Malignant pleural effusion in stage IV breast cancer: an experience from a sub-Saharan Tertiary Hospital

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Abstract

Background: Malignant pleural effusion described as effusion arising from direct infiltration of the pleura by cancer cells, occur in 2-23% of patients with breast cancer during the disease course. Breast cancer accounts for about one third of cases of malignant pleural effusion, second to lung cancer, and is associated with poor quality of life and increased mortality.

Methods: This was a retrospective analysis of 85 patients with breast cancer who were referred after detection of pleural effusion with a posteroanterior chest x-ray from the emergency or oncology unit to the cardiothoracic unit of the Lagos University Teaching Hospital between January 2011 and December 2012.

Results: A total of 85 patients were studied, with median age of 42 (25-72) years, 39(45.9%) patients were in 35-44 year group. The median disease free interval was 9 months. A high proportion of malignant pleural effusions were ipsilateral (85.9%), and haemorrhagic (61.2%). The 30 day mortality was 45.9%. The major determinants of mortality were the presence of massive haemorrhagic effusion, (OR = 19.2, 95% CI = 3.1-120.6, p = 0.002), and pulmonary metastatic deposit (OR = 94.7, 95% CI = 9.8-916.72.4, p <0.001).

Conclusion: Malignant pleural effusion is a common complication of stage IV breast cancer at our institution, with accompanying high 30 day mortality.

Key words: Malignant Pleural effusion, Stage IV Breast cancer, thoracostomy, mortality

Highland Med Res J 2017;17(2):100-103

Introduction

The recurrence of cancer cell following mastectomy occurs within the first 3-5 years,[1] in 18-45% of patients.[2,3] The most common site is in the bone, followed by local relapse, lung and liver.[1] Pleural and pericardial effusions are common and, when present, occur frequently over the course of the disease.[2,4] The identification of malignant cells in the pleural fluid, along with a positive parietal pleura biopsy can provide evidence that the primary disease has spread or progressed, and such progression has been associated with poor prognosis and a decreased life expectancy.[5] It has been reported that 70% of malignant pleural effusions were ipsilateral, 20% contralateral, and 10% bilaterally,[6] 11% are bloody in appearance, [7] and 3-10% are transudative in nature.[8]

The median survival time in malignant pleural effusion secondary to carcinoma of the breast is between 5-36 months.[9] We determined the prognostic influence of clinico-epidemiological profile of malignant pleural effusion secondary to breast cancer, and the 30 day mortality following the initial diagnosis.

Materials and Methods

This retrospective study was conducted at the Lagos University Teaching Hospital, a referral hospital located in metropolitan Lagos in Nigeria. The Human Research Ethics Committee approval of our institution was obtained. The patients were referred to the Cardiothoracic Unit from either the emergency or oncology departments after detection of pleural effusion with a posteroanterior chest x-ray. We analyzed the medical charts of patients diagnosed with malignant pleural effusion (MPE) at the cardiothoracic unit of our hospital between January 2011 and December 2012. Patients included are those with or without history of breast cancer now presenting with breast mass and pleural effusion, which had a core needle biopsy of the breast mass and pleural effusion cytological studies which confirmed presence of cancer cells. Patients with MPE secondary to other extra mammary primary tumors were excluded. Data collated included patients bio-data, age at diagnosis of MPE, location of the MPE in relation to the breast cancer (ipsilateral, contralateral and bilateral); physical, cytological and biochemical evaluation of the effusion. As well as treatment modalities (surgery, radiotherapy and chemotherapy) offered to the patient before the development of MPE,

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presence of extra pulmonary metastasis, and the 30 day mortality.

Procedure

All the MPEs were drained with chest tubes size between 28FR and 32FR and connected to underwater seal chest bottle with gravity assisted drainage. Laboratory results and chest radiological investigations were evaluated by qualified professionals experienced in cytopathology, histopathology and radiology.

The primary outcome determined the characteristics of malignant pleural effusion in cancer of the breast.

The secondary outcome(s) determined the 30 day mortality after diagnosis of malignant pleural effusion, and the determinants of 30 day mortality.

For the purpose of this study, the following definitions were used:

1. Disease free interval was described as the period between diagnosis and treatment of breast cancer and development of MPE.
2. Malignant pleural effusions was defined as effusions that result from the direct infiltration of the pleura by cancer cells.[3,6] Massive pleural effusion was defined as complete or almost complete opacification of a haemithorax on the chest x-ray.[13]
4. Thirty day mortality was described as death during initial hospitalization or within 30 days after the diagnosis of malignant pleural effusion.
5. Triple therapy was described as a combination of mastectomy, chemotherapy and radiotherapy for breast cancer management.

