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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Clinical, pathological, and molecular predictors of axillary lymph node metastases in young women with breast cancer

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SUMMARY

Introduction/Objective Breast cancer in women shows more aggressive biological characteristics, while the status of axillary lymph nodes remains the most important prognostic factor. The aim of this study was to determine the prevalence of axillary lymph node metastases and to identify histological and immunohistochemical predictors in patients under 40 years of age with breast cancer.

Methods A retrospective cohort study that included patients under 40 years of age with histopathologically confirmed breast cancer who underwent surgical treatment at the Department of Oncological Surgery, Clinical Hospital Center "Bežanijska kosa", between 2014 and 2024.

Results The study included 97 patients under 40 years of age (mean age 34.75 ± 3.74 years). Axillary lymph node metastases were identified in 48.5% of patients, while sentinel lymph node biopsy was positive in 26.8%. The most common molecular subtype was Luminal B (53.6%). Luminal B tumors were associated with younger age (p = 0.031) and higher body mass index (p = 0.007). HER2-positive and triple-negative tumors were more often of high histological grade (p = 0.003) and larger tumor size (p = 0.025), with a higher Ki-67 proliferation index (p = 0.001). Positive axillary lymph node status was significantly associated with Rh-positive blood type (p = 0.004), tumor size (p = 0.001), and mastectomy (p = 0.004).

Conclusion Breast cancer in women under 40 years of age is characterized by marked biological heterogeneity, with axillary lymph node metastases significantly associated with larger tumor size and more aggressive biological characteristics.

Keywords: breast cancer; biopsy; axillary lymph nodes; molecular subtypes

INTRODUCTION

Breast cancer is one of the most common malignancies in women, with an increasing frequency in younger ages, already after the age of 40 [1]. Although the incidence of breast cancer in women under 40 is lower than in older women [2, 3], the disease in this population often has more aggressive biological characteristics, including triple-negative and human epidermal growth factor receptor 2 (HER2)-positive subtypes, later diagnosis, and a poorer prognosis, with a higher risk of local recurrence and distant metastases [4, 5]. Despite the reduction in overall mortality due to advances in early detection and therapy, breast cancer in young women remains a significant clinical and public health challenge [6].

Metastatic disease is the main cause of mortality in breast cancer, responsible for more than 90% of deaths [7]. The metastatic process is complex and includes epithelial-mesenchymal transition, invasion, intravasation, survival in circulation, extravasation, and colonization of target tissues [7]. These processes are influenced by the interaction of tumor cells with the microenvironment, as well as specific signaling pathways that determine the organic tropism of metastases, including frequent dissemination to bones, lungs, liver, and brain [8]. Understanding the mechanisms of metastasis has enabled the identification of biological markers and the development of targeted therapeutic strategies [9].

The status of axillary lymph nodes is the most important independent prognostic factor in breast cancer [10]. Metastasis even in one axillary lymph node significantly increases the risk of distant disease and directly affects decisions on the application of adjuvant therapy [11]. Although the introduction of sentinel lymph node biopsy significantly reduced morbidity compared to classic axillary dissection, this approach carries the risk of false-negative findings [12]. Data show that a significant number of patients with a positive sentinel node do not have additional residual axillary disease, which calls into question the routine application of complete axillary dissection [13].

Recent randomized studies have shown that in selected patients with T1/T2 tumors and limited involvement of sentinel lymph nodes, axillary dissection can be safely omitted with adequate application of radiotherapy and systemic treatment, without jeopardizing

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oncological outcomes [14]. These findings emphasize the need to identify reliable clinical, pathological, and biological predictors of axillary metastases in order to avoid unnecessary surgical interventions.

To date, numerous factors have been identified as independent predictors of axillary lymph node involvement, including tumor size, lymphovascular invasion, histological grade, and molecular characteristics of the tumor [13, 15, 16]. Molecular subtypes of breast cancer further allow for risk stratification, with luminal A tumors having the most favorable prognosis, while luminal B, HER2-positive, and triple-negative cancers show a greater propensity for nodal and distant spread [17, 18]. In addition, radiological methods, especially magnetic resonance imaging (MRI), show potential in predicting axillary metastases, although their diagnostic accuracy is still not sufficient to replace histopathological evaluation [19, 20, 21].

The aim of the study was to determine the frequency of axillary lymph node metastases in women under 40 years of age with breast cancer and to examine the association of these metastases with the histological and immunohistochemical characteristics of the tumor.

