Pathological Proliferation Score (PrS) to Predict Genomic Risk Categories in Early Stage Breast Cancer

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ABSTRACT

Background: Five of the 16 cancer-related genes used to calculate the Recurrence score (RS) are proliferative genes. Appropriate utilization of an expensive test is important especially in areas of limited resources. A relatively inexpensive 'Pathological Proliferative score' (PrS) of a tumor may help group patients in risk categories correlating with the RS

Methods: We retrospectively studied 205 patients with Lymph node negative, hormone receptor (HR) positive, HER2 negative status (ODX candidates) between1990-2015 treated across three rural community oncology practices. Proliferation score was calculated by combining tumor grade, visual mitotic score and Ki67 immunostaining (on a scale of 1-3, lowest score of 3; highest score of 9). Log-rank test was used for survival analysis

Results: PrS correlated with ODX risk recurrence (p <0.001, Fischer's Exact test) [table 1]. PrS predicted FFP (p=0.014) at 10 years with PrS (3-4) 96%±2%, PrS (5-7) 91%±5% and PrS >(7-9) 75%±1%. It did not predict PFS (p=0.77), OS (p=0.84). Type of adjuvant treatment or none did not affect Low Prs(3-4) 10 yr PFS (p=0.18 and OS (p=0.33). Int/High PrS (5-9) showed benefit with adjuvant hormonal therapy compared to none at 10-year OS (p=<0.001), PFS (p=0.002) and FFP (p= 0.003). The 10 yr OS (p=0.75), PFS (0.76) and FFP (p=0.88) was not influenced by addition of adjuvant chemotherapy

Conclusions: PrS which may represent an inexpensive screening approach to identify patients with a low ODX RS that have excellent outcomes despite the type of adjuvant treatment. ODX testing is unlikely to re-categorize them. Higher (5-9) PrS was not predictive of chemotherapy benefit, unlike high ODX. Lack of standardization of Ki67 staining, retrospective nature of the study while important should be tested in an expanded and prospective setting

BACKGROUND

Five of the 16 cancer related genes used to calculate the Recurrence score are proliferative genes and weigh heavily in the final Recurrence Score (RS) (1). Appropriate utilization of an expensive test is important especially in areas of limited resources. In a low risk, clinical scenario (ER/PR Positive, Her2 Negative) a Score devised from Relatively inexpensive immunostaining of tumor cells for Ki67, visual scoring with Mitotic count (MC), and tumor grade (TG) may help determine a pathological 'Proliferative score' of a tumor and help group patients in risk categories correlating with the RS. We have previously determined that a low PrS predicts excellent outcomes and correlates with Freedom from Progression(2).

