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Clinicopathological and Genomic Identification of Breast Cancers with No Impact on Mortality

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Simple Summary: There are patients with breast cancer who will never metastasise. Tumour palpability is a prognostic variable for lower risk of developing metastases. PAM50 intrinsic subtypes were independently prognostic for long-term survival. In our study, patients with non-palpable, luminal tumours, < 1 cm, diagnosed on breast screening, never develop metastases. De-escalation of treatment should be considered

Abstract: Background. Implementing mammogram screening means that clinicians are seeing many breast cancers that will never develop metastases. The purpose of this study was to identify subgroups of breast cancer patients who did not present events related to long-term breast cancer mortality, taking into account diagnosis at breast screening, absence of palpability and axillary involvement, and genomic analysis with PAM50. Patients and Methods. To identify them, a retrospective observational study was carried out selecting patients without palpable tumour, without axillary involvement, and a genomic analysis was performed with PAM50. Results. The probability of distant metastasis-free interval (DMFI) of 337 patients was 0.92 (95% CI, 0.90-0.93) at 20 years and 0.96 (95% CI, 0.92-1.00) in 95 patients (28%) with available PAM50 tests. In 22 (23.15%) luminal A tumours and in 9 (9.47%) luminal B tumours smaller than 1 cm and in HER2 and basal type tumours there were no metastatic events (20-year DMFI of 1.00). Conclusion. Patients with nonpalpable breast cancer found at screening with negative nodes are at very low risk. It is possible to identify subgroups without metastatic events by determining the intrinsic subtype and tumour size less than 1 cm. De-escalation of treatment should be considered.

Keywords: Low-risk breast cancer; Metastasis; Observational study; Screening

1. Introduction

The expansion in breast screening (mammogram) programmes has resulted in clinicians seeing a large number of very early-stage breast cancers [1]. Advertising emphasises the benefits of detecting these preclinical lesions because intuition tells us that early-stage treatment of breast cancer should facilitate treatment and cure [2].

Mammography, as an effective screening test for breast cancer, should not only increase the incidence of preclinical disease, but should also decrease the incidence of metastatic cancer and cancer-related mortality. Otherwise, early detection efforts may be uncovering a reservoir of non-

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progressive, or very slowly progressive, breast cancers that were not destined to cause symptoms for the rest of the woman's life, nor her death, a phenomenon known as overdiagnosis [3].

If cancer is detected, it is impossible to know who has been overdiagnosed, as it is not possible to know how it would have evolved in the absence of screening. However, from the point of view of the clinician caring for these patients with very early breast cancer detected on screening mammography, it would be essential to be able to identify those whose diagnosis will have no impact on mortality because this would allow their treatment to be de-escalated in some way. To do so, the first requirement would be to demonstrate that a particular patient, diagnosed with breast cancer, will not have metastases, or breast cancer-related death, for an extended period of time. Secondly, the clinical, pathological and genomic characteristics of their tumours should be analysed and, thirdly, a clinical trial should be designed to de-escalate the treatments.

National registry studies can identify patients with breast cancer without any loss in life expectancy [4] and patients with certain breast cancers may have even higher relative survival than the general population if the cancer is detected incidentally or by mammogram screening, and patients also adopt other healthy behaviours (the healthy-user effect) [5].

Within the group of women diagnosed in breast screening, tumour palpability at diagnosis [6], a parameter that leads us to classify it as preclinical cancer, is a prognostic variable that helps to select those with a lower risk of developing metastases and with lower mortality [6]. Another way to identify breast cancers without a clear impact on mortality is the genomic analysis of the breast tumour. In a large prospective study, patients with ultra-low genomic risk determined by 70-gene signature (Mammaprint) had the best prognosis, with a reduced risk of distant metastasis or breast cancer-related death [7]. PAM50 intrinsic subtypes were independently prognostic for long-term breast cancer survival [8].

The purpose of this study was to identify subgroups of breast cancer patients who did not present events related to long-term breast cancer mortality, taking into account diagnosis at breast screening, absence of palpability and axillary involvement, and genomic analysis with PAM50.

2. Materials and Methods

2.1. Study Design

A retrospective, observational study of breast cancer patients from a public or opportunistic mammogram screening programme, with non-palpable breast tumours and without axillary involvement, treated in the Medical Oncology departments of two university hospitals between 2001 and 2014, was carried out.

