Original article

Prognostic significance of the Ki67 proliferation index in patients with breast cancer using 14% as the cut-off value

Robert Zorica [1], Damir Danolić [2], Marija Banović [3], Lucija Šušnjar [2], Luka Marcelić [2], Domagoj Dobranić [2], Šimun Puljiz [4], Mario Begović [5], Tomislav Bečejac [6], Mario Puljiz [2]

1 Oncology Department, Yeovil District Hospital, Higher Kingston, Yeovil, Somerset, United Kingdom
2 Department of Gynecologic Oncology, University Hospital Centre Sestre Milosrdnice-University Hospital for Tumors, Zagreb, Croatia
3 Poliklinika Leptir, Zagreb, Croatia
4 School of Medicine, University of Mostar, Mostar, Bosnia and Herzegovina
5 National Memorial Hospital dr. Juraj Njavro, Vukovar, Croatia
6 Clinical Department of Thoracic Surgery, University Hospital Centre Zagreb, Zagreb, Croatia

*Corresponding author: Domagoj Dobranić, dobranicdomagoj7@gmail.com

Abstract

Aims and background: Reference interval for Ki67 proliferation index, in breast cancer patients is still not determined. Therefore, the aim of this study was to evaluate prognostic value of Ki67 proliferation index in patients with invasive ductal carcinoma of the breast using 14% as the cut-off value.

Methods: Correlation of the patient's age, tumor size, tumor grade, nuclear grade, vascular invasion, axillary node status, estrogen receptor (ER)/ progesterone receptor (PR)/ human epidermal growth factor receptor 2 (HER2) status with Ki67 proliferation index was evaluated. We also analyzed survival outcomes according to Ki67 proliferative index.

Results: Ki67 proliferation index ≤14% was significantly associated with patient age >50 years (p<0.001), T1 (p<0.001) and T2 (p<0.002) tumors,negative axillary lymph nodes status (p<0.002), steroid hormone receptor positive tumors (p<0.001), absent vascular invasion (p<0.001), HER2 negative tumors (p<0.001), nuclear grade I (p<0.001) and nuclear grade II (p<0.015) tumors. This study found no correlation between the Ki67 proliferation index ≤14% and the tumor histological grade (p=0.251). Ki67 proliferation index>14% was significantly associated only with T1 tumors (p=0.036). Ki67 proliferation index did not have significant impact on survival(p=0.958).

Conclusion: 14% cut-off value for Ki67 proliferation index is not predicting survival in patients with invasive ductal carcinoma of the breast.

Zorica R, Danolić D, Banović M, Šušnjar L, Marcelić L, Dobranić D, Puljiz Š, Begović M, Bečejac T, Puljiz M. Prognostic significance of the Ki67 proliferation index in patients with breast cancer using 14% as the cut-off value. SEEMEDJ 2025; 9(S2); 30-9

Received: Sep 16, 2025; revised version accepted: Sep 23, 2025; published: Dec 29, 2025

KEYWORDS: breast cancer, Ki67 proliferation index, survival

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer and the leading cause of cancer mortality in women worldwide. The crude incidence of BC in Croatia is 134.7/100.000 women per year and it is responsible for 34.7 out of 100.000 deaths per women annually (1). Studies regarding BC have shown the presence of multiple prognostic factors utilized in clinical decision making (tumor size, histological grade, nodal status, lymphovascular invasion, hormone receptor status, HER-2 status and age) (2). In the last few decades, proliferative markers have been widely evaluated as prognostic factors for BC patients. Several papers evaluating one or more markers have been published, often with contradictory results (2). The use of Ki67 as a prognostic marker has been widely investigated. Nuclear Ki67 immuno-staining is one of the most commonly used proliferation marker in clinical practice (3). Mitotic index is considered to be a reliable prognostic factor, but evaluation of Ki67 immunohistochemistry has become more popular in evaluating proliferation (4). Ki67 is the proliferative marker strongly linked to cell cycle control. It was originally indentified by Gerdes and colleagues in the early 1980s (5). This protein is expressed in all proliferative cells, malignant and normal cells, and it is present during all active phases of the cell cycle expect G0 phase (3,6). With a significant relation between proliferative activity and tumor aggressiveness, Ki67 proliferation index is used as an established prognostic factor for various tumor types (6). Many studies have investigated the possible use of Ki67 as a prognostic marker for BC. The Colozza et al analyzed the prognostic and predictive role of Ki67 and other proliferative markers in thorough review of 132 articles including 159.516 BC patients (2). The authors appropriately point out that all studies concerning these markers were rated as level III or IV evidence, and demonstrate the difficulty in interpreting the literature due to lack of standardization of assay reagents, procedures, and scoring (2,7,8). The most recent meta-analysis was done by Stuart-Harris et al and it was based on 43 studies involving 15.790 patients. There searchers did not recommend adding Ki67 to the commonly used prognostic indices (9). Some studies have used 10% as the cut-off (arbitrary value) (10,11,12), whereas others have chosen mean, median, the optimal cut-off value or arbitrary values (Ki67 cut-off range 5-30%) (13-17), and these differences might be responsible for the difficulty in determining a standard threshold in daily practice (18). Healthy breast tissue can express low levels of Ki67 (<3%) (7).

