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# Metastatic patterns of breast cancer: a retrospective study in a Teaching Hospital in Ghana

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**Abstract**

***Background:*** Breast cancer is the most prevalent cancer among Sub-Saharan African women. In Ghana, there is an increasing incidence of breast cancer with a cumulative 5-year survival of 48%. The low survival has been attributed to the late stage of presentation, delays with diagnosis and limited treatment options. Breast cancer-associated morbidity and mortality are generally related to the clinical stage of the disease and are worse in metastatic disease.

***Objective:*** This study determined the time to metastases from the initial diagnosis of breast cancer and the patterns of metastases in a teaching hospital in Ghana.

***Methods:*** This study retrospectively reviewed consecutive cases of breast cancer managed from January 2009 to December 2011 at the Korle Bu Teaching Hospital, Accra, Ghana. Patient case records were reviewed, and data was extracted.

***Results:*** The median age of the patients was 50 years in the non-metastatic group and 51 years in the metastatic group. The median duration from diagnosis to detection of first metastasis was 10.5 months. Fifty-eight percent of participants had metastasis involving 1 site only and the rest had 2-5 sites of metastases. The most common sites of metastases were the lungs and pleura (41%), bones (31%), liver (23%) and brain (12%). Triple-negative and HER 2 enriched breast cancers were significantly associated with liver metastases. Breast cancer grade was significantly associated with multiple metastatic sites.

***Conclusion:*** The median time to metastases from initial diagnosis was less than 1 year, and two-fifths of patients had more than one site of metastases. It would be useful if clinicians aggressively monitor indications for metastases, especially in the common sites, and for patients at high risk of metastases, both at the initial breast cancer diagnosis and in the early post-treatment period.

**Keywords:** Breast cancer, metastases, Ghana

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## INTRODUCTION

Globally, breast cancer (BC) contributes to 23.8% of all female cancers and 15.4% of female cancer deaths, making it the most commonly diagnosed cancer and most frequent cause of cancer deaths in females [1]. In all regions of the world, breast cancer is the predominant cancer diagnosed in more than 80% (157 of 185) of countries [2]. Globally, an estimated 2.3 million new cases were diagnosed in 2022, accounting for a quarter of all new cancer cases in women [1]. An estimated 666,000 BC deaths occurred in women in 2022 [1,2]. It is the most prevalent cancer among Sub-Saharan African women with a lower average age of diagnosis, higher stage at presentation and higher proportion of triple-negative BC [3]. BC is the second leading cause of cancer death among women in low and medium Human Development Index countries [1]. In Ghana, there is an increasing incidence of BC, the leading female cancer [2], with the highest burden

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in the 35 - 45 year group [4]. It was estimated to cause 13% of all cancer deaths in 2022 with a 5 year prevalence of 83.8/100,000 [2]. Survival from breast cancer is influenced by stage of diagnosis, with overall 5-year survival in America being more than 99% for stage I disease, 93% for stage II, 75% for stage III and 29% for metastatic disease [5]. In Ghana, a study by Mensah et al. (2016) on the 5-year cumulative survival showed 91% for stage 0 & I disease, 60% for stage II, 34% for stage III and 15% for stage IV disease, with a cumulative 5-year survival of 48% [6].

