 1–98 trial." *J Natl Cancer Inst* 104 (2012): 441–51.
38. Sideras, K., Ingle, J.N., Ames, M.M., et al. "Coprescription of tamoxifen and medications that inhibit CYP2D6." *J Clin Oncol* 28 (2010): 2768–76.
39. Coleman, M.P., Quaresma, M., Berrino, F., et al. "Cancer survival in five continents: a worldwide population-based study (CONCORD)." *Lancet Oncol* 9 (2008).
40. Khatcheressian, J.L., Hurley, P., Bantug, E., et al. "Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update." *J Clin Oncol* 31 (2013): 961–65.
41. Senkus, E., Kyriakides, S., Penault-Llorca F., et al. "Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." *Ann Oncol* 24.6 (2013): 7–23.
42. Achiron, R., Lipitz, S., Sivan, E., Goldenberg, M., et al. "Changes mimicking endometrial neoplasia in postmenopausal, tamoxifen-treated women with breast cancer: a transvaginal Doppler study." *Ultrasound Obstet Gynecol* 6 (1995): 116–20.
43. Bertelli, G., Venturini, M., Del Mastro, L., et al. "Tamoxifen and the endometrium: findings of pelvic ultrasound examination and endometrial biopsy in asymptomatic breast cancer patients." *Breast Cancer Res Treat* 47 (1998): 41–6.
44. Fung, M.F., Reid, A., Faught, W., Le, T., et al. "Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen." *Gynecol Oncol* 91 (2003): 154–9.
45. Love, C.D., Muir, B.B., Scrimgeour, J.B., et al. "Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening." *J Clin Oncol* 17 (1999): 2050–4.
46. Markovitch, O., Tepper, R., Aviram, R., et al. "The value of sonohysterography in the prediction of endometrial pathologies in asymptomatic postmenopausal breast cancer tamoxifen-treated patients." *Gynecol Oncol* 94 (2004): 754–9.
47. Chalas, E., Costantino, J.P., Wickerham, D.L., et al. "Benign gynecologic conditions among participants in the Breast Cancer Prevention Trial." *Am J Obstet Gynecol* 192 (2005): 1230–9.
48. Syrjala, K.L., Yi, J.C., Ganz, P.A., Vora, S.R. Overview of psychosocial issues in the adult cancer survivor. Available from: [http://www.uptodate.com/contents/overview-of-psychosocial-issues-in-the-adult-cancer-survivor], last assessed Feb 17, 2016.
49. DeSantis, C.E., Lin, C.C., Mariotto, A.B., et al. "Cancer treatment and survivorship statistics, 2014." *CA Cancer J Clin* 64 (2014): 252.
50. Lerro, C.C., Stein, K.D., Smith, T., Virgo, K.S. "A systematic review of large-scale surveys of cancer survivors conducted in North America, 2000–2011." *J Cancer Surviv* 6.2 (2012): 115–45.
51. National Research Council. Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs // Ed. by N.E. Adler, A.E.K. Page. The National Academies Press. Washington D.C. (2007).
52. Institute of Medicine, National Research Council. From Cancer Patient to Cancer Survivor: Lost in Transition // Ed. by M. Hewitt, S. Greenfield, E. Stovall. The National Academies Press. Washington D.C. (2006).
53. Beckjord, E.B., Reynolds, K.A., van Londen, G.J., et al. "Population-level trends in posttreatment cancer survivors' concerns and associated receipt of care: results from the 2006 and 2010 LIVESTRONG surveys." *Psychosoc Oncol* 32.2 (2014): 125.
54. Forsythe, L.P., Kent, E.E., Weaver, K.E., Buchanan, N., et al. "Receipt of psychosocial care among cancer survivors in the United States." *J Clin Oncol* 31.16 (2013): 1961–9.
55. Greer, J.A., Solis, J.M., Temel, J.S., et al. "Anxiety disorders in long-term survivors of adult cancers." *Psychosomatics* 52 (2011): 417.
56. Costanzo, E.S., Ryff, C.D., Singer, B.H. "Psychosocial adjustment among cancer survivors: findings from a national survey of health and well-being." *Health Psychol* 28 (2009): 147.
57. Mitchell, A.J., Ferguson, D.W., Gill, J., et al. "Depression and anxiety in long-term cancer survivors compared with spouses and healthy controls: a systematic review and meta-analysis." *Lancet Oncol* 14 (2013): 721.
58. Mols, F., Husson, O., Roukema, J.A., van de Poll-Franse, L.V. "Depressive symptoms are a risk factor for all-cause mortality: results from a prospective population-based study among 3,080 cancer survivors from the PROFILES registry." *J Cancer Surviv* 7 (2013): 484.
59. Mosher, C.E., DuHamel, K.N., Rini, C.M., et al. "Barriers to mental health service use among hematopoietic SCT survivors." *Bone Marrow Transplant* 45 (2010): 570.
60. Sonmezer, M., Oktay, K. "Fertility preservation in patients undergoing gonadotoxic treatment or gonadal resection." Available from: [http://www.uptodate.com/contents/fertility-preservation-in-patients-undergoing-gonadotoxic-treatment-or-gonadal-resection], last accessed Feb 17, 2016.
61. Loren, A.W., Mangu, P.B., Beck, L.N., et al. "Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update." *J Clin Oncol* 31 (2013): 2500.
62. The Practice Committee of the American Society for Reproductive Medicine. "Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion." *Fertil Steril* 100 (2013): 1214.
63. The Ethics Committee of the American Society for Reproductive Medicine. "Fertility preservation and reproduction in patients facing gonadotoxic therapies: a committee opinion." *Fertil Steril* 100 (2013): 1224.
64. Das, M., Shehata, F., Moria, A., et al. "Ovarian reserve, response to gonadotropins, and oocyte maturity in women with malignancy." *Fertil Steril* 96 (2011): 122.

