



Patterns of lung metastasis on chest computed tomography scan studies in breast cancer patients and associated factors at St. Paul's hospital millennium medical college Addis Ababa, Ethiopia.

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Radiology & Medical Radiology Technology (MRT) Post-graduation Program**

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breast cancer patients and associated factors at St. Paul's hospital millennium
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ABSTRACT

Background: In Ethiopia, breast cancer is the most diagnosed cancer and the leading cause of cancer death in women. Computed tomography is often the preferred modality for monitoring metastatic disease due to its ability to determine the extent of local and metastatic disease. Lung metastasis represents a significant challenge in the management of breast cancer, affecting treatment decisions and prognosis.

Objective: To assess patterns of lung metastasis on chest CT scan studies in breast cancer patients and associated factors at St. Paul's hospital millennium medical college.

Methods: A facility based retrospective patients record review study was conducted by analyzing chest CT scan images of all patients who are diagnosed with Breast cancer with biopsy and lung metastasis with chest CT at St. Paul's Millennium Medical College (SPHMMC) in September 1, 2023- May 30, 2024. A template was prepared to collect data from the respective patient clinical records (charts as well as electronic medical recording/EMR) by the principal investigator and one trained radiology resident. Their CT findings were accessed from the radiology information system (RIS); Histopathology result was collected from EMR/chart or from pathology department, then data was entered into Epi info data version 4.6 and exported into SPSS version 26 for analysis. The presence of a statistically significant difference in the characteristics of the dependent and independent variables was assessed using the chi-square test, with a p-value of less than 0.05 indicating statistical significance.

Results: Out of the 165 patients studied, 164 (99.4%) were females and only 1 (0.6%) was male. 142 (86.2%) of the patients initially presented with stage IV disease. A higher proportion of patients accounting about 154 (93.3 %) had invasive ductal subtype breast carcinoma and 8 (4.8 %) had invasive ductal carcinoma. The majority of breast tumor subtypes were characterized by negative receptor status with the triple negative (ER, PR and HER 2 negative) status accounting for about 85 (51.5%). The most common lung metastasis pattern was multiple pulmonary nodules which was noted in 116 patients and the least common was endobronchial metastasis spread which was seen in only 2 (1.2 %) of the studied patients. No significant

association was found with the age demographic of the patients as well as histologic and molecular subtypes of breast cancer with the patterns of breast cancer metastasis.

Conclusion: The common age group of the patients in our study with advanced breast cancer and lung metastasis were relatively younger. Most of the participants are pre-menopausal and peri-menopausal. The commonest CT patterns for lung metastasis were multiple nodules. There was no statistically significant relationship between the histologic and molecular tumor characteristics and the likelihood of specific pattern of lung metastasis.

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Acronyms and Abbreviations

BC: Breast Cancer

ER: Estrogen Receptor

PR: Progesterone Receptor

HER 2: Human Epidermal Growth Factor

BLBC: Basal-like Breast cancer

PHGDH: Phosphoglycerate Dehydrogenase.

MRI: Magnetic Resonance Imaging

MRT: Medical Radiology Technology

MSc: Master of Science

RUL- Right Upper Lobe.

RML- Right Middle Lobe.

RLL- Right Lower Lobe.

LUL- Left Upper Lobe.

LLL- Left Lower Lobe

SPHMMC: Saint Paul Hospital Millennium Medical College

SPSS 26: Statistical Package for the Social Science

WHO – World Health Organization

1. INTRODUCTION

1.1. Background

Breast cancer is the most common public health problem and the major cause of cancer-related death worldwide (1). It is becoming a major public health problem in most of the developing countries (2).

A significant increase in breast cancer incidence is reported in most Sub-Saharan Africa countries suggesting an increasing public health problem.

In Ethiopia, breast cancer is the most diagnosed cancer and the leading cause of cancer death in women, accounting for about 32% of the total cases and 19.4% of all cancer deaths (1).

Breast cancer is also the most common malignant neoplasm among women in Addis Ababa. The Addis Ababa Cancer registry reports that breast cancer accounts for 34% of all female cancer cases, followed by cervical cancer at 16.6% (3). Furthermore, over two-thirds of breast cancers in Ethiopia are diagnosed at late stages of the disease (2). In addition to the late stage at diagnosis, access to evidence-based treatment is limited in Ethiopia, resulting in poor survival (2).

Widespread urbanization, changing patterns of reproductive and environmental risks factors, obesity, decreased physical activity, and increasing life expectancy are some of the common factors implicated in the steady rise in breast cancer incidence across low-income countries (3).

According to the World Health Organization (WHO) and American Cancer society, there are some recognized risk factors for breast cancer, including early menarche, late menopause, null parity, late age at first pregnancy (>30 years), non-breastfeeding mothers, hormonal contraceptives, hormone therapy after menopause, alcohol, cigarette smoking, obesity, physical in-activity, diet, and family history of breast cancer. However, several epidemiological studies conducted in different populations indicate that the incidence and mortality of breast cancer greatly differ between countries. This suggests that environmental and lifestyle factors may contribute to the development of breast cancer (1).

Breast cancer is a cancer type characterized by uncontrolled development and the spread of abnormal breast cells (1). It is a heterogeneous disease characterized by different morphological and molecular subtypes. Estrogen receptor (ER) and progesterone receptor (PR) analysis in

breast carcinomas were the first established biomarker assays with both prognostic and predictive power and they have been in use since the 1970s. Human Epidermal Growth Factor 2 (HER2) was discovered in the 1990s and HER2-targeted therapy was subsequently introduced; the introduction of targeted antibodies that interfere with HER2 signaling followed and their use has led to improved survival among breast cancer patients whose tumors overexpress HER2 (3).

Radiology plays a significant role in breast cancer management by early detection with screening mammography and ultrasound, staging and surveillance for recurrence after the initial treatment (4).

