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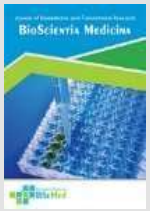

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Characteristics of Triple Negative Subtype Breast Cancer in Dr. Hasan Sadikin General Hospital for 5 Years (2019-2023): An Observational Study

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A B S T R A C T

Background: Triple-negative breast cancer has a percentage of 15% to 20% in breast cancer patients at the time of first diagnosis. Guidelines from St. Gallen guidelines, the American Society of Clinical Oncology, and the American College of Pathology state that triple-negative breast cancer is breast cancer with ER and PR expression <1%. As an aggressive subtype, outcomes are poor when compared with hormone receptor-positive. **Methods:** This research is an observational study. The research subjects in this study were triple-negative breast cancer patients in Dr. Hasan Sadikin General Hospital, Surgical Oncology division, West Java, Indonesia, from October 2018 - November 2023. There were 702 research subjects who would be studied. Characteristics of triple-negative breast cancer were taken from medical records. **Results:** The results showed that the average age of the subjects was 47 years. Based on histology, the most common was Invasive Carcinoma of no special type (86.75%), followed by Invasive lobular carcinoma (7.26%), medullary carcinoma (1.7%), micropapillary carcinoma (0.99%), metaplastic carcinoma (2.36%) and the least amount is Pleomorphic invasive lobular carcinoma (0.71%). The side of the breast affected is not significant, and the highest grade is 3. The involvement of lymph node metastases is due to aggressive tumor subtypes and lymphovascular invasion. Lymphovascular invasion is known to be a negative prognostic factor. It is a late stage for metastasis and local recurrence. **Conclusion:** Triple-negative breast cancer is breast cancer that has histopathological heterogeneity; most of the tumors are grade 3 and have significant metastases in regional lymph nodes. There is no significant relationship between grading and regional lymph node metastases. there is a significant relationship between lymphovascular invasion and regional lymph nodes metastases.

1. Introduction

Triple-negative breast cancer is breast cancer with a lack of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2). The percentage of triple-negative breast cancer cases is 15% to 20% at the time of first diagnosis, and it is known as an aggressive subtype; the outcome is poor when compared with hormone receptor-positive. It is a challenge for breast cancer researchers because of differences in response to standard chemotherapy and limited therapeutic options. Triple-negative breast cancer is a heterogeneous disease; it is difficult to find molecular targets for therapy. Biologically and clinically relevant subtypes contribute to identifying therapeutic targets, clinical research design, and patient risk stratification.[1,2]

Guidelines from St. Gallen guidelines, the American Society of Clinical Oncology, and the American College of Pathology state that triple-negative breast cancer is breast cancer with ER and PR expression <1%. It is widely accepted that triple-negative breast cancer represents an inhomogeneous, disseminated subtype, such as metaplastic, medullary, adenoid cystic, and apocrine carcinoma. Several markers were identified, such as cytokeratin

(CK) 5/6 and epidermal growth factor receptor (EGFR). There are subclassifications for triple-negative breast cancer: basal-like I and basal-like II (BL1 and BL2), mesenchymal (M), and luminal androgen receptor (LAR), based on retrospective data analysis by Lehmann and colleagues in 2016. Based on this division, analysis of immunohistochemical examination can be used as a prognosis and prediction. In clinical practice, it can be used as a parameter to predict survival or even response to therapy.[2-4]

2. Methods

This research is an observational study of the characteristics of triple-negative subtype breast cancer at Dr. Hasan Sadikin General Hospital, Surgical Oncology division, West Java, in the period October 2018 - November 2023. Sampling was carried out using the total sampling method with a total sample size of 702 patients. The inclusion criteria in this study were patients diagnosed with triple negative subtype breast cancer with tumor subtypes of invasive carcinoma of no special type, invasive lobular carcinoma, medullary carcinoma, micropapillary carcinoma, metaplastic carcinoma, and pleomorphic invasive lobular carcinoma. Each subtype will be analyzed for its characteristics based on histopathology, location, grading, and involvement of lymph node metastases and lymphovascular invasion. Exclusion criteria include incomplete data on patients diagnosed with triple negative subtype breast cancer in the medical record. The sample data that has been collected will be analyzed descriptively using proportions.

