CASE REPORT

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ADVANCED BREAST CANCER: CASE REPORTS AND STATISTICAL ANALYSIS

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Abstract. *Breast cancer is a pathology associated with high morbidity and mortality among women of all nations worldwide. The low efficiency or total absence of national screening programs, the presence of comorbid mental illnesses or dementia, general lack of information and underestimation of the problem among patients are factors that often lead to late diagnosis of breast cancer and, as a result, to high mortality. The article presents 2 clinical cases of advanced breast cancer in women who underwent surgical treatment in our clinic, which demonstrate the necessity of emergency reconstruction of Bulgarian national screening program. A brief statistical analysis of morbidity, mortality and effectiveness of screening in different countries is conducted.*

Key words: *breast carcinoma, locally advanced breast cancer, metastatic carcinoma*

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INRTODUCTION

Coverage of prophylactic mammograms in Bulgaria is one of the lowest in the European Union (EU), and according to the results of the trial conducted in 2019, over 24,1% of Bulgarian women have never been examined for breast cancer in their lifetime [12]. At the same time, mortality rate continues to increase, especially among young patients, and exceeds the average European rate. As a result, more patients in Bulgaria are diagnosed late, at the advanced stages, which greatly complicate treatment and leads to high mortality among all age groups.

CLINICAL CASE 1

A 35-year-old female patient, after a course of neoadjuvant radiotherapy, was admitted to a surgical clinic with complaints of purulent exudation and bleeding from a right mammary gland tumor formation. Physical examination revealed the presence of a 12 cm tumor with signs of decay, involving all quadrants of the gland, and 3-4 enlarged axillary lymph nodes (Figure 1).

The patient was admitted to the surgical clinic with hemoglobin level of 93 g/l. After short preoperative preparation and discussion, a mastectomy was performed. Under general anesthesia, a Stewart skin incision was made, and the right breast, along with the locally advanced tumor and the underlying major pectoral muscle fascia was removed. Axillary lymph node dissection was performed and a drain was placed and fixated. The postoperative period was uneventful. Morphologically, a centrally located ulcerated area (tumorous tissue in decay) measured

Fig. 1. Localization and appearance of the tumor before surgical treatment

11/10/6 cm with extensive necrosis was observed. Histologically, ductal carcinoma (NOS) with significant post-therapeutic pathomorphosis (giant cell transformation), necrosis, edema, and the presence of superficial ulceration over a wide area (ypT4b N1a R0 LV0 Pn0, RCB III) was diagnosed. Immunohistochemically, HER2 expression (3+) was discovered. Estrogen and progesterone receptors were absent. Ki-67 marked very high proliferative activity - 100%.

Patient was discharged in a satisfactory overall condition on the third day after the intervention, with indications of primary healing of the operative wound. Subsequently, based on the decision of the oncology committee, further chemotherapy, targeted and radiation therapy were advised.

CLINICAL CASE 2

A 68-year-old female presented to the emergency department with complaints of bleeding from a tumor formation originating from the left breast. Upon clinical examination, the patient's general condition was assessed as severely compromised, with apparent bradypsychia and disorientation. Physical examination revealed an ulcerated tumor with foci of necrotic tissue, located in the upper quadrants of the left breast above the areola, with an approximate diameter of 11 cm, one enlarged subclavicular and four parasternal lymph nodes with a size of 1-1.5 cm. In the left axilla, 3-4 enlarged lymph nodes were palpated, the largest measuring approximately 5 cm. Additionally, a second 7-8 cm tumor formation was identified on the right side in the lower medial and partially lateral quadrant. Palpation revealed 2-3 enlarged lymph nodes in the right axilla, 2-3 cm each (Figure 2).

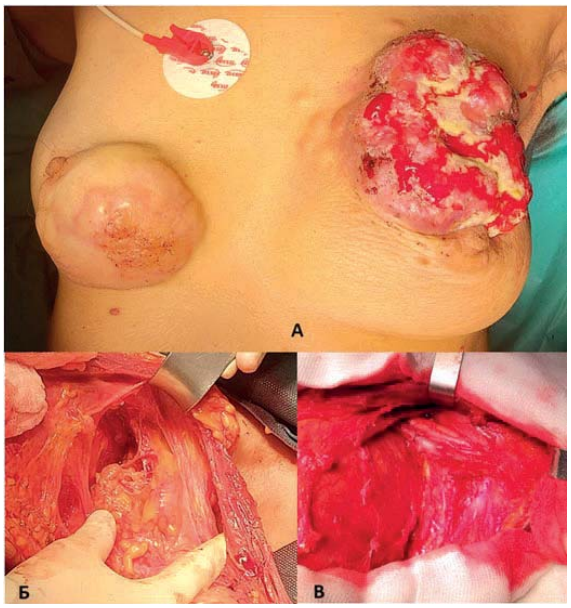

Fig. 2. Bilateral tumor formations before surgical treatment (A). Axillary lymph nodes before (B) and after (C) lymph node dissection

