Abstract: Breast cancer (BC) is a heterogeneous disease that encompasses several distinct entities with remarkably different characteristics. Histological type is one of important BC characteristics. Histological type is associated with differences in epidemiology, diagnostic issues, clinical course, prognosis. When we talk about BC, ductal and lobular carcinoma is usually what we have in mind. However, the other types that comprise less than 10% of BC are also very important. The rarity of many of these neoplasms does not allow large or randomized studies to define the optimal treatment. Many of the descriptions are from case reports and small series. The aim of this retrospective study was to analyze the data on rare breast cancers, to describe their main characteristics, and to calculate survival rates. We believe that the experience of our institution will contribute to the available data about these rare breast cancers and help in better understanding of this subgroup.

Keywords: Breast cancer, Histological type, Epithelial breast tumors, Rare histological types.

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1 Introduction

Breast cancer (BC) is a heterogeneous disease that encompasses several distinct entities with remarkably different characteristics. For many decades, invasive breast carcinomas were classified according to the histological type, grade and expression of hormone receptors. More recently, improvements in our understanding of the biology of breast cancer have led to a more specific classification of tumours according to their genetic expression and immunohistochemical staining characteristics. Different forms of the disease vary with regard to clinical behaviour, management options, and prognosis [1–3].

Histological type is one of very important characteristics of cancer. Histological type is associated with differences in epidemiology, diagnostic issues, clinical course, and prognosis. The World Health Organization (WHO) has presented a detailed classification of breast cancers [4]. Invasive epithelial tumours are divided into 19 different types. Most tumours are derived from mammary ductal epithelium (the terminal duct-lobular unit), and up to 75% of the diagnosed cases of infiltrating ductal carcinoma are defined as invasive ductal carcinoma, not otherwise specified (IDC-NOS). The second most common epithelial tumour type is invasive lobular carcinoma, which comprises 5–15% of the group. There are more than a dozen variants that are less common, but are still very well defined by the WHO classification. Here they will be referred to as “rare types of breast cancer”.

When we talk about breast cancer, ductal and lobular carcinoma is usually what we have in mind. However, the other types that comprise less than 10% of breast tumours are also very important. While several studies have examined the clinical, pathologic, and epidemiologic features of ductal and lobular invasive carcinomas as well as differences between these carcinomas, much less is known about the rarer histologic types of breast cancer— Including mucinous, tubular, medullary, and papillary carcinomas—and other epithelial tumours. The rarity of many of these neoplasms does not allow large or randomized studies to define the optimal treatment. Many of the descriptions of these cancers are from case reports and small series [5].

The aim of this retrospective study was to analyse the data on rare breast cancers, to describe their main characteristics, and to calculate survival rates. We believe that the experience of our institution will contribute to the available data about these rare malignant breast tumours and help in better understanding of this unique subgroup.
2 Materials and methods

A 7-year retrospective review of all breast resection specimens was completed in the Nacional Cancer Institute. Clinical records of patients diagnosed with rare epithelial breast malignancies were then reviewed for data regarding patient demographics, clinical characteristics, the extent of the disease, and the type of surgery, chemotherapy, and radiotherapy. Pathology reports were obtained from the National Centre of Pathology.

Between January 2000 and December 2006, 3,792 women were operated on at the Institute of Oncology. Among them 134 rare malignant epithelial tumours were detected. In the absence of adequate clinical follow-up data in the hospital records patients were excluded from the study. Thus, a total of 126 patients with rare epithelial tumours were included into the study.

The numeric variables were presented as mean ± SD. The vital status of the study group was assessed as of December 31, 2012, by passive follow-up, using data from the population registry.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors’ institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

3 Results

Demographic and clinical characteristics of 5 more frequent types of breast cancer are presented in Table 1. Treatment was administered in accordance with the standards of our Institute. All of the patients underwent surgery – breast conserving or mastectomy, depending on tumour size, localization, etc. In the cases of locally advanced breast cancer the neoadjuvant chemotherapy was given.