In order to study the association of Ki67 proliferation index with other prognostic and predictive factors of BC and with five year survival, we analyzed tissue samples from 177 patients surgically treated for invasive ductal carcinoma. Due to the fact that there is no standard Ki67 cut-off point, the aim of this study was to evaluate prognostic value of Ki67 proliferation index in invasive ductal carcinoma using 14% as the cut-off value.

Patients/Materials and methods

The current study utilized tissue from 177 patients who have undergone surgery for invasive ductal carcinoma of the breast at the University Hospital for Tumors, Zagreb, Croatia between September, 2002 and September, 2003. This time frame was chosen to assure a minimum of five years of follow-up data. The median age of patients was 59 years (range, 29-91). The following clinicopathological characteristics were analyzed: age, tumor size, tumor grade, nuclear grade, vascular invasion, axillary node status, estrogen receptor (ER)/ progesterone receptor (PR)/ human epidermal growth factor receptor 2 (HER2) status, Ki67 proliferation index and five year survival status. The patients were divided into two age groups, ≤50years and >50 years. Tumor size was defined as the largest diameter of the largest invasive tumor focus and it was classified as either ≤2 cm (T1), >2-5 cm (T2) or >5cm (T3). Formalin-fixed and paraffin-embedded tissue specimens were evaluated. A specialist pathologist assessed the histo¬pathological features of all cases. Tissue

sections of 3-5 μm were prepared from a representative part of each tumor sample to score several markers. Tumors were graded by the method of Bloom and Richardson (1957), with modifications as suggested by Elston and Ellis (1991).Vascular invasion was reported as present or absent. No attempt was made to distinguish between lymphatic and small blood vessel invasion. Vascular invasion was defined as neoplastic cells identified within an endothelial lined space. Axillary clearance was performed on all patients. Data obtained for each patient included presence and number of lymph node metastases. Axillary node status was reported as negative (pN0), 1-3positive lymph nodes (pN1) and 4 or more positive lymph nodes (pN2). ER, PR, HER2 status and Ki67proliferation index were determined by immunohistochemical methods on a selected tumor block. The routinely fixed, paraffin-embedded tissue sections were pretreated by boiling according to the DakoChemMate detection systems protocol. The antibodies used for steroid receptor assessment were mouse monoclonal anti-human ER, clone 1D5 (H 7098,Dako, Glostrup, Denmark) and mouse monoclonal anti-human PR, clone PgR 636 (M3569, Dako, Glostrup, Denmark). Cases were considered positive for ER and PR according to standardized guidelines using a cut-off of ≥10% stained tumor nuclei. Immunohistochemistry (IHC) using HercepTestTM (anti-Her2 polyclonal antibody ; Dako K 5204) on a Techmate automated staining system (Dako, Glostrup, Denmark) was used for HER2 assessment. All cases were graded individually with HER2 score 0, 1+, 2+ or 3+. IHC results showing a 2+ HER2 level were further tested by chromogenic in situ hybridization (CISH). The patients showing a 3+ HER2 level by IHC and/or HER2/neu gene amplification by CISH were described as being HER2 positive. Ki67 status was evaluated using monoclonal mouse anti-human Ki67, clone MIB-1 (M 7240,Dako, Glostrup, Denmark) antibody. Ki67 proliferation index was determined in the area with highest Ki67 nuclear labeling. A total of 1.000 proliferating and nonproliferating cells were counted, and the percentage of proliferating cells was calculated and reported as percent proliferating cells. Although there is no universal cut-off value for Ki67 proliferation index, in this study Ki67 proliferation index greater than 14% was classified as high. The Human Ethics Committee of the institution approved this study.

