LITERATURE REVIEW

Artificial intelligence-powered optimization of KI-67 assessment in breast cancer: enhancing precision and workflow efficiency. a literature review

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Abstract

Breast Cancer (BC) has evolved from traditional morphological analysis to molecular profiling, identifying new subtypes. Ki-67, a prognostic biomarker, helps classify subtypes and guide chemotherapy decisions. This review explores how artificial intelligence (AI) can optimize Ki-67 assessment, improving precision and workflow efficiency in BC management.

The study presents a critical analysis of the current state of AI-powered Ki-67 assessment. Results demonstrate high agreement between AI and standard Ki-67 assessment methods highlighting AI's potential as an auxiliary tool for pathologists. Despite these advancements, the review acknowledges limitations such as the restricted timeframe and diverse study designs, emphasizing the need for further research to address these concerns.

In conclusion, AI holds promise in enhancing Ki-67 assessment's precision and workflow efficiency in BC diagnosis. While challenges persist, the integration of AI can revolutionize BC care, making it more accessible and precise, even in resource-limited settings.

Keywords: Artificial Intelligence, Ki-67 Antigen, Prognosis, Pathologists, Breast Cancer

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Introduction

Unveiling Ki-67: A Key Player in Cell Proliferation and Cancer Research

Ki-67 is a protein found within the cell nucleus and is present during the active stages of the cell cycle, which include the G1, S, G2, and M phases. It serves as a commonly utilized marker for assessing cell proliferation, playing a significant role in cancer-related studies. A heightened Ki-67 index is indicative of tumour aggressiveness, making it a crucial factor in influencing treatment choices in most cancers.[1,2]

Ki-67's Role in Breast Carcinoma: Why It Matters

Breast cancer (BC) is responsible for approximately 1.7 million new cancer cases annually.[2] There has been a notable shift in the approach to BC research, transitioning from primarily morphological analysis to a molecular perspective. This shift has brought about significant advancements in the diagnosis and management of BC.[2] It has lead to the emergence of various morphological patterns, behaviours, responses to treatments, and molecular characteristics, resulting in the identification of new molecular subtypes.[1,2] Following the guidelines of the American Society of Clinical Oncology (ASCO), the utilisation of prognostic and predictive markers such as estrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor-2 (HER2) status has become standard practice in BC management.[3] Additionally, the assessment of Ki-67 proliferation has become routine in the evaluation of BC cases, mirroring its incorporation into the standard protocols for several other cancer types, including prostate, cervical, lung, soft tissue, neuroendocrine cancers, and gastrointestinal stromal tumours.[2]

Furthermore, Ki-67's significance extends to its role in distinguishing between Luminal A and Luminal B molecular subtypes of breast cancer. It is closely linked to the assessment of tumour aggressiveness and proliferation, thereby deciding the benefit of chemotherapy candidacy among Luminal BCs.[3]As a valuable prognostic biomarker for predicting patient survival and treatment response, it helps in clinical decision-making in patients with Luminal type of BC that can be spared from chemotherapy as a part of their treatment (overtreatment).[4] However, its utility as a sole clinical decision-making tool is questionable yet, therefore it is always assessed with the other clinical and prognosis assessment tools like Oncotype Dx, MammaPrint, Endo-Predict, and Prosigna etc.[4]

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Materials and Methods

The studies included in this literature review were identified through a comprehensive search of electronic databases, including PubMed, Embase, and Google Scholar from August 2023 to October 2023. The search was conducted to identify relevant articles published between January 2015 and July 2023. The following keywords and phrases were used: "Ki-67 assessment," "breast cancer," "artificial intelligence," "AI," "image analysis," "digital pathology," and variations thereof. The search strategy aimed to identify studies that investigated the application of AI in Ki-67 assessment for breast cancer.

Inclusion Criteria: Studies were included in this review if they met the following criteria: Published in peer-reviewed journals, Investigated the use of AI or machine learning techniques for Ki-67 assessment in breast cancer, included relevant information on study design, sample size, analysis methods, results, and conclusions.

