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Breast cancer relationship with sub molecular metastasis

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Abstract--The purpose of this research is to find out (1). Characteristics of breast cancer patients (2). Types of breast cancer subtypes (3). Location of breast cancer metastases (4). The relationship between breast cancer subtypes with the incidence of metastases. Methods This study used a retrospective control of breast cancer patients with metastases. The study subjects were 300 breast cancer patients who met the inclusion criteria which were divided into 150 metastatic patients in the case group and 150 patients without metastases in the control group. chi-square test. If the p value < 0.05, it is significant, with (OR) in identifying risk opportunities using the mantle-haenszel statistics common odds ratio estimate. Data analysis with (SPSS). Conclusion: Patients with breast cancer at Banten Hospital there were 65% of patients aged 55 years in the case group and 58.0%, the control group = 3.0 %, not married 42.0% and 52.0% menopause, 83.0% and 64.0% used hormonal contraception 5.0% and 4.0% patients did not breastfeed their babies with the case control

group. Most breast cancer metastases are located in the lung (48.5%), bone (26.5%), liver (19.5%), brain (5.5%) and other places (1.0%).

Keywords---breast cancer, molecular subtype, metastasis.

Introduction

Breast cancer as a type of cancer that is found throughout Banten, is the cause of death from cancer. (Purwadianto, Agus., 2014). Based on data from Globocan 2020, it is estimated that there are 2,261,420 million new cases, 12% of all cancer cases in the world. In each year lung cancer 12%, colorectal 10.0%, prostate 8%, and 6% stomach, with 684,996 = 7%, of which end in death. The mortality rate from breast cancer is higher in developing countries than in developed countries, with an incidence rate of 56, and 30 per 100,000 population, and mortality rates of 15.0 and 13 per 100,000 population in both developing and developed countries.

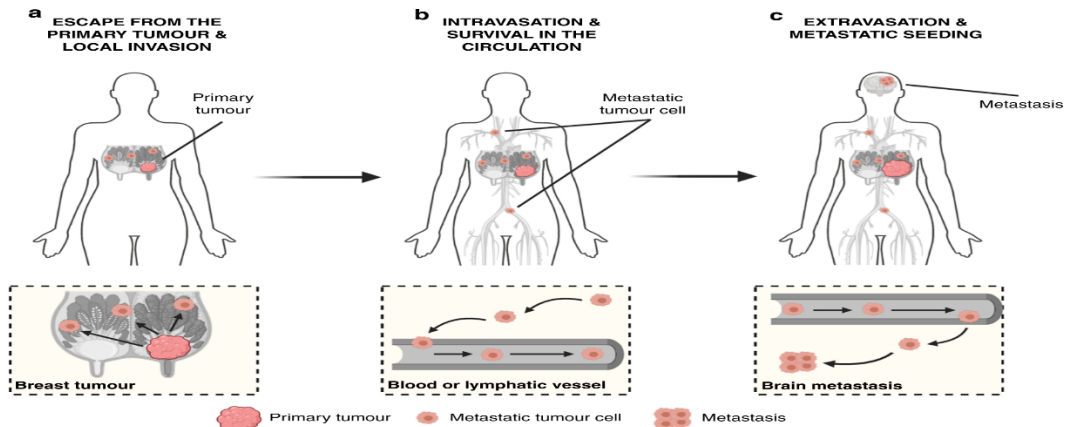


Figure 1. Metastasis in breast cancer
(Source: Nature.com)

Cancer in Indonesia, based on data from the Dharmais Cancer Hospital in 2019, breast cancer is the most common type of cancer with a prevalence reaching 20%, and as 35% among cancers in women. (Ponniah, Geethamalar., 2010). Meanwhile in Banten Province, based on data obtained from Banten Hospital, there were 7,100 outpatient cases and 610 inpatient breast cancer cases during the 2016-2019 period.

