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Evolving Role of Ki67 as a Predictive and Prognostic Marker in Breast Cancer

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Summary

Proliferation and autonomous growth are key hallmarks of malignancy and breast cancer is no exception to this [1]. Recently a lot of emphasis has been laid on proliferation in breast cancer with many emerging molecular techniques like Oncotype Dx utilizing proliferation genes as predictive tools to direct patient therapy [2]. However, given the high costs associated with these molecular tests there is constant effort to find suitable surrogate immunohistochemical markers. Ki67 (anti-MIB1) has emerged as a rapid and inexpensive method to detect proliferation in breast tumours. It has been an integral part of the biomarker profile along with estrogen receptor (ER), progesterone receptor (PR) and human epidermal receptor 2 (HER2), used as surrogates to assign breast carcinomas to various molecular subtypes [3]. There is robust data to show that Ki67 is an excellent prognostic and predictive marker.

As early as the 1980's high proliferation rates, as determined by high Ki67 index, were reported to be associated with poor outcome and early recurrences in breast cancer. A recent meta-analysis [4] concluded that high ki67 levels were associated with shorter overall survival. Another meta-analysis [5] showed a significantly worse disease free as well as overall survival for patients with positive Ki67 expression in node positive as well as node negative breast cancers. In addition, they also suggested usefulness of Ki67 in combination of other biomarkers especially, estrogen receptors (ER), as evidenced by its prognostic significance in ER positive, early breast cancers. This observation is further validated by the results of the study by Cuzick et al. [6], which demonstrated that a combination score of ER, PR, Her2 and Ki67 (IHC4 score) was not only prognostically significant; but also, comparable to gene-based assays like Oncotype Dx and PAM50.

Ki67 has also been used in clinical trials as a predictive marker to define pathologic response and compare drug efficacies. The Breast International Group (BIG) trial found high Ki67 in breast cancers predictive of a favorable response to adjuvant taxane-based therapy compared to non-taxane therapy. In the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) study and the P024 study comparing neoadjuvant vs. tamoxifen vs. combination of anastrozole and tamoxifen difference in the degree of suppression of Ki67 levels in the two arms of the study group correlated with difference in the recurrence [7]. There are a few trials underway looking at Ki67 levels to decide effectiveness of therapeutic agents in breast cancer [8].

Despite usefulness of Ki67 as a predictive and prognostic biomarker its use is fraught with controversies. There are no well-defined guidelines as to tissue fixation, staining techniques, interpretation of the stain and standardized cut-off values. The stain has been interpreted variously by different pathologists using different techniques ranging from manual rapid estimation to labour intensive meticulous counting of stained cells and automated counts. There is also no clear consensus about the number of cells to be counted to base the final Ki67 index value on. The inherent heterogeneity of the staining pattern has raised a concern whether to include just the hot-spots (focal areas with more intense staining) or base the estimate on the overall staining pattern of the entire tumour. Furthermore, there is a lack of consensus on cut-off values that can be universally used for risk stratification of patients with breast cancer. These limitations were highlighted by the Breast Cancer Working Group which included leading experts in the field [1]. Despite providing adequate guidelines for Ki67 interpretation, including pre-analytical and analytical, there was little inter-observer agreement even among experts on a follow-up study [9].

A review of literature reveals that, not only have the techniques of interpretation of the stain and cut-off levels varied according to the individual study, but also the patient cohorts included in these studies have differed from one another, making comparison between studies difficult [5,7,8]. This, in addition to the afore-mentioned controversies has further compounded the role of Ki67 as a predictive and prognostic marker. So the question is 'Can Ki-67 be reliably used as a marker for prediction and prognostication in breast cancer in routine pathology practice?'

It can very well be, but not until the shortcomings are addressed appropriately. One way of looking at the data is that, Ki67 has been found to be a predictive and prognostic factor across a spectrum of study populations, including node-positive and node-negative cancers, tumours belonging to different age groups and stage. This actually may work in favour of Ki67. Ki67 index may thus, be applicable in a wider population cohort; unlike molecular tests which are more likely to be beneficial in patients with node negative, hormone-receptor positive early breast cancers. The Breast Cancer Working Group has laid down certain guidelines for the pathologists to follow [1]. This is an encouraging first step towards standardization. As per the recommendations 10% neutral buffered formalin is the fixative of choice and MIB-1 antibody the gold standard immunohistochemical stain for Ki67 determination. Studies have shown that Ki67 antigen is stable in formalin and prolonged fixation times have little effect on antigen retrieval. MIB-1 has been a timed tested antibody and proved its utility in estimation of Ki67 index. Techniques to ensure adequate counterstaining of the tumour nuclei should be employed. No definite cut-off level for risk stratification has however been advocated. The current recommendation is that it should be determined based on individual laboratory or study. The current cut-off level as proposed by the St. Galen International Experts Consensus Group to differentiate luminal A from luminal B tumours is 14% [10]. However, there is a thought that a cut-off level of 20% may be better relevant clinically.

One study showed that Ki67 indexes determined by automated technique may be more reliable and more accurately classify patients to their molecular subtype [11]. However, breast is a heterogeneous tissue and selection of appropriate areas of tumour by a trained pathologist is essential. With the appropriate optimization of programs, digital image analysis can be used to validate Ki67 values.

In summary, there is good evidence in the literature that Ki67 can be a good predictive and prognostic factor. However, consensus over staining techniques, estimation of Ki67 and standardized cut-off values is lacking. Recommendations, as proposed by the Breast Cancer Working Group, are a good initial step towards harmonization. Automation techniques may be helpful in providing more objective solution but need further validation through future studies. Thus, Ki67 as a reliable factor for prognostication and prediction, though promising, is still not ready for use in routine practice.

References

1. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, et al. (2011) Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst 103: 1656-1664.
2. Wesolowski R, Ramaswamy B (2011) Gene expression profiling: changing face of breast cancer classification and management. Gene Expr 15: 105-115.
3. Cummings MC, Chambers R, Simpson PT, Lakhani SR (2011) Molecular classification of breast cancer: is it time to pack up our microscopes? Pathology 43: 1-8.
4. Stuart-Harris R, Caldas C, Pinder SE, Pharoah P (2008) Proliferation markers and survival in early breast cancer: a systematic review and meta-analysis of 85 studies in 32,825 patients. Breast 17: 323-334.
5. de Azambuja E, Cardoso F, de Castro G Jr, Colozza M, Mano MS, et al. (2007) Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. Br J Cancer 96: 1504-1513.
6. Cuzick J, Dowsett M, Pineda S, Wale C, Salter J, et al. (2011) Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. J Clin Oncol, 29: 4273-4278.
7. Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA (2010) Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol 11: 174-183.
8. Albarracin, C.a.D.S. (2014) Ki67 as a Biomarker of Prognosis and Prediction: Is it Ready for Use in Routine Pathology Practice? Current Breast Cancer Rep, 2014.
9. Polley MY, Leung SC, McShane LM, Gao D, Hugh JC, et al. (2013) An international Ki67 reproducibility study. J Natl Cancer Inst 105: 1897-1906.
10. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, et al. (2013) 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 24: 2206-2223.
11. Gudlaugsson E, Skaland I, Janssen EA, Smaaland R, Shao Z, et al. (2012) Comparison of the effect of different techniques for measurement of Ki67 proliferation on reproducibility and prognosis prediction accuracy in breast cancer. Histopathology 61: 1134-1144.