Histopathological Grading based on Tumor Margin according to BI-RADS Mammography in Breast Cancer

Shabrinna Ayasha[1] [ID], Lies Mardiyana[2,3]* [ID], Budi Utomo[3] [ID], Iskandar Ali[4,5] [ID]

[1]Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Radiology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Hospital, Surabaya, Indonesia.
[3]Indonesian Women Imaging Society (IWIS), Jakarta, Indonesia.
[4]Department of Public Health, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Hospital, Surabaya, Indonesia.
[4]Department of General Surgery, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo General Hospital, Surabaya, Indonesia.
[5]Indonesian Association of Oncology Surgeons Surabaya Chapter, Surabaya, Indonesia.

* Correspondence: lies.mardiyana@fk.unair.ac.id

A B S T R A C T

Introduction: Mammography is an X-ray technique used to take images of the breast. It is the primary diagnostic method for breast tumors. Breast imaging reporting and data system (BI-RADS) classification is needed to determine benign or malignant masses by accessing the mass's shape, margin, density, and other features. However, the tumor margin is the most helpful one. This study aimed to know the difference in the distribution of tumor margin types in each histopathological grading in breast cancer patients.

Methods: This was an observational analytic study with a comparative approach using secondary data from medical records of patients with breast cancer at the radio diagnostic and anatomical pathology installation of Dr. Soetomo General Academic Hospital, Surabaya, from January 2017 to December 2021. All statistical data were performed using the International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) version 27, with a $p<0.05$ considered statistically significant.

Results: Out of 235 cases, the highest distribution of breast cancer patients' age interval was 45-49 years old (20.9%), the primary tumor margin type was spiculated (64.3%), and the highest distribution of histopathological grading was grade 3 (53.2%). There was no significant difference between tumor margin and age of breast cancer patients ($p=0.815$), with spiculated tumor margin as the most common type in all age intervals. There was no significant difference ($p=0.163$) in the distribution of tumor margin types in each histopathological grading, with spiculated tumor margin as the most common type in every grade.

Conclusion: There was no significant difference between tumor margin and age of breast cancer patients, and there was no significant difference between tumor margin and histopathological grading.

Highlights:
1.The highest distribution of breast cancer patients' age based on the 5-year age interval was 45- 49 years old.
2.There was no significant difference between tumor margin and age of breast cancer patients.
3.There was no significant difference between tumor margin and histopathological grade.

Introduction

Breast cancer is caused by the growth of malignant tumor in the epithelial cells adjacent to the breast ducts or lobes.[1] The global burden of breast cancer is increasing rapidly and varies widely from country to country.[2] The World Health Organization (WHO) stated that in 2022, there were 2.3 million women with breast cancer and 685,000 deaths globally.[3] By the end of 2020, there had been 7.8 million women alive who were identified with breast cancer in the past five years, making breast cancer the most common worldwide.[4] In Indonesia, breast cancer also ranks first in the highest number of cancers, yet one of Indonesia's leading causes of cancer death.[5] Global Cancer Observatory (GLOBOCAN) data in 2020 showed that the number of new breast cancer cases reached 68,858 cases (16.6%) of the total 396,914 new cancer cases in Indonesia and reached more than 22,000 cases of death, of which 70% were detected in the end-stage.[6]

Early diagnosis and intervention are essential to improve quality of life. To detect and diagnose breast cancer, mammography is needed to show a more distinct and detailed image of breast tissue symptoms and assess the staging of the breast cancer itself.[7,8] The breast imaging reporting and data system (BI-RADS) grades or classifications are used to standardize the interpretation of mammograms among radiologists. The results are available to help refine mammography procedures worldwide. The system characterizes a mass by its shape, margin, and density.[9]

