

Retrospective evaluation of histopathological examinations in invasive ductal breast cancer of no special type: an analysis of 691 patients

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Abstract

Introduction: Invasive ductal carcinoma (IDC) is the most common type of breast cancer in women and accounts for about 80% of all breast cancers.

Material and methods: The material consisted of histological preparations derived from 691 patients treated for IDC-NST.

Results: In our own study material, invasive ductal breast cancer of no special type accounted for more than 60% of cases, with the largest percentage of tumors being classified as G2 (53.96%) and G3 (28.98%). In terms of tumor size, the most common IDC-NST tumors were those of stage T1c (34.59%) and T2 (35.31%). The incidence of lymph node involvement was also assessed to reveal that no lymph node metastases were present in 45.44% of IDC-NST tumors. In the histopathological analysis of IDC-NST, significant statistical correlation was demonstrated between the presence of lymph node metastases and the histological malignancy grade (N0/G1-G3 $p = 0.0103$; N1A/G1-G3 $p = 0.0498$; N1B/G1-G3 $p < 0.001$; N3/G1-G3 $p = 0.0027$; N4/G1-G3 $p < 0.001$), between the presence of lymph node metastases and the tumor size (N0/T1-T4 $p = 0.00295$; N1B/T1-T4 $p < 0.001$; N2/T1-T4 $p < 0.001$; N2A/T1-T2 $p < 0.001$; N4/T1-T4 $p < 0.001$; Nx/T1-T4 $p = 0.0447$), as well as between the histological malignancy grade and the tumor size (G1/T1-T4 $p < 0.001$; G1/2/T1-T4 $p < 0.001$; G2/3/T1-T4 $p < 0.0267$).

Conclusions: Own research demonstrated that the most common histological type of breast cancer is invasive ductal carcinoma of no special type (IDC-NST); statistically significant correlations were demonstrated in IDC-NST patients between the lymph node involvement status and the histological malignancy grade or tumor size as well as between the histological malignancy grade and the tumor size.

Key words: invasive ductal carcinoma of no special type, histological grade, tumor size, lymph node status.

Introduction

Breast cancer is a heterogeneous disease, comprising multiple entities associated with distinctive histological and biological features, clinical presentations and behaviors, as well as responses to therapy [1–5]. Inva-

sive ductal breast cancer is the most common type of breast cancer in women and accounts for about 80% of all breast cancers [6–8]. The terminology ductal is still being used for historical reasons and to date there is no evidence to suggest that these tumors arise from ductal epithelial cells [9–11]. The reason why it is sometimes referred to as “no special type” (NST) is that the cells under the microscope have no particular features that would classify them as a specific type of breast cancer [10, 11]. This is basically an acknowledgment that it has been impossible to classify the carcinoma as a particular type, and consequently it has been placed in this holding area until further classification strategies become available [11]. It is also not the case that such lesions necessarily derive from, or form, ductal structures; thus the term “no special type” is preferred by some pathologists over the name ductal [12]. Macroscopically, invasive ductal carcinoma NST occurs most often in the form of a hard tumor visible in the cross-section with an irregular contour [9, 11, 12]. Focal necrosis and an associated chronic inflammatory infiltrate may be seen. Histologically, there appear cords of cancer cells, as well as single cells infiltrating the stroma of breast cancer [8, 10, 12]. Microscopically, ductal carcinomas tend to form glandular structures, and the tumor cells show a variable degree of differentiation. Cytological characteristics of malignant cells are expressed in varying degrees [13]. Some of the tumors diagnosed as invasive ductal breast cancer of no special type (IDC-NST) show a low degree of anaplasia, while others show a high degree of anaplasia [11, 13]. Cancer cells can invade lymph vessels and blood vessels, as well as nerve trunks. About 80% of ductal/NST cancers show estrogen receptor (ER) positivity and about 25% are HER2-positive [7, 14].

The aim of this study was to evaluate the relationship between the histological grade, tumor size, and lymph node status in a group of 691 patients with IDC-NST.

