European Review for Medical and Pharmacological Sciences 2021; 25: 3990-3996

Comparative study of immunohistochemical determination of breast cancer molecular subtypes on core biopsy and surgical specimens

L. VUČKOVIĆ[1], A. KLISIC[2], J. RAONIĆ[1], J. VUĆINIĆ[1]

[1]Clinical Center of Montenegro, Department of Pathology, University of Montenegro-Faculty of Medicine, Podgorica, Montenegro
[2]Primary Health Care Center, University of Montenegro-Faculty of Medicine, Podgorica, Montenegro

Abstract. – OBJECTIVE: We aimed to compare the distribution of different molecular subtypes of invasive breast cancer (BC) between patients whose samples were obtained by core needle biopsy (CB) and surgical specimens (SS) and to assess the reliability of CB as a diagnostic method in this context.

PATIENTS AND METHODS: All patients (222) diagnosed with invasive BC were examined. Immunohistochemistry was performed on 40 samples obtained by CB and on 148 SS, while in 34 patients, the analysis was performed on both CB and SS. Molecular classification of BC was performed based on estrogen receptor (ER), progesterone receptor (PgR), Human epidermal growth factor receptor 2 (HER2), and Ki67 proliferative index status.

RESULTS: The most common molecular subtypes were Luminal A (43.2%) and Luminal B HER2- (29.7%). When comparing the frequencies of determined molecular subtypes, no difference was observed between samples obtained by CB and SS ($p>0.05$). Concordance analysis of molecular subtypes determined by immunohistochemistry on CB and SS was performed in 34 patients whose samples were obtained using both methods. No significant difference was observed in the designation of molecular subtype in relation to the sampling method ($p>0.05$). Results of immunohistochemistry analysis on CB and SS demonstrated good statistical agreement (Concordance rate=85.29%, Kappa=0.771, $p<0.001$).

CONCLUSIONS: CB might be a reliable method for the determination of the molecular subtype of invasive BC.

Key Words:
Breast cancer, Core biopsy, Surgery.

Introduction

Breast cancer (BC) is the most commonly diagnosed malignant tumor in women[1] and the leading cause of cancer-related death in females of the European continent[2].

In 2018, the estimated incidence of BC was 2,088,849 cases worldwide, with an estimated mortality of nearly 627,000 cases. In Montenegro, BC represented 36.8% of all malignancies diagnosed in women in 2018[3].

An increase in the incidence of BC was observed during the previous decade, which is mostly linked with the organization and implementation of screening programs for early detection of the disease[4]. At the same time, the mortality rate appears to be declining due to earlier diagnosis, as well as significantly more comprehensive treatment[1].

BC is a heterogeneous group of diseases[5]. According to St. Gallen Consensus, it is recommended to classify all BCs into the following molecular subtypes: Luminal A, Luminal B Human epidermal growth factor receptor 2 (HER2) negative (Luminal B HER2-), Luminal B HER2 positive (Luminal B HER2+), HER2 overexpressing (HER2+) and triple-negative BC (TNBC), based on immunohistochemical (IHC) detection of estrogen receptor (ER), progesterone receptor (PgR), HER2 and Ki67 proliferative index in tumor cells[1].

Treatment decisions for patients who suffer from BC are guided by clinical and radiological findings, as well as histopathological analysis of the tumor tissue[6,7].

Histopathological diagnosis is based on core needle biopsy (CB), which is guided by ultrasound or stereotaxically. It is essential to get CB samples before planning any treatment, and when this is not possible fine needle aspiration cytology (FNAC) is recommended[7]. As a sampling method, CB has a simpler technique and is associated with a lower rate of complications compared to surgery[8,9].

Corresponding Author: Aleksandra Klisic, MD, Ph.D; e-mail: aleksandranklisic@gmail.com

When preoperative systemic therapy is indicated, CB alone is expected to provide all the necessary information to guide the treatment. However, it could be argued that samples obtained by CB are less reliable in the diagnostic process compared to surgical specimens (SS) due to the smaller size of the sample, sampling errors, tumor heterogeneity and/or edge artifacts[10].

