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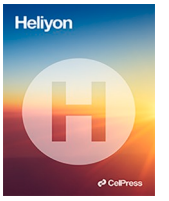

Research article

Assessing the long-term prognostic ability of the 70 gene expression signature MammaPrint in an Italian single-center prospective cohort study of early-stage intermediate-risk breast cancer patients

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ABSTRACT

Purpose: The aim of this study was to assess the prognostic performance of the 70-gene signature, MammaPrint, in an Italian single-center prospective cohort of early-stage intermediate-risk breast cancer (BC) patients.

Methods: A total of 195 eligible early BC cases were tested for genomic risk between 2006 and 2013. In this retrospective analysis, the association of genomic risk with distant metastasis-free survival (DMFS) and overall survival (OS) were assessed using Cox regression models, adjusting for clinical and pathological tumor characteristics.

Results: MammaPrint identified 118 (60.5 %) patients with genomically Low Risk tumors and 77 (39.5 %) patients with genomically High Risk tumors. Age, menopausal status, tumor size, receptor status, and nodal status were comparable between MammaPrint Risk categories. The median follow-up was 8.4 years for DMFS and 9.3 years for OS; 8-year follow-up was reported for both endpoints. The 8-year DMFS was 90.4 % (95 % CI 84.9–95.9) in patients with MammaPrint Low Risk tumors compared to 60.8 % (95 % CI 49.8–71.8) for patients with High Risk tumors. Patients with MammaPrint Low Risk tumors exhibited significantly superior 8-year OS (97.3 %; 95 % CI 94.4–100) compared with MammaPrint High Risk tumors (89.5 %; 95 % CI 82.6–96.4; $p = 0.028$). Multivariate analyses identified MammaPrint as significantly associated with 8-year DMFS and MammaPrint together with Progesterone Receptor positivity with 8-year OS.

Conclusion: The prognostic performance of MammaPrint was demonstrated in early-stage clinically intermediate to high-risk BC patients. Moreover, patients with MammaPrint Low Risk

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tumors had good outcome regardless of treatment regimen, thus supporting personalized treatment choices.

1. Introduction

Breast cancer is a public healthcare concern, with approximately 55,700 new diagnosed cases per year in Italy and 12,500 deaths in 2022 [1]. Breast cancer is a complex, heterogeneous disease, characterized by a mixture of molecular subtypes associated with different biological and clinical behaviors, which can be classified into different subtypes based on the hormonal receptor (HR) status, the expression of human epidermal growth factor 2 (HER2), as well as other biomarkers [2,3]. Hormone receptor positive (HR+) tumors account for 70–80 % of all tumors [1].

The standard of care in HR+/HER2-early-stage breast cancer setting is based either on surgery alone or combined with neoadjuvant chemotherapy and/or radiotherapy, followed by adjuvant systemic therapy, comprising endocrine (i.e., hormonal) therapy and chemotherapy [4]. It has been widely recognized since the 1990s that adjuvant chemotherapy significantly improves disease-free and overall survival in patients with poor prognostic features [5], where the most relevant factors were identified in age, tumor size, nodal status, histologic type of tumor, pathologic grade, and hormone-receptor status [6]. Conversely, in good prognosis patients, adjuvant chemotherapy appears to have limited beneficial effect and may have detrimental consequences in patients for whom toxic reactions are particularly deleterious [7].

In such a scenario, identifying groups of patients who could be spared of the toxicities of chemotherapies without compromising the prognosis has led to the development of multigene expression assays (MGA) in early HR + breast cancer. MGAs offer important information on the molecular background of the disease and provide criteria for a more accurate patient stratification for treatment decision-making [8]. The multigene assays that are most frequently used in clinical practice and commercially available are MammaPrint®, Oncotype DX®, Prosigna™, Endopredict [9]; among them, only MammaPrint® and Oncotype DX® are validated by prospective randomized phase 3 trials [10].