In another study in Ghana, which excluded breast cancer patients with stage 4 disease, it was shown that survival and recurrence outcomes in patients treated with standard-of-care therapy were significantly high and comparable to patients in high-income countries [7]. The low survival among African countries has been largely attributed to the late stage of presentation and diagnosis as well as the limited treatment [8]. For many women with symptomatic cancer, late presentation has been associated with a more advanced stage of the disease, resulting in poor survival outcomes [8,9]. In Ghana, the average duration of symptoms before presentation has been found to be 10 months [10]. As a result, almost two-thirds (57.6%) of the patients diagnosed with breast cancer present with Stage III-IV disease [11]. Globally, about 30% of patients diagnosed with early breast cancer will later develop metastases [12]. Few patients are first diagnosed with metastatic disease, while many others develop metastases months to years after initial diagnosis and treatment, usually for advanced tumours but occasionally also for early disease. Higher mean tumour size is associated with a greater risk of metastases [12]. The mean tumour size in patients without metastases was 2.2 cm compared to the 3.9 cm mean size of metastatic tumours [13]. The cancer-associated morbidity and mortality in BC are generally related to the extent or the clinical stage of the disease and are worse in metastatic disease. Metastases in breast cancer commonly affect vital organs such as the lungs, liver, brain and bone with resultant increasing burden of symptoms, decrease in quality of life and eventual mortality [6,14-16]. Multiple metastases have been found to be associated with lower overall survival as well as cancer-specific survival [17]. This study focused on the patterns of metastases among breast cancer patients in Ghana. The findings of this study will sensitise clinicians to monitor indications for metastases in the most likely sites and enable adequate acquisition of skills and logistics needed to effectively manage metastatic disease. Early identification of metastases requires less extensive treatment with fewer resources and is more tolerable for the patients.

## MATERIALS AND METHODS

### Study site

This study retrospectively reviewed the hospital records of consecutive cases of BC managed from 2009 to 2011 at the National Radiotherapy Oncology and Nuclear Medicine Centre (NRONMC), Korle Bu Teaching Hospital (KBTH), Accra, Ghana. The records of patients treated for BC at the NRONMC from January 2009 to December 2011 were retrieved from the records department, and all those meeting the inclusion criteria had their case records reviewed and data extracted. Patients were grouped into two - those with metastatic disease and those without, as at the time of data collection. Data was obtained on demography, socioeconomic characteristics, personal medical history and presenting symptoms of the cancer, histopathology, immunohistochemistry, stage of the disease at initial diagnosis, treatment given, the presence and site of metastases as well as last follow-up date.

### Data analysis

Descriptive statistics were reported for continuous variables as mean (± SD) if normally distributed or median [IQR] if skewed. Summary statistics for categorical variables were reported as frequencies and proportions. The association between body mass index (BMI) and the American Joint Committee on Cancer (AJCC) stage (18) was also determined by ordinal logistic regression and reported as an odds ratio (OR) with a 95% confidence interval [95% CI]. Chi-square test was used to test the association between the grade of cancer, age group, hormone status and the various sites and number of metastatic cancers. Stata® 14.1 was used for the statistical analysis, and $p < 0.05$ was considered statistically significant.

## RESULTS

Table 1 shows the socio-demographic and clinical characteristics of the study participants. A total of 285 patients were included in the review. The patients were grouped into either metastatic BC or non-metastatic BC at the time of the study, with 42.5% (n = 121) of patients categorised as metastatic, while 57.5% (n = 164) were non-metastatic. Most of the participants were female (96%), with a median age of 50.0 [42.0 - 61.0] years in the non-metastatic group and 51.5 [40.3 - 63.0] years in the metastatic group. Almost 60% of the participants were married. At least one co-morbidity was present in 38.0% (n = 46) of the metastatic BC group and 42.7% (n = 70) of the non-metastatic BC group, the commonest of which were hypertension in 31% and diabetes mellitus in 6% of all participants, in the metastatic and non-metastatic groups combined. Sixty-seven and seventy-four percent were overweight or obese in the metastatic and non-metastatic groups, respectively (Table 1).