The number of breast cancer patients in Banten Province is very high. Based on data from the Tangerang District General Hospital as a referral hospital in Banten Province, in 2019 there were 4,289 patients seeking treatment, 12% of which was comparable to 503 new patients. The patient is a patient with an advanced stage with a very high mortality rate.

The high mortality rate due to breast cancer is one of them with the incidence of metastases. That > 90% of deaths in breast cancer with the incidence of

metastases and complications. (Yodang, S., 2018). It is estimated that 5%-10% of patients have metastases at the time of first diagnosis, and 20%-40% develop metastases in the course of the disease, ending with a poor prognosis. Breast cancer is divided into several subtypes based on the expression of receptor genes in breast cancer tissue, namely luminal A, which is Estrogen Receptor positive and/or Progesterone receptor positive, Human Epidermal Growth Factor Receptor 2 negative, and Ki-67 14%), luminal B, which is Estrogen. Receptor positive and/or Progesterone positive, Human Epidermal Growth Factor Receptor 2 negative, and Ki-67>14%.

Positive Estrogen Receptor and/or positive Progesterone, Positive Human Epidermal Growth Factor Receptor 2, Positive Human Epidermal Growth Factor Receptor 2 i.e. (Wan, Desen., 2011). Estrogen Receptor negative, Progesterone negative, Human Epidermal Growth Factor Receptor 2 positive, and Basal Like or often known as Triple Negative Breast Cancer, Estrogen Receptor negative, Progesterone negative, Human Epidermal Growth Factor Receptor 2 negative.

Breast cancer is known as a cancer with high heterogeneity, both in terms of molecular characteristics that form the basis for subtypes of breast cancer, as well as tumor characteristics, biologic and clinicopathological behavior such as lymphovascular infiltration, and their response to various therapeutic modalities and prognosis. (Noviyani, R., Niruri, R., 2017). Each subtype of breast cancer is also known to describe different characteristics. In epidemiology, luminal subtype breast cancer is the most common and is associated with endogenous hormone exposure, while non-luminal subtype breast cancer occurs less frequently and is more associated with non-hormonal factors. However, the luminal type is known to have a better prognosis and five-year survival rate than the nonluminal type.

An understanding of the relationship between breast cancer subtypes and the tendency to metastasize from each of these breast cancer subtypes is a crucial matter to be investigated because it will be closely related to breast cancer related to metastatic screening methods, selection of adjuvant treatment to monitoring decisions and follow-up, which is ultimately expected can increase the efficiency and accuracy of treatment, and can reduce morbidity and mortality in breast cancer. (Nursalam., 2011). There have been studies on the relationship between breast cancer subtypes and the propensity to metastasize, these studies are very limited with inconsistent and very mixed results. Therefore, the authors are interested in conducting research on the relationship between breast cancer and sub-molecular metastases at RSU Banten.

Method

This study used a quantitative approach with a retrospective case-control study of breast cancer patients with sub-molecular metastases.

Data collection technique

The collection used in collecting data and information is through questionnaires in the form of questionnaires, in-depth interviews, and field observations. (Sugiyono., 2017). namely as follows:

1. Questionnaire as several written questions to obtain data from respondents regarding things they know. Respondents can give answers openly, with alternative answers determined, as an instrument in research.
2. Interviews were conducted to obtain data and information about problems related to research subjects. The research instrument used an interview guide and a checklist.
3. Observations using research instruments in the form of observation sheets, observation guides, observation guides and checklists.

Sampling

1. The research sample was taken using a convenience sampling technique, namely the research sample was taken from data that has been documented in medical records and met the inclusion and exclusion criteria of metastatic and non-metastatic breast cancer patients in 2016-2021.
2. The minimum sample size is determined by using the unpaired analytical test formula. The minimum sample size is determined by the formula. Based on the sample calculation formula, the samples in each research group were 124 so that the total sample as a whole was 228 subjects.

Discussion

Subject Characteristics

The characteristics of the subjects in this study can be seen as follows.