MammaPrint assesses the expression of 70 cancer-related genes and classifies the tumor into a High- and Low-risk group based on risk of developing distant metastases, with the objective of guiding personalized therapy [11]. MammaPrint was validated extensively targeting various populations (e.g., node-negative [11,12], node-positive patients [13], premenopausal [6,11], and postmenopausal patients [14,15]), confirming significant prognostic value in all cases. The prospective randomized trial MINDACT (NCT004433589) was a de-escalation trial, which confirmed that MammaPrint can identify patients at genomic low risk who can safely forego chemotherapy [16,17]. With 8.7-year median follow-up, the MINDACT trial demonstrated the ability of MammaPrint to identify clinically high risk patients with low genomic risk who had an excellent distant metastasis-free survival with endocrine therapy alone. The patients in this treatment arm showed no statistically significant difference in DMFS compared to the chemotherapy arm ($\Delta = 0.9$ % at 5 years), independent of nodal involvement.

An Italian local health authority, the ASST of Cremona (Cremona, Lombardy Region), has launched a prospective recruitment and data collection of early-stage, intermediate to high clinical risk breast cancer patients for whom MammaPrint was used as a tool to predict the risk profile. The objective of this analysis study is to confirm the prognostic value of MammaPrint in an Italian series of early-stage, intermediate to high risk early-stage breast cancer patients from a single-center cohort.

2. Methods

Formalin-fixed paraffin-embedded (FFPE) or fresh-frozen samples (n = 195) derived from surgically excised tumors from women diagnosed with early-stage (stage I-IIIA), intermediate to high clinical risk breast cancer were collected at Azienda Socio-Sanitaria Territoriale of Cremona (ASST-Cr) between 2006 and 2013.

Patients were included according to ASST-Cr criteria (>18 years, T1-2 or operable T3, N0-1, M0, unilateral tumors and multifocal tumors if identical histology had been proven).

Inclusion criteria for intermediate-risk patients were based on the decree issued by the Italian Ministry of Health, which considers factors such as tumor size, nodal involvement, and receptor status [18].

Clinicopathological data and demographics as well as information on therapy regimen were included in the dataset. Treatment decisions were guided by clinical characteristics with high risk patients receiving chemotherapy. Patients were eligible for endocrine therapy alone if they had HR + disease and showed endocrine responsiveness. This study was performed in line with the principles of the Declaration of Helsinki. The Val Padana Ethics Committee (nr 4791/06) approved the study protocol.

MammaPrint was used to stratify the tumor samples into Low Risk and High Risk of distant metastasis. Descriptive statistics were used to summarize patients and tumor characteristics: for comparison of baseline clinical and pathological variables between risk groups (i.e., MammaPrint Low Risk and High Risk) Fisher's exact test or Chi-Square tests were used.

Endpoints were distant metastasis-free survival (DMFS) and overall survival (OS). DMFS is defined as the time from diagnosis to the first distant metastatic recurrence or death from any cause, or censored at the last follow-up date. OS was defined as the time from surgery to death from any cause, or censored at the last follow-up date.

Follow-up data was collected until data lock on March 22, 2022. Kaplan-Meier survival curves were plotted for DMFS and OS distinguishing between MammaPrint Low Risk and High Risk groups and differences were assessed by log rank tests. The association between genomic risk and survival outcomes was assessed by performing univariate and multivariate Cox proportional hazard

regression analysis, and the effects were expressed as hazard ratios with corresponding 95 % confidence intervals (CI). Analyses were performed using R (version 4.2.3) or SPSS (version 27.0; SPSS inc., Chicago, IL, USA). Significance level was set at 0.05 and all p-values were two-sided.

3. Results

3.1. Clinical characteristics and treatment planning

The median age of patients was 57.3 years with a majority of patients over 50 years of age (70.3 %) and post-menopausal (69.3 %) (Table 1). The median size of tumors was 15.0 mm and median Ki-67 expression of 13.0. Of ER + tumors, 72.8 % were progesterone receptor positive and 3.1 % were HER2 positive. Vascular invasion was absent in 72.9 % of tumors, whereas lymphatic invasion was present in a 76.9 % of tumors (Table 1). Additionally, a majority of patients were lymph node negative (61.5 %) and had tumors of ductal histology (83.0 %) and intermediate grade (71.6 %). Regarding adjuvant systemic treatment, 50.5 % (n = 96) received

Table 1
Clinical characteristics for all patients and according to MammaPrint results (Low Risk versus High Risk groups).

