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REPEATED BREAST-CONSERVING SURGERIES AS REFLECTION OF THE EVOLUTION IN BREAST CANCER TREATMENT (CASE REPORT WITH LITERATURE REVIEW)

The clinical case of a patient with multicentric breast cancer who underwent organ-sparing surgery after neoadjuvant chemo-radiation therapy is presented. An ipsilateral cancer recurrence was diagnosed 8 years after the first operation. The repeated organ-sparing surgery (lumpectomy) was done with a good cosmetic result and without disease progression during 1-year follow-up. The literature review shows that neoadjuvant systemic therapy accounting for molecular subtypes of cancer has radically changed breast cancer surgeries. The evolution of surgical approaches in stage I—II breast cancer patients consists in the de-escalation of surgery from mastectomy to organ-sparing or oncoplastic surgery, minimally directed surgery, and repeated breast-conserving surgery. De-escalation of surgical interventions in the area of the regional lymphatic collector consists in the transition from total axillary lymphatic dissection to sentinel lymph node biopsy or targeted removal of metastatic lymph nodes. The repeated breast-conserving surgery can be safely performed for ipsilateral recurrence in patients with all molecular subtypes of breast cancer.

Keywords: breast cancer, repeated organ-sparing surgery, ipsilateral recurrence.

Today's breast cancer (BC) surgery is a primarily minimally targeted breast-saving and oncoplastic surgery. However, the local recurrence exists in approximately 5%—10% of patients. Ipsilateral recurrence after organ-sparing surgery can nullify all efforts of the oncology team to save the breast. Now the treatment approach to ipsilateral BC recurrence (IBCR) is gradually changing from salvage mastectomy to repeated breast-conserving surgery [1—3].

The molecular genetic studies (ER, PR, Her2, BRCA1/2, CDK4/6, p53, mTOR, etc.) have opened up the options for targeted pathogenetic approaches to BC treatment, and the neoadju-

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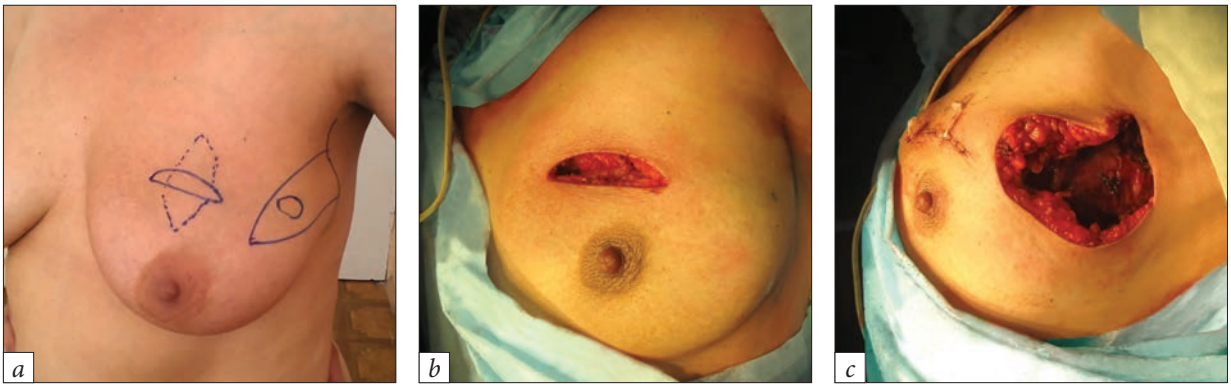

Fig. 1. Treatment of multicentric BC in a 44-year woman: *a*) multicentric cancer in the left breast; surgical planning of BC surgery after neoadjuvant treatment; *b*) lumpectomy; *c*) segmental breast resection with axillary dissection (level I—II)

