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Prognostic factors of Invasive Ductal Breast Carcinoma Non Special Type (NST). A Study of 98 cases.

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S u m m a r y: *Prognostic factors of histological subtypes in breast cancer, is still not well established, guidelines based on the histological subtype alone. The decisions for therapy are guided mostly independently of the histological subtype and are also guided by biomarkers and tumor stage. We analyzed a special histological subtype, Invasive Ductal Breast Carcinoma Non Special Type and correlated with patient's age, tumor grade, comedo type necrosis, necrosis, ER and PR receptors, Ki67 expression, HER2 status, pT tumor stage, pN lymph nodes stage, TNM classification and clinical tumor stage, in order to determine the factors which could predict the overall prognosis for this histological type.*

Study design: A total of 98 breast cancer cases with histological type, Invasive Ductal Breast Carcinoma Non Special Type (IDC NST), were retrospectively analyzed during 2020-2021.The minimum age of patients in our research was 32 years and the maximum was 95 years old, the mean was 59 years. Tumor's Grade was I in 2%, II in 35,7% and III in 62,2% of the cases. 40,8% of our cases had comedo type necrosis, while local or extensive necrosis was observed in 21,4%. ER and PR receptors expression was detected in 88,8% and in 86,7%, accordingly. The cell proliferation biomarker Ki67 was expressed >20% in 61,2% of the cases, 10-19% in 27,6%, and 1-9% in the rest11,2%, while the oncogene HER2 was overexpressed in 17,3% of all cases. Tumor

pathology stage was assessed for all cases and pT2 was identified in the majority (48,4%). Lymph nodes (axillary or sentinel, or both) were absent in 57,9% of all cases. IDC IST was related to clinical stages IIA (35,8%), followed by stages IA (29,5%), IIB (11.5%), and IIIC (9,5%). Invasive ductal breast carcinoma non special type is mostly characterized by certain prognostic factors such as, a higher grade of malignancy (grade III), a higher comedo type necrosis, a higher cellular proliferation (Ki67 >20%), a higher pT tumor stage (pt2), mostly without lymph nodes involvement (pN0), leading to II A, II B and III C clinical stages of TNM classification when combined with tumor histological grade, positive ER and PR receptors and negative overexpression to HER2. Furthermore, follow up and systematic research of the98 patients survival rate, may lead to new prognostic and preventive factors and targeted new therapies.

INTRODUCTION

Breast cancer is a significant global health challenge and it is the most commonly diagnosed cancer in the world with an estimated 2.26 million cases recorded in 2020, and is the leading cause of cancer mortality among females. Historically considered to be a disease of developed countries, but over half of breast cancer diagnoses and two-thirds of breast cancer related deaths are in the less developed regions of the world in 2020 [1]. The term, invasive breast carcinoma (IBC) no special type (NST) refers to a large and heterogeneous group of IBCs that cannot be classified morphologically as any of the others special histological types. Invasive Ductal Carcinoma (IDC) non special type (NST) and Invasive Lobular Carcinoma (ILC), subtypes, are the majority of breast cancer cases and have well-established prognostic factors and therapeutic procedures [2, 3, 4, 5]. NST is a group of cancers that does not present any specific differentiated features of other histological types of breast cancer. Among other breast cancers, can be distinguished numerous different types, often very rare, including mucinous breast cancer [6]. In our study, we try to evaluate prognostic factors for NST breast carcinomas, such as, necrosis, tumor size, tumor and nodes staging and number of infiltrated sentinel and axillary lymph nodes.

The most common used system for staging breast carcinoma is the TNM system [7]. This system gives information about the size of cancer at the primary site (T: Tumor), the regional lymph nodes (N: Nodes) and spread to distant metastatic sites (M: Metastasis). The T, N and M data are combined to define five stages (0, I, II, III and IV) that summarize information about the extent of regional disease and metastasis. This information is important for making decisions concerning the control of local disease, to determine the value of systemic therapy, and therefore, it could be considered as a prognostic factor [5]. Standard prognostic factors include, tumor dimension, number of infiltrated sentinel or axillary lymph nodes, or both, disease stage, tumor grade, necrosis comedo type or not, and lympho-vascular status. The presence of ER, PR receptors, HER2 biomarker, and the proliferative biomarker Ki67 were also considered.

Breast cancer in individuals aged <35years at diagnosis is rare (<5%) and potentially more aggressive, leading to large amount of chemotherapy [5]. The 10 year specific mortality rate associated with small, early–stage breast cancer has reported to be low up to 4% [8]. The 5 year relative survival rate of patients with localized breast cancer is >95%, which decreases to 85% when regional lymph nodes are involved and about 25% with metastatic disease.

