JBUON 2016; 21(5): 1113-1120
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Seven-year survey of classical and pleomorphic invasive lobular breast carcinomas in women from southeastern Serbia: Differences in clinicopathological and immunohistochemical features

Ivan R. Ilic[1], Nebojsa P. Djordjevic[2,3], Pavle J. Randjelovic[4], Nikola M. Stojanovic[2], Niko S. Radulovic[5], Ratko S. Ilic[1]

[1]Institute of Pathology, Faculty of Medicine, University of Nis, Nis; [2]Faculty of Medicine, University of Nis, Nis; [3]Surgical Clinic, Clinical Center Nis, Nis; [4]Department of Physiology, Faculty of Medicine, University of Nis, Nis; [5]Department of Chemistry, Faculty of Science and Mathematics, University of Nis, Nis, Serbia

Summary

Purpose: *The occurrence of different variants of invasive lobular carcinoma (ILC) of the breast is variable. For example, the pleomorphic variant of ILC has an incidence of around 5%; however, the number of analyzed cases of ILC is shadowed by the number of ductal type carcinoma (IDC). Thus, we aimed to analyze the classical and pleomorphic ILCs in women from southeastern Serbia.*

Methods: *Analyzed were 296 cases (11.91%) diagnosed with ILC, out of 2486 cases of all breast cancers (BCs), during a 7-year period (2005-2011) from southeastern Serbia. The differences in clinicopathological and immunohistochemical features (estrogen receptor/ER, progesterone receptor/PR, HER-2, Ki-67, BRCA-1, p53 and E-cadherin) of these cases of ILCs were assessed and compared.*

Results: *Pleomorphic ILC occurred relatively rarely compared to other variants, however almost one fifth of the ILC cases were pleomorphic. No statistically significant correlation was found between patient age, tumor stage and the presence/absence of multifocality (MFC), multicentricity (MCC) and bilaterality (BL) on one side, and ILC variant on the other. Only the expression of two prognostic and predictive immunohistochemical markers, important for endocrine therapy, ER and PR, showed significant correlation with the ILC variant.*

Conclusions: *Although higher tumor stage, incidence of multicentricity, overexpression of HER2 and higher p53 positivity were deemed to be characteristic of pleomorphic ILC, in our study that included a much larger number of cases than previous studies did, such correlations were not observed. Thus, it appears that the only two features of pleomorphic ILCs is absence of ER and PR positivity.*

Key words: *hormone receptors, immunohistochemistry, incidence of variants, lobular breast carcinoma, pleomorphic variant*

Introduction

ILC represents the second most common histological type of BC with approximately 5–15% of all BC c ases. The incidence of ILCs is increasing during the past two decades due to a larger application of hormone replacement therapy in postmenopausal women. It is known that both estrogen and progesterone exert an influence on the development of ILCs more than on any other histological BC type [1].

In addition to the classical variant, other variants such as pleomorphic, solid, alveolar, mixed and tubulolobular ILCs have been described [2].

Correspondence to: Ivan R. Ilic, MD, PhD. Institute of Pathology, Faculty of Medicine, University of Nis, Zorana Cjindjica 81, 18000 Nis, Serbia. Tel: +381 18 422664, Fax: +381 18 4238770, E-mail: ilicko81@gmail.com
Received : 03/02/2016; Accepted : 20/02/2016

Among them, besides the classical variant of ILC, the most clinically important variant is the pleomorphic ILC, with an aggressive biological behavior and similar infiltrating pattern as is seen in the classical ILC, but with more pleomorphic nuclei and overlapping features with those of infiltrating ductal carcinoma [3]. This variant is cytologically different, whereas other variants are mutually architecturally different. Also, a considerably worse prognosis and survival rate are reported for this type of ILC [3]. The poor prognosis of pleomorphic ILC is brought in connection with the high nuclear grade and overexpression of p53 and HER-2 proteins which are important characteristics of IDC [4]. In addition, there are up to 19% false-negative mammograms in patients with ILCs [5].

The occurrence of different variants of ILC was found to be variable [6,7]. For example, the pleomorphic variant of ILC was reported to have an incidence of around 5%; however, the number of analyzed cases of ILC was shadowed by the number of IDC [6,7].