Data related to patients and treatment received were collected retrospectively from the clinical records of the Medical Oncology departments. The Spanish register of deaths (*Índice Nacional de Defunciones*) was consulted for vital status and patients' date of death.

2.2. Inclusion and Exclusion Criteria

Women seen in the oncology clinic for breast carcinoma with the following characteristics: detected during the screening programme at the asymptomatic phase with non-palpable tumour and with no other signs or symptoms directly related to the tumour, such as skin retraction, bloody nipple discharge, or others, and with negative axillary nodes in diagnostic surgery. Tumours with histologic grade 1, 2 and 3, oestrogen and progesterone receptor positive and negative, HER2 negative and positive were permitted. Males and carcinomas in situ were excluded.

2.3. Data Analysis

Molecular analysis of gene expression of 50 genes allowed the tumour to be classified into one of 4 intrinsic subtypes: luminal A, luminal B, HER2-enriched and basal-like. Formalin-fixed, paraffin-embedded tumour tissue blocks and corresponding slides were obtained and reviewed by a pathologist who marked a representative area of the tumour. Tissue samples 1 mm in thickness were obtained from the area of the block corresponding to the marked slide. Two samples per box (or one

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sample if the primary tumour was less than 0.7 cm in diameter) were placed in plastic tubes with an identification number and sent to the reference laboratory. Tissue samples were deparaffinised and digested for RNA extraction. After assessment of their quality and concentration, the samples were processed and recorded in nCounter®. Samples were prepared with marker and capture probes, incubated in a thermocycler and transferred to the nCounter® preparation station. The reading was performed using a digital analyser. The analysis of the expression values was performed with the bioinformatics tool nSolver®.

The events collected were ipsilateral local recurrence after conserving surgery, postmastectomy local recurrence, regional lymph node recurrence, distant metastases, second primary invasive tumours (in ipsilateral or contralateral breast and other locations) and ipsilateral or contralateral breast carcinoma in situ. The dependent variable analysed was the distant metastasis-free interval (DMFI), defined as the interval between surgery and one of the following events: distant metastasis and death from breast cancer [9] (events related to breast cancer mortality).

A descriptive analysis of the variables related to patients, breast tumour and treatment (absolute and relative frequency, mean, median and standard deviation) was performed. For the comparison of qualitative variables, the chi-square test with Fisher's correction was applied and, for quantitative variables, the Student's t-test was used.

The Kaplan Meier method and the Log-Rank test for the comparison of survival curves were used to calculate survival. Cox regression with an independent variable was used to calculate the hazard ratio. SPSS version 21 was used for statistical analysis of the data. In the statistical analysis, $p<0.05$ was considered to indicate statistical significance.

3. Results

3.1. Patient Characteristics

Three hundred and thirty-seven patients met the inclusion and exclusion criteria. In 31 cases (9.20%) the immunohistochemical subtype was not available, 268 (79.50%) cases were hormone-sensitive, 23 (6.80%) were triple-negative and 15 (4.40%) were HER2. Of all of them, 96 (28.40%) intrinsic subtyping was available with PAM50 (57, 60% luminal A; 26, 27% luminal B; 6, 6.30% HER2; 7, 7.40% basal-like) (Figure 1). In one luminal A subtype patient the information on events and survival was not available.

