ORIGINAL ARTICLE PEER REVIEWED | OPEN ACCESS

Pure invasive micropapillary carcinoma of the breast: A 10-year case review of a rare and aggressive subtype of breast carcinoma

Diana Fernandes, Maria Olim Sousa, Ana Sílvia Pires-Luís, Carlos Gonçalves Dias, Conceição Leal, Joaquim Abreu de Sousa

ABSTRACT

Aims: Invasive micropapillary carcinoma (IMPC) is a special variant of breast carcinoma. The aim of this study was to investigate the relationship between clinicopathologic features of IMPC, lymph node metastasis and patients' outcome to verify if this subtype of breast carcinoma is associated with a poor prognosis. Methods: All cases of invasive carcinoma were reviewed in a 10-year period and 61 pure IMPC cases were identified. Clinical, histopathologic and immunohistochemical features, treatment type and outcome were evaluated. Chi-square test and Student's t-test were used for statistical analyses. Results were considered to be significant at p < 0.05. Results: All patients but 1 were women. Tumor size ranged from 0.3–10 cm. In 60 cases, 20 (33%) were grade 3. Of 49 patients with lymphatic permeation, 37 (76%) had lymphovascular invasion. Multifocality occurred in 21 (34%) cases and metastatic axillary nodes in 38 (62%). In 55 (90%) cases there was positivity for estrogen receptors and in 48 (79%) for progesterone receptors; HER2 was overexpressed in 21 (35%). Over a median follow-up of 61 months, six (10%) patients suffered disease progression. Disease-specific mortality rate was 5%. Conclusion: We found that lymph node metastasis was correlated with tumor size, high histologic grade, lymphovascular invasion, multifocality and HER2 positivity. Axillary lymph node metastasis and the burden of axillary node involvement were predicting factors related with poor prognosis. In this series, the cases with positivity for estrogen and progesterone receptors were associated with a more favorable outcome.

Keywords: Breast, Carcinoma, Invasive micropapillary subtype, Lymph node metastasis

Diana Fernandes[1], Maria Olim Sousa[1], Ana Sílvia Pires-Luís[2], Carlos Gonçalves Dias[3], Conceição Leal[4], Joaquim Abreu de Sousa[5]

Affiliations: [1]General Surgery Resident, General Surgery Department, Hospital Central do Funchal, SESARAM EPE, Madeira, Portugal; [2]Pathology Resident, Pathology Department, Instituto Português de Oncologia do Porto Francisco Gentil EPE, Porto, Portugal; Microscopy Department, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Portugal; [3]Surgical Oncology Specialist, Surgical Oncology Department, Instituto Português de Oncologia do Porto Francisco Gentil EPE, Porto, Portugal; [4]Breast Pathology Coordinator, Pathology Department, Instituto Português de Oncologia do Porto Francisco Gentil EPE, Porto, Portugal; [5]Head of Surgical Oncology Department, Surgical Oncology Department, Instituto Português de Oncologia do Porto Francisco Gentil EPE, Porto, Portugal.

Corresponding Author: Diana Fernandes, Avenida Luís de Camões n. 57, 9004-514 Funchal, Madeira, Portugal; Email: dianarfernandes@gmail.com

Received: 14 November 2017
Accepted: 30 November 2017
Published: 28 December 2017

How to cite this article

Fernandes D, Sousa MO, Pires-Luís AS, Dias CG, Leal C, Abreu de Sousa J. Pure invasive micropapillary carcinoma of the breast: A 10-year case review of a rare and aggressive subtype of breast carcinoma. Edorium J Surg 2017;4:41–49.

Article ID: 100024S05DF2017

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doi: 10.5348/S05-2017-24-OA-8

INTRODUCTION

Invasive micropapillary carcinoma (IMPC) is a special variant of breast carcinoma initially described by Fisher et al. in 1980, as an invasive papillary cancer with an exfoliative appearance [1]. Siriaunkgul and Tavassoli in 1993 first suggested the term 'invasive micropapillary carcinoma' of the breast and Luna-Moré et al. also later described it in 1994 [2, 3].

Invasive micropapillary carcinoma is composed of small, hollow or morula-like clusters of cancer cells, devoid of fibrovascular cores and surrounded by clear stromal spaces, characterized by a complete reversal of cell polarity (Figure 1). This is supported by an inside-out immunostaining pattern with MUC1 and EMA, which stain the cytoplasmic membrane oriented towards the stroma.

