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CLINICO-MORPHOLOGICAL FEATURES OF THE LUMINAL B SUBTYPE OF BREAST CANCER IN YOUNG WOMEN

Aim. To evaluate the clinical and morphological features of breast cancer (BC) of the luminal B subtype in young women to determine biological aggressiveness, response to neoadjuvant chemotherapy, and prognosis. **Materials and Methods.** A retrospective study included luminal B subtype BC patients under 40 years of age (n = 108) and over 55 years (n = 101) treated at the National Cancer Institute. All patients received neoadjuvant chemotherapy according to the ddAC-12T regimen. TNM stages, tumor differentiation grade, Ki-67 expression, hormone receptor status, response to the neoadjuvant chemotherapy (NAC) (RECIST 1.1), pathomorphology grade (Miller — Payne), disease-free (DFS) and overall survival (OS) were analyzed. **Results.** Patients of the younger age group were more likely to have G3 tumors (68% vs. 45%), high Ki-67 levels >35% (72% vs. 50%), and lymph node involvement (71% vs. 59%). The median estrogen receptor expression was 35% in the young patients vs. 65% in the older patients. Complete histological response to NAC was achieved in 26% of the young patients (vs. 9% in the older group). Five-year RFS in the young women was 82.4% vs. 94.1% in the older group. **Conclusions.** The luminal B subtype of BC in the young women is characterized by the higher proliferative activity, lower hormonal sensitivity, and more frequent lymph node involvement. Despite the response to NAC, this group demonstrates the worse DFS. The results confirm the need for personalized treatment strategies and improved early diagnosis programs in young patients.

Keywords: breast cancer, young age, Ki-67, luminal subtype, pathological response, neoadjuvant therapy.

Breast cancer (BC) incidence has increased rapidly in recent decades, especially among young women. BC is the leading cancer in women aged 15—39 years [1]. The young age is an independent adverse prognostic factor for BC, which is associated with the more aggressive course of the disease, a high risk of metastasis and recurrence, and lower survival rates. The clinicopathological and molecular biological features of BC in young patients differ from those in older age groups, which affects the course of the disease and response to therapy [1, 2].

Young women under 40 years of age are largely excluded from the organized BC screening programs, which primarily target women over 50 years.

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An analysis of the data from nine SEER registries (San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, and Metropolitan Atlanta) found that younger women were more likely to have BC at the later stages (II and III) than older women. In particular, stage II BC was diagnosed in 45.1% of women under 40 years of age compared to only 30.9% of women aged 40 years and older [3].

Even when mammographic screening is performed, younger women have a lower detection rate compared to postmenopausal women. This is due to the high density of breast tissue at a young age, which can mask the radiographic signs of early BC, making it more difficult to detect [4].

The lack of the systematic early detection measures leads to the delayed diagnosis of the disease, which contributes to the detection of BC at later stages. As a result, in a significant proportion of patients, preoperative (neoadjuvant) chemotherapy, the purpose of which is to reduce the volume of the tumor before surgery, becomes the first line of therapy [5]. Research shows that young BC patients who receive neoadjuvant chemotherapy (NAC) have the shorter interval to the start of the treatment compared to those who undergo primary surgery. This emphasizes the importance of the neoadjuvant approach in the therapeutic strategy for the young women, especially in the case of the aggressive biological characteristics of the tumor. Given these factors, improving approaches to early diagnosis and implementing personalized treatment strategies are critical to improving the prognosis and survival of patients in such age group [6].

The patients under 40 years of age with the luminal BC subtype demonstrate paradoxically lower survival rates compared to older patients with a similar subtype due to a combination of the biological aggressiveness of the tumor and late diagnosis [7]. The worse disease-free survival (DFS) in hormone receptor-positive BC (estrogen receptor [ER] or progesterone receptor [PR]) has been reported in younger age groups (<40 years) compared to older age groups [8]. Also, the poor outcome may result from the lack of access to medical care and delayed diagnosis among vulnerable young patients.

A number of studies suggest that ER expression plays a key role in the changes associated with reproductive history, as the hormonal shifts inherent in pregnancy and breastfeeding can alter the microenvironment of the mammary gland cells and create conditions conducive to the activation of the proliferative processes [9, 10].