Exclusion Criteria: Studies were excluded if they did not meet the inclusion criteria or if they were conference abstracts, posters, reviews, or duplicate publications.

Data from the selected studies were extracted and organized into a summary table (Table 1). The following

Table 1: Summary of Studies on AI-Assisted Ki-67 Assessment in Breast Cancer

Author Name	Study Design and Year	Sample Size	Analysis Methods	Results	Conclusion
1: Deng et al (29)	Observational study.2021	100	AI-assisted Ki-67 scoring using fully automatic and semi-automatic methods	The study demonstrates that both semi-automatic and automatic AI counting methods for Ki-67 scoring in clinical invasive ductal carcinoma (IDC) show high agreement with manual counting, with differences within 10% for 60-78% of cases. However, the Intra-class correlation coefficient (ICC) values suggest slightly better repeatability between the two AI methods compared to AI and manual counting.	AI counting is a valuable auxiliary tool for pathologists and can reduce the need for manual counting.
2: Chen et al. (30)	Retrospective observational study.2021	Data sets: GSE96058 (n=2976), GSE81538 (n=405), GSE163882 (n=222). The study employed fivefold cross-validation to evaluate the performance of their models and also tested the models on external data (using GSE96058 as training data and GSE81538 as testing data).	RNA sequencing data transformed into Artificial Image Objects (AIOs) and classified using Convolutional Neural Network (CNN) models	The proposed CNN model achieved a classification accuracy of approximately 82.1% and an AUC of about 0.891 for Ki67 status, and for Nottingham histologic grade (NHG), it achieved a weighted average categorical accuracy of around 82.0% and a weighted average AUC of approximately 0.931 using cross-validation. When tested on external data, it achieved an accuracy of approximately 82.6% and an AUC of about 0.883 for Ki67, and for NHG, it had an accuracy of around 76.4% and an AUC of approximately 0.882,	AIOs can transform RNA sequencing data into classification models for biomarkers, offering efficient and consistent results for clinical applications.

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				outperforming previous studies by approximately 10%.	
3. Xie et al (31)	Multicenteric retrospective study2022	The sample size for the tested 771 pairs of HE- and Ki-67-stained slides was used in the evaluation of the AI system's performance.	Scale-invariant feature transform SIFT-based AI system for Ki-67 calculation	The AI-based algorithm achieved a high accuracy of 93% in identifying breast cancer tissues in HE-stained slides, with an impressive area under the curve (AUC) of 0.98. After registration, the system attained a notable accuracy rate of 91.5% in calculating the Ki-67 index when compared to gold standard pathological reports, demonstrating its effectiveness in automating this process.	The AI-based system can enhance the accuracy and repeatability of Ki-67 index calculation in breast cancer.
4. Li et al (32)	Retrospective observational study2022	The study randomly assigned 300 invasive breast cancer specimens to a training set (150 cases) and a validation set (150 cases). Pathologists in the training set employed multiple methods, including AI, SRC, and manual counting, to assess Ki-67 labelling index (Ki-67LI). In the validation set, three pathologists used SRC and AI for Ki-67LI evaluation, aiming to determine inter-observer repeatability and agreement.	Evaluation of AI and standard reference card (SRC) for Ki-67LI	The study demonstrated that both the Ki-67 standard reference card (SRC) and artificial intelligence (AI) software exhibited very good inter-observer consistency, with ICC values exceeding 0.905 in homogeneous and heterogeneous groups. In the validation set, pathologists using SRC and AI achieved ICC values above 0.95 with the gold standard, indicating high reproducibility and agreement.	SRC and AI offer consistent results for Ki-67LI and can serve as standard methods for assessment.
5: Fulawka et al. (33)	Retrospective observational study2022	95	AI-based Ki-67 proliferation index calculation in Ductal carcinoma in situ.	The proposed deep learning model achieved a mean absolute error of 0.024 when estimating the Ki-67 proliferation index, offering a significant improvement over the current state-of-the-art solution.	AI-based method offers improved accuracy in Ki-67 index calculation compared to manual assessment.
6. Cai et al (34)	comparative observational stud2021	30 pathologists from five institutes with varying levels of experience to assess the Ki67 labelling index on 100 Ki67-stained	Pathologists conducted assessments in three rounds: visual assessment on a conventional microscope, assisted with reference cards,	The AI-empowered microscope improved Ki67 assessment reproducibility and accuracy, with experienced pathologists achieving an ICC of 0.937 and	The AI-empowered microscope enhances pathologists' consistency and accuracy in Ki67 assessment.