Moreover, E-cadherin immunoexpression was reported to be altered in IMPC [4]. These changes might be related to the higher frequency of lymphovascular invasion and lymph node metastasis.

Luna-More et al. reported two series of IMPC emphasizing the lymphotropism of this tumor and its frequent spread to axillary lymph nodes [3, 5]. Hence, IMPC is considered an aggressive variant of breast carcinoma. However, pure invasive micropapillary growth pattern is rarely observed and most series reported to date are small, describe mixed cases of IMPC with invasive ductal carcinoma, not otherwise specified, and have short follow-up intervals [6].

The aim of this study was to retrospectively analyze the clinicopathologic features and follow-up data of 61 patients diagnosed with pure IMPC, to verify the behavior and outcome of this subtype of breast carcinoma.

MATERIALS AND METHODS

Sixty-one cases of pure invasive micropapillary carcinoma of the breast, diagnosed and treated between January 2006 and December 2015 at the Instituto Português de Oncologia do Porto Francisco Gentil EPE, Portugal, were identified from the Department of Pathology files. Pure IMPC was morphologically defined as a tumor with exclusive micropapillary growth pattern. All cases with micropapillary carcinoma mixed with other patterns were excluded. In patients receiving neoadjuvant chemotherapy, the biopsy result prior to chemotherapy was in accordance with surgical specimens.

Patients' clinical features, follow-up and survival data were obtained from medical charts and registry records. For each patient, gender; age at diagnosis; size, grade and tumor multifocality; the presence of lymphovascular invasion and axillary lymph node metastasis; hormone receptors and HER2 overexpression status, therapeutic interventions (neoadjuvant and adjuvant treatments, type of surgery); disease recurrence; and disease-specific mortality were retrieved.

The tumors were graded using the Nottingham grading system [7]. Multifocality was defined as the existence of at least two foci of invasive tumor, with normal breast parenchyma in between [8]. Immunohistochemical (IHC) analysis was performed for estrogen receptors (ER), progesterone receptors (PR) and HER2 status. Results were considered positive for ER and PR if nuclear immunoreactivity was present in at least 10% of the neoplastic cells. For a case to be considered positive for HER2, strong membranous staining in at least 10% of the tumor cells was required [9] (Figure 2). Equivocal cases (2+) were evaluated by FISH, and cases with HER2 amplification were considered positive. Follow-up ranging from 6–122 months was available in all cases.