BI-RADS was developed by the American College of Radiologists (ACR) to reduce variability in radiologists' descriptions of findings used to diagnose. It also provides feedback to radiologists on their ability to detect and diagnose lesions with the goal of continual performance improvement.[10] Histopathological classification systems such as the Nottingham grading system (NGS) are also available to determine the extent of breast cancer. The grade is determined by pleomorphism, duct formation, and cell mitosis.[11,12] It is used as a prognostic factor that will show the invasive potential of the tumor. Clinicians are supported in making appropriate patient treatment options based on their severity. As it is widely used, this study aimed to analyze whether the tumor margins in the data of breast cancer patients at Dr. Soetomo General Academic Hospital, Surabaya, were the same as the tumor margins criteria in the atlas of the BI-RADS category that had been developed. Therefore, determining the grade is very important for clinicians to use as further treatment options.[13]

Methods

This was an observational analytic study with a comparative approach using secondary data from medical records of patients with breast cancer at the radio diagnostic and anatomical pathology installation of Dr. Soetomo General Academic Hospital, Surabaya, from January 2017 to December 2021. This study compared BI-RADS and grading based on triple diagnosis: the combination of modalities, physical examination, imaging (mammography and ultrasound), and fine needle aspiration cytology (FNAC) was more accurate than any modality.[14]

Subjects were sampled using the consecutive sampling technique. Research samples were medical records that met the inclusion criteria: 1) Tumor margin findings in mammography before surgery; 2) Found more than one mass in one breast or both breasts; 3) Had tissue biopsies and/or breast cancer diagnosed surgery and were diagnosed based on histopathological results showing cancer and grading according to NGS criteria. Exclusion criteria were: 1) Mammography results did not match the BI-RADS assessment 2013; 2) Histopathological results did not include/according to the results of histopathological grading based on NGS. From the total of 452 cases, 235 subjects fulfilled the criteria. This study was conducted after receiving permission from the ethics committee of Dr. Soetomo General Academic Hospital, Surabaya (No. 1137/LOE/301.4.2/XI/2022).

Data Analysis

Research data was categorical using the International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) version 27 with the Kruskal Wallis method.[15] Results are displayed in tabular form (a table with rows and columns) with percentages.

Results

Out of 452 cases of breast cancer, 217 cases were excluded due to mammography criteria that did not align with the BI-RADS assessment 2013 and histopathological results that did not align with the effects of histopathological grading based on NGS.

Table 1. Frequency distribution

Characteristics	n = 235	Percentage (%)
Age Group (years old)		
<40	22	9.4
40-44	42	17.9
45-49	49	20.9
50-54	34	14.5
55-59	35	14.9
60-64	36	15.3
65-69	12	5.1
≥70	5	2.1
Tumor Margin		
Circumscribed	14	6.0
Obscured	13	5.5
Microlobulated	19	8.1
Indistinct	38	16.2
Spiculated	151	64.3
Grading		
I	32	13.6
II	78	33.2
III	125	53.2

Source: Research data, processed

A total of 235 cases were included in this study. Table 1 shows the characteristics of breast cancer based on age, tumor margin, and histopathological grading. From the age intervals based on a 5-year survival rate, the most frequent were patients in the age range of 45-49 years old, with 49 patients (20.9%), followed by 40-44 years old, with 42 patients (17.9%), and the least was patients aged ≥70

years old, with 5 patients (2.1%). The frequency of spiculated tumor margin showed the highest of all types, with 151 patients (64.3%), and obscured as the least, with

13 patients (5.5%). Higher grade of breast cancer (grade III) showed a higher prevalence among all grades, 125 (53.2%) in breast cancer patients.

