Original paper

Prevalence of biological types of breast cancer and their influence on disease staging and therapeutic management – a single-center study

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According to the St. Gallen 2011 consensus, proper qualification of breast cancer patients for treatment requires taking into consideration the division into biological types of neoplasms. The goal of this work was to assess the prevalence of all biological types of breast cancer in the population of Kuyavian-Pomeranian province. We determined the influence of particular types of neoplasms on the degree of disease progression and the choice of therapeutic management.

The study was conducted on a group of 2653 patients treated surgically due to malignant breast tumors in the Oncology Centre in Bydgoszcz. In the analyzed clinical material we determined the biological type of cancer as well as other prognostic factors. The most commonly identified types of cancer were luminal B1 type (38.4%) and luminal A type (27.4% of cases), followed by a triple-negative type, luminal B2 type and HER2-positive type (respectively: 11.4%, 10.2%, and 6.9% of patients). Estrogen receptors were present in 81.1% and progesterone receptors in 71.4% of subjects. HER2 overexpression was identified in 17.3% of patients.

Routine use of a biology-based division into cancer types influences the choice of anti-cancer treatment. Diagnosis of luminal A type of tumor more commonly than other biological types of cancer coexists with lower clinical and pathological disease staging. It allows for more frequent use of sparing surgical techniques in patients. It also makes systemic neoadjuvant chemotherapy unnecessary in the majority of patients (differences in such cases exhibit statistical significance of $p < 0.0001$).

Key words: breast cancer, prognostic factors, biology-based cancer types, disease staging, surgical treatment, neoadjuvant chemotherapy.

Introduction

The possibility of obtaining good long-term treatment outcomes among breast cancer patients largely depends on the degree of disease progression. It is also a result of proper antineoplastic treatment [1] and is influenced by the risk factor status [2].

Breast cancer is the most common malignant disease in women in Poland and other developed countries [2]. Poland is one of the countries characterized

by a dynamic increase in the number of new cases of breast cancer. In 2010, the number of new cases was more than 30% higher than 10 years before [3].

According to the classification of identified risk factors in breast cancer proposed by the College of American Pathologists, three groups may be distinguished [4] (first group – prognostic factors of proven value used in management of the treatment; second group – factors being tested in clinical trials; third group – factors that do not meet current criteria for the first and second group). The group of factors with the greatest prognostic value includes primary lesion size, axillary lymph node status, histological type and grading of the lesion, as well as tumor steroid receptor status.

As demonstrated by the results of subsequent studies, the primary division of prognostic factors into groups became partially outdated and had to be updated [5, 6]. The expansion includes human epidermal growth factor receptor 2 (HER2) status, level of proliferation markers (Ki-67 mitotic index) and the biological type of breast cancer, which became indispensable when making decisions regarding the planned course of treatment [2, 7, 8, 9, 10, 11, 12, 13].

Over the last several years the importance of determining the biology-based cancer type has grown. According to Cheang *et al.* [10] and Nielsen *et al.* [14], it requires determination of estrogen receptor (ER), progesterone receptor (PgR), and HER2 receptor status as well as the Ki-67 mitotic index value. The obtained results enable identification of the cancer type [luminal A type: ER(+) and/or PgR(+), HER2(–), Ki-67 < 14%; luminal B1 type: ER(+) and/or PgR(+), HER2(–), Ki-67 ≥ 14%; luminal B2 type: ER(+) and/or PgR(+), HER2(+), Ki-67 ≥ 14%; HER2(+); HER2-positive type – *ERBB2(+)*: ER(–), PgR(–), HER2(+); triple-negative type – *basal-like*: ER(–), PgR(–), HER2(–)] [8]. According to the 2011 St. Gallen consensus, classification of breast cancer into biological types is included in generally accepted standards of treatment [8].

Current literature provides only limited information on the prevalence of biological types of breast cancer all over Poland and in particular regions of our country. Statistical data from several reports on the problem describe small populations of patients or use a simplified classification of this malignancy [15, 16].

