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The Relationship of Breast Cancer Subtypes with the Event of Metastasis in Dr. M. Djamil Hospital Padang

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ABSTRACT

Background: One of the high mortality rates from breast cancer is related to the incidence of metastases. It is known that >90% of deaths in breast cancer are related to the incidence of metastases and the complications that follow. Breast cancer is divided into several subtypes based on the expression of receptor genes in breast cancer tissue, namely Luminal A, Luminal B, HER 2 and Triple Negative Breast Cancer (TNBC). This study aims to determine the relationship between breast cancer subtypes and the incidence of metastases in Dr. M. Djamil Padang. **Methods:** This study used a retrospective case-control study to breast cancer patients with metastatic at Dr M Djamil Hospital, Padang from 2016-2021. The research subjects were 260 breast cancer patients who met the inclusion criteria. The study subjects were divided into 130 patients as the case group with metastases and 130 patients as the control group with no metastases. To determine the relationship between breast cancer subtypes and the incidence of metastases, the chi-square test was used. If the p value <0.05, it can be concluded that it is significant. Furthermore, analysis is continued to obtain an odds ratio (OR) in identifying risk opportunities with Cochran's and Mantle-Haenszel statistics common odds ratio estimate. The data were analysed using the Statistical Package for Social Sciences (SPSS) program. **Result:** Characteristics of the subjects in this study can be seen that there is a relationship between hormonal contraception, T and N status with the incidence of metastasis (p <0.05). Patients with metastases were more common with breast cancer subtypes luminal B (61.5%), HER2+ (21.5%), TNBC (14.6%) and luminal A (2.3%). The most common locations for breast cancer metastases were lung (48.5%), bone (26.2%), liver (19.2%), brain (5.4%) and other places (0.8%). There was a relationship between breast cancer subtypes and the incidence of metastasis (p<0.038). The highest risk of metastases was in patients with TNBC subtype with OR = 7.74 (95% CI 1.72-34.79). There was no relationship between breast cancer subtypes with metastatic location (p>0.05) and breast cancer subtypes TNBC had a risk (OR) of 9.60 (95% CI 1.96-47.14) times increasing the risk of metastases in brain. **Conclusion**: It can be concluded that there was a relationship between breast cancer subtypes and the incidence of metastasis.

1. Introduction

Breast cancer is the most common type of cancer found worldwide, and is the fifth most common cause of cancer death among all types of cancer. Based on data from Globocan 2020, it is estimated that there are 2,261,419 million new cases (11.7% of all cancer cases in the world) each year beating lung cancer (11.4%), colorectal (10.0%), prostate (7. 3%), and stomach (5.6%), with 684,996 (6.9%) of them ending in death.[1] In Indonesia, based on data obtained from the Dharmais Cancer Hospital in 2018, breast cancer is the most common type of cancer with a prevalence of 19.18%, and is 34.30% among all cancer incidences in women.[2]

One of the high mortality rates from breast cancer is related to the incidence of metastases. It is known that >90% of deaths in breast cancer are related to the incidence of metastases and the complications that follow.[3]

Breast cancer is divided into several subtypes based on the expression of receptor genes in breast cancer

tissue, namely Luminal A (Estrogen Receptor positive and/or Progesterone receptor positive, Human Epidermal Growth Factor Receptor 2 negative, and Ki-67 14%), Luminal B (Estrogen Receptor positive). Receptor positive and/or Progesterone positive, Human Epidermal Growth Factor Receptor 2 negative, and Ki-67>14% or Estrogen Receptor positive and/or Progesterone positive, Human Epidermal Growth Factor Receptor 2 positive), Human Epidermal Growth Factor Receptor 2 Positive (Estrogen Receptor negative, Progesterone negative, Human Epidermal Growth Factor Receptor 2 positive), and Basal Like or often known as Triple Negative Breast Cancer (TNBC) (Estrogen Receptor negative, Progesterone negative, Human Epidermal Growth Factor Receptor 2 negative).[4]

Breast cancer is known as a cancer with high heterogeneity, both in terms of the molecular characteristics that form the basis for the division of breast cancer subtypes, or tumour characteristics, biologic behaviour and clinicopathology such as lymphovascular infiltration, and their response to various therapeutic modalities to prognosis.[5,6] Molecular subtypes also correlate with the risk of local and regional recurrence or distant metastasis of breast cancer.[7]

Although there have been several studies examining the relationship between breast cancer subtypes and metastasis, these studies are still very limited with inconsistent and very mixed results. Based on this background description, a study was conducted to determine whether there was a relationship between breast cancer subtypes with the event of metastasis in Dr. M. Djamil Hospital Padang.

