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Original Article

Assessment of Risk Factors for Distant Metastases of Breast Cancer

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ABSTRACT

Background: *Breast cancer is the most prevalent cancer among Bangladeshi women (27.4%) and the second most common among both sexes (12.5%). Late-stage illness with distant metastases in low-income communities has a poor prognosis.* ***Objective:*** *The purpose of this research was to identify potential causes of distant metastases.* ***Materials and Methods****: This case control study was done from July 2017 to June, 2018 in National Institute of Cancer Research and Hospital (NICRH), Mohakhali, Dhaka.* ***Results:*** *In the case group, about 25% involved lymph node numbers > 5, whereas in the control group it was nearly 13%; the p-value was 0.035 (<0.05).The primary tumor involved the underlying blood vessel in 35.7% of participants in the case group and only 15.5% of participants in the control group; the p-value was 0.05 (i.e., 0.029). Primary tumors of stages III and IV were present in 54.7% of patients in the case group and only 22.6% of patients in the control group. On the other hand, I was more in the control (28.5%) group than the case group (11.9%). Positive surgical margin (p = 0.034, OR = 4.8; 95% CI: 1.126–20.460); positive lymph node > 5 (p = 0.007, OR = 4.11; 95% CI: 1.48–11.41); involvement of vessels (p = 0.016, OR = 2.99; 95% CI: 1.227–7.317); stage of primary tumor (p = 0.002, OR = 5.81; 95% CI: 1.85–18.15).* ***Conclusion:*** *The higher number of affected lymph nodes (>5), involvement of underlying vessels, positive surgical margin and higher stage (stage III & IV) at diagnosis are statistically significant risk factors*

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for distance metastases of breast cancer.

Keywords: *Breast cancer; Distant metastasis; Risk factors.*

INTRODUCTION

Breast cancer is the top cancer in women globally. Breast cancer rates are up, but early detection and personalized treatments have lowered death rates in wealthy countries. LMICs, like Indonesia, have higher case fatality rates than high-income countries [1,2,3]. LMICs have higher mortality rates due to various factors like demographics, socioeconomic status, and healthcare systems [4]. Cancer kills mainly due to distant spread [5,6]. 1/3 of breast cancer patients will develop distant spread, even those diagnosed early [7]. Spotting risks for metastasis can aid breast cancer treatment.

Cancer is a major non-communicable disease on the rise globally. Breast cancer is widespread globally.2nd most common cancer with 1.7M new cases and 25% of all cancer types.Breast cancer rates vary from 19.4 to 89.7 per 100,000 people across regions.Breast cancer hits younger women harder in developing countries.Breast cancer peaks in Asian women in their 40s and in Western women in their 60s [7]. Breast cancer is deadlier in developing countries than in high-income ones. Over 60% of breast cancer deaths in 2012 happened in developing countries [8].

Breast cancer is the top cancer in women (27.4%) and second in both genders (12.5%) in Bangladesh.69% of women's cancer deaths are caused by a hidden burden.Breast cancer rate in Bangladesh: 22.5 per 100000 women.Bangladeshi women aged 15-44 have the highest rate (19.3 per 100000) of breast cancer compared to other cancers.More Bangladeshi women than men (84.1 vs 79.5 million). 45M women can reproduce, 13.5M are <50 [9]. Breast cancer info in Bangladesh is scarce. Breast cancer rates in West Bengal, India are comparable to those in Bangladesh (ASR 25.2 per 100,000).Bangladesh's NICRH hospital registry tracks new cancer cases. NICRH diagnosed 1373 cases of breast cancer in 2014. Breast cancer patients averaged 42.97 years old (SD ± 10.873, age range 15–94). 55% had given birth before, while only 7.2% had not. Breast cancer can spread to various body parts, with the bone being the most common site. Metastatic breast cancer treatment varies by tumor location and may involve surgery, radiation, chemo, biological, or hormonal therapy [10]. Breast cancer can come back quickly or after a few years. Risk changes with time based on molecular and clinical factors.ER-negative and HER2-positive tumors have higher recurrence and death rates within 1-3 years. ER+/HER2- patients have lower rates in early years but still have recurring rates after 5 years. Tamoxifen helps at first, but after 5 years, most relapses and deaths happen. Breast cancer targets differently by subtype. Breast cancer can spread to bones, lungs, liver, brain, and lymph nodes. ER+ tumors have a low incidence rate and good prognosis in the first five years. Rate rises after 5 years (up to 40%). Bones are commonly affected, but not so much the brain. TN breast tumors have a poor prognosis, with high incidence and early metastases [11,12]. TN tumors often target vital organs like the brain and lungs. HER2+ tumors are highly aggressive.

