Nusantara Medical Science Journal
Volume 7 Issue 1, January - June 2022
P-ISSN: 2460-9757, E-ISSN: 2597-7288
Nationally Accredited Journal, Decree No. 36/E/KPT/2019.

Original Article

Survivability Rates Based on Molecular Subtype, Stage and Metastasis of 36 months cohort in Breast Cancer Patients

Adi Wijayanto[1], John S. L. A. Pieter[1], Prihantono[1], Salman Ardy Syamsu[1], Nilam Smaradhania Thaufix[1], Amirullah Abdi[2]

[1]Department of Surgery, Subdivision of Oncology, Faculty of Medicine,Universitas Hasanuddin, Makassar, Indonesia
[2]Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia

Corresponding Author:
Name: Adi Wijayanto
Email: yengbedah@gmail.com

ARTICLE INFO

Keywords:
Breast Cancer; Overall Survival; Disease Free Survival; Subtype; Stage; Metastasis;

How to cite:
Wijayanto A., Pieter J.S.L.A., Prihantono, Syamsu SA., Thaufix NS., Abdi A. (2022). Survivability Rates Based on Molecular Subtype, Stage and Metastasis in Breast Cancer Patients. Nusantara Medical Science Journal, 7(1), 29-38

DOI:
10.20956/nmsj.v7i1.20092

ABSTRACT

Introduction: *Breast cancer treatment is carried out at the early stage of the disease, and a comprehensive assessment of the subtype, stage, and incidence of metastases is required. This study aims to determine breast cancer patients' overall survival (OS) and disease-free survival (DFS) based on subtype, stage, and incidence of metastases.* ***Methods:*** *An observational analytic study with a retrospective cohort design was performed on eligible breast cancer patients at Wahidin Sudirohusodo Hospital from 2016 to 2019. Univariate analysis, and the Kaplan-Meier survival log-rank method (Mantel-Cox), were used to determine differences in survivability rates (OS and DFS) based on subtype, stage, and incidence of metastases.* ***Results:*** *A total of 172 breast cancer patients from 32 years to 84 years with a mean age of 53.5 years. The most subtypes were Luminal A (34.9%) patients, and the least was Luminal B (15.7%) patients. A total of 85 (49.4%) patients survived during these three years, while 87 (50.6%) died. Based on the results of statistical tests in this study, there were no significant differences between the subtypes with DFS and OS, but on the contrary, there was a significant difference between the stage and incidence of metastases with OS*

and DFS (p<0.05). ***Conclusions:*** *There were no statistically significant differences between the subtypes with OS and DFS. This study showed a significant difference between the stage and incidence of metastases with OS and DFS.*

1. INTRODUCTION

The incidence of breast cancer globally was 14.9 million new cases in 2012. It is predicted to increase by 22 million new cases in the next two decades.[1] In Indonesia, the estimated incidence of breast cancer is 40.3 per 100,000 women, or 48,998 new cases per year. This figure represents 30.5% of all types of cancer in women or 16.4% of all types of cancer in men and women. This data suggests 6 cases of breast cancer every hour in Indonesia.[2] Data obtained from the South Sulawesi Provincial Health Office stated that cases of breast cancer in Makassar city in 2012 amounted to 671 cases, of which there were 337 new cases, 319 old cases, and 15 deaths. In 2014, the incidence tended to increase, with the majority of sufferers being women aged 45-54 years.[3]

Many therapeutic modalities have been used and provide good results, particularly if treatment is carried out at an early stage of disease progression.[4] Patients come in advanced conditions, so early detection and comprehensive assessment are needed.[5] Molecular subtypes of breast cancer cells were developed as an initial step in selecting therapy and predicting the prognosis of breast cancer patients.[6] In the 2013 St Gallen consensus, breast cancer subtypes were grouped into Luminal A, Luminal B, HER-2 positive and triple-negative types. The luminal molecular subtype was influenced by Estrogen Receptor (ER), Progesterone Receptor (PR), Her-2, and Ki67 levels. Molecular subtypes are useful for determining the type of therapy to be given and describing the prognosis of each subtype. Luminal A & B subtypes usually give a better prognosis, and the HER-2 (+) and triple-negative molecular subtypes give a poor prognosis in patients with breast cancer.[7]

This study aims to determine the relationship between molecular subtypes, stages, and metastases with Disease-Free Survival (DFS) and Overall Survival (OS) in breast cancer patients at RSUP Dr Wahidin Sudirohusodo and as reference data to better evaluate, detect and treat breast cancer.

