BIOMEDICINSKA ISTRAŽIVANJA
2023;14(1):21–28

UDK: 616-073:618.19-006
DOI: 10.59137/BII202301299M

Original article

Could Apparent Diffusion coefficient (ADC) be used as an imaging marker for proliferative activity in breast carcinoma?

Jelena Marić[1], Jasmina Boban[2,3], Tatjana Ivković-Kapicl[2,3], Dragana Djilas[2], Viktorija Vučaj-Ćirilović [2,3], Dragana Bogdanović-Stojanović[4]

[1]General hospital "Sveti Vračevi", Bijeljina, Republic of Srpska, Bosnia and Herzegovina

[2]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

[3]Oncology Institute of Vojvodina, Center for Diagnostic Imaging, Sremska Kamenica, Serbia

[4]Health Medic Clinic, Novi Sad, Serbia

Primljen – Received: 24/11/2021
Prihvaćen – Accepted: 16/01/2023

Corresponding author:
Jelena Marić, MD
Srpske vojske 53, 76300 Bijeljina
maric.jelena@live.com

Summary

Introduction. Multiparametric magnetic resonance mammography (mMRM) has an important role in detection, evaluation and follow-up of breast lesions. The aim of this study was to explore whether imaging parameters, in particular ADC, can be used as a biomarker of cell proliferation in breast cancer.

Methods. This cohort-study included 67 lesions in 50 female patients who underwent mMRM on a 3T scanner. Percutaneous biopsies and surgical excisions were performed after imaging in period up to 3 weeks. The Ki67 index was assessed microscopically. Seven Ki67 categories were defined: 0–5%, 10–20%, 20–40%, 40–50%, 50–80% and over 80%. Methods of descriptive statistics were used; correlations were determined using Pearson's correlation test. ROC curve was constructed and analyzed for determination of "cut-off" values for diagnostic potential. Statistical significance was set at $p < 0.05$.

Results. Different subtypes of breast carcinomas were involved: ductal carcinoma (59.9%), lobular carcinoma (17.9%), metastatic carcinoma (10.5%), ductal carcinoma in situ (9%), and tubular carcinoma (3%). It was not possible to determine whether there was significant difference in values of ADC for histological subtypes of breast carcinoma because of small number of samples in some groups. The cut off value of ADC for breast carcinoma was 0.792 (sensitivity 98.6%, specificity 65.7%). There was no significant difference in values of ADC for categories of Ki67. There was no significant correlation between ADC mean and Ki67 for all histological subtypes of breast carcinomas ($r = 0.156$, $p = 0.243$).

Conclusion. ADC cannot be used as a reliable imaging marker for proliferative activity in breast cancer.

Key words: breast cancer, ADC, DWI, Ki67

Introduction

Magnetic resonance mammography (MRM) is a novel diagnostic and screening modality based on morphology and kinetic features of the breast lesion [1]. It has an important role in follow-up, as well as in detection and evaluation of breast lesions. Diffusion-weighted

imaging (DWI) is a MRI technique based on Brown motion of water molecules reflecting tissue cellularity and integrity of cell membranes [2]. This diffusion of water in tissue can be quantified by apparent diffusion coefficient (ADC) [3, 4]. ADC can be divided in 3 sub-parameters: ADC mean, ADC minimum and ADC maximum [4]. Mean ADC is most frequently used in clinical and experimental investigations.

Usually, benign breast lesions show a decrease in DWI signal and higher apparent diffusion coefficient (ADC) values compared to breast cancers which have lower values [5–7]. This means that ADC values can discriminate malignant and benign breast lesions. Also, it has been shown that ADC correlated inversely with cell count of investigated lesions [8]. Association with proliferation, e.g. Ki67 receptor are very important because the fact that it predicts behavior of several tumors [4, 8]. According to the literature, breast carcinomas with high expression of Ki67 had lower ADC values in comparison to tumors with low Ki67 expression [8].

Utility ADC as a biomarker of tumor proliferation is controversial due to several issues. Firstly, wide spectrum of correlations coefficient between ADC and Ki67 was reported [9–13]. Secondly, most reports about association between ADC and Ki67 investigated small samples ranging from 11 to 50 patients/tumors [9, 12, 13]. There only few studies investigated collectives over 100 patients [10, 11, 14].

Some studies showed that ADC_{min} had stronger correlations with Ki67 [15] and can better reflect proliferation potential of malignant lesions.