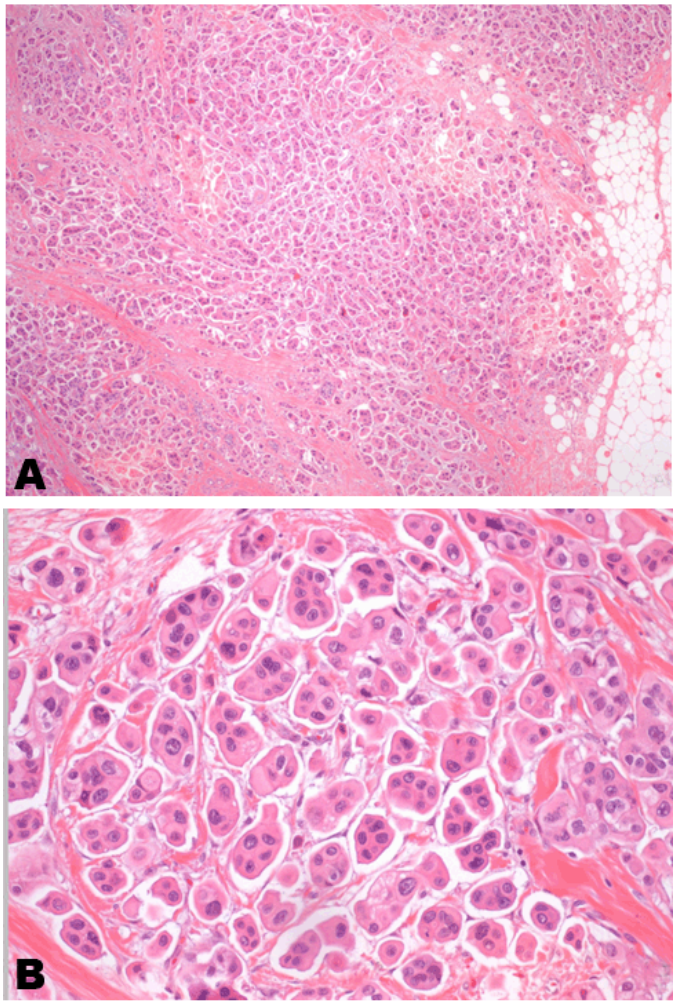

Figure 1: Invasive micropapillary carcinoma of the breast: cuboidal or columnar cells in aggregates without fibrovascular core, surrounded by empty stromal spaces and presenting reverse polarity (H&E stain, A: x40; B: x200).

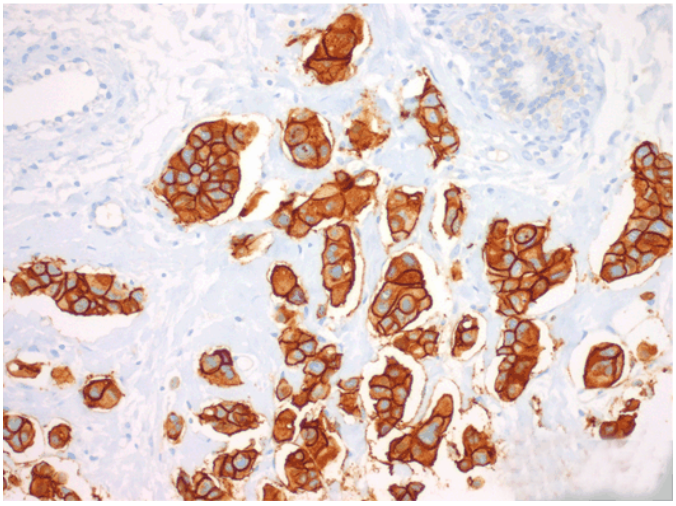

Figure 2: HER2 immunohistochemical staining, positive (3+) (x200). In this series, HER2 overexpression was found in 21 (35%) tumors.

Statistical analyses were verified in their categorical variables by chi-square test and in their numerical variables with student's t-test. Results were considered to be significant at $p < 0.05$.

RESULTS

Of the 61 patients, 60 were female and 1 was male. The patient's age at presentation ranged from 32 to 78 years (mean 54.0 years). The initial clinical manifestation was a palpable mass in 33 patients (54%) and a mammographic abnormality in 28 patients (46%). All patients underwent mammography, breast ultrasound and biopsy before surgery or neoadjuvant chemotherapy.

Regarding therapeutic interventions, 14 (23%) received neoadjuvant chemotherapy: one patient received an anthracycline-based therapy alone and 13 were treated with a combination of anthracyclines and taxanes; 25 (41%) were submitted to breast conserving surgery (BCS) and sentinel lymph node biopsy (SLNB); 16 (26%) to total mastectomy and SLNB; 4 (7%) underwent BCS and axillary lymph node dissection (ALND); and 16 (26%) had modified radical mastectomy. Of the 41 patients initially submitted to SLNB, 16 (39%) required a subsequent ALND due to positive lymph node metastasis.

Of all cases, 51 (84%) received radiotherapy; 55 (90%) received adjuvant hormonal therapy; 17 (28%) had trastuzumab; and adjuvant chemotherapy was given to 38 (62%) patients: four patients received an anthracycline-containing therapy alone, 32 were treated with a combination of anthracyclines and taxanes and two patients received a CMF regimen (cyclophosphamide, Methotrexate and 5-fluorouracil combination). Of the total mastectomies performed, in two patients (13%) immediate breast reconstruction was done. In all cases of SLNB, a triple technique with lymphoscintigraphy, radiotracer and blue dye was performed.

The tumor size ranged from 0.3–10 cm (mean 2.7 cm). Twenty-one (34%) patients had multifocal tumors composed of separate neoplastic foci. In 60 cases, according to the Nottingham grading system, 38 (63%) tumors were classified as grade 2; 20 (33%) as grade 3; and 2 (3%) as grade 1. Of 49 patients with lymphatic permeation, 37 (76%) had lymphovascular invasion. Of the 61 surgical specimens, axillary lymph node metastases were identified in 38 (62%) cases. The tumor size, multifocality, histological grade 3 and lymphovascular invasion, correlated positively with lymph node metastasis ($p < 0.05$ in all cases) (Table 1).