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		slides from invasive breast cancer patients.	and assisted with an AI-empowered microscope.	mean error of 4.36%, and inexperienced pathologists reaching an ICC of 0.923 and mean error of 4.71%.	
7. Zehra et al (35)	Descriptive study2023	60 cases of invasive ductal carcinoma (IDC) stained with Ki67 antibody.	Automated detection of Ki67 compared to manual eyeball method	Automated Ki67 scoring demonstrated strong positive concordance with manual scoring ($p < 0.001$), indicating the potential of automated methods to improve consistency, reproducibility, and accuracy in breast cancer diagnosis with AI support.	Automated scoring of Ki67 staining has the potential to eliminate issues of consistency and accuracy.
8. Abele et al (36)	Retrospective observational study2023	The evaluation was conducted using a dataset of 204 slides, which included 72 Ki-67 slides, 66 ER slides, and 66 PR slides.	The study involved assessing the intra-observer agreement between pathologists in scoring breast cancer core biopsies stained for Ki-67, ER, and PR using both manual scoring and AI assistance under varying preanalytical conditions, including different staining systems, scanners, and antibodies.	With AI support, agreement rates for pathologists improved to 87.6% for Ki-67 and 89.4% for ER/PR, compared to lower interobserver agreement (Krippendorff's α, 0.69) in conventional quantification.	AI assistance enhances the reliability of immunohistochemical scoring for Ki-67, ER, and PR quantification.

information was extracted from each study: author name, study design and year, sample size, analysis methods, results, and conclusions. The summary table was used to facilitate the comparison and synthesis of findings across studies. The findings from the selected studies were synthesized and analyzed to provide an overview of the current state of research on AI-assisted Ki-67 assessment in breast cancer. The synthesis focused on key outcomes such as the accuracy, reproducibility, and efficiency of AI methods in comparison to manual assessment. Additionally, any variations in study design, AI algorithms used, and the impact of AI on clinical practice were explored.

Quality Assessment: The quality of the included studies was assessed using relevant quality appraisal tools, such as the Newcastle-Ottawa Scale (NOS) for observational studies.[5] This assessment aimed to evaluate the methodological rigor and potential biases in the selected studies.

Discussion

Over time, the assessment of cellular proliferation in malignant cells has undergone a significant evolution. Various methods have been employed, including thymidine uptake, flow cytometry to detect S-phase cells, manual counting of mitotic figures through microscopic examination, the utilization of immunohistochemical (IHC) staining for Ki-67 expression, and newer methods now like; molecular multi-gene assays such as Oncotype DX and MammaPrint Endo predict, and Prosigna etc.[4-7]

The monoclonal antibody Ki-67 has endured the test of time and has proven to be a valuable IHC marker for assessing cellular proliferation in various tumour tissue samples.[4,8] It effectively highlights cells in the G1, S, G2, and mitotic phases of the cell cycle while exhibiting minimal expression in quiescent (G0) and early G1 phases.[9,10] In general, the proliferative index determined through IHC aligns well with the S-phase fraction measured by flow cytometry.[11] However, the widespread use of Ki-67 in routine clinical practice is hindered by various factors. These include pre-analytical, analytical, and post-analytical variables, the use of different Ki-67 assays, a lack of standardization, and inconsistent reproducibility, all of which limit its routine clinical utility.[12] Nevertheless, in modern clinical practice, Ki-67 is considered a reliable indicator of response to systemic therapeutic strategies and serves as a prognostic biomarker in certain malignancies.

The use of Ki-67 in the breast for neoadjuvant therapy: A Beneficial Tool?