The goal of this study was to assess the frequency of occurrence of biological breast cancer types in population of Kuyavian-Pomeranian province of Poland. We also determined the impact of specific types of neoplasms on disease advancement and choice of therapeutic management (mainly with regard to the possibility of application of sparing surgical techniques and the need for systemic neoadjuvant chemotherapy).

Material and methods

Study group

A group of 2653 consecutive breast cancer patients was subject to surgical treatment in the Department of Clinical Breast Cancer and Reconstructive Surgery of the Oncology Center in Bydgoszcz (1715 patients treated in 2011-2012 – retrospective group; 938 patients treated in 2014 – the clinical material collected prospectively).

The study included 2374 patients diagnosed with ductal or lobular type of invasive cancer. We also included cases of invasive breast cancer diagnosed on the basis of histopathological assessment performed after preoperative chemotherapy (in some patients it made unequivocal identification of one of two mentioned histological cancer types impossible).

Patients with other forms of invasive breast cancer (99 patients), breast malignancies of non-epithelial origin (16 patients), secondary breast tumors (metastasis of another tumor to the mammary gland – 6 patients) and cases of in-situ intraductal carcinoma (158 patients) were excluded from the study.

In the analyzed group of patients we determined the biological type of breast cancer (according to the criteria specified above) and the status of selected prognostic factors: presence of hormone receptors (ER and PgR), expression of the HER2 receptor, Ki-67 index value, histological type of cancer and histological grading of the neoplasm.

In order to assess clinical staging (cTNM) the results of the physical examination and preoperative imaging studies were used. In order to determine pathological disease stage (pTNM) we used information from the pathology report [17]. The analysis included patients who had not been subjected to induction or neoadjuvant treatment.

Menopausal status of patients was determined based on the data from physical examination. Perimenopausal age was identified in the absence of menstrual bleeding in a non-pregnant patient (or in the presence of menstrual cycle disorders) in the period of two years from the last regular menstruation. No additional assessment of steroid hormone levels in the serum was performed in those patients.

When determining the proportion of patients subjected to breast-conserving treatment (BCT) we took into consideration cases where the primary surgical procedure had to be radicalized (patients required extension of surgical treatment to simple mastectomy). We also established the proportion of patients referred for sentinel lymph node biopsy (SLNB). In the course of qualification for sparing surgical procedures we applied generally accepted rules of therapeutic management [18].

Immunohistochemistry

ER, PgR and HER2 receptors and Ki-67 protein were determined immunohistochemically in standard 4-5 μm sections, cut from breast cancer tissue, fixed in 10% buffered formaldehyde and embedded in paraffin. The ER, PR and HER2 receptors were labeled immunohistochemically using an automated slide stainer (Bench MarkXT, Ventana), after heating to 60°C. All procedures, including antigen retrieval and blocking of endogenous peroxidase activity, were performed automatically by the Benchmark system. After deparaffinization and antigen retrieval the antibodies anti-ER (SP1 250), anti-PgR (clone 1E2) and 4B5 were applied for 20 minutes. Antibodies' binding sites were visualized using ultra View Universal DAB Detection Kit (Ventana Medical Systems, SA), according to the manufacturer's instructions. After counterstaining with hematoxylin, sections were dehydrated and coverslipped using a mounting medium (Consul Mount; Thermo Fisher Scientific Inc. Waltham, MA, USA).

For Ki-67 expression, 4-5 μm sections, after heating to 60°C, were deparaffinized and antigen retrieved in high pH buffer (Dako, Carpinteria, CA, USA) in PT Link equipment (Dako, Carpinteria, CA, USA). The subsequent steps of immunostaining were done using Autostainer Link 48 (Dako, Carpinteria, CA, USA). After blocking the activity of endogenous peroxidase with hydrogen peroxide, sections were incubated with anti-Ki-67 (for 20 minutes). Antigen-linked antibodies were visualized using the system EnVision+ System-HRP and diaminobenzidine (Dako, Carpinteria, CA, USA), then the slides were stained with hematoxylin and preparations were coverslipped (Consul Mount; Thermo Fisher Scientific Inc. Waltham, MA, USA).