Blood analysis showed anemic syndrome (Hb-90g/l), elevated inflammatory markers (WBC-12,6*10^9g/l, CRP-3,14 mg/dL), and liver enzymes (ALT-59U/l, AST-290U/l), LDH-2080 U/l. The patient was admitted to the surgical clinic and after a brief preoperative preparation bilateral mastectomy with lymph node dissection was performed. The surgery was concluded with non-libera skin plasty and placement of 2 tube drainages in each axilla. The postoperative period was relatively normal and patient was discharged on the 7th day post-op.

Morphologically, an exophytic-growing, ulcerated lesion with dimensions of 11/10/5cm was identified on the left side, histologically corresponding to poorly differentiated invasive ductal carcinoma NST with well-defined desmoplastic and moderately expressed lymphoplasmacytic stromal reaction and presence of lymphovascular invasion: G3pT4bN1aR0 Pn-LV+ER-PR-HER2/3+/Ki67 – nuclear expression in 80% of neoplastic nuclei. On the right side, a 7/6/8 cm tumor formation with heterogeneous cut surface, mucinous areas, and hemorrhages was identified, histologically corresponding to moderately differentiated mucinous carcinoma with infiltration into the fatty tissue, and weakly expressed desmoplastic and lymphoplasmacytic stromal reaction G2pT3N0R0Pn-LV-PR-ER-IS-2, PS-3 (10-33%), TS-5 – corresponding to a 50% chance of therapeutic response, HER2/1+/. Ki-67 – over 10% proliferative activity.

On the 3rd day after discharge, exudation from the surgical wound was observed during a follow-up examination. Further laboratory tests revealed anemia, with Hb level dropped to 70 g/l, and significant hypoproteinemia (albumin – 19 g/l, total protein – 52 g/l). The patient was readmitted and started on conservative therapy including intravenous infusions, blood products, antibiotics, low-molecular-weight heparin, hepatoprotectors, and analgesics. Wound revision was performed and new drains were placed. Microbiologically Streptococcus beta-haemolyticus and Pseudomonas aeruginosa were isolated. Improvement in the general condition and a decrease in CRP from 18,07 mg/dl to 14,36 mg/dl were observed after treatment was initiated. During second admission patient started showing signs of depression, refusing food and rehabilitation. On the 4th day after wound revision, a sudden deterioration with signs of deepening hepatic (ALT – 174U/l, AST – 2704 U/l), renal (urea increased to 15,1 mmol/l, K-6,5 mmol/l, creatinine-170 mmol/l), and respiratory (Sat-67%) failure was noted. Extreme bradycardia followed by asystole was registered. Resuscitation measures were unsuccessful. Exitus letalis was claimed.

LITERATURE REVIEW

According to the World Health Organization (WHO) data, 2,3 million new cases of breast cancer were registered in 2020 alone, with the mortality rate of 685,000 [1, 18, 19, 20].

The leading positions among the members of the EU for breast cancer mortality in the age group 75+ in 2020 were occupied by Slovakia (220,3 cases per 100,000 population with a decrease to 189,7 in 2021), Luxembourg (220,3 cases, with a downward trend to 169,6 cases in 2021 and a new increase to 221,5 in 2022). The lowest mortality in 2020 in this age category was observed in Spain, Cyprus and Croatia (114,7; 119,4 and 125,9 cases per 100,000 respectively).

Among women in 55-74 age group, the highest mortality rates in 2020 were registered in Malta, Hungary and Bulgaria (83,3; 74,3 and 67,0 deaths per 100,000 population), and the lowest, again, in Spain (39,6 respectively).

In the 35-54 years' category, the leading position is occupied by Latvia with a mortality rate of 24,2 cases per 100,000 population. At the same time, 3,8 and 2 times lower rates were demonstrated by Luxembourg and Sweden.

The highest mortality among women aged 25-34 was observed in Lithuania (3,4 cases per 100,000 population). Meanwhile death rates in this group in Malta and Estonia were close to zero.

The average European breast cancer mortality in 2020 (the latest available data for Portugal and Romania is from 2019) among female patients aged 25-34 is 1,86 + 0,78; among 35-54 year olds – 16,38 ± 3,3; in categories 55-74 years – 56,596 ± 9,38 and 75+ years – 161,82 ± 30,76 per 100,000 population, respectively.