Another more specific and accurate pathology staging is the American Joint Committee on Cancer (AJCC) system and has both clinical and pathologic staging systems for breast cancer. The pathologic stage (also called the surgical stage) is determined by examining tissue removed during an operation. Sometimes, if surgery is not possible right away or at all, the cancer will be given a clinical stage instead. This is based on the results of a physical exam, biopsy, and imaging tests. The clinical stage is used to help plan the treatment. Sometimes, though, the cancer has spread further than the clinical stage estimates, and may not predict the patient's outlook as accurately as a pathologic stage. In both staging systems, 7 key pieces of information are used: The extent (size) of the tumor (Tx, T0, T1a, T1b, T1c, T2, T3, T4a, T4b, T4c, T4d), the spread to nearby lymph nodes (Nx, N0, Nmi, N1a, N1b, N2a, N2b, N3a, N3b, N3c), the spread (metastasis) to distant sites (Mx, M0, M1), Estrogen Receptor (ER) status, Progesterone Receptor (PR) status, Grade of the cancer (G), and the presence or absence of overexpressed protein Human Epidermal Receptor2 (HER2). Once all these factors have been determined, this information is combined in a process called stage grouping to assign an overall stage. However, the addition of information about ER, PR, HER2, and grade has made stage grouping for breast cancer more complex than for other cancers [9].

MATERIALS AND METHODS

Several number of 98 formalin-fixed paraffin embedded tissue blocks of female patients with diagnosed breast carcinoma NST type and median age the 59 years, were collected during May 2018 up to February 2022 in Histopathological Laboratory of Hippokration General Hospital, but the most cases were during 2020-2022. We evaluated the clinical data and reviewed pathological findings regarding Invasive Ductal NST breast cancers. Paraffin blocks were cut into sections (3μm). The sections were next stained with different methods for diagnostic purposes. Preparations stained with hematoxylin and eosin (H&E) were used to define the tumor histological type [5], and histological grade of malignancy. Two independent pathologists evaluated tumor slides. Consent for participation in the study or the use of their biopsy was given from all participants.

Immunohistochemistry (IHC) for all 98 cases for Her2, ER, PR and ki67 was studied by the VENTANA-BenchMark-XT computerized automated system, using the ultraview Universal DAB Detection Kit. Three-micrometer-thickness tissue sections were used. The used antibodies were:

1. HER2 rabbit monoclonal antibody (clone Cerb2).
2. Estrogen receptor (ER) rabbit monoclonal antibody (clone SP1).
3. Progesterone receptor (PR) rabbit monoclonal antibody (clone 1E2).
4. Ki67 cellular marker of proliferation (clone Mib-1).

The ultraview Universal DAB Detection Kit detects specific mouse and rabbit primary antibodies bound to an antigen for paraffin-embedded tissue sections. The specific antibody is located by a cocktail of enzyme labeled secondary antibodies (HRP Multimer). The complex is then visualized with hydrogen peroxide substrate and, 3'-diaminobenzidine tetrahydrochloride (DAB) chromogen, which produces a brown precipitate that is readily observed by light microscopy. The staining protocols followed for the four immunostains (HER2, ER, PR and Ki67) were in accordance with standard staining protocols of VENTANA-BenchMark-XT computerized automated system for each antibody.

The IHC results and scores were recorded independently by two pathologists, followed by a common review for agreement.

- 0+ negative score
- 1+ negative score
- 2+ equivocal score
- 3+ positive score

DATABASE DESIGN-DATABASE CREATION-STATISTICAL ANALYSIS

The original database was created with the help of Microsoft Office Excel, then the data was encoded, and a new database was produced in SPSS with the data of 98 breast cancer patients. The research process included the descriptive and inductive analysis of 12 variables from the patients' medical record: 1) patient's age, 2) tumor grade, 3) comedo type necrosis, 4) necrosis, 5) ER receptors, 6) PR receptors, 7) Ki67 expression, 8) Her2 status, 9) pT tumor stage, 10) pN lymph nodes stage, 11) TNM classification and, 12) tumor clinical stage. The analysis of the results confirmed by using the distribution of percentage frequencies through Frequencies and Descriptive Statistics [10].

