ANALYSIS OF THE MAMMAPRINT BREAST CANCER ASSAY IN AN OLDER US GENERAL HOSPITAL POPULATION

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Introduction

Breast cancer patients with similar pathological staging can have markedly different rates of disease-free and overall survival. A key challenge in breast cancer management is to accurately determine a patient's risk of developing distant metastasis at the time of primary diagnosis. This information can then be used to tailor metastasis-preventing treatment for high-risk patients.

A 70-gene microarray gene expression signature was previously discovered at the Netherlands Cancer Institute (NKI) to identify younger breast cancer patients (age < 55 years) with lymph-node negative disease who are at low risk of developing distant metastasis and might therefore be spared further adjuvant chemotherapy (1, 2). This diagnostic test known as "MammaPrint™" was recently validated in an independent cohort (3). Many breast cancer patients, however, are older and post-menopausal with a lower overall risk of distant metastasis. A molecular diagnostic test with high negative predictive value for distant metastasis in this subgroup could spare many older women adjuvant treatment.

Methods

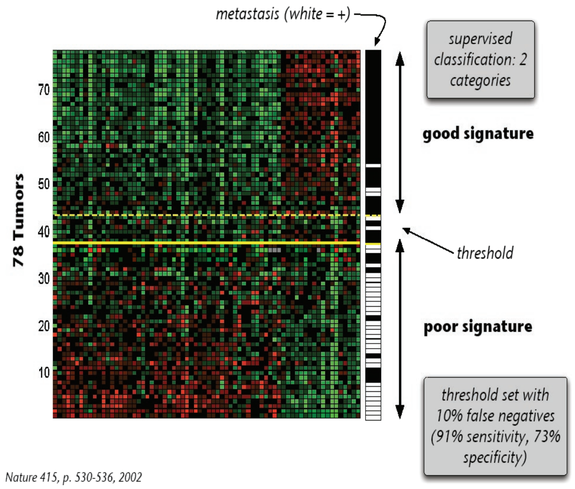
We determined the negative and positive predictive value of the MammaPrint assay in breast cancer patients who were consecutively diagnosed and treated at the Massachusetts General Hospital (MGH) between 1985 and 1997. Primary tumors from 101 patients with node negative, invasive breast cancer (median age 62 years) were subjected to microarray expression analysis using this previously reported 70-gene expression signature and were classified as being at either low or high risk for distant metastasis.

References:
(1) van 't Veer LJ, Dai H, van de Vijver MJ et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002; 415(6871):530-536.
(2) van de Vijver MJ, He YD, van't Veer LJ et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002; 347(25):1999-2009
(3) Buyse M, Loi, S, et al. Validation and Clinical Utility of a 70-Gene Prognostic Signature for Women With Node-Negative Breast Cancer, JNCI. 2006 17, 1183-92.

The 70-gene MammaPrint Prognostic Profile

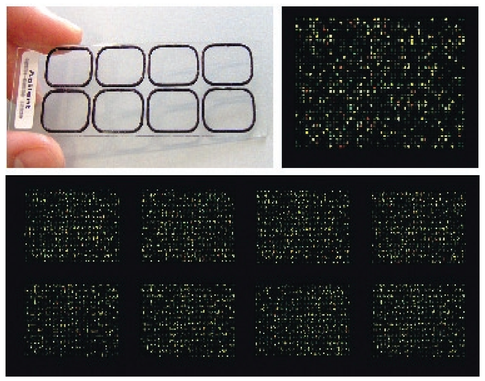
A gene-expression signature, predictive breast cancer metastases, was discovered using an initial cohort of 78 patients with or without metastatic disease[1].

The profile was subequently validated on a larger cohort of 295 patients[2] and now forms the basis of the MammaPrint® breast cancer prognostic test.



Nature 415, p. 530-536, 2002

MammaPrint®: A Customised 8-pack Microarray



The MammaPrint 8 pack is a single 1"x3" slide with eight sub-arrays each with 1,900 microarray probes, allowing eight simultaneous hybridizations.

Test samples are hybridized against a breast cancer RNA pool, incorporating a Cy3/Cy5 dye-swap, to compensate for potential differences in dye incorporation properties.

Clinicopathologic features of node-negative MGH and NKI patients.