Anti-HER2 therapy boosts prognosis and extends patient lifespan. Therapy works for outside lesions, but brain metastasis is still a challenge. Cancer can come back locally or spread elsewhere, and the factors that predict each are different. Local recurrences in women increase distant metastases risk. Younger women with early lymphatic invasion and local recurrence within 2 years are at high risk for distant spread. Extensive intraductal component or inadequate initial surgery lowers risk.13Better early breast cancer treatment = fewer distant metastasis in women. Cancer deaths per 100,000 people have dropped for 20 years straight, from 215.1 in 1991 to 171.8 in 2010. 20% drop = 1,340,400 fewer cancer deaths (952,700 men, 387,700 women). Cancer death rates dropped from 1991 to 2010, but not for white women over 80 [13].

OBJECTIVE

The goal of this study was to identify tertiary care hospital-based risk factors for distant metastases in breast cancer among women in Bangladesh.

MATERIALS & METHODS

The Dhaka-based National Institute of Cancer Research and Hospital (NIRCH) conducted this case-control study. It took 12 months, from July 2017 to June 2018, to complete this investigation. Patients over the age of 18 with a diagnosis of breast cancer with metastases who were admitted to NICRH's Medical Oncology, Radiation Oncology, or Surgical Oncology departments were included in the study. And for the control group, we chose individuals who had breast cancer, received treatment for breast cancer, returned here for follow-up care, but showed no signs of metastasis. Purposive sampling with specific inclusion and exclusion criteria was used to acquire the sample. The total number of people in the sample was 126.Out of those, 42 were chosen as cases and 84 as controls.

Inclusion criteria

- Patients diagnosed with metastatic breast cancer will be selected as cases.
- Patient diagnosed with breast cancer and got treatment for breast carcinoma minimum 2 years before but had not yet developed any features of metastasis cancer will be selected as control
- Cases and controls must both be at least 18 years old.
- Admitted patients for cases and patients coming for follow up clinic as control.

Exclusion criteria

- Aged below 18 years.
- Having any other clinical features not from metastatic breast cancer.
- Those who refused to give consent for this study.

Study procedure: Factors such as age, tumor size, lymph node status, tumor grade, time between primary and first metastatic relapse, treatment factors, loco-regional treatment, adjuvant medical treatment, hormone receptor status, margin status, peritumoral vascular invasion, morphologic factors of carcinoma, menopausal status, breastfeeding, delayed diagnosis, inadequate, or incomplete treatment, etc. were all taken into account.

Data collection: Face-to-face interviews utilizing a standardized data sheet were used to compile the acquired information. Documents and medical records provided all additional necessary information. Histopathology and imaging results from

CT scans or ultrasounds were documented. The staging and recording of it were completed.

Data analysis: For this investigation, we used the chi-square test. Regression analysis was used for multivariate analysis. SPSS for Windows, version 22, was used for the study's statistical analysis. Tables, figures, charts, and diagrams illustrate the findings. The 95% confidence threshold was used.

Ethical consideration: The research procedure for this study was approved by the relevant ethics committee and research review committee before it could begin. Every participant in this trial was fully briefed on the study's potential benefits and drawbacks. Patients were only included in the study once they gave their informed, written consent.

RESULTS

The purpose of this case-control study was to pinpoint the causes of breast cancer that has spread far beyond the original tumor. Those who experienced the development of distant metastases following breast cancer treatment were classified as cases, while those who did not experience the same were classified as controls. Various socio-demographic characteristics, behavioral factors, treatment factor, grading, staging, clinical features were sought and analyzed.