2. Methods

This study used a retrospective case-control study to breast cancer patients with metastatic at Dr M Djamil Hospital, Padang from 2016-2021.

The research subjects were 260 breast cancer patients who met the inclusion criteria. The study subjects were divided into 130 patients as the case group with metastases and 130 patients as the control group with no metastases.

To determine the relationship between breast cancer subtypes and the incidence of metastases, the chi-square test was used. If the p value <0.05, it can be concluded that it is significant. Furthermore, analysis is continued to obtain an odds ratio (OR) in identifying risk opportunities with Cochran's and Mantle-Haenszel statistics common odds ratio estimate. The data were analysed using the Statistical Package for Social Sciences (SPSS) program.

3. Result

In this study, it was found that there was a relationship between a history of hormonal contraception, T and N status with the incidence of metastasis ($p<0.05$). However, there was no relationship between age, marital status, menopausal status, breastfeeding history, grade, ER, PR, HER2 and Ki67 with the incidence of metastasis ($p>0.05$). (Table 1)

Table 2 shows that patients with metastases are more common with breast cancer subtypes luminal B (61.5%), HER2+ (21.5%), TNBC (14.6%) and luminal A (2.3%). Meanwhile, in patients who did not have metastases, the subtypes of breast cancer were luminal B (60.0%), HER2+ (24.6%), luminal A (8.5%) and TNBC (6.9%). Table 5.3 shows that the most common locations for breast cancer metastases are lung (48.5%), bone (26.2%), liver (19.2%), brain (5.4%) and other places (0.8%).

Table 1 Subject characteristics

Characteristic	Category	Group		p-value
		Case (f/%)	Control (f/%)	
Ages	< 50 years	52 (40,0)	55 (42,3)	0,801
	≥ 50 years	78 (60,0)	75 (57,7)	
Marriage	Not married	4 (3,1)	0 (0)	0,122
	Married	126 (96,6)	130 (100,0)	
Menopause	Yes	55 (42,3)	67 (51,5)	0,172
	No	75 (57,7)	63 (48,5)	
Hormonal Contraception	Yes	108 (83,1)	83 (63,8)	**0,001***
	No	22 (16,9)	47 (36,2)	
Breast Feeding	Yes	124 (95,4)	125 (96,2)	1,000
	No	6 (4,6)	5 (3,8)	
Grade	I	3 (2,3)	7 (5,4)	0,219
	II	106 (81,5)	109 (83,8)	
	III	21 (16,2)	14 (10,8)	
T Status	T1	0 (0)	4 (1,5)	**<0,001***
	T2	4 (3,1)	22 (16,9)	
	T3	26 (20,0)	55 (42,3)	
	T4	100 (76,9)	49 (37,7)	
N Status	N0	3 (2,3)	36 (27,7)	**<0,001***
	N1	57 (43,3)	69 (53,1)	
	N2	50 (38,5)	20 (15,4)	
	N3	20 (15,4)	5 (3,8)	
ER	Positive	66 (50,8)	78 (60,0	0,170
	Negative	64 (49,2)	52 (40,0)	
PR	Positive	63 (48,5)	75 (57,7)	0,172
	Negative	67 (51,5)	55 (42,3)	
HER2	Positive	60 (46,2)	64 (49,2)	0,710
	Negative	70 (53,8)	66 (50,8)	
KI67	>20 %	127 (97,7)	119 (91,5)	0,054
	<20 %	3 (2,3)	11 (8,5)	