Table 2 shows the association between BMI and AJCC stage of cancer at initial BC diagnosis. Table analysis indicates that among both the metastatic BC and non-metastatic BC groups, participants with BMI category of obesity have increased odds of having AJCC stage IV BC diagnosis compared with normal weight participants (OR = 3.62; [95% CI: 1.34 - 9.77], p = 0.011 and OR = 2.81, [95% CI:1.02 - 7.75], p = 0.046 respectively) (Table 2). Table 3 shows the association between the initial cancer stage and

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the subsequent development of metastases. Table analysis indicates that the initial cancer stage is significantly associated with the development of metastases, with all 4 study participants with initial cancer stage I remaining non-metastatic, whilst 36% each of initial stage II and II study participants developed metastases ($p < 0.001$). The median duration of symptoms prior to presentation was 12.0 (5.5 – 12.0) months for the patients with metastases and 8.5 (5.3 – 12.0) months for the non-metastatic patients, but this was not statistically significant (p-value 0.443) (Table 3). The commonest sites of metastatic disease were the lungs and pleura (41%), bones (31%), liver (23%) and brain (12%). Most of the participants with metastases had one site involved (58%), 28% had metastases at 2 sites and the rest had between 3 to 5 sites involved. The median duration

Table 1. Socio-demographic and clinical characteristics of study participants

| Characteristic | | Metastatic BC | Non-metastatic BC |
|---|---|---|---|
| | | n, %[1] | n, %[1] |
| | | N=116 | N=155 |
| Age, median [IQR], years | | 51.5 [40.3-63.0] | 50.0 [42.0-61.0] |
| Sex | | N=121 | N=164 |
| | Male | 5 (4.1) | 7 (4.3) |
| | Female | 116 (95.9) | 157 (95.7) |
| Marital status | | N=108 | N=141 |
| | Single | 29 (26.9) | 43 (30.4) |
| | Married | 60 (55.6) | 84 (59.6) |
| | Divorced | 15 (13.9) | 8 (5.7) |
| | Widowed | 4 (3.7) | 6 (4.3) |
| Presence of co-morbid condition | | N=121 | N=164 |
| | Present | 46 (38.0) | 70 (42.7) |
| | Absent | 75 (62.0) | 94 (57.3) |
| Co-morbid condition[$] | | N=46 | N= 70 |
| | Hypertension | 29 (63.0) | 59 (84.3) |
| | Diabetes Mellitus | 5 (10.9) | 12 (17.1) |
| | Asthma | 7 (15.2) | 6 (8.6) |
| | Other cancer | 1 (2.2) | 3 (4.3) |
| | Hyperlipidaemia | 1 (2.2) | 1 (1.4) |
| | Others | 3 (6.5) | 4 (5.7) |
| BMI category | | N=121 | N=164 |
| | Underweight | 6 (4.9) | 8 (4.9) |
| | Normal weight | 34 (28.1) | 34 (20.7) |
| | Overweight | 28 (23.10) | 58 (35.4) |
| | Obese | 53 (43.8) | 64 (39.0) |

$May sum up >100 as one patient may present with >1 co-morbidity; 1Column percentages

Table 2. Association between BMI and AJCC stage at Initial diagnosis among BC patients