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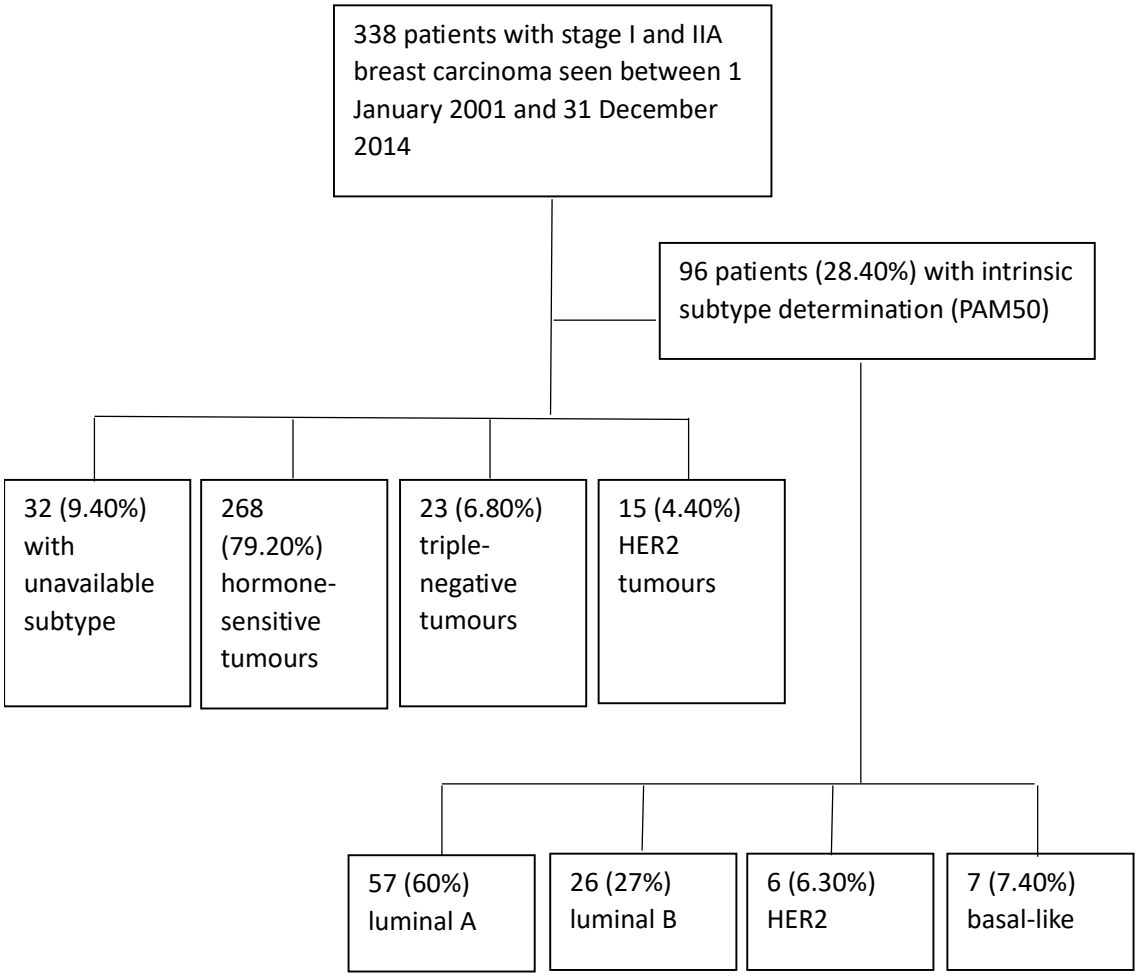

Figure 1. Flow chart of the study.

Figure 1.

The median age was 56 years, with a range between 38 and 71. Participation in the public screening programme was from the age of 45 up until 2013, and the presence of younger women in the study (65, 19.20% premenopausal) is explained as a result of opportunistic screening. All were referred from breast screening (302, 89.30% public and 36, 10.70% opportunistic). The vast majority had full functional capacity. Of the patients, 93.20% had no or few comorbidities. Most of the carcinomas (82.50%) were of the invasive ductal type, stage I (77.20%), with a median tumour size of 1.20 cm, mean histologic grade in half of the cases and a median Ki67 proliferative index of 12%. Oestrogen receptors were positive in 88.50% of tumours and progesterone receptors in 76%. Regarding HER2, 4.40% were positive.

Some 88.80% of the women underwent breast-conserving surgery and 68.60% underwent axillary lymph node-sparing surgery. Among the patients, 73.10% were treated with adjuvant hormone therapy for 5 years, and one third with 3-6 months of adjuvant chemotherapy.

Table 1 shows the patients' characteristics.

Table 1. Characteristics of the 338 patients in the study.