Socio-demographic characteristics

The majority of both the cases (35.7%) and controls (38.7%) were found to be between the ages of 41 and 50 (**Table-I**)

Table I: Age-bracketed distribution of study participants (N = 126)

Age group In years	Case %	Control %
20-30	14.3	4.7
31 – 40	30.9	33.3
41 – 50	35.7	38.1
51 – 60	19.0	16.7
> 60	0	7.1

Table II shows that Infertility, very early or late age of conception or prolonged use of hormonal contraceptive use was also analyzed but none of these was found to have significant difference in these two groups.

Table II: Pregnancy- and hormone-related factors in the drug usage of the study's subjects (N=126)

Risk factors	Case N	Control N	$\chi 2$ value	P value
Infertility				
Yes	2	3	0.11	0.74
No	40	81		
Age at conception				
Extreme age	12	21	0.18	0.66
Normal age	30	63		
Prolong use of hormonal contraceptive				

Prolonged use	25	39	1.92	0.66
Not use	17	45		
Exclusive breast feeding				
Yes	31	68	0.84	0.35
Not breast feeding	11	16		
State of menopause				
Pre menopause	13	18	1.36	0.24
Post menopause	29	66		

Factors of the primary tumor

The two groups were compared regarding primary tumor grading and staging, histopathologic lesion pattern, lymph node involvement, lymph node positivity rate, surgical margin status, and initial lesion hormonal receptors. The primary tumor histopathology of the case and control groups is depicted in **Figure I**. The ductal carcinoma rate was 90.5% in the case group and just 77.4% in the control group. However, for 17.8% of the control group, information was unavailable. The significance level was determined using a Chi-square test. Since the p-value for 2 = 3.46 was greater than 0.05, the result was not statistically significant.

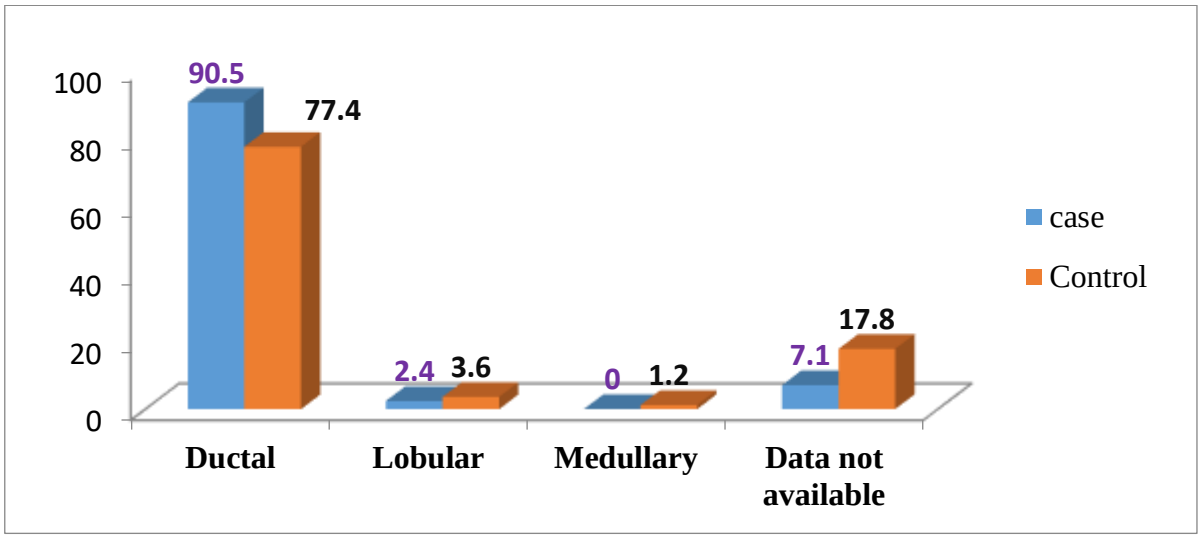

Fig 1: The Bar diagram of the primary tumor according to Histopathology (N=126)

Four patients in case group had surgical positive margin, but it was only one in the control group. $\chi 2$= 8.14, since p-value was 0.043 (<0.05), the result was statistically significant (**Table III**). In case group about 25% had involved in lymph node number > 5, whereas in the control group it was nearly 13%. $\chi 2$= 10.44, since p-value was 0.035 (<0.05), the result was statistically significant (Table 4). Logistic regression done to compute Odds Ratio (OR).