Assessment of immunohistochemically stained sections

The hormonal nuclear receptors' (ER and PgR) status was assessed semiquantitatively with simultaneous evaluation of expression intensity (IS) and percentage (PS) of labeled neoplastic cells. IS was assessed using the following scale: 0 – no staining, 1 – low staining intensity, 2 – moderate staining intensity, 3 – high staining intensity. PS was assessed using a 6-grade scale, as follows: 0 – no labeled neoplastic cells, 1 – immunoreactivity in up to 1% of neoplastic cells; 2 – immunoreactivity in > 1-10% of neoplastic cells, 3 – immunoreactivity in >10-33.3% of neoplastic cells, 4 – immunoreactivity in >33.3-66.6% of neoplastic cells, 5 – immunoreactivity in more than 66.6% of neoplastic cells.

Immunohistochemically determined HER2 receptor expression was assessed using the 4-grade scale specified by the American Society of Clinical Oncology/College of American Pathologists [19]. According to these criteria, cancers with no membrane staining were classified as HER2 0 (negative). Cancers with weak and heterogeneous HER2 membrane expression were classified as HER2 1+ (negative). Cancers with weak or heterogeneous membrane expression present in at least 10% of cancer cells were qualified as HER2 2+ (ambiguous). Cancers classified as HER2 3+ (positive) showed strong, uniform HER2 membrane expression for at least 30% of cancer cells.

Ki-67 expression was analyzed by assessing the percentage of breast cancer cell nuclei that express the tested antigen. In order to enable statistical comparisons, the acquired results were divided into percentage ranges corresponding to proliferation grades as indicated by Goldhirsch *et al.* [20]. The following ranges of Ki-67 values were distinguished: below 15% (low proliferation index), 15-30% (intermediate proliferation index), and above 30% (high proliferation index). In the case of the latter interval calculations were performed on two separate groups of patients: Ki-67 values of 31-45% and >45%.

Moreover, while determining the steroid receptor status (ER, PgR), we evaluated the consequences of changes in the diagnostic criteria regarding those studies. According to the 2009 St. Gallen conference guidelines, positive estrogen and progesterone receptor status is determined by the presence of color reaction regardless of the percentage of marked cells [20]. This accepted consensus replaced a previous one, based on which the test result was positive when over 10% of evaluated cells were stained.

Statistical analysis

The data are presented in tables as numbers and percentage values in groups as well as mean tumor sizes with standard deviations. Statistical analyses were performed using Statistica software by StatSoft Co. (v. 10, StatSoft Inc. 2011). The χ^2 test was used for comparison of proportions of qualitative variables. ANOVA test was used for analysis of a continuous variable (tumor size); post-hoc tests were performed using Tukey's method. Differences were considered statistically significant if the p value was below 0.05.

Results

The study group included 2367 women and 7 men; mean patient age was 58.0 ±11.2 years (22 to 90 years). As many as 67.5% of patients were in postmenopausal age (Table I).

In 47.5% of patients the primary tumor size did not exceed 2 cm (clinical assessment – cT1). Stages I and II of clinical disease progression were diagnosed most frequently in the analyzed group – 44.5% and 44.2% of patients, respectively.