Material and methods

The material consisted of histological preparations derived from 691 patients treated for IDC-NST. The material for the study came from biopsy, excisional biopsy, and modified radical mastectomy. Histological and immunohistochemical studies were performed at the Department of Pathology, Military Medical Institute in Warsaw. Samples of tumors were fixed in 10% phosphate buffered formalin. Paraffin blocks were cut into sections with a thickness of 4 μm each. The obtained sections were stained with different methods for diagnostic purposes. Preparations stained with hematoxylin and eosin were used to identify tumor type (WHO classification), tumor grade including tubule formation, intensity of division, and degree of mitotic index of neoplastic cells as the mean number of mitoses in neoplastic cells counted in 10 fields of vision at an objective magnification of 400 \times (surface field 0.17 mm^2). Routinely, patients with IDC-NST had a basic immunohistochemical profile assessed, i.e. expression of estrogen receptor (ER), HER2 (Figure 1 A) and progesterone receptor (PgR) (Figure 1 B).

Statistical analysis

All statistical analyses were performed with SPSS software version 12.0 for Windows. If the expected size was less than 5, the chi-square (χ^2) test was used with Yates' correction.

The correlations between variables were assessed using Spearman's rank or Cramer's V coefficient. The Spearman rank-order correlation is the nonparametric version of the Pearson product-moment correlation. It measures the strength of association between two ranked variables. To find the relation between qualitative (nominal) variables which cannot be ranked, Cramer's V coefficient was calculated.

To determine the relationship between the degree of histological malignancy (G), lymph node

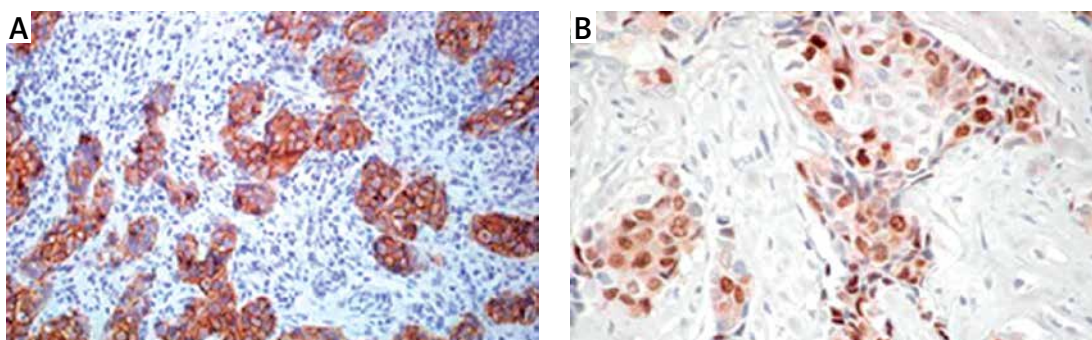


Figure 1. Immunohistochemical image of invasive ductal carcinoma of no special type of the breast (IDC-NST): **A** – Strong, circumferential staining in > 30% of invasive ductal carcinoma of no special type cells was scored as 3+, interpretation – positive for HER2 amplification, original magnification, 20 \times ; **B** – Showing positive nuclear staining of progesterone receptor in IDC-NST of the breast, original magnification, 20 \times

metastasis (pN) and tumor size (pT), lymph node metastasis (pN) and the degree of histological malignancy (G), and tumor size (pT) and metastatic lymph nodes (pN) in IDC-NST, the value of Cramer's V coefficient was determined (a value of 0 indicated no relationship between variables). In order to investigate the correlation between the degree of histological malignancy (G), lymph node metastasis (pN) and tumor size (pT), lymph node metastasis (pN) and the degree of histological malignancy (G), and tumor size (pT) and metastasis to the lymph nodes (pN) in patients with IDC-NST, Spearman's rho coefficient was determined. The results were considered as statistically significant if the *p* value was ≤ 0.05 .