Neo-adjuvant chemotherapy (NACT) has become a standard procedure in locally advanced breast cancer, those desiring breast-conserving surgery with size reduction potential, ipsilateral axillary lymph node involvement, and aggressive subtypes like triple-negative or HER2-positive, impacting adjuvant therapy choices.[13] However, evaluating treatment response through clinical and radiological means often proves to be unreliable. To obtain an accurate assessment of response, the gold standard remains the pathological evaluation of the excised tumour bed. This assessment is essential for categorizing the pathological response after NACT, which correlates with the survival outcomes.[8,10]

The predictive value of Ki-67 in neoadjuvant chemotherapy response is firmly established, with numerous studies indicating that an elevated Ki-67 index is a reliable predictor for achieving a pathological response (pCR) during neoadjuvant chemotherapy.[14-19] It is important to note that predicting pathological response also depends on factors like ER/PR/Her2neu status, molecular subtype, tumour size, age of the patient, menopausal status, number of involved lymph nodes, PDL1 status in conjunction with the Ki67 index.[3,14,15,20]

The behaviour of the Ki-67 indexes following neoadjuvant chemotherapy varies, as it can decrease, increase, or remain unchanged.[4,10,21,22] As elevated pre-treatment Ki-67 values are associated with an increased likelihood of achieving a pathologic complete response, a high Ki-67 proliferation rate post-neoadjuvant treatment is indicative of an unfavourable prognosis.[23] Notably, the predictive value of Ki-67 varies between Her2-positive and hormone receptor-positive BCs, with lower predictive values observed for Her2-positive tumours. Therefore, the Ki-67's role in the neoadjuvant setting is considered supportive, and there is a call for further data collection, recording, and analysis to better understand its utility.[24]

The use of Ki-67 in the breast for adjuvant therapy: A Beneficial Tool?

The recommendation for using cyclin-dependent kinase (CDK) 4/6 inhibitor, such as abemaciclib, in the adjuvant setting for high-risk ER-positive/HER2-negative early-stage breast cancer, as seen in the MonarchE trial, is contingent on a meticulous evaluation of the Ki-67 index. This underscores the importance of selecting a standardized Ki-67 antibody and consistent interpretation practices. It further underscores that Ki-67 serves as both a prognostic and predictive marker in breast cancer, elevating its significance beyond a routine immunostain.[4,25] However, a pertinent question remains about the establishment of uniform reporting for Ki-67 and the definition of cutoff values for low and high Ki-67 indices, which would facilitate the stratification of patient groups.[26]

The 2009 St. Gallen recommendations on the treatment of early breast cancer consensus created three groups for Ki-67 levels: Low (≤15%), Intermediate (16% to 30%), and High (≥30%) (Joerger, Senn et al. 2009).[27] In 2013 St. Gallen changed the cut-off point to 20%.[28] Based on the data from the monarchE clinical trial, the FDA approved Abemaciclib in combination with endocrine therapy for the adjuvant treatment of hormone receptor-positive/HER2-negative, node-positive, early breast cancer with a Ki-67 score ≥20%. Patients with a Ki-67 ≥20% were shown to have a clinically meaningful increased risk of developing the invasive disease within 2 years as compared with those with Ki-67 <20%, which further validates the prognostic value of Ki-67 at this specific cutoff point. A 20% cut-off is considered clinically relevant for calculating recurrence and survival outcomes as per the trial results.[29] The most informative Ki-67 expression levels for prognosis are typically observed when the level is either less than 5% (indicating low proliferation) or greater than 30% (indicating high proliferation), as accurately distinguishing values within the intermediate range can be technically challenging.[3]

Enhancing Ki-67 Assessment Consistency: Key Factors and Challenges to Consider

Ki-67 plays a crucial role in decision-making for adjuvant/neoadjuvant treatments and prognosis in breast cancer, though its utility remains uncertain as a single assessment tool.[14,15] Its assessment is greatly influenced by pre-analytical factors, including fixation methods, specimen type, and surgical procedures, as well as analytical considerations such as staining standards and pathologist expertise.[4] Post-analytical variables, including storage and data capture methods, also come into play. The International Ki-67 in Breast Cancer Working Group (IKWG) provides valuable insights, advocating for core biopsies, stringent quality control, and standardised procedures.[4] However, the complexity of the IKWG scoring method, involving software proficiency and time, poses challenges in routine pathology settings.[4] Alternate, simpler scoring methods are explored, including visual estimation and automated approaches, each with its own set of pros and cons. Inter-laboratory reproducibility hinges on meticulous adherence to guidelines for specimen handling, antigen retrieval, and data capture.[4]