Imaging modalities such as ultrasound and computed tomography (CT) are suitable screening and diagnostic tools for monitoring cancer diseases. Radiological assessment of BC metastasis is crucial for the successful staging and management of patients. CT is a common modality used to evaluate the chest, abdominal viscera, pelvic soft tissues, and related bones. In practice, contrast medium is utilized to enhance the radiologic features of pathologies observed in non-contrast procedures. The literature shows the varying imaging features of BC metastases, even though they may conform to certain patterns in some organs (5).

Although, there is paucity of studies in Ethiopia in assessing the patterns of chest metastasis in breast cancer patients few studies have been done in black women in some African countries like Gana and Nigeria. The aim of this study is to determine the pattern of lung metastasis in patients with breast cancer.

1.2. Statement of the Problem:

Most often, distant metastases of breast cancer are not observed during the initial diagnosis. Less than 10% of all newly diagnosed breast cancer patients will have obvious distant metastatic disease at the time of initial diagnosis. Breast cancer metastases may arise between 2 and 5 years after the initial diagnosis if not appropriately managed. The most common sites of distant tumor metastasis are the liver, lung, bone, soft tissue, and adrenal glands (5).

The thorax is a common site of metastasis, which may involve the lymph nodes, bone, lung, pleura, or heart and pericardium (6).

Lung metastatic lesions can have multiple patterns including solitary pulmonary nodule, multiple pulmonary nodules, airspace patterns metastasis, lymphangitic metastasis and endobronchial

metastasis. The lung pleura can also be involved with metastatic lesions which often manifests as pleural effusion. (6)

Aggressive breast cancer is well documented in women of the black African race. Radiologic examinations in routine BC examinations for metastases should be encouraged to promote early detection of cancer spread to local and distant sites for management. There is limited relevant literature to better understand lungs metastatic patterns in breast cancers in developing countries. Literature on metastatic breast cancer is frequently reported from developed countries where technological advancement is evidently better (5).

In this study, the radiological pattern and features of the lung metastases among patient with advanced breast cancer patients were examined, which is frequently reported in developed countries where technological advancement is evidently better (5).

With early recognition of the commonest patterns of lung metastasis in breast cancer patients, early aggressive treatment options can be implemented to save the patient. Diagnosing and treating lung metastasis in breast cancer patients timely and effectively is paramount, especially in developing countries like Sub Saharan regions where there is high prevalence of breast cancer.

1.3 Significance of the Study:

According to my literature review, even though different patterns of metastasis on chest CT scan studies in breast cancer patients was assessed in multiple studies, little has been done on chest CT patterns of metastasis lung metastasis in breast cancer patients. To my knowledge, there are no such studies done in Ethiopia.

This study is very valuable in detecting early lung metastasis on chest CT scan studies by recognizing the multiple patterns, thereby assisting clinicians for early diagnosis and management of patients. This study can also be an input for other future studies.

This research study can contribute valuable data insights to the existing body of knowledge on lung metastasis on chest CT scan studies.

The findings on this research study can also spark further collaborative research efforts among other clinicians particularly oncologists to address the challenges of early recognition and diagnosis of breast cancer lung metastasis.

2. LITERATURE REVIEW

Metastasis is a complex process that involves the spread of cancer cells from the primary tumor to distant organs. One of the common sites of metastasis in breast cancer patients is the lung. Understanding the chest CT scan patterns of lung metastasis in breast cancer patients is crucial for accurate diagnosis and treatment planning. In this literature review, we will explore the existing research findings related to the patterns of lung metastasis in breast cancer patients and identify potential areas for future research.

2.1. Prevalence of breast cancer

Breast cancer is one of the commonest malignancies and have a high burden on clinicians. Tolessa L et al highlighted that Breast cancer is the most common public health problem and the major cause of cancer-related death worldwide in general and Ethiopia in particular (1).

In a study on Breast cancer in Ethiopia and Evidences for geographic difference in the distribution of molecular subtypes in Africa by hadgu E et al, Breast cancer is also the most common malignant neoplasm among women in Addis Ababa (3).

2.2. Metastasis in breast cancer patients

In a Prospective review of computed tomography images from the study on Radiologic patterns of distant organ metastasis in advanced breast cancer patients by Jimah BB et al, Less than 10% of all newly diagnosed BC patients will have obvious distant metastatic disease at the time of initial diagnosis. BC metastases may arise between 2 and 5 years after the initial diagnosis if not appropriately managed. The most common sites of distant tumor metastasis are the liver, lung, bone, soft tissue, and adrenal glands (5).

It has been observed that the magnitude of lung metastasis is quite high. Jung JI et al revealed that the thorax was a common site of metastasis, which may involve the lymph nodes, bone, lung, pleura, or heart and pericardium (6).

In a prospective review of CT images on the literature on Radiologic patterns of distant organ metastasis in advanced breast cancer patients diagnosed with chest metastasis, Bashir J et al highlighted that the lungs (77.4%) and lymph nodes (64.5%) were the most frequent sites of metastasis. Only 9.7% and 3.2% patient showed pleural effusion and pulmonary artery metastasis, respectively (10).

Most of the lung metastases were nodular (91.7%), while (16.7%) showed consolidation. Of the patients with nodular lesions, (81.8%) and (18.2%) had single and multiple nodules, respectively. The upper lobes (bilateral: 45.5%, right-40.9%, and left-9.1%) were the most common locations for nodules in those patients with lung metastasis (10).

2.3. Factors associated with lung tropism of metastasis.

It has been observed that luminal breast tumors tend to metastasize to bone, while basal-like breast cancer (BLBC) displays a lung tropism of metastasis. The study by Xiao et al. described the distinct metastatic patterns of different subtypes of breast cancer. This finding suggests that there may be specific molecular and biological mechanisms underlying the lung tropism of metastasis in BLBC, which warrants further investigation (7).