The aim of this study was to investigate the occurrence and clinicopathological characteristics of the two relatively similar (classical and pleomorphic) ILC variants in women from southeastern Serbia in a 7-year period.

Methods

From 2486 cases diagnosed with BC during a 7-year period (January 2005-April 2011), belonging to different histopathological types, 296 (11.91%) cases of ILCs belonging to either classical or pleomorphic variants were found. Tissue samples of ILC were obtained by breast-conserving surgery or mastectomy with axillary dissection in the Clinical Center Nis and other clinical centers from southeastern Serbia. The samples were routinely processed, embedded in paraffin and archived together with their corresponding histopathological diagnosis and clinical documentation in the Center of Pathology of the Clinical Center Nis. Data concerning patients' age, tumor stage and presence of metastases in axillary lymph nodes was obtained from the archive. All microscopic slides were reevaluated during the collection of the data for this study.

MFC was determined on the microscopic level by evaluating the presence of larger number of morphological centers for cancer development and that pertained to the same morphological unit of the breast, i.e. lobule (within 5 cm). The presence of a larger number of BCs appearing in the same breast, with at least 5 cm of normal tissue inbetween (both uni- and bi-quadrant ones), was taken as indicative of MCC. The local presence of lobular or ductal carcinoma in situ were part of the multicentric/multifocal diagnosis.

Immunohistochemical staining was performed for the characteristic areas of tumors (1-2 paraffin blocks per case), from microscopically selected samples (regions), based on standard H&E staining. Tissue from the paraffin molds was cut into 4 µm thick sections, placed on super frost glass slides and stained immunohistochemically for the presence of ER (Monoclonal Mouse Anti-Human Estrogen Receptor α (ER); Clone 1D5; Code N1575, Ready-to-use; DAKO, Glostrup Denmark), PR (Monoclonal Mouse Anti-Human Progesterone Receptor (PR); Clone PgR 636; Code N1630, Ready-to-use; DAKO, Glostrup Denmark), HER-2 receptor (Polyclonal Rabbit Anti-Human c-erbB-2 Oncoprotein; Code A0485, 1:250 - 1:350; DAKO, Glostrup Denmark), BRCA1 protein (Monoclonal Mouse Anti-Human BRCA1; Clone GLK-2; Code M3606, 1:50; DAKO, Glostrup Denmark), p53 protein (Monoclonal Mouse Anti-Human p53 Protein; Clone DO-7; Code N1581, Ready-to-use; DAKO, Glostrup Denmark), Ki-67 antigen (Monoclonal Mouse Anti-Human Ki-67 Antigen, Clone MIB-1; Code N1633, Ready-to-use; DAKO, Glostrup Denmark) and E-cadherin (Monoclonal Mouse Anti-Human E-cadherin; Clone NCH-38; Code M3612, 1:50; DAKO, Glostrup Denmark). After the sections were processed following the manufacturer's instructions, visualization was effectuated using diaminobenzidine (DAB) and counterstaining with Mayer's hematoxylin.

Scoring was done on at least 100 cancer cells per slide where medium to strong staining was considered positive. Cancer cells stained with ER or PR antibodies were considered positive for these markers when 1% of cancer cells with strong nuclear staining was present or 10% of cancer cells showed medium to weak nuclear staining. Positivity of HER-2 was noted when more than 10% of cancer cells had complete and intense membranous staining. Cases with HER-2 2+ were subjected to CISH staining and were further evaluated as HER-2 positive or negative cases. Ki-67 index (all samples were taken before the application of neoadjuvant therapy) was assessed based on the percentage of cancer cells positive for Ki-67 as being low (<15%) or high (>15%). Medium to strong nuclear staining by p53 antibody was taken as positive when more than 10% of the stained cancer cells were present. BCs were considered BRCA1 positive when BRCA1 staining of the nucleus was decreased (compared to the positive inner control) or absent and/or positive in the cytoplasm of cancer cells. ILCs are typically E-cadherin negative (loss of expression) except in the cases of its aberrant membranous expression (decreased expression) and even then its expression is lower than in the normal positive ductal epithelium (positive inner control).

Statistics

The acquired data were presented in contingency tables.