Comparisons between groups were evaluated with the chi-squared test or Fisher's exact test. Patient survival curves were drawn using the Kaplan-Meier method and analyzed by the log-rank test. The hazard ratios and corresponding 95% confidence intervals (CIs) were calculated with Cox's proportional hazards model. Univariate and multivariate Cox's proportional hazards models were used to explore the associations of variable with five year survival. For all tests, differences at $p<0.05$ were considered statistically significant.

Results

Data were analyzed using statistical software SPSS 15. Ki67 expression was low (≤14%) in 156 samples, and high (>14%) in 21 samples. The associations between Ki67 proliferation index and clinicopathological variables are presented in Table 1 and Table 2.

Ki67 proliferation index ≤14% was significantly associated with patient age >50 years ($p<0.001$), T1 ($p<0.001$) and T2 ($p<0.002$) tumors, negative axillary lymph nodes status ($p<0.002$), steroid hormone receptor positive tumors ($p<0.001$), absent vascular invasion ($p<0.001$), HER2 negative tumors ($p<0.001$), nuclear grade I ($p<0.001$) and nuclear grade II ($p<0.015$) tumors. This study found no correlation between the Ki67 proliferation index ≤14% and the tumor histological grade ($p=0.251$). Ki67 proliferation index >14% was significantly associated with T1 tumors ($p=0.036$). Patient's age at diagnosis ($p=0.439$), axillary lymph nodes status ($p=0.449$), steroid hormone receptor status ($p=0.754$), vascular invasion ($p=0.209$), HER2 status ($p=0.757$),nuclear grade ($p=0.273$, $p=0.246$) and histological grade ($p=0.184$, $p=0.194$) did not have significant relationship with Ki67 proliferation index >14%.

Table 1. Clinical and pathological characteristics of patients with low Ki67 expression (≤14%)

Characteristics of patients	Number of patients N(%)	p value
Age		
≤50	38 (24)	
>50	118(76)	p<0.001
Tumor size		
T1	106 (68)	p<0.001
T2	41 (26)	p<0.002
T3	9 (6)	
Axillary lymph node status		
negative	84 (54)	p<0.002
1-3 positive lymph nodes	36 (23)	
≥4 positive lymph nodes	36 (23)	
Steroid receptor status		
negative	46 (29)	
positive	110 (71)	p<0.001
Vascular invasion		
absent	140 (90)	p<0.001
present	16 (10)	
*HER2 status		
negative	113 (73)	p<0.001
positive	43 (27)	
Nuclear grade		
I	86 (55)	p<0.001
II	56 (36)	p<0.015
III	14 (9)	
Histological grade		
I	58 (37)	p=0.251
II	58 (37)	
III	40 (26)	

*HER2, Human epidermal growth factor receptor 2

After five years, 136 patients were available for the follow-up examination. The mean survival rate of patients with Ki67 proliferation index ≤14% was 50.3±1.5 months (HR 0.262, 95% CI42.27-53.34) and the mean survival rate of patients with Ki67 proliferation index>14% was 51.4±3.8 months (HR 0.272, 95% CI 43.97-58.88) . The median overall survival (OS) of patients with Ki67 proliferation index ≤14% was 60 months and the median OS of patients with Ki67 proliferation index >14% was 50 months. The 5-year cumulative survival rate among patients with Ki67 proliferation index ≤14%was 76.9% and with Ki67 proliferation index>14% was 76.2%. The difference in survival was not statistically significant (Mantel-Cox p=0.958).

Table 2. Clinical and pathological characteristics of patients with high Ki67 expression (>14%)

Characteristics of patients	Number of patients N(%)	p value
Age		
≤50	9 (43)	p=0.439
>50	12 (57)	
Tumor size		
T1	13 (62)	p=0.036
T2	7 (33)	
T3	1 (5)	
Axillary lymph node status		
negative	12 (57)	p=0.449
1-3 positive lymph nodes	6 (29)	
≥4 positive lymph nodes	3(14)	
Steroid receptor status		
negative	9 (43)	
positive	12 (57)	p=0.754
Vascular invasion		
absent	15 (71)	p=0.209
present	6 (29)	
*HER2 status		
negative	12 (57)	
positive	9 (43)	p=0.757
Nuclear grade		
I	4 (19)	p=0.273
II	12 (57)	
III	5 (24)	p=0.246
Histological grade		
I	2 (9)	
II	9 (43)	p=0.184
III	10 (48)	p=0.194