Characteristics of the 338 patients	N	%
Age, median (range)	56 (38-71)	
Functional capacity (ECOG)[1]		

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0	296	87.60
1	40	11.80
2	1	0.30
3	1	0.30
Comorbidity[2]		
0	83	24.60
1	21	6.20
2	211	62.40
3	20	5.90
4	1	0.30
6	2	0.60
Menopause status		
Premenopausal	65	19.20
Postmenopausal	273	80.80
Breast screening mammogram		
Public	302	89.30
Opportunistic	36	10.70
Histological type		
Ductal	279	82.50
Lobular	21	6.20
Others	38	11.20
Stage		
I	261	77.20
IIA	75	22.20
Unknown	2	0.60
Tumour (pT)		
pT1mi	8	2.40
pT1a	21	6.20
pT1b	101	29.90
pT1c	161	47.60
pT2	44	13
Unknown	3	0.90
Tumour size (cm), median (range)	1.20 (0.06-5)	
Histological grade		
1	106	31.40
2	167	49.40
3	49	14.50
Unknown	16	4.70
Ki67 proliferative index, median (range)	12 (1-90)	
Oestrogen receptors		
Positive	299	88.50
Negative	34	10.10
Unknown	5	1.50
Progesterone receptors		
Positive	258	76.30
Negative	75	22.20
Unknown	5	1.50
HER2		
Positive	15	4.40
Negative	318	94.10
Unknown	5	1.50
Breast surgery		

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Conserving	300	88.80
Mastectomy	38	11.20
Axillary surgery		
Sentinel lymph node biopsy	232	68.60
Axillary lymphadenectomy	98	29
None	8	2.40
Adjuvant systemic treatment		
Hormone therapy	152	45
Chemotherapy	28	8.30
Chemotherapy-hormone therapy	95	28.10
None	58	17.20
Unknown	5	1.50
Hormone therapy		
Tamoxifen	106	43.60
Aromatase inhibitor	59	24.30
Tamoxifen-aromatase inhibitor	76	31.30
Ovarian ablation	2	0.80
Chemotherapy		
Anthracyclines	67	54
Anthracyclines and taxanes	37	29.80
Others	20	16.10

[1] Measured by the ECOG *(Eastern Collaborative Oncology Group)* scale [10][2] Measured by the Charlson scale [11].

3.2. Event Analysis

The median follow-up of patients was 142 months (1-249). During this time, 72 patients suffered an event (21.30%), which are shown in Table 2.

Table 2. Events in the 338 patients.

Events	N %
Local recurrence	164.70
After conserving surgery	133.80
After mastectomy	3 0.90
Regional recurrence	3 0.90
Metastasis	185.30
Liver	6 1.80
Bone	5 1.50
Lung	5 1.50
Central nervous system	2 0.60
Skin	1 0.30
Peritoneum	1 0.30
Others	2 0.60
Secondary invasive primaries	319.30
Breast	10 3
Ipsilateral	3 0.90
Contralateral	7 2.10
Non-breast	216.30
Colorectal	4 1.20
Ovarian	3 0.90
Endometrial	3 0.90
Pancreatic	2 0.60
Lung	1 0.30

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Thyroid	1 0.30
Bladder	1 0.30
Vulva	1 0.30
Carcinoid tumour	1 0.30
Soft tissue sarcoma	1 0.30
Non-Hodgkin's lymphoma	1 0.30
Multiple myeloma	1 0.30
Oncocytoma	1 0.30
Secondary non-invasive primaries	7 2.10
Ductal carcinoma in situ of the ipsilateral breast	5 1.50
Ductal carcinoma in situ of the contralateral breast	2 0.60
Deaths	30 9
From breast carcinoma	164.80
From other causes	123.60
Due to unknown causes	2 0.60

In the 22 patients with tumours of luminal intrinsic subtype A and size less than 1 cm, there were no events related to breast cancer mortality. In the 34 patients with tumours of luminal intrinsic subtype A and size greater than 1 cm, there were 2 events related to breast cancer mortality. Likewise, in the 9 patients with luminal intrinsic subtype B and size less than 1 cm, there were no events related to breast cancer mortality. Again, in the 17 patients with luminal B tumours and size greater than 1 cm, there was 1 event related to breast cancer mortality.

In the 6 patients with intrinsic HER2 subtype and in the 7 with basal-like subtype, no metastatic events occurred (Table 3).

Table 3. Metastatic and non-metastatic events in relation to intrinsic subtype and tumour size less than or greater than 1 cm.