Leveraging Artificial Intelligence (AI) Advancements for Enhanced Ki-67 Assessment in Breast Cancer: A Path

Towards Precision and Efficiency

AI, or artificial intelligence, refers to advanced computer systems capable of performing tasks that typically require human intelligence, such as analyzing complex data and making informed decisions.[32-34] Leveraging AI advancements, supported by studies in literature, enhances Ki-67 assessment in breast cancer.[30,31] It provides standardised data capture, precise image analysis, predictive models, and quality control, streamlining tasks and improving patient outcomes when integrated into clinical workflows.[30-38] Table 1 shows the case studies conducted in tabular form.

Several studies have explored the application of artificial intelligence (AI) in enhancing Ki-67 assessment in breast cancer diagnosis. Deng et al. conducted an observational study with 100 cases, demonstrating that both semi-automatic and automatic AI counting methods showed high agreement with manual counting for Ki-67 scoring.[30] Similar results were reported by other multicenter retrospective studies which attained a high accuracy of 93% in identifying breast cancer tissues and 91.5% in calculating the Ki-67 index using an AI-based algorithm.[32,36] While Li et al. assessed AI and standard reference card (SRC) methods, revealing excellent inter-observer consistency and Fulawka et al. developed a deep learning model with a mean absolute error of 0.024 for Ki-67 index estimation, showcasing improved accuracy using AI-based models in Ki 67 assessment.[33-34]

For classifying Ki67 status classification, Chen et al. employed a retrospective observational study with large datasets, achieving remarkable accuracy and area under the curve (AUC) using a Convolutional Neural Network (CNN) model for Ki67 status classification.[31] Another study found that an AI-empowered microscope improved Ki-67 assessment reproducibility and accuracy.[35] Abele et al. revealed that AI assistance enhances the reliability of immunohistochemical scoring for Ki-67, ER, and PR quantification.[37] Finally, Boden et al. showed that human-in-the-loop corrections improve the accuracy of Ki-67 proliferation assessment. These studies collectively emphasize the potential of AI to enhance Ki-67 assessment, offering accuracy, consistency, and efficiency benefits in breast cancer diagnosis.[38]

Study Limitations

The literature review's limitations include a restricted timeframe of studies published from January 2015 to July 2023, potentially missing relevant research beyond this period. Additionally, it does not encompass grey literature like conference abstracts or unpublished reports, which could offer valuable insights. The diverse study designs, ranging from observational to retrospective and comparative, may hinder direct comparisons. Variable sample sizes across studies may impact generalizability and statistical power. Different AI algorithms and technologies employed make direct performance comparisons challenging. Furthermore, while AI aids Ki-67 assessment, interlaboratory variability in specimen handling, staining, and data capture may persist, affecting consistency. The complexity of the Ki-67 assessment, influenced by pre-analytical, analytical, and post-analytical factors, may not be fully addressed in the reviewed studies. Lastly, some studies provide cross-sectional data, potentially missing the evolving nature and long-term impact of AI-assisted Ki-67 assessment in breast cancer diagnosis and treatment. These limitations should guide future research in the field of AI-powered Ki-67 assessment in breast cancer.

The future implications of AI-powered Ki-67 assessment in breast cancer for Low- and Middle-Income Countries (LMICs)

The future implications of AI-powered Ki-67 assessment in breast cancer for Low- and Middle-Income Countries (LMICs) are promising. AI can enhance diagnostic accuracy, reduce healthcare disparities, and improve cost-efficiency in resource-limited settings. It enables telepathology services, facilitates capacity building, and supports data collection for tailored treatment strategies. Integration with mobile health technologies expands access to remote areas. However, challenges include addressing ethical considerations and ensuring responsible AI adoption. Overall, AI holds great potential to advance breast cancer diagnosis and care in LMICs, provided that infrastructure and ethical guidelines are appropriately developed and implemented.