Table III: The OR for margin of surgery

Group	OR	Std. Err	z	P	95% Conf. interval
Margin of surgery					
Positive or close	4.8	3.55	2.12	0.034	1.126 – 20.460

Interpretation = Odds of presenting with negative margin of surgery compared to positive or close margin was 4.8 times more likely among cases in comparison to control group.

Table IV: The OR for Lymph node number

Group	OR	Std. Err	z	P	95% Conf. interval
Lymph node number					
1-5	2.30	1.13	1.69	0.091	0.87 - 6.06
> 5	4.11	2.14	2.71	0.007	1.48 – 11.41

Interpretation= Odds of presenting with 1-5 lymph nodes compared to zero nodes was 2.3 times more likely among cases in comparison to the control group (**Table IV**).

Similarly, odds of presenting with 6 or more lymph nodes compared to zero nodes were 4.1 times more likely among cases in comparison to the control group.

The primary tumor involved the underlying blood vessel in 35.7% participants in case group and only 15.5 % participants of the control group (**Figure 2**).

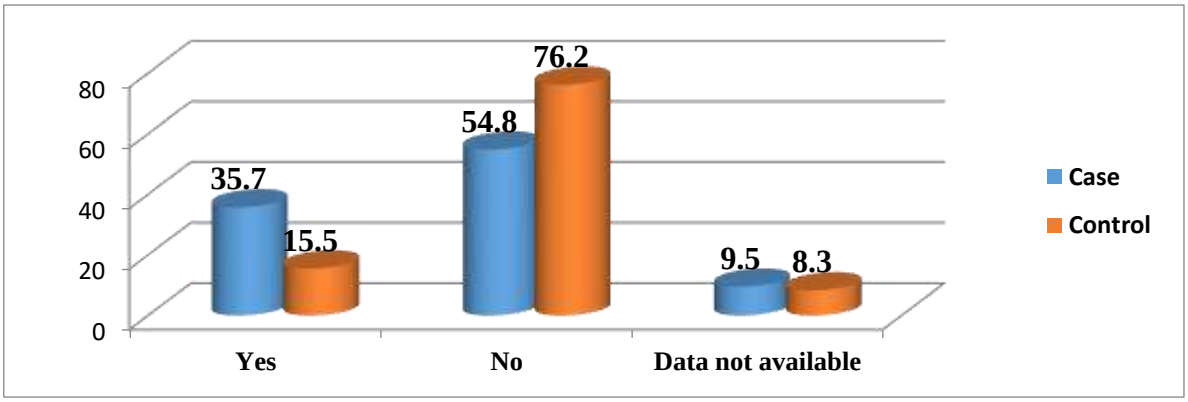

Fig 2: The Bar diagram Distribution of study subjects according to blood vessel involvement (N=126).

The significance level was determined using a Chi-square test. $\chi 2 = 7.06$, since p-value was <0.05 (i.e.0.029), the result was significant. Logistic regression done to compute OR (**Table V**).

Table V: The OR for vessel involved

Group	OR	Std. Err	z	P	95% Conf. interval
Vessel involved					
Yes	2.99	1.364	2.41	0.16	1.227 – 7.317

Interpretation= Odds of involvement of the vessels was 2.9 times more likely among cases in comparison to the control group. In the control group 33.3% tumor was in grade I and 34.5% were in grade II. On the other hand, 35.7% tumor was in grade III in case group and 9.5% were in grade IV. None of the participants in the control group had a tumor group IV (**Figure – III**).