Intrinsic subtype and tumour size	N and %	Events (N and %)	Events not related to breast cancer mortality	Events related to breast cancer mortality
Luminal A	**56/95 (58.90%)**	**9/56 (16.10%)**	**7/56 (12.50%)**	**2/56 (3.50%)**
< 1 cm	**22 (39.30%)**	**3/56 (5.30%)**	**3/56 (5.30%)**	**0/56 (0%)**
> 1 cm	**34 (60.70%)**	**6/56 (10.70%)**	**4/56 (7.10%)**	**2/56 (3.60%)**
Luminal B	**26/95 (27.30%)**	**6/26 (23%)**	**5/26 (19.20%)**	**1/26 (3.80%)**
< 1 cm	**9 (34.60%)**	**3/26 (11.50%)**	**3/26 (11.50%)**	**0/26 (0%)**
> 1 cm	**17 (65.40%)**	**3/26 (11.50%)**	**2/26 (7.70%)**	**1/26 (3.80%)**
HER2 Enrichment	**6/95 (6.30%)**	**1/6 (16.70%)**	**1/6 (16.70%)**	**0/6 (0%)**
< 1 cm	**0 (0%)**			
> 1 cm	**6 (100%)**	**1/6 (16.70%)**	**1/6 (16,70%)**	**0/6 (0%)**
Basal like	**7/95 (7.30%)**	**1/7 (14.30%)**	**1/7 (14.30%)**	**0/7 (0%)**
< 1 cm	**4 (57.10%)**	**0/7 (0%)**	**0/7 (0%)**	**0/7 (0%)**
> 1 cm	**3 (42.90%)**	**1/7 (14.30%)**	**1/7 (14.30%)**	**0/7 (0%)**

3.3. Survival Analysis

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The distant metastasis-free interval probability at 5, 10, 15 and 20 years was 0.98 (95% CI, 0.96-0.99), 0.94 (95% CI, 0.91-0.97), 0.92 (95% CI, 0.90-0.93) and again 0.92 (95% CI, 0.90-0.93), respectively.

Figure 2 shows the distant metastasis-free probability curve.