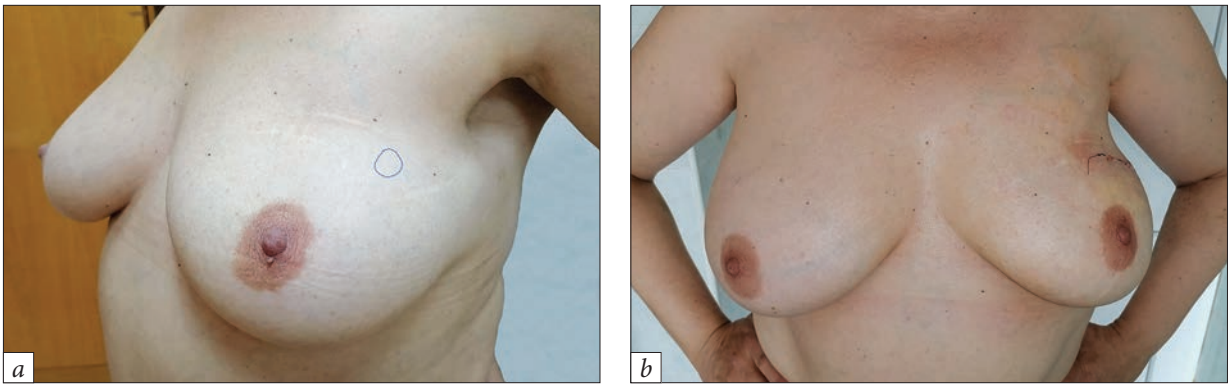

Fig. 2. Treatment of IBCR: *a*) IBCR (marked with a circle) located between previews scars; *b*) on day 5 after repeated BC surgery

vant treatment methods have in turn changed the surgical options for BC patients [4—5].

The purpose of the study is to show the possibility of repeated organ-sparing surgeries in BC patients, presenting a special clinical case with a review of scientific publications on this topic.

Clinical case

The clinical case is multicentric BC in a 44-year-old woman. Two tumors (35 × 33 mm and 44 × × 41 mm) and enlarged axillary lymph nodes (28 × 12 mm) were diagnosed in the left mammary gland. Core biopsies of each tumor with histological examination confirmed the presence of moderately differentiated invasive ductal carcinoma (G2). Immunohistochemistry (IHC) evaluation: luminal A subtype of BC (ER 83%, PR 78%, HER2 negative, Ki67 15%). The patient provided informed consent for participating in the study.

Treatment was as follows:

a) neoadjuvant chemotherapy: CAF regime × × 3 cycles. Results: tumors' shrink from 35 × × 33 mm to 15 × 15 mm and from 44 × 41 mm to 13 × 13 mm, the size of axillary lymph nodes (LN) became 10 mm. In general, the tumors decreased by 57%—70% of their initial size;

b) neoadjuvant radiation therapy (RT; Co-60) of 2.2—2.5 Gy daily. The dose of the whole breast irradiation was 35.2 Gy, the axillary LN — 35.2 Gy, subclavicular LN — 36.8 Gy, and supra-

clavicular LN — 40.9 Gy. Results in one month after RT: the ultrasound and mammography recorded the size of both breast tumors at 10 mm, and the axillary LN were not visualized;

c) given the significant tumor regression, the breast conserving surgery (BCS) was performed with the removal of one tumor by lumpectomy (between upper quadrants) and the other tumor by segmental lateral radical breast resection with axillary lymph node (level I—II) dissection (Fig. 1). Surgical samples after lumpectomy and radical segmental resection (R0) were larger than the volume of residual tumors, and even larger than the size of the tumors at the time of diagnosis.

A significant treatment pathomorphosis was revealed during histological examination of residual cancer tissue, which consisted in the degenerative changes and formation of calcifications in the tumor's bed; the resection margins were clear; in 8 removed LN, hyperplasia was found. Thus, the postoperative diagnosis was established as "cancer of the left breast pT2(2) N0M0G2, IIA stage, luminal A subtype". The patient completed chemotherapy cycles and started taking hormonal treatment (tamoxifen).

IBCR was detected after 8 years of disease-free period during the follow-up ultrasound and mammography. The recurrent tumor (11 × × 9 mm) was located in the upper-external quadrant of the left breast between two postoperative scars (Fig. 2, *a*). The second BCS (lumpectomy) was done under the general anesthesia. Histology confirmed the invasive ductal carcinoma G2 with negative margins (R0) of surgical sample. IHC: ER 100%, PR 15%, HER2 negative, Ki67 70%. The cosmetic outcome was good in general (Fig. 2, *b*). After this surgery, the patient received 4 cycles of chemotherapy, local radiotherapy (39.6 Gy) to the left breast, and continued endocrine therapy with an aromatase inhibitor. During one-year follow-up, no relapses or distant metastases were detected during ultrasound and computed tomography examinations. This clinical case shows that with consistent careful observation of patients after primary BCS, it is possible to detect a small recurrent tumor, which will allow one to perform repeated BCS.

In total, 4.8% of women who underwent BCS at the Ternopil Regional Cancer Hospital in 2010—2018 have repeated organ-sparing surgeries due to loco-regional ipsilateral recurrence, while the median time of ipsilateral recurrence was 6.2 years.