Studies that compared the results of immunohistochemistry (IHC) determined molecular subtypes of BC between the samples obtained by CB and SS are scarce. Regarding the possibility of a heterogeneous antigen distribution within the tumor, the main objective of the present study was to determine whether there is a statistically significant difference in IHC assignment of molecular subtype to the invasive BC in CB samples (in cases where preoperative systemic therapy was planned) and SS (in patients who were initially treated surgically). Importantly, to our knowledge, there are no studies that examined this issue in Montenegro.

Patients and Methods

We analyzed 222 women diagnosed with invasive BC during 2019 in the Clinical Center of Montenegro. The study was approved by the Institutional Ethical Committee, and informed consent was obtained from each patient.

Samples were obtained by CB and during surgery (SS). Invasive BC was initially confirmed on CB samples for all patients. In patients who were candidates for preoperative systemic therapy, ER and PgR, HER2 and Ki67 were determined on samples obtained by CB. In cases where surgery was the initial treatment of choice, the same analysis was performed on SS. CB samples were obtained using 14 Gauge needle, taking at least 4 samples from each patient for histopathological analysis. Each CB and SS were fixed in 10% buffered formalin from 6 to 72 hours. Histochemical staining using hematoxylin-eosin was performed in all samples, followed by IHC staining in order to determine the status of ER, PgR, HER2, and Ki67 proliferation index. After IHC analysis of HER2 receptor status, all patients whose score was 2+ were retested using the Dual-color dual-hapten *in situ* hybridization (D-DISH) method.

IHC staining was performed using ER (Monoclonal rabbit anti-human estrogen receptor α, clone EP1, FLEX ready to use, DAKO, Carpinteria, CA and Glostrup, Denmark), PgR (Monoclonal mouse anti-human progesterone receptor, clone PgR 636, FLEX ready to use, DAKO, Carpinteria, CA and Glostrup, Denmark), Ki67 (Monoclonal mouse anti-human Ki67 antigen, Clone MIB-1, FLEX Ready to use, DAKO, Carpinteria, CA and Glostrup, Denmark) and HER2 (Monoclonal rabbit primary antibody, anti-HER2/neu (4B5), Ventana BenchMark GX (Roche Diagnostics, Basel, Switzerland) antibodies on paraffin-embedded samples of tumor tissue, of both CB and SS. The staining procedure was performed in Autostainer Link 48, DAKO, Carpinteria, CA and Glostrup, Denmark (ER, PgR, Ki67) and Ventana BenchMark GX (Roche Diagnostics, Basel, Switzerland) (HER2). ER, PgR, and HER2 status was determined according to the American Society of Clinical Oncology/College of American Pathology (ASCO/CAP) recommendations, while Ki67 proliferative index was assessed upon reviewing nuclear positivity distribution over the whole slide for both CB and SS. If Ki67 expression was uniformly distributed over the entire slide, 500–2000 cells were chosen from different microscope fields; otherwise, 2000 cells were counted in both hotspot and negative areas of the specimen. Ki67 expression was scored as the percentage of positive invasive tumor cells with any nuclear staining and recorded as the mean percentage of positive cells[11].

Based on the results of IHC analysis, all cases were classified into molecular subtypes according to St. Gallen consensus criteria[7].

Statistical Analysis

Statistical analysis was carried out in IBM® SPSS® Statistics version 20.0 software (IBM SPSS Statistics for Windows, Armonk, NY, USA), using both descriptive and inferential statistical methods, i.e., Mann-Whitney test, Chi-square test with Yates correction, and the Kappa test were used where appropriate. The p-values <0.05 (two-sided tests) were regarded to be statistically significant.