METHODS

Type of study, place, and period of research

This study was designed as a retrospective cohort study and included female patients under the age of 40 with a histopathologically confirmed diagnosis of breast cancer who were surgically treated at the Oncology Surgery Department of the "Bežanijska Kosa" Clinical Hospital Center in the period from 2014 to 2024.

All data used in the research were anonymized and encrypted, and the analysis was conducted in accordance with the ethical principles of patient privacy protection. The study was approved by the Ethics Committee and the Expert Council of University Clinical Hospital Center "Bežanijska Kosa." The research did not use personal data that could lead to the identification of female patients.

Source and collection of data

Medical documentation, including electronic medical records from the hospital database used in daily clinical work, was used as a data source. Data on demographic, clinical, surgical, histopathological, and immunohistochemical characteristics of tumors were collected from the available documentation.

The following parameters were analyzed: patient age, body weight (kg), body height (cm), body mass index (BMI), categorized as underweight, normal body weight, overweight, and obesity, blood group and Rhesus factor (Rh factor), affected breast (left/right), type of surgical intervention performed (sparing operation or mastectomy), tumor size, histological type of tumor (ductal, lobular, mucinous, medullary), histological grade (G1, G2, G3), estrogen and progesterone receptor status (positive/negative), HER2 status (positive/negative), Ki-67 proliferative index, and molecular subtype of breast cancer (Luminal A, Luminal B, HER2-positive, and triple negative).

In addition, data on the status of lymph nodes were analyzed, including the performance and results of sentinel lymph node biopsy (not performed/negative/positive), application of axillary lymphadenectomy (not performed/negative/positive), the total number of removed and histopathologically examined lymph nodes, the total number of positive lymph nodes, as well as the number of positive sentinel and axillary lymph nodes.

Statistical analysis

Statistical data processing was performed using the IBM SPSS Statistics for Windows, Version 19.0. (IBM Corp., Armonk, NY, USA). The level of statistical significance was set at $p < 0.05$. Final results are presented as categorical variables (absolute and relative frequencies) and continuous variables (mean ± standard deviation).

Nonparametric tests were used to analyze differences between groups, including the χ^2 test for categorical variables, the Mann–Whitney U test for comparing two independent groups, and the Kruskal–Wallis test for comparing multiple groups.

RESULTS

A total of 97 patients with breast cancer under 40, with an average age of 34.75 ± 3.74 years, were included in the study. Most of the respondents were Rh-positive (81.4%) and blood type A (47.4%). The average BMI was 23.32 ± 4.79, with the largest number of female patients having a normal body weight (62.9%) (Table 1).

The left breast was most often affected (51.5%), and in most patients a sparing surgical intervention was used

Table 1. Sociodemographic and anthropometric characteristics of female patients

Variables		Number	Percentage (%)
Body mass index categories	Malnutrition	9	9.3
	Normal body weight	61	62.9
	Excessive body weight	18	18.6
	Obesity	9	9.3
Rh	Negative	18	18.6
	Positive	79	81.4
Blood type	A	46	47.4
	B	16	16.5
	AB	9	9.3
	O	26	26.8
Parameters	Minimum	Maximum	Mean value ± SD
Age	22	40	34.75 ± 3.74
Body weight (kg)	32	130	65.81 ± 14.3
Body height (cm)	150	185	167.92 ± 6.77
Body mass index	12.04	42.45	23.32 ± 4.79

SD – standard deviation; Rh – Rhesus factor

Table 2. Clinical, surgical, histopathological, and immunohistochemical characteristics of the tumor

Variables		Number	Percentage (%)
Breast	Left	50	51.5
	Right	47	48.5
Operation	Economical	54	55.7
	Mastectomy	43	44.3
Histopathological finding	Ductal	88	90.7
	Mucinous	2	2.1
	Medullary	2	2.1
	Lobular	5	5.2
Gradus of the tumor	First	2	2.1
	Others	74	76.3
	Third	21	21.6
Estrogen receptor	Negative	22	22.7
	Positive	75	77.3
Progesterone receptor	Negative	25	25.8
	Positive	72	74.2
HER2	Negative	62	63.9
	Positive	35	36.1
Luminal category	Luminal A	23	23.7
	Luminal B	52	53.6
	HER2-positive	7	7.2
	Triple negative	15	15.5
Parameters	Minimum	Maximum	Mean value ± SD
Tumor size	4	70	23.9 ± 12.96
Ki_67_percent	1	90	35.22 ± 3.17

SD – standard deviation; HER – human epidermal growth factor receptor; Ki_67 – marker of proliferation Ki-67

(55.7%). Histopathologically, invasive ductal carcinoma predominated (90.7%), with the most common histological grade being II (76.3%). Most tumors were positive for estrogen (77.3%) and progesterone receptors (74.2%), while HER2 positivity was recorded in 36.1% of patients. The most common molecular subtype was Luminal B (53.6%), followed by Luminal A (23.7%), triple-negative (15.5%), and HER2-positive tumors (7.2%) (Table 2).