The aim of this study was to explore associations between the mean ADC values and Ki67 in different types of breast tumors, and whether imaging parameters, in particular ADC, can be used as a biomarker of cell proliferation in breast cancer.

Methods

This randomized retrospective cohort-study included 67 lesions in 50 females who underwent MRM in period from January 2013 to January 2017. The study was approved by ethical committee. Percutaneous biopsies and surgical excisions were performed after imaging in period up to 3 weeks. The including criteria were age over 18 and female gender. The excluding criteria were absence of subsequent histological finding and contraindications for MRM.

All patients signed a fully informed written consent for taking part in the study.

Magnetic Resonance Mammography (MRM)

MRM in all patients was performed on 3T scanner (Siemens Trio Tim, Erlangen, Germany), using a dedicated 36-channel coil, in the prone position. DWI was integrated in conventional protocol that consisted of non-fat-suppressed T2-weigthed turbo spin echo transversal, non-fat-suppressed and fat suppressed T1-weighetd transversal sequences and STIR sagittal sequence, followed by dynamic contrast study (fat-suppressed 3D T1-weighted Fast Low Angle Shot (FLASH) transversal tomograms). Gadolinium contrast agent was injected in the dose of 0.1mmol/kg, at the rate 2.5 ml/s, followed by 25 ml saline injection. Parameters for dynamic contrast study were: time of repetition/ time of echo (TR/TE) 4.2 ms/1.6 ms, flip angle (FA) 15°, field of view (FOV) 340x340 mm, matrix size 512x410, slice thickness 2mm, time of acquisition 86s. Diffusion-weighted imaging was performed prior to contrast study, using echo-planar imaging (EPI) sequence in the axial plane, with b values of 750, 1000 and 1500 s/mm2. Parameters for this sequence were: TR/TE 8400 ms/98 ms, FOV 340x170 mm, matrix size 192x96, slice thickness 4 mm. Apparent diffusion coefficient (ADC) maps were created during the post-processing by using available software provided by the manufacturer (Syngo, Siemens Healthcare). The region of

interest (ROI) was selected manually including only solid parts of tumor.

Percutaneous biopsies or surgical excision obtained tissues samples that underwent histological examination. Core biopsy was performed using Bard Magnum biopsy instrument and needles of 14 G. Three to twelve tissue samples were taken and put into formalin. Histological report contained histological finding according to WHO Classification of the breast tumors [16]. The Ki67 index was assessed microscopically. In the „hot spot" within the tumor (area with highest number of positive nuclei) scoring was performed. The Ki67 index was expressed as the percentage of Ki-67 positive malignant cells in 1000 malignant cells. We defined seven Ki67 categories: 0–5%, 10–20%, 20–40%, 40–50%, 50–80% and over 80%.

Statistical analysis was performed using SPSS ver. 19.0 (IBM, Chicago, IL, USA). Methods of descriptive statistics were used (mean, standard deviation, minimum, maximum). Differences between variables were tested using chi-square test. Correlations were determined using Pearson's correlation test. For determination of cut off value for diagnostic and prognostic potential of variable, Receiver Operating Characteristic (ROC) curves were constructed. Statistical significance was set at value $p < 0.05$.

Results

The study included 50 females with 67 detected breast lesions. Histologically, there were different subtypes of breast carcinomas involved. Most frequently, ductal carcinoma (59.9%), followed by lobular carcinoma (17.9%), metastatic carcinoma (10.5%), ductal carcinoma in situ (9%), and tubular carcinoma (3%) were reported. Mean ADC values and distribution of pathohistological subtypes of breast carcinoma are summarized in table 1. Since in category tubular carcinoma were only two cases, it was not possible to determine whether there was significant difference in values of ADC in different histological subtypes of breast carcinoma.

Mean values and standard deviations of ADC and defined groups of Ki67 are summarized in table 2 and shown in figure 1.

