Proliferative Score in Predicting Recurrence Risk of Breast cancer

Ajaz Bulbul, MBBS, MD[1], Denice Taso-Wei[2], Sadaf Rashad[3] ,Susan Groshen[2], Imran Siddiqui[2], Janice Lu[2], Vyas Dake[1], Corey Hotlwick[1], Kenzi Griego[1], Venkata Prashanthi[1], Debu Tripathy[4]

1. Kymera Independent Physicians, Carlsbad, New Mexico, United States, 88220; 2. Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California, United States, 90033; 3. All Saints School of Medicine, Chicago, Illinois, United States, 60301; 4. University of Texas MD Anderson Cancer Center, Houston, Texas, United States, 77030.

ABSTRACT

Background: Oncotype DX® (ODX) is a validated clinical genomic tool that needs to be efficiently utilized especially in areas of limited resources. Proliferative genes weigh heavily in calculating Recurrence score (RS). Ki67 is a nuclear protein highly expressed in the S phase and not in G0 phase. 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.

Methods: We retrospectively studied 205 patients with Lymph node negative, hormone receptor (HR) positive, HER2 negative status (ODX candidates) treated at our community oncology practice. Proliferation score was calculated by combining tumor grade, mitotic score and Ki67 (on a scale of 1-3). Freedom from disease progression (FFP) was calculated from date of surgery to the date of progression or last follow-up. Fisher's exact test was used to test association of baseline characteristics with Ki67 and mitotic score. Log-rank test was used for survival analysis.

Results: There was significant association of Proliferation score (PrS) and FFP, (p=0.014), [table 2]. Patients with Proliferation Score 3-4 had FFP 96%±2% at 10 yr. post surgery compared 75%±1% with PrS >7. 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 or T stage. Patients with Ki67 <10% had 95%±1% FFP at ten-year post surgery, (p=0.001) based on log-rank test, however (p 0.25) based on Wald Chi-square test after adjusted by tumor grade using proportional Cox model [table 2]. Ninety percent of low/intermediate Ki67 (≤20%) patients did not receive chemotherapy. PrS was significantly associated with Ki67 (p<0.001) and ODX (p<0.001)[table4].The baseline characteristics are reviewed in [table 1]

Conclusion: Low Proliferation Score (PrS) when derived from Ki67 and pathological data is predictive of excellent outcomes and genomic testing is unlikely to re-categorize such patients. The limitations of discrepancies with lack of standardization of Ki67 staining and retrospective nature of the study while important should be tested in an expanded and prospective setting

BACKGROUND

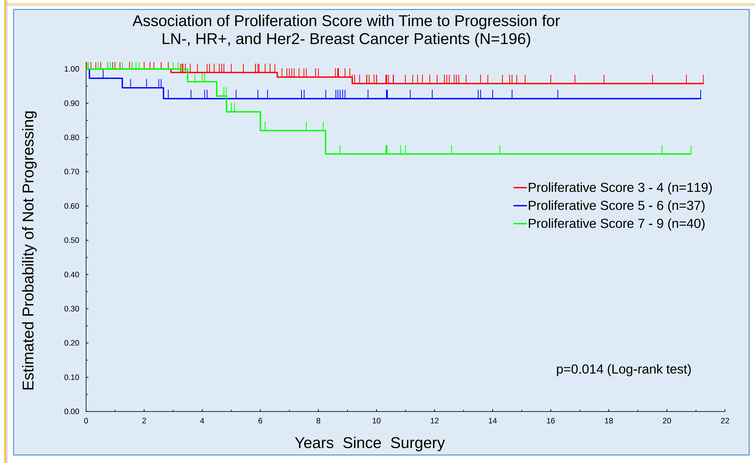
Five of the 16 cancer related genes used to calculate the Recurrence score are proliferative genes and weigh heavily in the final score(1). Ki67 is a nuclear protein highly expressed in the S phase and not in G0 phase(2). The Ki-67 proliferation index is widely used and recommended by the 2013 St. Gallen guidelines(3) but not currently recommended by other expert panels like ASCO(4). 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 similar prognostic value to that of genomic signatures(5, 6)

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 3]. 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

There was significant association of Proliferation score (PrS) and FFP (p=0.014) [table 2]. Patients with Proliferation Score 3-4 had 96%±2 FFP at 10 year post surgery compared 75%±1% for patients with PrS >7. 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. Ki67 was significantly associated with FFS (p=0.001), but no more significant after adjusted by tumor grade [table 2]. 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%
Unknown	1	

Table 1: Clinical Characteristics of Patients with Breast Cancer

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)

	Proliferative Score (n=190)			
Genomic Risk (ODX)	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 4: Correlation of ODX with PrS |* p-value based on Fisher's Exact test

Table 2: 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, 28.04)		0.95±0.04	0.76±0.09	1.30 (0.52, 3.27)		0.83±0.08	0.67±0.10	1.36 (0.58, 3.19)	

*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

- Low Ki67 by itself or when combined with pathological data is predictive of excellent outcomes and genomic testing may unlikely re-categorize such patients
- 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 proliferation score and FFP (p=0.014) at 5 and 10 years
- The limitations of discrepancies with lack of standardization of Ki67 staining(7) 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

REFERENCES

- 1.Kalinsky K, Lim EA, Andreopoulou E, Desai AM, Jin Z, Tu Y, et al. Increased Expression of Tumor Proliferation Genes in Hispanic Women with Early-Stage Breast Cancer. Cancer Invest. 2014;32(9):439-44.
- 2.Bologna-Molina R, Mosqueda-Taylor A, Molina-Frechero N, Mori-Estevez AD, Sánchez-Acuña G. Comparison of the value of PCNA and Ki-67 as markers of cell proliferation in ameloblastic tumor. Med Oral Patol Oral Cir Bucal. 182013. p. e174-9.
- 3.Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thurlimann B, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013;24(9):2206-23.
- 4.Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007;25(33):5287-312.
- 5.Ignatiadis M, Breast Cancer Translational Research Laboratory IJB, Université Libre de Bruxelles, Brussels, Belgium, Medical Oncology Clinic DoM, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium, Azim HA, Breast Cancer Translational Research Laboratory IJB, Université Libre de Bruxelles, Brussels, Belgium, Desmedt C, et al. The Genomic Grade Assay Compared With Ki67 to Determine Risk of Distant Breast Cancer Recurrence. JAMA Oncology. 2017;2(2):217-24.
- 6.Tobin NP, Lindstrom LS, Carlson JW, Bjohle J, Bergh J, Wennmalm K. Multi-level gene expression signatures, but not binary, outperform Ki67 for the long term prognostication of breast cancer patients. Mol Oncol. 2014;8(3):741-52.
- 7.Polley M-YC, Leung SCY, Gao D, Mastropasqua MG, Zabaglo LA, Bartlett JMS, et al. An international study to increase concordance in Ki67 scoring. Modern Pathology. 2015;28(6):778-86.