The effectiveness of primary and repeated organ-sparing surgery in BC treatment: a review

The surgical treatment of BC has changed dramatically during the past 100—130 years: from mastectomy of William Halsted (1889) to breast conserving surgery of Bernard Fisher (1985), and nowadays to the minimally-targeted breast surgery or even omitting of breast surgery. The clinical trials of B. Fisher (Pittsburgh, PA, USA) transformed the way of BC treatment, and to him hundreds of thousands of women owe the preservation of mammary glands with an adequate quality of life [6, 7].

On the other hand, today oncologists feel confident about the choice of treatment options based on the molecular genetic subtypes of BC (luminal A, luminal B/triple-positive, HER2-positive, triple-negative). Better understanding of BC pathogenesis opened the possibilities to use neoadjuvant systemic treatment (NAST). NAST is used for downstaging operable BC, especially of triple-negative (TNBC) and HER2-positive, to reduce the extent of surgery and offer to patient the possibility of breast-conserving options in case of pathological complete response (pCR) [8—10]. However, therapeutic methods cannot yet achieve complete success in BC treatment, and surgery remains, but it no longer occupies a leading position, as before.

The volume of surgical interventions in BC has changed significantly in the last two decades. Neoadjuvant systemic therapy made its adjust-

ments. It has been proven that such molecular subtypes of BC as triple negative and Her2-positive are extremely sensitive to systemic neoadjuvant therapy, which now leads to the complete pathohistological response (pCR, ypT0) in 60%—80% of patients [4, 9, 11]. After NAST, the following several surgical options are practiced for BC stage I—II: organ-sparing surgery, subcutaneous mastectomy with breast reconstruction or oncoplastic bilateral subcutaneous mastectomy. The rate of BCS has increased now up to 70% in Western countries. However, the rate of bilateral mastectomy after NAST has also increased over the past decade despite increasing BCS eligibility and increasing complete response to NAST [12—15].

A complete imaging response is not the same as a complete histological response. That is why lumpectomy or minimally targeted removal of breast tissue with Magseed in the tumor bed is recommended. A pathological complete response to NAST predicts an excellent prognosis and can be accurately determined by percutaneous image-guided vacuum-assisted core biopsy (VACB). Usually, patients eligible for BCS require clipping of the tumor prior to the initiation of NAST. The clips allow a robust pre-operative localization of the tumor bed. The minimally invasive biopsy technique guided by breast imaging has a potential to accurately predict the complete remission of BC after NAST, which makes the non-operative BC treatment a feasible choice [5, 9, 11, 16]. However, some patients can avoid even such a minimal surgery: in some cases, breast radiation therapy is prescribed, in the others — only observation during hormonal treatment [4, 9, 11, 12].

Radiothertapy (RT) is a universal target treatment for all molecular subtypes of BC. Thus, it appears to be more appropriate to irradiate a breast tumor in neoadjuvant setting than to irradiate the tumor-free breast after surgery. The use of RT in combination with neoadjuvant chemotherapy allows consolidating the effectiveness of chemotherapy, reducing the number of its cycles, and also obtaining an ablastic effect before organ-sparing surgery. Surgery is usually performed 4—8 weeks after the last RT session. In these cases, the local complications of postoperative healing are insignificant and do not affect the BCS results [17—19].

More recently, mastectomy has been recommended for patients with primary multicentric tumors. However, three prospective clinical trials undergoing BCS after NAST showed that the recurrence and DFS, as well as overall survival (OS) of patients with multicentric or multifocal tumors were not inferior compared to patients with unifocal tumors if clear surgical margins (R0) can be obtained [20]. Our experience confirms these data as well.

Regional lymph nodes. The data collected from the Netherlands Cancer Registry show an overall trend toward de-escalation of axillary surgery in patients with BC treated with NAST. In cN0 patients, an overall increase in sentinel lymph node biopsy (SLNB) was only seen from 11% in 2006 to 94% in 2016. SLNB performance after NAST increased from 33 to 62%. In cN+ patients, an overall decrease in axillary lymph node dissection (ALND) was seen from 99% in 2006 to 53% in 2016 [21].

The axillary pCR rates reach more than 50% in TNBC and 80% in HER-2 positive patients receiving trastuzumab plus pertuzumab. Therefore, those who may reach axillary pCR are unlikely to benefit from ALND [22, 23].

The role of SLNB and the data supporting its use are different from those with clinically negative and clinically positive nodes prior to chemotherapy. SLNB instead of ALND has become a standard of care for patients with clinically lymph node-negative (cN0) BC. Nevertheless, for those with cN+ BC, ALND is still the standard local treatment for axillary regions. On the other hand, the German AGO Breast Committee permits the omission of SLNB in elderly patients with cN0 status under certain conditions:

≥ 70 years, pT1, hormone receptor-positive, and HER2-negative [11, 24, 25].