2. METHODS

This study is an observational analytic study with a retrospective cohort study design. All study designs were approved by the Hasanudin University Faculty of Medicine Ethics Committee (recommendation number 264/UN4.6.4.5.31/PP36/2021). The population of this study was all patients diagnosed with breast cancer who came to Dr. Wahidin Sudirohusodo Makassar from 2016 to 2019.

Population and Sample

The study population was selected based on inclusion and exclusion criteria. Inclusion criteria included: Patients with breast cancer aged 20 - 70 years, metastatic detected by a radiological examination (chest rontgen, ultrasound, CT scan, or MRI), had

undergone mastectomy surgery / Breast-Conserving Treatment (BCT). While the exclusion criteria included: Suffering from other cancers, having already undergone mastectomy / BCT but the molecular subtype was not clear, smoked, and suffering from liver cirrhosis.

Data Collection

Medical record data taken as research data included age at diagnosis of breast cancer, clinical stage based on TNM, metastases and their location, diagnosis, outcome, subtype, histopathological grading, tumour location, overall survival (follow-up for 36 months), and disease-free survival (follow-up for 36 months).

Molecular Subtype Determination and Breast Cancer Staging

The molecular subtype classification used is Luminal A, Luminal B, Her 2+, and Triple Negative. The luminal A subtype was identified based on the expression of ER/PR + hormone, HER-2 – expression, and Ki67 expression with a value of less than 14% on the immunohistochemical examination. The luminal B subtype was identified based on the expression of ER/PR + hormone, HER-2 + expression, and Ki67 expression with a value of less than 20% on the immunohistochemical examination. Her 2+ subtype was identified based on ER/PR hormone expression and HER-2 3+ expression on immunohistochemical examination. Triple-Negative subtypes were identified based on ER/PR- hormone expression and HER-2- expression on immunohistochemical examination. All samples came from tumour tissue made in paraffin blocks and examined using ER, PR, HER-2, and Ki-67 reagents at the Anatomical Pathology Laboratory and Medical Record Installation at Wahidin Sudirohusodo Hospital Makassar.

The stage classification based on the clinical stage of the TNM system is recommended by the International Union Against Cancer (IUAC) from World Health Organization(WHO) / American Joint Committee on Cancer (AJCC), judging by the size of the primary tumour (T), regional lymph nodes (N), and metastases (M).[8] Classification based on metastasis is cancer has spread beyond the place of origin, causing symptoms according to the location of the appearance of the metastases. The most common sites of breast cancer metastases are bone, liver, lung, and brain.[9]

Statistical Analysis

Data were statistically analyzed using SPSS version 22 (IBM SPSS Statistics for Windows, Version 22.0. IBM Corp., Armonk, NY). Data were analyzed by univariate and survival. Univariate was conducted to determine the distribution of patient characteristic data. Using the log-rank method (Mantel-Cox), Kaplan-Meier survival analysis was used to determine differences in patient survivability based on subtype, stage, and incidence of metastases.

3. RESULTS

The total number of breast cancer patients included in this study at Wahidin Sudirohusodo Hospital Makassar, Subdivision of Surgical Oncology, who met the inclusion criteria was 172 participants. The characteristics of the research participant can be seen in Table 1. The percentage of breast cancer cases was mostly found at the age of 50-59 years (31.4%), and the lowest was at the age of 80-89 years (1.7%). The highest

patient stage was stage 3b (45.9%), and the least was stage 2 (2.9%). The most histopathological type was the IDC type (66.3%). Based on histopathological grading, the highest grade was intermediate grade (72.7%), and the least grade was low grade (11.6%). The most common breast cancer subtype was the Luminal-A type (34.9%), and the least was the Luminal-B type (15.7%). Based on the location, the most common tumours are found in the right breast (57.6%), Left (37.2%) and bilateral (5.2%). Based on the diagnosis, the most is Carcinoma Mammae (86.0%). Based on the outcome, the percentage of patients who lived was 49.4%, and those who died were 50.6%. Based on the incidence of metastases, the percentage without metastases was 62.8% and with metastases 37.2%, with the most common sites of metastases being bone (18.6%), followed by lung (14.0%) and liver (4.7%).