Variables	All cases (N = 195)	MammaPrint Low Risk (n = 118, 61 %)	MammaPrint High Risk (n = 77, 39 %)	p-value
Age[a], **median (95 % CI)**	57.3 (55.8–58.8)	56.8 (54.8–58.8)	58.2 (55.8–60.5)	0.377
Age, **category**				1.000
≤50 years	58 (29.7)	35 (29.7)	23 (29.9)	
>50 years	137 (70.3)	83 (70.3)	54 (70.1)	
Menopausal status				0.523
Post-	133 (69.3)	78 (67.2)	55 (72.4)	
Tumor size (mm), **median (95 % CI)**	15.0 (13.9–16.1)	14.6 (13.4–15.9)	15.6 (13.7–17.4)	0.417
PR status				0.050
Positive	142 (72.8)	92 (78.0)	50 (64.9)	
HER2 status				0.210
Positive	6 (3.1)	2 (1.7)	4 (5.3)	
Vascular invasion				0.307
Absent	132 (67.7)	77 (70.0)	55 (77.5)	
Present	49 (25.1)	33 (30.0)	16 (22.5)	
Not determined	14 (7.2)			
Lymphatic invasion				0.419
Absent	18 (9.2)	12 (27.3)	6 (17.6)	
Present	60 (30.8)	32 (72.7)	28 (82.4)	
Not determined[b]	117 (60)			
Tumor grade				<0.001
G1 (good)	11 (5.7)	9 (7.6)	2 (2.6)	
G2 (intermediate)	139 (71.3)	95 (80.5)	44 (57.9)	
G3 (poor)	44 (22.5)	14 (11.9)	30 (39.5)	
Not determined[b]	1 (0.5)			
LN status				0.441
Negative	115 (59.0)	74 (63.8)	41 (57.7)	
Positive	72 (37.0)	42 (36.2)	30 (39.5)	
Not determined[b]	8 (4.0)			
Ki-67[a], median (95 % CI)	13.0 (11.6–14.4)	10.4 (9.0–11.8)	17.3 (14.6–20.0)	<0.001
Tumor histology, ductal				0.170
No	33 (16.9)	24 (20.3)	9 (11.8)	
Yes	161 (82.5)	94 (79.7)	67 (88.2)	
Not determined[b]	1 (0.5)			
Surgery type				1.000
Mastectomy	26 (13.3)	16 (13.6)	10 (13.0)	
Lumpectomy	169 (86.7)	102 (86.4)	67 (87.0)	
Neoadjuvant treatment				0.534
ET only	5 (2.6)	3 (2.5)	2 (2.6)	
CT only	6 (3.1)	3 (2.5)	3 (3.9)	
CT + ET	39 (20.0)	20 (16.9)	19 (24.7)	
None	145 (74.4)	92 (78.0)	53 (68.8)	
Adjuvant treatment				<0.001
ET only	96 (50.5)	84 (72.4)	12 (16.2)	
CT only	7 (3.7)	0	7 (9.5)	
CT + ET	80 (42.1)	30 (25.9)	50 (67.6)	
None	7 (3.7)	2 (1.7)	5 (6.8)	

Data represented as n(%), unless otherwise specified.
p-values are derived from Fisher's exact test for binary variables and Chi-squared test for categorical variables.
[a] The variable is assumed to be continuous and normally distributed; p-value from two-sided *t*-test on equality of means between groups is reported.
[b] Patients listed as "not determined" for each category were not included in statistical comparisons.

endocrine treatment only whereas 45.8 % (n = 87) received chemotherapy with or without endocrine treatment (Table 1).