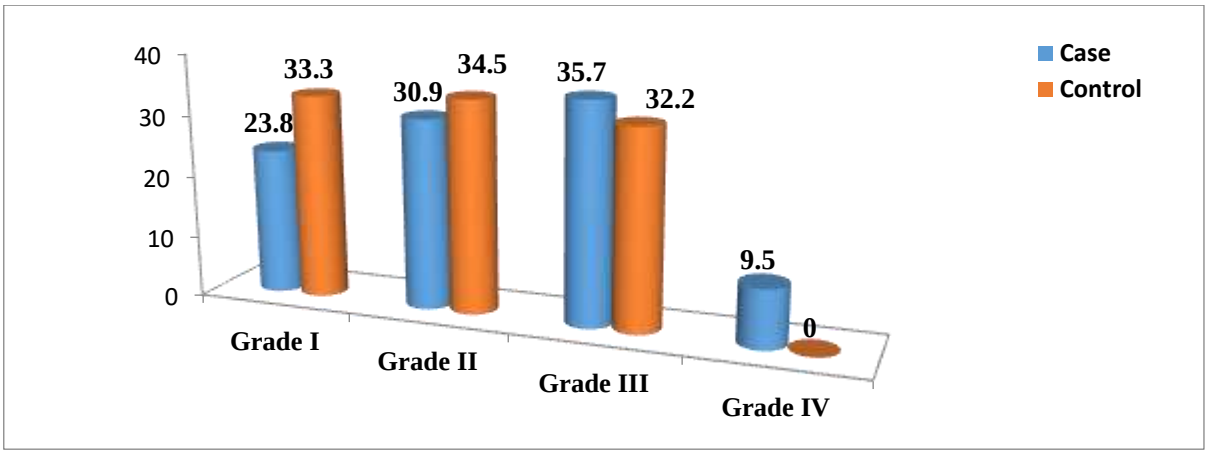

Fig 3: The Bar diagram shows the distribution of study subjects according to grading of the primary tumor (N=126).

The significance level was determined using a Chi-square test. $\chi 2$= 9.05, since p-value was <0.05 (i.e.0.029), the result was significant. Logistic regression done to compute OR (**Table VI**).

Table VI: The OR for tumor grade

Group	OR	Std. Err	Z	P	95% Conf. interval
Grading					
Grade II	1.255	0.623	0.46	0.648	0.473 – 3.325
Grade III	1.970	0.935	1.43	0.153	0.777 – 4.996

Meaning = Cases were 1.25 times more likely than controls to appear with a grade-II tumor compared to a grade-I tumor. Similarly, the likelihood of presenting with a tumor of grade 3 or 4 was 1.97 times that of presenting with a tumor of grade 1. The primary tumor's stage was compared between the case and control groups. According to the results, only 22.6% of the patients in the control group had a primary

tumor at stage III (**Table VII**), while 54.7% of the patients in the case group did. However, the Stage I group was more in control (28.5% vs. 11.9%) than the control group. Chi-square = 0.001, significance level. (**Table VIII**)

Table VII: The primary tumor stage distribution of the research population (N=126).

Hormone receptor type	Case		Control		χ2 value	P value
	N	%	N	%		
Stage I	5	11.9	24	28.5	13.59	0.001
Stage II	14	33.3	41	48.8		
Stage III & IV	23	54.7	19	22.6		

Table VIII: The OR for staging of the primary tumor

Group	OR	Std. Err	Z	P	95% Conf. interval
staging of the primary tumor					
Stage II	1.63	0.95	0.85	0.395	0.52 – 5.11
Stage III&IV	5.81	3.37	3.03	0.002	1.85 – 18.15

Most of the participant had estrogen receptor positive (ER + ve) that was 23.8% in case group and 50% in the control group. On the other hand, 30.9 % of case subject had HER2 +ve and only 17.8% in control group. The triple negative case was 38.1% in case group and 23.8 % in control group (**Figure 4**).