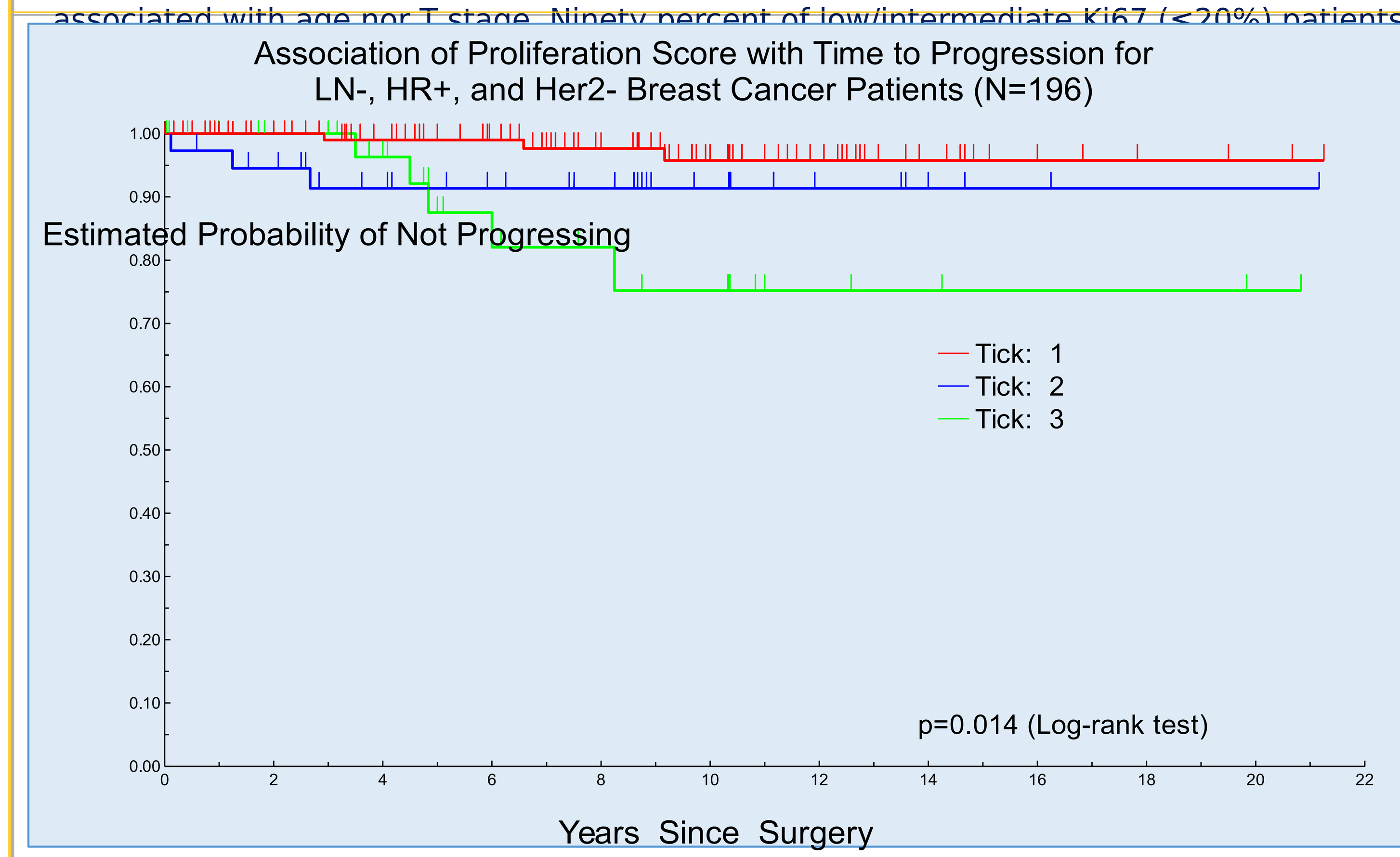
Ki67 is a nuclear protein highly expressed in the S phase and not in G0 phase(3). The Ki-67 proliferation index is widely used and recommended by the 2013 St. Gallen guidelines(4) but not currently recommended by other expert panels like ASCO(5). Relatively inexpensive immunostaining of tumor cells with standard pathological data may help determine the proliferative index of a tumor and help group patients in risk categories correlating with the Recurrence Score (RS). Ki67 index may be an alternative or adjunct to more expensive molecular tools. Assessment of tumor proliferative index by Ki67 immunohistochemistry and standard pathological grade may represent a relatively inexpensive screening approach to identify patients with a low risk of recurrence and may have a

METHODS

We retrospectively studied 205 patients between Jan. 1989 – Oct. 2015, Median age 64 (30 – 91) with node negative, hormone receptor (HR) positive, and HER2 negative status (Oncotype DX® candidates--ODX) diagnosed and treated at our community Oncology practice. Median time to follow-up was 8.9 (0.03, 26.8) Years. We devised a Proliferation score (PrS) which was calculated by combining tumor grade, mitotic score and Ki67 (on a scale of 1-3) with 1 score for each. The Minimum possible score of 3 and maximum score of 9 [Table 4]. Freedom from disease progression (FFP) was calculated from date of surgery to the date of progression or last follow-up (FFP). Overall Survival was calculated from date of surgery to date of death or last follow-up (OS) and progression free survival was calculated from date of surgery to date of progression or death whichever came first or last follow-up (PFS). Fisher's exact test was used to test the association of baseline characteristics with Ki67 and Mitotic score. Log-rank test was used for testing the association of proliferative score, Ki67, Mitotic score with FFP, OS and PFS. Cox proportional model was used to test the association adjusted by tumor grade

RESULTS

PrS correlated with ODX risk recurrence (p <0.001, Fischer's Exact test) [table 2]. PrS predicted FFP (p=0.014) at 10 years [Table 4] with PrS (3-4) 96%±2%, PrS (5-7) 91%±5% and PrS >(7-9) 75%±1%. It did not predict PFS(p=0.77), OS(p=0.84). The Positive predictive value (PPV) of Low Prs (3-4) was 87% for low ODX, and the PPV of high Prs (7-9) was 89% for Int/High ODX p<0.001 (Fisher's exact test). Type of adjuvant treatment or none did not affect Low Prs(3-4) 10 yr PFS (p=0.18 and OS (p=0.33). Int/High PrS (5-9) showed benefit with adjuvant hormonal therapy compared to none at 10-year OS (p=<0.001), PFS (p=0.002) and FFP (p= 0.003). The 10 yr OS (p=0.75), PFS (0.76) and FFP (p=0.88) was not influenced by addition of adjuvant chemotherapy. Ki67 was significantly associated with tumor grade (p<0.001), ODX (p=0.032) and mitotic index (p<0.001) but not associated with age nor T stage. Ninety percent of low/intermediate Ki67 (<20%) patients did not receive chemotherapy.