Differences in proportions were analysed by Fisher's exact test. Statistical significance was set at $p<0.05$.

Table 1. Occurrence, mean age and tumor stage in patients with classical and pleomorphic invasive lobular breast carcinoma

ILC variant	*Patients, N (%)*	*Mean age ± SD (years)*	*Number of cases with different tumor stage*									
			T1	*p*	*T2*	*p*	*T3*	*p*	*T4*	*p*	*Tx*	*p*
Classical	243 (82.1)	58.0 ± 11.1	67	1.0	93	0.7	11	0.32	24	1	49	0.4
Pleomorphic	53 (17.9)	57.5 ± 13.6	14		22		4		5		8	

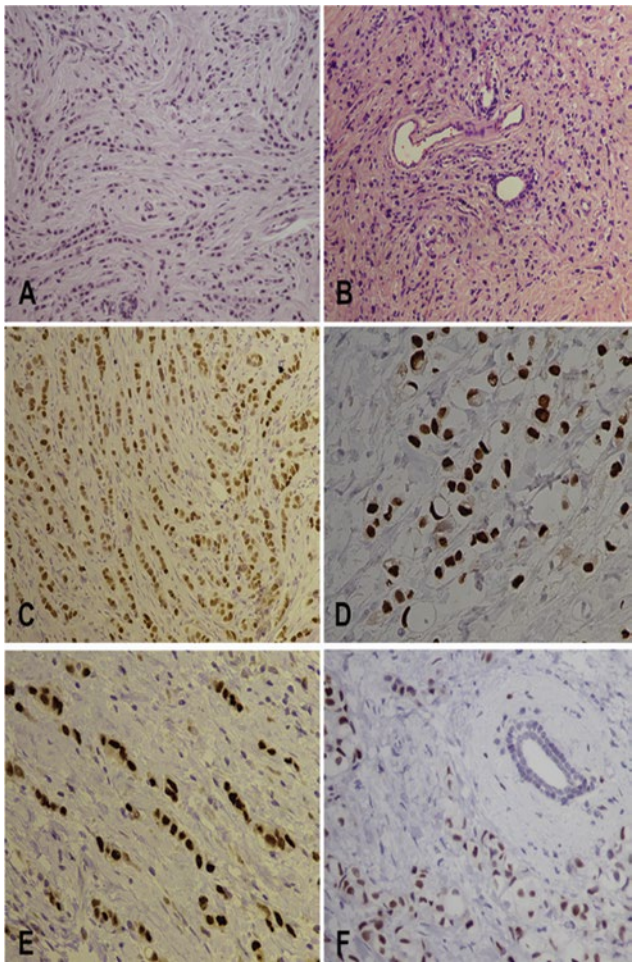

Figure 1. Histological and immunohistochemical differences between classical and pleomorphic ILC. **(A):** Classical variant of ILC with characteristic "single files" (H&E x200); **(B):** Pleomorphic variant of ILC with dispersed tumor cells (H&E x200); **(C):** Moderate expression of estrogen receptors in the classical variant of ILC (LSAB x200); **(D):** Strong expression of progesterone receptors in the pleomorphic variant of ILC ("signet ring" cell type) (LSAB x400); **(E):** Strong nuclear expression of progesterone receptors in the classical variant of ILC (LSAB x400); **(F):** Moderate nuclear expression of progesterone receptors in the pleomorphic variant of ILC (LSAB x400).

Statistical packages used were Jandel Sigma Stat 2.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5.03. (San Diego, CA, USA).

Results

The percentile abundance of ILCs was 11.9% of all BCs, while the incidence of ILCs in females from southeastern Serbia varied in the range of 0.11-0.76‰. Microscopic analysis was done on a total of 296 cases of ILC, from which 82.1% were diagnosed as classical variant, whereas the rest (17.9%) were classified as pleomorphic (Table 1). Additionally, other variants of ILC were present but were much less frequent (30 cases in total), and, thus, we did not take them into consideration throughout the study. The cases where the tumor growth, frequently seen near the preserved ductal structures, was linear around the stromal collagen fibers (forming the so-called single files), with relatively small equal nuclei, were classified as classical ILC (Figure 1A). When cancer cells were larger than those in the classical ILC (greater cellular atypia and pleomorphism), with more abundant eosinophilic cytoplasm and eccentrically located nuclei (apocrine or histiocytoid differentiation or dominant truly signet ring cells), these cases were characterized as pleomorphic ILC variant (Figure 1B).