Table 2. Comparison of age and grading based on tumor margin

Characteristics	Tumor Margin (n%)					p-value
	Circumscribed	Obscured	Microlobulated	Indistinct	Spiculated	
Age group (years old)						
<40	0 (0)	1 (7.7)	4 (21.1)	2 (5.3)	15 (9.9)	
40-44	3 (21.4)	2 (15.4)	3 (15.8)	8 (21.1)	26 (17.1)	
45-49	2 (14.3)	3 (23.1)	5 (26.3)	8 (21.1)	32 (21.1)	
50-54	3 (21.4)	2 (15.4)	2 (10.5)	5 (13.2)	22 (14.5)	0.815
55-59	5 (35.7)	2 (15.4)	1 (5.3)	8 (21.1)	19 (12.5)	
60-64	1 (7.1)	1 (7.7)	3 (15.8)	5 (13.2)	26 (17.1)	
65-69	0 (0)	1 (7.7)	1 (5.3)	1 (2.6)	9 (5.9)	
≥70	0 (0)	1 (7.7)	0 (0)	1 (2.6)	3 (2.0)	
Histopathological grading						
I	4 (28.6)	2 (15.4)	3 (15.8)	3 (7.9)	20 (13.2)	
II	1 (7.1)	2 (15.4)	5 (26.3)	15 (39.5)	55 (36.4)	0.163
III	9 (64.9)	9 (69.2)	11 (57.9)	20 (52.6)	76 (50.3)	

Source: Research data, processed

Table 2 compares age and grading based on tumor margin. The distribution of age based on tumor margin showed that spiculated was the most common type in each age range, and there was no significant difference (*p*=0.815) in the distribution of tumor margin types in each age range of breast cancer patients.

In the distribution of histopathological grading based on tumor margin, spiculated remained the highest among all types, and there was no significant difference (*p*=0.163) in the distribution of tumor margin types in each grading in breast cancer patients at Dr. Soetomo General Academic Hospital, Surabaya, from January 2017 to December 2021.

Discussion

This study found that the highest distribution of breast cancer patients at Dr. Soetomo General Academic Hospital, Surabaya, in 2017-2021 based on the 5-year age interval was 45-49 years old, with 49 patients (20.9%), followed by a range of 40-44 years old with 42 patients (17.9%). At the same time, the distribution of breast cancer was rarely found in the age range of 70 years old and above. This result is similar to the Surveillance, Epidemiology, and End Results (SEER) results conducted by the National Cancer Institute (NCI), according to which the incidence of breast cancer corresponds to childbearing age.[16] It increased at a lower rate.[16]

This study aligns with a study conducted in 2019, in which 19,503 female patients diagnosed with breast cancer in Turkey were studied.[17] The median age of patients at diagnosis was 51 years old, while the mean age was 51.8 years old.[17] Age interval 45-49 years old was the most populated (16.5%).[17]

This study is also similar to a survey of 2,166 Malaysian citizens diagnosed with primary breast cancer between 2010 and 2014.[18] All subjects were then divided by age into three groups: young women (under 40 years old), middle-aged women (40-59 years old), and older women (over 60 years old).[18] However, the results showed that more than half of the respondents (54.4%) were middle-aged women

at the time of initial diagnosis, followed by Chinese women (62.9%), Malaysian women (27.0%), Indians (9.0%), and others (1%).[18]

Spiculated tumor margin was the highest distribution type amongst breast cancer patients at Dr. Soetomo General Academic Hospital, Surabaya, in 2017-2021, which was 151 patients (64.3%). The second highest was indistinct type, with 38 patients, or approximately equal to 16.2% of all types. The obscured type of tumor margin was the lowest, with only 13 patients (5.5%). Another study conducted in Austria explained that among 49 female patients with breast cancer, most of them had spiculated margin tumors (56%) and indistinct (33%).[19] Mammographic features of tumor margin based on the BI-RADS assessment category that best describes malignancy is spiculated type. It is similar to the study conducted in 2020, which stated that the BI-RADS C5 category showed 100% malignancy, and spiculated was the most frequently found type in the BI-RADS C5 (56.8%) and C4c (5.9%), followed by a microlobulated margin type of 96.5%, it was significantly associated with malignancy (*p*=0.003).[20] Highly suspicious mammographic findings are usually very dense, irregularly shaped, spiculated, and have poorly defined/indistinct margins.[21]