Table 1 Subject characteristics

No	Characteristics	Category	Group	
1	Age	< 50 years	52(40,0)	55(42,0)
		≥ 50 years	78(60,0)	75(58,0)
2	Marital status	Not married yet marry	4(3,0)	0 (0)
			126 (97,0)	130(100,0)
3	Menopausal status	Menopause	55(43,0)	67(52,0)
		Not Menopause yet	75(58,0)	63(49,0)
4	Contraceptive History Hormonal	Yes	108(83,0)	83(64,0)
		Not	22(17,0)	47(36,0)
5	Breastfeeding history	Yes	124 (96,0)	125 (96,0)
		Not	6(5,0)	5(4,0)
6	Grade	I	3(2,5)	7(6,0)
		II	106(82,0)	109 (84,0)
		III	21(16,5)	14(11,0)
7	T status	T1	0(0)	4(2,0)
		T2	4(3,0)	22(17,0)
		T3	26(20,0)	55(42,0)
		T4	100 (77,0)	49(38,0)
8	N Status	NO	3(2,5)	36(28,0)

		N1	57(43,0)	69(53,0)
		N2	50(39,0)	20(16,0)
		N3	20(15,5)	5(4,0)
9	ER	Positive	66(51,0)	78 (60,0)
		Negative	64(49,0)	52(40,0)
10	PR	Positive	63(49,0)	75(58,0)
		Negative	67(52,0)	55 (42,0)
11	HER2	Positive	60(46,0)	64 (49,0)
		Negative	70(54,0)	66 (50,8)
12	KI67	>20 %	127 (98,0)	119(92,0)
		<20 %	3(2,5)	11(9,0)

Based on table 1, it is known that the characteristics of the subject are 60% of patients aged more than 50 years in the case group and 58% in the control group. For hormonal risk factors, there were only 3% who were not married in cases, 43% and 52% of patients had menopause, 84% and 64% of patients used hormonal contraception and 5% and 4% of patients who did not breastfeed their babies in the case and control groups. (Mohammed, A. A., 2021). On the histopathological level, the highest frequency was found in grade 2, namely 82% and 84%, respectively. The highest T status was at T4 77% and T3 43% in controls. Meanwhile, the highest N status was in N1 44% and 54% in the case and control groups.

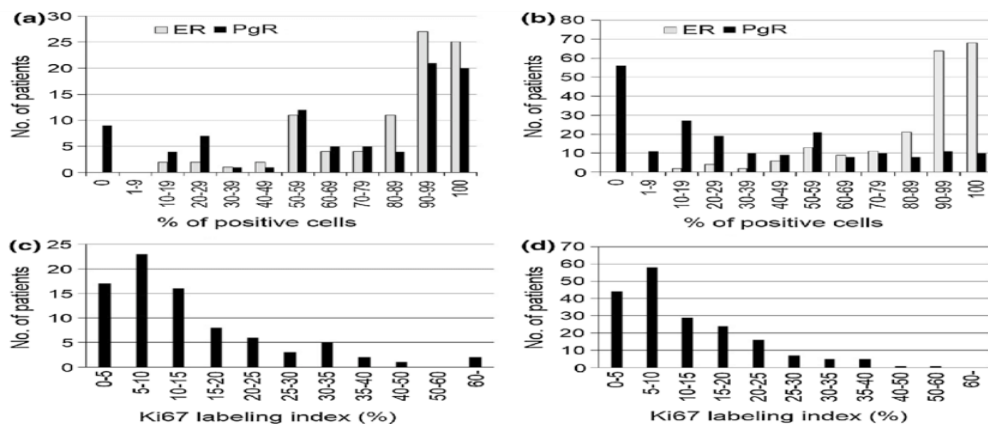


Figure 2 Expression of estrogen receptor (ER) and progesterone receptor (PgR) (Source: researchgate.net)