| | AJCC Stage | | | | OLR Odds ratio [95% CI] | p-value |
|---|---|---|---|---|---|---|
| AJCC Stage | Stage I | Stage II | Stage III | Stage IV | | |
| | n, %[1] | n, %[1] | n, %[1] | n, %[1] | | |
| Metastatic BC patients BMI category | N=0 | N=22 | N=38 | N=26 | | |
| Normal weight | - | 8 (36.4) | 14 (36.8) | 3 (11.5) | 1.00 | |
| Underweight | - | 1 (4.6) | 4 (10.5) | 0 (0) | 1.07 [0.21-5.48] | 0.940 |
| Overweight | - | 3 (13.6) | 12 (31.6) | 3 (11.5) | 1.62 [0.55-4.77] | 0.384 |
| Obese | - | 10 (45.5) | 8 (21.1) | 20(76.9) | 3.62 [1.34-9.77] | 0.011 |
| Non-metastatic BC patients BMI category | N=4 | N=39 | N=66 | N=0 | | |
| Normal weight | 3 (75.0) | 11 (28.2) | 13 (19.7) | - | 1.00 | |
| Underweight | 0 (0) | 2 (5.1) | 3 (4.6) | - | 1.92 [0.28-12.93] | 0.504 |
| Overweight | 0 (0) | 15 (38.5) | 22 (33.3) | - | 1.88 [0.70-5.06] | 0.214 |
| Obese | 1 (25.0) | 11 (28.2) | 28 (42.4) | - | 2.81 [1.02-7.75] | 0.046 |
| BC patients (All) BMI category | N=4 | N=61 | N=104 | N=26 | | |
| Normal weight | 3 (75.0) | 19 (31.2) | 27 (26.0) | 3 (11.5) | 1.00 | |
| Underweight | 0 (0) | 3 (4.9) | 7 (6.7) | 0 (0) | 1.40 [0.41-4.81] | 0.593 |
| Overweight | 0 (0) | 18 (29.5) | 34 (32.7) | 3 (11.5) | 1.45 [0.71-2.97] | 0.306 |
| Obese | 1 (25.0) | 21 (34.4) | 36 (34.6) | 20 (76.9) | 2.84 [1.41-5.74] | 0.004 |

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Table 3. Association between initial cancer stage at diagnosis and subsequent metastases

| Characteristic | | Metastatic BC n, %[1] | Non-metastatic BC n, %[1] | p-value |
|---|---|---|---|---|
| Initial Cancer Stage | | | | *<0.001* |
| | Stage I | 0 (0) | 4 (100) | |
| | Stage II | 22 (36.1) | 39 (63.9) | |
| | Stage III | 38 (36.5) | 66 (63.5) | |
| | Stage IV | 26 (100) | 0 (0) | |
| Median duration of symptoms in months | | 12.0 (5.5 – 12.0) | 8.5 (5.3 – 12.0) | p= 0.443 |

Table 4. Characteristics of metastatic disease

| Characteristic | | Frequency (%) |
|---|---|---|
| Site of metastasis[$] | | *N=121* |
| Lung | | 49 (40.5) |
| | Bone | 37 (30.6) |
| | Liver | 28 (23.1) |
| | Brain | 15 (12.4) |
| | Contra-lateral axillary lymph nodes | 4 (3.3) |
| | Other sites | 23 (19.0) |
| Number of metastatic sites | | *N=90* |
| | 1 site | 52 (57.8) |
| | 2 sites | 25 (27.8) |
| | 3 sites | 10 (11.1) |
| | 4 sites | 1 (1.1) |
| | 5 sites | 2 (2.2) |
| Duration between diagnosis and 1st metastasis, median [IQR], months | | 10.5 [4.8-24.0] |

Table 5. Association between number of metastatic sites and age, tumour subtype and grade