The luminal B-like BC subtype is characterized by a higher aggressiveness and significantly worse prognosis compared to the luminal A-like BC variant. Despite the positive ER expression, luminal B-like tumors often activate the alternative growth signaling pathways. A worse prognosis in patients with the luminal B-like BC subtype (HER2-negative) may be due to the activation of the EGFR and PI3K/AKT/mTOR signaling cascades, which compensate for or enhance tumor growth in conditions of reduced hormonal sensitivity [11].

Particular attention is paid to the hypothesis of postpartum involution, by which changes in the extracellular matrix occur in breast tissue after lactation accompanied by activation of collagen remodeling and structural reorganization of collagen fibers [12]. This may stimulate the BC development with the involvement of collagen, cyclooxygenase-2 (COX-2), and activation of mechanisms inherent in wound-healing processes [12, 13].

Therefore, the aim of the work was to study the clinical and morphological features and course of the luminal B subtype of BC in women under 40 years of age by analyzing the response rates to NAC, the level of proliferation, and hormonal sensitivity, compared to women older than 55 years.

Materials and Methods

We have performed a retrospective analysis of the data on 108 women under the age of 40 with luminal B BC who were treated at the National Cancer Institute in 2021—2024. For comparison, a control group of 101 women older than 55 years from the National Cancer Registry was selected ensuring matching on the key clinical parameters (tumor type, hormonal status, and absence of metastases at the time of diagnosis). In these groups, a number of clinical and morphological features and the results of treatment have been analyzed.

All patients were treated by a standardized scheme of a dense AC regimen (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 14 days) with the subsequent transition to weekly administration of paclitaxel 80 mg/m^2. The results were assessed using computed tomog-

raphy (RECIST 1.1) before the start of the preoperative course and after it. Tumor pathomorphosis was assessed using the Miller — Payne grading system, which includes five stages of tumor regression: 1 — Lack of appropriate morphological response to treatment; 2 — Reduction in the number of tumor cells but their preservation of more than 30%; 3 — Marked reduction in tumor cells but their preservation within 10%—30%; 4 — Less than 10% viable tumor cells in the residual tumor; 5 — Complete absence of tumor cells (pathological complete response, pCR).

All patients had a localized or locally advanced BC. Immunohistochemically, all tumors were characterized by positive ER expression (ER 1^+–3^+), with low or absent PR expression (PR 0–2^+ in most cases), negative HER2/neu status (in 100% of cases), and a Ki-67 proliferation index of ≥15%, which met the criteria for determining the luminal B subtype according to international recommendations (ESMO, 2023).

The statistical analysis was performed using «IBM SPSS Statistics, version 26». For the analysis of categorical variables, the χ^2 test or Fisher's exact test was used, for quantitative variables — Student's *t*-test or Mann — Whitney U-test. The significance was established at $p < 0.05$.

Results and Discussion

The clinical and morphological analyses revealed significant differences between the groups of BC patients of different age (Table). The regional lymph node involvement (N1—N2) was significantly more common in the younger women compared to patients of the older age. At the same time, the primary tumor size was smaller in the young women, while T3—T4 tumors were found more often in the older group. This may be possible due to the fact that in the older cohort, the diagnosis was more often made at the asymptomatic stage during screening.

In terms of the histological differentiation, poorly differentiated tumors (G3) predominated in the young patients (68%) while in the older cohort, G3 grade was revealed in 45% of cases ($p < 0.05$). This indicates the prevalence of more aggressive cancer at a young age. The proliferative activity determined by the Ki-67 index was also significantly higher in the young patients: the average level was 45.6% (95% CI: 42.3—49.1) versus 32.8% (95% CI: 30.1—35.5) in the older patients ($p < 0.01$). Ki-67 >35% was found in 72% women under 40 years of age and 50% women 55+ years of age ($p < 0.05$), which further indicates the higher biological activity of tumors in the younger group.

In terms of the hormonal profile, the young patients had a moderate or low expression of ER— a median of 35%, with more than half of cases having an ER level ≤50%. PR were negative or weakly positive (0–10%) in 57% of patients. In the older cohort, the median ER level was 65%, with a predominance of strong expression. PR positivity (≥20%) was observed in 57% of patients.