3. Results

The results showed that the median age of the subjects was 47 years. Based on the histological, it was found that the most common types of triple-negative breast cancer were Invasive Carcinoma of no special type, reaching 86.75%, Invasive lobular carcinoma 7.26%, Medullary carcinoma 1.7%, Micropapillary carcinoma 0.99%, Metaplastic carcinoma was 2.56%, and the smallest number was Pleomorphic invasive lobular carcinoma, only 0.71%. The most common locations were found on the right breast with a total of 372 (52.99%), the left with a total of 323 (46.01%), and bilaterally with a total of 8 (1.13%). In grading, there are 123 in grade 2 (17.52%) and 579 in grade 3 (82.47%), and there are 277 involved in regional lymph node metastases (39.45%) and 199 for lymphovascular invasion (27.2%) as in Table 1.

Table 1. Characteristics of research subjects.

Variable	Proportion (%)
Age	
Mean	46.27 ± 14.3 years
Median	47 years
Histology	
ICNST	609 (86.75%)
ILC	51 (7.26%)
Medullary carcinoma	12 (1.7%)
Micropapillary carcinoma	7 (0.99%)
Metaplastic carcinoma	18 (2.56%)
Pleomorphic ILC	5 (0.71%)
Tumor grade	
Grade 2	123 (17.52%)
Grade 3	579 (82.47%)
Tumor location	
Right	372 (52.99%)
Left	323 (46.01%)
Bilateral	8 (1.13%)
Regional lymph node metastases	
Positive (+)	277 (39.45%)
Negative (-)	425 (60.54%)
Lymphovascular invasion	
Positive (+)	191 (27.2%)
Negative (-)	511 (72.79%)

Table 2. Analysis of subject characteristics with each subtype.

Characteristic	ICNST	ILC	Medullary carcinoma	Micropapillary carcinoma	Metaplastic carcinoma	Pleomorphic ILC
Grading						
Grade 2	100 (14.2%)	15 (2.13%)	2 (0.28%)	0 (0%)	5 (0.71%)	1 (0.14%)
Grade 3	509 (72.5%)	36 (5.12%)	10 (1.4%)	7 (0.99%)	13 (1.85%)	4 (0.56%)
Location						
Right	315 (44.8%)	37 (5.27%)	5 (0.71%)	2 (0.28%)	7 (0.99%)	4 (0.56%)
Left	287 (40.8%)	11 (1.56%)	7 (0.99%)	5 (0.71%)	11 (1.56%)	1 (0.14%)
Bilateral	5 (0.71%)	3 (0.43%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Regional lymph node metastases						
Positive (+)	234 (33.3%)	39 (5.56%)	1 (0.14%)	2 (0.28%)	1 (0.14%)	0 (0%)
Negative (-)	476 (66.7%)					
Lymphovascular invasion						
Positive (+)	158 (22.5%)	26 (3.7%)	2 (0.28%)	1 (0.14%)	3 (0.42%)	1 (0.14%)
Negative (-)	552 (77.5%)					

As the results of the analysis in Table 2 show, it can be seen that there is a relationship between the characteristics of triple-negative subtype breast cancer and histopathology, location, grading, involvement of lymph node metastases, and lymphovascular invasion. Invasive Carcinoma of no special type was found to be the most common in 609 cases (86.75%), with Grade 2 being 100 cases (14.2%) and Grade 3 being 509 (72.5%), on the right side being 315 cases. (44.8%), left side in 287 cases (40.8%) and bilateral in 5 cases (0.71%), regional lymph node metastasis in 234 cases (33.3%), and lymphovascular invasion in 158 cases (22.5%). The invasive Lobular Carcinoma subtype was 51 (7.26%), with Grade 2 being 15 cases (2.13%) and Grade 3 being 36 (5.12%), on the right side 57 cases (5.27%), left side 11 cases (1.56%) and bilateral in 3 cases (0.43%), regional lymph node metastasis in 39 cases (5.56%) and lymphovascular invasion in 26 cases (3.7%). Medullary carcinoma subtype was 12 (1.7%), with Grade 2 being 2 cases (0.28%) and Grade 3 being 10 (1.4%), on the right side being 5 cases (0.71%), the left were 7 cases (0.99%) and there were no bilateral cases, regional lymph node metastasis was 1 case (0.14%) and lymphovascular invasion was 2 cases (0.28%). Micropapillary carcinoma subtype was 7 (0.99%), with Grade 2 and Grade 3 not being found in 7 (0.99%), on the right side in 2 cases (0.28%), on the left side in 5 cases (0, 71%) and there were no bilateral cases, regional lymph node metastasis was 2 cases (0.28%) and lymphovascular invasion was 1 case (0.14%). Metaplastic carcinoma subtype was 18 (2.56%), grade 2 was found in 5 cases (0.71) and grade 3 was 13 (1.85%). On the right side, there were 7 cases (0.99%); on the left side, there were 11 cases (1.56%), and there were no bilateral cases; regional lymph node metastasis was 1 case (0.14%), and lymphovascular invasion was 3 cases (0.42%). The pleomorphic carcinoma subtype was 5 (0.71%), Grade 2 was obtained in 1 case (0.14), and Grade 3 was found in 4 (0.56%). On the right side, there were 4 cases (0.56%), on the left side there was 1 case (0.14%), and there were no bilateral cases, no regional lymph node metastases and lymphovascular invasion were found in 1 case (0.14%).