The standard regimen after breast conserving therapy included irradiation of the whole breast, with or without including regional nodes, as defined by extent of disease. Whole-breast RT was delivered using 3D-CRT. A total dose of 54 Gy in 27 daily fractions was given. In locally advanced disease, irradiation of the breast (or chest wall), supraclavicular, axilla lymph nodes was planned. Post mastectomy radiation therapy was given in cases of T3/4 tumours, positive resection margins and in cases of ≥ 4 involved lymph nodes. Conventional dose fraction regimen of a total of 50 Gy with 2.0 Gy per daily fractions was given.

Adjuvant chemotherapy was given according to the risk factors of cancer relapse: patients’ age, tumour size, amount of affected regional lymph nodes, etc.

In the cases of hormone-dependent tumours, the adjuvant hormone therapy was given.

Because of the small number of patients in each subgroup and different treatment given, we did not evaluate the influence of different treatment modalities on survival.

The routine application of the immunohistochemical analysis for HER2 status at our Institute started only in 2005. Thus, in most cases, the HER2 status was unknown, and therefore it is not presented in Table 1.

4 Other rare types

4.1 Micropapillary carcinoma

Two cases were detected. The mean age at the time of the diagnosis was 57.62 years. One patient was premenopausal, and one – postmenopausal. Both patients presented with stage III of the disease, with metastases in lymph nodes. One tumour was 2.2 cm, and the other one was 4.7 cm in size. One case presented with a moderately differentiated tumour, and the other with a poorly differentiated tumour. ER were positive in both cases. One patient died, and the other survived. The mean survival was 4.20 (± 4.07) years.

4.2 Adenoid cystic carcinoma

Three cases were found. The mean age was 54.90 (±16.56) years. One patient was premenopausal, and two were postmenopausal. In two cases, the patients presented with stage I of the disease, with a metastatic disease. One tumour was 2.2 cm, and the other one was 4.7 cm in size. One case presented with a moderately differentiated tumour, and the other with a poorly differentiated tumour. ER was negative in all cases. One patient survived, while two died.

4.3 Secretory carcinoma

One patient was found. At the time of the diagnosis, she was 43.31 years old, and was premenopausal. She presented with stage I of the disease, with a 1.2-cm tumour,
and without lymph node involvement. The tumour was well differentiated. The ER was negative. This patient is still alive. The mean survival time was 8.40 years.

### 4.4 Apocrine carcinoma

Three cases were detected. The mean age was 63.0 (± 24.09) years. One patient had stage I, one patient had stage II, and another one had stage III of the disease. The median tumour size was 2.1 cm. One patient had no lymph node involvement, while two other patients had metastases in the lymph nodes. Two tumours were moderately differentiated, and one was poorly differentiated. ER was negative in two cases, and was positive in one case. Two of the patients are still alive, and one patient died. The mean survival was 6.46 years.

