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IMPORTANCE OF MICROCALCIFICATIONS IN MAMMOGRAPHIC DIFFERENTIATION OF THE INVASIVE DUCTAL BREAST CANCER AND OF THE DUCTAL CARCINOMA IN SITU

ZNAČAJ MIKROKALCIFIKACIJA U MAMOGRAFSKOJ DIFERENCIJACIJI INVAZIVNOG DUKTALNOG CARCINOMA DOJKE I DUKTALNOG KARCINOM IN SITU

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Abstract

Introduction: Microcalcifications represent a significant and reliable sign of the presence of the malignant breast lesion.
Aim: The aim of the paper is to radiologically evaluate the type and distribution of suspicious microcalcifications, in patients with invasive ductal carcinoma (IDC) and ductal carcinoma in situ (DCIS).
Material and Methods: Retrospective analysis includes the evaluation of the type and distribution of suspicious microcalcifications, in patients with histologically verified malignant lesions: invasive ductal carcinoma (N1=40 pts.) and ductal carcinoma in situ (N2=40 pts.). Standardised mediolateral oblique and cranicaudal views were selected for the evaluation of the images, taken on the full-field digital mammograph (FFDM «Selenia», Institute of Oncology and Radiology of Serbia, Belgrade), on the dedicated workstation of the mammography unit, with the aid of the software for lesion evaluation.
Results: Eight patients with invasive ductal carcinoma (20%) had no suspicious microcalcifications, as opposed to the patients with ductal in situ carcinoma, where all patients had suspicious microcalcifications ($p<0.05$). In the subgroup of patients with invasive ductal carcinoma, the most frequent type of microcalcifications included the fine pleomorphic calcifications (75%). In patients with ductal carcinoma in situ, amorphous (57.5%) and linear/branching microcalcifications were more frequent than other types (55%).
Conclusion: The results of this study show that the amorphous microcalcifications segmental distribution usually detected in the subgroup with DCIS, which coincides with published results. With acceptable sensitivity and specificity, amorphous microcalcifications and linear distribution segment represents a specific mammographic findings in the detection of DCIS.

Keywords:
microcalcifications,
invasive ductal carcinoma,
ductal carcinoma in situ,
mammography

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SAŽETAK

Uvod: Mikrokacifikacije predstavljaju značajan, a ponekad i jedini znak razvoja maligne lezije u dojkama.
Cilj: Cilj istraživanja podrazumeva mamografsku evaluaciju mikrokalcifikacija-procenu tipa i distribucije kod ispitanica sa invazivnim duktalnim karcinomom dojke (IDC) i duktalnim karcinomom in situ (DCIS).
Materijal i metode: Retrospektivno ispitivanje podrazumeva evaluaciju tipa i distribucije mikrokalcifikacija kod ispitanica sa histološki verifikovanim malignim lezijama: četrdeset ispitanica (N1=40) sa IDC, odnosno četrdeset ispitanica sa DCIS (N2=40). Analiza materijala podrazumeva izbor standardnih mamografskih projekcija: mediolateralne kose (MLO) i kraniokaudalne (CC). Svi snimci su urađeni na digitalnom mamografu (FFDM "Selenia" u Institutu za onkologiju i radiologiju Srbije), analizirani su na radnoj stanici mamografske jedinice, a uz primenu namenskog softvera za evaluaciju snimaka i analizu parametara praćenja.
Rezultati: Kod 8 ispitanica sa IDC (20%), nisu detektabilne mikrokalcifikacije, za razliku od ispitanica sa DCIS, gde su kalcifikacije detektabilne ($p < 0,05$). Od suspektnih mikrokalcifikacija, kod ispitanica sa IDC, najčešće se javljaju fine pleomorfne mikrokalcifikacije (75%), dok se kod ispitanica sa DCIS sa većom učestalošću javljaju amorfne (57,5%) i linearne/granajuće (55%) u odnosu na ostale tipove.
Zaključak: Rezultati ove studije pokazuju da se amorfne mikrokalcifikacije segmentne distribucije obično otkrivaju u podgrupi sa DCIS, što se poklapa sa objavljenim rezultatima. Sa prihvatljivom senzitivnošću i specifičnošću, amorfne mikrokalcifikacije, segmentne i linearne distribucije predstavljaju specifične mamografske nalaze u detekciji DCIS-a.