| | | Number of metastatic sites | | | | | |
|---|---|---|---|---|---|---|---|
| Characteristic | | 1 site n, %[1] | 2 sites n, %[1] | 3 sites n, %[1] | 4 sites n, %[1] | 5 sites n, %[1] | p-value[#] |
| Age group (years) | | | | | | | 0.537 |
| | <40 | 8 (44.4) | 6 (33.3) | 4 (22.2) | 0 (0) | 0 (0) | |
| | 40-49 | 19 (70.4) | 5 (18.5) | 2 (7.4) | 0 (0) | 1 (3.7) | |
| | 50-59 | 8 (47.1) | 6 (35.3) | 2 (11.8) | 0 (0) | 1 (5.9) | |
| | ≥60 | 17 (60.7) | 8 (28.6) | 2 (7.4) | 1 (3.6) | 0 (0) | |
| ER status | | | | | | | 1.000 |
| | Positive | 9 (56.3) | 6 (37.5) | 1 (6.3) | 0 (0) | 0 (0) | |
| | Negative | 15 (50.0) | 10 (33.3) | 3 (10.0) | 1 (3.3) | 1 (3.3) | |
| PR status | | | | | | | 0.109 |
| | Positive | 4 (30.8) | 7 (53.9) | 1 (7.7) | 1 (7.7) | 0 (0) | |
| | Negative | 20 (62.5) | 8 (25.0) | 3 (9.4) | 0 (0) | 1 (3.1) | |
| HER 2 status | | | | | | | 0.843 |
| | Positive | 6 (66.7) | 3 (33.3) | 0 (0) | 0 (0) | 0 (0) | |
| | Negative | 17 (51.5) | 10 (30.3) | 4 (12.1) | 1 (3.0) | 1 (3.0) | |
| Hormone positive | | | | | | | 0.556 |
| | Yes | 9 (47.4) | 8 (42.1) | 1 (5.3) | 1 (5.3) | 0 (0) | |
| | No | 15 (57.7) | 7 (26.9) | 3 (11.5) | 0 (0) | 1 (3.9) | |
| TNBC | | | | | | | 0.347 |
| | Yes | 8 (47.1) | 5 (29.4) | 3 (17.7) | 0 (0) | 1 (5.9) | |
| | No | 15 (57.7) | 9 (34.6) | 1 (3.9) | 1 (3.9) | 0 (0) | |
| Grade of cancer | | | | | | | *0.001* |
| | I | 4 (57.1) | 0 (0) | 1 (14.3) | 1 (14.3) | 1 (14.3) | |
| | II | 15 (55.6) | 12 (44.4) | 0 (0) | 0 (0) | 0 (0) | |
| | III | 4 (30.8) | 5 (38.4) | 4 (30.8) | 0 (0) | 0 (0) | |

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Table 6. Association between Breast cancer subtype and metastases

| Characteristic | | Metastatic BC n, %[1] | Non-metastatic BC n, %[1] | p-value |
|---|---|---|---|---|
| Hormone positive | | | | 0.744 |
| | Positive (N=61) | 27 (44.3) | 34 (55.7) | |
| | Negative (N=89) | 37 (41.6) | 52 (58.4) | |
| HER2 Neu Enriched | | | | 0.024 |
| | Positive (N=31) | 20 (64.5) | 11 (35.5) | |
| | Negative (N=98) | 39 (39.8) | 59 (60.2) | |
| Triple-Negative Breast Cancer | | | | 0.063 |
| | Present (N=61) | 21 (34.4) | 40 (65.5) | |
| | Absent (N=82) | 41 (50.0) | 41 (50.0) | |

Table 7. Association between metastatic sites and breast cancer subtype

| | Lung | | | Vertebrae | | | Liver | | |
|---|---|---|---|---|---|---|---|---|---|
| | Yes n, %[1] | No n, %[1] | p-value | Yes n, %[1] | No n, %[1] | p-value | Yes n, %[1] | No n, %[1] | p-value |
| Hormone status | | | 0.355 | | | 0.105 | | | 0.350 |
| Positive | 10 (35.7) | 17 (47.2) | | 10 (58.8) | 17 (36.2) | | 4 (30.8) | 23 (45.1) | |
| Negative | 18 (64.3) | 19 (52.8) | | 7 (41.2) | 30 (63.8) | | 9 (69.2) | 28 (54.9) | |
| Triple Negative | | | 0.233 | | | 0.648 | | | 0.046 |
| Yes | 11 (42.3) | 10 (27.8) | | 5 (29.4) | 16 (35.6) | | 7 (58.3) | 14 (28.0) | |
| No | 15 (57.7) | 26 (72.2) | | 12 (70.6) | 29 (64.4) | | 5 (41.7) | 36 (72.0) | |
| HER2 | | | 0.168 | | | 0.093 | | | 0.044[#] |
| Positive | 6 (24.0) | 14 (41.2) | | 3 (17.7) | 17 (40.5) | | 1 (8.3) | 19 (40.4) | |
| Negative | 19 (76.0) | 20 (58.8) | | 14 (82.3) | 25 (59.5) | | 11 (91.7) | 28 (59.6) | |