Table I. Breast cancer patients referred for surgical treatment – clinical data

Features	2011-2012 n = 1562 (%)	2014 n = 812 (%)	Total n = 2374 (%)	p
Age (years)				
< 40	85 (5.4)	43 (5.3)	128 (5,4)	0.9183
40-60	854 (54.6)	392 (48.3)	1246 (52.5)	0.0035
> 60	623 (39.9)	377 (46.4)	1000 (42.1)	0.0023
Menopausal status				
premenopausal	317 (20.3)	93 (11.5)	410 (17.3)	< 0.0001
perimenopausal	208 (13.3)	147 (18.1)	355 (15.0)	0.0019
postmenopausal	1033 (66.1)	569 (70.1)	1602 (67.5)	0.0484
men	4 (0.3)	3 (0.4)	7 (0.3)	0.6407
Size of primary tumor – clinical assessment (cT)				
T1	739 (47.3)	389 (47.9)	1128 (47.5)	0.7812
T2	673 (43.1)	328 (40.4)	1001 (42.2)	0.2063
T3	66 (4.2)	41 (5.0)	107 (4.5)	0.3711
T4	84 (5.4)	54 (6.7)	138 (5.8)	0.2002
Classification of clinical stage assessment (cTNM)				
I A	681 (43.6)	375 (46.2)	1056 (44.5)	0.2265
II A	440 (28.2)	265 (32.6)	705 (29.7)	0.0260
II B	269 (17.2)	76 (9.4)	345 (14.5)	< 0.0001
III A	76 (4.9)	32 (3.9)	108 (4.5)	0.2876
III B	80 (5.1)	49 (6.0)	129 (5.4)	0.3577
III C	13 (0.8)	6 (0.7)	19 (0.8)	0.7909
IV	3 (0.2)	9 (1.1)	12 (0.5)	0.0034
Histological type of the tumor				
invasive ductal	1297 (83.0)	668 (82.3)	1965 (82.8)	0.6684
invasive lobular	179 (11.5)	76 (9.4)	255 (10.7)	0.1176
invasive (post-chemotherapy)	86 (5.5)	68 (8.4)	154 (6.5)	–
Grade of histological malignancy				
G1	97 (6.2)	28 (3.4)	125 (5.3)	0.0037
G2	972 (62.2)	591 (72.8)	1563 (65.8)	< 0.0001
G3	358 (22.9)	111 (13.7)	469 (19.8)	< 0.0001
unknown	135 (8.6)	82 (10.1)	217 (9.1)	–
Size of primary tumor – pathological assessment (pT; n = 2057)				
T1	813 (59.4)	387 (56.2)	1200 (58.3)	0.1649
T2	509 (37.2)	281 (40.8)	790 (38.4)	0.1132
T3	30 (2.2)	10 (1.5)	40 (1.9)	0.2806
T4	16 (1.1)	10 (1.5)	26 (1.3)	0.4381
Tx	1 (0.1)	0 (0.0)	1 (0.0)	–

Table I. Cont.

Features	2011-2012 n = 1562 (%)	2014 n = 812 (%)	Total n = 2374 (%)	p
Axillary lymph node status – pathological assessment (pN; n = 2057)				
N0	856 (62.5)	485 (70.3)	1341 (65.2)	0.0005
N1	289 (21.1)	112 (16.3)	401 (19.5)	0.0095
N2	121 (8.8)	59 (8.6)	180 (8.8)	0.8795
N3	97 (7.1)	24 (3.5)	121 (5.9)	0.0011
Nx	6 (0.4)	8 (1.2)	14 (0.7)	–
Estrogen receptor status				
positive	1271 (81.4)	654 (80.5)	1925 (81.1)	0.5952
negative	286 (18.3)	156 (19.2)	442 (18.6)	0.5930
unknown	5 (0.3)	2 (0.2)	7 (0.3)	–
Progesterone receptor status				
positive	1141 (73.0)	554 (68.2)	1695 (71.4)	0.0141
negative	416 (26.6)	256 (31.5)	672 (28.3)	0.0119
unknown	5 (0.3)	2 (0.2)	7 (0.3)	–
HER2 receptor status				
positive	265 (17.0)	146 (18.0)	411 (17.3)	0.5415
negative	1277 (81.8)	662 (81.5)	1939 (81.7)	0.8577
unknown	20 (1.3)	4 (0.5)	24 (1.0)	–
Ki67 value				
0-14%	476 (30.5)	207 (25.5)	683 (28.8)	0.0107
15-30%	479 (30.7)	317 (39.0)	796 (33.5)	< 0.00001
31-45%	151 (9.7)	97 (11.9)	248 (10.4)	0.0965
> 45%	239 (15.3)	154 (19.0)	393 (16.6)	0.0214
unknown	217 (13.9)	37 (4.6)	254 (10.7)	–
Molecular type of the breast cancer – St Gallen 2011				
luminal A	446 (28.6)	204 (25.1)	650 (27.4)	0.0697
luminal B1	572 (36.6)	339 (41.7)	911 (38.4)	0.0153
luminal B2	159 (10.2)	84 (10.3)	243 (10.2)	0.9392
HER2 positive	106 (6.8)	58 (7.1)	164 (6.9)	0.7844
triple-negative	176 (11.3)	94 (11.6)	270 (11.4)	0.8273
unknown	103 (6.6)	33 (4.1)	136 (5.7)	–
Surgical procedures				
BCT	784 (50.2)	461 (56.8)	1245 (52.4)	0.00229
SLNB	999 (64.0)	627 (77.2)	1626 (68.5)	< 0.00001
Systemic neoadjuvant/preoperative treatment				
chemotherapy	185 (11.8)	120 (14.8)	305 (12.8)	0.0381
endocrine therapy	8 (0.5)	4 (0.5)	12 (0.5)	0.8325
no	1369 (87.6)	688 (84.7)	2057 (86.6)	0.0490