Table 2. Tumor variant distribution based on the presence/absence of MFC, MCC and bilateral BC

Group	*Classical*	*Pleomorphic*	*p value*
non-MFC/MCC/BLBC	223	49	1
MFC	8	0	0.3584
MCC	10	4	0.2859
Bilateral BC	2	0	1
Total	243	53	

For abbreviations see text

No statistically significant difference was found between patient age and ILC variant (Table 1, p=0.7834). The results also showed that there was no correlation between tumor stage (pT) and ILC variant (Table 1, p>0.05). Also, no statistically significant difference was found between the presence of axillary lymph node metastasis and tumor variant (Figure 2, p>0.05). No correlation was found between the ILC variant and the presence/absence of MFC, MCC and BL BCs (Table 2, p>0.05).

Statistical analysis of the obtained data in-

Table 3. Frequency of the expression of ER and PR receptors and HER-2 and Ki67 index in invasive lobular carcinoma variants

ILC variant	*ER score*		*p value*	*PR score*		*p value*	*HER-2 score*		*p value*	*Ki67 index*		*p value*
	negative	*positive*		*negative*	*positive*		*negative*	*positive*		*low*	*high*	
Classical	42	201	0.0025	69	171	0.0043	162	30	0.6682	10	27	0.2318
Pleomorphic	19	34		26	27		31	7		0	4	

Table 4. The relation between tumor variant and the expression of BRCA1 and p53 protein and the loss or decrease of membrane E-cadherin

ILC variant	*BRCA1 score*		*p value*	*p53*		*p value*	*E-cadherin*		*p value*
	negative	*positive*		*negative*	*positive*		*loss*	*decrease*	
Classical	10	23	0.3095	56	41	0.9895	11	9	0.7104
Pleomorphic	6	7		11	8		8	5	

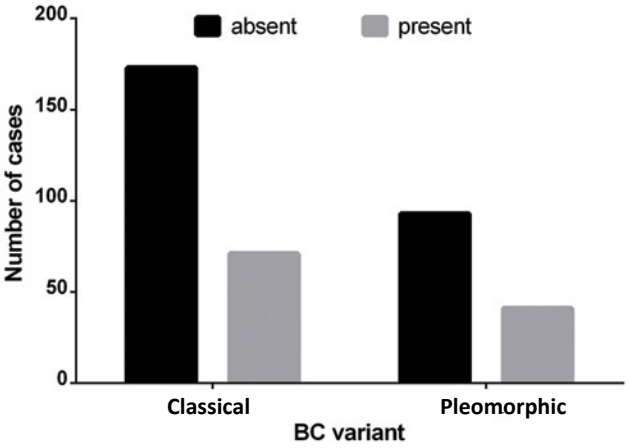

Figure 2. Analysis of axillary lymph node metastases in patients with classical and pleomorphic ILCs (p>0.05).

dicated that patients with the classical variant of ILC showed a more frequent expression of ER and PR than those with the pleomorphic variant (Table 3, Figures 1 C, D, E and F). On the other hand, the results revealed that there was no correlation between ILC variant and the expression of HER-2 (Figures 3A and B) and Ki-67 protein (Table 3). Analysis of the relations between tumor variant and the presence of BRCA1 and p53 (Figures 3C and D) disclosed no statistically significant correlations (Table 4). Fisher's analysis demonstrated no correlation between the expression of E-cadherin (Figures 3E and F) and the ILC variants (Table 4).

Discussion

The frequency of occurrence of different variants of ILCs is debatable, and the results of our study showed that the classical variant was present in 82.1% of the cases, while the pleomorphic one was diagnosed in 17.9% of all ILCs (Table 1). Talman et al. [6] revealed that in a group of 860 patients with ILC, the presence of classical ILCs was 83%, while the pleomorphic one appeared in only 5.7%. A general notion is that the pleomorphic variant is present in 0.67% of all BCs, and less than 5% of lobular BC [7].