Based on the biomolecular profile, the case group was ER positive as much as 51%, PR 49%, Her 2 = 47% and KI 67 > 20% = 98% while in the control group ER positive was 60%, PR 58%, Her 2 = 50 % and KI 67 > 20% by 92%

Types of Breast Cancer Subtypes

The types of breast cancer subtypes in the research subjects can be seen in the table as follows:

Table 2 Types of breast cancer subtypes

No	Breast cancer subtype	Group		
		Case (f/%)	Control (f/%)	Total
1	Luminal A	3(4)	11(8)	14 (5)
2	Luminal B	80(60)	78(60)	158 (62)
3	HER2+	28(20)	32(25)	60(25)
4	TNBC	19(15)	9(7)	28(10)
5	Total	150(100,0)	150(100,0)	300(100,0)

Based on table 2 above, it is known that patients with metastases are more common with breast cancer subtypes luminal B (60.5%), HER2+ (22.5%), TNBC (15.5%) and luminal A (3.3%).). Meanwhile, in patients who did not have metastases, the subtypes of breast cancer were luminal B (60.0%), HER2+ (24.6%), luminal A (9.5%) and TNBC (6.9%).

Location of Breast Cancer Metastases

The location of breast cancer metastases in research subjects can be seen in table 3 as follows:

Table 3 Locations of breast cancer metastases

No	Organ metastases	Case (f/%)	Control (f/%)
1	Bone	34	26
2	Brian	7	5
3	Lungs	62	49
4	Heart	25	29
5	Another place	1	1

Based on table 3 above, it is known that the most common locations for breast cancer metastases are lung (49%), bone (26%), liver (19%), brain (6%) and other places (1%).

Relationship between breast cancer subtypes and metastases

The relationship between breast cancer subtypes and the incidence of metastases in research subjects can be seen as follows.

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

Breast cancer subtype	Group				
	Case (f/%)	Control (f/%)	Total (f/%)	p-value f/%)	OR(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)		3,80 (1,01-13,99)*

HER	28(21,5)	32(25,0)	60 (23,1)		3,20 (0,81-12,67)
TNBC	19(14,6)	9(6,9)	28 (10,8)		7,70 (1,72-34,90)*

*p<0,05 significant

Based on table 4 above, it can be seen that there is a relationship between breast cancer subtypes and the incidence of metastases ($p < 0.05$). (Nindya, S., Suroso, B., 2016). The highest probability of metastatic events occurred in patients with TNBC subtype with OR = 7.70 (94% CI 1.70-34.80) followed by luminal B with OR = 3.80 (95% CI 1.01-13.99).

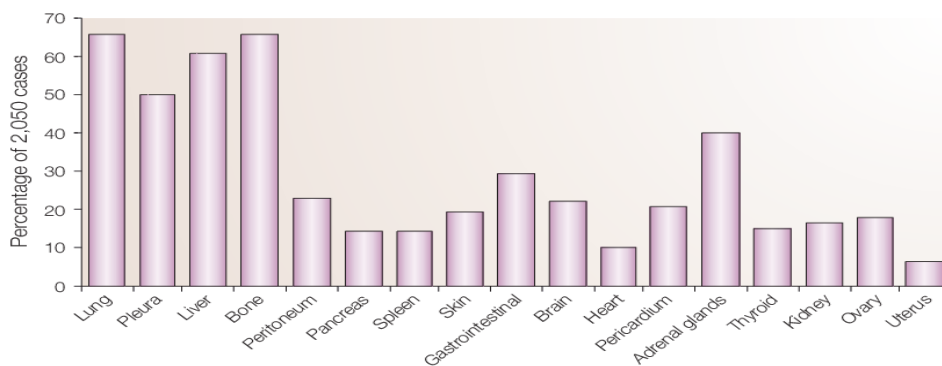


Figure 3. Breast cancer metastases markers
(Source: semanticscholar.org)

Relationship between breast cancer subtypes and metastatic sites

The relationship between breast cancer subtypes and the location of metastases in research subjects can be seen as follows.