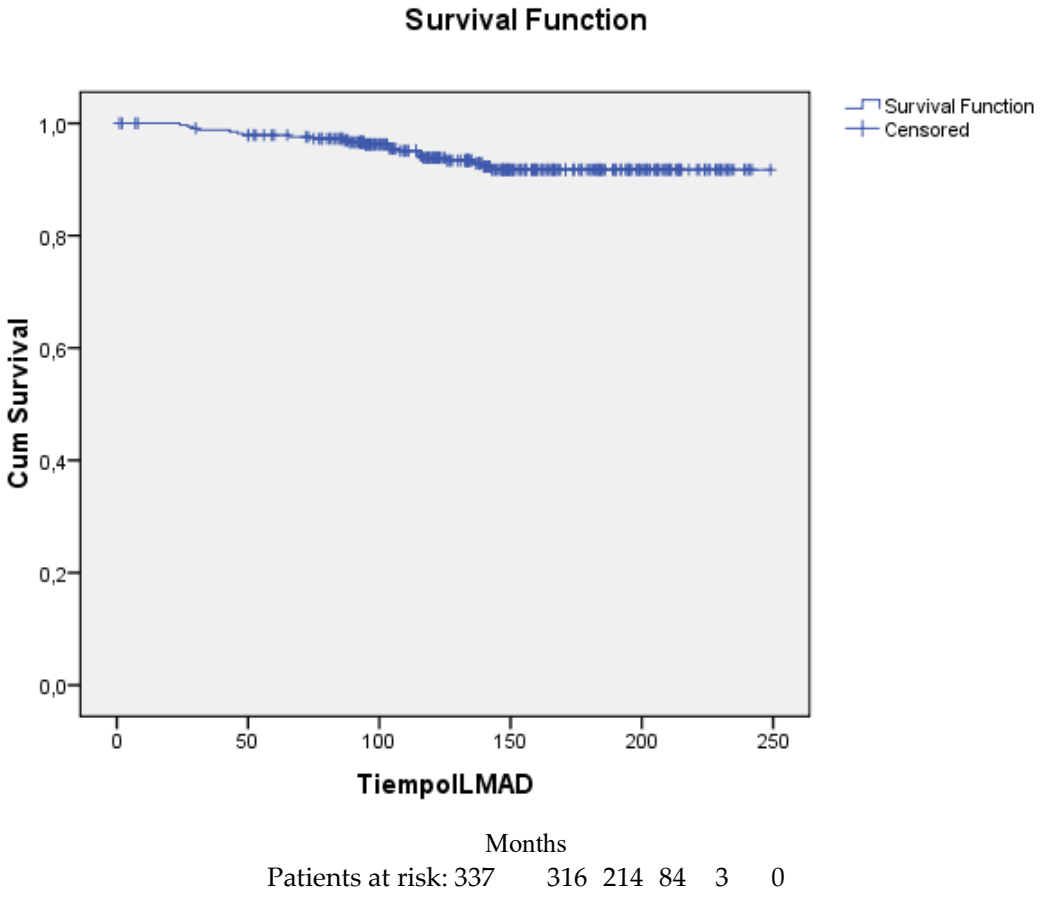

Figure 2. Distant metastasis-free interval probability curve for the 337 patients.

In the 95 patients with available intrinsic subtype determination the distant metastasis-free interval probability at 5 years was 1.00 and at 10 years, 15 years and 20 years was 0.96 (95% CI, 0.92-1.00).

Figure 3 shows the distant metastasis-free interval probability curve for the 95 patients with intrinsic subtype determined by PAM50.

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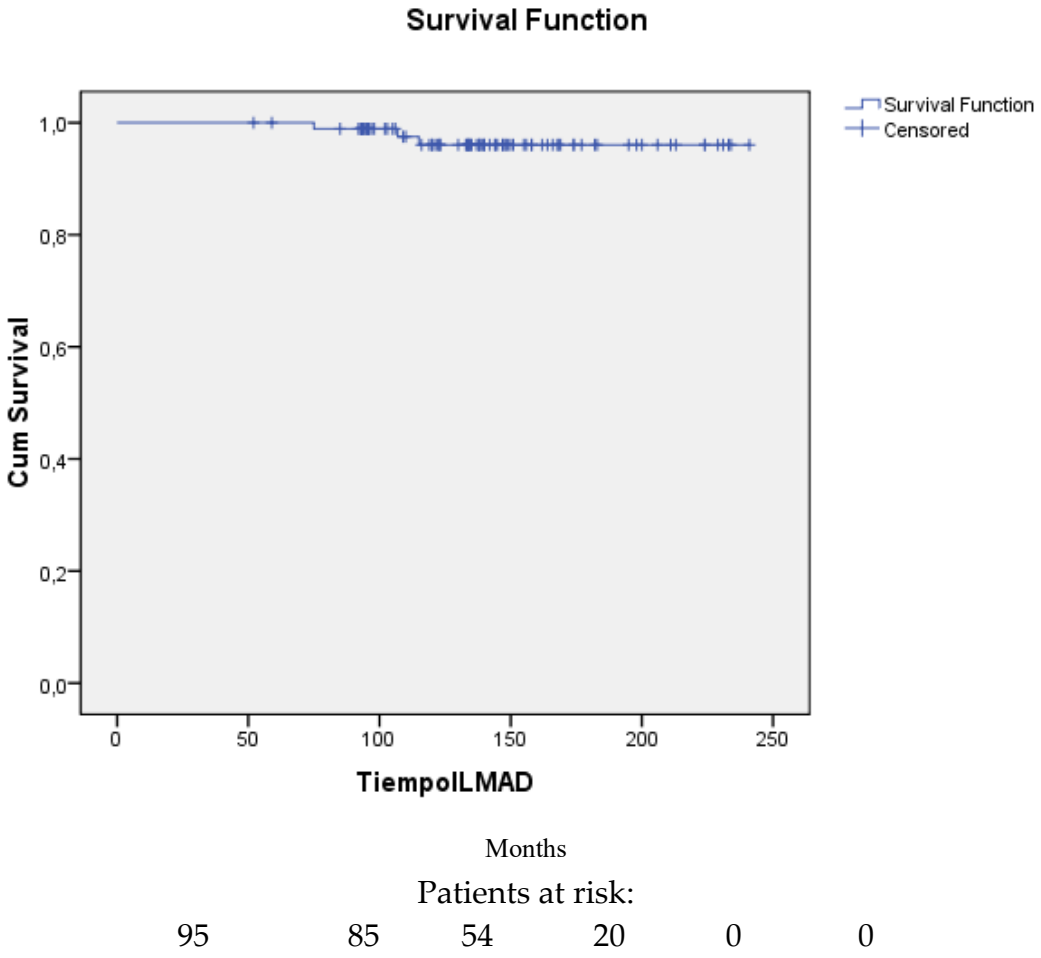

Figure 3. Distant metastasis-free interval probability curve for 95 patients with intrinsic subgroup determination by PAM50.