Table 3. Characteristics of removed sentinel and axillary lymph nodes in women under 40 years of age with breast cancer

Variables		Number	Percentage (%)
Sentinel glands	They were not done	26	26.8
	Done	71	73.2
The result of the sentinel gland examination	It was not done	26	26.8
	Negative	45	46.4
	Positive	26	26.8
Axillary dissection	They were not done	41	42.3
	Done	56	57.7
The result of examination of the axillary glands	It was not done	41	42.3
	Negative	9	9.3
	Positive	47	48.5
Total number of glands examined	Only sentinels removed	41	42.3
	Sentinel and axillary removed	30	30.9
	Only axillary removed	26	26.8
Total positive glands	Negative sentinel and axillary	44	45.4
	Sentinel only positive	6	6.2
	Positive only axillary	27	27.8
	Positive sentinel and axillary	20	20.6

Sentinel lymph node biopsy was performed in 73.2% of patients, with positivity determined in 26.8%. Axillary lymph node dissection was performed in 57.7% of women, and axillary metastases were confirmed in 48.5%. In total, an average of 10.52 ± 9.24 lymph nodes were removed per patient, with an average of 2.16 ± 3.63 positive nodes. Only positive sentinel nodes were present in 6.2% of patients, only axillary nodes in 20.6%, while both sentinel and axillary nodes were positive in 27.8% of subjects (Table 3).

Analysis in relation to molecular subtypes revealed that patients with Luminal B tumors were statistically significantly younger compared to the Luminal A subtype ($p = 0.031$) and had a higher BMI ($p = 0.007$). Luminal A and Luminal B tumors were significantly more often of histological grade II, while HER2-positive and triple-negative tumors were predominantly of high grade ($p = 0.003$). Tumor size was significantly smaller in Luminal A and Luminal B subtypes compared to HER2-positive and triple-negative tumors ($p = 0.025$). The Ki-67 index increased statistically significantly from Luminal A to triple-negative tumors ($p = 0.001$) (Table 4).

When analyzing factors associated with axillary lymph node positivity, it was found that axillary metastases are significantly more common in Rh-positive patients ($p = 0.004$), in larger tumors ($p = 0.001$), and in patients who underwent mastectomy ($p = 0.004$). The number of removed and positive lymph nodes was significantly higher in patients with positive sentinel and axillary lymph nodes ($p = 0.001$) (Table 5).

DISCUSSION

Breast cancer in women under the age of 40 is a distinct clinical entity that differs from the disease in the older population in terms of biological characteristics, patterns of spread, and therapeutic challenges. In our study, the average age of female patients at diagnosis was in the middle of the fourth decade of life, which is in accordance with previously published data indicating that in this age group the disease is often diagnosed during the reproductive period, with significant long-term consequences for quality of life [22].

Anthropometric analysis in our sample showed that most patients had a normal body mass, while significant differences in BMI were observed depending on the molecular subtype of the tumor. In particular, it was observed that patients with Luminal B carcinoma had a higher BMI compared to other subtypes, while patients with triple negative tumors had the lowest BMI values. Although the relationship between body mass and tumor biology is complex and insufficiently elucidated, previous studies indicate that metabolic status may influence the hormonal environment and proliferative potential of tumors, particularly in hormone-dependent subtypes [23].

In terms of localization and histopathological characteristics, in our study the left breast was most

Table 4. Comparison of sociodemographic and clinical-pathological parameters according to molecular (luminal) subtypes of breast cancer in women under 40 years of age

