Post-Recurrence-Survival After Treatment in Breast Cancer Patients: Identifying Associated Factors

Abu Khaled Muhammad lqbal[1*] Nasima Akhter[2] Md. Jahangir Kabir[3] Md. Rassell[4] A.K.M. Minhaj Uddin Bhuyian[5]
Mayin Uddin Mahmud[6] Md. Yunus Haroon Chowdhury[7] M Mizanur Rahman[8]

Abstract

Background: Globally breast cancer is the most common deadly cancer and major health problem in women. Recurrence of breast cancer is a major clinical manifestation and represents the principal cause of breast cancer related deaths. During diagnosis most of the breast cancer patients are detected and treated in a curative state with some patient's experiences recurrence following completion of treatment after a certain period. Therefore, explore the associated factors related to recurrence of breast cancer would be helpful in estimating the treatment outcomes and predicting the prognosis. This study aimed to evaluate the factors related to recurrences and post recurrent mortality for five years after primary treatment among breast cancer patients.

Materials and methods: In this prospective cohort study on patients selected between 2014-2016 who developed recurrence after primary treatment of breast cancer,they were evaluated, treated and followed up for five years from the primary treatment. Data was compiled as age, molecular subtypes, type of operation, margin status, treatment status, sociodemographic profile. Death was analyzed considering the time period, age of the patient and molecular profile of the tumor.Kaplan-Meier methods were used for survival estimation and for comparing mean survival among different groups, the Log-Rank test was utilized.

1. Associate Professor of Surgical Oncology
   Chittagong Medical College, Chattogram.

2. Lt. Colonel & Classified Specialist in Surgery
   BNS Patenga Hospital, Chattogram.

3. Associate Professor of Surgical Oncology
   National Institute of Cancer Research and Hospital, Dhaka.

4. Associate Professor of Surgical Oncology
   BSMMU, Dhaka.

5. Associate Professor of Surgical Oncology
   National Institute of Cancer Research and Hospital, Dhaka,

6. Assistant Professor (CC) of Surgery
   Chittagong Medical College, Chattogram.

7. Associate Professor of Surgery
   Chittagong Medical College, Chattogram.

8. Professor Surgical Oncology (Retired)
   National Institute of Cancer Research and Hospital, Dhaka.

*Correspondence: Dr. Abu Khaled Muhammad lqbal
        Cell : 01711 13 29 50
        E-mail: khaledcum06@gmail.com

Results: Mean age at the time of primary treatment was 41.6 years, 55.7% was below 40 years of age, 78.7% had mastectomy, 21.6% underwent an unplanned lumpectomy, margin positivity was noticed in 17% of cases, 34% failed to receive axillary surgery. Regarding treatment status, 71% received incomplete treatment (p=.049) and larger tumor-17% (T3+T4) had more recurrences (p=.05). Out of 86 informed cases 59 died (68.6%) within five years of primary treatment. More death was noticed in younger and hormone negative groups. Highest survival was seen in the HR+veolder group and increased survival in younger ages demonstrated by Kaplan-Meier curve.

Conclusion: Incomplete treatment is an associated factor apart from younger age and molecular factors for recurrence in breast cancer treatment. Recurrence is an important risk factor for poor survival after breast cancer treatment.

Key words: Breast cancer; Recurrence; Risk factor; survival.

Introduction

Breast cancer is the second leading cancer having 11.6% and responsible for 66 % of all cancer related deaths.[1] Recurrence is a fatal outcome of breast cancer treatment. Relapse is seen in about 4-15% after successful treatment in different reports after surgical treatment including both Breast Conservation Surgery (BCS) and mastectomy.[1,2] In Post mastectomy cases without radiation treatment, locoregional Recurrence (LRR) was found to be between 4% to 35% in breast cancer patients. It depends on several risk factors.[3]

For early breast cancer surgery, systemic therapy and radiotherapy are the key elements of treatment for the purpose of cure. In locally advanced cancer neoadjuvant systemic treatment are practiced as per different international guidelines and recommendations.[4,5] There are episodes of metastasis or local recurrences even after adequate treatment. Vast majority of the studies are seen in the literature belong to first world. There is no sufficient data on final outcome of treatment when there is insufficient or inadequate treatment.