Table 1. Patient characteristic

Characteristic	Number of patient (N=172)	Proportion (%)
Age		
30-39 year	13	7.6
40-49 year	46	26.7
50-59 year	54	31.4
60-69 year	43	25.0
70-79 year	13	7.6
80-89 year	3	1.7
Histopathology Grade		
Low	20	11.6
Intermediate	125	72.7
High	27	15.7
Stage		
II	5	2.9
IIIa	8	4.7
IIIb	79	45.9
IIIc	15	8.7
IV	65	37.8
Histopathology		
ADC	19	11.0
ICM	33	19.2
IDC	114	66.3
ILC	4	2.3
Malignant Phyllodes	1	.6
Subtype		
Luminal A	60	34.9
Luminal B	27	15.7
Her2+	47	27.3
Triple negative	38	22.1
Tumor location		
Right	99	57.6

Left	64	37.2
Bilateral	9	5.2
Diagnosis		
Breast cancer	148	86.0
Fungating breast cancer	21	12.2
Recurrent breast cancer	3	1.7
Outcome		
Survive	85	49.4
Non-survive	87	50.6
Metastasis		
No Metastasis	108	62.8
Metastasis	64	37.2
Metastasis Location		
Bone	32	18.6
Liver	8	4.7
Lung	24	14.0

ADC: Adenoid Cystic Carcinoma; ICM: Invasive Micropapillary Carcinoma; IDC: Invasive Ductal Carcinoma; ILC: Invasive Lobular Carcinoma

In general, at the end of the 36-month follow-up, DFS duration was between 2-36 months with a mean of 19±11.3 months. Meanwhile, the duration of OS also varied between 5-36 months, with a mean of 28.27±9.4 months (Table 2).

Table 2. Descriptive Statistic of DFS and OS duration (n=172)

Variable	Minimum	Maximum	Mean	SD
DFS duration (Month)	2.00	36.00	19.00	11.317
OS duration (Month)	5.00	36.00	28.27	9.463

DFS: *Disease Free Survival*; OS: *Overall Survival*

The mean duration of OS between the subtypes in Luminal A (33.67 months) was longer than that in the Luminal B subtype (27.40 months). The mean duration of DFS between the subtypes in Luminal A (24.53 months) was longer than that in the Luminal B subtype (20.69 months). Based on the Kaplan-Meier analysis using the log-rank (Mantel-Cox) overall survival rate and disease-free survival by subtype, there was no significant difference between subtypes in terms of survivability (p=0.795) and recurrence rate (p=0.601) (Table 3 and Figure 1).

Table 3. OS and DFS of breast cancer based on subtype, stage and metastasis

Characteristic	*Mean* OS ± SD (Month)	*p-value*	*Mean* DFS ± SD (Month)	*p-value*
Subtype				
Luminal A	29.30 ± 1.14	0.795	24.53 ± 1.58	0.601
Luminal B	27.40 ± 1.83		20.69 ± 1.00	
Her-2	28.08 ± 1.43		22.73 ± 2.07	
Triple Negative	27.50 ± 1.56		21.41 ± 2.25	
Stadium				
II	36.00 ± 0.00	**<0.0001**	28.20 ± 4.98	**<0.00001**

IIIa	32.75 ± 2.06		27.50 ± 4.32	
IIIb	32.60 ± 0.81		23.58 ± 1.17	
IIIc	33.53 ± 0.97		25.53 ± 1.89	
IV	20.64 ± 1.06		10.18 ± 0.81	
Metastasis				
No metastasis	32.95 ± 0.62	**<0.001**	30.26 ± 1.00	**<0.00001**
Metastasis	20.37 ± 1.04		10.42 ± 0.90	
Overall	28.27 ± 0.72		22.72 ± 1.02	

Statistical Test: Log-Rank (Mantel-Cox). *OS: *Overall Survival*, DFS: *Disease Free Survival*