Grade 3 was the histopathological grading with the most distribution of breast cancer patients, with 125 patients (53.2%). Meanwhile, grade 2 had a distribution of 78 patients (33.2%), and grade 1 had 32 patients (13.6%) of breast cancer patients at Dr. Soetomo General Academic Hospital, Surabaya, in 2017-2021. This study is similar to the findings in 2019, in which the distribution of grading 10 (9%), 32 (29%), and 58 (61.81%) were grades I, II, and III, respectively.[22] Meanwhile, this study slightly has a different result from the study conducted in 2020, which discovered that global female breast cancer grading showed that most patients developed when their tumors were already grade 2, and some patients developed at grade 3.[23] It was obtained from the results of 343 cases, 24 patients (7%) had grade I NGS.[23] Two hundred forty-four patients (71%) were grade II, and 75 (22%) were grade III.[22]

This study conducted a comparison between clinical features of breast cancer, which were tumor margin and the age of patients. Results showed no significant difference between tumor margin and age of breast cancer patients (p=0.815), with spiculated tumor margin as the most common type in all age intervals. There have never been detailed studies examining comparisons, while there are those that compare mammography findings of BI-RADS assessment categories and the age of breast cancer patients. Based on the study of age-related positive predictive values of the BI-RADS category 4, conducted in 2021, BI-RADS C4c had the highest distribution in all age groups (≤35 years old, >35 to 60 years old, and >60 years old). It was also stated that malignant cases in C4c were dominant, meaning the higher type of tumor margin based on the BI-RADS assessment categories that described malignancy could be expected as the highest distribution.[24]

In this study, a comparison between mammography findings based on the BI-RADS category of tumor margin and histopathological grading by NGS on breast cancer patients at Dr. Soetomo General Academic Hospital, Surabaya, showed that the spiculated tumor margin type had the highest distribution in every grade (I-III). There was no significant difference (p=0.163) in the distribution of tumor margin types in each histopathological grading. Based on a study conducted on 606 women with breast cancer in Japan over five years, spiculated margins were significantly lower in patients with grade 3 cancer (p<0.001). It occupied the highest number in grade 1 and 2. As for grade 3, microlobulated was the most common. Moreover, in grade 1 tumors, significant differences were found between those with an indistinct and microlobulated or spiculated margin (p=0.030 and p=0.003) and those with spiculated and indistinct or microlobulated margins (p<0.001).[25]

Mammographic presentation in spiculated mass was present in 72% of low-grade lesions but only in 24% of high-grade lesions. It is preferentially seen in slow-growing lesions that trigger a strong and progressive stroma reaction that will create spicules anatopathologically. These spicules correspond to connective tissue composed of varying proportions of fibrosis and elastosis and are responsible for their retractable nature and, thus, their spiculate aspect in imaging.[26]

Strength and Limitations

The strength of this study is that it compared histopathological grading based on the tumor margin of breast cancer, which could enhance the accuracy of mammography diagnosis by investigating whether tumor morphology, specifically grading, correlates with breast. However, due to its limitation in collecting the data manually, it was time-consuming.

Conclusion

The highest distribution of breast cancer patients' age based on the five-year age interval was 45-49 years old, with spiculated as the most common tumor margin type, and primarily third grade. There was no significant difference between tumor margin and age of breast cancer patients, with spiculated tumor margin as the most common type in all age intervals. There was no significant difference between tumor margin and histopathological grading, with spiculated tumor margin as the most common type in every grade.

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Conflict of Interest

The authors stated there is no conflict of interest.

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Ethical Clearance

This study had received ethical clearance from the Ethics Committee for Health Research Dr. Soetomo General Academic Hospital, Surabaya (No. 1137/LOE/301.4.2/XI/2022) on 11/17/2022.

Authors' Contributions

The study was designed by SA, LM, BU, and IA. SA is in charge of handling the ethical clearance process. Taking data by SA. SA analyzed the data. SA and LM interpret the data. SA authored the manuscript. LM, BU, and IA provided advice. SA, LM, BU, and IA revised the document. All authors reviewed and approved the final version of the manuscript.

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