Results

Samples of 222 patients diagnosed with invasive BC were analyzed. IHC was performed on 40 samples obtained by CB and 148 SS, while 34 patients had their IHC analysis performed on both CB and SS. The age distribution of the

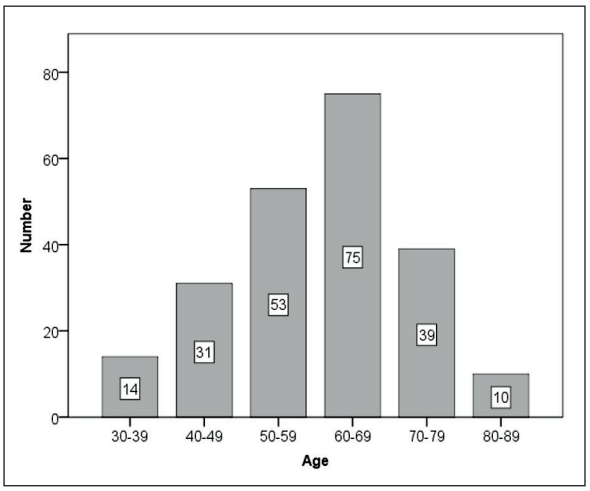

Figure 1. Age distribution of patients diagnosed with breast cancer.

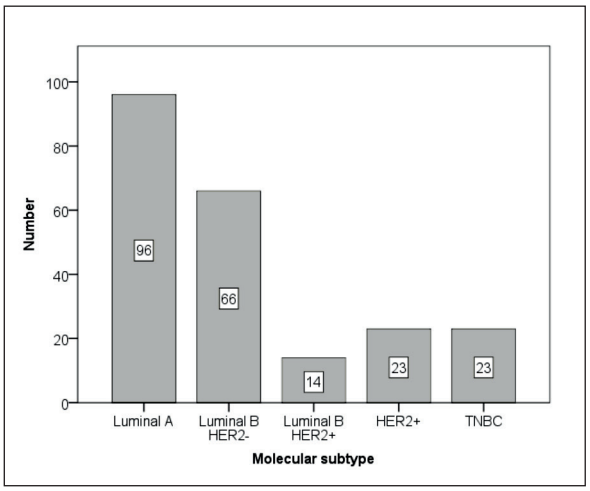

Figure 2. Frequency of different molecular subtypes in patients diagnosed with invasive breast cancer.

patients is shown in Figure 1. The average age at diagnosis was 60.7 ± 12.3 years (the youngest woman was 30 years old, while the oldest one was 87 years old). The majority were between 50 and 69 years old (57.7%), while 20.3% of newly diagnosed patients were under the age of 50.

The frequency of different molecular subtypes in the examined group of patients is shown in Figure 2. In cases where IHC analysis was performed on both CB and SS, results of the latter were taken into account. Overall, the most common subtypes were Luminal A (43.2%) and Luminal B HER2- (29.7%). HER2+ and TNBC were diagnosed in 10.4%, while Luminal B HER 2+ was diagnosed in 6.3% of patients.

The results of statistical analysis (Table I) showed that patients with established Luminal A molecular subtypes were significantly older compared to patients with Luminal B subtypes, both HER2- and HER2+ ($p<0.05$). Also, patients diagnosed with HER2+ subtype were significantly older compared to those diagnosed with Luminal B HER2+ ($p<0.05$).

The frequency of different molecular subtypes in the group of patients whose samples were obtained by CB is shown in Table II. In this group, the most common subtypes were Luminal A (35%) and Luminal B HER2- (32.5%). TNBC, HER2+, and Luminal B HER2+ represented 15%, 12.5%, and 5% of cases, respectively.

In surgically obtained specimens (Table III), Luminal A and Luminal B HER2- subtypes were also the most common ones, found in 46.2% and 27.5% of cases, respectively. HER2+ was diagnosed in 9.9%, TNBC in 9.3%, and Luminal B HER2+ in 7.1% of cases.

Table I. Comparison of mean age at the time of diagnosis for patients with different molecular subtypes.