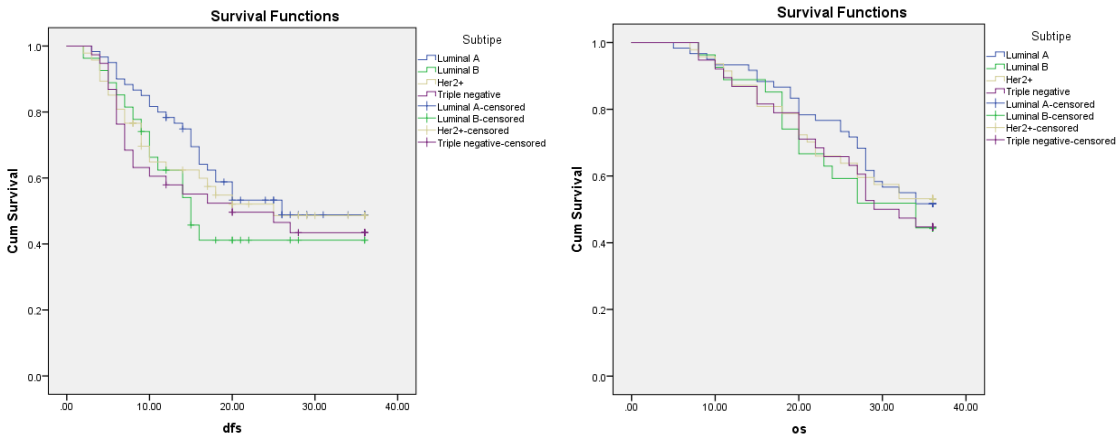

Figure 1. Comparison OS and DFS duration based on subtype

The mean duration of OS with stage II (36 months) is longer than stage IV (20.64 months). The mean duration of DFS with stage II (28.2 months) is longer than stage IV (10.18 months). Based on the Kaplan-Meier analysis using the log-rank (Mantel-Cox) overall survival rate and disease-free survival by stage, there was a significant difference between stage and survivability (p=0.0001) and recurrence rate (p=0.00001) (Table 3 and Figure 2).

The mean duration of OS with metastases seen in patients without metastases (32.95 months) was longer than those with metastases (20.37 months). The mean duration of DFS with the incidence of metastases seen in patients without metastases (30.26 months) was longer than those with metastases (10.42 months). Based on the Kaplan-Meier analysis using the log-rank (Mantel-Cox) overall survival rate and disease-free survival with the incidence of metastases, there was a significant difference in the incidence of metastases to the survivability rate (p=0.001) and recurrence rate (p=0.00001) (Table 3 and Figure 3).