BREAST CANCER SURVIVORS. EARLY DIAGNOSIS – SUCCESSFUL TREATMENT – QUALITY OF LIFE: MULTIDISCIPLINARY APPROACH

T.F. Tatarчук, MD, professor, corresponding member of NAMS of Ukraine, deputy director for research work, Chief of the Endocrine Gynecology Department, SI "Institute of Pediatrics, Obstetrics and Gynecology, NAMS of Ukraine"

I.I. Smolanka, MD, professor, Chief oncologist of the Ministry of Health of Ukraine, head of the Scientific and Research Department of Breast Tumors and its Reconstructive Surgery, National Cancer Institute of the NAMS of Ukraine

O.V. Popkov, PhD, gynecologist

Breast cancer is the leading cause of cancer-related deaths in European women. Breast cancer diagnosis is widely represented in women with such risk factors as exposure of endogenous and exogenous estrogens, some genetic predispositions, low parity and others. Consumption of fat, alcohol leads to the rising breast cancer incidence of last decades. Breast cancer occurs mostly after 50 years. Genetic BRCA1 and BRCA2 polymorphism, family history allows supposing breast cancer in 10% of women in risk group. In Ukraine radiation played a great role due to Chernobyl atomic station catastrophe in 1986.

In a treatment of breast cancer different methods are used in a combination. Primary surgery and systemic approaches include radiation therapy, hormone therapy and chemotherapy. Important role belongs to a chemotherapy and post-treatment after surgical intervention.

Chemotherapy is recommended in the vast majority of triple-negative, HER2-positive breast cancer and in high-risk luminal HER2-negative tumors (evidence level I, A). The absolute benefit from chemotherapy is more pronounced in estrogen receptors negative tumors. The most frequently used regimens contain anthracyclines and/or taxanes, although in selected patients the CMF therapy (cyclophosphamide, methotrexate, and fluorouracil) may still be used. Endocrine therapy is indicated in all patients with detectable estrogen receptors expression irrespective of the use of chemotherapy and/or targeted therapy (evidence level I, A).

Routine physical examinations with a careful taking history are the most valuable measures of detecting breast cancer recurrence. The European Society for Medical Oncology recommends regular visits every 3 to 4 month in the first 2 years, every 6 month from years 3 to 5 and annually thereafter.

Keywords: breast cancer, radiation therapy, hormone therapy, chemotherapy.

ТІ, ХТО ВИЖИВ ПІСЛЯ РАКУ МОЛОЧНОЇ ЗАЛОЗИ. РАННЯ ДІАГНОСТИКА – УСПІШНЕ ЛІКУВАННЯ – ЯКІСТЬ ЖИТТЯ: МІЖДИСЦИПЛІНАРНИЙ ПІДХІД

Т.Ф. Татарчук, д. мед. н., професор, член-кор. НАМН України, заст. директора з наукової роботи, зав. відділенням ендокринної гінекології ДУ «ІПАГ НАМН України»

І.І. Смолянко, д. мед. н., професор, головний онкохірург МОЗ України, зав. науково-дослідним відділенням пухлин грудної залози та її реконструктивної хірургії НІР МОЗ України

О.В. Попков, к. мед. н., лікар-гінеколог

Рак молочної залози є основною причиною смертності від онкологічних захворювань у європейських жінок. Рак молочної залози широко виявляється у жінок із такими факторами ризику, як вплив ендогенних та екзогенних естрогенів, деякі генетичні схильності, низький паритет та інші. Надмірне споживання жирів, алкоголю зумовлює зростання захворюваності на рак молочної залози в останні десятиліття. Рак молочної залози розвивається в основному після 50 років. Поліморфізм генів BRCA1 і BRCA2, обтяжений сімейний анамнез дозволяє припустити наявність раку молочної залози у 10% жінок групи ризику. В Україні велику роль відіграє радіаційний фон, обумовлений катастрофою на Чорнобильській атомній електростанції в 1986 р.