Previous publications indicated that the classical lobular carcinoma, but not the other variants, occurred in younger-aged patients, where a high incidence of ILC was in the 40-49 years age group, and the median age of patients with classical ILC was 48.7±9.9 [8]. This was not the case in our study, since the patients included in our study were significantly older (57 years) (Table 1). However, the study of Fu and co-workers [8] and a more recent study of Jung et al. [9] also demonstrated that the occurrence of ILC in women in their 40's was visibly connected to the geographical origin of patients with ILC. This is in good agreement with the fact that ILCs often occurred in older women (older than 50 years) in Western countries [9]. On the other hand BRCA1 positive pleomorphic ILCs can occur in much younger patients, and this possibly explains the large discrepancy in the average patient age, 35 to 80 [10].

According to our results (Table 1), although tumors of both ILC variants were classified as T2 in a much higher percentage than in other stages, there were no statistically significant correlations between the tumor stage and variant. Recently, in much smaller study (22 cases of pleomorphic and 47 cases of classical ILCs), the authors provided evidence for statistically significant differences in T stage for these two variants [11]. The lack of cor-

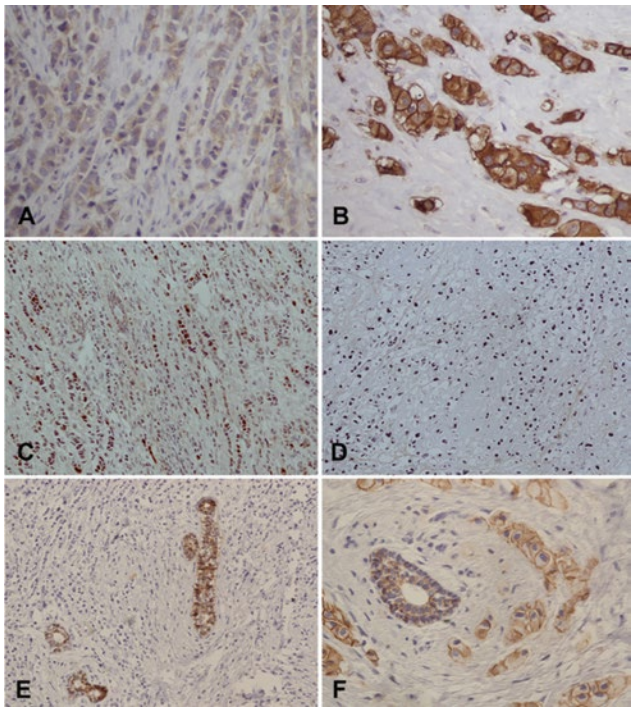

Figure 3. Immunohistochemical differences between classical and pleomorphic ILC. **(A)**: Weak and incomplete membrane staining of HER-2 receptors in the classical ILC (LSAB x400); **(B):** Strong and complete membrane staining of HER-2 receptors in more than 10% of tumor cells in the pleomorphic variant of ILC (LSAB x200); **(C):** Moderate and strong immunohistochemical nuclear expression of p53 in the classical variant of ILC (LSAB x200); **(D):** Absence of immunohistochemical nuclear expression of p53 in the pleomorphic variant of ILC (LSAB x200); **(E)**: Absence of E-cadherin membrane expression in the invasive parts of the classical variant of ILC (LSAB x200); **(F)**: Aberrant E-cadherin membrane expression in the invasive parts of the pleomorphic variant of ILC (LSAB x400).

relation in our study could partially be explained by the fact that for almost one fifth of the classical ILC cases the tumor stage (T) could not be macroscopically determined (Table 1). Another reason for the discrepancy might be the high number of Tx cases that the mammographic interpretation of ILCs is often quite difficult and its sensitivity varies between 57 and 89%. The characteristic diffuse infiltrating growth pattern is only one of the possible obstacles in interpretation, and also the relatively low or equal radiographic opacity compared to normal fibroglandular tissue can represent an issue (sometimes even a 50-mm lesion can still be occult) [5]. When staging primary tumors according to the greatest size of the tumor mass, mistakes can be made if additional macroscopically invisible focus(es) was (were) present or if mammographically the tumor was manifested as an architectural distortion that corresponded to a palpable area of thickening [2].