Variables		Luminal A	Luminal B	HER2-enriched	Triple negative	p
Body mass index*		23.1 ± 3.09	24.41 ± 5.31	23.91 ± 4.68	19.64 ± 3.36	0.007
Body mass index categories	Malnutrition	0 (0%)	5 (9.6%)	0 (0%)	4 (26.7%)	0.017
	Normal body weight	15 (65.2%)	30 (57.7%)	5 (71.4%)	11 (73.3%)	
	Excessive body weight	8 (34.8%)	9 (17.3%)	1 (14.3%)	0 (0%)	
	Obesity	0 (0%)	8 (15.4%)	1 (14.3%)	0 (0%)	
Histopathological finding	Ductal	22 (95.7%)	45 (86.5%)	7 (100%)	14 (93.3%)	0.461
	The others	1 (4.3%)	7 (13.5%)	0 (0%)	1 (6.7%)	
Gradus of the tumor	The first	0 (0%)	2 (3.8%)	0 (0%)	0 (0%)	0.003
	Others	21 (91.3%)	43 (82.7%)	3 (42.9%)	7 (46.7%)	
	The third	2 (8.7%)	7 (13.5%)	4 (57.1%)	8 (53.3%)	
Tumor size*		29.61 ± 13.45	20.35 ± 10.32	26 ± 21.09	26.47 ± 13.39	0.025
Ki_67_percent*		14.57 ± 4.24	37.13 ± 21.56	49.29 ± 20.09	53.67 ± 24.67	0.001
The result of the sentinel gland examination	It was not done	6 (26.1%)	15 (28.8%)	3 (42.9%)	2 (13.3%)	0.609
	Negative	11 (47.8%)	22 (42.3%)	4 (57.1%)	8 (53.3%)	
	Positive	6 (26.1%)	15 (28.8%)	0 (0%)	5 (33.3%)	
The result of examination of the axillary glands	It was not done	10 (43.5%)	21 (40.4%)	3 (42.9%)	7 (46.7%)	0.373
	Negative	0 (0%)	5 (9.6%)	2 (28.6%)	2 (33.3%)	
	Positive	13 (56.5%)	26 (50%)	2 (28.6%)	6 (40%)	

*Continuous variable presented as mean ± SD;
HER – human epidermal growth factor receptor; Ki_67 – marker of proliferation Ki-67

Table 5. Comparison of sociodemographic and clinical-pathological parameters in relation to the status of sentinel and axillary lymph nodes in women under 40 years of age with breast cancer

Variables		Sentinel			Axillary		
		Not done/negative	Positive	p	Not done/negative	Positive	p
Rhesus factor	Negative	15 (21.1%)	3 (11.5%)	0.221	15 (30%)	3 (6.4%)	0.004
	Positive	56 (78.8%)	23 (88.5%)		35 (70%)	44 (93.6%)	
Operation	Economical	42 (59.2%)	12 (46.2%)	0.356	35 (70%)	19 (40.4%)	0.004
	Mastectomy	29 (40.85%)	14 (53.8%)		15 (30%)	28 (59.6%)	
Tumor size*		23.31 ± 12.78	25.5 ± 13.58	0.348	19.92 ± 10.24	28.13 ± 14.26	0.001
Ki_67_percent*		33.97 ± 22.82	38.62 ± 24.23	0.381	35.72 ± 23.25	34.68 ± 23.32	0.831
Total glands removed per woman*		8.34 ± 8.54	16.46 ± 18.56	0.001	4.26 ± 5.82	17.17 ± 7.36	0.001
Total positive glands per woman*		1.66 ± 3.84	3.54 ± 32.56	0.001	0.2 ± 0.61	4.26 ± 4.3	0.001

*Continuous variable presented as mean ± SD;
Ki_67 – marker of proliferation Ki-67

often affected, and the dominant histological type was invasive ductal carcinoma, with the predominant histological grade being II. This distribution is consistent with the findings of previous studies examining breast cancer in younger women and confirms that, despite the younger age, the basic histopathological features often follow the patterns seen in the general population [22, 23].

Immunohistochemical analysis in our sample showed a predominance of hormone receptor-positive tumors, with a significant proportion of HER2-positive and triple-negative cancers. According to the molecular classification, Luminal B and Luminal A subtypes were most frequently represented. Recent studies continue to demonstrate that Luminal B remains the predominant molecular subtype among young women with breast cancer, supporting our finding that more than half of the patients belonged to this molecular category [24, 25].

Analysis of molecular subtypes in our work showed clear differences in histological grade, tumor size, and proliferative index. Luminal A and Luminal B tumors were more often in histological grade II and had smaller dimensions compared to HER2-positive and triple-negative tumors, which were predominantly of higher grade. Contemporary studies have confirmed that HER2-positive and triple-negative tumors are characterized by higher histological grade, increased proliferative activity, and more aggressive biological behavior, which is consistent with our findings [25, 26, 27].

The Ki-67 proliferative index in our study showed a statistically significant increase from Luminal A to Luminal B, HER2-positive, and triple-negative tumors. Recent evidence continues to support Ki-67 as an important marker of tumor aggressiveness and treatment response, particularly in biologically heterogeneous breast cancers, which corresponds to the progressive increase observed across molecular subtypes in our cohort [25].