MammaPrint testing identified 118 (61 %) of patients with genomically Low Risk tumors and 77 (39 %) of patients with MammaPrint High Risk tumors. Age, menopausal status, tumor size, receptor status, and nodal status were comparable between both genomic risk categories (Table 1). In contrast, patients with MammaPrint High Risk tumors had a higher frequency of grade 3 tumors (39.5 %) relative to Low Risk tumors (11.9 %; $p < 0.001$) (Table 1). Yet, a sizable proportion of approximately 1 out of 3 patients with a grade 3 tumor had a genomically Low Risk. Median Ki-67 expression was also significantly higher in MammaPrint High Risk tumors compared with Low Risk tumors ($p < 0.001$). Regarding adjuvant treatment, a significantly higher proportion of Low Risk patients received Endocrine Treatment only (72.4 %) compared with High Risk patients (16.2 %). However, 30 (25.9 %) patients with genomically Low Risk tumors received additional chemotherapy, as treatment regimen was based on clinical factors. Lastly, a majority of patients with genomically High Risk tumors (n = 57; 77.1 %) received adjuvant chemotherapy and only 12 patients in this group received endocrine therapy only (Table 1).

The role of progesterone receptor (PR) positivity as a prognostic factor was particularly evident in this study. PR positivity was significantly associated with improved long-term outcomes, specifically in terms of distant metastasis-free survival (DMFS) and overall survival (OS) in early-stage, intermediate-risk breast cancer patients. In the analysis, PR-positive tumors had a 49 % lower risk of distant metastasis compared to PR-negative tumors (HR = 0.51; 95 % CI 0.27–0.96; $p = 0.036$). In the multivariate analysis for OS, the difference was even more pronounced, with PR-positive patients showing an 86 % lower risk of death (HR = 0.14; 95 % CI 0.03–0.67; $p = 0.014$).

3.2. MammaPrint is accurately prognostic of 8-year outcome

The median follow-up was 8.4 years for DMFS and 9.3 years for OS; 8-year follow-up was reported for both endpoints. Univariate and multivariate Cox proportional hazard regression analyses were performed to determine the association between genomic risk and survival outcomes. The 70-gene expression signature, MammaPrint, was significantly associated with both DMFS and OS after adjustment for clinico-pathological variables in a multivariate analysis (hazard ration for DMFS, 0.24; 95 % CI, 0.10 to 0.59; and hazard ratio for OS, 0.15; 95 % CI, 0.02 to 0.91 for patients at genomically Low Risk versus those at High Risk of recurrence) (Tables 2–5).

At 8 years, 41 DMFS events were observed, 11 (9.3 %) in MammaPrint Low Risk patients and 30 (39.0 %) among patients with genomically High Risk tumors. The 8-year DMFS was 90.4 % (95 % CI 84.9–95.9) in patients with MammaPrint Low Risk tumors, which was significantly higher compared to High Risk tumors (60.8 %; 95 % CI 49.8–71.8) (Fig. 1a). Additionally, 8-year DMFS was comparable between patients with MammaPrint Low Risk tumors who received endocrine treatment only (92.8 %, 95 % CI 87.3–98.3) versus those who received both endocrine and chemotherapy (89.8 %, 95 % CI 78.8–100; $p = 0.655$) (Fig. 1b). Interestingly, of 5 patients with a MammaPrint High Risk, who did not receive any adjuvant treatment, 4 had an event at 8 years.

At 8 years, 11 death events were observed, 3 out of 118 (2.5 %) in MammaPrint Low Risk tumors and 8 out of 77 (10.4 %) in High Risk tumors. Patients with MammaPrint Low Risk tumors exhibited an 8-year OS of 97.3 % (95 % CI 94.4–100), which was significantly higher compared with MammaPrint High Risk tumors (89.5 %, 95 % CI 82.6–96.4; $p = 0.028$) (Fig. 2a). When stratified by nodal status (Fig. 2b), 8-year OS was highest in patients with MammaPrint Low Risk, lymph node negative tumors (98.6 %, 95 % CI 95.9–100) and MammaPrint Low Risk, lymph node positive tumors (94.9 %, 95 % CI 88.0–100), followed by MammaPrint High Risk, lymph node negative tumors (92.7 % 95 % CI 84.7–100), and lowest in MammaPrint High Risk, lymph node positive tumors (83.0 %, 95 % CI 69.5–96.5). Among patients with genomically Low Risk tumors (Fig. 2c), there was no significant difference in 8-year OS between those that received endocrine treatment only (97.5 % 95 % CI 94.0–100) versus those that received both endocrine and chemotherapy (96.6 % 95 % CI 89.9–100; $p = 0.796$).