The lymph node status (presence of metastases) is very important during the evaluation of BC, especially in those patients with the classical variant of ILCs. These tiny areas of metastases are sometimes missed out, even with the use of immunohistochemical methods, so in such cases the false-negative result can simply be a missed small metastasis [12]. Between the two analyzed variants of ILCs, the pleomorphic one is more prone to developing of distant metastases than the classical one [10]. On the other hand the pleomorphic variant is more prone to producing macro-metastases, which is a characteristic of ductal carcinoma [12]. A recent publication also point to the fact that there are no significant differences between the presence of axillary lymph node metastases and ILC variants [13], and this was noted in our study as well. Other authors concluded that there are no differences in patient age, lymph node status and expression of hormone receptors between different variants of ILC [14].

MFC/MCC are generally considered to be more common, even specific, for lobular BC [15]. Also ILC is suggested to be more often bilateral, have larger tumor size and microscopic MFC as a cause of the tendency for ductal spreading and MCC [16]. Certain published data point to the fact that the incidence of bilateral BC is more frequent in patients with classical ILC than in patients with other ILC variants [17]. However, others reported that pleomorphic ILCs tend to be multicentric and bilateral [10]. On the other hand, the results of our study revealed no statically significant correlation between tumor variants with either MFC, MCC or BL of ILC, with almost all cases (272 patients) belonging to the non-MFC/MCC/BL BC group ($p>0.05$, Table 2).

Besides ER positivity, the positivity of PR contributes to the prediction of BC independently of the ER reaction [18]. There is a low probability that the gene encoding PR is estrogen-dependent; the discovery of alternative estrogen mechanisms provided new insights into the concept that a low number of cases with ER(-)/PR(+) carcinomas are likely to respond to endocrine therapy. This proved to be of paramount importance in patients with ER (+) BC in women of all ages [19,20]. The statistically significant frequency of occurrence of both ER and PR were observed in patients with the classical variant of ILC (Table 4). There are contradictory studies that dealt with the differences in ER and/or PR expression of the classical and pleomorphic ILCs, where it was stated that the expressions of these two markers completely differed or were identical for the two variants [3,10,21,22].

Also, some additional relations were established between lower nuclear grade and ER(+)/PR(+) in patients with classical ILCs, but there was relatively rare occurrence of the same characteristics in those with the pleomorphic variant [23].

The presence of HER-2 and its overexpression or amplification in BC, represents one of the most important characteristics of BC because of the use of trastuzumab as first-line therapy for these patients [24]. One of the parameters put forward for an easier differentiation between the classical and pleomorphic ILCs is HER-2 expression; overexpression of HER-2 is observed in the pleomorphic ILCs [22]. In our study, HER-2 expression was found to occur more frequently in patients with the pleomorphic variant (22.6%) than in those with the classical one (15.6%), but without statistically significant correlation (Table 2).

In comparison to other histological types of BC, Ki-67 index in ILC is known to be positive in around 14% (median value) of the cases, which is considered as a low value of Ki-67 index [25]. Most publications on this subject indicated that the expression of Ki-67 was more frequent in patients with pleomorphic ILCs than in those with classical ILCs [26], and this was not substantiated by our results. Since the Ki-67 index was in good correlation with the response to chemotherapy of ILCs [27,28], it could be possibly brought in connection with the noted high Ki-67 index in patients with classical ILCs, known to better respond to chemotherapy, in our study (72.9% of cases). Newer studies proved that the determination of Ki-67 index, after a short endocrine therapy, increased survival predictions, thus making this marker useful for the detection of primary cancer, the choice of therapy, as well as the prediction of survival [29].

The regulation of cell growth and differentiation, as well as cell transformation, is under the influence of tumor suppressor genes. The p53 gene, involved in regulation of several important cell functions [3], is commonly present in its mutated form in BC, however it does not occur in normal breast tissue, ductal hyperplasia, atypical ductal hyperplasia and cases of lobular neoplasia [30]. The suggestions that the accumulation of p53 is in association with increased tumor aggressiveness [31] was not corroborated in our study (Table 4). The p53 positivity in the classical ILC was present in 42.3% of the cases, while in the pleomorphic ILCs, it was present in almost the same percent (42.1%), indicating that there was no correlation with the suggested theory of aggressiveness.