Ključne reči:
mikrokalcifikacije, intraduktalni karcinom, duktalni karcinom in situ, mamografija

Introduction

Microcalcifications are defined as localized calcium deposits in the breast tissue, which represent an early diagnostic sign of breast cancer (1). The current strategy for evaluating and managing microcalcifications makes the important assumption that the microcalcifications are present within or are closely related to the most important underlying pathologic change in the breast (2). Microcalcifications occur as a consequence of breast inflammation, progression of fibroadenoma, intraductal papilloma, cystic and fibrotic changes, but may also be actively secreted, as is the case with malignant lesions (3). Microcalcifications are one of the main categories of abnormalities detectable by mammograms (4). International guidelines recommend that breast ultrasound can be used as an additional test, but not as a primary method of screening for breast cancer (5). Therefore, mammography is the gold stanadrd in diagnostic estimation of early detection of the breast cancer (6,7). Mammography has a sensitivity of 63 to 95% and sensitivity increases with the presence of palpable lumps and reduces dense breasts (8).

Around 50% of non-palpable breast cancers are detectable on mammograms, based only on microcalcifications, as around 90% of ductal carcinomas in situ are detected due to calcifications (9). DCIS is a complex clinical entity that is highly variable in its appearance, biology, and behavior (10). This carcinoma is characterized by malignant proliferation of the epithelium lining of the ducts of the middle and larger size without any evidence of invasion, i.e., without breaking the basal membrane (9). Cell necrosis occurs in the central part of a duct creating a necrotic detritus in which calcium deposits tend to accumulate. This change is one of the pre-invasive lesions with malignant potential. There is a general consensus that DCIS represents a noninvasive, nonobligate precursor of invasive breast cancer (11). Therefore, the early diagnosis and management of DCIS are critical in preventing the development of invasive cancer (12,13). It has been proposed that the biological aggressiveness of breast cancer can also be predicted by mammographic characteristics (13,14). Thus, detection of microcalcifications in breast tissue enhances the choice in therapeutic modalities, as well as the outcome of the patients having breast cancer (15). The association between pattern of mammographic microcalcifications and histological findings related to more aggressive disease can be helpful in optimal surgery planning, in patients with screen-detected DCIS, regarding the extent of breast intervention and consideration of synchronous sentinel node biopsy (16). The development of imaging techniques and the widespread adoption of screening programs, resulted in dramatically increased incidence of ductal carcinoma in situ (DCIS), which currently accounts for about 20–25% of newly diagnosed breast cancer cases (17-19).

Invasive ductal beast cancer is a cancer that may have the highest degree of malignancy. It is also considered as the predominant histologic type of breast cancer, which is the most frequent cause of death of women in the developed countries (20). Typical feature of this carcinoma is the proliferation of the cells through the ducts by breaking the basal membranes, which leads to stromal invasion of breast tissue, making it 80% of all breast cancers (21).

The aim of the research involves mammographic evaluation of microcalcifications – the type and extent in patients with invasive ductal breast cancer (IDC) and ductal carcinoma in situ (DCIS).

Material and methods

Retrospective analysis involves evaluation of the type and distribution of microcalcifications with hystologically verified malign lesions. Forty patients (N1=40) with IDC, and the same number of patients with DCIS (N2 = 40), were included in the analysis, aged between 40 and 55 years. The examinees with IDC were aged 49.6 +/- 6.5, while the examinees with DCIS were 48.5 +/- 7.3 years old, with insignificant dfference ($p > 0.5$).

The included patients were analysed with standard mammographic projections: mediolateral oblique (MLO) and cranio-caudal (CC). All the images were taken by a digital mammogram (FFDM «Selenia», Hologic, Bedford MA, USA) at the Institute of Oncology and Radiology of Serbia, and they were analysed retrospectively in the period from September 2014 – March 2015, at the dedicated workstation within the mammographic unit.Dedicated software for image evaluation and analysis of tracking parameters was applied for the analysis (R2 CAD, Hologic, Bedford, MA, USA), on adequate screens of the 5MP system, with the resolution 2048 x 2560 (Barco N.V, Kortrijk, Belgium).

Characterization of microcalcifications was defined in accordance with the standardised recommendations ACR (ACR BI-RADS Atlas, 5thEdition, 2013) (22), and the significance of the existence of difference between two independent samples. It was expressed as a proportion, with the level of significance 0.05, tested with the Z-test.