Breast cancer has been found to spread preferentially to the lung, brain, bone, and liver, a phenomenon known as organ tropism. Jin et al. highlighted the importance of understanding the molecular biology of breast cancer lung metastasis and its therapeutic implications. This knowledge underscores the need for comprehensive imaging modalities such as chest CT scans to detect and characterize lung metastases in breast cancer patients (8).

Cao et al identified the potential of liposomes coated with isolated macrophage membrane to target lung metastasis of breast cancer. This innovative approach opens up opportunities for developing targeted imaging agents for detecting lung metastases in breast cancer patients (9).

The study by Xiao et al demonstrated Cathepsin C as a promoter of breast cancer lung metastasis through its modulation of neutrophil infiltration and neutrophil extracellular trap formation. These findings shed light on the intricate interplay between cancer cells and the immune microenvironment in the context of lung metastasis (7).

Samanta et al suggested that PHGDH expression is required for mitochondrial redox homeostasis, breast cancer stem cell maintenance, and lung metastasis. This connection between metabolic pathways and lung metastasis highlights the potential of metabolic imaging techniques in evaluating lung metastases in breast cancer patients (10).

While the existing research provides valuable insights into the patterns and mechanisms of lung metastasis in breast cancer patients, several knowledge gaps and future research directions can be identified. Firstly, there is a need to further elucidate the specific molecular and biological factors that drive the lung tropism of metastasis in BLBC. Additionally, the development of novel imaging agents targeting the unique features of lung metastases in breast cancer is an area that warrants further exploration. Furthermore, understanding the interactions between cancer cells, immune cells, and the microenvironment in the context of lung metastasis can open new avenues for targeted therapies and imaging modalities. Finally, integrating multi-omics approaches with advanced imaging techniques such as chest CT scans can provide a comprehensive understanding of the spatial and molecular heterogeneity of lung metastases in breast cancer patients. In conclusion, the literature review has highlighted the diverse patterns and underlying mechanisms of lung metastasis in breast cancer patients. By integrating the existing research findings and identifying potential future research directions, this review provides a comprehensive overview of the current state of knowledge on chest CT scan patterns of lung metastasis in breast cancer patients.

2.4. Chest CT Patterns of lung metastasis.

In a review of computed tomography patterns of metastatic breast cancer patients undergoing treatment at a private oncology center in Ghana, Mensah et al observed that, the common sites of breast cancer metastasis in those patients were lymph nodes, lung, bone, liver, pleura and heart in descending order. The commonest CT metastatic patterns were, nodular for lung metastasis. There was a significant association between the molecular subtypes and the proportion of patients with lung metastasis. (4)

Prospective computed tomography images to evaluate Radiologic patterns of distant organ metastasis in advanced breast cancer patients were reviewed by B.B Jimah et al. They highlighted that the lungs (77.4%) and lymph nodes (64.5%) were the most frequent sites of metastasis. Only (9.7%) and (3.2%) patients showed pleural effusion and pulmonary artery metastasis, respectively. Most of the lung metastases were nodular (91.7%), while (16.7%) showed consolidation. Of those patients with nodular lesions, (81.8%) and (18.2%) had single and multiple nodules, respectively. The upper lobes (bilateral: 45.5%, right: 40.9%, and left: 9.1%) were the most common locations for nodules in patients with lung metastasis. (5)

In a ten year review of patterns of breast cancer metastasis at radiotherapy clinic in Ibadan, T.N elemulu et al. Revealed that lungs are the commonest sites of distant organ metastasis, compared to other distant organs. (11)

3. OBJECTIVES

3.1. General objectives

- To assess patterns of lung metastasis on chest CT scan studies in breast cancer patients and associated factors at St. Paul's hospital millennium medical college.

3.2. Specific objectives

- To assess CT patterns of lung metastasis in breast cancer patients.
- To investigate the potential association between the CT patterns of lung metastasis and the molecular and histological subtypes of breast cancer.
- Assess the potential associations between metastasis patterns and clinical parameters such as age and gender.

4. METHODS AND MATERIALS

4.1. Study Area:

The study was conducted in St. Paul's Hospital Millennium Medical College (SPHMMC) which is one of the tertiary referral hospitals directly under the Federal Ministry of Health in Addis Ababa, Ethiopia. It is a teaching hospital for the health science students enrolled in various undergraduate and postgraduate programs. The hospital has a total bed capacity of more than 700 beds, and on average sees 1200 emergency and outpatient clients daily. The hospital college provides both academic and service in various clinical disciplines.

In 2016 close to 40 % of the annual outpatient visits to the hospital also visits the department of radiology and MRT. Annually more than 7500 CT scan is done among which, 30% of this are chest CT.

4.2. Study Period

The study was conducted from February 1, 2024- July 30, 2024 GC.

4.3. Study Design

A facility based retrospective patient's clinical records review study design was employed. Reports of chest CT images of those patients with Biopsy proven Breast cancer with lung metastasis was assessed for the way they were written/reported. Chest CT Images of these patients was reassessed for the metastasis patterns. Structure data collecting template was prepared to collect data based on a review of literature.

4.4. Study population

4.4.1 Source Population

All patients diagnosed with breast cancer with lung metastasis in SPHMMC during the study period.

4.4.2. Study Population:

All patients with breast cancer with lung metastasis at SPHMMC who fulfill the inclusion criteria from September 1/2023 to May 30/2024 GC.

4.4.3. Study Units

Medical records of all patients who had chest CT and breast histopathology result during the study period.

4.5. Sampling size determination and sampling procedure:

4.5.1. Sample size determination:

The total number of patients who has breast cancer and lung metastasis between September 2023 and May 2024 were 165. All of these patients were included in this study. Therefore, the sample size for our study was 165 patients.