| | Brain | | | Contra-lateral nodes | | |
|---|---|---|---|---|---|---|
| | Yes n, %[1] | No n, %[1] | p-value | Yes n, %[1] | No n, %[1] | p-value[#] |
| Hormone status | | | 0.362 | | | 1.000 |
| Positive | 6 (54.5) | 21 (39.6) | | 0 (0) | 27 (42.9) | |
| Negative | 5 (45.5) | 32 (60.4) | | 1 (100) | 36 (57.1) | |
| Triple Negative | | | 0.225 | | | |
| Yes | 2 (18.2) | 19 (37.2) | | 0 (0) | 21 (34.4) | 1.000 |
| No | 9 (81.8) | 32 (62.8) | | 1 (100) | 40 (65.6) | |
| HER2 | | | 0.483[#] | | | 0.339[#] |
| Positive | 5 (45.5) | 15 (31.3) | | 1 (100) | 19 (32.8) | |
| Negative | 6 (54.5) | 33 (68.7) | | 0 (0) | 39 (67.2) | |

between diagnosis and first metastatic disease was 10.5 months (Table 4). Table 5 shows that there is an association between the grade of cancer and the number of sites. Whilst 57.1% (n = 4) of the Grade I BC participants had one site involved, 30.8% (n = 4) of Grade III BC participants had three sites involved (p = 0.001) (Table 5). Other analyses indicated that the grade of the cancer and the age of the patient were not significantly associated with the different metastatic sites (p > 0.05) (data not shown).

Analysis of Table 6 indicates that HER 2 enriched breast cancer is associated with metastases (p = 0.024), but other cancer subtypes (hormone positive and TNBC) were not significantly associated (p > 0.05). Table 7 shows the association between the various BC subtypes and the metastatic sites. Table analysis indicates that none of the BC subtypes was associated with lung, vertebrae, brain or contra-lateral node sites of metastasis (p > 0.05). However, Triple negative and HER2 positive BC subtypes were significantly associated with liver metastases (p = 0.046 and p = 0.044 respectively).

## DISCUSSION

This study has described the characteristics of non-metastatic and metastatic breast cancer patients managed in a tertiary hospital in Ghana. It determined the median time to metastases after breast cancer diagnosis to be 10 months with 42% having metastases to multiple sites. It also

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identified an association between liver metastases and tumour subtypes. The median age for metastatic and non-metastatic BC was 51.5 and 50.0 years, respectively. This relatively young age group affected by breast cancer in low- and middle-income Countries (LMICs) has been reported by other studies [3,19]. Four percent of patients are males, which is slightly higher than the 2.4% and 2.9% prevalence of male BC reported by earlier studies in Ghana [19,20]. It is, however, known that male breast cancer has a higher frequency in Africa [21]. About 4 in 10 of the patients had co-morbidities, with the commonest being hypertension, followed by diabetes mellitus, affecting 31% and 6% of the total number of patients. This is quite comparable to the prevalence of hypertension and diabetes of 28.3% and 6%, respectively, found in studies involving adult Ghanaians [22,23].

Sixty-seven and seventy-four percent of the patients were either overweight or obese in the metastatic and non-metastatic groups, respectively. About two-thirds being overweight /obese in this study is much higher than 41.5% rate found in adult females seeking care at a secondary health facility in Accra [23]. This could be because obesity is a known risk factor for developing postmenopausal breast cancer [24]. A study done on the effect of obesity on prognosis following early breast cancer found obesity to be an independent predictor for developing distant metastases [25]. It is important to take note of these co-morbidities as the chemotherapeutic medications (namely anthracyclines and, to a lesser extent, taxanes) and immunotherapy (trastuzumab) used for the treatment of BC have cardiotoxic effects [26]. Patients who are overweight, obese, hypertensive or diabetic are at increased risk of these cardiotoxic effects and should, therefore, be identified and monitored closely [26,27].