Results

Benign microcalcifications were not found in either group of patients. The parameter: type of microcalcifications in subgroups is presented in **Table 1**.

Table 1. Evaluation of the frequency of detectable microcalcifications, according to the type, with the patients with IDC (N1= 40) and DCIS (N2 = 40).

Type of microcalcifications	**IDC, N1=40**	**DCIS, N2=40**	**p**
Benign	0/40	0/40	
Suspected	32/40 (80%)	40/40 (100%)	p < 0.05 (p = 0.003)
amorphic	9/32 (28.1%)	**23/40 (57.5%)**	p < 0.05 (p = 0.01)
rough heterogenous	3/32 (09.4%)	8/40 (20%)	p > 0.05 (p = 0.2)
fine pleomorphic	**24/32 (75%)**	12/40 (30%)	p < 0.05 (p = 0.0002)
linear/branching	6/32 (18.7%)	**22/40 (55%)**	p < 0.05 (p = 0.002)
No microcalcifications	8/40 (20%)	**0/40**	p < 0.05 (p = 0.003)

Within the group of patients with IDC, suspicious microcalcifications were detected in 80% (32/40), while all the patients with DCIS i.e, 100% had suspicious microcalcifications (40/40) ($p < 0.05$). Within the group of patients with DCIS, the most frequently detected type included amorphic (23/40, 57.5%) and linear/branching microcalcifications (22/40, 55.0%). Both types are more frequent in the group of patients with DCIS, than in the groups of patients with IDC ($p < 0.05$). Within the group of patients with IDC, fine pleomorphic microcalcifications are most frequently detected (24/32, 75%). This type of microcalcifications is detected much more frequently in the subgroup of the examinees with IDC, than those with DCIS ($p = 0.0002$), (**Figure 1**).

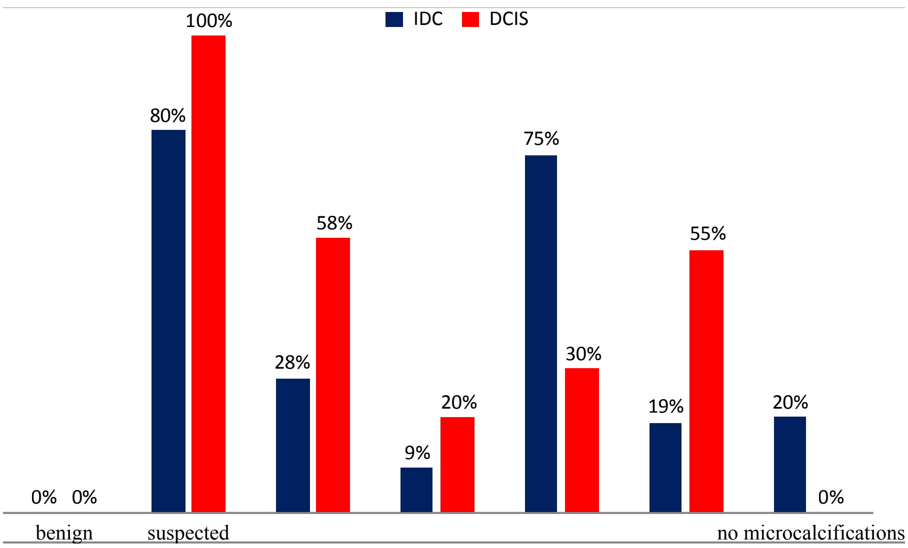

Figure 1. Evaluation of the frequency of detectable microcalcifications according to the type in the patients with IDC (N1 = 40) and DCIS (N2 = 40).

As far as the evaluation of extensiveness, based upon the parameters where microcalcifiction distribution is concerned (**Table 2, Figure 2**), diffuse and regional distribution pattern was not discovered in either group of patients.

In the sugroup of the patients with DCIS, the most frequent type of distribution is segment (21/40, 52.5%), followed by the linear distribution (18/40, 45.0%). The frequency of both types of distribution is statistically significantly different from the subgroup with histologically verified IDC: the segmental type of distribution (p=0.0004) and the linear type of distribution (p<0.05) are more frequent in DCIS (**Figure 3**). In the subgroup of the patients with IDC, clustered microcalcificatios are most frequently detected (28/32, 87.5%), mostly within the tumor, with the frequency considred different compared to thepatients with DCIS (p < 0.05).