Statistical analysis

Data were presented as mean ±SD, median (IQR), frequency, percentage. Odd ratio and 95% CI as needed. Factors associated with the 30 day mortality were identified using binary logistic regression. Variables considered for the regression analysis included age >50 years, disease free intervals >6 months, the location of MPE (ipsilateral, contralateral, bilateral). As well as no medical treatment prior to presentation, the presence of massive serous-sanguineous fluid, ipsilateral upper limb oedema, and pulmonary metastatic deposit. The variables with $p < 0.20$ were further analysed using a stepwise, multivariate, logistic regression analysis. A p value of <0.05 was considered significant for all tests. All analyses were performed using the Statistical Package for Social Sciences for Windows version 20 (SPSS, Chicago, IL).

Results

A total of 85 patients with a diagnosis of MPE secondary to breast cancer were studied. All had closed thoracostomy tube drainage, a total of 92 procedures were performed; 7(15.2%) were bilateral and 78(84.8%) unilateral. There were 73(85.9%) and 52(61.2%) patients with ipsilateral pleural effusion, and haemorrhagic effusion respectively, Table 1.

Table 1. Characteristics of pleural effusion complicating stage IV breast cancer in Lagos, Nigeria

Variables	Frequency	Percent
Location of effusion		
Ipsilateral pleural effusion	63	74.1
Contralateral pleural effusion	12	14.1
Bilateral effusion	10	11.8
Type of effusion		
Haemorrhagic effusion	52	61.2
Serosanguinous effusion	33	38.8

The median disease free interval was 9 (0-20) months. A high proportion of MPE presented between 6.1-12 months 40 (47.1%), followed by 0-6 months with 27 (31.76%), and the least >18 months 3 (3.53%). At the time of presentation with MPE, 26 (30.6%) patients had no previous treatment. Patients who had single therapy were 6 (7.1%), which included surgery alone 5 (5.9%) and chemotherapy alone in one patient (1.2%).

Table 2. The distribution of mortality of patients with pleural effusion complicating stage IV breast cancer by age range in Lagos, Nigeria

Age range, years	30 day mortality No	Frequency Yes	P value
25-34	8	3	0.32
35-44	18	21	
45-54	10	10	
55-64	9	3	
≥65	1	1	

Those who had double therapy were 29(34.1%), which included surgery and chemotherapy in 27(31.8%), and surgery and radiotherapy 2(2.4%), while those who received triple therapy were 24(28.3%). Pulmonary parenchymal metastatic deposits were observed in 39 (45.9%) patients, ipsilateral upper limb lymphedema occurred in 15 (17.7%), and bony deposits in only one patient (1.2%). The 30 day mortality following the diagnosis of MPE was 39 (45.9%).

The median age was 42 (25-72) years, MPE occurred mostly among the 35-44 year group and this constituted 39 (45.9%) of cases followed by the 45-54 year group with 20 (23.5%) as shown in Table 1. The proportion of patient with 30 day mortality in the different age group

were similar, p = 0.32.

Table 3 shows the factors influencing 30 day mortality after malignant pleural effusion subjected to binary regression. The factors identified to be significantly associated with 30 day mortality in bivariate analysis were harvested and subjected to multivariate analysis.

Table 3. Univariate analysis of determinants of 30 day mortality in patients with pleural effusion complicating stage IV breast cancer in Lagos, Nigeria

Variable	Odd Ratio	95% CI	p value
Age >50 years	0.69	0.24-2.01	0.50
Diagnosis > 6months	6.228	0.20-1.27	0.14
Ipsilateral pleural effusion	0.56	0.16-1.9	0.35
Contralateral pleural effusion	1.79	0.52-6.18	0.5
Bilateral pleural effusion	1.91	0.49-7.32	0.34
Haemorrhagic effusion	22.5	5.98-84.6	<0.001
Upper limb lymph oedema	11	2.23-52.64	<0.001
Pulmonary metastatic deposit	128.4	13.9-1179.4	<0.001
No treatment	2.2	0.87-5.61	0.91

The result of the multiple logistic regression analysis for 30 day mortality is shown in Tables 4. The dependent variable in table 4 is 30 day mortality, 0 No -or- 1- Yes. Patients with massive haemorrhagic effusion were about 19 times more likely, (OR = 19.2, 95% CI = 3.1-120.6), p = 0.002, to die within 30 day than those with serosanguinous effusion.

Table 4. Multivariate analysis of factors influencing 30 day mortality in patients with of pleural effusion complicating stage IV breast cancer in Lagos, Nigeria

Variable		Odd Ratio	95% CI	p value
Haemorrhagic effusion	No			
	Yes	19.2	3.1-120.6	0.002
Upper limb lymph oedema	No			
	Yes	2.9	0.36-23.6	0.32
Pulmonary metastatic deposit	No			
	Yes	94.7	9.8-916.72.4	<0.001
Diagnosis >6 months	No			
	Yes	1.97	0.8-4.9	0.40

While patients with pulmonary metastatic deposit were about 95 times likely, (OR = 94.7, 95% CI = 9.8-916.7), p <0.001, to die within 30 day of MPE. However, the presence of upper limb oedema (p = 0.40) and diagnosis >6 months (p = 0.32) were not significant predictor of 30 day mortality.