4. Discussion

In this retrospective attempt to identify subgroups of breast cancer patients who did not present events related to long-term breast cancer mortality, taking into account diagnosis at breast screening, absence of palpable anomalies, and no axillary involvement, and genomic analysis with PAM50, we found that patients with luminal intrinsic subtypes A and B and tumours smaller than 1 cm (32.62%) never develop metastatic events. The low representation of HER2 (6.30%) and basal (7.30%) tumours also did not develop metastases. As has been shown before, patients with tumours smaller than 1 cm, with luminal A, HER2 and triple-negative subtypes on immunohistochemistry did not develop metastases [12].

Breast screening detects slow-growing cancers, the vast majority of which tend to be of the luminal subtype. In our study, the proportion of HER2 or basal-like breast cancers has been lower than the known proportion for all age groups [13,14]. Specifically, the age, represented by a low number of young women in our study, where the presentation of these aggressive tumour subtypes is more frequent, justifies this lower proportion of HER2 and basal tumours. Likewise, the aggressive behaviour of these rapidly growing tumour subtypes with a shorter preclinical detectable phase, justifies their lower frequency in our study as these tumours often emerge clinically between screening cycles [14]. HER2 and basal cancers detected by screening mammography are usually diagnosed at an earlier stage, and their prognosis was better than those detected by symptoms [15].

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As we said in the introduction, the next step, once the subgroups of breast cancer patients who, having undergone standard treatment, will not develop metastases have been identified, would be to de-escalate the treatment. If we exclude progressive preclinical cancers [16] (HER2 and basal), the adjuvant systemic treatment of women with luminal tumours and tumours smaller than 1 cm is hormone therapy. De-escalating this treatment would be possible in this subgroup of patients because the effect of hormone therapy on the development of metastases is limited [17]. In fact, in the Mindact trial, which had an 8-year follow-up, the distant metastasis-free interval and overall survival of low-risk stage I patients treated with adjuvant hormone therapy was not statistically different from those who did not receive this treatment [17], using propensity score matching methodology to select a group of patients receiving hormone therapy and another not receiving hormone therapy. A drawback of refraining from using adjuvant hormonal therapy is that this treatment not only reduces distant relapses, but also locoregional recurrences and second contralateral or ipsilateral breast cancers [17]. As we have seen in the event analysis of our study, the number of locoregional recurrences and second primary breast tumours is similar to the number of metastases. The follow-up period of the Mindact trial of 8 years and that of our study of almost 12 years seem short due to the considerable risk of late recurrence of these luminal tumours, with recurrences up to 32 years after diagnosis [18]. For this reason, it is impractical to design a controlled clinical trial to answer research questions that require decades of follow-up and also require events that will almost never occur.

In fact, at present, de-escalation measures could already be applied in this patient population. For example, based on the SOUND non-inferiority trial [19], the results of which suggest that breast cancer patients with tumours of less than 2 cm and ultrasonographically negative axillary lymph nodes, can safely avoid any axillary surgery [19], the patients identified in our study could also be offered the choice to abstain from axillary surgery.

Likewise, women with luminal A tumours could also be offered abstinence from adjuvant radiotherapy after conserving surgery, based on the results of the LUMINA trial [20].

Finally, as we have seen [17], in patients with low-risk stage I breast cancer, the beneficial effect of hormone therapy on the distant metastasis-free interval is limited and has to be counterbalanced by its side effects [21], and should be discussed with these patients at very low risk of distant metastasis [17,21]. The Canadian LA LEAST trial compares 2 years of endocrine therapy in women over 50 years of age whose node-negative breast cancers are low risk according to the Prosigna score [22], also as a form of de-escalation. However, one must be very careful about combining several forms of de-escalation at the same time, for example, omitting radiotherapy and hormone therapy at the same time [23]. Just like for ductal carcinoma in situ [24], dose reduction of hormone therapy could be explored in this group of very low-risk patients. There are no data with dose reduction of aromatase inhibitors, but there are data with reduction to 5 mg per day of tamoxifen [24].