BCT – breast-conserving treatment; SLNB – sentinel lymph node biopsy

Ductal type of invasive breast carcinoma was diagnosed in 82.8% and lobular type in 10.7% of patients. Invasive breast carcinoma without specific diagnosis was identified in 6.5% of subjects (154 patients subjected to neoadjuvant preoperative chemotherapy). A total of 65.8% of patients were diagnosed with intermediate grade of malignancy (G2).

In 58.3% of subjects (patients who had undergone primary surgical treatment) the size of the tumor as indicated by histopathological examination did not exceed the diameter of 2 cm (pT1).

Presence of estrogen receptors was identified in tumor cells of 81.1% of patients and progesterone receptors were found in 71.4% of patients. HER2 overexpression (or *c-erbB-2* gene amplification) concerned 17.3% of patients from the study group, and in 28.8% of subjects the Ki-67 mitotic index did not exceed 14%.

Luminal B1 cancer was the most frequently diagnosed biological type of cancer in the study group (38.4% of patients), followed by luminal A type of tumor (27.4% of patients). Detailed data regarding the remaining biological types of cancer and other analyzed clinical variables are presented in Table I.

Breast sparing surgery was performed in 1245 (52.4%) patients, and 1626 (68.5%) patients were referred for treatment with the intention of sparing axillary lymph nodes (sentinel node biopsy procedure). As many as 13.4% of all patients required systemic neoadjuvant or induction chemotherapy.

The lowest degree of neoplastic disease progression (determined by the size of primary tumor – cT, pT and axillary lymph node status – pN) was identified in patients with luminal A type of breast carcinoma. Observed differences between results acquired in this group of patients and the remaining subjects exhibited statistical significance (Table II; does not display patients excluded due to incomplete data). Breast-conserving surgery was possible in 65% of patients with luminal A type of tumor. Almost 83% of those patients were qualified for sentinel lymph node biopsy. Conserving treatment was the least often possible in patients with HER2-positive type of cancer (respectively 34.1% and 49.4% of patients).

Discussion

Introducing determination of HER2 receptor status and the Ki-67 mitotic index value enabled widespread use of breast cancer classification into biological types. Distinguishing cancer types enabled comprehensive consideration of the prognostic value of a group of factors characterized by high prognostic significance [10, 14].

The most frequently diagnosed biological cancer types in our study group were the luminal B1 type (38.4% of patients) and luminal A type (27.4% of cases).

As indicated by studies of Adamczyk *et al*., luminal A type was the most commonly identified biological type of breast carcinoma among patients treated surgically in the Institute of Oncology in Cracow (about 60% of cases), followed by a triple negative type (about 25% of patients) [15]. However, the analysis encompassed a small, preselected group of patients (108 women). Moreover, the authors applied simplified criteria for the diagnosis of luminal A (ER+, PgR+, HER2–) and luminal B (ER+, PgR+, HER2+) types of cancer, which did not take into consideration the value of the Ki-67 mitotic index.

Yang *et al*. [16] did not take advantage of the value of the Ki-67 index either. The authors presented an analysis of a group of 804 patients treated at oncological centers in Warsaw and Lodz in 2000-2003. Applying the above-mentioned criteria for diagnosis of luminal A and luminal B types of breast cancer, the authors identified them in 68.7% and 6% of cases, respectively. The HER2-positive type was diagnosed in 7.6% of patients and triple negative type in 11.8%. It is therefore not possible to compare the data reported in those two studies with our results.