Targeted axillary dissection (TAD) after neoadjuvant chemotherapy for BC has proven safe and led to de-escalation of axillary surgery. When the sentinel lymph node is not a clipped node, lymphoscintigraphy (SPECT-CT) or triple mapping technique may be used for axillary staging after neoadjuvant therapy [21, 24, 26, 27].

Second conservative treatment has emerged as an option for patients with a second ipsilateral breast tumor event after BCS and breast irradiation. Mastectomy remains current standard surgical procedure for IBCR. However, the multivariate analysis and the propensity score matching cohort analysis demonstrated that there was no difference in the terms of distant disease-free survival, 5-year OS, and cumulative incidence of the third breast event between repeat lumpectomy and mastectomy in patients with IBCR [28, 29].

Patients with the ER-positive/HER2-negative subtype of IBCR had a significantly better second IBCR-free survival rate than those with other subtypes of IBCR (88% *vs.* 75%). Multivariate analysis revealed that the ER status was a significantly independent predictive factor for the second IBTR-free survival. Patients in the low-risk group could safely undergo repeated lumpectomy without RT for IBCR [30, 31].

An analysis of 42 observational studies from the MEDLINE and EMBASE databases showed that the pooled second local recurrence rate after repeat BCS (rBCS) was 15.7%, and 10.3% after salvage mastectomy. The pooled 5-year OS was 86.8% and 79.8% for rBCS and salvage mastectomy, respectively [3].

In another study at a median follow-up of 10.7 years following initial BCS and 6.5 years following IBCR, there were no differences in BC specific survival (BCSS) or OS between re-conservation treatment (RCT) and mastectomy. These results support wider consideration of RCT in the management of IBCR, especially in the setting of an older age and longer disease-free interval [2].

There are several ways to identify early relapse using molecular biomarkers. The recent studies have reported that circulating tumor DNA (ctDNA) detection in the post-definitive therapy can identify the relapse with a median lead-time of 11 months before imaging. However, none of the patients who achieved pCR had detectable ctDNA at the presurgical time point, and no patients who were ctDNA-positive at the presurgical time point achieved pCR. It seems that highly proliferative and more aggressive tumors have higher ctDNA detection rates [32].

An increasing number of studies have explored the possibility of evaluating the levels of circulating miRNAs as molecular biomarkers for diagnosis or prognosis. It was shown that three-miRNA panel (miR-9-5p, miR-34b-3p, miR-146a-5p) in serum could be used as a non-invasive biomarker in the diagnosis of invasive ductal carcinoma of the breast [33].

Thus, today we have many convincing facts about the effectiveness of primary and repeated organ-sparing surgery in BC treatment. The molecular methods allow one not only to diagnose subtypes of primary and recurrent BC but also to determine the tactics and strategy of patients' treatment and serve predictors of the disease prognosis.

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ПОВТОРНІ ОРГАНОЗБЕРІГАЛЬНІ ОПЕРАЦІЇ
ЯК ВІДОБРАЖЕННЯ ЕВОЛЮЦІЇ ЛІКУВАННЯ РАКУ МОЛОЧНОЇ
ЗАЛОЗИ (КЛІНІЧНИЙ ВИПАДОК З ОГЛЯДОМ ЛІТЕРАТУРИ)

Представлено клінічний випадок хворої на мультицентричний рак молочної залози, якій було виконано органозберігальну операцію після неоад'ювантної хіміопроменевої терапії. Іпсилатеральний рецидив раку було діагностовано через 8 років після першої операції. Повторна органозберігальна операція (лампектомія) проведена з хорошим косметичним результатом і без прогресування захворювання протягом одного року спостереження. У літературному огляді показано еволюцію хірургічного лікування раку молочної залози від мастектомії до мінімально-таргетної хірургії. Підкреслено, що неоад'ювантна системна терапія з урахуванням молекулярних підтипів кардинально змінила хірургію раку молочної залози. Еволюція хірургічних підходів у хворих на рак молочної залози I—II стадії полягає у деескалації хірургії від мастектомії до органозберігальної або онкопластичної операції, мінімально спрямованої хірургії та повторної операції зі збереженням грудей. Деескалація хірургічного втручання в зоні регіонарного лімфатичного колектора полягає в переході від тотальної пахвової лімфатичної дисекції до біопсії сторожового лімфатичного вузла або прицільного видалення метастатичних лімфатичних вузлів. Повторні операції зі збереженням молочної залози можна безпечно проводити в разі іпсилатерального рецидиву у хворих з усіма молекулярними підтипами раку молочної залози.

Ключові слова: рак молочної залози, повторні органозберігальні операції, іпсилатеральний рецидив.