RESULTS

The minimum age of patients in our research was 32 years and the maximum was 95 years old, the mean was 59 years (Table 1). 57,1% of cases concerned the right breast and the 42,9% the left breast. Tumor's Grade was I in 2%, II in 35,7% and III in 62,2% of the cases (Table 2). In our study, in 40,8% of our cases comedo type necrosis was observed while local or extensive necrosis was observed in 21,4% (Tables 3, 4). ER receptors expression was detected in 88,8% (Table 5) and PR receptors expression in 86,7% (Table 6). The cell proliferation biomarker Ki67 was expressed>20% in 61,2% of the cases, 10-19% in 27,6% and 1-9% in the rest 11,2%(Table 7), while the oncogene HER2 was overexpressed in 17,3% of all the cases (Table 8). Tumor pathology stage (pT stage) was assessed for all cases and pT2 was identified in the majority 48,4% (Table 9). Lymph nodes infiltration (axillary or sentinel, or both) were absent in 57,9% of all the cases (Table 10). TNM and clinical classification are presented in Tables 11, 12.

DISCUSSION

Invasive breast carcinomas are morphologically divided according to their growth patterns and degree of differentiation which shows their resemblance to the normal breast epithelial cells. Tumor type reflects useful prognostic information of breast cancer. The 60% to 75% of breast cancers have no special type of characteristics such us, invasive ductal carcinoma of no special type. These special types that show distinct prognostic significance are relatively rare. Consequently, the role of histological typing in clinical management and the decision making is currently limited [11]. In a large study, Henson and colleagues [12], who studied survival rates in 22,616 cases of breast cancer, showed that patients with histological Grade I stage II disease had the same overall survival as those with Grade III and stage I disease. The authors also found that patients with Grade I tumors of less than 2cm in size had an excellent prognosis, with 99% 5-year survival, even when they presented with positive lymph nodes (LN). The Nottingham group [13] had similar results in a study, which included 2,219 operable breast cancer cases with long-term follow-up. These results provide evidence that histological grade, when used in conjunction with LN stage, can improve the prediction of outcome for individual patients. There is compelling evidence that histological grade can predict in an accurate way tumor behavior, especially in earlier small tumors (stage pT1), more than other 'time-dependent' prognostic factors like tumor size (pT1a, pT1b, and pT1c) [14, 15, 16, 17]. It has also been demonstrated by studies that grade is an independent prognostic factor in specific subgroups of breast cancer, including ER-positive or negative ER breast cancer patients [18, 19].

In another study, the authors showed that tumor size, pT stage, lympho-vascular invasion (LVI), estrogen (ER) status, hormone receptor (HR) status, and triple negative breast cancer (TNBC) were associated with sentinel lymph nodes (SLN) metastasis. Although, pT stage, histological grade and TNBC were independent predictive factors for SLN involvement. In this study, it was demonstrated in one hand that pT stage and histological grade provided positive,

and in another hand, TNBC provided negative prediction about SLN metastasis in early stage breast cancer patients with clinically negative axillary lymph nodes [20].

Finally, the existence of so many factors that go into stage grouping for breast cancer, it's not possible to describe every combination that might be included in each stage[21].Thus, the many different possible combinations lead to the conclusion that women who have the same stage of breast cancer might have different factors to determine their stage. In our study, the mean age of patients was 59 years old. Most of our cases were Grade III (62.2%), the cell proliferation biomarker Ki67 was also high in 59,4% of cases. The classification category IB, wasn't present in our cases, but it could be determined with combination of Grade III (62,2%), HER2 expression negative (82,7%), ER (88,8%) and PR (86,7%) expression positive or with combination of Grade II (35,7%), HER2 expression positive (17,3 %), ER (88,8%) and PR (86,7%) receptors positive. On the contrary, in our study classification category IIIB with combination of Grade II (35,7%), HER2 expression negative (82,7%), ER (11,2%) and PR (13,3%) receptors negative was observed in 4,2% of all the cases. In our study most of the cases of IDC IST were clinical stage IIA (35,8%), followed by IA (29,5%), IIB (11,5%), and IIIC (9,5%) stages.

CONCLUSIONS

In this research of 98 cases of Invasive Ductal Breast Carcinoma Non Special Type (IDC NST), it was observed that this histological type is mostly characterized by certain prognostic factors such as, a higher grade of malignancy (grade III), a higher comedo type necrosis, a higher cellular proliferation (Ki67 > 20%), a higher pT tumor stage (pT2) mostly without lymph nodes involvement (pN0), leading to II B, III B and III C clinical stages of TNM classification when combined with tumor histological grade, positive ER and PR receptors and negative overexpression to HER2. Therefore, concerning the IDC IST, a furthermore follow up and systematic research of the survival rate of the 98 patients, may lead to new prognostic and predictive factors and targeted new therapies.