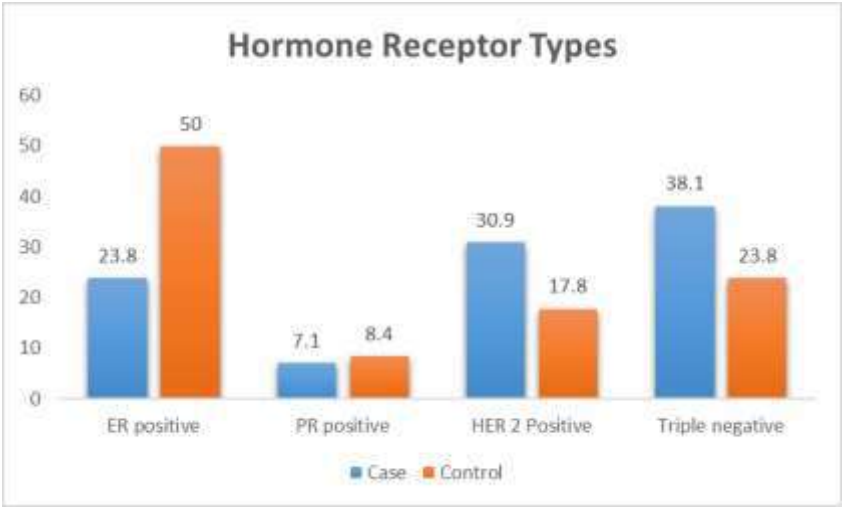

Figure 4: Hormone receptor presence was used to stratify the study individuals.

The significance level was determined using a Chi-square test. $\chi 2 = 8.86$, since p-value was 0.031 (<0.05), the result was significant.

Table IX: The OR for receptor status of the tumor

Group	OR	Std. Err	z	P	95% Conf. interval
Receptor status of the tumor					
Only ER or PR positive	1.604	0.853	0.89	0.374	0.565 – 4.551
Only HER2 Positive	1.435	0.755	0.69	0.492	0.511 – 4.02
Triple negative	1.666	0.867	0.98	0.326	0.601 – 4.620

Interpretation= Odds of having only ER or PR receptor positive compared to both ER and PR or all three receptors being positive was 1.6 times more likely among cases in comparison to the control group. Odds of having only HER2 receptor positive compared to both ER and PR or all three receptors being positive was 1.4 times more likely among cases in comparison to the control group. Odds of having all three receptors negative compared to both ER and PR or all three receptors positive was 1.7 times more likely among cases in comparison to the control group (**Table IX)**.

Factors associated with treatment of the primary tumor:

Various factors regarding treatment of the initial treatment – as type of surgery, use of radiotherapy, chemotherapy or hormonal therapy, use of local or foreign medicine, delay in the treatment was analyzed.

Table X: The distribution of various treatment factors of the participants (N=126)

	Case		Control		$\chi 2$ value	P value
	N	%	N	%		
Type of surgery					4.0	0.135
Lumpectomy	4	9.5	14	16.7		
Mastectomy	34	81.0	68	80.9		
Surgery not done	4	9.5	2	2.4		
Source of chemotherapeutic drugs						
Local	30	78.9	74	89.2	2.25	0.134
Foreign	8	21.1	9	10.8		

Table X shows Mastectomy was done in 81% in case group, and 80.9% in control group. P is 0.135 that is not significant. The source of chemotherapeutic agent

were from local source 78.9% in case group, and 89.2% in control group and it also showed no significant statically difference (p=0.134). Thirty-two participants out of 42 cases (76.2%) develop distant metastases within 2 years of treatment of initial diagnosis (**Figure 5**). 2-5 years disease free was 19.1% of case group.