Type		Mean difference	Sig.	95% confidence interval	
				Lower bound	Upper bound
Luminal A	Luminal B HER 2-	5.152	.030	.33	9.97
Luminal A	Luminal B HER 2+	13.412	.000	4.76	22.07
Luminal A	HER 2 +	2.204	.921	-5.08	9.49
Luminal A	TNBC	6.653	.067	-.29	13.59
Luminal B HER 2-	Luminal B HER2+	8.260	.085	-.67	17.19
Luminal B HER 2-	HER 2 +	-2.948	.824	-10.55	4.66
Luminal B HER 2-	TNBC	1.501	.980	-5.78	8.78
Luminal B HER 2+	HER 2 +	-11.208	.029	-21.67	-.74
Luminal B HER 2+	TNBC	-6.759	.367	-16.99	3.47
HER 2 +	TNBC	4.449	.664	-4.65	13.55

Table II. Frequency of molecular subtypes in samples obtained by core biopsy.

Molecular subtype	Number	%	Cumulative
Luminal A	14	35.0	35.0
Luminal B HER2-	13	32.5	67.5
Luminal B HER2+	2	5.0	72.5
HER2+	5	12.5	85.0
TNBC	6	15.0	100.0
Total	40	100.0	

Table III. Frequency of molecular subtypes in surgically obtained samples.

Molecular subtype	Number	%	Cumulative
Luminal A	84	46.2	46.2
Luminal B HER2-	50	27.5	73.6
Luminal B HER2+	13	7.1	80.8
HER2+	18	9.9	90.7
TNBC	17	9.3	100.0
Total	182	100.0	

When comparing the frequencies of determined molecular subtypes, no statistically significant difference was observed between the samples obtained by CB and SS ($p>0.05$).

Concordance analysis of molecular subtypes determined by IHC on CB and SS was performed in 34 patients whose samples were obtained using both methods (Table IV). No statistically significant difference was observed in the designation of molecular subtype in relation to the sampling method ($p>0.05$). Furthermore, results of IHC analysis on CB and SS demonstrated good statistical agreement (Concordance rate=85.29%, Kappa=0.771, $p<0.001$).

Discussion

As far as we know, this is the first study that examined CB as a diagnostic procedure in BC and the first comparative study of the immunohistochemical determination of BC molecular subtypes on CC and SS in the female population in Montenegro. In the present study, which included 222 women diagnosed with BC, the average age at diagnosis was 60.7 ± 12.3 years. More than half of women were diagnosed between 50 and 69 and one-fifth before the age of 50. Our results are in accordance with the previous reports[7].

It is now generally accepted that BC is not a unique process and that there are significant differences in histological, molecular, and clinical characteristics within this entity. Gene expression profiling by deoxyribonucleic acid (DNA) microarray has identified five molecular subtypes but, given the fact that this method is expensive and not widely available, IHC determination of the molecular subtype represents a good alternative[12-14].

Table IV. Concordance analysis of determined molecular subtypes on core biopsy and surgical specimens.

	OP							
	Luminal A	Luminal B HER 2-	Luminal B HER2+	HER 2+	TNBC	Total	Concordance rate (%)	Kappa (*p*-value)
Luminal A	15	1	0	0	0	16	85.29	0.771
Luminal B HER 2-	3	8	1	0	0	12		($p = 0.000$)
Luminal B HER 2+	0	0	1	0	0	1		
HER2+	0	0	0	1	0	1		
TNBC	0	0	0	0	4	4		
Total	18	9	2	1	4	34		

The selection of the most suitable therapeutic approach depends on the determination of the molecular subtype, which also represents an important factor in predicting the disease outcome[15].

The results of the present study showed that Luminal A is the most common molecular subtype (43.2%), followed by Luminal B HER2- (29.7%). Overall, 72.9% of cases were ER and PgR positive and HER2 negative (Luminal A and Luminal B HER2-) BCs.

Kumar et al[12] also found that the most common subtype was Luminal A (34%). TNBC was present in 25% of cases; both Luminal B and HER2+ subtypes were found in 18% of the cases, while 5% belonged to the Unclassified subtype.

Errahhali et al[16] also showed in a study conducted on a series of 2260 cases of BC that the most common molecular subtype was Luminal A (61.1%), and less frequent subtypes were Luminal B, HER2+, and TNBC, with the frequency of 16.1%, 14.2%, and 8.6%, respectively.