*HER2, Human epidermal growth factor receptor 2

Discussion

The number of tumor markers in oncology that have emerged as clinically useful is quite small. There are many studies which have investigated Ki67 expression and clinical outcome in a variety of malignancies. Studies of its use as a marker of cell proliferation have shown that the percentage of Ki67 positive cells can be used to stratify patients into good and poor prognostic groups (19). It is clear that Ki67 expression is of prognostic value for many types of malignant tumor (lung cancer, soft tissue tumors, astrocytoma) (20). Ki67 has been assayed in many studies as a prognostic marker in BC (2,9,18). The most studies show a strong, statistically significant correlation with clinical

outcomes (20). Jacquemier et al studied 162 patients with breast cancer all treated with the same standard adjuvant chemotherapy. Ki67 expression was a significant indicator of disease-free survival, both on univariate and multivariate analysis (21). High level of Ki67 expression is often associated with an early recurrence of BC after mastectomy (22). The current guidelines of the American Society of Clinical Oncology do not include Ki67 in the list of required routine biological markers (7,8). Ki67 is not standard prognostic factor in BC patients, because of a lack of perspicuity regarding how Ki67 levels should influence clinical decisions (23).

Antibody MIB-1 is the most widely used to recognize Ki67 in conventional fixed tissue sections (18). Scoring system is based on the percentage of tumor cells stained by the antibody. There is no standard cut-off value for Ki67 proliferation index. The most common threshold definitions are mean or median values, the best cut-off value or an established arbitrary value (range 3.5-40%) (7,18,24). Each laboratory scored Ki67 using its own method, without standardizing scoring methodology (19,25). In several reports 10% cut-off values were used. Seshardi et al studied 707 patients with BC, using 10% cut-off value for Ki67 proliferation index. This study confirmed that tumor-cell proliferation fraction, as measured by MIB-1 count, is the most useful parameter of BC prognosis, with the exception of ER, tumor size and the number of axillary nodes involved (26). Few studies showed no prognostic value for Ki67 proliferation index, using 10% cut-off value (27,28,29). The meta-analysis done by de Azambuja et al confirmed a significant association between high Ki67 levels and the risk of recurrence and death in patients with early BC. However, the analysis could not confirm that Ki67 is an independent prognostic factor (8,18). In this meta-analysis, various studies used different cut-off values, range 3.5-34%. Although there is no universal cut-off value for Ki67 proliferation index, Cheang et al. showed that, using the cases which were subtyped by gene expression profile, the best Ki67 proliferation index cut-off value to distinguish luminal B from luminal A BC was 14% (8,23,30). Luminal B tumors have poorer outcomes than luminal A tumors (23). Veronese et al studied 127 patients with BC using 14% median cut-off value for Ki67 proliferation index and showed that detection of proliferative activity on paraffin sections with MIB-1 monoclonal antibody represents a valuable tool to obtain kinetic data on "routine" histological samples and, above all, give prognostic evaluations on the clinical outcome of BC patients (17). In this context, we analyzed a series of breast cancer for which the follow-up was sufficient for prognostic evaluation. According to Fitzgibbons et al, Ki67 reference intervals and performance characteristics must be determined by each individual laboratory (19). We arbitrary used 14% cut off value for Ki67 proliferation index. Our study comparing Ki67 proliferation index and clinicopathological features, found a good correlation between these parameters. Low Ki67 expression was significantly associated with favorable prognostic variables. The comparison of Ki67 proliferation index with the important prognostic variable lymph-node staging revealed major association. Low Ki67 expression was significantly associated with negative axillary lymph nodes. Similarly, low Ki67 expression was significantly correlated with patient age >50 years, tumor size less than five centimeters, steroid hormone receptor positive tumors, absent vascular invasion, HER2 negative tumors, nuclear grade I and nuclear grade II tumors. These finding confirm results of other studies (7,31,32) and these data indirectly suggest that patients with a higher Ki67 expression have a worse prognosis. In our study, Ki67 proliferation index above 14% did not reveal any major association with clinicopathological features. We also showed that Ki67 proliferation index did not have significant impact on survival. These results are similar with the results of Ferguson et al (31).