There is a large number of research on risk factors

for recurrence of breast cancer, but relatively less on mortality after a local recurrence. Factors causing the recurrence of breast cancer is multifactorial. Research findings showing that disease factors like tumor grade, large tumor size, axillary nodal involvement, lymphovascular invasion, high nuclear grade and negative hormone receptors status and positive HER-2 status had a higher risk of recurrence.[6]

Patient-factors like age and menopausal status, treatment-factors like margin status, chemotherapy and antihormonal treatment also had influence on treatment outcome[7]. Some reports revealed that there are more chances of developing distant metastases and death in patients who experience a local recurrence than without a local recurrence.[8] Risk factors like extent of recurrent disease, paucity of hormone receptor expression, lymph node involvement of the primary tumor, older age at diagnosis and a short disease-free interval are presumed to enhance the mortality rate.[9,10]

There are variation of the occurrence and recurrence of breast cancer in Asian populations with other parts of the globe.[10] Other than tumor and biological factors less emphasis was given on the influence of socioeconomic status, treatment profile, awareness, education status which might play role on the outcome of the breast cancer treatment and survival.

This study was designed and intended to identify the probable associated factors related to recurrence and post-recurrent mortality within five years of the primary treatment among the underprivileged women. It finally analyzed time and cause of death after primary surgical treatment.

Materials and methods
Case selection:It is a prospective cohort study carried out on patients who presented from 2014 to 2016 in the department of Surgical Oncology of National Institute of Cancer Research and Hospital (NICRH) Dhaka Bangladesh, with symptoms and signs of recurrences after primary treatment of breast cancer. In this study which was performed on 126 suspected recurrent cases among them 118 patient diagnosed as a recurrent breast cancer. Total 21 patients were excluded due to absent of previous documents (16) and declined

to enroll (5). They were offered the required treatment of the recurrent problems. Follow up study continued for five years after the time of primary surgical treatment. Breast cancer patients from different corners of the country attended in the outpatient department after new diagnosis, partially treated cases and for follow up after previous treatment. After proper scrutiny, all diagnosed recurrent breast cancer cases who consented to participate in the investigation group were included. Their previous documents of diagnosis and treatment were thoroughly checked. There was approval of the study from the institutions' ethical committee (Ref. no-NICRH/ Ethics/2015/197).

The documents of previous diagnosis, histopathology report, immunochemistry report, their hospital discharge certificate was examined. As per the patient's notification and physical examination they were categorized as local, locoregional and distant metastatic group. Core needle biopsy was done from the locoregional lumps. Metastatic work up with ultrasonography of the breast and abdomen, CT scan of the chest and isotope bone scan was done. To confirm the distant metastasis in lung and liver, CT guided FNAC was performed and for suspected brain metastasis brain MRI was done.

Local recurrence included lump over the chest wall, skin, previous scar or within breast parenchyma.Locoregional recurrence comprised breast and axillary node involvement. Distant recurrence included lung, bone, brain, ovary or liver.

After completion of the diagnostic work up, decision was made in a multidisciplinary team meeting for further planning of treatment. Surgery (Wide local excision, mastectomy or axillary dissection), chemotherapy, endocrine therapy and radiotherapy were offered to the patients according to their requirement.

After receiving appropriate treatment, each patient was under follow up in the Outpatient Department, they were in touch with telephone also. Total health status, time and mode of death was noted in case of death cases. Death time was recorded up to five years from the time of primary treatment. Distribution of the patients were arranged as the flow chart (Figure 1).

After thorough history taking regarding their demography, family status, sociocultural and treatment history, all relevant findings were collected, taken in structured data sheet which were later compiled in computer. Thereafter, data were collected in SPSS version 23 by which data analysis was done.

Results

Mean age of the patients was 41.6 SD 9.3, over 55% are in the group of below 40 years (Younger). People came from low income community as the data shows nearly 59 percent earn below 1500$ annually for a family. On the other hand nearly 60% achieved just primary education or no education (Table I). Data manifest that 21% had history of unplanned lumpectomy, more than 17 % had margin involvement. Nearly half (46.5%) of the cases recurred within two years. More than two third (71%) of the patients (p= .049) failed to receive complete adjuvant chemotherapy or radiotherapy treatment. Molecular profile showed over 60 % had TNBC and HER2 expressed tumor (Table II) among 81 examined cases.