The analysis by Mazouni *et al*. also did not take the Ki-67 mitotic index into consideration [21]. The authors found a similar percentage distribution of cancer types as in the previously mentioned studies. Among 1194 patients treated due to primary breast carcinoma during 2004-2010, the luminal A type of neoplasm was diagnosed in 63.2% of patients (ER+, PgR+, HER2- and G1 or G2), luminal B1 type in 13.8% (ER+, PgR+, HER2- and G3), luminal B2 type in 6.9% of cases (vs 10.2% in our clinical material), HER2-positive type in 5.0% of patients (vs 6.9%), and triple negative type in 11.1% (vs 11.4%).

The St. Gallen criteria for division of breast cancer into three biological types [8] provide an unequivocal and reproducible method for distinguishing specific groups of patients. It is particularly important in the case of luminal A breast cancer type. In our study, comparison of clinical data from luminal A patients with other groups demonstrated statistically significant differences (Table II).

Results similar to those presented in our study were also obtained by Puig-Vives *et al*. [22]. Analysis of prevalence of particular cancer types in a population of patients inhabiting the regions of Spain's Mediterranean coast revealed that in 68.7% of patients the tumor exhibited expression of steroid receptors and lacked HER2 overexpression (luminal A or B1 type). Luminal B2 type was found in 12.5% of cases, HER2-positive type in 7.0%, and triple-negative type in 11.8% of patients. The study was based on data analysis in a very large group of patients (3480 patients). Similar rates of distribution of specific biological types of breast cancer in European patient populations were also found in other studies [23, 24, 25].

Table II. Relationship between biological type of breast cancer, clinical and pathological staging and type of therapeutic management (years 2011-2012 and 2014)

Clinical data	Luminal A n (%)	Luminal B1 n (%)	Luminal B2 n (%)	HER2 (+) n (%)	Triple-negative n (%)	p, multivariate analysis
Tumor size – cT (%):						
T1	426 (65.5)$^{B1\ B2\ H\ TN}$	408 (44,8)$^{A\ H\ TN}$	97 (39.9)$^{A\ H}$	46 (28.0)$^{A\ B1\ B2}$	96 (35.6)$^{A\ B1}$	< 0.0001
T2	198 (30.5)$^{B1\ B2\ H\ TN}$	423 (46.4)^{A}	118 (48.6)^{A}	81 (49.4)^{A}	127 (47.0)^{A}	
T3	18 (2.8)$^{H\ TN}$	37 (4.1)^{H}	10 (4,1)^{H}	15 (9.1)$^{A\ B1\ B2}$	18 (6.7)^{A}	
T4	8 (1.2) $^{B1\ B2\ H\ TN}$	43 (4.7)$^{A\ H\ TN}$	18 (7.4)$^{A\ H}$	22 (13.4)$^{A\ B1\ B2}$	29 (10.7)$^{A\ B1}$	
mean tumor size – pT (mm)	18.23 ±11.01$^{B1\ B2\ H\ N}$	21.33 ±11.11$^{A\ TN}$	23.53 ±11.39 ^{A}	25.44 ±14.71^{A}	25.99 ±15.85$^{A\ B1}$	< 0.0001
Tumor size – pT (%):						
T1	462 (73.4) $^{B1\ B2\ H\ TN}$	446 (55.9)$^{A\ B2\ TN}$	94 (46.8) $^{A\ B1}$	60 (48.8) ^{A}	82 (39.8)$^{A\ B1}$	< 0.0001
T2	147 (23.4) $^{B1\ B2\ H\ TN}$	334 (41.9)$^{A\ TN}$	99 (49.2) ^{A}	57 (46.3) ^{A}	116 (56.3)$^{A\ B1}$	
T3	14 (2.2)	12 (1.5)	4 (2.0)	3 (2.4)	4 (1.9)	
T4	6 (1.0)	6 (0.8)	4 (2.0)	3 (2.4)	4 (1.9)	
Lymph node status pN (%):						
N0	460 (73.6)$^{B1\ B2\ H}$	488 (61.4)^{A}	114 (57.3)$^{A\ TN}$	70 (57.9) ^{A}	139 (67.8)^{B2}	< 0.0001
N1	115 (18.4)	180 (22.6)^{TN}	39 (19.6)	23 (19.0)	33 (16.1)^{B1}	
N2	30 (4.8)$^{B1\ B2\ H\ TN}$	78 (9.8)^{A}	26 (13.1)^{A}	16 (13.2) ^{A}	19 (9.3)^{A}	
N3	20 (3.2)$^{B1\ B2\ H\ TN}$	49 (6.2)^{A}	20 (10.0)^{A}	12 (9.9) ^{A}	14 (6.8)^{A}	
BCT (%)	421 (64.8)$^{B1\ B2\ H\ TN}$	496 (54.4) $^{A\ B2\ H\ TN}$	108 (44.4)$^{A\ B1\ H}$	56 (34.1)$^{A\ B1\ B2}$	106 (39.3)$^{A\ B1}$	< 0.0001
SLNB (%)	538 (82.8)$^{B1\ B2\ H\ TN}$	635 (69.7) $^{A\ B2\ H\ TN}$	141 (58.0)$^{A\ B1}$	81 (49.4)$^{A\ B1}$	155 (57.4)$^{A\ B1}$	< 0.0001
Neoadjuvant/ preoperative treatment (%)	22 (3.4)$^{B1\ B2\ H\ TN}$	116 (12.7) $^{A\ B2\ H}$	42 (17.3)$^{A\ B1\ H\ TN}$	42 (25.6)$^{A\ B1\ B2}$	66 (24.4)$^{A\ B2}$	< 0.0001