Conclusion

Reference intervals for Ki67 proliferation index are still not determined. There is no agreement on the methodology to be used for Ki67 proliferation index evaluation. Our results lead us to conclusion that the 14% cut-off value for Ki67

proliferation index is not good enough to stratify patients into good and poor prognostic groups.

Acknowledgement. No acknowledgment.

Disclosure

Funding. No specific funding was received for this study.
Competing interests. None to declare.

References

1. Šupe Parun A, Čukelj P, Tešić V, Jelavić M, Brkljačić B. Results of the National Breast Cancer Screening Program in Croatia (2006-2016). Croat Med J. 2022 Aug 31;63(4):326-334. doi: 10.3325/cmj.2022.63.326.

2. Colozza M, Azambuja E, Cardoso F, Sotiriou C, Larsimont D, Piccart MJ. Proliferative markers as prognostic and predictive tools in early breast cancer: where are we now? Ann Oncol. 2005;16(11):1723-39.

3. Reyal F, Hajage D, Savignoni A, Feron JG, Bollet MA, Kirova Y et al. Long-term prognostic performance of Ki67 rate in early stage, pT1-pT2, pN0, invasive breast carcinoma. PLoS One. 2013;8(3):e55901.

4. Jalava P, Kuopio T, Juntti-Patinen L, Kotkansalo T, Kronqvist P, Collan Y. Ki67 immunohistochemistry: a valuable marker in prognostication but with a risk of misclassification: proliferation subgroups formed based on Ki67 immunoreactivity and standardized mitotic index. Histopathology. 2006;48(6):674-82. DOI: 10.1111/j.1365-2559.2006.02402.x

5. Gerdes J, Schwab U, Lemke H,Stein H. Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. Int J Cancer. 1983; 31: 13-20.

6. Kobayashi T, Iwaya K, Moriya T, Yamasaki T, Tsuda H, Yamamoto J et al. A simple immunohistochemical panel comprising 2 conventional markers, Ki67 and p53, is a powerful tool for predicting patient outcome in luminal-type breast cancer. BMC ClinPathol. 2013; 6;13:5. doi: 10.1186/1472-6890-13-5.

7. Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA. Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol. 2010;11(2):174-83. doi: 10.1016/S1470-2045(09)70262-1

8. Henry NL, Somerfield MR, Dayao Z, Elias A, Kalinsky K, McShane LM, et al. Biomarkers for Systemic therapy in metastatic breast Cancer: ASCO Guideline Update. Journal of Clinical Oncology. 2022 Sep 20;40(27):3205–21. Available from: https://doi.org/10.1200/jco.22.01063

9.Stuart-Harris R, Caldas C, Pinder SE, Pharoah P. Proliferation markers and survival in early breast cancer: a systematic review and meta-analysis of 85 studies in 32,825 patients. Breast. 2008; 17: 323-34. doi: 10.1016/j.breast.2008.02.002

10. Hlupic L, Jakic-Razumovic J, Bozikov J, Coric M, Belev B, Vrbanec D. Prognostic value of different factors in breast carcinoma. Tumori.2004;90:112–119.

11. Robertson S, Stålhammar G, Darai-Ramqvist E, Rantalainen M, Tobin NP, Bergh J, et al. Prognostic value of Ki67 analysed by cytology or histology in primary breast cancer. Journal of Clinical Pathology. 2018 Mar 27;71(9):787–94. Available from: https://doi.org/10.1136/jclinpath-2017-204976

12. Fresno M, Molina R, Perez del Rio MJ, Alvarez S, Diaz-Iglesias JM, Garcia I et al. p53 expression is of independent predictive value in lymph node-negative breast carcinoma. Eur J Cancer. 1997; 33: 1268–1274. doi: 10.1016/S0959-8049(97)00096-8

13. Arima N, Nishimura R, Osako T, Okumura Y, Nakano M, Fujisue M, et al. Ki-67 index value and progesterone receptor status can predict prognosis and suitable treatment in node-negative breast cancer patients with estrogen receptor-positive and HER2-negative tumors. Oncology Letters. . 2018 Oct 29; Available from: https://doi.org/10.3892/ol.2018.9633

14. Gonzalez MA, Pinder SE, CallagyG, Vowler SL, Morris LS, Bird K,Bell JA et al. Mini chromosome maintenance protein 2 is a strong independent prognostic marker in breast cancer. J ClinOncol. 2003; 21: 4306–4313. DOI: 10.1200/JCO.2003.04.121

15. Goodson WH, Moore DH III, Ljung BM II, Chew K, Mayall B, Smith HS et al.The prognostic value of proliferation indices: a study with in vivo bromodeoxyuridine and Ki-67. Breast Cancer Res Treat.2000;59: 113-123.