When it comes to surgical treatment, breast-sparing surgery was more often applied in our sample. Modern therapeutic concepts favor breast conservation when it is oncologically safe, especially in younger patients, in whom aesthetic and psychosocial aspects are of particular importance. At the same time, the decision on the scope

of the surgical intervention must be coordinated with the characteristics of the tumor and the status of the axillary lymph nodes. The status of axillary lymph nodes is one of the most important prognostic factors in breast cancer. In our study, sentinel lymph node biopsy was used in most patients, while axillary dissection was performed in part of the subjects, with a high percentage of confirmed axillary metastases in that group. Recent prospective studies suggest that axillary surgery can be safely de-escalated in carefully selected patients; however, the relatively high prevalence of axillary metastases in our cohort indicates that young women still require careful axillary assessment [26, 27, 28].

In our sample, axillary lymph node positivity was significantly associated with larger tumor size and the choice of mastectomy as the surgical method. Several recent predictive models have identified tumor size as one of the strongest predictors of axillary lymph node involvement, which is fully consistent with the results of our study [29].

Literature data additionally indicate that the frequency of lymphatic metastases differs among molecular subtypes of breast cancer. Recent studies continue to demonstrate significant differences in nodal involvement among molecular subtypes, emphasizing the biological heterogeneity of breast cancer and the importance of individualized risk assessment [24]. These data are in agreement with the findings of our study and confirm the heterogeneity of the biological behavior of breast cancer in young women.

Overall, our results confirm that breast cancer in women younger than 40 years is a heterogeneous disease in which molecular subtype, histological characteristics of the tumor and axillary lymph node status play a key role in the assessment of biological behavior and planning of therapy. Similar conclusions have been reported in recent international and regional studies, including data from Serbia, highlighting the persistent prognostic importance of axillary lymph node status despite advances in molecular classification and systemic therapy [30].

CONCLUSION

This retrospective cohort study showed that axillary lymph node metastases are common in women under 40 years with breast cancer and are associated with adverse histopathological and immunohistochemical tumor characteristics. Lymph node involvement was particularly related to larger tumor size and more extensive surgical treatment, supporting its role as an important indicator of local disease progression. These findings emphasize the value of careful preoperative axillary assessment and molecular tumor classification in planning individualized treatment for young women with breast cancer. Further prospective studies with larger patient cohorts are warranted to validate these findings.

Ethical compliance statement: We confirm that we have read the journal's position on issues involving ethical publication and affirm that work is consistent with those guidelines.

Ethical standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest: None declared.

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Клинички, патолошки и молекуларни предиктори метастаза у аксиларним лимфним чворовима код младих жена са раком дојке

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САЖЕТАК

Увод/Циљ Рак дојке код жена показује агресивније биолошке карактеристике, док статус аксиларних лимфних чворова остаје најважнији прогностички фактор. Циљ ове студије био је да се утврди преваленција метастаза у аксиларним лимфним чворовима и да се идентификују хистолошки и имунохистохемијски предиктори код болесница млађих од 40 година са раком дојке.

Методе Ретроспективна кохортна студија обухватила је болеснице млађе од 40 година са хистопатолошки потврђеним раком дојке које су подвргнуте хируршком лечењу на Одељењу за онколошку хирургију Клиничко-болничког центра „Бежанијска коса", између 2014. и 2024. године.

Резултати Студија је обухватила 97 болесница млађих од 40 година (просечна старост 34,75 ± 3,74 године). Метастазе у аксиларним лимфним чворовима идентификоване су код 48,5% болесница, док је биопсија сентинел лимфних чворова била позитивна код 26,8%. Најчешћи молекуларни подтип био је Луминал Б (53,6%). Луминални Б тумори били су повезани са млађом животном доби ($p = 0,031$) и вишим индексом телесне масе ($p = 0,007$). *HER*2-позитивни и троструко негативни тумори су чешће били високог хистолошког степена ($p = 0,003$) и веће величине тумора ($p = 0,025$), са вишим *Ki*-67 индексом пролиферације ($p = 0,001$). Позитиван статус аксиларних лимфних чворова био је значајно повезан са *Rh*-позитивном крвном групом ($p = 0,004$), величином тумора ($p = 0,001$) и мастектомијом ($p = 0,004$).

Закључак Рак дојке код жена млађих од 40 година карактерише изражена биолошка хетерогеност, при чему су метастазе у аксиларним лимфним чворовима значајно повезане са већом величином тумора и агресивнијим биолошким карактеристикама.

Кључне речи: рак дојке; биопсија; аксиларни лимфни чворови; молекуларни подтипови