Table 5 The relationship between breast cancer subtypes and the location of metastases

Subtype Breast cancer	Another place					Total	p-value f/%
	Bone (f/%)	Brain (f/%)	Lungs (f/%)	Heart (f/%)	Another place (f/%)		
Luminal A	1(3,0)	0 (0)	1(1,7)	1 (4,0)	0 (0)	3 (2,3)	0,198
Luminal B	24(71,0)	23(61,8)	1(100,0)	80(29,0)	(57,1)	(68,0)	(61,5)
HER	6(17,6)	1 18 3	(12,0)	028 (14,3)	(28,6)	0	(22,0)
TNBC	3(8,8)	48(12,7)	4(16,0)	0	19(57,1)	0	(14,8)

*p<0,05 significant

Based on table 5 above, it can be seen that there is no relationship between breast cancer subtypes and the location of metastases ($p > 0.05$). The risk

opportunities for breast cancer subtypes based on each metastatic location can be seen as follows.

Table 6 Risk opportunities for breast cancer subtypes by location of significant metastases; n/a, not account

subtype Breast cancer	OR metastatic site (94% CI)			
	Bone	Brain	Lungs	Haert
Luminal A	0,70 (0,06-7,96)	-	1,90 (0,17-21,60)	0,47 (0,04-5,35)
Luminal B	1,75 (0,74-3,96)	4,35(0,81-3,30)	1,45(0,71-,95)	0,71(0,28-1,78)
HER	1,39 (0,51-3,80)	1,70(0,19-4,60)	2,29(0,63-8,30)	0,44 (0,18-1,05)
TNBC	2,07 (0,56-7,60)	9,60(1,96-7,14)	1,35(0,51-3,60)	0,88 (0,26-2,95)

*p<0,05 significant

Based on table 6, it is known that the TNBC breast cancer subtype has a risk opportunity (OR) of 9.60(94% CI 1.96-47.10) times increasing the risk of brain metastases.

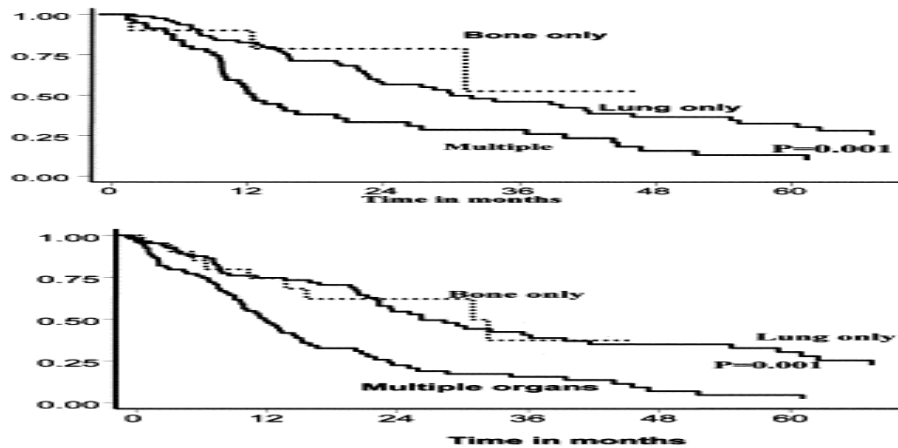


Figure 4. The risk of breast cancer subtypes at the site of metastasis (Source: semanticscholar.org)

Discussion

Subject Characteristics

This study with subjects amounted to 270 breast cancer patients. The study subjects were divided into 130 patients as the case group with metastases and 130 patients as non-metastatic cases. (Nursalam., 2013). Identification of risk factors associated with metastases is very important in determining breast cancer medical and monitoring after treatment. Therefore, the identification of factors associated with an increased risk of metastases, subtypes of breast cancer as well

as several interventions on potential factors to reduce risk are important studies in the field of oncology.