The number of sentinel lymph nodes ranged from one to eight (mean 2.4). Among 41 patients submitted to SLNB, 18 (44%) had lymph node metastasis. In 2 (11%) cases, lymph node involvement corresponded to micrometastasis and in 16 (89%) to macrometastasis. In 7 (39%) cases of positive SLNB, the sentinel lymph node was the only node with carcinoma metastasis. The number of metastatic sentinel lymph nodes varied from one to three (mean 1.2).

The number of axillary lymph nodes dissected ranged from 9–42 (mean 16.3). Among 36 patients submitted to ALND, 29 (81%) had lymph node metastasis. The number of metastatic axillary lymph nodes varied from 1–21 (mean 7.4).

Immunohistochemically, hormone receptor analysis was positive for estrogen in 55 (90%) cases and for progesterone in 48 (79%). Overexpression of HER2 was found in 21 (35%) tumors. HER2 positivity correlated with lymph node metastasis ($p < 0.05$) but there was no significant difference in axillary node metastasis depending on the status of ER or PR ($p = 0.513$ and $p = 0.949$, respectively) (Table 1).

Follow-up was available in all 61 cases, ranging from 6–122 months. The mean follow-up period was 61 months. Recurrence occurred in 6 (10%) patients. The time to recurrence ranged from 5–102 months (mean 59 months). Local recurrence was detected in two (3%) cases and distant organ metastasis was discovered in 4 (7%). Of the 61 patients, 3 (5%) died of disease with widespread metastasis, 58–108 months after the initial diagnosis (mean 81 months). There was a correlation between the frequency of positive nodes and a worse prognosis (58% had positive lymph nodes in the alive with no disease (AND) group versus 100% in the alive with recurrent disease/died of disease (ARD/DOD) group, $p < 0.05$) (Table 2). A significant difference was similarly found between the nodal tumor burden and the outcome. Patients in the ARD/DOD group had higher mean number of metastatic nodes than patients in the AND group (12.3 versus 3.0, respectively, $p < 0.05$) (Table 2). Age at diagnosis, tumor size, histological high grade, lymphovascular invasion, multifocality and ER, PR and HER2 status were not predictive of adverse outcome.

Table 1: Relationship between clinicopathological features and axillary lymph node metastasis

	Negative ALNM	Positive ALNM	p-value
Number of patients	23 (38%)	38 (62%)	—
Mean tumor size (cm)	1.3	3.6	< 0.05*
Grade 3	4 (17%)	16 (43%)	< 0.05§
LVI	7 (44%)	30 (91%)	< 0.05§
Multifocal tumor	4 (17%)	17 (45%)	< 0.05§
Estrogen receptors positive	20 (87%)	35 (92%)	0.513§
Progesterone receptors positive	18 (78%)	30 (79%)	0.949§
HER2 positive	4 (17%)	17 (45%)	< 0.05§

Abbreviations: ALNM: Axillary Lymph Node Metastasis, LVI: Lymphovascular Invasion, HER2: Human Epidermal Growth Factor Receptor 2
* Student's t-test, $p < 0.05$
§ Chi-square test, $p < 0.05$

Table 2: Relationship between clinicopathological features and patients' outcome

	AND	ARD/DOD	p-value
Number of patients	55 (90%)	6 (10%)	—
Mean age	54.0	53.7	0.950*
Mean tumor size (cm)	2.4	5.7	0.066*
Grade 3	17 (31%)	3 (50%)	0.361§
Lymphovascular invasion	33 (75%)	4 (80%)	0.805§
Multifocal tumor	18 (33%)	3 (50%)	0.339§
Estrogen receptors positive	50 (91%)	5 (83%)	0.554§
Progesterone receptors positive	45 (82%)	4 (67%)	0.375§
HER2 positive	19 (35%)	3 (50%)	0.454§
Axillary lymph node metastasis	32 (58%)	6 (100%)	< 0.05§
Mean number of ALNM	3.0	12.3	< 0.05*