Site of recurrence: All patients presented in the series with some sort of locoregional recurrent lumps (Table III). Data explored 69% cases recurred within the same site, over 7 % developed in the contralateral breast, over 18 % had isolated axillary recurrence. In the distant metastatic group, lung (14.4%) followed by bone (9.2%) was the metastatic site.

In total, mortality could be analyzed among 86 patients as 11 patients dropped from the follow up list who couldn't be traced even on phone (Figure 1). There was information about 57 deaths among them (TableIV). Two molecular data were missed. In the hormone negative groups there were documents of 38 patients, 50% were below 40 years age group, over 39% died within first two years of primary treatment including all age groups. Survival estimation shows that TNBC had marked negative outcome on younger patients. In total 27(31.3%) patients survived more than five years in this group.

The cumulative five-year survival rates by the Kaplan-Meier method (Figure 2A and Figure 2B) calculated by indicator of factors like age and molecular profile status (HR+ve,HER2+ve and

TNBC) displayed (Table IV). In the over 40 years (Gr A) group highest survival was seen in HR+ve and TNBC group (p=0.741). In the younger group (Gr B), though there was much mortality with TNBC as shown in the table, survival curve expressed also highest survival in TNBC and HR+ve patients (p=0.167) in the curve.

Table I Patient particulars

Variables	Sub group	Frequency	Percent (%)
Age	≤40 yrs	54	55.7
	>40 yrs	43	44.3
Family history	Yes	15	15.5
	No	82	84.5
Economical status Annual income	<1500 $	57	58.8
	>1500 $	40	21.2
Site	Unilateral	87	89.7
	Bilateral	10	10.3
Type of operation	Mastectomy	76	78.4
	Lumpectomy	21	21.6
Resection margin status (93)	Free	77	82.7
	Involved	16	17.2
Time of recurrence	<1 years	16	16.5
	1-2 years	29	29.9
	>2 years	52	54.6
Education status	Primary education or below	60	59.8
	Illiterate	(31)	
Treatment place	Secondary school or above	37	40.2
	Other institute	91	93.8
	NICRH	8	8.2

Table II Relationship of recurrence with different factors

Variables with number		Time of Recurrence		Total	Percentage	p
		≤2 years	>2 years		(%)	value
Type of operation (97)	Mastectomy	50	26	76	78.3	0.741
	Lumpectomy	13	8	21	21.7	
Tumor grade (51)	Moderately differentiated	24	13	37	72.5	0.611
	Poorly differentiated	8	6	14	27.5	
Axillary dissection (76)	Yes	30	20	50	65.7	0.14
	No	24	6	26	34.2	
Nodal metastasis (36)	Yes	17	10	27	75	0.443
	No	4	5	9	25	
Treatment profile (97)	Complete	14	14	28	28.8	.049
	Incomplete	49	20	69	71.3	
Tumor Stage (53)	T1-T2	30	14	44	83.1	.05
	T3-T4	3	6	9	16.9	
Molecular profile: Receptor Status (81)	HR+ve	20	11	31	38.2	0.949
	Her2 expression	11	7	18	22.2	
	TNBC	21	11	32	39.5	

Table III Site of recurrence /metastasis

Area	Site	Frequency	Percentage (%)
Locoregional (97)	Ipsilateral breast	67	69
	Opposite breast	7	7.2
	Ipsilateral axilla	43	44.3
	Only axilla	18	18.5
	opposite axilla	7	7.2
Distant (32)	lung	14	14.4
	liver	5	5.1
	Bone	9	9.2
	Brain	4	4.1

Table IV Mortality according to age and molecular profile on year basis

Molecular profile	1 yr		2 yr		3 yr		5 yr		>5 yr		Total
	GrA	GrB	GrA	GrB	GrA	GrB	GrA	GrB	GrA	GrB	
HR+ve	3	0	3	0	1	3	5	0	2	2	19
Her2 +ve	0	1	0	2	2	0	1	0	0	2	8
TNBC	3	3	2	4	2	4	0	5	4	3	30
											57+2 (Missing data= 59)