*p<0.05 significant

Table 2. Breast cancer subtypes

Subtype	Group		Total
	Case (f/%)	Control (f/%)	
Luminal A	3 (2,3)	11 (8,5)	14 (5,4)
Luminal B	80 (61,5)	78 (60,0)	158 (60,8)
HER2+	28 (21,5)	32 (24,6)	60 (23,1)
TNBC	19 (14,6)	9 (6,9)	28 (10,8)
Total	130 (100,0)	130 (100,0)	260 (100,0)

Table 3. Locations of breast cancer metastases

Metastasis	F	%
Bone	34	26,2
Brain	7	5,4
Lung	63	48,5
Liver	25	19,2
Others	1	0,8

Table 4 shows that there is a relationship between subtypes of breast cancer and the incidence of metastases (p<0.05). The highest chance of metastatic risk was in patients with TNBC subtype with OR = 7.74 (95% CI 1.72-34.79) followed by luminal B with OR = 3.76 (95% CI 1.01-13.99).

Table 4. The relationship between breast cancer subtypes and the incidence of metastases

Subtype	Group		Total	p-value	OR (95% CI)
	Case (f/%)	Control (f/%)			
Luminal A	3 (2,3)	11 (8,5)	14 (5,4)	**0,038***	0,13 (0,03-0,58)
Luminal B	80 (61,5)	78 (60,0)	158 (60,8)		**3,76 (1,01-13,99) ***
HER2+	28 (21,5)	32 (24,6)	60 (23,1)		3,21 (0,81-12,67)
TNBC	19 (14,6)	9 (6,9)	28 (10,8)		**7,74 (1,72-34,79) ***

Table 5 shows that there is no relationship between breast cancer subtypes and the location of metastases (p>0.05). The risk for breast cancer subtypes based on each metastatic location can be seen in table 6.

Table 5. Relationship between breast cancer subtypes and the location of metastases

Subtiype	Metastasis					Total	p-value
	Bone (f/%)	Brain (f/%)	Lung (f/%)	Liver (f/%)	Other (f/%)		
Luminal A	1 (2,9)	0 (0)	1 (1,6)	1 (4,0)	0 (0)	3 (2,3)	0,196
Luminal B	24 (70,6)	2 (28,6)	36 (57,1)	17 (68,0)	1 (100,0)	80 (61,5)	
HER+	6 (17,6)	1 (14,3)	18 (28,6)	3 (12,0)	0	28 (21,5)	
TNBC	3 (8,8)	4 (57,1)	8 (12,7)	4 (16,0)	0	19 (14,6)	

Table 6. Risk for breast cancer subtypes based on each metastatic site

Subtype	Metastasis OR (95% CI)			
	Bone	Brain	Lung	Liver
Luminal A	0,70 (0,06-7,99)	n/a	1,91 (0,17-21,57)	0,47 (0,04-5,35)
Luminal B	1,74 (0,74-3,97)	4,33 (0,81-23,26)	1,44 (0,71-2,92)	0,71 (0,28-1,78)
HER+	1,39 (0,51-3,78)	1,69 (0,19-14,63)	0,44 (0,18-1,04)	2,29 (0,63-8,30)
TNBC	2,07 (0,56-7,59)	**9,60 (1,96-47,14) ***	1,35 (0,51-3,61)	0,88 (0,26-2,91)

Table 6 shows that the TNBC breast cancer subtype has a risk (OR) of 9.60 (95% CI 1.96-47.14) times increasing the risk of brain metastases.

4. Discussion

In this study, the risk factors for the use of hormonal contraception were associated with the incidence of metastases in breast cancer (p = 0.001). This was also stated by *Jamnasi (2016)* where 17% of patients with metastatic breast cancer had a history of using hormonal family planning. Hormonal family planning has been known as a risk factor for breast cancer. Research by *Hasnita et al (2019)* explains that the use of hormonal family planning is the most dominant hormonal risk factor in the incidence of breast cancer. The use of hormonal birth control containing estrogen and progesterone will cause a proliferative effect on the ductal epithelium of the breast and if followed by loss of control in apoptosis, it will result in continuous tissue proliferation without being able to be controlled.[8,9,10]