Abbreviations: AND: Alive with No Disease, ARD: Alive with Recurrent Disease, DOD: Died of Disease, HER2: Human Epidermal Growth Factor Receptor 2, ALNM: Axillary Lymph Node Metastasis
*Student's t-test, $p < 0.05$
§Chi-square test, $p < 0.05$

DISCUSSION

Breast carcinomas are a heterogeneous group of tumors with numerous histologic morphologies. Invasive micropapillary carcinoma of the breast is a distinct subtype but also a poorly recognized histologic variant of invasive ductal carcinoma. The incidence of IMPC in all primary breast cancers is estimated to be 2.6–6% [4, 6, 10–13]. Pure IMPC is a rare entity, representing approximately 0.9–2% of all breast carcinomas [2, 13, 14]. However, the incidence of IMPC has been increasing since 2008 mostly due to better recognition of this histologic variant from pathologists [15]. In our series, we identified 61 cases. This is one of the largest published series of carcinomas of the breast with exclusively pure micropapillary component.

Moderate relationship between each histologic subtype and its biologic behavior has been revealed in some studies. Some phenotypes represent more aggressive variants associated with poor short-term treatment results [16, 17]. Zekioglu et al. reported that 50% of IMPC between 1 and 2 cm had positive lymph nodes and 83% of >2 cm had lymph node metastases [12]. Moreover, Paterakos et al. have suggested that sentinel lymph node biopsy may not benefit patients with IMPC due to the likelihood of positive lymph nodes [13]. In our study, mean tumor size was 2.7 cm, ranging from 0.3–10 cm, which meant the risk of axillary lymph node metastasis was high.

Some studies have reported that IMPC of the breast is associated with a higher histologic grade and a particular lymphotropic character [3, 4, 6, 12, 18, 19]. Guo et al. described that high-grade IMPC presented with more positive lymph nodes per case, demonstrating that high histologic grade was correlated with the range of lymph node metastasis [11]. In our study, up to 96% of 60 cases had IMPC with histologic grade 2/3, which is in accordance with the findings of previous series.

Lymphatic vessels invasion is usually a marker of lymph node metastasis. Of 49 patients with lymphatic permeation, we identified 37 cases (76%) with lymphatic vessel invasion. Invasive micropapillary carcinoma is known to have high frequency of lymphatic and axillary lymph node spread. Its incidence has been described as ranging from 72 to 91% [5, 6, 9, 13]. In our study, this incidence was 62% and the burden of metastatic nodal disease was high. Of these cases with positive lymph nodes, 55% had three or more metastatic nodes. However, all cases with sentinel lymph node macrometastasis were radically treated with axillary lymph node dissection, which may have contributed to the overall better outcome of the patients.

Some series have reported estrogen receptors positivity in IMPC of the breast ranging between 25% and 91%, [4, 9, 11, 12, 17, 20, 21] and progesterone receptors positivity between 13% and 82% [4, 9, 17, 20, 21]. In our series, estrogen receptors and progesterone receptors expression was detected in 90% and 79%, respectively, which is in agreement with previously reported data. The HER2 overexpression status is not consensual in literature. It has been reported to be in the range of 36–100% [4, 11, 12, 20, 21]. In the present study, HER2 was overexpressed in only 35% of the tumors.

Many studies suggested that IMPC appears to be an exception to the general rule that ER positivity is commonly associated to better-differentiated tumors with a favorable outcome. However, one study revealed a poor prognosis in patients with IMPC lacking estrogen receptor expression [15]. Similarly, Luna-Moré et al. have reported that ER positivity was the most powerful predictor of patient survival [22]. More recently, Gokce et al described that ER and PR negativity, as well as HER2 overexpression in all IMPC cases, either pure or mixed forms, significantly correlates with higher local recurrence rates. This study also suggested that ER positivity is associated with longer overall survival in breast cancer patients, regardless of the histologic type of cancer [23]. Thus, the high positivity of estrogen and progesterone receptors and the low rate of HER2 overexpression may explain the favorable outcome observed in our patients.

Table 3 summarizes the comparison between our data and clinicopathological data from previously published series of IMPC of the breast.