Table 1. Mean ADC values and distribution of histological subtypes of breast carcinoma

Histological subtype of breast carcinoma	N (frequency)	ADC (x 10^{-3} mm2/s) (3rd–1st quartile)	max	min
Ductal invasive carcinoma	40 (59.9%)	0.68 (0.87–0.52)	1	0.06
Lobular carcinoma	12 (17.9%)	0.72 (0.82–0.55)	0.98	0.27
DCIS	6 (9%)	0.78 (0.88–0.52)	0.89	0.63
Metaplastic carcinoma	7 (10.5%)	0.68 (0.85–0.50)	0.95	0.22
Tubular carcinoma	2 (3%)	0.78 (0.81–0.75)	0.83	0.73

Table 2. Mean ADC values and standard deviations distribution of defined groups of KI 67

ADC	Ki67						
	0–5%	5–10%	10–20%	20–40%	40–50%	50–80%	> 80%
Mean value	0.7145	0.5571	0.5839	0.584	0.604	0.732	0.728
ST deviation	0.19811	0.34368	0.19626	0.25628	0.14188	0.34518	0.15503

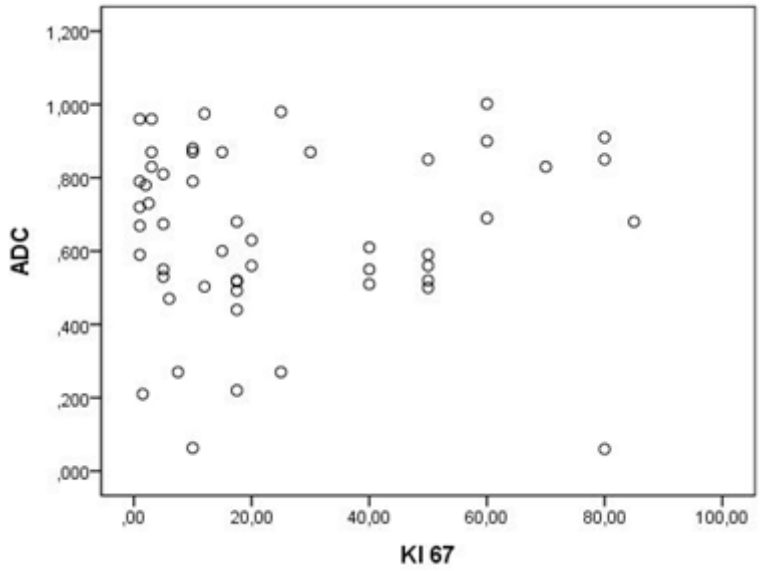

Figure 1. Values of ADC for defined categories of Ki67

There was no significant difference in values of ADC and Ki67.

The pooled correlation coefficient between ADC mean and Ki67 for all histological subtypes of breast carcinomas was r = 0.156 (p = 0.243). There was no significant correlation between parameters. Pearson's correlation coefficients and mean ADC for each category of Ki67 are shown in table 3 and figure 2.

ROC curve for malignant lesions is shown in figure 3. The cut off value of ADC for malignant lesions was 0.792 (sensitivity 98.6%, specificity 65.7%).

Table 3. Correlation coefficients between ADC mean and defined groups of KI 67 in breast carcinoma

Ki67	ADC
0–5%	r = -0.053, p = 0.85, n=15
5–10%	r = 0.356, p = 0.489, n = 6
10–20%	r = -0.426, p = 0.168, n = 12
20–40%	r = -0.225, p = 0.667, n = 6
40–50%	*n=5
50–80%	r = -0.404, p = 0.368, n = 7
>80%	r = 0.288, p = 0.420, n = 10
pooled KI 67	r = 0.156, p = 0.243, n=58

