



# The Role of Ki-67 in Breast Cancer



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## 1. Introduction

Breast cancer is a heterogeneous disease of uncontrolled cellular proliferation. A core biopsy assesses histological grade; a prognostic factor graded 1-3. It is measured by differentiation, nuclear pleomorphism, and proliferation, according to the Nottingham-Bloom-Richardson (NBR) grading method<sup>1</sup>. However, it is only concordant with the result on excision tissue in 67%<sup>2</sup> of cases, with proliferation being the weakest point with a concordance of 58%<sup>2</sup>.

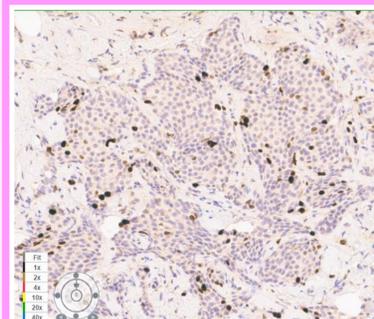
Ki-67 is nuclear protein expressed during cell division so hence a measurement of proliferation, therefore could be used to improve histological grade assessment<sup>3</sup>. However, there are no cut-off points for high, intermediate, and low Ki-67 scores.

## 2. Aims

1. Compare concordance of histological grade on core biopsy and excision tissue.
2. Create cut-off points, incorporate Ki-67 into histological grade, and re-compare concordance on core biopsy and excision tissue.
3. Assess the reproducibility of cut-off points

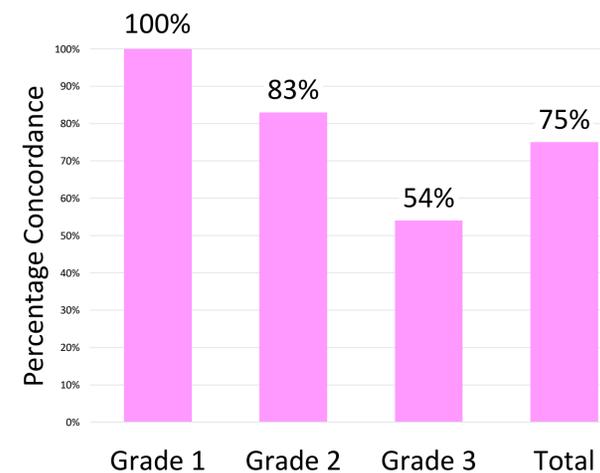
## 3. Methods

Ki-67 is detected by immunohistochemical staining with MM1 antibody on the Lecia Bond III staining platform. A labelling index score is calculated as the percentage of cells expressing Ki-67 within the total number of cancer cells. The Ki-67 score will be divided using two cut-off points and combined with tubule formation and nuclear grade to calculate the histological grade. The first cut-off point distinguishes between low and intermediate; the second between intermediate and high.

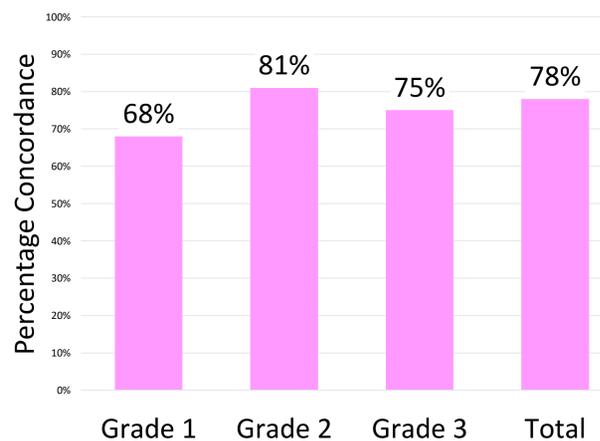


Cancer cells positively stained for Ki-67 appear brown.