In this study, risk factors such as age, marital status, menopausal status, history of hormonal contraception and breastfeeding were found, the use of hormonal contraception was 83.5% in the case group. Where there are 16.5% of patients with metastatic breast cancer have a history of using hormonal contraceptives. Hormonal contraception has been known as a risk factor for breast cancer. (Hasnita et al., 2019). The use of hormonal contraceptives as the most dominant hormonal risk factor in the incidence of breast cancer. Hormonal contraceptives 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, will result in continuous tissue proliferation that cannot be controlled.

Tumor size as a predictor to see the survival rate of breast cancer patients. (Husen, A., Hardian., 2016). Shows the relationship between breast cancer tumor size and lymph node metastasis and infiltration. The same thing was also shown in this study where the T status was highest at T4 76.5% and T3 42.5% in controls, which means that the higher the T value, the higher the possibility for metastases to occur. Infiltration into the skin and chest wall (T4a-c) carries a higher risk for distant metastases. Something that could explain the relationship between tumor size and risk of metastases as 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.

In today's era of genomic profiling, immunohistochemistry is developing rapidly in the management of breast cancer. N status remains as an important determinant as a guide in decision making on treatment, survival rates, metastases in breast cancer patients. (Anita., 2016). Therefore, in addition to tumor size, the risk of metastases is also associated with N status. In this study, N status was found at most 44.0% N1 while N negative or NO was found only 2.5% in the case group, which means positive N status. have a role in increasing the risk of metastatic breast cancer. This study found positive N status was associated with metastasis in the case group and also found positive axillary lymph nodes (N1-3) had a higher risk of distant metastases.

Breast Cancer Subtype

In this study, it was found that in the case group, the subtypes of breast cancer were luminal B (60.5%), HER2+ (22.5%), TNBC (13.6%) and luminal A (2.5%). (Aslinda, et al., 2013). Meanwhile, in the control group, breast cancer subtypes were luminal B (60.0%), HER2+ (25.0%), luminal A (8.5%) and TNBC (7.0%). The frequency of breast cancer subtypes at RSU Banten are luminal A 20.0%, luminal B 29.0%, Her 2 = 23.0% and TNBC 29.0%. Luminal B subtype as a subtype with positive hormonal receptors, Her 2 positive/negative and Ki-68 > 22. (Rasjidi, Imam., 2010). The number of metastases in Luminal B compared to Luminal A was related to the abundance of KI 68 expression. That the level of Ki-67 expression was positively correlated with tumor size and the number of lymph node metastases. These findings suggest that the high expression of Ki-68 plays a central role in promoting the pathogenesis and progression of breast cancer. In

addition, Ki-68 plays an important role in promoting the genesis and metastasis of breast cancer.

Location of Breast Cancer Metastases

In this study, the most common locations for breast cancer metastases were lung (49.0%), bone (26.0%), liver (19.0%), brain (5.0%) and the ovaries (1.0%). This study showed 16.5 lungs as the most common site (13.0%), followed by bone (12.0%), pleura (9.0%), liver (6.0%), and brain (2.0%). (Astuti, D., 2010). However, different results were obtained by Xiao et al (2018), namely bone (3.28%), followed by lung (2.0%), liver (1.0%), and brain metastases (0.5%). This occurs because of differences in diagnosing breast cancer metastases, especially in bone. In this study, breast cancer patients were not subjected to a bone scan, which is a necessary examination if the histopathological or clinical examination of lesions >6 cm in size and suspected of having distant metastases.

This study showed that the most common sites for metastases were the lungs. The lungs had a higher expression of chemokine ligand 12 (CXCL12) than other organs, while breast cancer cells overexpressed chemokine receptor 4 (CXCR4). (Deni, Syamsuddin., 2013). Organs that have higher CXCL12 expression are associated with a common site of occurrence in target organs of distant metastases. The CXCR4-CXCL12 interaction promotes the migration of breast cancer cells to target organs for distant metastases in breast cancer.