Results

Pathological examination of tumors obtained from 1122 patients suffering from breast cancer was carried out. The age of the patients ranged from 30 to over 81 years, with a mean age of 60.47 ± 5.07 years. Patients were divided into seven age groups: under 30 years; from 31 to 40 years; from 41 to 50 years; from 51 to 60 years; from 61 to 70 years; from 71 to 80 years; and over 81 years (Figure 2). Among 1122 cases of breast cancer, there were 118 (10.52%) invasive lobular carcinomas (ILC), 691 (61.59%) IDC-NST, 29 (2.58%) ductal carcinomas in situ (DCIS), 3 (0.27%) lobular carcinomas in situ (LCIS), and 281 (25.04%) cases of other breast cancers (Figure 3). Regarding the histological grade of malignancy, the largest group of IDC-NST comprised grade 2 (53.96%) and grade 3 (28.98%) (G2 and G3) tumors (Table I, Figure 4). During the analysis of the pre-operative

staging of the studied cancers, it was found that the largest group of IDC-NST tumors consisted of those assessed as T1c (34.59%) and T2 (35.31%) (T1c – larger than 1 cm, up to 2 cm in diameter; T2 – larger than 2 cm but not larger than 5 cm in diameter). None of the patients had tumor size of type T4a or T1d. Moreover, the size of the tumor of type T1a, T3, and T4b was found in fewer than 2% of patients with IDC-NST (Table I). The lymph node status was also assessed during the study. It was noted that in all investigated IDC-NST cases, women without metastasis to regional lymph nodes constituted the largest group (pN0) (45.44%). Furthermore, N1 and Nx was found in 14.47% and 2.89%, respectively. In less than 0.5% of the study group, the N1B and N4 lymph node status was found (Table I). In 60.64% of patients, no distant organ metastases (M0) were identified, and in 39.36% those could not be assessed (Mx). Based on the analysis of the results of the relationship between histological grade (G) and lymph node status (pN) in NST-IDC patients, and assuming the significance level of $p = 0.05$ in the study, statistically significant correlations were found for N0, N1A, N1B, N3, N4 and G1–G3 (N0/G1–G3 $p = 0.0103$; N1A/G1–G3 $p = 0.0498$; N1B/G1–G3 $p < 0.001$; N3/G1–G3 $p = 0.0027$; N4/G1–G3 $p < 0.001$) (Table II).

The obtained results allowed us to evaluate the relationship between tumor size and lymph node metastasis in IDC-NST. We found a correlation between the size of T1-T4 tumor and lymph node status assessed as N0, N1B, N2, N2A, N4, and Nx (N0/T1–T4 $p = 0.00295$; N1B/T1–T4 $p < 0.001$;