16. Davey MG, Hynes SO, Kerin MJ, Miller N, Lowery A. KI-67 as a prognostic biomarker in invasive breast cancer. Cancers. 2021 Sep 3;13(17):4455. Available from: https://doi.org/10.3390/cancers13174455

17. De Gregorio A, Friedl T, Hering E, Widschwendter P, 8 N, Bekes I, et al. Ki67 as Proliferative Marker in Patients with Early Breast Cancer and Its Association with Clinicopathological Factors. Oncology. 2021 Jan 1;99(12):780–9. Available from: https://doi.org/10.1159/000517490

18. de Azambuja E, Cardoso F, de Castro G Jr, Colozza M, Mano MS, Durbecq V et al. Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. Br J Cancer. 2007;96(10):1504-13. doi: 10.1038/sj.bjc.6603756

19. Roncati L, Barbolini G, Piacentini F, Piscioli F, Pusiol T, Maiorana A. Prognostic Factors for Breast Cancer: an Immunomorphological Update. Pathology & Oncology Research. 2015 Nov 20;22(3):449–52. Available from: https://doi.org/10.1007/s12253-015-0024-7

20. Zhu XL, Chen L, Huang B, Wang Y, Ji L, Wu J, et al. The prognostic and predictive potential of Ki-67 in triple-negative breast cancer. Scientific Reports. 2020 Jan 14;10(1). Available from: https://doi.org/10.1038/s41598-019-57094-3

21. Jacquemier JD, Penault-Llorca FM, Bertucci F, Sun ZZ, Houvenaeghel GF, Geneix JA, et al. Angiogenesis as a prognostic marker in breast carcinoma with conventional adjuvant chemotherapy: a multiparametric and immunohistochemical analysis. J. Pathol. 1998; 184; 130-135. doi: 10.1078/0344-0338-00177

22. Rothschild H, Clelland E, Mujir F, Record H, Wong J, Esserman LJ, et al. Predictors of early versus late recurrence in invasive lobular carcinoma of the breast: Impact of local and systemic therapy. Annals of Surgical Oncology. 2023 Jul 18;30(10):5999–6006. Available from: https://doi.org/10.1245/s10434-023-13881-x

23. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst 2009;101(10):736–750. doi: 10.1093/jnci/djp082

24. MacGrogan G, Mauriac L, Durand M, Bonichon F, Trojani M, de Mascarel I et al. Primary chemotherapy in breast invasive carcinoma: predictive value of the immunohistochemical detection of hormonal receptors, p53, c-erbB-2, MiB1, pS2 and GST pi. Br J Cancer. 1996; 74: 1458–65.

25.Caly M, Genin P, Ghuzlan AA, Elie C, Freneaux P, Klijanienko J et al. Analysis of correlation between mitotic index, MIB1 score and S-phase fraction as proliferation markers in invasive breast carcinoma. Methodological aspects and prognostic value in a series of 257 cases. Anticancer Res. 2004; 24: 3283–3288.

26. Bertheau P, Lehmann-Che J, Varna M, Dumay A, Poirot B, Porcher R, et al. p53 in breast cancer subtypes and new insights into response to chemotherapy. The Breast. 2013 Aug 1;22:S27–9. Available from: https://doi.org/10.1016/j.breast.2013.07.005

27. Kono M, Fujii T, Matsuda N, Harano K, Chen H, Wathoo C, et al. Somatic mutations, clinicopathologic characteristics, and survival in patients with untreated breast cancer with bone-only and non-bone sites of first metastasis. Journal of Cancer. 2018 Jan 1;9(19):3640–6. Available from: https://doi.org/10.7150/jca.26825

28. Bukholm IR, Bukholm G, Holm R, Nesland JM. Association between histology grade, expression of HsMCM2, and cyclin A in human invasive breast carcinomas.J ClinPathol.2003;56(5):368-73.