BC metastases commonly involve bone, lung, liver and /or brain [16]. Similarly, this study found that the commonest sites of distant metastases were the lungs and pleura (41%), bones (31%), liver (23%) and brain (12%). This is similar to a study that examined radiological images in metastatic breast cancer patients in Ghana, which found the three commonest sites of distant metastases to be lung (55.3%), bone (44.6%) and liver (39.8%) (28). Metastases may involve solitary or multiple organs, usually 2 or 3 sites. Metastases to 4 organs are rare [16]. Most patients in this study had metastasis to one site only, with 28% having metastases to 2 sites, while 14% had between 3-5 metastatic sites. Survival outcomes differ depending on the site and multiplicity of metastases, the cancer subtypes and the performance status of the patient [17]. Patients who develop bone metastases only have the most favourable outcomes [13], whereas those who develop brain metastasis have the worst survival [16]. Other studies have shown patients with lung metastasis having the longest overall survival [29]. In a study on patients with brain metastasis, those with solitary metastasis and favourable performance status (ECOG 0 & 1) had significantly better prognoses [30]. Luminal A metastases are mostly solitary, while HER 2 positive and hormone receptor-negative tumours and younger patients tend to have multiple metastases [12,31]. Considering the relatively young age of breast cancer patients in this present study, it is not surprising that as many as 4 in 10 of those with metastases had multiple sites of involvement. Younger patients have been found to have larger tumours with a higher likelihood of lymph node involvement and hence are diagnosed at more advanced stages [32], which, together with the increased likelihood of aggressive breast cancer subtypes [32,33], increases the chances of multiple metastases.

Similar to the findings in this study, a study in Ghana on metastatic patterns found the lung and pleura to be the most common distant sites [28]. Other studies in different localities globally have found bone metastases to be the first site of breast metastases in the majority of patients [13,31,34]. This is because bone metastases are more common in hormone receptor-positive tumours [12,13,31,34], and it is known that there is a higher proportion (or twice as many) of hormone-positive tumours in Caucasians than in people of African descent whilst Triple Negative Breast Cancer (TNBC) is far more common in Africans [35]. Visceral metastases are said to be more common in triple-negative cancers [13,36], and therefore, it is not surprising that this study found lung and pleural metastasis to be more common than bone metastasis. This study found a significant association between triple-negative and HER 2 breast cancers with liver metastases.

HER 2 enriched breast cancers in this study were more likely to metastasise (Table 6, p-value = 0.024), as has been found in another study [12], while other studies suggest triple-negative breast cancers are more likely to develop visceral metastases [36]. At the time of this study in Ghana, anti-HER 2 therapy was not covered by the National Health Insurance scheme and, so most HER 2 positive patients did not receive that treatment option. This may account for the seemingly high likelihood of metastasis from HER 2 positive BC.

All the tumours diagnosed at stage 1 in this study, though few, remained non-metastatic, while about two-thirds of the stage 2 and 3 tumours became metastatic. Significantly fewer T1 tumours develop metastatic disease than bigger-sized tumours [13]. It has been found that the mean time to development of metastases is 29 months [12], while another study found the median time to development of metastases to be 51.3 months [29]. Our median time to metastases of 10 months is rather short, but this is not surprising given the fact that the majority of our patients present with advanced disease, which is more likely to metastasise. There is, however, the inherent limitation in determining the time to metastases from the time of diagnosis, which varies from patient to patient and in LMICs, is usually delayed. As such comparing this time to metastases in our patients with patients from HICs may not be appropriate.