4.6 Inclusion and Exclusion criteria

4.6.1. Inclusion criteria:

All Patients with pathological proven breast cancer with lung metastasis, either with resection or core biopsy, with both primarily reported paper and images(CT) at SPHMMC between September 1/2023 to May 30/2024 GC are included.

4.6.2. Exclusion criteria:

- Patients with single (solitary) and multiple small sub cent metric lung nodules with no interval size change during follow up CT scan studies.
- Patients with other known synchronous or metachronous cancer diagnosis.

4.7. Study Variables

- **Dependent Variables**

- Patterns/morphology of lung metastasis on chest CT.

- **Independent Variables**

- **Socio-demographic variables.**

- Sex
 - Age
 - Menopausal status
 - Parity.

- **Site of cancer**

- **Stage at presentation.**

- **Histologic subtype.**

- **Histologic grade.**

- **Molecular subtype.**

- **Laterality of tumor.**

4.8 Operational Definitions:

- **Patterns of lung metastasis on chest CT-** These are the distribution and morphologic appearances of lung metastatic lesions on chest CT scan studies. They can be single (solitary pulmonary nodules) or multiple pulmonary nodule, airspace pattern metastasis (consolidations), Lymphangitic metastasis (lymphangitis carcinomatosa) and endobronchial. (6).
- **Site of cancer-** The involved part of the lung. Can be right lung, left lung or bilateral. (6).
- **Laterality of tumor-** Specific site of the metastatic lesion on chest CT. can be Right upper lobe, Right lower lobe, Left upper lobe, Left lower lobe, Bilateral upper lobe, Bilateral lower lobe and Middle lobe. (6).
- **Stage at presentation-** Is the degree of spread of cancer. From stage I to stage IV. (12).
- **Histologic subtype-** Are the microscopic cellular subtypes of the cancer. Can be Invasive ductal carcinoma, Invasive lobular carcinoma, anaplastic carcinoma, inflammatory breast carcinoma, malignant phyllodes tumor, Mucinous carcinoma, medullary carcinoma, Metaplastic carcinoma and Colloid carcinoma. (13)
- **Histologic grade-** A histologic measure of how closely a cancer cell resembles that of a normal cell. Graded from grade I to grade III. (13)
- **Molecular subtype-** Classification of breast cancer according to various gene expression. Can be Luminal A, Luminal B, HER-2, ER, PR and Triple negative. (13).

4.9 Data Collection Tools and Techniques

Data collection was done by the principal investigator and trained third year radiology residents. The data was collected by filling the data collecting template for each patient.

Data collection method

- The Chest CT report which is approved by consultant radiologists was accessed from radiology information system (RIS) by using patient medical record number. Post biopsy histopathology was collected from the pathology department or from patient medical record (either the chart or EMR will be used).

Data collectors:

- Data was collected by the principal investigator and one trained radiology resident from June 1-20, 2024. The principal investigator gave training on the basics of questionnaire and how to use it before the data is collected. The principal investigator and clinical advisor revised the collected data. Data collectors were given a detailed training about the aim of the study, the elements of the questionnaire, and how to handle the completed questionnaire.

4.10. Quality control

- Data quality was managed by training and appropriate supervision of data collectors
- Data was checked its completeness, clarity and accuracy
- Data was entered by using kobotoolbox and imported to SPSS version 26.
- The quality checking was also done daily after data collection and correction was made before the next data collection measures. Data clean up, cross checking and double entry was done before analysis.

4.11. Data Analysis

The collected data was coded, cleaned, stored and transferred to Statistical Package for Social Sciences, version 26 (SPSS v26). The data was analyzed using SPSS version 26 software. Descriptive statistics using measures of frequency were used to summarize categorical variables. Then the information was presented by using simple frequencies, summary measures, tables and figures.

Pearson chi-square test or Fisher Exact (observation <5) was used to assess the relationships between age categories, histologic subtypes as well as molecular subtypes of chest CT patterns of lung metastasis of breast cancer. Fisher exact test was used to determine whether the above independent variables participation of the CT patterns of breast cancer's spread to the chest was substantial. The results are presented in tables and charts.

4.12. Ethical Consideration

Ethical clearance was obtained from the institutional review board (IRB) of St. Paul hospital millennium medical college, Addis Ababa. The study was conducted without individual informed consent, because retrospective data collation will be used as part of routine patient care.

Confidentiality was assured by avoiding writing names of patients. Privacy of patients and confidentiality of information was respected. There was is no risk or benefit in taking part in the survey by individual patients.

4.13. Plans for Dissemination:

The final outcome of the study will be submitted to department of Radiology and MRT, SPHMMC, in the form of written document. Also the result will be presented for fulfillment of final year post graduate course in radiology to the department and all other interested bodies. The output will also be submitted to be published in the Peer-reviewed reputable journals.

5. RESULTS

5.1. Demographic characteristics of patients.

Out of the 165 patients studied, 164 (99.4%) were females and only 1 (0.6%) was male. The mean age of patients was about 43 with a standard deviation of 10.9 years. The majority 90(54.5) were less than 45 years.

96(58.2) patients were premenopausal and 68 (41.2) were post-menopausal. 140 of the patients were multi-parous and 24 were nulliparous.

The site of breast cancer in the studied patients were comparable with 82 (49 %) of having left side breast cancer whereas 83 (50.3%) of them had right side breast cancer.

142 (86.2%) of the patients initially presented with stage IV disease while only 2 (1.2%) were presented initially with stage I disease.

Table 1. Sociodemographic characteristics of patients with breast cancer lung metastasis at SPHMMC from September 2023-May 2024.