Relationship between breast cancer subtypes and metastases

Breast cancer has been recognized as a heterogeneous disease with the most basic differences in molecular changes and clinical course. That there is a relationship between specific breast cancer subtypes with the incidence of metastases ($p < 0.06$). Results in other studies showed the same results. (Firdaus, V. R. P., 2016). Breast cancer subtype as known as one of the determining factors in metastatic organotropism in breast cancer. That the highest risk of metastases occurred in patients with TNBC subtype with OR = 7.8 (95% CI 1,7234.80) followed by luminal B with OR = 3.8 (95% CI 1.01-14.00). The results were consistent with the TNBC subtype having the highest rate of distant metastases (28.0%).

In Triple negative as 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 is highly invasive. (Halimatussakdiah., Unardi., 2017). The potential for metastasis and recurrence is high, and the prognosis is poor. Systemic chemotherapy is the choice because the triple negative subtype has no expression of ER, PR, and 18.0 HER-2 so it is not sensitive to hormonal treatment.

Relationship between breast cancer subtypes and metastatic sites

In this study, there was no relationship between breast cancer subtypes and the location of metastases ($p > 0.05$). (Faith, Rasjidi, H. S., 2016). The possible risk of breast cancer subtypes based on each metastatic site can be demonstrated in this

study. In this study, the TNBC breast cancer subtype had a risk opportunity (OR) of 9.60 (95% CI 1.96-47.15) times increasing the risk of brain metastases. These results are consistent with those described by Xiao (2018) for the TNBC subtype having a higher chance of risk in brain (OR, 1.95), liver (OR, 1.35), and lung (OR, 1.35) metastases. but the rate of bone metastases was significantly lower (OR, 0.65).

Brain metastases are one of the main complications associated with TNBC subtypes and threaten the survival of TNBC patients. (Marpaung, M. R. A., et. al., 2020). The unique biological characteristics of TNBC cancer cells favoring brain invasion and metastasis, destruction of the BBB, formation of a highly permeable brain barrier, and alteration of the central nervous system microenvironment all play key roles in the formation of brain metastases in TNBC

Conclusion

1. The main conclusions of the study may be presented in a short Conclusions Breast cancer patients at Banten Hospital there were 65% of patients aged over 55 years in the case group and 58.0% in the control group, only 3.0% were unmarried in cases, 42.0% and 52.0% patients menopausal, 83.0% and 64.0% of patients used hormonal contraception and 5.0% and 4.0% of patients who did not breastfeed their babies in the case and control groups. Histopathology was mostly grade 2, namely 82.0% and 84.0%. The highest T status was at T4 77.0% and T3 42.0% in controls. Meanwhile, the highest N status was in N1 43.0% and 53.0% in the case and control groups. Biomolecular profile, in the case group ER positive was 50.8%, PR 48.5%, Her 2 46.0% and KI 68 > 22% was 98.0% while in the control group ER positive was 62%, PR 58, 0%, Her 2 49.0% and KI 68 > 22 % by 92.5%.
2. Patients with metastases were mostly found with breast cancer subtypes luminal B (62.0%), HER2+ (22.0%), TNBC (15.0%) and luminal A (2.0%). In patients who did not experience metastases, the subtypes of breast cancer were luminal B (60.0%), HER2+ (25.0%), luminal A (9.0%) and TNBC (7.0%).
3. The most common locations for breast cancer metastases are lung (48.5%), bone (26.5%), liver (19.5%), brain (5.5%) and other places (1.0%).
4. There is a relationship between subtypes of breast cancer and the incidence of metastases ($p < 0.038$). The highest probability of metastatic event as in patients with TNBC subtype with OR = 8.0 (95% CI 1.72-34.80)
5. There is no relationship between breast cancer subtypes with metastatic location ($p > 0.06$) and breast cancer subtype TNBC has a risk opportunity (OR) of 9.60 (95% CI 1.96-47.15) times increasing the risk of developing breast cancer brain metastases

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