Table 2. Evaluation of the distribution of microcalcifications according to the type with the patients with IDC (N1 = 40) i DCIS (N2 = 40).

Calcifications	**IDC, N1=40**	**DCIS, N2=40**	**p**
diffuse	0/40	0/40	
regional	0/40	0/40	
clustered	**28/32 (87.5%)**	1/40 (2.5%)	p < 0.05 (p = 0)
linear	0/40	**18/40 (45%)**	p < 0.05 (p = 0)
segmental	4/32 (12.5%)	**21/40 (52.5%)**	p < 0.05 (p = 0.0004)

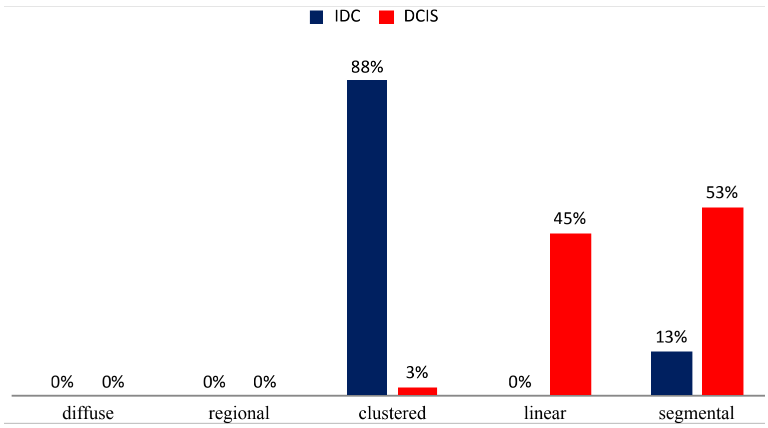

Figure 2. Evaluation of the distribution of microcalcifications according to the type in patients with IDC (N1= 40) i DCIS (N2 = 40).

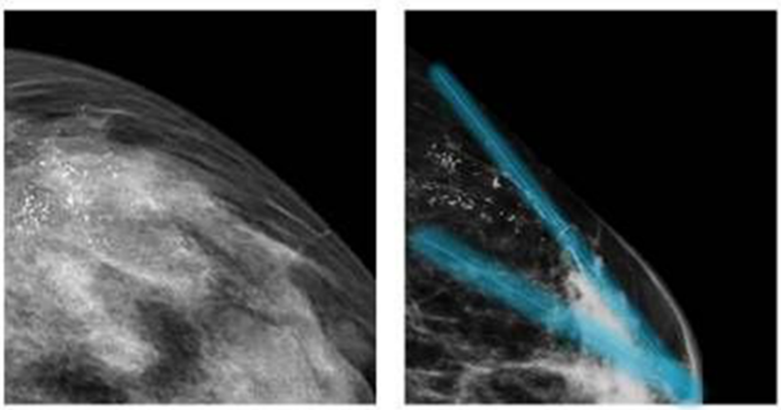

Figure 3. Detail – Digital mammography: pleomorphic microcalcifications of segmental distribution with apex towards mammila – extensive ductal carcinoma in situ (CC and MLO projection).

A significant difference of the frequency of the types of the suspicious microcalcifications was noticed between IDC and DCIS (p < 0.05): amorphic, rough heterogenous and linear/branching, were more frequently detected within the group of patients with DCIS, while fine pleomorphic microcalcifications are more often detected in patients with IDC (p = 0.0002).

As far as the distribution of microcalcifications is concerned, the clustered microcalcifications, occur more often within the group of patients with IDC (p < 0.05), while the microcalcifications of segmental distribution (p = 0.0004), as well as linear (p = 0.0001), occur more often within the patients with DCIS.