Variables	Category	Frequency (%)
Age	<45	90 (54.5)
	≥45	75 (45.5)
Sex	Female	164 (99.4)
	Male	1 (0.6)
Menopausal status *	Post menopause	68 (41.2)
	Pre menopause	96 (58.2)
Parity	Multi-parouse	140 (84.8)
	Nulliparouse	24 (14.5)
Site of cancer	Left	82 (49.7)
	Right	83 (50.3)
Stage at presentation	Satge I	2 (1.2)
	Satge II	9 (5.5)
	Satge III	11 (6.7)
	Satge IV	142 (86.1)
	Unspecified	1 (0.6)

*1 individual is male

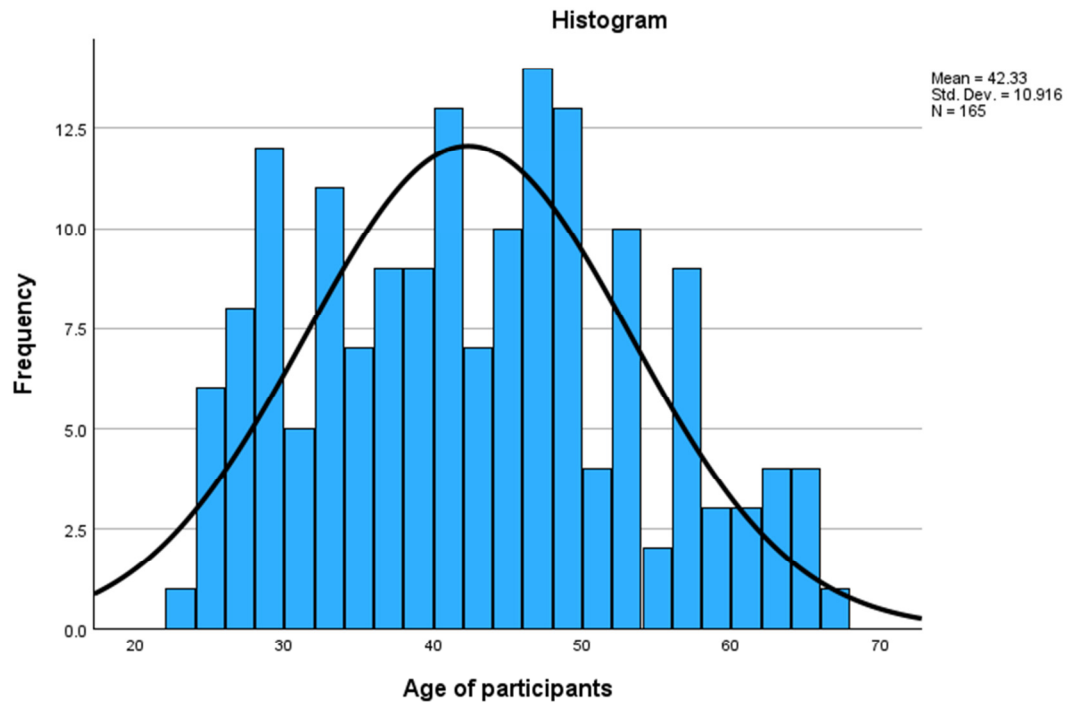


Figure 1. Age of patients with breast cancer lung metastasis distribution and frequency at SPHMMC from September 2023-May 2024.

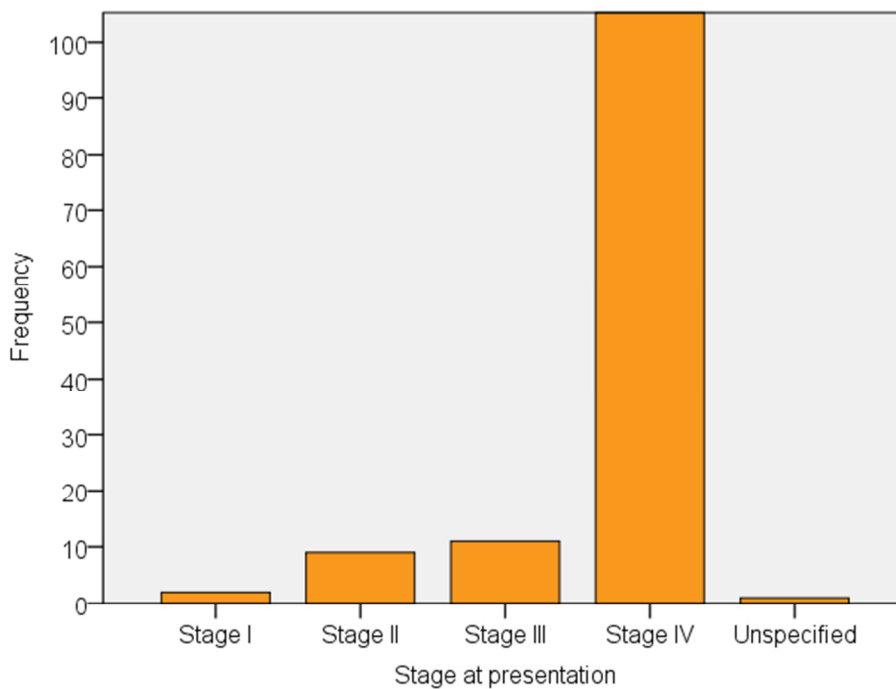


Figure 2. Stage at presentation of patients with breast cancer lung metastasis frequency at SPHMMC from September 2023-May 2024.

5.2. Characteristic of breast cancer.

A higher proportion of patients accounting about 154 (93.3 %) had invasive ductal subtype breast carcinoma and 8 (4.8 %) had invasive lobular carcinoma.

Only 1 patient had a record of the histologic grade of the breast cancer and the rest, 164 were no documented.

The majority of breast tumor subtypes were characterized by negative receptor status with the triple negative (ER, PR and HER 2 negative) status accounting for about 85 (51.5%). 34 (20.6%) had positive estrogen and progesterone receptor status, while triple positive (ER, PR, HER2 positive) accounted for only about 7 (4.2%).