Tumor size is a predictor to see the survival rate of

breast cancer patients. Research conducted by *Laura S et al (2005)* showed that there was a relationship between breast cancer tumor size and lymph node metastasis and infiltration. The same thing was also shown in this study where T status in breast cancer patients was associated with the incidence of metastases, which means that the higher the T value, the higher the probability of metastases ($p < 0.001$). This is in line with the results of research by *Anwar et al (2020)* which explains that infiltration into the skin and chest wall (T4a-c) has a higher risk for distant metastases. Something that could explain the relationship between tumor size and the risk of metastases is that as cancer cells progress, cancer cells accumulate a specific set of genetic events to have the ability to spread to regional lymph nodes and distant organs. [11,12,13,14]

In this study, N status was found to be associated with the incidence of metastases in breast cancer ($p < 0.001$). This study is in line with the results of the *Jamnasi (2016)* study which found a positive N status associated with metastasis in the case group. This was also found by other studies such as *Anwar et al (2020)*, who found positive axillary lymph nodes (N1-3) to have a higher risk of distant metastases.[8,13]

In this study, it was found that in the case group, the subtypes of breast cancer were luminal B (61.5%), HER2+ (21.5%), TNBC (14.6%) and luminal A (2.3%). Meanwhile, in the control group, breast cancer subtypes were luminal B (60.0%), HER2+ (24.6%), luminal A (8.5%) and TNBC (6.9%). The luminal B subtype is a subtype with positive hormonal receptors, Her 2 positive/negative and Ki-67 > 20. The number of metastases in Luminal B compared to Luminal A is related to the amount of KI 67 expression.[15]

In this study, the most common locations for breast cancer metastases were lung (48.5%), bone (26.2%), liver (19.2%), brain (5.4%) and the ovaries (0.8%). %). This is in accordance with a study by Anwar et al (2020) which showed the lungs were the most common site (12.7%), followed by bone (12.3%), pleura (8.8%), liver (5 .5%), and brain (1.9%) but different results were obtained by Xiao et all (2018) namely bone (3.28%), followed by lungs (1.52%), liver (1, 20%), and brain metastases (0.35%).[13, 16, 17]

This study found that there was a relationship between specific breast cancer subtypes and the incidence of metastasis ($p<0.05$). This result is reinforced by the results of another study by Xiao et al (2016) which showed the same results. Breast cancer subtype as we know is one of the determining factors in metastatic organotropism in breast cancer. [17.18]

This study explains that the highest risk of metastases is in patients with TNBC subtype with OR = 7.74 (95% CI 1.72-34.79) followed by luminal B with OR = 3.76 (95% CI 1, 01-13.99). This result is also in accordance with what was stated by Anwar (2020) that the TNBC subtype has the highest rate of distant metastases (27.3%). Triple negative is a subtype of breast cancer with ER, PR, and HER-2 negative. This subtype has the worst prognosis compared to other subtype classifications. The triple negative subtype has high invasiveness, high potential for metastasis and recurrence, and poor prognosis. [19,20]

In this study, there was no relationship between breast cancer subtypes and the location of metastases ($p>0.05$). TNBC had a risk (OR) of 9.60 (95% CI 1.96-47.14) times increasing the risk of brain metastases. These results are consistent with those described by Xiao (2018) for TNBC subtypes having a higher chance of risk in brain (OR, 1.95), liver (OR, 1.35), and lung (OR, 1.34) metastases.) but the rate of bone metastases was significantly lower (OR, 0.64).[17]

We are trying to investigate whether there is an association between breast cancer subtypes and the incidence of metastases that will be useful for the management of these patients. However, this study has some limitations related to the retrospective case-control design based solely on secondary data. Analysis of disease duration, treatment effect, and comorbid contribution was also not possible. Larger studies involving multiple centre or population-based studies with longer periods are needed to confirm this study.

5. Conclusion

In this study, it was proven that there was a relationship between breast cancer subtypes and the incidence of metastasis and TNBC Subtype had a risk

9.60 times increasing the risk of brain metastases.

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