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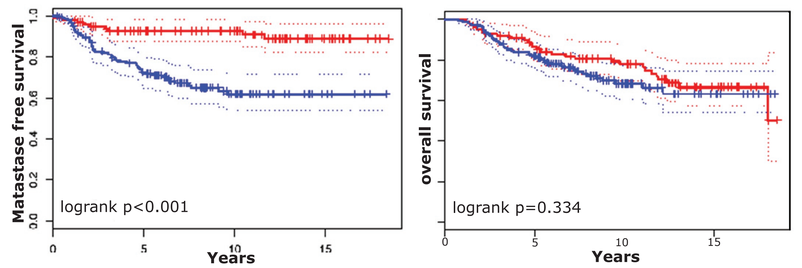
		MGH		NKI		p-value
Age	<40 yr	4	4%	36	24%	<0.001
	40-44 yr	6	6%	42	28%	
	45-49 yr	14	14 %	49	32%	
	50-54 yr	8	8%	24	16%	
	>=55 yr	69	68%	0	0%	
	total	101		151		
Tumor size						0.008
	<= 2cm	72	71%	82	54%	
	> 2cm	29	29%	69	46%	
Histologic grade						<0.001
	I	5	5%	34	23%	
	II	54	53%	46	30%	
	III	41	41%	71	47%	
	medullary carcinoma	1	1%	0	0%	
Estrogen receptor						0.180
	negative	20	20%	42	28 %	
	positive	81	80%	109	72%	
Surgery						0.015
	breast conserving	44	44%	90	60%	
	mastectomy	57	56%	61	40%	
Hormonal therapy						<0.001
	yes	24	24%	6	4%	
	no	77	76%	145	96%	
Chemotherapy						<0.001
	yes	22	22%	6	4%	
	no	79	78%	145	96%	

Comparison of clinical features of the both cohorts revealed thatmost patients in the MGH cohort were post-menopausal. Significant differences in age, tumor size, and histologic grade between the 100 MGH and 151 NKI node-negative patients (p <= 0.01) were observed, Notably, MGH patients also had a significantly higher rate of treatment with both adjuvant chemotherapy and hormonal therapy (p < 0.001).

Overall clinical outcome of node-negative MGH versus NKI patients.

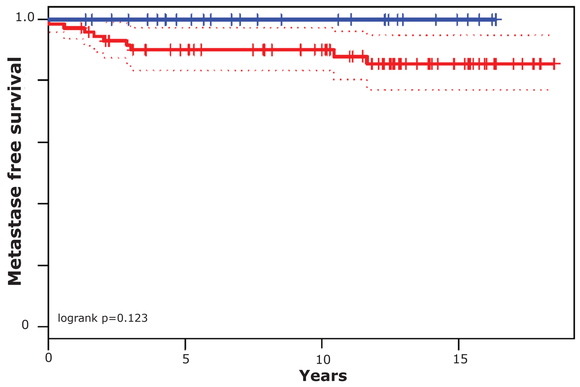


Kaplan-Meier curves of time to metastasis and overall survival for the MGH and lymph-node negative NKI cohorts (Red = MGH, Blue = NKI node-negative, Dotted = 95% CI).

A strikingly lower rate of distant metastasis as a first event in the MGH cohort compared with the NKI node-negative cohort (p < 0.001)). Notably, the MGH and NKI node-negative cohorts did not differ significantly in overall survival, despite the low metastasis rate in MGH patients. This was due to death from causes other than breast cancer in the older MGH population.

Molecular classification of node-negative MGH patients, 100% NPV

The negative predictive value (NPV) of the 70-gene signature was 100% at 5 years in the MGH cohort, which was comparable to a NPV of 93% at 5 years in the node-negative NKI cohort.
All patients that did develop distant metastases in the MGH cohort were predicted as high risk patients (n=9).



Kaplan-Meier curves of time to metastasis for node-negative MGH cohort based on classification with the 70-gene signature (Red = high-risk signature, Blue = low-risk signature.

Conclusion

The MammaPrint assay was originally designed to identify younger breast cancer patients at low risk for distant metastasis, who might consequently be spared systemic treatment. We show here that the same signature can accurately identify older breast cancer patients at lower risk for recurrence after adjuvant treatment.