It is important to note that the history of diagnosing was also age-specific. In the group of women aged 55+, 52.5% cancer cases were detected during routine mammographic screening, which contributed to the detection of tumors at an early stage. In the younger cohort, only 22 women (20.4%) underwent screening, while the rest presented due to symptoms such as palpable mass,

Clinical and morphological features of the studied BC cases

Index	Age of BC patients	
	< 40 years (n = 108)	> 55 years (n = 101)
N category		
Regional LN lesions (N1—N2)	77 (71%)	60 (59%)
N1 (1—3 LN)	61 (56.5%)	47 (46.5%)
N2 (≥4 LN)	16 (14.8%)	13 (12.9%)
None (N0)	31 (28.7%)	41 (40.6%)
T category		
T1—T2	69 (64%)	49 (49%)
T3—T4	39 (36.1%)	52 (51.5%)
Differentiation grade		
G3 (low)	73 (68%)	45 (45%)
G2 (moderate)	35 (32%)	56 (55%)
Ki-67 expression		
Average	45.6 %	32.8 %
>35%	78 (72%)	50 (50%)
Receptor status		
ER median (%)	35 %	65 %
ER ≤50%	57 %	24 %
PR 0—10%	57 %	43 %
PR ≥20%	43 %	57 %

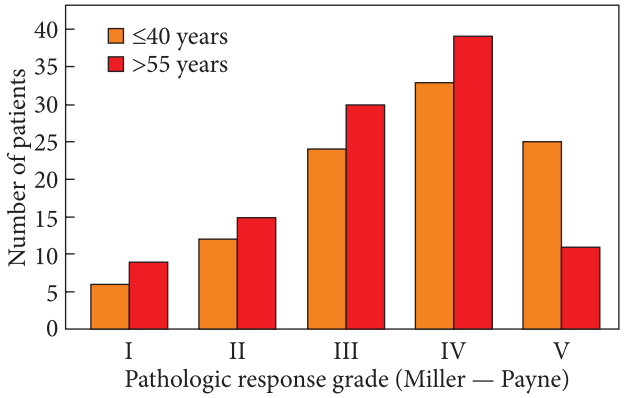

Fig. 1. Distribution of pathologic response grades in the study groups

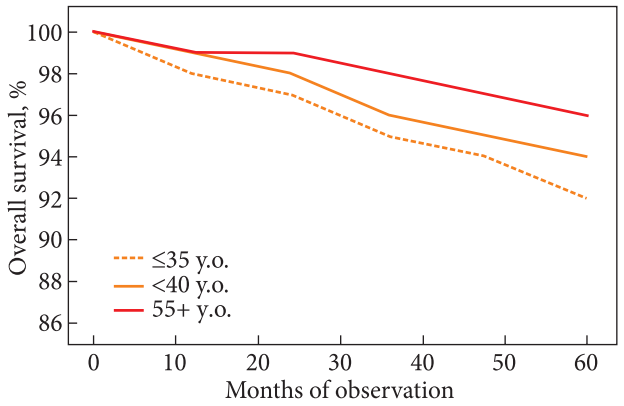

Fig. 2. Kaplan — Meier survival curves of BC patients by age groups

pain, or changes in the shape of the breast. This partly explains the higher frequency of the lymph node involvement and the greater cancer aggressiveness in the young women. Thus, in patients under 40 years of age, tumors with the higher proliferative activity, lower differentiation grade, higher frequency of LN involvement, and lower level of hormonal sensitivity were more often recorded, which comprehensively indicated the more aggressive biological course even within the ER-positive luminal B subtype.

The objective responses to the treatment according to RECIST 1.1 were assessed based on the computed tomography data, including disease stabilization (DS), partial (PR), and complete response (CR). In the group under 40 years of age, PR was observed in 51 women, CR in 22, DS in 33, and disease progression in 2 patients. In the older group, PR was recorded in 42 women, DS in 49, and CR in 10 women ($p < 0.05$).

We detected that in young women, the frequency of grade IV and V pathomorphosis (Fig. 1) was higher compared to the group of older women. The complete histological response (grade V) was observed in 26% of young patients versus 9% in the older group, and grade IV was observed in 40% of the young patients versus 30% in the older group. This indicated the better response to neoadjuvant chemotherapy in the younger group. At the same time, it should be noted that the complete pathomorphological response, according to postoperative histological analysis, did not always correspond to CR by computed tomography. In 12 patients in the younger group, in whom complete pathomorphosis was confirmed, CT showed only PR or DS according to RECIST 1.1.