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TABLES AND DIAGRAMS

Table 1. Age of Invasive Ductal Carcinoma NST

AGE		
N	Valid	98
Mean		59,4694
Minimum		32
Maximum		95

Diagram 1. Age of Invasive Ductal Carcinoma NST

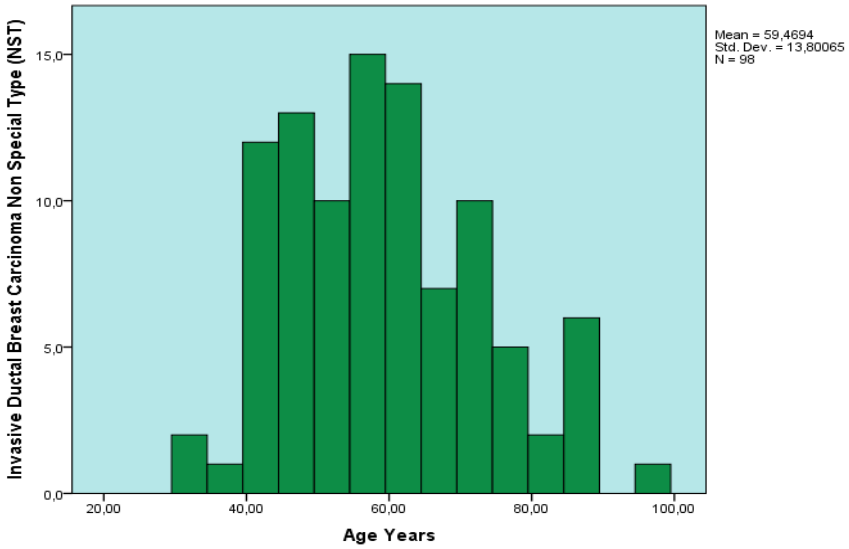

Table 2. Grade of Invasive Ductal Carcinoma NST

Grade				
		Frequency	Percent	Valid Percent
Valid	I	2	2,1	2,1
	II	35	35,7	35,7
	III	61	62,2	62,2
	Total	98	100,0	100,0

Table 3. Comedo Type Necrosis of Invasive Ductal Carcinoma NST

Comedo Type Necrosis				
		Frequency	Percent	Valid Percent
Valid	NO	58	59,2	59,2
	YES	40	40,8	40,8
	Total	98	100,0	100,0

Table 4. Local or extensive necrosis of Invasive Ductal Carcinoma NST

Necrosis local or extensive				
		Frequency	Percent	Valid Percent
Valid	NO	77	78,6	78,6
	YES	21	21,4	21,4
	Total	98	100,0	100,0

Table 5. ER Receptors of Invasive Ductal Carcinoma NST

ER Receptors				
		Frequency	Percent	Valid Percent
Valid	NEGATIVE	11	11,2	11,2
	POSITIVE	87	88,8	88,8
	Total	98	100,0	100,0

Table 6. PR Receptors of Invasive Ductal Carcinoma NST

PR Receptors				
		Frequency	Percent	Valid Percent
Valid	NEGATIVE	13	13,3	13,3
	POSITIVE	85	86,7	86,7
	Total	98	100,0	100,0

Table 7. Ki67 expression of Invasive Ductal Carcinoma NST

Ki67 expression				
		Frequency	Percent	Valid Percent
Valid	>20%	60	61,2	61,2
	10-19%	27	27,6	27,6
	1-9%	11	11,2	11,2
	Total	98	100,0	100,0

Table 8. HER2 overexpression of Invasive Ductal Carcinoma NST

HER2 overexpression				
		Frequency	Percent	Valid Percent
Valid	NEGATIVE	81	82,7	82,7
	POSITIVE	17	17,3	17,3
	Total	98	100,0	100,0

Table 9. Tumor pT stage of Invasive Ductal Carcinoma NST

Tumor pT stage				
pT stage		Frequency	Percent	Valid Percent
Valid	pT1a	7	7,4	7,4
	pT1b	8	8,4	8,4
	pT1c	26	27,3	27,3
	pT2	46	48,4	48,4
	pT3	3	3,2	3,2
	pT4a	3	3,2	3,2
	pT4b	2	2,1	2,1
	Total	95	100,0	100,0

Three cases are missing because pathology was unavailable.