Table 2. Histological subtype, grades of histology's, molecular subtypes and laterality of primary tumor of patients with breast cancer lung metastasis at SPHMMC from September 2023-May 2024.

Variables	Category	Frequency (%)
Histological sub type	Inflammatory breast carcinoma	1 (0.6)
	Invasive ductal carcinoma	154 (93.3)
	Invasive lobular carcinoma	8 (4.8)
	Medullary carcinoma	1 (0.6)
	Mucinous carcinoma	1 (0.6)
Grade of histology	Unspecified	164 (99.4)
	Grade II	1 (0.6)
Molecular sub-type	ER PR HER-2	7 (4.2)
	ER PR	33 (20.0)
	HER-2	4 (2.4)
	Luminal A	19 (11.5)
	PR ER	1 (0.6)
	Triple negative	85 (51.5)
	Unspecified	16 (9.7)
Laterality of primary tumor	Left	82 (49.7)
	Right	83 (50.3)

5.3. Patterns of breast cancer metastasis and associated factors.

The most common lung metastasis pattern was multiple pulmonary nodules which was noted in 116 patients and the least common was endobronchial metastasis spread which was seen in only 2 (1.2 %) of the studied patients.

Most of the metastatic lesions (112) were diffusely distributed throughout the lung parenchyma, while right middle lobe metastatic lesion was only noted in 2 patients

No significant association was found with the age demographic of the patients as well as histologic and molecular subtypes of breast cancer with the patterns of breast cancer metastasis.

Table 3. CT Patterns of metastasis and location of nodules of patients with breast cancer lung metastasis at SPHMMC from September 2023-May 2024.

Variables	Category	Frequency (%)
Patterns of metastasis	Consolidation	7 (4.2)
	Endo-bronchial	2 (1.2)
	Lymphangitic carcinomatosis	19 (11.5)
	Multiple pulmonary nodules	116 (70.3)
	Solitary pulmonary nodule	21 (12.7)
Location of nodules	Bilateral LL	9 (5.5)
	Bilateral UL	3 (1.8)
	Diffuse	112 (67.9)
	LLL	13 (7.9)
	LUL	5 (3.0)
	RLL	10 (6.1)
	RML	2 (1.2)
	RUL	11 (6.7)

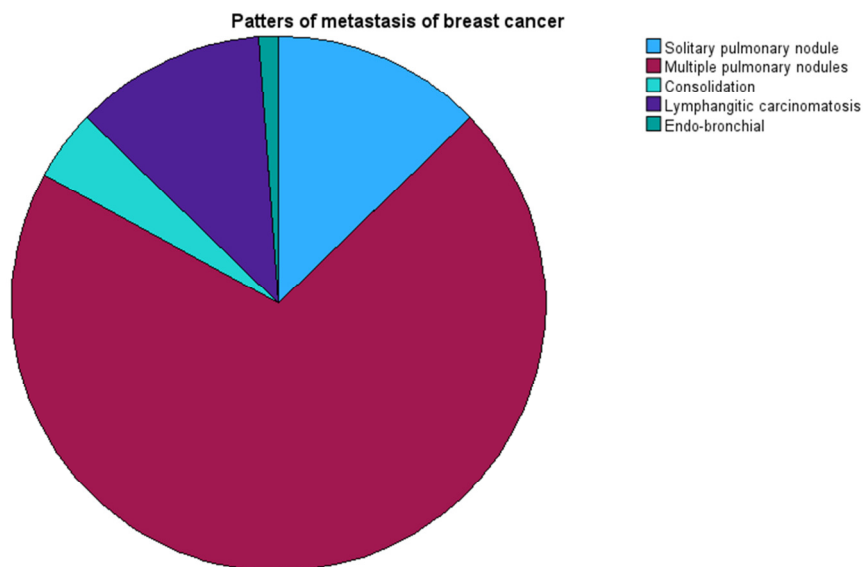


Figure 3. Patters of lung metastasis of patients with breast cancer lung metastasis at SPHMMC from September 2023-May 2024.

The Chi-Square test statistic is approximately 6.99, and the p-value is approximately 0.136. Since the p-value is greater than 0.05, we fail to reject the null hypothesis. This suggests that there is no significant association between the age range and the patterns of metastasis of breast cancer (Table 4).

Table 4. Association between age and patterns of metastasis of breast cancer at SPHMMC from September 2023-May 2024.

			Patters of metastasis of breast cancer					Total	P-value
			Solitary pulmonary nodule	Multiple pulmonary nodules	Consolidation	Lymphangitic carcinomatosis	Endo-bronchial		
Age range of participants	<45		14	64	4	6	2	90	0.136
	>=45		7	52	3	13	0	75	
Total		Count	21	116	7	19	2	165	

Chi-square test with Fisher's exact test p-value.

The Chi-Square test statistic is approximately 10.92, and the p-value is approximately 0.814. Since the p-value is significantly greater than 0.05, we fail to reject the null hypothesis. This suggests that there is no significant association between the histological subtypes of breast cancer and the patterns of metastasis in the given data (Table 5).

Table 5. Association between histological subtypes of breast cancers and patterns of metastasis of breast cancer at SPHMMC from September 2023-May 2024.

		Patters of metastasis of breast cancer					Total	P-value
		Solitary pulmonary nodule	Multiple pulmonary nodules	Consolidation	Lymphangitic carcinomatosis	Endo-bronchial		
Histological subtypes of breast cancer	Invasive ductal carcinoma	20	108	6	18	2	154	0.814
	Invasive lobular carcinoma	1	6	1	0	0	8	
	Inflammatory breast carcinoma	0	0	0	1	0	1	
	Mucinous carcinoma	0	1	0	0	0	1	
	Medullary carcinoma	0	1	0	0	0	1	
Total		21	116	7	19	2	165	

Chi-square test with Fisher's exact test p-value.