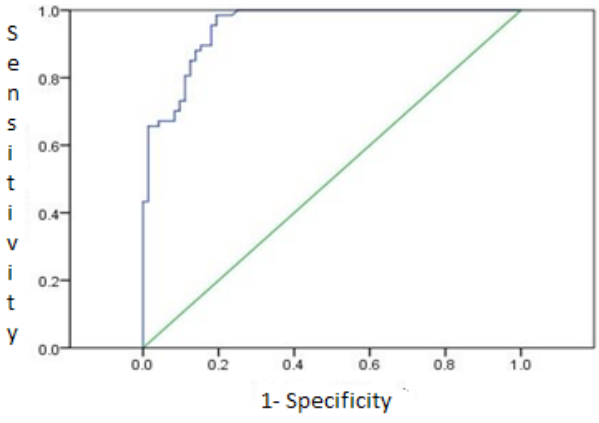

Figure 2. ADC values vs. Ki67

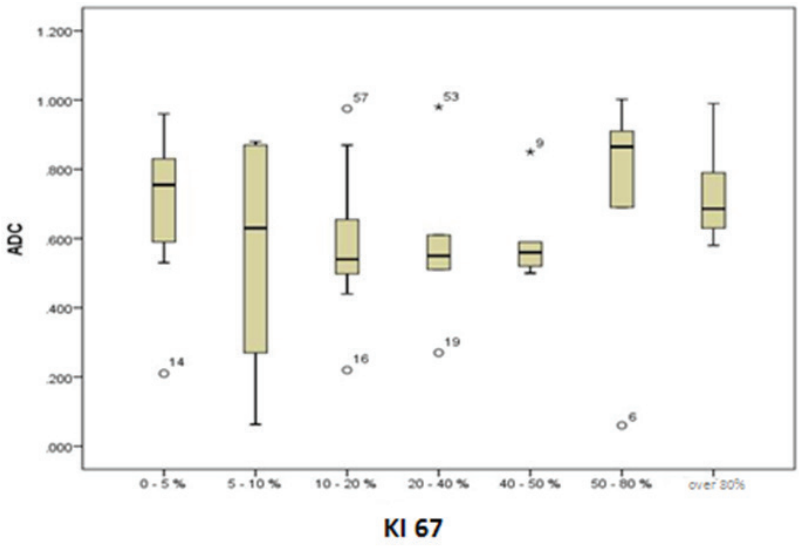

Figure 3. ROC curve for malignant breast lesions

Discussion

Ki67 is a marker of cell proliferation and can predict the prognosis for patients with breast carcinoma [17, 18]. Because of this, it is important to predict expression of Ki67 on imaging parameters. ADC reflects water diffusion in tissue and is in inverse correlation with cell number in tumors [19], and statistically significant correlation with nucleic size/volume [4]. Some previous studies showed the phenomenon that ADC can be associated with Ki67 [4, 15]. It is unknown the exact cause of this association. Ki67 is shown to be responsible for cell proliferation as nuclear cell protein synthesized through the whole mitosis except the G0 phase [20, 21]. Also, it is possible that mitotic phases may an increase of cytoplasmic proteins and cytoplasmic viscosity [22]. This may lead to decrease ADC.

Reported data about associations between ADC and Ki67 in breast cancers are very inconsistent. Some studies identified significant correlations between parameters [23, 24], other did not. It is suggested that that ADC can be used as a biomarker for proliferation in ovarian cancer. But ADC cannot be used as a proliferation biomarker in breast cancer because of weak correlations between ADC and Ki67. Interpretation of results of previous studies is difficult because of different study design and analysis. Different values of Ki67 expression are used to discriminate cancers with low or high proliferative activity [8, 25, 26], and some defined more than two Ki67 categories.

In previous studies, several problems were identified. Firstly, some studies contained relatively small patient samples which were examined with use of different MRI equipment with different technical parameters (field strength, DWI sequences and b-values). Secondly, published correlation coefficients were various due to different subjects included, different ratio of histological subtypes of tumors or different method of analysis (ROI size, location, etc.).

The cut off values of mean ADC was determined for malignant lesions in our study. The cut off ADC value for malignant lesions was 0.792 (sensitivity 98.6%, specificity 65.7%). Therefore, ADC could be used as marker for distinguishing malignant lesions of breast with very good sensitivity, but low specific-

ity. This could be improved with use of dynamic contrast-enhanced magnetic resonance mammography (DCE-MRM).

Our study has some limitations. Firstly, it contained relatively small patient sample. Therefore, it could not identify if there was significant associations between ADC and histological subtypes of breast cancer, or Ki67 and subtypes of breast cancer because of small sample in some histological groups. Secondly, we did not calculate correlation coefficients for each histological subtype included, because the included tumors represent the most frequent subtypes of breast carcinoma and we consider these should be analyzed as a group. Thirdly, we used different MRI equipment and methods of analysis (first of all, b values, size and positioning of ROI).

Conclusion

In conclusion, weak correlations between ADC and Ki67 in breast cancer were found, thus ADC cannot be used as a reliable imaging marker for proliferative activity in this entity. However, ADC can be used as a marker for distinguishing malignant lesions of breast with high sensitivity, but low specificity that could be improved using dynamic contrast-enhanced magnetic resonance mammography (DCE-MRM).

Funding source. The authors received no specific funding for this work.