Discussion

Breast cancer is a global problem, and 1.7 million new cases are diagnosed per year (23). Breast cancer is the most common cancer among women worldwide and ranks second in cancer-related deaths after colon cancer (24). Approximately 60% of deaths due to breast cancer occur in developing countries (DCs), whereas in the United States (US), an estimated 249.260 new cases of breast cancer are diagnosed each year, and mortality due to this disease is decreasing. Developing countries have limited healthcare resources and use different strategies to diagnose breast cancer. Despite advances in medicine, breast cancer is diagnosed in the advanced stages in countries with limited resources (25). In Serbia, according to the latest report by the Institute of Public Health "Dr Milan Jovanović - Batut" annually 2.675 women are diagnosed with breast cancer. The incidence rate in Serbia of breast cancer per 100,000 inhabitants is 99.7, while the mortality rate was 44.0. In 2013 in Serbia, the screening program that aims to demonstrate efficacy in reducing mortality begun - such as by a larger number of lesions in the breast to detect at an early stage of the disease and thus to establish adequate treatment (26). In the US, 70% of women undergo mammographies and from that reason, death rate concerning breast cancer has been declining in the past twenty years (27). This decrease is caused by introducing the well-spread mammographic screening programs from 1960s, which led to diagnosis at an early nonmetastatic stage and treatment. Also, with the development and standardising of chemotherapeutic protocols, decrease of mortality is expected. According to the conclusions of the National Health institute, the frequency of the invasive ductal carcinoma detection, increased from 1.87 per 100.000 in 1973, to 32.5 per 100.000 in 2004. The increase is attributed to the introduction of screening mammography and early lesion detection. Total frequency of detecting lesions at an early stage has been doubled since 1976 (28).

The morphology and distribution characteristics proved to be a helpful tool in diagnosis of calcifications (29). Gershon-Cohen et al. were the first to report that the irregular, clustered appearance of calcifications was associated with breast cancer in 1962. The shape of microcalcifications is a major criterion for distinguishing malignant versus benign tissue. Malignant microcalcifications tend to be more irregular, which corresponds to the most important clinical indications of malignancy i.e. linear or branching microcalcifications (30). Combining morphology and distribution descriptors for suspicious microcalcifications provides accurate risk stratification (31). According to research, linear branching microcalcifications are related with a more aggressive type of DCIS (32). The survival of women with masses or linear/linear-branching calcifications (i.e. casting calcifications) is considerably worse than the survival of women with other types of lesions, suggesting that the calcifications are associated with duct-forming invasive cancer (30).

Microcalcifications are detectable in DCIS and their type and distribution are of vital importance in setting radiological diagnosis with categorization and recommendation for histological verification, especially with nonpalpable lesions, where standardized regular radiological examinations are the only way of diagnosing lesions in due time.

The most common types of suspicious microcalcifications in DCIS are amorphous (57.5%) and linear/branching (55%), followed by fine pleomorphic (30%) and rough heterogenous (20%). The results confirm the previously published ones, and contribute to differentiation according to the current ACR BI-RADS categorisation, as well as defining of the types and distribution of microcalcifications. D'Orsi stated that amorphous microcalcifications of linear and segmental distribution represent specific mammographic result, with acceptable sensitivity and specificity in detection of DCIS (33).

According to research in Japan, the most common type of micocalcifications comprised of the pleomorphic and linear/branching microcalcifications, while the largest number of microcalcifications are linear and segmental distiribution (34). Also, the investigations conducted in Norway, indicate that high grade DCIS has a typical segmental distribution (35). Holland et al. stated that the amorphic, linear/branching microcalcifications were considered the most common ones in poorly differentiated DCIS, while the tendency towards clustered microcalcifications remained characteristic of the high-grade DCIS, evolving towards the invasive form (36). Segmental distribution is also considered typical for DCIS, which was also proved by the results of this research. Slanetz et al. stated the detection of a tumor shadow in a small number of DCIS, pointing further to the tendency towards the dominant segmental distribution of microcalcification, instead of clustering, which was also confirmed in the results of this research. It was in the group of the patients with IDC where fine pleomorphic microcalcifications, with the tendency to cluster, were the most common type (36,37). The most common types of the distribution of microcalcifications, within the examinees patients with DCIS, include the segmental (52.5%) and linear microcalcifications (45%). For the group of patients with IDC, microcalcifications are not always detectable, however, those detected include fine pleomorphic microcalcifications. As far as the distribution of microcalcifications IDC is concerned, the most frequent type of distribution included clustered microcalcifications.

Within the evaluation of both parameters: type and distribution of microcalcifications, amorphous microcalcifications of segmental distribution are most frequently detected in the subgroup with DCIS, which is considered in correlation with the published results, while the less frequently encountered clustered microcalcifications within the tumor are related to the IDC.

Limitations of this research include retrospective design and the limited number of the partcipants involved.

Further research in the field is needed, including a larger number of patients, analysis according to histological type and grade, as well as the corelation with other imaging modalities, such as magnetic resonance imaging.

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