This study found the median duration of having symptoms prior to first presentation, although the difference was not

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statistically significant, was 12 months for metastatic breast cancer as compared to 8.5 months for non-metastatic cancer`. We consider this observation to be of clinical significance because longer duration prior to presentation has been found to be associated with more advanced disease and poorer survival [8,37]. Possible reasons for this delay in presentation, though not explored by this study, could be inadequate knowledge about breast cancer symptoms, uncertified complementary and alternative medicine (CAM) options and lack of access to appropriate health facilities [38,39]. It is possible, however, that some metastatic disease is wrongly classified as non-metastatic, and the actual duration of metastasis has been underestimated.

The risk of micrometastatic disease at presentation in advanced breast cancer is relatively high, hence the need for increased surveillance [40]. Unfortunately, limited resources in LMICs lead to a less-than-ideal metastatic work-up of cancer patients. In instances where appropriate high-resolution radiological investigations are available, access to the service may be limited by cost. For instance, in our practice, even though some individuals may afford CT imaging, the majority end up with chest X-ray and abdominal ultrasound scans, which are relatively more affordable but less sensitive in the detection of metastases [41]. Few patients undergo radio-isotope bone scans even though the service is available in our institution. PET scan is currently not available in Ghana, although it is available in South Africa. kenya and recently in Nigeria, meaning patients will have to travel to any of these countries to access the service. The associated travel and service costs invariably become a barrier to accessing this medical imaging option. Anecdotally, in our practice, there have been instances of the occurrence of metastasis weeks to a few months after surgery or chemotherapy and sometimes during treatment, suggesting that metastasis might have been present but missed at diagnosis.

The authors consider that these limitations may lead to the underdiagnosis and underreporting of metastatic disease. Availability and accessibility of comprehensive facilities for a thorough metastatic work-up of all newly diagnosed breast cancer patients would significantly influence the identification and appropriate treatment of those that are metastatic ab initio. Until then, efforts to improve the timely diagnosis of metastatic disease should be heightened with the available resources and made more affordable for the majority, aiming to minimise underdiagnoses and undertreatment and better estimate the true time frame to metastasis.

Whereas some studies have found the pattern of metastatic disease to be related to grade, nodal status, Ki 67 and receptor status [12,13,34], and another study found that high-grade tumours have a higher frequency of pulmonary and hepatic metastases as compared to low-grade tumours with more pleural and bone metastases [42], in this study, the age of the patient and grade of the cancer were not significantly related to the site of metastases. A major limitation of this study is that this is a retrospective review, and many of the patients have been lost to follow-up as such survival outcomes could not be evaluated. It is recommended that prospective studies be carried out to assess breast cancer survival in relation to the patterns of metastases.

### Conclusion

The median duration from diagnosis to metastases was less than 1 year, with the commonest sites being lung and pleura, bone, liver and brain in descending order. As much as 40% had 2-5 metastatic sites, and grade 3 cancers were significantly associated with multiple metastatic sites. Liver metastases were associated with triple-negative and HER 2 enriched BC. Considering that the median time to metastases from initial diagnosis was less than 1 year, and two-fifths of patients had more than one site of metastases, it may be more impactful and beneficial if clinicians aggressively monitor indications for metastases in these common sites. This could be done both during the initial diagnosis of breast cancer and also in the early post-treatment period since most of our patients present with larger tumours or are generally present late. Patients who present with high-risk disease with an increased likelihood of developing metastatic disease should be consequently managed aggressively. Early diagnosis and treatment remain the hallmark of improving the outcome of breast cancer management in Africa.

## DECLARATIONS

### Ethical consideration

Ethical approval was obtained from the Ethics and Protocol Review Committee of the Korle-Bu Teaching Hospital with approval number [KBTH-STC/IRB/00067/2018].

### Consent to publish

All authors agreed on the content of the final paper.

### Funding

None

### Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

### Author contributions

FD, JN, SE, HAA, EN, and JNCL participated in conceptualising, reviewing, and editing the manuscript. FD wrote the original draft, and EN performed the data analysis.

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**Availability of data**

Data is available upon request to the corresponding author.

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