Ethical approval. The Ethics Committee of the General hospital "Sveti Vračevi", Bijeljina, Republic of Srpska, Bosnia and Herzegovina, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

References:

1. Rahbar H, Patridge SC. Multiparametric MR imaging of breast cancer. Magn Reson Imaging Clin N Am 2016;24(1):223–8.
2. Kuhl CK, Shrading S, Strobel K, Schild HH, Hilgers RD, Bieling HB. Abbreviated breast magnetic resonance imaging (MRI): first post-contrast subtracted images and maximum-intensity projection - a novel approach to breast cancer screening with MRI. J Clin Oncol 2014;32(22):2304–10.
3. Fornasa F. Diffusion-weighted Magnetic Resonance Imaging: What Makes Water Run Fast or Slow? J Clin Imaging Sci 2011;1:27.
4. Surov A, Caysa H, Wienke A, Spielmann RP, Fiedler E. Correlation between different ADC fractions, cell count, Ki-67, total nucleic areas and average nucleic areas in meningothelial meningiomas. Anticancer Res 2015;35(12):6841–6.
5. Bostan TB, Koç G, Sezgin G, Altay C, Gelal MF, Oyar O. Value of apparent diffusion coefficient values in differentiating malignant and benign breast lesions. Balkan Med J 2016;33(3):294–300.
6. Marini C, Lacconi C, Giannelli M, Cilotti A, Moretti M, Bartolozzi C. Quantitative diffusion-weighted MR imaging in the differential diagnosis of breast lesion. Eur Radiol 2007;17(10):2646–55.
7. Guo Y, Cai YQ, Cai ZL, Gao YG, An NY, Ma L, et al. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. J Magn Reson Imaging 2002;16(2):172–8.
8. Choi SY, Chang YW, Park HJ, Kim HJ, Hong SS, Seo DY. Correlation of the apparent diffusion coefficiency values on diffusion-weighted imaging with prognostic factors for breast cancer. Br J Radiol 2012;85(1016):e474–9.

9. Kim SH, Cha ES, Kim HS, Kang BJ, Choi JJ, Jung JH, et al. Diffusion-weighted imaging of breast cancer: correlation of the apparent diffusion coefficient value with prognostic factors. J Magn Reson Imaging 2009;30(3):615–20.
10. Martincich L, Deantoni V, Bertotto I, Redana S, Kubatzki F, Sarotto I, et al. Correlations between diffusion-weighted imaging and breast cancer biomarkers. Eur Radiol 2012;22(7):1519–28.
11. Shin HJ, Kim SH, Lee HJ, Gong G, Baek S, Chae EY, et al. Tumor apparent diffusion coefficient as an imaging biomarker to predict tumor aggressiveness in patients with estrogen-receptor-positive breast cancer. NMR Biomed 2016; 29(8):1070–8.
12. Mori N, Ota H, Mugikura S, Takasawa C, Ishida T, Watanabe G, et al. Luminal-type breast cancer: correlation of apparent diffusion coefficients with the Ki-67 labeling index. Radiology 2015;274(1):66–73.
13. Sun K, Chen X, Chai W, Fei X, Fu C, Yan X, et al. Breast Cancer: Diffusion Kurtosis MR Imaging-Diagnostic Accuracy and Correlation with Clinical-Pathologic Factors. Radiology 2015;277(1):46–55.
14. Surov A, Clauser P, Chang YW, Li L, Martincich L, Partridge SC, et al. Can diffusion-weighted imaging predict tumor grade and expression of Ki-67 in breast cancer? A multicenter analysis. Breast Cancer Res 2018;20(1):58.
15. Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia 2009;11(2):102–25.
16. Sinn HP, Kreipe H. A Brief Overview of the WHO Classification of Breast Tumors, 4th Edition, Focusing on Issues and Updates from the 3rd Edition. Breast Care (Basel) 2013;8(2):149–54.
17. Li L, Han D, Wang X, Wang Q, Tian J, Yao J, et al. Prognostic values of Ki-67 in neoadjuvant setting for breast cancer: a systematic review and meta-analysis. Future Oncol 2017;13(11):1021–34.
18. Tao M, Chen S, Zhang X, Zhou Q. Ki-67 labeling index is a predictive marker for a pathological complete response to neoadjuvant chemotherapy in breast cancer: a meta-analysis. Medicine (Baltimore) 2017;96(51):e9384.
19. Surov A, Meyer HJ, Wienke A. Correlation between apparent diffusion coefficient (ADC) and cellularity is different in several tumors: a meta-analysis. Oncotarget 2017;8(35):59492–9.
20. He X, Chen Z, Fu T, Jin X, Yu T, Liang Y, et al. Ki-67 is a valuable prognostic predictor of lymphoma but its utility varies in lymphoma subtypes: evidence from a systematic meta-analysis. BMC Cancer 2014;14:153.
21. Schlüter C, Duchrow M, Wohlenberg C, Becker MH, Key G, Flad HD, et al. The cell proliferation-associated antigen of antibody Ki-67: a very large, ubiquitous nuclear protein with numerous repeated elements, representing a new kind of cell cycle-maintaining proteins. J Cell Biol 1993;123(3):513–22.
22. Valentine MT, Perlman ZE, Mitchison TJ, Weitz DA. Mechanical properties of Xenopus egg cytoplasmic extracts. Biophys J 2005;88(1):680–9.
23. Onishi N, Kanao S, Kataoka M, Iima M, Sakaguchi R, Kawai M, et al. Apparent Diffusion Coefficient as a Potential Surrogate Marker for Ki-67 Index in Mucinous Breast Carcinoma. J Magn Reson Imaging 2015;41(3):610–5.
24. Shen L, Zhou G, Tong T, Tang F, Lin Y, Zhou J, et al. ADC at 3.0 T as a noninvasive biomarker for preoperative prediction of Ki67 expression in invasive ductal carcinoma of breast. Clin Imag 2018;52:16–22.
25. Zhuang Z, Zhang Q, Zhang D, Cheng F, Suo S, Geng X, et al. Utility of apparent diffusion coefficient as an imaging biomarker for assessing the proliferative potential of invasive ductal breast cancer. Clin Radiol 2018;73(5):473–8.
26. Molinari C, Clauser P, Girometti R, Linda A, Cimino E, Puglisi F, et al. MR mammography using diffusion-weighted imaging in evaluating breast cancer: a correlation with proliferation index. Radiol Med 2015;120(10):911–8.