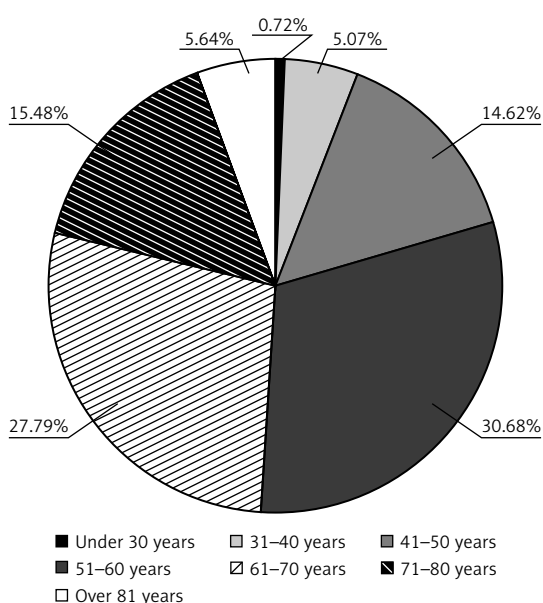


Figure 2. Age distribution of patients with IDC-NST

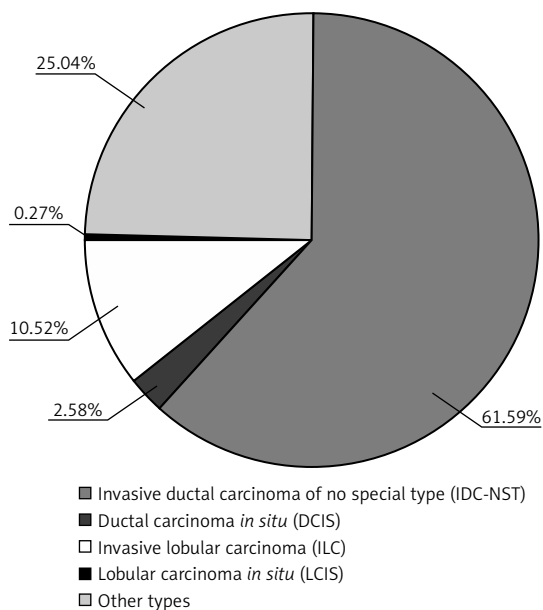


Figure 3. Histological types in the group of 1122 patients with breast cancer

N2/T1–T4 $p < 0.001$; N2A/T1–T2 $p < 0.001$; N4/T1–T4 $p < 0.001$; Nx/T1–T4 $p = 0.0447$) (Table II).

The analysis of the relationship between tumor size and lymph node metastasis allowed us to evaluate the clinical severity of the disease in patients with IDC-NST. Tumor, node, and metastasis (TNM) staging showed that the most common group was pT1N0 (39.74%) (clinical stage I) followed by pT2N0 (clinical stage IIA) (25.26%), pT1N1 (clinical stage IIA) (14.90%), and pT2N1 (clinical stage IIB) (12.52%) (Table III). Based on the analysis of the test results, we also examined the relationship between tumor size (pT), and the degree of histological malignancy (G). Our study demonstrated a statistically significant relationship between histological grade G1, G1/2, and G2/3, and tumor size T1–T4 (G1/T1–T4 $p < 0.001$; G1/2/T1–T4 $p < 0.001$; G2/3/T1–T4 $p < 0.0267$) (Table IV). We also examined the relationship between histological grade of the tumor, its size, and the presence of metastases to distant organs (Tables V, VI), but no statistically significant differences between the studied variables were found.

Discussion

Invasive ductal carcinoma of no special type is the most common form of microscopic breast cancer. According to most authors, it represents approximately 80% of all malignant breast tumors. In the literature it is assumed that the clinical picture of IDC-NST differs from that of clinical invasive lobular breast carcinoma (ILC) [11]. The main differences relate to patient age, tumor size at diagnosis, multifocal growth rate of cancer, and incidence of cancer in the other breast. Other important diagnostic markers are the degree of histological grade, lymph node status, and presence of distant metastases.

Our study was carried out in a group of 691 patients with IDC-NST. That group was isolated from 1122 patients with breast cancer. In our study, a detailed analysis of basic histopathological features of IDC-NST, such as the histological grade, primary tumor size, lymph node status, presence of distant metastases, and the clinical severity of the disease was carried out.

In our study the ages of the patients ranged from 30 to over 81 years, with a mean age of 60.47 years. Patients were divided into seven age groups: under 30 years; from 31 to 40 years; from 41 to 50 years; from 51 to 60 years; from 61 to 70 years; from 71 to 80 years, and over 81 years.

The data showed that the mean age of patients with IDC-NST is lower than the mean age of patients with ILC [15, 16]. According to the results of Silverstein *et al.*, the mean age of patients with IDC-NST was 52.5, according to Tubiana-Hulin *et al.*

Table I. Clinicopathologic characteristics of IDC-NST

Parameter	Number of patients with IDC-NST (total = 691)	
	N	%
Age (mean \pm SD)	60.47 \pm 5.07	
Tumor stage (pT):		
T1	2	0.29
T1a	13	1.88
T1b	55	7.96
T1c	239	34.59
T1d	0	0.00
T2	244	35.31
T3	9	1.30
T4	32	4.63
T4a	0	0.00
T4b	6	0.87
Unknown	91	13.17
Nodal stage (pN):		
N0	314	45.44
N1	100	14.47
N1A	41	5.93
N1B	3	0.43
N2	34	4.92
N2A	25	3.62
N2B	4	0.58
N3	15	2.17
N3A	17	2.46
N4	3	0.43
Nx	20	2.89
Unknown	115	16.64
Tumor grade (G1–3):		
G1	52	7.48
G2	375	53.96
G3	200	28.98
G1/2	2	0.29
G2/3	8	1.15
Unknown	54	7.81
Metastases (pM):		
Mx	272	39.36
M0	419	60.64