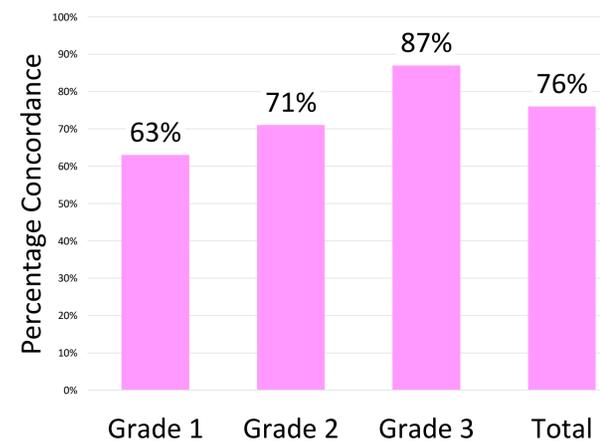
## 4. Aims 1 and 2 Results



1. NBR grading system

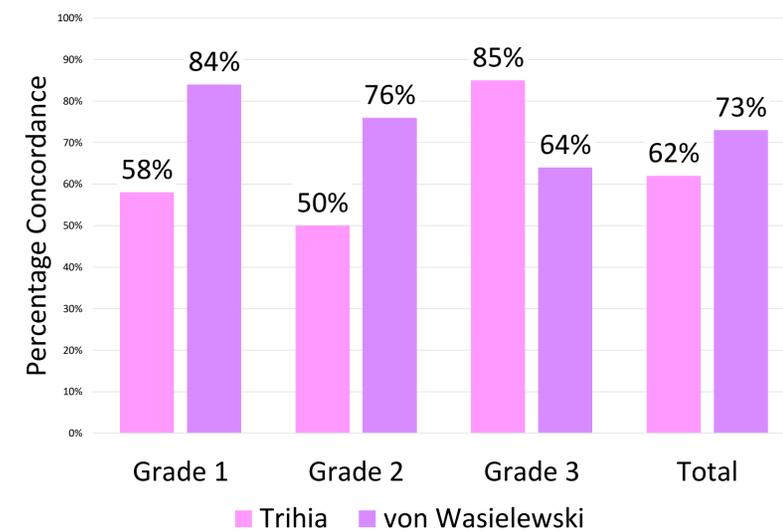


2. Grading with Ki-67 cut-off points 1% and 20%.



3. Grading with Ki-67 cut-off points 1% and 18%.

## 5. Aim 3 Results



4. Grading with Ki-67 cut-off points from Trihia et al and von Wasielewski et al.

## 6. Aim 1 Discussion

100% of grade 1, 83% of grade 2, and 54% of grade 3 carcinomas received the same histological grade on core biopsy and excision tissue, when using the NBR grading method. The total concordance was 75% (bar chart 1). 25% discrepancy is still higher than desired, therefore suggesting room for improvement. These results are similar to Harris *et al*<sup>2</sup>. Grade 3 concordance was lowest at 54% so it was important that this was improved with the Ki-67 score.

## 7. Aim 2 Discussion

The best total concordance of 78% was found using cut-off points 1% and 20% (bar chart 2), and the best grade 3 concordance of 87% was found using cut-off points 1% and 18% (bar chart 3).

The discrepancy found when using these cut-off points is due to problems with mitotic activity assessment, Ki-67 scoring, grading on excision tissue, or discrepancy in tubule formation or nuclear grade. The latter is a common issue, as in Harris *et al*<sup>2</sup>, tubule formation and nuclear grade showed discrepancies of 18% and 27%, respectively. Problems with Ki-67 scoring can be removed by manual counting, DIA, and training in further study.

When using the NBR grading method, 1% of cases were miss-graded by a factor of 2 grades. However, the discrepancies found using Ki-67 were all only by a factor of 1 grade, therefore no grade 1 carcinomas will be miss-graded as grade 3 and receive chemotherapy when Ki-67 is used as the measurement of proliferation.

## 8. Aim 3 Discussion

Trihia *et al* and von Wasielewski *et al* used a Ki-67 score as the measurement of proliferation in the histological grade. Trihia *et al* used cut-off points of 9.5% and 15.5% and yielded total concordance of 88%<sup>4</sup> and von Wasielewski *et al* used cut-off points of 10% and 20% and yielded 97%<sup>5</sup> full agreement or deviation by one grade. These cut-off points were applied to the Ki-67 score from this data set to evaluate their reproducibility. The total concordance results of 62% and 73% (bar chart 4) are very dissimilar to the papers' results, which suggests the cut-off points are not translational.

## 9. Conclusion

This study has shown that the concordance of histological grade on core biopsy and excision tissue is not as desired when the NBR method is used. Cut-off points for optimum total concordance are 1% and 20%, and for optimum grade 3 concordance are 1% and 18%. It is likely the cut-off points are unique to each Ki-67 score.

## 10. Acknowledgments

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## 11. References

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