Table 2
8 year DMFS, Univariate analysis.

Variable	Hazard Ratio	95 % CI	p-value
MammaPrint	4.71	2.36–9.40	<0.001
Age	1.01	0.98–1.04	0.657
Post-menopausal status	1.35	0.66–2.77	0.407
Node positive	1.71	0.89–3.28	0.108
Ductal tumor	1.25	0.53–2.98	0.614
Tumor size	1.01	0.98–1.05	0.483
Tumor grade, G3	2.22	1.17–4.22	0.015
Vascular invasion present	1.12	0.54–2.35	0.761
PR positive	0.51	0.27–0.96	0.036
Ki-67	1.03	1.00–1.06	0.048
Treatment			
CT	1.85	0.99–3.47	0.055
ET	0.18	0.09–3.47	<0.001
ET vs. None	0.08	0.03 -0.21	<0.001
CT vs. None	0.52	0.15–1.84	0.309
CT + ET vs. None	0.19	0.08–0.48	<0.001

Abbreviations: CI, confidence interval; PR, progesterone receptor; CT, chemotherapy; ET, endocrine therapy.

Table 3
8 year DMFS, Multivariate analysis.

Variable	Hazard Ratio	95 % CI	p-value
MammaPrint	0.24	0.10–0.58	0.001
Age	1.01	0.96–1.06	0.810
Post-menopausal status	1.23	0.36–4.22	0.740
Node positive	1.61	0.69–3.77	0.272
Ductal tumor	1.03	0.35–3.04	0.954
Tumor size	1.00	0.96–1.05	0.882
Tumor grade, G3	1.24	0.52–2.93	0.626
Vascular invasion present	0.85	0.31–2.30	0.745
PR positive	0.76	0.34–1.69	0.501
Ki-67	1.01	0.97–1.04	0.819

Abbreviations: CI, confidence interval; PR, progesterone receptor.

Table 4
8 year OS, Univariate analysis.

Variable	Hazard Ratio	95 % CI	p-value
MammaPrint	3.96	1.05–14.91	0.042
Age	0.94	0.89–0.99	0.015
Post-menopausal status	0.55	0.17–1.80	0.323
Node positive	2.85	0.83–9.72	0.095
Ductal tumor	2.19	0.28–17.14	0.454
Tumor size	1.05	1.01–1.09	0.015
Tumor grade, G3	1.22	0.32–4.61	0.767
Vascular invasion present	1.36	0.34–5.43	0.665
PR positive	0.20	0.06–0.69	0.011
Ki-67	1.01	0.96–1.07	0.625
Treatment			
CT	2.97	0.79–11.18	0.108
ET	0.84	0.11–6.59	0.871
ET vs. None	0	–	0.985
CT vs. None	0.37	0.10–1.44	0.153
CT + ET vs. None	1.61	0.20–13.10	0.656

Abbreviations: CI, confidence interval; PR, progesterone receptor; CT, chemotherapy; ET, endocrine therapy.

Table 5
8 year OS, Multivariate analysis.

Variable	Hazard Ratio	95 % CI	p-value
MammaPrint	0.15	0.02–0.91	0.039
Age	0.94	0.86–1.04	0.226
Post-menopausal status	1.89	0.24–14.87	0.546
Node positive	0.83	0.12–5.52	0.844
Ductal tumor	1.27	0.14–11.18	0.829
Tumor size	1.05	0.10–1.11	0.058
Tumor grade, G3	0.41	0.07–2.58	0.344
Vascular invasion present	2.33	0.34–16.03	0.391
PR positive	0.14	0.03–0.67	0.014
Ki-67	0.99	0.92–1.07	0.829

Abbreviations: CI, confidence interval; PR, progesterone receptor.

4. Discussion

Genomic assays such as MammaPrint can accurately predict a patient's risk of distant metastasis, which can be used to guide planning of adjuvant treatment. Here, we evaluated the prognostic ability of MammaPrint at 8 years in an Italian cohort of patients with clinically intermediate to high risk early-stage breast cancer.