29. Kröger N, Milde-Langosch K, Riethdorf S, Schmoor C, Schumacher M, Zander AR et al. Prognostic and predictive effects of immunohistochemical factors in high-risk primary breast cancer patients.Clin Cancer Res. 2006;12(1):159-68. doi: 10.1158/1078-0432.CCR-05-1340

30. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ; Panel members. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011.

Ann Oncol. 2011;22(8):1736-47. doi: 10.1093/annonc/mdr304

31. Ferguson NL, Bell J, Heidel R, Lee S, Vanmeter S, Duncan L et al. Prognostic value of breast cancer subtypes, Ki-67 proliferation index, age, and pathologic tumor characteristics on breast cancer survival in Caucasian women.Breast J. 2013;19(1):22-30. doi: 10.1111/tbj.12059

32. Ermiah E, Buhmeida A, Abdalla F, Khaled BR, Salem N, Pyrhönen S et al Prognostic value of proliferation markers: immunohistochemical ki-67 expression and cytometric s-phase fraction of women with breast cancer in libya.J Cancer. 2012;3:421-31. doi: 10.7150/jca.4944.

Author contribution.

Acquisition of data: RZ, DDan, MBan, LŠ, LM, DDob, ŠP, MBeg, TB, MP
Administrative, technical, or logistic support: RZ, DDan, MBan, LŠ, LM, DDob, ŠP, MBeg, TB, MP
Analysis and interpretation of the data: RZ, DDan, MBan, LŠ, LM, DDob, ŠP, MBeg, TB, MP
Conception and design: RZ, DDan, MBan, LŠ, LM, DDob, ŠP, MBeg, TB, MP
Critical revision of the article for important intellectual content: RZ, DDan, MBan, LŠ, LM, DDob, ŠP, MBeg, TB, MP
Drafting of the article: RZ, DDan, MBan, LŠ, LM, DDob, ŠP, MBeg, TB, MP
Final approval of the article: RZ, DDan, MBan, LŠ, LM, DDob, ŠP, MBeg, TB, MP
Guarantor of the study: RZ, DDan, MBan, LŠ, LM, DDob, ŠP, MBeg, TB, MP
Provision of study materials or patients: RZ, DDan, MBan, LŠ, LM, DDob, ŠP, MBeg, TB, MP

Prognostičko značenje granične vrijednosti od 14% proliferativnog indeksa Ki67 kod pacijentica s karcinomom dojke

Sažetak

Ciljevi: Referentni interval za Ki67 proliferacijski indeks još uvijek nije točno određen. Zbog toga je cilj ovog istraživanja bio procijeniti prognostičku vrijednost Ki67 proliferacijskog indeksa u bolesnika s invazivnim duktalnim karcinomom dojke, koristeći 14% kao cut-off vrijednost.

Metode: Procjenjivali smo poveznicu između pacijentove dobi, veličine tumora, gradusa tumora, gradusa jezgre, vaskularne invazije, statusa aksilarnih limfnih čvorova, statusa estrogenskih receptora (ER)/progesteronskih receptora (PR)/receptora ljudskog epidermalnog faktora rasta 2 (HER2) s Ki67 proliferacijskim indeksom. Također smo analizirali preživljenje povezano s Ki67 proliferacijskim indeksom.

Rezultati: Ki67 proliferacijski indeks ≤ 14% bio je značajno povezan s dobi pacijenta >50 godina ($p < 0,001$), T1 ($p < 0,001$) i T2 ($p < 0,002$) tumorima, negativnim aksilarnim limfnim čvorovima ($p < 0,002$), s tumorima s pozitivnim receptorima za steroidne hormone ($p < 0,001$), s odsutnom vaskularnom invazijom ($p < 0,001$), HER 2 negativnim tumorima ($p < 0,001$), nuklearnim gradusom I ($p < 0,001$) i nuklearnim gradusom II ($p < 0,015$). U ovom istraživanju nismo pronašli poveznicu između Ki67 proliferacijskog indeksa ≤ 14% i tumorohistološkog gradusa ($p= 0,251$). Ki67 proliferacijski factor > 14% bio je značajno povezan samo s T1 tumorima ($p = 0,036$). Ki67 proliferacijski factor nije imao veliki utjecaj na preživljenje ($p= 0,958$).

Zaključak: 14% cut-off vrijednost Ki67 proliferacijskog indeksa nije prediktivni faktor preživljenja u pacijenata s invazivnim duktalnim karcinomom dojke.

Ključne riječi: karcinom dojke, proliferativni indeks Ki67, preživljenje