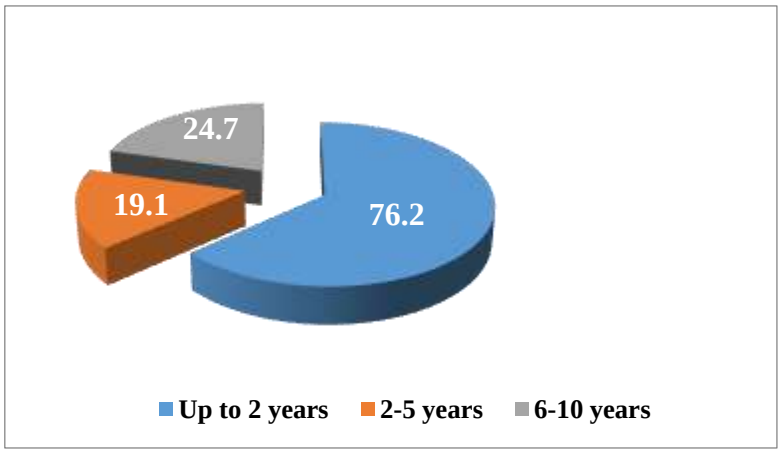

Figure 5: Disease free interval of cases (in percentage) N=42

Sites of metastases

Bone and liver were the commonest site for distant metastases - 21.4% in each site (**Figure 6**). On the other hand 35.7% had metastases in multiple sites of the body as liver, bone, lung, brain etc.

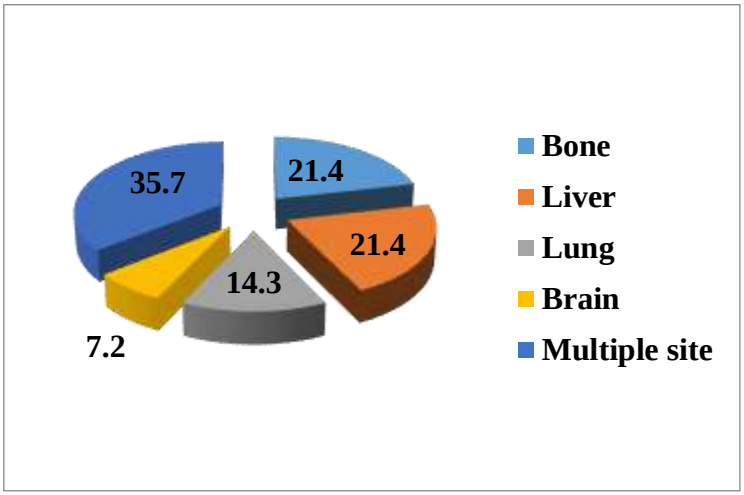

Figure 6: Distribution of metastatic sites of the case group (in percentage) N=42

DISCUSSION

Breast cancer is very common among malignancies in women. About 90% of breast cancer deaths are attributable to distant metastases [14]. Age at diagnosis, family history, cancer stage, receptor type, histologic and nuclear grade, and treatment outcomes all play a role in a breast cancer survivor's likelihood of experiencing a recurrence [15]. In the present study, mean

age in case group was 42.67 ±9.27 years, whereas in the control group it was a bit higher that is 45.13±9.60 years. The average age of breast cancer patients was reported to be 46.8 and 47 years old, respectively, in hospital-based studies conducted in Delhi and Jaipur [16,17]. Bangladeshi women, on average, develop breast cancer at the age of 41.0, ten years earlier than white women in the United States [18]. Despite improvements in treatment, people who are diagnosed at a younger age have a higher risk of recurrence [19]. In this study also we found the mean age is lower in the control group though statistically not significant.

In our series, ductal carcinoma was the most common histological subtype among both cases (95.5%) and controls (77.4%). The current study's results are very similar to those published in India. [19] The infiltrating ductal carcinoma type was also shown to be the most prevalent in the US population [20]. Although breast cancer is common in middle-aged women, local recurrence is common in the young patients [21]. In an early radical mastectomy series, Lewis and Reinhoff found a 67% crude local recurrence rate in patients aged 20-29 years and a 41% rate in patients aged 30-39 years, whereas in women aged >40 years, the local failure rate was 21% to 25% [22].