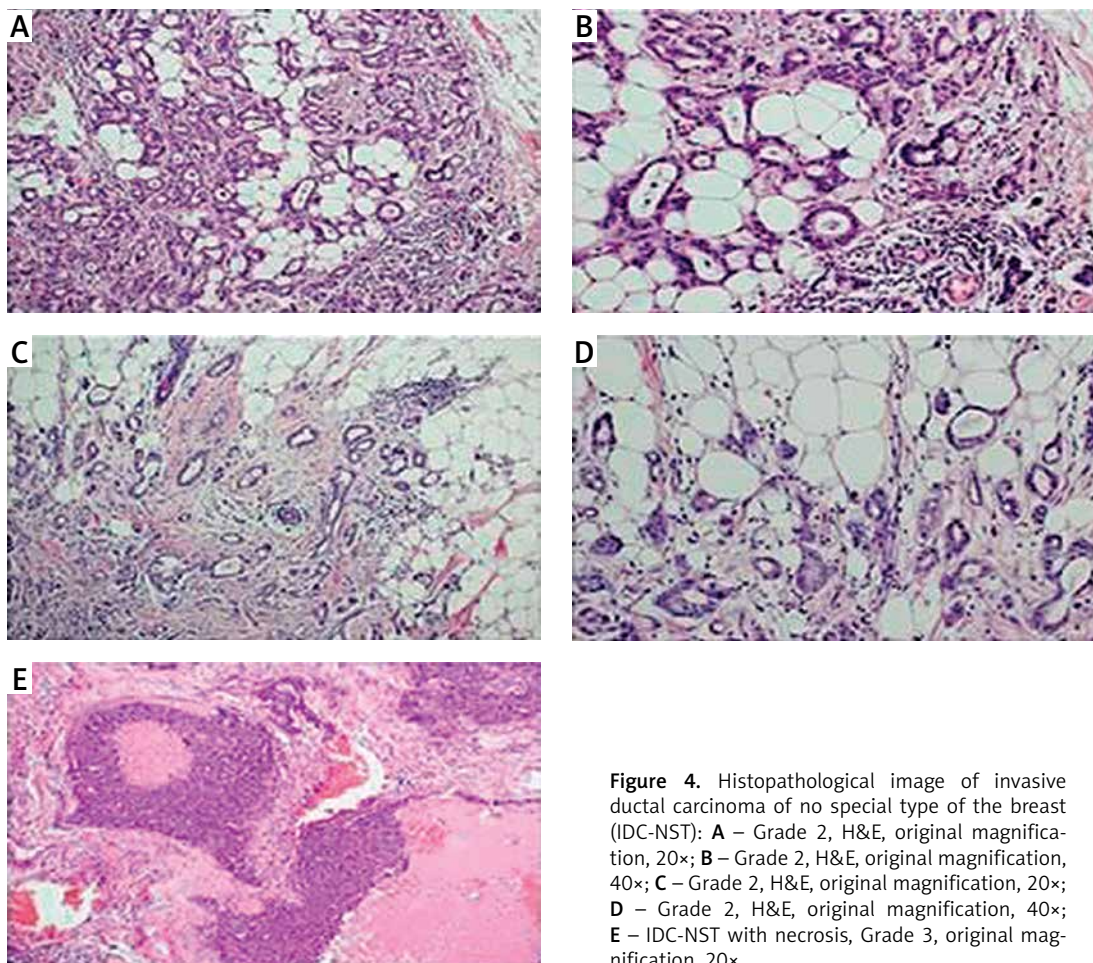


Figure 4. Histopathological image of invasive ductal carcinoma of no special type of the breast (IDC-NST): **A** – Grade 2, H&E, original magnification, 20×; **B** – Grade 2, H&E, original magnification, 40×; **C** – Grade 2, H&E, original magnification, 20×; **D** – Grade 2, H&E, original magnification, 40×; **E** – IDC-NST with necrosis, Grade 3, original magnification, 20×