The majority of patients in this study were identified as genomically Low Risk and these patients had excellent 8-year overall survival (97.3 %) compared to patients with MammaPrint High Risk tumors (89.5 %), with no significant benefit from chemoendocrine therapy compared with endocrine therapy alone. These data are comparable to the 8-year overall survival among patients with clinically high risk, genomically Low Risk tumors in MINDACT treated with endocrine (94.3 %) or chemoendocrine therapy (95.7 %) [17]. Patients with MammaPrint Low Risk tumors had superior outcomes compared to High Risk tumors regardless of nodal status. These data are supported by multivariate analyses at 8 years, which demonstrate that clinical factors such as node positivity, tumor

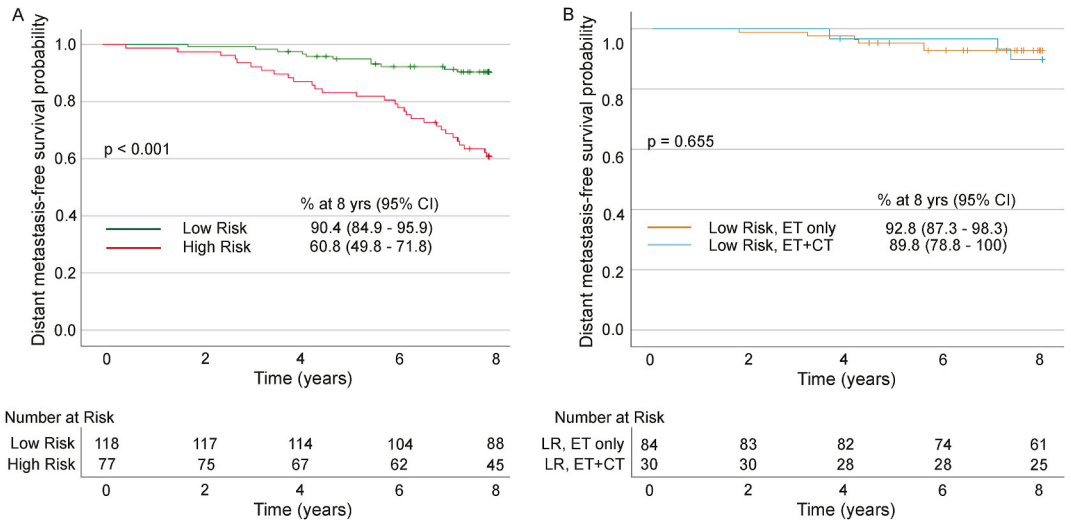

Fig. 1. Association of MammaPrint with 8-year Distant Metastasis-Free Survival. (a) DMFS in patients with MammaPrint Low Risk and High Risk tumors. (b) DMFS among patients with MammaPrint Low Risk tumors further stratified by treatment regimen (ET only vs ET + CT). Significance was assessed by using log-rank test. Abbreviations: DMFS, distant metastasis-free survival; ET, endocrine treatment; CT, chemotherapy.

grade, and Ki-67 are not associated with outcomes, whereas MammaPrint remained a strong predictor. Our findings underscore the prognostic value of PR-positivity in early-stage intermediate-risk breast cancer. PR-positive patients demonstrated significantly better long-term outcomes, with a 49 % lower risk of distant metastasis and an 86 % lower risk of mortality compared to PR-negative patients. These results suggest that PR status, in conjunction with MammaPrint, provides a more precise risk stratification, supporting the consideration of endocrine therapy alone for PR-positive patients to reduce overtreatment with chemotherapy.

The differences by genomic risk for this Italian cohort are even more pronounced when evaluating DMFS, which incorporates recurrence risk, where 8-year DMFS among patients with MammaPrint Low Risk tumors (90.4 %) was 29.6 % higher than among patients with MammaPrint High Risk tumors (60.8 %). Importantly, similar DMFS probabilities were observed among patients with clinically high risk, genomically Low Risk tumors who were treated with endocrine therapy and chemoendocrine therapy. Among patients with clinically high risk, genomically Low Risk tumors in MINDACT, 8-year DMFS probabilities for patients treated with endocrine therapy versus chemoendocrine therapy were also similar [17]. The 8-year outcomes observed in this study are comparable to the RASTER study, where patients with node-negative clinically high risk, MammaPrint Low Risk tumors had a 10-year distant recurrence-free interval (DRFI) of 95.5 % regardless of adjuvant treatment, compared to 88.7 % in patients with MammaPrint High Risk tumors [19].