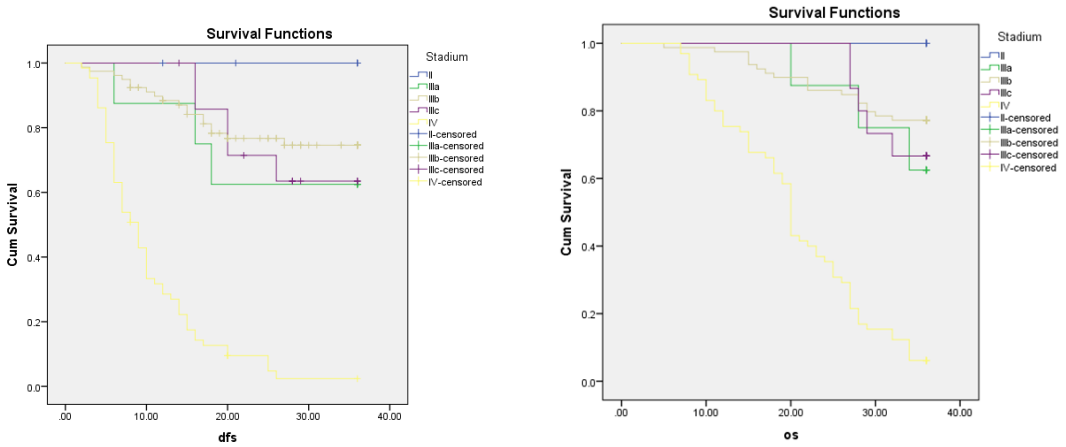

Figure 2. Comparison OS and DFS duration based on stage

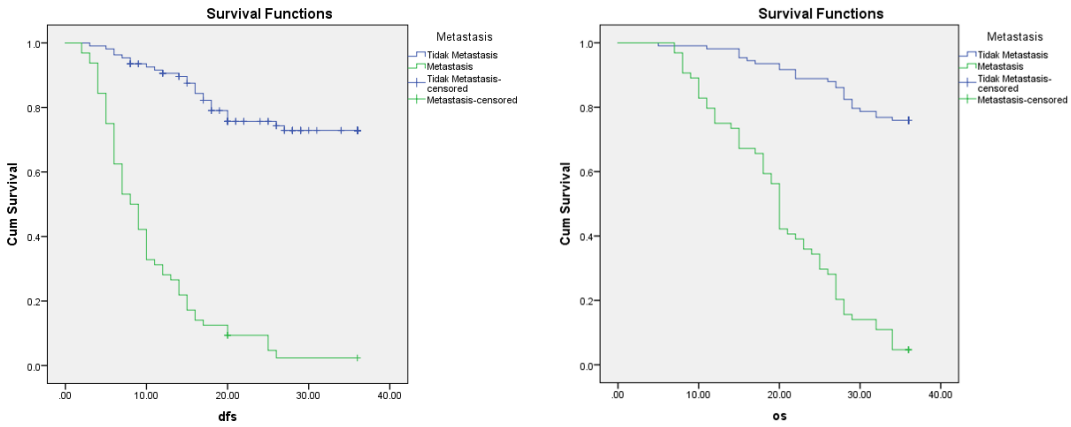

Figure 3. Comparison OS and DFS based on metastasis occurrence

4. DISCUSSIONS

Based on the results of this study, patients with breast cancer who met the inclusion criteria were 172 research subjects. The subjects of this study were examined for subtype, stage, and incidence of metastases. Subjects were also retrospectively followed in the cohort to determine disease progression or whether metastases had occurred. Furthermore, the patient's progress was followed for 36 months with survival analysis, whether the patient had a postoperative relapse (DFS) and when the patient died from being diagnosed (OS).

The subjects of this study consisted of an age range of 32 years to 84 years, with a mean age of 53.5 years. This recent result is not different from what McPherson et al. reported that the incidence of breast cancer increases with age, doubles every ten years until menopause, then decreases drastically.[10]

The most subtypes in this study were Luminal A which consisted of 60 (34.9%) patients, and the least was Luminal B, only 27 (15.7%) people. A total of 85 (49.4%) patients survived during these three years, while 87 (50.6%) died. Based on the results of statistical tests in this study, there was an insignificant relationship between subtypes with DFS and OS. The present result is not in line with the research conducted by

Yinghao su et al. in China, which reported that the Triple Negative and HER2 subtypes were associated with poorer outcomes than the Luminal A subtype.[11] The triple-negative and HER2+ subtypes metastasize to vital organs such as the brain and lungs more often than the Luminal A subtypes, so they have the potential to cause earlier death in patients.[12] Recent study showed that in both BCSS and OS, patients with bone metastasis had the best survival, whereas patients with brain metastasis had the lowest.[13] In this study, a predominant luminal A subtype was found that might influence the significance of its association with poorer prognosis. Other factors such as early detection, stage, spread, and delay in receiving treatment in breast cancer patients in this study can be considered the cause of no significant relationship.

In this study, stage IIIb was the most advanced stage (79 patients, 45.9%), followed by stage IV (65 patients, 37.8%). The mean duration of OS at stage II (36 months) is longer than stage IV (20.64 months). The mean duration of DFS at stage II (28.2 months) was longer than in stage IV (10.18 months) and statistically showed a significant relationship between stage and OS and DFS ($p<0.05$). The recent result is in line with a study from Simon et al., who concluded that the 5-year Overall Survival was highest in stage 1 breast cancer patients, as much as 96.84% compared to advanced stages.[14]

There were 64 (37.2%) patients who had metastases in the tumour, and 108 (62.8%) did not have metastases. The most common location for metastases was bone in as many as 32 (18.6%) people. The mean duration of OS with no metastases (32.95 months) was longer than that of metastases (20.37 months). The mean duration of DFS with no metastases (30.26 months) was longer than that with metastases (10.42 months). So that statistically shows a significant relationship between metastasis with OS and DFS in this study. The recent result is in line with the research conducted by Zegarac et al., which showed an extension of Disease-Free Survival and Overall Survival time above 24 months in breast cancer patients with metastases to the liver who underwent metastasectomy.[15] There is an association between the biological properties of breast cancer cells with their metastatic ability, thus determining the prognosis. Metastases to the brain can cause a lower survivability rate than metastases to other organs.[13]