Most studies usually report IMPC associated to a poor prognosis. The lymphotropism, aggressive clinical behavior, short disease-free interval and overall survival of IMPC of the breast have been described in the literature [5, 6, 9, 13, 18]. However, some authors defend that, despite its propensity for multiple node involvement, the outcome for IMPC patients is similar to that of infiltrating ductal carcinoma, not otherwise specified, with similar axillary lymph node status [6]. In our series, adequate follow-up data were available in all 61 patients with mean

Table 3: Clinicopathological data from breast invasive micropapillary carcinoma series published to date

Study	Year	N	Mean age	Size (cm)	Grade 3	LVI	ALNM	ER	PR	HER2
Siriangkul and Tavassoli[2]	1993	9	62	0.8-3	33	33	44	—	—	—
Middleton et al[18]	1999	14	50	3-6.2	36	71	100	25	13	100
Tresserra et al[20]	1999	15	52	0.6-4.7	60	—	60	—	—	—
Paterakos et al[13]	1999	21	55	3.6	67	—	95	62	50	81
Luna-Moré et al[22]	2000	68	54.2	4.1	43	59	91	75	46	36
Walsh and Bleiweiss[9]	2001	80	58.8	0.1-10	68	63	72	91	70	59
*Nassar et al[6]	2001	83*	61	4	58	15	77	71	—	—
Pettinato et al[4]	2004	62	57	0.7-10	87	63	93	32	20	95
Zekioglu et al[12]	2004	53	52.5	0.5-9.0	82	76	69	68	61	54
*Gokce et al[23]	2013	103*	52.8	0.4-9.5	41	—	—	70 (101)	77 (88)	42 (80)
Present study	2017	61	54	0.3-10	33	76 (49)	62	90	79	35

Abbreviations: LVI: Lymphovascular Invasion, ALNM: Axillary Lymph Node Metastasis, ER: Estrogen Receptors, PR: Progesterone Receptors, Her2: Human Epidermal Growth Factor Receptor 2.
Data are shown in percentage.
* In the series of Nassar et al. [6] and Gokce et al. [23], the micropapillary pattern in the majority of their cases (79% and 81%, respectively), comprised only a minor proportion of the tumor.

follow-up period of 61 months (range 6–122 months). There were only 6 (10%) recurrences in 61 patients with time to recurrence ranging from 5–102 months (mean 59 months). Local recurrence was detected in two (3%) cases and 4 (7%) patients developed distant organ metastasis.

Luna-More et al. described that 20 (37%) patients were dead, within 42 months after the initial diagnosis [22]. In the study of Middleton et al the follow-up in 10 cases showed that 50% of the patients died of disease [18]. Zekioglu et al. reported that 10 (28%) in 36 patients died of disease within nine years [12]. In our study, only three patients (5%) died of disease with widespread metastasis in an average of 81 months of follow-up. Our follow-up data is compared to other series published to date in Table 4.

Yerushalmi et al. [24] and Acevedo et al. [25] have reported a review of literature concerning rare breast tumors indicating its clinical, epidemiological and treatment characteristics and patients' outcome. Table 5 shows a comparison between our series of pure IMPC and other rare breast tumors regarding clinical features, main histopathological characteristics, axillary lymph node involvement and prognosis.

Table 4: Follow-up data of breast invasive micropapillary carcinoma series published to date

Study	N	Recurrence	Mean follow-up (months)	Died of disease	Mean follow-up (months)
Siriangkul and Tavassoli[2]	5	1 (20%)	—	—	—
Middleton et al[18]	10	9 (90%)	24	5 (50%)	36–144
Tresserra et al[20]	15	4 (27%)	14.3	—	—
Luna-Moré et al[22]	54	—	—	20 (37%)	42
Nassar et al[6]	83	43 (52%)	—	38 (46%)	2–144
Pettinato et al[4]	41	29 (71%)	30	20 (49%)	12–126
Zekioglu et al[12]	36	27 (75%)	—	10 (28%)	108
Gokce et al[23]	87	47 (54%)	—	21 (24%)	5–132
Present study	61	6 (10%)	59	3 (5%)	58–108

Table 5: Comparison between our series of pure invasive micropapillary carcinoma and other rare breast carcinomas