There is no significant relationship between tumors with grade 3 (high grade) and metastases in regional lymph nodes in patients with triple-negative breast carcinoma (p-value 0,755), as shown in Table 3. Table 4 shows that there is a significant relationship between lymphovascular invasion and metastases in regional lymph nodes in the axilla (p value 0,009).

Table 3. Relationship between tumor grade and regional lymph node metastases.

		Regional Lymph node metastases			Chi-Square (p-value)
		+	-	Total	
Grade	2	73	50	123	0.755
	3	352	227	579	
Total		425	277	702	

Table 4. Relationship between lymphovascular invasion and regional lymph node metastasis.

		Lymphovascular invasion			Chi-Square (p-value)
		-	+	Total	
Metastases regional lymph node	-	390	125	425	0.009
	+	133	54	277	
Total		511	191	702	

4. Discussion

Triple-negative breast cancer is breast carcinoma, with an incidence of 10%–15% of all breast cancers. Tumor with aggressive character, high risk of local recurrence, and distant metastasis to the lung, liver, and brain with a poor prognosis. At diagnosis, axillary lymph node involvement and large tumors are often found. Tumor heterogeneity in triple-negative breast cancer is a concern as a reason for differences in clinical outcomes, with varying responses to chemotherapy with or without radiation. Triple-negative breast cancer has limited therapeutic options, high rates of recurrence, metastasis, and poor prognosis. Neoadjuvant chemotherapy significantly increases PCR (Pathology complete response) compared with hormone receptor-positive subtype and improved prognosis. Molecular heterogeneity and cells that grow more rapidly than other subtypes of breast cancer, chemotherapy is more effective in cells that grow quickly, Chemosensitive triple-negative breast cancer (cytotoxic agents) such as anthracyclines and taxanes, which is standard therapy in high-risk patients. Currently, there is targeted therapy for triple-negative breast cancer, namely PARP inhibitors (Olaparib and talazoparib) for patients with BRCA mutations and Programmed death-ligand 1. Atezolizumab and Pembrolizumab are anti-PDL-1. Improved biomarkers are needed to provide information for better patient selection.[5-7]

Lehmann and colleagues divided into 7 subtypes: immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), luminal androgen receptor (LAR), unstable (UNS) subtype and two basal-like subtypes (BL1 and BL2). Then, this subclassification into 4 groups: basal-like I and basal-like II (BL1 and BL2), mesenchymal (M), and luminal androgen receptor (LAR) based on a retrospective analysis by Lehmann and colleagues in 2016. This classification can be used for prognostic, predictive, and proof-of-concept purposes in discovering new drugs and clinical research designs. Approximately 50% to 80% of initial breast cancer diagnoses are invasive carcinoma of no special type, and approximately 20% are invasive lobular carcinoma. In special type histopathology, special characters are found in the cells and special molecular behavior. The most common types of this are medullary carcinoma, metaplastic carcinoma, apocrine carcinoma, mucinous carcinoma, cribriform carcinoma, tubular carcinoma, neuroendocrine carcinoma, classic lobular carcinoma, and pleomorphic lobular carcinoma.[8,9]