Table II. Relationship between degree of malignancy (G1–G3), tumor size and lymph node status (pN) in IDC-NST

Tumor	G1	G2	G3	G1/2	G2/3	P-value	T1	T1a	T1b	T1c	T1d	T2	T3	T4	T4b	P-value
Invasive ductal carcinoma of no special type (IDC-NST):																
N0	32	184	81	1	2	0.0103*	1	7	33	143	0	117	1	9	0	0.00295*
N1	3	47	38	1	1	0.1201	1	1	6	33	0	42	1	4	1	0.9211
N1A	8	22	7	0	1	0.0498*	0	0	5	18	0	16	0	1	0	0.9832
N1B	0	2	1	0	0	< 0.001*	0	0	0	5	0	0	0	0	0	< 0.001*
N2	1	17	17	0	0	0.2193	0	0	0	10	0	13	2	8	0	< 0.001*
N2A	2	12	8	0	1	0.5508	0	0	1	3	0	13	1	3	4	< 0.001*
N3	1	2	9	0	0	0.0027*	0	0	1	4	0	7	2	1	0	0.03123
N3A	0	10	6	0	1	0.2921	0	0	0	4	0	8	1	2	1	0.432
N4	0	2	1	0	0	< 0.001*	0	0	0	1	0	1	0	1	0	< 0.001*
Nx	5	76	29	0	1	0.3318	0	2	10	12	0	11	0	1	0	0.0447*

*Statistically significant results ($p \leq 0.05$).

it was 49, and according to Sastre-Garau *et al.* it was 56 [16–19]. In studies by Mersin *et al.*, the mean age of patients with IDC-NST was 42 years [13]. According to the WHO, the mean age of patients with IDC-NST is from 1 to 3 years lower than

in patients with ILC [20]. In our study, the mean age of patients with IDC-NST was 60.47 years.

In the study by Yeatman *et al.*, 11.8% of patients with IDC were less than 39 years old [21], whereas in our study, women diagnosed with IDC-

NST less than 39 years old accounted for 5.79%. It should be noted, however, that for most of the authors, the differences in the mean age of patients with IDC are small and statistically insignificant [20–22].

Most of the data in the literature confirm that at the time of cancer diagnosis, the primary tumor in patients with IDC-NST is on average smaller in size than the primary tumor in patients with ILC [16–18, 21]. In studies by Yeatman *et al.*, the average size of the primary tumor in patients with IDC-NST was 2.2 cm, and in 4.5% of patients the tumor was classified as T3 [21]; in the study by Moland *et al.*, in only 3% of patients with IDC the primary tumor was classified as T3 [23]. In the studies by Silverstein *et al.*, the average size of the primary tumor in the group of patients with IDC was 2.3 cm [17]. In the material of Tubiana-Hulin *et al.* including 742 patients with IDC, 21.4% had a primary tumor of T3 stage [16]. In our study, the largest group among IDC-NST tumors consisted of those assessed as T1c (34.59%) and T2 (35.31%), and patients with IDC-NST classified as T3 and T4 accounted for 1.3% and 0.87%, respectively (Table I).

In the microscopic evaluation of IDC-NST the following features are very important: the degree of cancer differentiation, invasion of the vascular space by cancer cells, and the status of regional lymph nodes. The quoted authors agreed that in

Table III. Clinical classification of IDC-NST

Tumor size staging	Node involvement staging	Clinical stage	Percent
T1*	N0	I	39.74
T1*	N1	IIA	14.90
T2	N0	IIA	25.26
T2	N1*	IIB	12.52
T3	N0	IIB	0.21
T3	N1*	IIIA	0.21
T3	N2*	IIIA	0.65
T4*	N0–N2*	IIIB	6.48

*T1 includes T1a, T1b, T1c, T1d; T4 includes T4a, T4b; N1 includes N1A, N1B; N2 includes N2A.