Overall, these data confirm that patients with genomically Low Risk tumors derive little to no benefit from chemotherapy and could forego the addition of adjuvant chemotherapy, similar to previous studies, including MINDACT and RASTER [16,17,19,20]. Thus, among patients with genomically Low Risk tumors, 25.9 % could have avoided overtreatment with adjuvant chemotherapy, with related adverse events such as neutropenia, nausea, neuropathy, cardiotoxicity and associated costs to the healthcare system, and would likely continue to have comparable long-term outcomes as those treated with endocrine therapy alone if MammaPrint had been used to guide treatment decisions. In addition, patients with MammaPrint High Risk tumors had worse outcomes at 8 years than those with Low Risk tumors. Further analysis by treatment or nodal status among patients with genomically High Risk tumors were limited due to small numbers in this cohort. However, patients with MammaPrint High Risk tumors in previous studies had clinically meaningful benefit from the addition of chemotherapy to endocrine therapy [17,20]. As a result, the 12 patients with MammaPrint High Risk tumors who only received endocrine therapy would likely benefit from the addition of chemotherapy.

This study presents several key strengths that contribute to its significance in supporting the clinical implementation of MammaPrint in guiding treatment decisions for breast cancer patients in Italy. One of the major strengths of this study is the extended follow-up period, which provides robust evidence on the prognostic value of MammaPrint. Using a well-validated multigene test, such as MammaPrint, adds significant value to this study. MammaPrint has been extensively validated in various populations and confirmed by the prospective randomized trial MINDACT. Although the analysis was retrospective, the study benefits from a prospective cohort design where patients were recruited consecutively, thus minimizing selection bias and enhancing the reliability of the findings. Additionally, this study focuses on a clinically intermediate-risk population, an area of significant uncertainty in treatment planning. By demonstrating that patients with MammaPrint Low Risk tumors can safely forego chemotherapy without compromising long-term outcomes, this study directly impacts clinical decision-making. Despite its strengths, this study also has several limitations such as the single-center design, the retrospective analysis and the small sample size. Last but not least this study is non-randomized and observational, which is why treatment decisions were following guideline recommendations at the time which were more likely based on clinical features.