Type of tumor	%[a]	Clinical features	Main histologic features	ER	PR	HER2	ALNM	Outcome
Pure tubular	2	Small spiculated mass	Open tubules of single-layered epithelial cells and cellular desmoplastic stroma	+	+	-	Low (4–17)	Excellent
Invasive cribiform	0.3–3	Frequently clinically occult	Infiltrating components presenting >90% in a cribriform growth pattern	+ (96)	+ (86)	- (98)	Low	Excellent
Mucinous	1–4	Palpable lump; well-defined and lobulated lesion	Abundant production of extracellular and/or intracellular mucin	+ (96)	+ (80)	-	Low (3–15)	Excellent
Solid papillary	1.7	Palpable, central mass; bloody nipple discharge; older women	Round, well-defined nodules composed of low-grade ductal cells (with NE and mucinous differentiation) separated by fibrovascular cores	+	NA	NA	Low (13)	Excellent
Apocrine	0.3–4	Small size mass	Large round nuclei and eosinophilic, granular and sharp-bordered cytoplasm	-	-	+	Low	Favorable
Neuroendocrine	0.1	Undistinguished from other types	NE markers (mainly chromogranin or synaptophysine) in >50% of cells	+	+	-	Low	Uncertain

Table 5: *(Continued)*

Medullary	5	Well delineated and soft on palpation	Syncytial growth pattern, large vesicular nuclei and prominent nucleoli, circumscribed margins, important lymphocytic infiltrate	-	-	-	Low (27)	Favorable
Secretory	Rare[b]	Painless and firm mass	Intracellular/extracellular secretion and granular eosinophilic cytoplasm	-	-	-	Low	Indolent course
Adenoid cystic	0.1	Unilateral, small breast lump	Cribriform, tubular or solid cells	-	-	-	Low (2)	Favorable
Acinic cell	Rare[b]	Well-defined mass on mamography	Salivary gland-like tumors of the breast with serous differentiation	-	-	-	Low (17)	Favorable
High grade small-cell NE	Rare[b]	Well-defined mass on mamography	NE markers (neurone-specific enolase, PGP 9.5, chromogranin and synaptophysin) >50% of cells; + for cytokeratin CAM5.2, AE1/3 and cytokeratin 7	+	+	-	High (59)	Poor
Metaplastic	<1%	Circumscribed or indistinct lesion on mamography	Adenocarcinoma with dominant metaplastic component (of epithelial or mesenchymal origin)	-	-	- (0-8)	Low (20)	Poor
Lipid-rich	1–2%	Higher density than adjacent tissue	~90% of cells contain abundant cytoplasmic neutral lipids	-	-	+ (71)	High (80)	Poor
Pure invasive micropapillary[c]	0.9–2	Palpable lump; high density lesion, speculated margins	Small, hollow clusters of cells, devoid of fibrovascular cores and surrounded by clear stromal spaces	+ (90)	+ (79)	- 35)	High (62)	Excellent

Abbreviations: ER: Estrogen Receptors, PR: Progesterone Receptors; HER2: Human Epidermal Growth Factor Receptor 2, ALNM: Axillary Lymph Node Metastasis, NE: Neuroendocrine, NA: Not Available, PGP 9.5: Protein Gene Product 9.5
Data are shown in percentage.
[a] Percentage of all breast cancers
[b] Less than 40 cases described in the literature
[c] Pure invasive micropapillary carcinoma series of the present study

CONCLUSION

Our data suggest that multifocal tumors, lymphovascular invasion, lymph node metastasis and the lymphotropic nature of invasive micropapillary carcinoma could explain its aggressive behavior. We found that axillary lymph node metastasis and the degree of axillary node involvement were predicting factors related with poor prognosis. Nevertheless, high levels of estrogen receptors and progesterone receptors and lacking of HER2 overexpression indicate that some cases have been associated with a better prognosis and longer overall survival. The low recurrence and mortality rates observed in our study, comparing with previously published data in literature, may be explained by these biological characteristics and by radical treatment decisions regarding axillary lymph node dissection. Further studies with molecular profiling tests and genomic analysis are needed to verify this correlation and elucidate the prognostic and predictive features of this unique variant of breast carcinoma.

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Acknowledgements
We acknowledge the Surgical Oncology and the Pathology Departments for their support and the Records Department for giving us access to data used in this study.

Author Contributions
Diana Fernandes – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Maria Olim Sousa – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Ana Sílvia Pires-Luís – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Carlos Gonçalves Dias – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Conceição Leal – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Joaquim Abreu de Sousa – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission
The corresponding author is the guarantor of submission.

Source of Support
None

Conflict of Interest
Authors declare no conflict of interest.

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