IDC-NST, the percentage of patients with highly and moderately differentiated carcinoma (G1, G2) is lower than in ILC [13, 16, 18, 23–27]. According to the results obtained by Mersin *et al.*, patients with highly and moderately differentiated cancer accounted for 46.6% of patients with IDC [13].

In the studies by Sastre-Garau *et al.*, well-differentiated carcinoma was found in 22% of patients with IDC and poorly-differentiated cancer in 15% [18]. In the group of patients studied by

Table IV. Relationship between tumor size (pT) and degree of malignancy (G1–G3) in IDC-NST

Tumor	T1	T1a	T1b	T1c	T1d	T2	T3	T4	T4b	P-value
Invasive ductal carcinoma of no special type (IDC-NST):										
G1	0	3	13	26	0	9	0	0	1	< 0.001*
G2	1	2	25	137	0	127	5	15	3	0.6333
G3	1	2	11	59	0	88	4	14	1	0.1129
G1/2	0	0	0	1	0	1	0	0	0	< 0.001*
G2/3	0	1	1	1	0	3	0	1	0	0.0267*

*Statistically significant results ($p \leq 0.05$).

Table V. Relationship between degree of malignancy (G1–G3) and metastases to distant organs (pM) in IDC-NST

Tumor	G1	G2	G3	G1/2	G2/3	P-value
Invasive ductal carcinoma of no special type (IDC-NST):						
M0	23	165	108	2	3	0.2993
Mx	29	153	72	0	4	0.2993

Table VI. Relationship between tumor size (pT) and metastases to distant organs in IDC-NST

Tumor	T1	T1a	T1b	T1c	T1d	T2	T3	T4	T4b	P-value
Invasive ductal carcinoma of no special type (IDC-NST):										
M0	0	3	25	95	0	128	4	14	1	0.43587
Mx	2	6	29	138	0	116	4	20	2	0.43587

Tubiana-Hulin *et al.*, those with highly and moderately differentiated IDC accounted for 45.4% [16]. In the studies by Mathieu *et al.*, 63% of patients with IDC had highly or moderately differentiated carcinoma [26]. In the studies of Cristofanilli *et al.*, poorly differentiated cancer was found in 56% of patients with IDC [25].

In our study, 7.48% of patients had well-differentiated IDC-NST, 53.96% had moderately differentiated IDC-NST, and 28.98% had poorly differentiated IDC-NST. In patients with IDC, lymph node metastasis was found more frequently than in patients with ILC [16–19, 28]. In the studies by Silverstein *et al.*, metastases to axillary lymph nodes were found in 37% of patients with IDC [17], while in our study, lymph node metastases were found in 34.58% of patients with IDC-NST. Tubiana-Hulin *et al.* in their study found no metastases to lymph nodes in 43.3% of patients with IDC [16]. In our study, no metastases were found in 45.44% of patients with IDC-NST. In order to investigate the correlation between clinical features of IDC-NST, Spearman's rho coefficient was determined. The obtained results indicated a correlation between the degree of histological grade (G1 and G2) and lymph node metastasis [G1/pN (–0.70743); G2/pN (–0.72177)]. Moreover, a correlation between the size of the tumor pT1c and lymph node metastasis [T1c/pN (–0.86715)] was found.

In conclusion, IDC-NST constitutes more than a half of all diagnosed histological types of breast cancer in women. The most common among patients with IDC-NST are cases showing grade 2 (G2). Among IDC-NST cases, the most common are T1c and T2. The largest group of patients with IDC-NST consisted of those in whom the disease severity was as assessed as I and IIA. A relationship was found between IDC-NST of histological grades 1 and 2 and presence of metastasis to lymph nodes. In more than a half of the patients with IDC-NST, there were no metastases to distant organs.

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Conflict of interest

The authors declare no conflict of interest.

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