Of particular note is the fact that in such Asian countries as, for example, South Korea, the breast cancer mortality rate among 25-54-year-old female patients is 1,4 times, among 55-74-year-old – 3 times, and among women over 75 – 6 times lower than average European rates. In Japan and China (according to the latest available mortality data in Hong Kong from 2017), the corresponding coefficients among patients aged 55-74 years is 1,5 times lower, and among patients over 75 years old – 3 times lower than the European average rates (Figure 3).

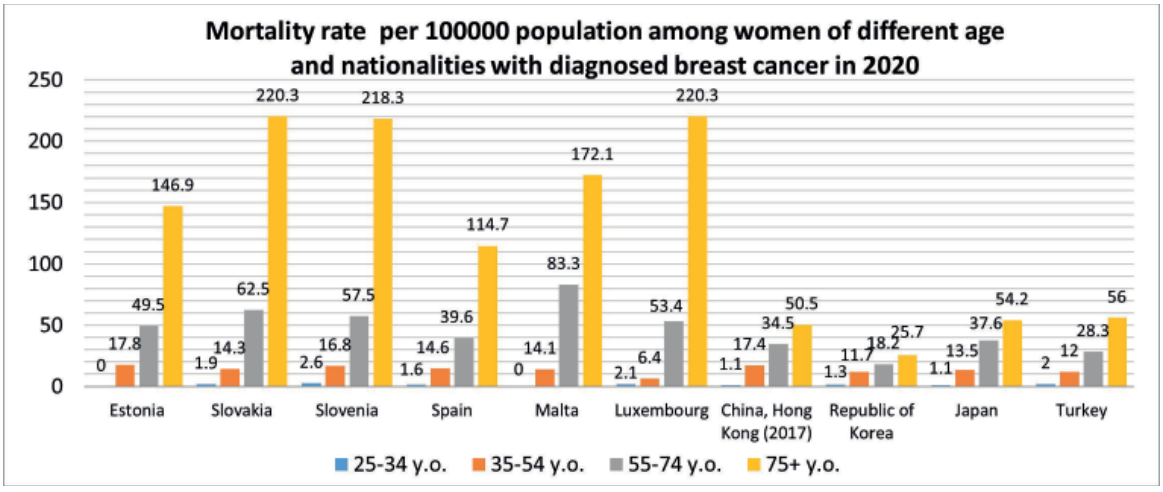

Fig. 3. Breast cancer mortality rates per 100,000 population in women of different ages from different countries in 2020 according to WHO data

In Bulgaria, the breast cancer mortality remains high. Among young patients aged 25-34 years, the mortality rate increased from 0,9 per 100,000 population in 2018 to 2,3 in 2021, almost reaching the level recorded in 2017. Among the age category 75+, 1,2 times increase was registered in mortality rate in 2021 compared to 2017. No significant dynamics were noted among patients of 55-74 and 35-54 year old categories during the period between 2017-2021 years (Figure 4).

Constantly increasing breast cancer morbidity and mortality in the world and in Bulgaria justifies the relevance of issues related to diagnosis and treatment of this pathology. Low coverage of preventive examinations and screening on the one hand, and extremely low self-awareness among women on the other, both lead to late diagnosis and unsatisfactory treatment results. The described clinical cases illustrate these trends.

About 4% of all patients in the EU and about 8,5% in the USA are diagnosed at the stage of locally advanced breast carcinoma [2]. In some Muslim countries as Uzbekistan, the same coefficient reaches 60-65% [7, 17].

About 17-40% of patients are being referred for neoadjuvant systemic therapy [8]. In primary inoperable locally advanced carcinomas, in order to reduce the size of the tumor formations, neoadjuvant radiotherapy is recommended, which according to the data of Sousa et al. also increased both 3- and 5-year overall (83% and 68% vs. 48% and 35%) and 3- and 5-year relapse-free (76% and 71% vs. 53% and 47%) survival rates conditional on pathologic response over 90% [3]. However, according to another retrospective cohort study which includes 41618 patients with locally advanced breast cancer, there was no statistically significant difference in overall 5-year survival between patients who underwent preoperative radiotherapy and a control group where radiotherapy was not performed [4]. According to a separate data, neoadjuvant chemotherapy is associated with achieving a satisfactory 10-year survival, – 65,1% in IIIA, 41,2% in IIIB and 26,7% in IIIC stages of breast cancer [5].