BRCA-1 is used as an immunohistochemical marker with its mutations practically undetectable in patients with sporadic occurrence of BC. Our analyses showed no statistically significant correlation between the ILC variants and BRCA-1 expression (Table 4). Also, the majority of our cases (23 of the classical and 7 of the pleomorphic variant) were BRCA-1 positive, which is not in agreement with the results of a recent study of the Greek population, where out of 8 ILCs none were BRCA-1 positive [32].

The expression of E-cadherin is useful for the differentiation of ILC and IDC. Additionally, we did not note a difference in E-cadherin expression between the two mentioned ILC variants (no statistically significant differences). However, loss of E-cadherin expression was observed in somewhat larger percentage for the pleomorphic variant of ILC (62%) than for the classical one (55%; Table 4). These findings can be brought into connection with publications where a number of pleomorphic ILCs was reported to have aroused from high grade IDCs of the rare ER positive and E-cadherin negative phenotype. However, the similarities between the pleomorphic and the classical variant of ILC (ER and PR positivity, loss of E-cadherin) suggest that many pleomorphic ILCs are not just IDCs with the loss of E-cadherin expression [4].

Conclusion

Although suggested to occur relatively rarely compared to other variants of ILC (<5%), the present study, that included patients from southeastern Serbia, revealed a much higher incidence (almost one fifth of the cases) of the pleomorphic variant. The frequency of ER and PR positivity of the classical variant was statistically significantly higher than in the pleomorphic variant which is in good agreement with the better response of the classical variant to hormone therapy and with the generally accepted attitudes towards hormone receptors expression in ILC variants. However, other pointed characteristics of the pleomorphic ILC, such as higher tumor stage, incidence of MCC, overexpression of HER-2 and higher p53 positivity, were not observed.

Acknowledgement

This work was funded by the Ministry of Education, Science and Technological Development of Serbia (Project 172061 and 175092).

Conflict of interests

The authors declare no confict of interests.