	Number Patients	Percent
Stage		
1	131	65%
2	67	33%
3	2	1%
Unknown	3	
Genomic Risk(n=85)		
Low	54	64%
Intermediate	14	16%
High	17	20%
Unknown	120	
Surgery		
Bilateral Mastectomy	10	5%
Mastectomy	47	23%
Modified Radical Mastectomy	48	23%
Lumpectomy	100	49%
Adjuvant Hormonal Rx		
No	19	9%
Yes	185	91%

Table 1: Clinical Characteristics of Patients with Breast Cancer

Genomic Risk (ODX)	Proliferative Score (n=190) 3 – 4 (n=119)	5 – 6 (n=37)	7 – 9 (n=40)	p-value *
Low	41 (87%)	11 (58%)	2 (11%)	<0.001
Intermedium	6 (13%)	7 (37%)	1 (5%)	
High	0 (0%)	1 (5%)	16 (84%)	

Table 2: Correlation of ODX with PrS |* p-value based on Fisher's Exact test

Table 3: Pathological Proliferation Score

Proliferation Score	1 (Low)	2 (Intermediate)	3 (High)
Ki67	<10%	10-20%	>20%
Mitotic Index	1 (Low)	2 (Intermediate)	3 (High)
Tumor Grade	1 (Low)	2 (Intermediate)	3 (High)

Table 4: Association of Ki67, Proliferation Score with Freedom from Progression (FFP), Overall Survival (OS) and Progression Free Survival (PFS)

	N	Time to Progression (yrs.)				Overall Survival (yrs.)				Progression Free Survival (yrs.)			
		Prob. of FFP at 5 Yrs.	Prob. of FFP at 10 Yrs.	HR (95% CI)	p-value	Prob. of OS at 5 Yrs.	Prob. of OS at 10 Yrs.	HR (95% CI)	p-value	Prob. of PFS at 5 Yrs.	Prob. of PFS at 10 Yrs.	HR (95% CI)	p-value
Ki67 Status					<0.001*				0.28*				0.15*
<10%	134	0.97±0.01	0.95±0.02	1.00	0.25^	0.91±0.03	0.84±0.04	1.00	0.49^	0.90±0.03	0.80±0.04	1.00	0.28^
10 – 20%	33	0.97±0.03	0.97±0.03	1.00 (0.12, 8.54)		0.92±0.06	0.86±0.08	1.09 (0.37, 3.21)		0.92±0.06	0.86±0.08	0.89 (0.30, 2.52)	
>20%	29	0.81±0.10	0.62±0.14	7.28 (2.08, 25.49)		0.89±0.08	0.67±0.13	2.05 (0.83, 5.10)		0.78±0.10	0.54±0.14	2.18 (0.94, 5.07)	
Proliferative Score					0.014*				0.84*				0.77*
3 – 4 (Low)	119	0.99±0.01	0.96±0.02	1.00		0.91±0.03	0.82±0.04	1.00		0.90±0.03	0.79±0.05	1.00	
5 – 6 (Int)	37	0.91±0.05	0.91±0.05	3.32 (0.67, 16.47)		0.91±0.05	0.87±0.06	1.15 (0.48, 2.76)		0.89±0.05	0.84±0.07	1.17 (0.52, 2.63)	
7 – 9(High)	40	0.88±0.07	0.75±0.10	6.67 (1.59,		0.95±0.04	0.76±0.09	1.30 (0.52,		0.83±0.08	0.67±0.10	1.36 (0.58,	

*p-value based on log-rank test | ^p-value based on Wald Chi-square test after adjusted by tumor grade using proportional Cox model

CONCLUSIONS

We devised a Proliferation score (PrS) which was calculated by combining tumor grade, mitotic score and Ki67 (on a scale of 1-3)

There was significant association of PrS and ODX Categories. **A Low (3-4) PrS is predictive of a Low RS**. ODX these patients are unlikely to re-categorize them and is predictive of excellent 10 yr. outcomes. Adjuvant hormonal treatment did not improve PFS, OS in our very Low PrS patients (PrS-3)

Higher (5-9) PrS patients unlike the high ODX, did not identify the benefit of adjuvant chemo, therefore, pts with high PrS would benefit from testing for ODX and may benefit from genomic testing to enhance our confidence in treatment recommendations and overcome the limitations of discrepancies with lack of standardization of Ki-67 staining while still efficiently utilizing these expensive tests

There was significant association of proliferation score and FFP (p=0.014) at 5 and 10 years

The limitations of discrepancies with lack of standardization of Ki67 staining(8) and retrospective nature of the study while important should be tested in an expanded and prospective setting

ODX is a validated clinical genomic tool that could be efficiently utilized especially in areas of limited resources and representative pathological data when carefully evaluated can be very informative

"PrS" may represent a relatively inexpensive screening approach to identify patients with a low risk of recurrence. Representative pathological data when carefully evaluated can be very informative and cost efficient

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