statistically significant: ^{A} vs. luminal A; ^{B1} vs. luminal B1; ^{B2} vs. luminal B2; ^{H} vs. HER2(+); ^{TN} vs. triple-negative
purple color = $p < 0.05$; blue color = $p < 0.01$; green color = $p < 0.001$; red color = $p < 0.0001$

Presence of differences in prevalence of particular biological breast cancer types among women, representatives of various races, was demonstrated in studies encompassing European and Asian patient populations. According to Su *et al*., higher prevalence of HER2-positive cancer is found in the population of Chinese women – about 13.7% of cases [26]. Thus, it is significantly higher than that observed in Europe and North America (4-8% of patients) [21, 22, 23, 24, 25, 27], including our clinical material (7.3% of patients).

On the other hand, triple negative type is more common among the northern African American population than among Caucasians. Its prevalence varies from 14% (postmenopausal patients) to 39% (premenopausal patients) of all breast cancers [27, 28]. Most authors report higher prevalence of this type of cancer among young patients and coexistence with higher disease staging regardless of the analyzed population.

As noted by Zubor *et al*., who analyzed cases of breast cancer in Slovakia and Turkey, there are significant differences with regard to the presence of steroid receptors and HER2 expression in neoplastic cells. Expression of ER and PgR was noted in 54.6% of patients in Slovakia and 49.0% in Turkey ($p < 0.001$). However, an inverse correlation was related to the presence of HER2 receptor (21.2% vs 28.5%) [29]. The report did not analyze the prevalence of specific biological types of breast cancer. However, it did provide valuable information regarding prevalence of previously mentioned prognostic factors in both patient groups.

Analysis of clinical data in breast cancer patients taking into consideration biological types of neoplasm may provide proof of significant diversity among this group of patients. A study in the Institute Gustave Roussy in Villejuif showed that it concerned age, menopausal status of patients, as well as the possibility of performing breast-sparing surgery and sentinel lymph node biopsy. Lymph node metastases were most often found in patients with luminal B1 and HER2-positive types of cancer (in both cases the differences were statistically significant, with $p < 0.001$) [21].