Conclusion

In summary, the integration of artificial intelligence (AI) in Ki-67 assessment offers significant advancements in breast cancer care. This review underscores AI's potential as a valuable tool for pathologists, demonstrating a high level of agreement with traditional methods. Challenges, including variability and complexity, call for further research. Nevertheless, AI holds promise in improving accuracy and accessibility, particularly in resource-limited settings, revolutionizing breast cancer diagnosis and treatment. Addressing these challenges and harnessing AI's benefits should be a priority in future research and clinical practice.

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Abbreviation:

BC - Breast Cancer
AI - Artificial Intelligence
ER - Estrogen Receptor
PR - Progesterone Receptor
HER2 - Human Epidermal Growth Factor Receptor-2
ASCO - American Society of Clinical Oncology
LMICs - Low- and Middle-Income Countries
NACT - Neoadjuvant Chemotherapy
pCR - Pathological Complete Response
IDC - Invasive Ductal Carcinoma
AUC - Area Under the Curve
CNN - Convolutional Neural Network
NHG - Nottingham Histologic Grade
SRC - Standard Reference Card
DIA - Digital Image Analysis
IKWG - International Ki-67 in Breast Cancer Working Group
IHC - Immunohistochemical
ICC - Intra-class Correlation Coefficient
RNA - Ribonucleic Acid
GSE - Gene Expression Omnibus Series