Для лікування раку молочної залози використовуються поєднання різних методів. Після первинного хірургічного втручання застосовуються методи системної терапії, що включають променеви, гормональну терапію та хіміотерапію. Важлива роль належить хіміотерапії і подальшому лікуванню після хірургічного втручання.

Хіміотерапія рекомендується в переважній більшості випадків потрійного негативного, HER2-позитивного раку молочної залози і за високого ризику раку молочної залози люмінального підтипу (HER2-негативного) (рівень доказовості I, A). Абсолютна користь від хіміотерапії більш виражена при ER-негативних пухлинах. Найбільш часто живані схеми включають антрацикліни та/або таксани, хоча у окремих хворих може, як і раніше, використовуватися ЦМФ-терапія (циклофосамід, метотрексат, фторурацил). Ендокринна терапія показана всім хворим з ER-позитивним раком молочної залози незалежно від застосування хіміотерапії та/або таргетної терапії (рівень доказовості I, A).

Звичайні медичні огляди з ретельним збором анамнезу є найціннішими способами виявлення рецидиву раку молочної залози. Європейське суспільство медичної онкології рекомендує здійснювати регулярний огляд пацієнток кожних 3–4 місяці протягом перших 2 років після лікування, кожних 6 місяців в період від 3 до 5 років, а далі щороку.

Ключові слова: рак молочної залози, променева терапія, гормональна терапія, хіміотерапія.

ВЫЖИВШИЕ ПОСЛЕ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ. РАННЯЯ ДИАГНОСТИКА – УСПЕШНОЕ ЛЕЧЕНИЕ – КАЧЕСТВО ЖИЗНИ: МЕЖДИСЦИПЛИНАРНЫЙ ПОДХОД

Т.Ф. Татарчук, д. мед. н., профессор, член-корр. НАМН Украины, зам. директора по научной работе, зав. отделением эндокринной гинекологии ГУ «ИПАГ НАМН Украины»

И.И. Смолянко, д. мед. н., профессор, главный онкохирург МОЗ Украины, зав. научно-исследовательским отделением опухолей грудной железы и ее реконструктивной хирургии НИР МЗ Украины

А.В. Попков, к. мед. н., врач-гинеколог

Рак молочной железы является основной причиной смертности от онкологических заболеваний у европейских женщин. Рак молочной железы широко выявляется у женщин с такими факторами риска, как воздействие эндогенных и экзогенных эстрогенов, некоторые генетические предрасположенности, низкий паритет и другие. Избыточное потребление жиров, алкоголя обуславливает рост заболеваемости раком молочной железы в последние десятилетия. Рак молочной железы развивается в основном после 50 лет. Полиморфизм генов BRCA1 и BRCA2, отягощенный семейный анамнез позволяет предположить наличие рака молочной железы у 10% женщин группы риска. В Украине большую роль играет радиационный фон, обусловленный катастрофой на Чернобыльской атомной электростанции в 1986 г.

Для лечения рака молочной железы используется сочетание различных методов. После первичного хирургического вмешательства применяются методы системной терапии, включающие лучевую, гормональную терапию и химиотерапию. Важная роль принадлежит химиотерапии и последующему лечению после хирургического вмешательства.

Химиотерапия рекомендуется в подавляющем большинстве случаев тройного негативного, HER2-положительного рака молочной железы и при высоком риске рака молочной железы люминального подтипа (HER2-негативного) (уровень доказательности I, A). Абсолютная польза от химиотерапии более выражена при ER-негативных опухолях. Наиболее часто применяемые схемы включают антрациклины и/или таксаны, хотя у отдельных больных может по-прежнему использоваться ЦМФ-терапия (циклофосамид, метотрексат, фторурацил). Эндокринная терапия показана всем больным с ER-положительным раком молочной железы независимо от использования химиотерапии и/или таргетной терапии (уровень доказательности I, A).

Обычные медицинские осмотры с тщательным сбором анамнеза являются самыми ценными способами выявления рецидива рака молочной железы. Европейское общество медицинской онкологии рекомендует проводить регулярный осмотр пациенток каждые 3–4 месяца в течение первых 2 лет после лечения, каждые 6 месяцев в период от 3 до 5 лет, а затем ежегодно.

Ключевые слова: рак молочной железы, лучевая терапия, гормональная терапия, химиотерапия.