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Gene expression profiling to predict the risk of locoregional recurrence in breast cancer

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Background

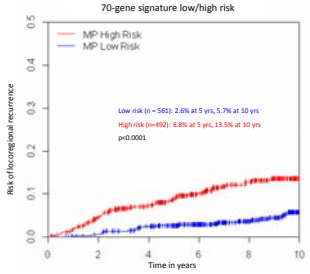
The 70-gene signature (Mammaprint®) has been developed to predict the risk of distant metastases in breast cancer and select those patients who will have benefit in survival from adjuvant treatment. Aside from distant metastases, the development of locoregional recurrence is a significant predictor of survival. Given the strong association between locoregional recurrence and distant recurrence, we hypothesize that the 70-gene signature will be predictive of locoregional recurrence as well.

Methods

We updated follow-up and radiotherapy details for all 1053 individual breast cancer patients treated at the NKI-AVL who previously participated in various 70-gene signature validation studies. Diagnosis was between 1984 and 2006. All patients were primarily treated surgically with either breast conserving surgery or mastectomy. Adjuvant treatment consisted of radiotherapy, chemotherapy and/or endocrine therapy as indicated, according to the treatment guidelines at the time. Known risk factors for locoregional recurrence including age, tumor free resection margins, tumor size, grade, ER status, nodal irradiation and tumor bed boost were included in our analysis in addition to the 70-gene signature result. Risk of locoregional recurrence in all subgroups was calculated using R 2.15.2.

Results

Through 10 years of follow-up, 80 locoregional recurrences occurred. Patients with a 70-gene signature high risk result (n = 492) had a locoregional recurrence risk of 8.8% (95%CI: 6.3-11.3) at 5 years and 13.5 % (95%CI: 10.2-16.8) at 10 years, which was 2.6% (95%CI: 1.2-4.0) at 5 years and 5.7% (95%CI:3.5-7.9) at 10 years for patients with a low risk 70-gene signature (n = 561)(p<0.0001).

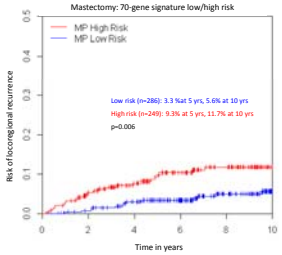


Characteristics	MP Low risk	MP High risk	P value
≤ 50 years	188	232	
> 50 years	373	260	
Mastectomy	298	257	
Local RT	151	147	0.13
No local RT	147	110	
Breast conserving surgery	253	217	
Local RT	249	216	0.38
No local RT	4	1	
Average tumor diameter (mm)	22	24	
Node positive	271	266	
Node negative	281	224	
Grade 1	233	52	
Grade 2	259	154	
Grade 3	48	275	
ER positive	542	318	
ER negative	16	173	
PR positive	448	318	
PR negative	97	255	
HER2 positive	20	100	
HER2 negative	441	320	
Endocrine therapy	263	212	
Chemotherapy	105	188	

Results

When treated with breast conserving surgery, patients with a low risk 70-gene signature result had a 1.5% risk of locoregional recurrence at 5 years and 4.3% at 10 years. Patients with a high risk 70-gene signature result had a 8.6% risk of recurrence at 5 years and 14.0% at 10 years (p<0.001).

70-gene signature low risk patients, treated with a mastectomy had a 3.3% risk of locoregional recurrence at 5 years and 5.6% at 10 years. Patients with a high risk 70-gene signature result had a 9.3% risk of recurrence at 5 years and 11.7% at 10 years (p=0.006).



Univariate analysis	HR	95% CI	P
MammaPrint	2.89	(1.80-4.62)	<0.001
Grade 2	1.87	(0.96-3.65)	0.067
Grade 3	3.23	(1.68-6.19)	<0.001
ER status	0.52	(0.32-0.84)	0.008
Endocrine Therapy	0.52	(0.32-0.84)	0.008
Chemotherapy	1.13	(0.70-1.81)	0.625
Surgery	1.06	(0.67-1.68)	0.796
Radiotherapy	0.82	(0.49-1.37)	0.45
Boost	0.83	(0.49-1.42)	0.5
Size (per 5 mm)	1.02	(0.93-1.12)	0.664
Age (per 10 yrs)	0.74	(0.61-0.90)	0.002
Nodal Status	1.03	(0.93-1.14)	0.571

Multivariate analysis	HR	95% CI	P
MammaPrint	2.27	(1.24-4.15)	0.008
Grade 2	1.89	(0.87-4.09)	0.105
Grade 3	2.27	(0.96-5.35)	0.062
ER status	0.9	(0.49-1.63)	0.719
Endocrine Therapy	0.63	(0.36-1.09)	0.099
Chemotherapy	0.56	(0.31-1.00)	0.049
Surgery	0.83	(0.44-1.54)	0.552
Radiotherapy	0.74	(0.38-1.45)	0.386
Boost	0.86	(0.46-1.60)	0.63
Size (per 5 mm)	0.99	(0.87-1.13)	0.894
Age (per 10 yrs)	0.77	(0.62-0.97)	0.027
Nodal Status	1.13	(1.01-1.28)	0.039

Results

Patients with a high risk 70-gene signature had an approximately 3 times higher risk of locoregional recurrence than patients with a low risk 70-gene signature (univariable hazard ratio (HR) 2.89; 95%CI: 1.80-4.63). Adding the 70-gene signature to a Cox proportional hazard model containing age, size, grade, ER status, involvement of axillary lymph nodes, surgical treatment and adjuvant treatment (radiotherapy, chemotherapy and/or endocrine therapy), significantly improved the model (likelihood ratio: p=0.007). In that model, the multivariable HR for high versus low 70-gene signature risk was 2.27 (95%CI:1.24-4.15). No significant difference in the admission of radiotherpy was seen between patients who received breast conserving surgery and patients who underwent a mastectomy.

Conclusion

The 70-gene signature is able to predict the risk of locoregional recurrence. We observed a significantly lower incidence of locoregional recurrence in patients with a low risk 70-gene signature result compared to those with high risk 70-gene signature result, independent of known risk factors. Patients with high risk 70-gene signature cancers are eligible for extensive adjuvant treatment (radiotherapy, chemotherapy and/or endocrine therapy) to reduce the risk of distant as well as locoregional recurrence. Patients with low risk 70-gene signature cancers are eligible for more limited local treatment strategies.

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