The mortality in patients who had no medical intervention prior to the diagnosis of MPE was 55.2% compared to those who had some medical intervention 39.7%, p = 0.09.

The 30 day mortality was similar in patients below 50 years (47.8%) and above 50 years (38.9%), p = 0.5.

The 30 day mortality was similar in patients with bilateral MPE (60%) and unilateral MPE (44%), p = 0.340.

Discussion

We have demonstrated that malignant pleural effusion secondary to breast cancer is not uncommon at our institution. The median age for the development of MPE was 42 (25-72) years, which is close to a value of 45 ±1.24 years reported in an earlier study at our institution.[10] The age at presentation did not influence the 30 day mortality. Our observation is contrary to a previous study which reported that breast cancer has a worse prognosis when diagnosed before the age of 50 years.[5]

The median disease free interval was 9 (0-20) months, which is lower than 13(0-84) months reported in earlier studies.[5] The shorter interval in our study was attributed to limited access to proper oncological service coupled with delayed presentation with advanced cancer, probably following refusal of treatment especially mastectomy.

It is observed that a higher proportion of MPE were ipsilateral, and right sided. A similar observation have been made by other researchers.[6] The presence of a high proportion of MPE on the right side has been attributed to the increase pulmonary surface area on the right side, which may encourage the spread of cancer cell to the right pleural.[11]

We observed few cases of contralateral and bilateral MPE. This is in agreement with previous reports that effusions on both side and opposite side of breast cancer are few but not a rare occurrence.[6] Blood stained pleural effusion was noticed in 61.2% of MPE in the present study, which is higher than 11% previously documented.[8] The presence of blood stained MPE has been attributed to a direct invasion of blood vessels by tumor cells or from tumor induced angiogenesis.[12] Secondary pulmonary metastatic deposits, infiltration of axillary nodes, ipsilateral lymph oedema and bone metastasis was observed in our study. The lymphedema seen we attributed to obstruction of the lymphatic drainage secondary to axillary nodal obstruction, surgical clearance and radiation therapy.

The treatment modalities for breast cancer before development of MPE in the present study vary from mastectomy or radiation to a combination of surgery and chemotherapy, surgery and radiation, or triple regimen. Despite the availability of oncology services in tertiary

hospitals in the country, 30.6% patients had no medical treatment, and only presented at the hospital when in respiratory distress from massive pleural effusion. The variation in treatment regimens for breast carcinoma observed by us has been documented by other scholars. [12] We attribute the lack of treatment by some of the patients before the development of MPE to inadequate health care facilities as oncology services are available only in few centers in the country, and financial incapability of the patient, which may mitigate against seeking health care services early. The 30 day mortality was similar in patients who had no basic treatment (55.2%) and those who received one form of medical intervention (39.7%) before presentation. We attributed our observation to late presentation in our environment.

All patients in our study had thoracostomy with chest tube drainage, which suggested that the patients were in some form of respiratory distress before presentation at the hospital. In a similar study, only 45% of patients diagnosed with MPE had thoracocentesis which may indicate that the patients presented early in their disease course when compared to our patients.[13]

The 30 day mortality (45.9%). was higher in our study than 15-37% reported earlier,[12] but within the range of 32-77% reported for one year mortality in a group of patients with MPE of various aetiology in developed countries.[12] Our observation may be because a considerate number of patients had no medical intervention prior to presentation. Some of our patients presented with advanced disease condition with metastatic pulmonary deposits, extra pulmonary metastasis (axillary nodes, lymphatic and bone), and complications arising from chemotherapy or radiation. The 30 day mortality in patients with bilateral MPE (60%) was higher than unilateral MPE (44%) in our study; however, the difference was insignificant. On the contrary, in a general study of patients with pleural effusion, patients with bilateral pleural effusion, relative to unilateral, had a higher risk of death at 30 days (17% versus 47%), and at 1 year (36% versus 69).[12] The major determinant of mortality in our patients included the presences of haemorrhagic effusion, and pulmonary metastatic deposit. However, the age, disease free interval period before presentation, treatment modalities, the side or site of effusion had no influence on the mortality.

The limitations to our study include it been a retrospective study. Hence, we were unable to exploit confounding risk factors implicated in patients' outcome after the diagnosis of malignant pleural effusion. It is a single institution study with a relative small size. Nevertheless, we have illustrated that MPE is not uncommon in stage IV breast carcinoma, and is associated with a high mortality rate.

Conclusion

Malignant pleural effusion is not uncommon following stage IV breast cancer at our institution, and it is associated with high 30 day mortality. The determinant of mortality included the presence of massive haemorrhagic effusion, and pulmonary metastatic deposit.

Conflict of interest

The authors have no potential conflict of interest.

Source(s) of funding support: No support.

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