References

1. Colditz GA. Estrogen, estrogen plus progestin therapy, and risk of breast cancer. Clin Cancer Res 2005;11:909s-917s.
2. Tavassoli FA, Devilee A (Eds): Pathology and genetics of tumours of the breast and female genital organs. IARC Press, Lyon, 2003.
3. Radhi JM. Immunohistochemical analysis of pleomorphic lobular carcinoma: higher expression of p53 and chromogranin and lower expression of ER and PgR. Histopathology 2000;36:156-160.
4. Simpson PT, Reis-Filho JS, Lambros MBK et al. Molecular profiling pleomorphic lobular carcinomas of the breast: evidence for a common molecular genetic pathway with classic lobular carcinomas. J Pathol 2008;215:231-244.
5. Veltman J, Boetes C, van Die L, Bult P, Blickman JG, Barentsz JO. Mammographic detection and staging of invasive lobular carcinoma. Clin Imaging 2006;30:94-98.
6. Talman ML, Jensen MB, Rank F. Invasive lobular breast cancer. Prognostic significance of histological malignancy grading. Acta Oncol 2007;46:803-809.
7. Rosen PP (Ed): Rosen's breast pathology (2nd Edn). Lippincott, Williams and Wilkins, Philadelphia, 2001, pp 627-652.
8. Fu L, Tsuchiya S, Matsuyama I, Ishii K. Clinicopathologic features and incidence of invasive lobular carcinoma in Japanese women. Pathol Int 1998;48:348-354.
9. Jung SY, Jeong J, Shin SH et al. The invasive lobular carcinoma as a prototype luminal A breast cancer: A retrospective cohort study. BMC Cancer 2010;10:664-671.
10. Butler D, Rosa M. Pleomorphic lobular carcinoma of the breast, A morphologically and clinically distinct variant of lobular carcinoma. Arch Pathol Lab Med 2013;137:1688-1692.
11. Jung HN, Shin JH, Han BK, Ko EY, Cho EY. Are the imaging features of the pleomorphic variant of invasive lobular carcinoma different from classic ILC of the breast? Breast 2013;22:324-329.
12. Wei S, Bleiweiss IJ, Nagi C, Jaffer S. Characteristics of breast carcinoma cases with false-negative sentinel lymph nodes. Clin Breast Cancer 2014;14:280-284.
13. Jacobs M, Fan F, Tawfik O. Clinicopathologic and biomarker analysis of invasive pleomorphic lobular carcinoma as compared with invasive classic lobular carcinoma: an experience in our institution and review of the literature. Ann Diagn Pathol 2012;16:185-189.
14. Frost AR, Terahata S, Siegel RS et al. An analysis of prognostic features in infiltrating lobular carcinoma of the breast. Mod Pathol 1995;8:830-836.
15. Foote Jr FW, Stewart FW. A histologic classification of carcinoma of the breast. Surgery 1946;19:74-99.
16. DiCostanzo D, Rosen PP, Gareen I, Franklin S, Lesser M. Prognosis in infiltrating lobular carcinoma: An analysis of "classical" and variant tumors. Am J Surg Pathol 1990;14:12-23.
17. du Toit RS, Locker AP, Ellis IO, Elston CW, Nicholson RI, Blamey RW. Invasive lobular carcinomas of the breast-The prognosis of histopathological subtypes. Br J Cancer 1989;60:605-609.
18. Yamashita H, Yando Y, Nishio M et al. Immunohistochemical evaluation of hormone receptor status for predicting response to endocrine therapy in metastatic breast cancer. Breast Cancer 2006;13:74-83.
19. Fisher B, Redmond C, Brown A et al. Influence of tumor estrogen and progesterone receptor levels on the response to tamoxifen and chemotherapy in primary breast cancer. J Clin Oncol 1983;1:227-241.
20. Dowsett M, Allred C, Knox J et al. Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the Arimidex, Tamoxifen, alone or in combination trial. J Clin Oncol 2008;26:1059-1065.
21. Middleton LP, Palacios DM, Bryant BR, Krebs P, Otis CN, Merino MJ. Pleomorphic lobular carcinoma: morphology, immunohistochemistry, and molecular analysis. Am J Surg Pathol 2000;24:1650-1656.
22. Oliveira TM, Elias J, Melo AF et al. Evolving concepts in breast lobular neoplasia and invasive lobular carcinoma, and their impact on imaging methods. Insights Imag 2014;5:183-194.
23. Hoda SA. Invasive lobular carcinoma. In: Hoda SA, Brogi E, Koerner FC, Rosen PP (Eds): Rosen's breast pathology (4th Edn). Lippincott, Williams and Wilkins, Philadelphia, 2014, pp 855-893.
24. Murphy CG, Fornier M. HER2-positive breast cancer: beyond trastuzumab. Oncology-NY 2010;24:410-415.
25. Nishimura R, Osako T, Okumura Y et al. Ki-67 as a prognostic marker according to breast cancer subtype and a predictor of recurrence time in primary breast cancer. Exp Ther Med 2010;1:747-754.
26. Cha I, Weidner N. Correlation of prognostic factors and survival with classical and pleomorphic variants of invasive lobular carcinoma. Breast J 1996;2:385-393.
27. Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA. Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol 2010;11:174-183.
28. Urruticoechea A, Smith IE, Dowsett M. Proliferation marker Ki-67 in early breast cancer. J Clin Oncol 2005;23:7212-7220.
29. Dowsett M, Smith IE, Ebbs SR et al. IMPACT Trialists Group. Group: prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. J Natl Cancer Inst 2007;99:167-170.
30. Naidu R, Yadav M, Nair S, Kutty MK. Immunohistochemical analysis of p53 expression in primary breast carcinomas. Anticancer Res 1998;18:65-70.
31. Pratap R, Shousha S. Breast carcinoma in women under the age of 50: relationship between p53 immunos-

taining, tumour grade and axillary lymph node status. Breast Cancer Res Treat 1998;49:35-39.
32. Triantafyllidou O, Vlachos IS, Apostolou P et al. Epidemiological and clinicopathological characteristics of BRCA-positive and BRCA-negative breast cancer patients in Greece. JBUON 2015;20:978-984.