**TX: Primary tumor cannot be assessed. T0: No evidence of primary tumor. Tis: Carcinoma in situ (DCIS, or Paget disease of the breast with no associated tumor mass). T1 (includes T1a, T1b, and T1c): Tumor is 2 cm (3/4 of an inch) or less across.T1=Tumor is ≤ 1mm. T1a=Tumor is >1mm ≤ 5mm. T1b=Tumor is >5mm≤ 10mm.T1c=Tumor > 10mm ≤ 20mm. T2: Tumor is more than 2 cm but not more than 5 cm (2 inches) across. T3: Tumor is more than 5 cm across. T4 (includes T4a, T4b, T4c, and T4d): Tumor of any size growing into the chest wall or skin. This includes inflammatory breast cancer. T4a=tumor into chest wall.T4b=Tumor into skin. Tc=Tumor into chest wall and skin. Td=Inflammatory breast cancer [9].*

Table 10. Lymph nodes pN stage of Invasive Ductal Carcinoma NST

Lymph nodes (axillary or sentinel, or both), pN stage				
		Frequency	Percent	Valid Percent
Valid	pN0	55	57,9	57,9
	pN1a	14	14,7	14,7
	pN1b	6	6,3	6,3
	pN1c	3	3,2	3,2
	pN2a	8	8,4	8,4
	pN3a	7	7,4	7,4
	pN3c	2	2,1	2,1
	Total	95	100,0	100,0

Three cases are missing because pathology was unavailable.

**N0(mol+): Cancer cells cannot be seen in underarm lymph nodes (even using special stains), but traces of cancer cells were detected using a technique called RT-PCR. RT-PCR is a molecular test that can find very small numbers of cancer cells. N1: Cancer has spread to 1 to 3 axillary (underarm) lymph node(s), and/or cancer is found in internal mammary lymph nodes (those near the breast bone) on sentinel lymph node biopsy. N1mi: Micrometastases (tiny areas of cancer spread) in the lymph nodes under the arm. The areas of cancer spread in the lymph nodes are at least 0.2mm across, but not larger than 2mm. N1a: Cancer has spread to 1 to 3 lymph nodes under the arm with at least one area of cancer spread greater than 2 mm across. N1b: Cancer has spread to internal mammary lymph nodes on the same side as the cancer, but this spread could only be found on sentinel lymph node biopsy (it did not cause the lymph nodes to become enlarged). N1c: Both N1a and N1b apply. N2: Cancer has spread to 4 to 9 lymph nodes under the arm, or cancer has enlarged the internal mammary lymph nodes. N2a: Cancer has spread to 4 to 9 lymph nodes under the arm, with at least one area of cancer spread larger than 2 mm. N2b: Cancer has spread to one or more internal mammary lymph nodes, causing them to become enlarged. N3: Any of the following: N3a: either: Cancer has spread to 10 or more axillary lymph nodes, with at least one area of cancer spread greater than 2 mm, or Cancer has spread to the lymph nodes under the collarbone (infraclavicular nodes), with at least one area of cancer spread greater than 2 mm. N3b: either: Cancer is found in at least one axillary lymph node (with at least one area of cancer spread greater than 2 mm) and has enlarged the internal mammary lymph nodes, or Cancer has spread to 4 or more axillary lymph nodes (with at least one area of cancer spread greater than 2 mm), and to the internal mammary lymph nodes on sentinel lymph node biopsy. N3c: Cancer has spread to the lymph nodes above the collarbone (supraclavicular nodes) on the same side of the cancer with at least one area of cancer spread greater than 2 mm [9].*

Table 11. TNM Classification of Invasive Ductal Carcinoma NST

TNM Classification				
		Frequency	Percent	Valid Percent
Valid	T1aN0M0	6	6,3	6,3
	T1aN1M0	1	1,1	1,1
	T1bN0M0	6	6,3	6,3
	T1bN1M0	1	1,1	1,1
	T1bN2M0	1	1,1	1,1
	T1cN0M0	17	17,8	17,8
	T1cN1M0	7	7,4	7,4
	T1cN3M0	2	2,1	2,1
	T2N0M0	23	24,2	24,2
	T2N1M0	11	11,5	11,5
	T2N2M0	7	7,4	7,4
	T2N3M0	5	5,2	5,2
	T3N1M0	2	2,1	2,1
	T3N3M0	1	1,1	1,1
	T4aN0M0	1	1,1	1,1
	T4aN1M0	1	1,1	1,1
	T4aN3M0	1	1,1	1,1
	T4bN0M0	2	2,1	2,1
	Total	95	100,0	100,0

Three cases are missing because pathology was unavailable.

Table 12. Clinical stage of Invasive Ductal Carcinoma NST

Clinical stage				
		Frequency	Percent	Valid Percent
Valid	I A	28	29,5	29,5
	II A	34	35,8	35,8
	II B	11	11,5	11,5
	II C	1	1,1	1,1
	III A	8	8,4	8,4
	III B	4	4,2	4,2
	III C	9	9,5	9,5
	Total	95	100,0	100,0

Three cases are missing because pathology was unavailable.