Da li vidljivi koeficijent difuzije (ADC) može biti imidžing marker za proliferativnu aktivnost kod karcinoma dojke?

Jelena Marić[1], Jasmina Boban[2,3], Tatjana Ivković-Kapicl[2,3], Dragana Đilas[2], Viktorija Vučaj-Ćirilović [2,3], Dragana Bogdanović-Stojanović[4]

[1]JZU bolnica "Sveti Vračevi", Bijeljina, Republika Srpska, Bosna i Hercegovina

[2]Univerzitet u Novom Sadu, Medicinski fakultet, Novi Sad, Srbija

[3]Institut za onkologiju Vojvodine, Centar za imidžing dijagnostiku, Sremska Kamenica, Srbija

[4]Poliklinika "Health Medic", Novi Sad, Srbija

Uvod. Multiparametrijska magnetno-rezonantna mamografija (mMRM) ima važnu ulogu u detekciji, evaluaciji i praćenju tumora dojke. Cilj ove studije je da ispita da li imidžing parametar, konkretno Apparent Diffusion Coefficient (ADC), može biti marker za proliferativnu aktivnost kod karcinoma dojke.

Metode. Ova kohortna studija uključila je 67 lezija kod 50 pacijentkinja koje su pregledane mMRM na skeneru 3T. Perkutane biopsije i hirurške ekscizije izvođene su posle snimanja u periodu do tri nedelje. Ki67 indeks je procenjen mikroskopski. Sedam Ki67 kategorija je definisano: 0–5%, 10–20%, 20–40%, 40–50%, 50–80% i više od 80%. Korišćene su metode deskriptivne statistike. Korelacije su određene korišćenjem Pirsonovog korelacionog testa. Konstruisana je i analizirana ROC kriva za određivanje "cut-off" vrednosti i dijagnostičkog potencijala. Statistička značajnost je bila postavljena na $p < 0,05$.

Rezultati. Različiti podtipovi karcinoma dojke su bili zastupljeni: duktalni karcinom (59,9%), lobularni karcinom (17,9%), metastatski karcinom (10,5%), duktalni karcinom in situ (9%) i tubularni karcinom. "Cut off" vrednost ADC za karcinom dojke bila je 0,792 (senzitivnost 98,6%, specifičnost 65,7%). Nije postojala statistički značajna razlika u vrednostima ADC za različite kategorije Ki67. Nije postojala statistički značajna korelacija između srednje vrednosti ADC i Ki67 na nivou celog uzorka ($r = 0,156$, $p = 0,243$).

Zaključak. ADC se ne može koristiti kao pouzdan imidžing marker za proliferativnu aktivnost kod karcinoma dojke.

Ključne reči: karcinom dojke, ADC, difuzioni imidžing, Ki67