The surgical treatment of locally advanced carcinomas follows global trends and aims to achieve oncological radicality on the one hand and a good cosmetic result on the other [6]. Complemented by adjuvant cytotoxic, targeted, endocrine therapy, radiotherapy, surgical treatment increases overall survival in patients with advanced carcinoma [16]. However, in addition to neoadjuvant systemic therapy, earlier diagnosis helps to increase the percentage of organ-preserving surgeries. For example, in South Korea in 2017, about 8,6% of all newly discovered breast cancer cases were classified as stage III and IV, and the percentage of performed mastectomies for the same year turned out to be 2 times lower than in 2002 [9, 15]. In 2019, the percentage of newly discovered advanced cases drops to 7,5%, and the amount of organ-preserving surgical interventions reaches a country record of 68,6% [10]. Such results are achieved thanks to a functioning national screening program that has been generally available in South Korea since 2002, and covered about 60% of patients of 40-year-old and older with preventive mammograms in 2015. In Japan the same coefficient during 2016 reached 45% [11].

In Bulgaria, on the other hand, in 2017 only 20,6% of the target group of patients had undergone prophylactic mammography. According to EUROSTAT data for 2019, 24,1% of Bulgarian women have never been examined for breast cancer in their lifetime, and this indicator among EU countries is higher only in Romania, where it reaches 71,6% [12]. Finland and Sweden remain leaders in the EU in breast cancer screening, and in these countries the percentage of patients who had at least once undergone preventive mammography according to the 2019 data was 99% and 97,7%, respectively [13].

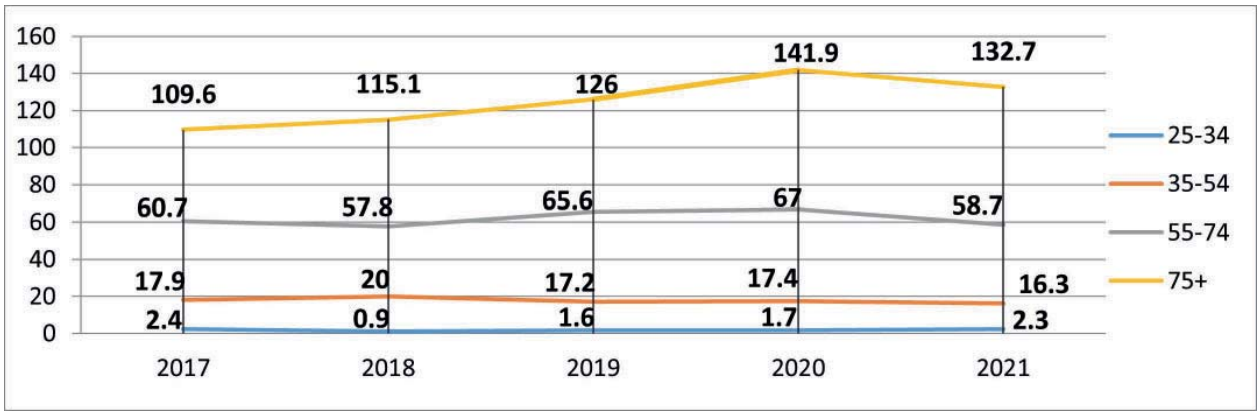

Fig. 4. Breast cancer mortality rates per 100,000 population in women of different ages in Bulgaria for the period between 2017 and 2021 according to WHO data

It has been proven that participation of 70-75% of patients from the target group in screening programs allows significantly reduction of the mortality rate. Moreover, 8,8 and 5,7 deaths per 1000 women in Sweden and Great Britain were averted thanks to regular breast cancer screening among patients of 50 years and older in the last 20 years [14].

CONCLUSIONS

Breast cancer is the leading localization of the oncological process in women in the world, with high morbidity and mortality.

The death rate in young female patients aged 25-34 in Bulgaria has been continuously increasing since 2018 and reaches 2,3 cases per 100,000 population in 2021.

According to the World Health Organization data for 2020, the breast cancer mortality rate in the Republic of Bulgaria exceeds the corresponding coefficients in South Korea by 1,3; 1,5; 3,7 and 5,5 times for females aged 25-34, 35-54, 55-74 and 75+ years, respectively. For the same year, among the 55-74 age group, mortality in Bulgaria was 1,18 times higher compared to the European average.

According to the EUROSTAT data in Bulgaria in 2017, 79,4% of the target patient group were not covered by prophylactic mammograms, and information is missing for subsequent years.

Low awareness among the population and inefficiency of screening leads to late diagnosis of breast cancer, unsatisfactory treatment results and high mortality; it also makes oncoplastic and organ-preserving surgeries challenging and often technically impossible to perform.

Described case reports illustrate the existing trends in Bulgaria and show the necessity of national screening program immediate reformation, as well as oncological institutions reorganization.

The article highlights the importance of the popularization of the information related to the breast cancer prevention and prophylactic as it is a socially significant disease.

Conflict of interests: *Authors declare no conflict of interests*

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