More the number of lymph node involved, more is the chance of recurrence. In this study about 25% of the study population of case group had involved in lymph node number > 5, whereas in control group it was nearly 13%. $\chi 2$= 10.44, since p-value was 0.035 (<0.05), the result was statistically significant. This result coincides with the findings of another study where they found distant metastases were significantly predicted by the total number of lymph nodes affected (p=0.008) in a one-way analysis. Greater the lymph nodes counted involved, higher was the incidence of recurrence [23]. Truong in his multivariate analysis, he finds that axillary lymph node involvement of more than 25% is associated with local recurrence following mastectomy.

Another very critical and important risk factor includes surgical margin. We observed that the positive margin rate was 12.1% in this investigation, 69.1% had negative margin, and among the control group, only 1.2% had positive margin and 85.7% had negative margin. There is a statically significant difference (p <0.05) ensures that positive surgical margin is a risk factor for distant metastases. Numerous studies have indicated that local recurrence rates are reduced by doing a more thorough excision of the tumor. Based on these findings, it appears that both complete local and complete distant tumor management require "adequate" initial tumor excision. [22] Following CS and RT for invasive breast cancer, patients with positive microscopic margins have been demonstrated to experience a much greater rate of local recurrence than those with negative margins in the majority of follow-up studies [24]. Lack of radiotherapy treatment acts as risk factor for local recurrence. Radiotherapy significantly reduces the incidence of local recurrence (14% vs. 49%) and distant metastases (6% vs. 35%) in the 3083 patients of the Danish Breast Cancer Cooperative Group randomized to receive adjuvant radiotherapy or not following surgery. Woodward found that the local control of tumor was improved by radiotherapy regardless of primary tumor size or lymph node status when comparing two groups of patients who had or had not

received chest wall radiotherapy after surgery [28]. According to Fordor, pT1 and pT2 N+ patients who undergo irradiation have an 8% risk of recurrence and a 52% and 41% chance of survival after 15 years, respectively [25]. According to Morrow[26], Combining initial chemotherapy, surgery, and radiation therapy allows for excellent local control of disease in patients with large and locally advanced breast tumors. Eugène Marquis Comprehensive Cancer Center study on 75 cases showed As far as local control goes, the benefits of chemotherapy appear to be minimal. either in the form of neoadjuvant or in the form of adjuvant therapy. Neoadjuvant debulks the tumour, while adjuvant kills any remaining malignant cells not detected clinically or pathologically. The reason behind the difference in our result may be delay in commencing RT. In the perspective of Bangladesh, there occurs technical delay in scheduling RT and during this period patients are advised chemotherapy. So, instead of being part of a combined protocol, chemotherapy is given as an alternative view to halt the disease process till patient receives RT. Hence the outcome may not be up to expectation.

Histologic grading of the primary tumour is also important to predict the prognosis of the disease. In this study most of the control group patients had the initial tumor grading I & II (68 % of the total) but in case group grade III & IV is much more than the control group and that is stastically significant (p=0.029) . It implies that higher the grade, more is the chance of distant metastases. The Danish Breast Cancer Cooperative Group analyzed data from 3083 patients, high histologic grade was discovered to increase the likelihood of a distant recurrence. [27] Finally, the stage of the tumour at the initial diagnosis was an important factor to cause local recurrence. It implies that risk for local recurrence was low at stages IA, IB and IIA, and high beyond stage IIA. More advanced stage had more risk for recurrence. Tumor stages 2 and 3 had a greater rate of local recurrence when analyzed separately. Overall survival rates calculated using actuarial data were 98% at 1 year, 94% at 3 years, and 88% at 5 years. In a multivariate study, advanced stage was the component most strongly linked to shortened survival and a bad prognosis. The risk of a tumor returning was proportional to its initial stage of development [28,30].

CONCLUSION

In our opinion, there are a number of potential causes of breast cancer to spread to other parts of the body. The increase in number of affected lymph nodes, positive surgical margin, involvement of underlying vessels and higher stage at diagnosis are statistically significant risk factors for distant metastases. Patients with distant metastases tend to be young and have low levels of education. Knowledge about the disease and its treatment, prognosis is not known to the patients. So there is delay in the diagnosis and initiation of treatment. Due to poverty and ignorance many of them did not complete the treatment also. All these factors also contribute to the distant metastases of breast cancer.

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