This study has several limitations, including the number of samples for each group being not homogeneous, which can affect the study results, and there is a loss of follow-up. More in-depth research is needed on other clinicopathological parameters such as comorbidities (diabetes mellitus, hypertension, and others), age, menopausal status, and tumour size to DFS and OS with a larger and heterogeneous study sample.

5. CONCLUSION

Based on this study, there was no significant difference between the subtypes with OS and DFS. The factors of early detection, stage, spread, and delay in receiving treatment in breast cancer patients in this study can be considered as the cause of the absence of significant differences in this study. There was a significant difference between the stage and the presence of metastases with OS and DFS.

ACKNOWLEDGMENTS

Nothing to declare

REFERENCES

1. Ghoncheh M, Mahdavifar N, Darvishi E, Salehiniya H. Epidemiology, Incidence and Mortality of Breast Cancer in Asia. *Asian Pac J Cancer Prev*. 2016;17(sup3):47-52. doi:10.7314/APJCP.2016.17.S3.47
2. The International Agency for Research onCancer (IARC). Global Cancer Observatory. Accessed February 20, 2022. https://gco.iarc.fr/
3. Health Department of South Sulawesi Province. 2014 Non-Communicable Disease Case Report. Published online 2014.
4. Nguyen D, Yu J, Reinhold WC, Yang SX. Association of Independent Prognostic Factors and Treatment Modality With Survival and Recurrence Outcomes in Breast Cancer. *JAMA Netw Open*. 2020;3(7):e207213. doi:10.1001/jamanetworkopen.2020.7213
5. Ginsburg O, Yip CH, Brooks A, et al. Breast cancer early detection: A phased approach to implementation. *Cancer*. 2020;126(S10):2379-2393. doi:10.1002/cncr.32887
6. Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. *World J Clin Oncol*. 2014;5(3):412-424. doi:10.5306/wjco.v5.i3.412
7. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol Off J Eur Soc Med Oncol*. 2013;24(9):2206-2223. doi:10.1093/annonc/mdt303
8. Arnone P, Zurrida S, Viale G, et al. The TNM classification of breast cancer: need for change. *Updat Surg*. 2010;62(2):75-81. doi:10.1007/s13304-010-0014-y
9. Kimbung S, Loman N, Hedenfalk I. Clinical and molecular complexity of breast cancer metastases. *Semin Cancer Biol*. 2015;35:85-95. doi:10.1016/j.semcancer.2015.08.009
10. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. *BMJ*. 2000;321(7261):624-628. doi:10.1136/bmj.321.7261.624
11. Su Y, Zheng Y, Zheng W, et al. Distinct distribution and prognostic significance of molecular subtypes of breast cancer in Chinese women: a population-based cohort study. *BMC Cancer*. 2011;11:292. doi:10.1186/1471-2407-11-292
12. Kennecke H, Yerushalmi R, Woods R, et al. Metastatic Behavior of Breast Cancer Subtypes. *J Clin Oncol*. 2010;28(20):3271-3277. doi:10.1200/JCO.2009.25.9820
13. Wang R, Zhu Y, Liu X, Liao X, He J, Niu L. The Clinicopathological features and survival outcomes of patients with different metastatic sites in stage IV breast cancer. *BMC Cancer*. 2019;19(1):1091. doi:10.1186/s12885-019-6311-z

14. Simon SD, Bines J, Werutsky G, et al. Characteristics and prognosis of stage I-III breast cancer subtypes in Brazil: The AMAZONA retrospective cohort study. *Breast Edinb Scotl*. 2019;44:113-119. doi:10.1016/j.breast.2019.01.008
15. Zegarac M, Nikolic S, Gavrilovic D, et al. Prognostic factors for longer disease free survival and overall survival after surgical resection of isolated liver metastasis from breast cancer. *J BUON Off J Balk Union Oncol*. 2013;18(4):859-865.

Conflict of Interest Statement:

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.