References

1. Ishibashi N, Maebayashi T, Aizawa T, Sakaguchi M, Nishimaki H, Masuda S. Correlation between the Ki-67 proliferation index and response to radiation therapy in small cell lung cancer. Radiat Oncol 2017;12:16. doi: 10.1186/s13014-016-0744-1
2. Davey MG, Hynes SO, Kerin MJ, Miller N, Lowery AJ. Ki-67 as a Prognostic Biomarker in Invasive Breast Cancer. Cancers (Basel) 2021;13:4455. doi: 10.3390/cancers13174455
3. Andre F, Ismaila N, Allison KH, Barlow WE, Collyar DE, Damodaran S, et al. Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update. J Clin Oncol 2022;40:1816-37. doi: 10.1200/JCO.22.00069
4. Finkelman BS, Zhang H, Hicks DG, Turner BM. The Evolution of Ki-67 and Breast Carcinoma: Past Observations, Present Directions, and Future Considerations. Cancers (Basel) 2023;15:808. doi: 10.3390/cancers15030808
5. Bae JM. A suggestion for quality assessment in systematic reviews of observational studies in nutritional epidemiology. Epidemiol Health 2016;38:e2016014. doi: 10.4178/epih.e2016014
6. Nielsen TO, Leung SCY, Rimm DL, Dodson A, Acs B, Badve S, et al. Assessment of Ki67 in Breast Cancer: Updated Recommendations From the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst 2021;113:808-19. doi: 10.1093/jnci/djaa201
7. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817-26. doi: 10.1056/NEJMoa041588
8. Abubakar M, Figueroa J, Ali HR, Blows F, Lissowska J, Caldas C, et al. Combined quantitative measures of ER, PR, HER2, and KI67 provide more prognostic information than categorical combinations in luminal breast cancer. Mod Pathol 2019;32:1244-56. doi: 10.1038/s41379-019-0270-4
9. Bullwinkel J, Baron-Lühr B, Lüdemann A, Wohlenberg C, Gerdes J, Scholzen T. Ki-67 protein is associated with ribosomal RNA transcription in quiescent and proliferating cells. J Cell Physiol 2006;206:624-35. doi: 10.1002/jcp.20494
10. Aboushousha T, Hammam O, Safwat G, Eesa A, Ahmed S, Esmat ME, et al. Differential Expression of RAGE, EGFR and Ki-67 in Primary Tumors and Lymph Node Deposits of Breast Carcinoma. Asian Pac J Cancer Prev 2018;19:2269-77. doi: 10.22034/APJCP.2018.19.8.2269
11. Hashmi AA, Hashmi KA, Irfan M, Khan SM, Edhi MM, Ali JP, et al. Ki67 index in intrinsic breast cancer subtypes and its association with prognostic parameters. BMC Res Notes 2019;12:605. doi: 10.1186/s13104-019-4653-x
12. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J, et al. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst 2011;103:1656-64. doi: 10.1093/jnci/djr393
13. Korde LA, Somerfield MR, Carey LA, Crews JR, Denduluri N, Hwang ES, et al. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. J Clin Oncol 2021;39:1485-50. doi: 10.1200/JCO.20.03399
14. Cabrera-Galeana P, Muñoz-Montaño W, Lara-Medina F, Alvarado-Miranda A, Pérez-Sánchez V, Villarreal-Garza C, et al. Ki67 Changes Identify Worse Outcomes in Residual Breast Cancer Tumors After Neoadjuvant Chemotherapy. Oncologist 2018;23:670-8. doi: 10.1634/theoncologist.2017-0396
15. Turner BM, Katerji H, Zhang H, Hicks DG. Biomarker and multigene assay testing in ER positive, HER-2 negative breast carcinomas: an international guidelines-based approach. Hum Pathol Rep 2021;26:e300574. Doi: 10.1016/j.hpr.2021.300574.
16. Colleoni M, Bagnardi V, Rotmensz N, Viale G, Mastropasqua M, Veronesi P, et al. A nomogram based on the expression of Ki-67, steroid hormone receptors status and number of chemotherapy courses to predict pathological complete remission after preoperative chemotherapy for breast cancer. Eur J Cancer 2010;46:2216-24. doi: 10.1016/j.ejca.2010.04.008
17. Fasching PA, Heusinger K, Haeberle L, Niklos M, Hein A, Bayer CM, et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer 2011;11:486. doi: 10.1186/1471-2407-11-486
18. Alba E, Lluch A, Ribelles N, Anton-Torres A, Sanchez-Rovira P, Albanell J, et al. High Proliferation Predicts Pathological Complete Response to Neoadjuvant Chemotherapy in Early Breast Cancer. Oncologist 2016;21:150-5. doi: 10.1634/theoncologist.2015-0312
19. Jain P, Doval DC, Batra U, Goyal P, Bothra SJ, Agarwal C, et al. Ki-67 labeling index as a predictor of response to neoadjuvant chemotherapy in breast cancer. Jpn J Clin Oncol 2019;49:329-38. doi: 10.1093/jjco/hyz012
20. Burcombe RJ, Makris A, Richman PI, Daley FM, Noble S, Pittam M, et al. Evaluation of ER, PgR, HER-2 and Ki-67 as predictors of response to neoadjuvant anthracycline chemotherapy for operable breast cancer. Br J Cancer 2005;92:147-55. doi: 10.1038/sj.bjc.6602256
21. Qin Q, Gao F, Jiang W, Tan Q, Mo Q, Wei C. Effect of neoadjuvant chemotherapy on expressions of estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, and Ki-67 in breast cancer. Chin Med J (Engl) 2014;127:3272-7.
22. Zhang L, Hao J, Guo J, Zhao X, Yin X. Predicting of Ki-67 Expression Level Using Diffusion-Weighted and Synthetic Magnetic Resonance Imaging in Invasive Ductal Breast Cancer. Breast J 2023;2023:6746326. doi: 10.1155/2023/6746326
23. Chen R, Ye Y, Yang C, Peng Y, Zong B, Qu F, et al. Assessment of the predictive role of pretreatment Ki-67 and Ki-67 changes in breast cancer patients receiving neoadjuvant chemotherapy according to the molecular classification: a retrospective study of 1010 patients. Breast Cancer Res Treat 2018;170:35-43. doi: 10.1007/s10549-018-4730-1

24. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30:1674. doi: 10.1093/annonc/mdz189
25. Fung S, Blair HA. Abemaciclib: A Review in Early Breast Cancer with a High Risk of Recurrence. Target Oncol 2023;18:287-94. doi: 10.1007/s11523-023-00952-y
26. Kanyılmaz G, Yavuz BB, Aktan M, Karaağaç M, Uyar M, Fındık S. Prognostic Importance of Ki-67 in Breast Cancer and Its Relationship with Other Prognostic Factors. Eur J Breast Health 2019;15:256-61. doi: 10.5152/ejbh.2019.4778
27. Jörger M, Senn HJ, Thürlimann B. St. Gallen 2009 recommendations on the treatment of early breast cancer: consensus and controversy. Memo-Mag Eur Med Onc 2009;2:229-31. Doi: 10.1007/s12254-009-0163-1.
28. Ignatiadis M, Buyse M, Sotiriou C. St Gallen International Expert Consensus on the primary therapy of early breast cancer: an invaluable tool for physicians and scientists. Ann Oncol 2015;26:1519-20. doi: 10.1093/annonc/mdv259
29. Polewski MD, Nielsen GB, Gu Y, Weaver AT, Gegg G, Tabuena-Frolli S, et al. A Standardized Investigational Ki-67 Immunohistochemistry Assay Used to Assess High-Risk Early Breast Cancer Patients in the monarchE Phase 3 Clinical Study Identifies a Population With Greater Risk of Disease Recurrence When Treated With Endocrine Therapy Alone. Appl Immunohistochem Mol Morphol 2022;30:237-45. doi: 10.1097/PAI.0000000000001009
30. Deng Y, Li FL, Qin HY, Zhou YY, Zhou QQ, Mei J, et al. Application Test of the AI-Automatic Diagnostic System for Ki-67 in Breast Cancer. Sichuan Da Xue Xue Bao Yi Xue Ban 2021;52:693-7. doi: 10.12182/20210460202.
31. Chen X, Chen DG, Zhao Z, Balko JM, Chen J. Artificial image objects for classification of breast cancer biomarkers with transcriptome sequencing data and convolutional neural network algorithms. Breast Cancer Res 2021;23:96. doi: 10.1186/s13058-021-01474-z
32. Xie N, Zhou H, Yu L, Huang S, Tian C, Li K, et al. Artificial intelligence scale-invariant feature transform algorithm-based system to improve the calculation accuracy of Ki-67 index in invasive breast cancer: a multicenter retrospective study. Ann Transl Med 2022;10:1067. doi: 10.21037/atm-22-4254
33. Li L, Han D, Yu Y, Li J, Liu Y. Artificial intelligence-assisted interpretation of Ki-67 expression and repeatability in breast cancer. Diagn Pathol 2022;17:20. doi: 10.1186/s13000-022-01196-6
34. Fulawka L, Blaszczyk J, Tabakov M, Halon A. Assessment of Ki-67 proliferation index with deep learning in DCIS (ductal carcinoma in situ). Sci Rep 2022;12:3166. doi: 10.1038/s41598-022-06555-3
35. Cai L, Yan K, Bu H, Yue M, Dong P, Wang X, et al. Improving Ki67 assessment concordance by the use of an artificial intelligence-empowered microscope: a multi-institutional ring study. Histopathology 2021;79:544-55. doi: 10.1111/his.14383
36. Zehra T, Shams M, Ahmad Z, Chundriger Q, Ahmed A, Jaffar N. Ki-67 Quantification in Breast Cancer by Digital Imaging AI Software and its Concordance with Manual Method. J Coll Physicians Surg Pak 2023;33:544-7. doi: 10.29271/jcpsp.2023.05.544
37. Abele N, Tiemann K, Krech T, Wellmann A, Schaaf C, Länger F, et al. Noninferiority of Artificial Intelligence-Assisted Analysis of Ki-67 and Estrogen/Progesterone Receptor in Breast Cancer Routine Diagnostics. Mod Pathol 2023;36:100033. doi: 10.1016/j.modpat.2022.100033
38. Bodén ACS, Molin J, Garvin S, West RA, Lundström C, Treanor D. The human-in-the-loop: an evaluation of pathologists' interaction with artificial intelligence in clinical practice. Histopathology 2021;79:210-8. doi: 10.1111/his.14356.