6. DISCUSSION.

This study provides a detailed analysis of the demographic, clinical, and pathological characteristics of 165 breast cancer patients, emphasizing the patterns of metastasis. The data reveal several critical insights and highlight significant areas for potential intervention and improvement in breast cancer management.

The overwhelming majority of patients were female (99.4%), which is consistent with the known higher prevalence of breast cancer in women. The mean age of patients was 43 years, with a standard deviation of 10.9 years, indicating a relatively young patient cohort. More than half of the patients (54.5%) were younger than 45 years, emphasizing the need for targeted screening and awareness programs for younger women, who may not typically be prioritized for breast cancer screening. Once more; most of these patients are between the age of 40 and 50 years. This means that most of the patients are young, premenopausal and peri-menopausal. This is similar to the studies done in Ghana reported in 2009, 2012 and 2016 respectively which was about 43-46 years (14, 15, 16). The mean age is lower than similar studies done in Nigeria and Ghana which was reported as a mean age of 48 years and 51.2 years respectively (17, 18).

This distribution suggests that hormonal factors play a significant role in the development and progression of breast cancer in this cohort. Additionally, 140 patients were multiparous, while 24 were nulliparous, indicating that reproductive history may influence breast cancer risk and outcomes.

Breast cancer is a disease of older women in developed countries which is contrary to the finding in developing countries (19). A majority of patients were premenopausal (58.2%), while 41.2% were postmenopausal, this is similar from a study done in university of Ibadan, Nigeria (20). This distribution suggests that hormonal factors play a significant role in the development and progression of breast cancer in this cohort. But it is in sharp contrast with the developed countries where premenopausal patients accounted for less than one-third of the patients. Adebamowo et al reported a much higher incidence of 80% of premenopausal women in Nigerian breast cancer patients (21).

Additionally, 140 patients were multiparous, while 24 were nulliparous, indicating that reproductive history may influence breast cancer risk and outcomes. These would have been the reverse since the higher the number of full term pregnancies, the greater the protection from breast cancer and that there is a reduction in risk of breast cancer by 7% for each birth after the first, in the absence of breast feeding, also women who breast feed reduces their risk compared to those who do not (22).

The laterality of breast cancer showed an almost equal distribution, with 49% of patients having left-sided breast cancer and 50.3% having right-sided breast cancer. This finding aligns with existing literature, which does not show a strong preference for either side in breast cancer occurrence.

One of the most concerning findings was the stage at initial presentation. A significant majority (86.2%) of patients were diagnosed at stage IV, while only 1.2% were diagnosed at stage I. This late-stage presentation underscores substantial challenges in early detection and diagnosis. There is a critical need for improved public health strategies, enhanced screening programs, and increased awareness to facilitate earlier detection and intervention.

Histologically, invasive ductal carcinoma was the most common subtype, accounting for 93.3% of cases, while invasive lobular carcinoma was present in 4.8% of cases. Notably, only one patient had a documented histologic grade, suggesting a need for more comprehensive pathological documentation in clinical practice. This is also the finding in the study done in Nigeria (20). Invasive carcinoma was also the highest histologic type in about 86.8 % of the patient population in the study done in Ghana (21). This also compares with work done by Edmund et al. in KBTH in 2013 which found 91.9% of breast cancers to be invasive ductal carcinoma. This was followed by invasive lobular carcinoma similar to what was noted in this study (23).

The receptor status of breast tumors revealed that the majority were triple-negative (ER, PR, HER2-negative), accounting for 51.5% of cases. This subtype is known to have a poorer prognosis and fewer treatment options compared to hormone receptor-positive subtypes. Estrogen and progesterone receptor-positive tumors accounted for 20.6%, while triple-positive

tumors (ER, PR, HER-2-positive) accounted for only 4.2%. which is also close to the findings in the study by Mensah et al. who reported triple negative 66%, luminal A, 19% and HER2-rich, 9.5% as the top three (24).

Regarding lung metastasis patterns, multiple pulmonary nodules were the most common, observed in 116 patients, while endobronchial metastasis was the least common, seen in only 2 patients. Most metastatic lesions were diffusely distributed throughout the lung parenchyma, with only 2 patients having metastases localized to the right middle lobe. The above findings regarding the CT patterns of lung metastasis supported by the reports from previous studies conducted in developing African countries Nigeria and Ghana (25, 26). This was in contrast to Thomas et al. who in their autopsy series found lymphangitic spread as the commonest pattern. The difference in findings has been explained by the limited sensitivity of CT scan in identifying lymphatic spread of breast cancer (27).

Statistical analysis revealed no significant association between age, histological subtypes, and patterns of metastasis. The Chi-Square test statistic for age demographics was approximately 6.99 with a p-value of 0.136, indicating no significant association between age and patterns of metastasis. Similarly, the Chi-Square test for histological subtypes yielded a statistic of 10.92 with a p-value of 0.814, suggesting no significant association between histological subtypes and metastasis patterns.

In conclusion, this study highlights the critical need for early detection and comprehensive documentation in breast cancer management. The high prevalence of late-stage presentation and triple-negative breast cancer underscores the challenges faced in treating this population. Further research is essential to develop targeted interventions and improve outcomes for breast cancer patients, particularly those at higher risk of advanced disease and poor prognosis.

7. STRENGTH AND LIMITATIONS.

The study explores an under-researched area in Ethiopia, which can be considered as a strength. The key limitations noted were the sample size, number of subjects, and the single facility involved. The study involved only patients with advanced breast cancer from one teaching hospital in Ethiopia and was therefore not representative of the Ethiopian population. Hence, the findings may not be generalizable to other centers in Ethiopia, as patients served by other tertiary facilities may present a different pattern of metastasis due to socio-demographic characteristics, CT scan quality, and the accuracy of imaging interpretations. The study is only a metastasis positivity rate based on imaging criteria determined by the authors based on previous studies. The retrospective nature of the study made it difficult to elicit information that was not available in the patient's record which may have affected important proportions in the study.