In studies that included different populations, despite the differences in methodology and tissue processing methods applied to determine Er, PgR, HER2, and Ki67, two-thirds of BCs were ER and PgR positive ones (HR)[8].

Similar results were obtained by a large study conducted in 2010 patients in the USA, which showed that 72.7% of diagnosed BCs were HR+/HER2-. However, the authors suggested that subtype distributions varied by age, race, ethnicity, country-level poverty, stage, and grade of the tumor. Compared to patients diagnosed with HR+/HER2- tumors, those diagnosed with the other three subtypes were somewhat more likely to be younger, belong to minority racial or ethnic groups, live in countries with higher poverty levels, and have a later stage and higher Bloom-Richardson grade disease[17].

The present study showed that patients with established molecular Luminal A subtype were significantly older compared to patients with Luminal B (both HER2- and HER2+ subtypes), as were the patients diagnosed with HER2+ compared to Luminal B HER2+ molecular subtype.

These results are in accordance with the results of other authors. Namely, Howlader et al[17] demonstrated that patients with triple-negative, HR+/HER2+ and HR-/HER2+ BC were 10% to 30% less likely to be diagnosed at an older age compared to HR+/HER2- patients, and 6.4-fold to 20.0-fold more likely to present with high-grade disease. Similarly, in a large epidemiological study on a series of 2544 patients with BC, Kwan et al[18] showed that, in contrast to Luminal A cases, Luminal B, triple-negative and HER2-overexpressing cases tend to be younger at diagnosis.

Continuously emerging BC molecular profiling data keep emphasizing the potential impact of tumor heterogeneity on the diagnostic process due to the existence of biologically and histologically different zones[19]. Lately, a number of authors have questioned the reliability of assessment of ER, PgR, HER2, and Ki67 expression on CB samples of invasive BC[20-26].

A large meta-analysis that included the data from 27 published studies shows that CB has a high diagnostic value in evaluating biomarkers in BC, indicating that CB may be a reliable procedure for ER, PgR, and HER2 determination[27]. However, very few published papers show the reliability of the determination of molecular subtypes in CB samples in the available literature.

When comparing the frequencies of IHC determined molecular subtypes in 222 cases in total, the present study found no significant difference between the samples obtained by CB and SS.

Concordance analysis of molecular subtypes on CB and SS, performed in 34 paired samples, showed no statistically significant difference in the designation of molecular subtype, demonstrating good statistical agreement.

A similar result was reported by Meattini et al[28], with the concordance rate of 87.1% (Kappa=0.78), in a study of 101 patients. According to their results, CB showed good accuracy in the evaluation of estrogen and progesterone receptors, HER2 status, and molecular subtype. Chen et al[1], who analyzed 298 patients, reported a somewhat lower concordance rate of 77.2% (Kappa=0.65), mainly due to intra-tumoral heterogeneity of Ki67 expression, resulting in misclassification of approximately 14% of HR+/HER2- cases as Luminal A instead of Luminal B on CB.

A relatively small sample size of the examined specimens is the limitation of the current study. However, it represents the entire group of samples analyzed during 2019 in Montenegro related to this pathology as it is the first study that investigated the reliability of CB as a diagnostic procedure in this country. Also, TNBC can be subdivided into 6 subtypes: basal-like 1 (BL1), BL2, Mesenchymal stem-like (MSL), Mesenchymal (M), Luminal androgen receptor (LAR), and Immunomodulatory (IM)[29]. Although we did not make such a subdivision in the current study, this could be a useful suggestion for our future investigations.

New studies with large sample size are needed to confirm our results.

Conclusions

Given the results obtained, it can be concluded that CB, as a minimally invasive diagnostic procedure, might be a reliable method for the determination of the molecular subtype in patients with invasive BC. Keeping in mind that BC represented more than two-thirds of all malignancies diagnosed in women in 2018, this procedure seems to be of utmost importance for the timely diagnosis of the mentioned malignancy in the female population in Montenegro.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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