The overall survival (OS) (Fig. 2) was 93.5% in the young group compared to 97.0% ($p < 0.05$) in the older group. However, subgroup analysis of OS showed that very young women (<35 years) had lower OS rates (87.8%).

Five-year recurrence-free survival (RFS) was significantly lower in younger women, with recurrence diagnosed in 17.6% cases, corresponding to a RFS of 82.4%, while in the older group, RFS was equal to 94.1% ($p < 0.05$). This confirms the higher cancer aggressiveness.

Luminal B subtype of BC is recognized worldwide as a biologically heterogeneous disease that poses significant clinical challenges, especially in younger women. Meta-analyses consistently demonstrate a higher risk of recurrence and worse survival rates in luminal B subtype BC patients [15, 16].

The luminal B subtype of BC is considered clinically important due to its heterogeneity, high proliferative activity, more frequent development of drug resistance, and poorer response to hormone therapy, which distinguishes it from the luminal A subtype. Among young women (under 40 years of age), the luminal B subtype is detected significantly more often than in older patients, and has a worse prognosis and survival rates compared to other molecular subtypes.

Our data are consistent with European studies indicating that young age is an independent adverse prognostic factor for the luminal B subtype of BC. The results are also consistent with the data from large international projects such as METABRIC, plasmaMATCH, and The Cancer Genome Atlas (TCGA), which indicate significant intra-group variability within ER-positive tumors [17, 18]. In

particular, studies [19, 20] showed that young age is associated with lower rates of RFS and OS specifically in patients with luminal BC subtypes.

Additionally, study [11] showed that in women younger than 40 years, the luminal B subtype is associated with the higher rates of locoregional recurrence after surgery, highlighting the need to develop personalized treatment and follow-up approaches for young patients with this BC subtype.

Given the above, it is important to pay special attention to early diagnosis and individualization of treatment of the luminal B subtype of breast cancer in young women to improve prognosis and increase survival rates.

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КЛІНІКО-МОРФОЛОГІЧНІ ОСОБЛИВОСТІ ЛЮМІНАЛЬНОГО В ПІДТИПУ РАКУ МОЛОЧНОЇ ЗАЛОЗИ В МОЛОДИХ ЖІНОК

Мета. Оцінити клініко-морфологічні особливості люмінального В підтипу раку молочної залози (РМЗ) у жінок віком до 40 років та порівняти їх із контрольної групою жінок віком понад 55 років для з'ясування біологічної агресивності та відповіді на неоад'ювантну хіміотерапію та прогнозу. **Матеріали та методи.** Проведено ретроспективне дослідження, яке включало 108 хворих віком до 40 років із люмінальним В підтипом РМЗ та 101 хвору віком понад 55 років. Усі хворі отримували неоад'ювантну хіміотерапію (НАХТ) за схемою ddAC-12T. Аналізували стадії TNM, ступінь диференціювання пухлин, рівень експресії Ki-67, статус гормональних рецепторів, відповідь на НАХТ (RECIST 1.1), ступінь патоморфозу (Miller — Payne), безрецидивну та загальну виживаність. **Результати.** У пацієнток молодшої вікової групи частіше спостерігалися пухлини G3 (68% проти 45%), високий рівень Ki-67 >35% (72% проти 50%), ураження лімфатичних вузлів (71% проти 59%). Медіана експресії рецептора естрогену становила 35% у молодих проти 65% у старших. Повна гістологічна відповідь на НАХТ досягнута у 26% молодих пацієнток (проти 9%). П'ятирічна безрецидивна виживаність у молодих жінок склала 82,4% проти 94,1% у старшій групі. **Висновки.** Люмінальний В підтип РМЗ у молодих жінок характеризується вищою проліферативною активністю, нижчою гормональною чутливістю та частішим ураженням лімфатичних вузлів. Попри кращу відповідь на НАХТ, ця група демонструє гірші показники безрецидивної виживаності. Отримані результати підтверджують необхідність персоналізованих стратегій лікування та удосконалення програм ранньої діагностики у молодих хворих.

Ключові слова: рак молочної залози, молодий вік, Ki-67, люмінальний підтип, патологічна відповідь, неоад'ювантна терапія.