### Table 1: Demographic and clinical characteristics of 5 of more frequent types of breast cancer

|                      | Mucinous carcinoma | Metaplastic carcinoma, unspecified | Medullary carcinoma | Papillary carcinoma | Tubular carcinoma |
|----------------------|--------------------|-----------------------------------|--------------------|---------------------|-------------------|
| **Patients**         |                   |                                   |                    |                     |                   |
| n                    | 62                 | 14                                | 14                 | 11                  | 6                 |
| %                    | 49.2%              | 11.1%                             | 11.1 %             | 8.7 %               | 4.8 %             |
| **Mean age**         | 63.48 (±13.75)     | 64.80 (±7.22)                     | 53.99 (±14.74)     | 68.70 (±12.06)      | 52.16 (±10.15)    |
| **Menopausal status**|                   |                                   |                    |                     |                   |
| premenopausal        | 15                 | -                                 | 6                  | -                   | 4                 |
| postmenopausal       | 46                 | 14                                | 8                  | 11                  | 2                 |
| **Stage of disease** |                   |                                   |                    |                     |                   |
| I                    | 17 (27.4%)         | 3 (21.4%)                         | 5 (35.7%)          | 3 (27.3%)           | 5 (83.3%)         |
| II                   | 33 (53.2%)         | 3 (21.4%)                         | 9 (64.3%)          | 8 (72.7%)           | 1 (16.7%)         |
| III                  | 10 (16.1%)         | 7 (50.0%)                         | -                  | -                   | -                 |
| IV                   | 2 (3.2%)           | 1 (7.1%)                          | -                  | -                   | -                 |
| **Mean tumor size (cm)** |       |                                   |                    |                     |                   |
| Min.                 | 0.5                | 1.5                               | 0.7                | 0.1                 | 0.6               |
| Max.                 | 11                 | 12                                | 5.5                | 8.0                 | 1.5               |
| **Lymph node status**|                   |                                   |                    |                     |                   |
| negative             | 44                 | 4                                 | 9                  | 9                   | 5                 |
| positive             | 16                 | 9                                 | 4                  | 1                   | 1                 |
| unknown              | 2                  | 1                                 | 1                  | 1                   | -                 |
| **Tumor grade**      |                   |                                   |                    |                     |                   |
| G1                   | 31                 | -                                 | -                  | 7                   | 6                 |
| G2                   | 24                 | 1                                 | 2                  | 3                   | -                 |
| G3                   | 6                  | 13                                | 5                  | 1                   | -                 |
| **ER**               |                   |                                   |                    |                     |                   |
| positive             | 51                 | -                                 | -                  | 7                   | 5                 |
| negative             | 5                  | 13                                | 11                 | 2                   | -                 |
| unknown              | 6                  | 1                                 | 3                  | 2                   | 1                 |
| **Status**           |                   |                                   |                    |                     |                   |
| alive                | 47 (76%)           | 4 (28.6%)                         | 12 (85.7%)         | 7 (67%)             | 6 (100%)          |
| dead                 | 15                 | 10                                | 2                  | 4                   | -                 |
| **Mean survival time (years)** | | 6.61 (±2.29) | 2.25 (±2.34) | 8.26 (±2.91) | 6.03 (±3.20) | 9.68 (±3.18) |
4.5 Solid neuroendocrine carcinoma

Four cases were detected. The mean age was 69.37 years. All patients were postmenopausal. The median tumour size was 2.5 cm. Two patients presented with stage I, and two—with stage II of the disease. Two tumours were well differentiated, and two were poorly differentiated. ER was negative in two tumours, was positive in two tumours as well. All patients are still alive.

4.6 Neuroendocrine small cell carcinoma

A 49 year-old patient presented with a 2.5-cm tumour with no lymph node involvement. Stage II of the disease was diagnosed. The tumour was poorly differentiated, and the ER was negative. The patient is still alive after 7 years following the diagnosis.

4.7 Metaplastic carcinoma with squamous cell differentiation

Three cases were detected. Mean age of the patients was 45.45 years. Mean tumour size was 4.8 cm. Two cases presented with stage II, and one with stage III of the disease. In one case, the involvement of lymph nodes was found. One tumour was moderately differentiated, and two were poorly differentiated. Only one patient is still alive. The mean survival was 4.13 years.

Also, there were two cases of mixed-type epithelial carcinomas.

5 Discussion

The main reason for applying a classification system to invasive breast carcinoma is to obtain a correlation with prognosis and tumour biology. Invasive carcinomas may be sub-divided morphologically according to their histological type and histological grade. The relationship between histological type and prognosis is known: the excellent prognosis group comprises tubular, cribriform, and mucinous carcinomas; the good prognosis group includes tubular mixed, mixed ductal NST/special type, and classical lobular carcinoma; the average prognosis group consists of mixed lobular, medullary, and atypical medullary carcinoma; and the poor prognosis group is composed of ductal NST, mixed ductal, and solid lobular carcinoma [6].

We think that presenting data on rarer histological forms of breast cancer is important in order to prognosticate the outcome and to select optimal treatment, even though for many tumours, prognosis based on histological type alone is known to be less accurate than that using grade and type together [7].

According to the Nacional Cancer Institute data, mucinous carcinoma was the main “rare” form of breast cancer (BC), comprising 49.2% of rare forms of BC and 4.3% of all breast cancers. Literature indicates that cribriform carcinoma (5-6% of all BC) is more common among the rare forms of BC, while mucinous, micropapillary, and tubular carcinoma comprise ca. 2% of all BC each [5, 8]. According to our findings, ca. 11.1% of rare BC cases were metaplastic (1% of all BC), medullary, and tubulo-lobular carcinoma; papillary carcinoma was somewhat less common (8.7%), while tubular carcinoma comprised 4.8% of rare BC (0.5% of all BC). Thus, according to our findings, metaplastic carcinoma was detected somewhat more frequently, compared to the incidence indicated in literature.