The strengths of this study include its large cohort of patients with long-term follow-up and reliable data based on individual medical records. However, this study suffered from biases, such as the low availability of material for the determination of the PAM50 genomic study and the biases associated with retrospective studies, such as selection bias.

5. Conclusion

Our study provides novel insights into the epidemiology of very low-risk breast cancer. Oncologists and other health care professionals should be aware that there are patients with breast cancer who will never metastasise, particularly women diagnosed on breast screening with non-palpable, luminal subtype tumours smaller than 1 cm and node negative. Our study advocates further research to optimise treatment de-escalation to prevent overtreatment.

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Aguilar, Encarnación Benítez-Rodríguez and José Manuel Baena-Cañada; Funding acquisition, José Manuel Baena-Cañada; Investigation, Salvador Gámez-Casado, Lourdes Rodríguez-Pérez, Cristina Bandera-López, Andrés Mesas-Ruiz, Alicia Campini-Bermejo, Marta Bernal-Gómez, Manuel Zalabardo-Aguilar, Julio Calvete-Candenas, Gala Martínez-Bernal, Lidia Atienza-Cuevas, Marcial Garcia-Rojo, Encarnación Benítez-Rodríguez, Bella Pajares-Hachero, María José Bermejo-Pérez and José Manuel Baena-Cañada; Methodology, Salvador Gámez-Casado, Lourdes Rodríguez-Pérez, Cristina Bandera-López, Andrés Mesas-Ruiz, Alicia Campini-Bermejo, Marta Bernal-Gómez, Manuel Zalabardo-Aguilar, Julio Calvete-Candenas, Gala Martínez-Bernal, Lidia Atienza-Cuevas, Marcial Garcia-Rojo, Encarnación Benítez-Rodríguez, Bella Pajares-Hachero, María José Bermejo-Pérez and José Manuel Baena-Cañada; Project administration, José Manuel Baena-Cañada; Resources, José Manuel Baena-Cañada; Software, Salvador Gámez-Casado, Lourdes Rodríguez-Pérez, Cristina Bandera-López, Andrés Mesas-Ruiz, Alicia Campini-Bermejo, Marta Bernal-Gómez, Manuel Zalabardo-Aguilar, Julio Calvete-Candenas, Gala Martínez-Bernal, Lidia Atienza-Cuevas, Marcial Garcia-Rojo, Encarnación Benítez-Rodríguez, Bella Pajares-Hachero, María José Bermejo-Pérez and José Manuel Baena-Cañada; Supervision, Encarnación Benítez-Rodríguez and José Manuel Baena-Cañada; Validation, Salvador Gámez-Casado, Lourdes Rodríguez-Pérez, Cristina Bandera-López, Andrés Mesas-Ruiz, Alicia Campini-Bermejo, Julio Calvete-Candenas, Gala Martínez-Bernal, Lidia Atienza-Cuevas, Encarnación Benítez-Rodríguez, Bella Pajares-Hachero, María José Bermejo-Pérez and José Manuel Baena-Cañada; Visualization, Lourdes Rodríguez-Pérez, Cristina Bandera-López, Andrés Mesas-Ruiz, Alicia Campini-Bermejo, Marta Bernal-Gómez, Manuel Zalabardo-Aguilar, Gala Martínez-Bernal, Lidia Atienza-Cuevas, Marcial Garcia-Rojo, Encarnación Benítez-Rodríguez, Bella Pajares-Hachero, María José Bermejo-Pérez and José Manuel Baena-Cañada; Writing – original draft, José Manuel Baena-Cañada; Writing – review & editing, Salvador Gámez-Casado, Lourdes Rodríguez-Pérez, Cristina Bandera-López, Andrés Mesas-Ruiz, Alicia Campini-Bermejo, Marta Bernal-Gómez, Manuel Zalabardo-Aguilar, Julio Calvete-Candenas, Gala Martínez-Bernal, Lidia Atienza-Cuevas, Marcial Garcia-Rojo, Encarnación Benítez-Rodríguez, Bella Pajares-Hachero, María José Bermejo-Pérez and José Manuel Baena-Cañada.

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