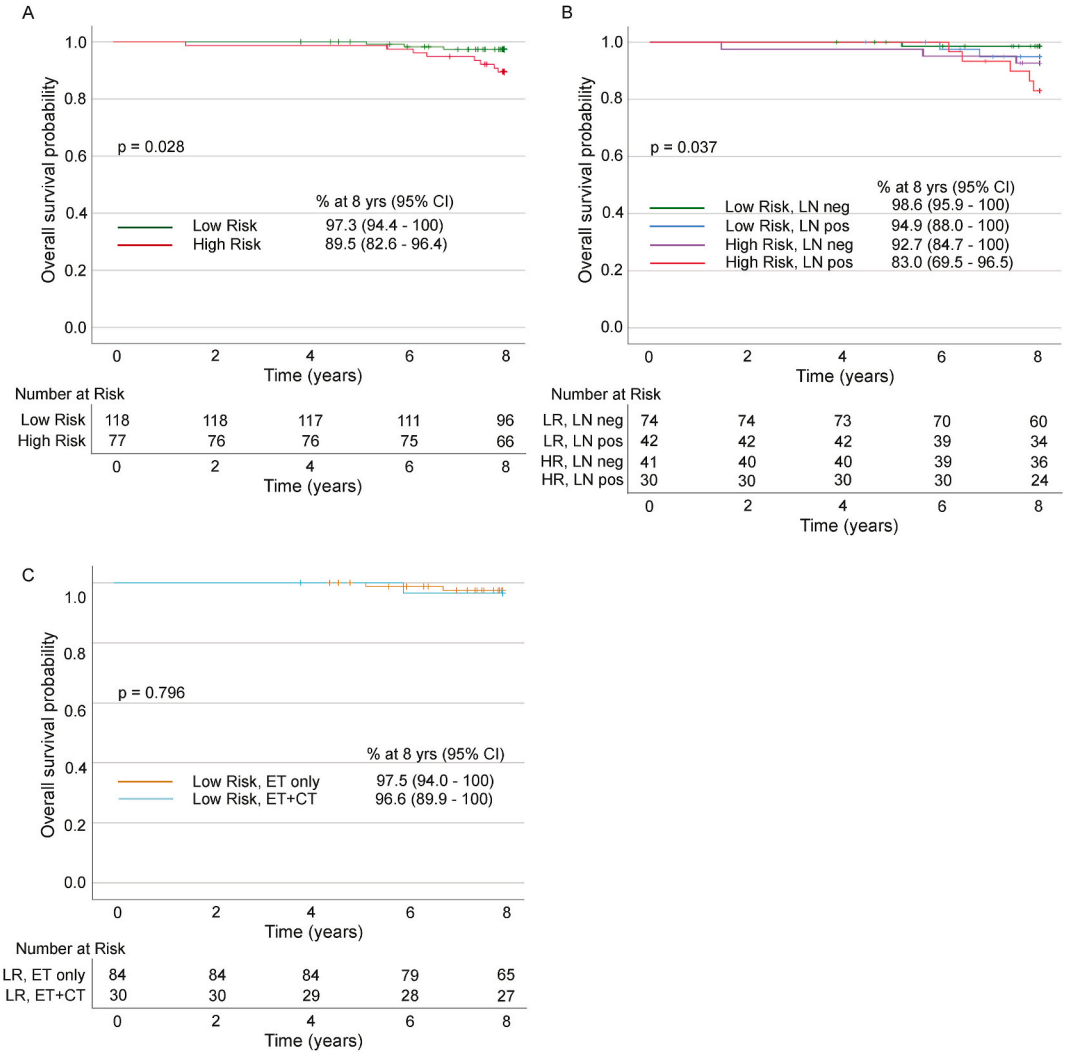

Fig. 2. Association of MammaPrint with 8-year Overall Survival. (a) OS in patients with MammaPrint Low Risk and High Risk tumors. (b) OS in patients with MammaPrint Low Risk and High Risk tumors further stratified by lymph node status. (c) OS among patients with MammaPrint Low Risk tumors further stratified by treatment regimen (ET only vs ET + CT). Significance was assessed by using log-rank test. Abbreviations: OS, overall survival; LN neg, lymph node-negative; LN pos, lymph node-positive; ET, endocrine treatment; CT, chemotherapy.

5. Conclusions

This study confirms the prognostic value of MammaPrint in an Italian series of early-stage intermediate to high-risk breast cancer patients from a single-center cohort. Only MammaPrint and not clinical factors were associated with DMFS at 8 years by multivariate analysis. In addition, patients with clinically intermediate to high risk, MammaPrint Low Risk tumors had excellent outcomes regardless of treatment regimen, further supporting the utility of MammaPrint in providing accurate information to guide personalized treatment planning from either core biopsies or surgical samples. These data, along with previous studies, suggest treatment can be optimized in this group of genomically Low Risk tumors to receive endocrine therapy alone with no evidence of significant benefit from added chemotherapy and potential savings to be generated for the national healthcare system.

CRediT authorship contribution statement

Daniele Generali: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andrea Rocca:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Carla Strina:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Manuela Milani:** Writing – review &

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Ethics approval

From 2006 to 2013, 195 patients treated at Azienda Socio-Sanitaria Territoriale Cremonda (ASST-Cr) were included in this study. This study was performed in line with the principles of the Declaration of Helsinki. The Val Padana Ethics Committee (nr 4791/06) approved the study protocol.

Consent to participate

Informed consent was obtained from all participants included in the study.

Consent to publish

This manuscript does not include any individual persons' details, so patient consent for publication is not applicable in this case. All authors listed approved the present manuscript and consented to its publication.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The clinical datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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