8. CONCLUSION.

The common age group of the patients in our study with advanced breast cancer and lung metastasis were relatively younger. Most of the participants are pre-menopausal and perimenopausal. The commonest CT patterns for lung metastasis were multiple nodules. There was no statistically significant relationship between the histologic and molecular tumor characteristics and the likelihood of specific pattern of lung metastasis.

9. RECOMMENDATION.

Based on the findings of this study, several recommendations can be made to improve the management and outcomes of breast cancer patients:

1. Enhanced Screening and Early Detection Programs:

- A. **Targeted Screening for Younger Women:** Given that more than half of the patients were younger than 45 years, it is essential to develop screening guidelines that include younger women. Public health initiatives should focus on increasing awareness about breast cancer risks and symptoms in younger populations.
- B. **Regular Screening for High-Risk Groups:** Increased surveillance for premenopausal women and those with a family history of breast cancer could lead to earlier detection and better prognosis.

2. Improved Access to Healthcare Services:

- A. **Addressing Late-Stage Presentation:** With a significant majority of patients presenting at stage IV, it is crucial to enhance access to healthcare services. This includes reducing barriers to regular medical check-ups and diagnostic services, especially in underserved areas.
- B. **Community Outreach and Education:** Implement community outreach programs to educate the public about the importance of early detection and regular breast examinations.

3. Comprehensive Clinical Documentation:

- A. **Detailed Pathological Reporting:** Encourage comprehensive documentation of histologic grades and molecular subtypes of breast cancer. This will aid in better understanding the disease and tailoring treatment plans more effectively.
- B. **Standardized Reporting Protocols:** Develop and implement standardized protocols for documenting and reporting breast cancer characteristics in clinical settings.

4. Focus on Triple-Negative Breast Cancer:

A. Research and Treatment Development: Given the high prevalence of triple-negative breast cancer in this study, there should be a concerted effort to research and develop targeted therapies for this aggressive subtype.

B. Clinical Trials and New Therapies: Encourage participation in clinical trials to explore new treatment options for triple-negative breast cancer patients.

5. Hormonal and Reproductive Health Education:

A. Education on Hormonal Influences: Provide education on the impact of hormonal factors and reproductive history on breast cancer risk. This can help women make informed decisions about their health and lifestyle.

B. Support Services for High-Risk Women: Establish support services and counseling for women at high risk of breast cancer, particularly those who are premenopausal and multiparous.

6. Monitoring and Management of Metastatic Disease:

A. Advanced Imaging and Diagnostic Tools: Utilize advanced imaging techniques to monitor the spread of breast cancer and manage metastatic disease more effectively.

B. Personalized Treatment Plans: Develop personalized treatment plans based on the patterns of metastasis, ensuring that patients receive the most appropriate and effective therapies.

7. Policy and Advocacy:

A. Advocate for Policy Changes: Work with policymakers to advocate for changes that support early detection, research funding, and access to healthcare services for breast cancer patients.

B. Public Health Initiatives: Promote public health initiatives aimed at reducing the incidence of late-stage breast cancer through education, early detection, and improved healthcare access.

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11. ASSURANCE OF PRINCIPAL IVESTIGATOR.

I the undersigned agree to accept all responsibilities for the scientific and ethical conduct of the research project, I will provide timely progress report to my advisor and seek the necessary advice and approval from my primary advisor in the course of the research. I will communicate timely to my advisors all stakeholders involved in the study including any source funding for this research.

- Name of data collector _____
- Signature _____
- Date _____

Approval of primary advisor

- Name of data collector _____
- Signature _____
- Date _____

Approval of co-advisor

- Name of data collector _____
- Signature _____
- Date _____

12. ANNEX: Developed structured data collecting Template

S.no	Variables	Response	Code
1.Patient characteristic			
1.1	Sex	• M • F	
1.2	Age	• < 45 years. • >=45 years.	
1.3	Menopausal status	• Pre-menopausal, • post-menopausal, • Not documented.	
1.4	Parity	1. Null parity 2.Multiparity (2-4 children) 3.Grand multiparity (>= 5 children) 4. Not documented.	
1.5	Site of cancer	1. Right 2. Left 3. Bilateral	
2	Stage at presentation	• Stage I • Stage II • Stage III • Stage IV.	

		• Unspecified.	
3	Histologic subtypes	• Invasive ductal carcinoma. • Invasive lobular carcinoma. • Anaplastic carcinoma. • Inflammatory breast carcinoma. • Malignant phylloides tumor. • Mucinous carcinoma. • Medullary carcinoma. • Metaplastic carcinoma. • Colloid carcinoma. • Unspecified.	
3.1	Grade of histology	• Grade I. • Grade II. • Grade III. • Unspecified	
4	Molecular subtypes	• Luminal A. • Luminal B. • HER-2. • ER. • PR. • Triple negative. • Unspecified.	
5	Laterality of primary tumor.	• Left. • Right. • Bilateral.	

6	Morphology/patterns of lung metastasis.		
6.1	Morphology of lung lesions	• Nodules. • Consolidation. • Lymphangitic. • Endo-bronchial.	
6.2	Single nodules.	• Yes. • No.	
6.3	Multiple nodules	• Yes • No	
6.4	Location of nodules.	• Right upper lobe. • Right lower lobe. • Left upper lobe. • Left lower lobe. • Bilateral upper lobe. • Bilateral lower lobe. • Middle lobe.	

Submitted by:

Name of student

Signature

Date

Approved by:

1. _____

Major Advisor

Signature

Date

2. _____

Co-Advisor

Signature

Date