In the histopathological subtype, invasive carcinoma of no special type is the most frequent type, accounting for around 40% to 75% of all types of invasive breast carcinoma. In this descriptive study, it was found that invasive carcinoma of no special type was most commonly found in 609 cases (86.75%), more than research by Nascimento and friends. With grading, grade 2 was 100 cases (14.2%), and grade 3 was 509 (72.5%); there was no correlation with the side of the affected breast. Invasive lobular carcinoma is the second most common histological subtype, accounting for approximately 5-15% at first diagnosis and in advanced age. In this study, the Invasive lobular carcinoma subtype was found in 51 (7.26%), with grade 2 in 15 cases (2.13%) and grade 3 in 36 (5.12%), bilateral cases in 3 cases (0.43%) and an average age of 47 years. Medullary carcinoma is a rare histopathological type, accounting for less than 5% of all cases. has a good prognosis among other invasive breast carcinomas. Generally occurs in BRCA1 mutation carriers. In this study, the Medullary carcinoma subtype was found to be 12 (1.7%), in accordance with research by Makki J. Medullary carcinoma was correlated with the IM (immunomodulatory) subtype, with a good prognosis

even though it was high-grade on histology, in this study grade 2 was obtained as many as 2 cases (0.28%) and grade 3 as many as 10 cases (1.4%).[10-13]

Invasive micropapillary carcinoma is a rare subtype, accounting for approximately 2% of all invasive carcinomas. This subtype often involves extensive skin and lymph node invasion. poor prognosis and low survival. In this study, there were 7 subtypes of micropapillary carcinoma (0.99%), and grade 3 was 7 (0.99). Solid papillary carcinoma has a good prognosis; there are mutations in IDH2 R172 and PIK3CA, low local recurrence, and low regional metastases to the axillary lymph nodes; in this study, regional lymph node metastases were found in 2 cases (0.28%). Metaplastic carcinoma is an aggressive subtype of breast carcinoma with characteristics of metaplastic differentiation (squamous, spindle, and mesenchymal). Found in less than 1% of all invasive carcinomas. It is rare to find metastases to the axillary lymph nodes. In this study, there were 12 medullary carcinoma subtypes (1.7%), with Grade 2 in 2 cases (0.28%) and Grade 3 in 10 (1.4%) and lymph node metastasis in 1 case (0.14%), according to the research of Makki J. Metaplastic carcinoma is a squamous type or mesenchymal differentiation type, high grade and is associated with a low survival rate and resistance to chemotherapy. Metaplastic carcinoma also has a high presentation of TP53 mutations and proliferation via the PI3K and WNT pathways. Low-grade variants of metaplastic carcinoma are adenosquamous and fibromatosis-like carcinoma. Pleomorphic lobular carcinoma is characterized by a larger cell size than classic invasive lobular carcinoma, with a very large number of eosinophils in the cytoplasm. This variant often occurs in negative hormonal receptors with high expression of P53 and the HER2/neu subtype. In this study, the Pleomorphic lobular carcinoma subtype was 5 (0.71%), Grade 2 was obtained in 1 case (0.14), and grade 3 as many as 4 (0.56%).[14,15]

Lymphovascular invasion is an invasion of the lymphatic blood vessels by a thrombus from the tumor. It is an advanced stage for metastasis and local recurrence. Lymphovascular invasion is known to be a negative prognostic factor, defined as tumor cells appearing in the endothelium (both the lymphatic system and blood vessels) in an area surrounded by invasive carcinoma cells. As an early indicator, lymphovascular invasion was found in 24% of all patients. In this study, lymphovascular invasion was found positive in 191 patients (27.2%), 158 cases (22.5%) in invasive carcinoma of no special type, 26 cases (3.7 %) in invasive lobular carcinoma, 2 cases (0.28%) in medullary carcinoma, 2 cases (0.28%) in micropapillary carcinoma, 3 cases (0.42%) in metaplastic carcinoma cases, 1 case (0.14 %) in cases of pleomorphic invasive lobular carcinoma.[16-19]

5. Conclusion

Triple-negative breast cancer is a subtype of breast cancer with 15% to 20% at first diagnosis and is known as an aggressive subtype with poor outcomes. The average age of patients is 47 years. Based on histology, the most common is invasive carcinoma of no special type, followed by invasive lobular carcinoma, medullary carcinoma, micropapillary carcinoma, and metaplastic carcinoma, and the least number is pleomorphic invasive lobular carcinoma. The side of the breast affected was not significant, and the highest grade was 3. There is no significant relationship between grade 3 (high grade) and regional lymph node metastases (p-value 0.755). There were 39.45% metastases to the lymph nodes because the patients had received neoadjuvant chemotherapy. lymph node metastatic involvement due to aggressive tumor subtype. Lymphovascular invasion was found in 27.2%, which is known as a negative prognostic factor. This is an advanced stage for metastasis and local recurrence. There was a significant relationship between lymphovascular invasion and regional lymph node metastases (p-value 0.009).

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