Some rare forms of BC are more characteristic for younger or older patients – e.g. medullary and micropapillary carcinomas are more common during the early postmenopausal period. The age at which rare forms of breast cancer were diagnosed was similar to that indicated in other literature sources – i.e. papillary carcinoma was more common in older women (median age–68.7 years), while tubular carcinoma in somewhat younger patients (median age – 52.16 years). Literature indicates that metaplastic carcinoma is usually detected in ca. 56-year-old patients [9], while the median age of women with metaplastic carcinoma registered at our institution was somewhat older at 64.8 years.

In addition to that, our findings showed that the detected metaplastic carcinomas were larger. The mean tumour size reached 4.1 cm, while tubular carcinomas were usually smaller at the time of detection with mean tumour size of 1.1 cm.

With respect to stages, stage IV breast cancer at Nacional Cancer Institute was diagnosed only in cases of mucinous (2/62 cases, 3.2%) and metaplastic carcinoma (7.1%). Our findings clearly indicated that BC in early stages was more commonly detected in cases of mucinous carcinoma: according to our findings, stage I-II mucinous carcinoma was detected in 80% of cases, stage I-II medullary carcinoma – in 100% of cases; meanwhile, metaplastic carcinoma was more frequently detected in more advanced stages – stage III tumour was found in as many as 50% of patients. The study also clearly showed that, compared to other forms, metaplastic carcinoma was more frequently associated with metastases to lymph
nodes; according to our findings, metastases in axillary lymph nodes were detected in as many as 64.3% of cases of metaplastic carcinoma, compared to only 9.1% in case of papillary carcinoma.

The study also showed that the presence of oestrogen receptors (ER+) was detected in 82% of cases of mucinous carcinoma, while the highest percentage of ER+ tumours was observed in tubular (100%) carcinomas. Literature presents analogous results.

According to the Nacional Cancer Institute data, micropapillary carcinoma, as indicated in literature, is a rather aggressive form of cancer; only two cases were detected, but both cases were stage III cancer, and one patient did not survive. According to literature, the prognosis for this type is poor, and lymph nodes are positive in 72-77% of cases [10].

Adenoid cystic carcinoma, where prognosis, according to literature is moderate, appeared to be rather aggressive according to the Nacional Cancer Institute data. Only three cases of this cancer were detected, and only one patient is still alive.

One case of secretory carcinoma was detected in a 43-year-old patient. Literature also indicates that this form is typically found in premenopausal women. This tumour has excellent prognosis, and the patient treated at Nacional Cancer Institute is still alive.

Concerning the prognosis, the best results within the period of 5-10 years after the diagnosis were observed in cases of tubular (100% of survivors) and medullary carcinomas (85.7% of survivors). Poor prognosis was characteristic of metaplastic carcinoma (71.4 % of patients died). These results correspond to those presented in literature, indicating that the prognosis for tubular carcinoma is excellent, while that for metaplastic carcinoma is poor.

We collected these data in order to clarify what information can be obtained from the histological type of BC, and what prognosis can be expected. Currently, gene expression studies that reveal the molecular makeup of breast cancer are becoming increasingly common [11,12].

There is an international consensus that the Nottingham Grading System (NGS) should be considered as the ‘gold standard’ for breast cancer grading. The adoption of the objective criteria of NGS has been shown to overcome many of the previous problems of reproducibility of grading, problems that resulted from using a variety of approaches [13].

6 Conclusions

Rare epithelial breast cancers are a heterogeneous group of malignancies with different behaviours and prognoses.

Since these forms of breast cancer are indeed rare, the description of the experience of our Clinic is important because each case helps to understand these tumours, their characteristics, and the course of the disease. Our results are in accordance with most data from other studies. The most favourable histological types were mucinous, tubular and tubulo-lobular, while shortest survival time was with metaplastic carcinoma.

The more information about these tumours we obtain the better possibilities we will have for selecting optimal treatment tactics for each patient.

Conflict of interest statement: Authors state no conflict of interest.

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