Similar dependence between cancer type and percentage of nodal metastases was corroborated by other authors. The risk of lymph node lesions increased in cases of cancers exhibiting HER2 overexpression [27, 30]. However, it was notably lower among patients with luminal A type of cancer and triple negative tumors [31, 32] (in our study this proportion was 26.4% and 32.2%, respectively).

Due to a high proportion of lymph node metastases noted among patients with luminal B1 and HER2-positive cancers (exceeding 50% of the total number of cases – vs 38.6% and 42.1%, respectively, in our material), Reyal *et al*. suggested the need for consideration of SLNB in these groups of patients [30]. However, possible changes in patient qualification for this type of procedure proposed by the authors have not been widely accepted.

In the analyzed clinical material we found statistically significant differences with regard to the percentage of axillary lymph node metastases. They were particularly apparent when comparing the results obtained from patients with luminal A breast cancer type and the remaining groups of patients (including a proportion of patients without metastases – pN0, as well as more advanced axillary infiltration – pN2 and pN3). Division of breast cancer into biological types may therefore be helpful in determining the risk of metastases to the local lymphatic system.

As shown by research conducted at a center in Izmir, there is an increased risk of axillary lymph node metastases among breast cancer patients regardless of biological type of neoplasm. It is enabled by determination of chemokine receptor 4 (CXCR4) expression. Elevated CXCR4 expression was found in 90% (in HER2-positive breast cancer) to 78.5% of patients (luminal A type of cancer) with metastases to the axillary fossa [33]. Use of tests determining the degree of expression of selected gene panels may also be helpful [34, 35]. According to the authors' suggestions, these tests may be a valuable addition to the panel of prognostic factors used to date. However, their broader application requires analyses on larger groups of patients.

Depending on the studied group, in our clinical material breast sparing treatment was possible in 34.1% to 64.9% of cases (least frequently in HER2-positive cancers). On the other hand, between 49.4% (also HER2-positive cancer) and 82.8% of patients were qualified for the sentinel lymph node procedure.

A similar relationship involving the possibility of BCT was noted by Puig-Vives *et al*. [22]. An analysis performed on a population of women living in southern Spain showed that breast-conserving treatment was least often possible in patients with HER2-positive type of cancer – 39.1% of cases. It was directly related to the presence of the greatest proportion of tumors exceeding 5 cm in diameter (10.8% of cases) or 2-5 cm in diameter (54.2%), as well as multifocal lesions (23.5% of patients) in this group of patients.

It should be remembered that the primarily established biological type of cancer might change. As reported by Abolinš *et al*., a patient with HER2-positive breast cancer underwent conversion of the primary tumor as a result of immunotherapy (trastuzumab). A triple negative type of cancer diagnosed on the basis of immunohistochemical examination of metastatic lesions required modification of treatment

[36]. As suggested by the authors, similar lesions might also apply to other combinations of results.

Within the described groups of patients, different frequency of occurrence of analyzed prognostic factors was observed. It involved especially clinical stage assessment and grade of histological malignancy, progesterone receptor status as well as age and menopausal status of the patients (statistically significant differences). In the second time period application of breast-conserving treatment was more often possible.

Conclusions

Classification of breast cancer into biological types enables comprehensive application of a group of highly valuable prognostic factors. It may therefore increase the likelihood of appropriately determining the degree of clinical and pathological disease progression as well as predicting long-term treatment outcomes.

Naturally, introduction of the previously mentioned classification of biological types of breast cancer does not solve all of the problems that appear in the course of treatment planning. The biological type of breast cancer allows for precise determination of systemic treatment. It particularly pertains to indications for chemotherapy (neoadjuvant, adjuvant) and the choice of drugs in targeted treatment (especially anti-HER2 biological therapy). However, the choice of appropriate procedure is still determined by the result of clinical examination of the patient (physical examination, imaging studies). So far we have been unable to replace the significance of primary tumor size assessment as well as lymph node status in that regard.

Diagnosis of luminal A type of breast cancer more often than other biological types coexists with lower disease staging (in clinical as well as pathological assessment). It allows for more frequent use of surgical sparing techniques and reduced need for use of systemic neoadjuvant therapy (differences noted in such cases are statistically significant – $p < 0.05$).

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