Group A :>40 yr
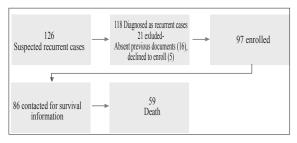Group B: ≤40 yr

Figure 1 Showing flow chart of steps of study of cases and death within five years of primary treatment
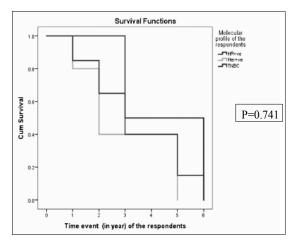

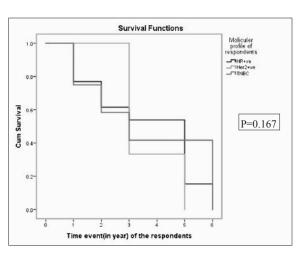**Figure 2A** Kaplan-Mayer curve showing survival in >40 yrs group distributed as molecular subtype

Figure 2B Kaplan-Mayer curve showing survival in <40 yrs group distributed as molecular subtype

Discussion

Return of the cancer after treatment is designated as recurrence. In breast cancer treatment it is claimed as the worse outcome. Though many factors were contemplated in the past, some are labelled as definite risk factors.[11] Recurrence is seen after mastectomy (9-28%) in early breast cancer cases, about 30-40% develop distant metastasis among them. In world literature it has been widely discussed about the influence of age and molecular factors for the locoregional recurrence and distal metastasis. In Arab, younger age (<40) in Japan HER2 and axillary status, in China lymph node involvement status and in Thailand, ER,PR and HER status and ,position of axillary lymph node metastasis are settled issues as prognostic indicators for early or late recurrence.[12,13,14,15] There are also descriptions about lymphovascular invasion, high tumor grade, negative hormone status, involved margin, lack of adjuvant systemic therapy which play great role for recurrence.[16,17] According to National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial, in case of locoregional relapse there are 3 times chances of distant relapse and 2.5 times increased risk of mortality.[18] In a large meta-analysis it was concluded that radiotherapy reduces recurrence by almost half.[19]

In Bangladesh, NICRH has to bear huge load to deal with cancer patients especially for the people with low socioeconomic status and who are in a bad shape of the disease. On an average about 1400-1500 breast cancer patients take their

services annually from this institute. In the specified time we could finally compiled the mentioned recurrent cancer patients. It is markedly observable that patients of younger age (<40) outnumbered the older age group. Another issue is that hormone negative patients presented more with recurrence. This number neither matches with the existing number of treated patients in our institute nor globally.[1,20] There was huge disparity and a question of competency at the care giver level as described in the study.

Breast cancer incidence rate varies markedly in Asia and Western countries. Age incidence is much lower in this part of the world.[21] In Bangladesh though there is no national registry yet, institutional data shows mean age is below 45 years.[20] It is described in multiple studies that breast cancer in young women is biologically more aggressive, so report says initial locoregional recurrence may be a source of distal spread.[22,23] In multiple studies it is seen that over 40 percent hormone positive tumors of women below 40 years were noncompliant of taking tamoxifen and chemotherapy for longer time as suffer from amenorrhea and other related uncomfortable complications. This nonadherence towards endocrine therapy may also be a cause of early recurrence and mortality.[24,25] There is also enough evidence that relationship of young age at diagnosis with cancer subtype has cancer specific survival.[26] Studies in Japan after a long term follow up in early breast cancer showed that young age, margin positivity and absence of radiation therapy had significant chances of recurrences.[27]

In the current series, in the recurrence group, under 40-years (Younger) population were 55% and in the mortality group they were double than the older (Over 40) group.

Influence of molecular subtypes of ER, PR and HER-2 status on recurrence were widely studied with various findings. In a study by A. J. Lowery et al. over 12000 patients of breast conservation versus mastectomy, recurrence was much reduced in number in HR positive patients and increased in HR negative patients.[28,29]

Nguyen D et al. showed in their findings thatluminal A as baseline, the HER-2 and basal subtypes were the only factors associated with increased local recurrence and other factors like margin status, tumor size, age, nodal status played a significant role.[29] Similarly Dent et al. also found in both the groups of mastectomy and BCT.[10] TNBC groups had overall more incidences for recurrences than non TNBC.[30]

Nguyen D et al. reached to a conclusion from two large trials that HER-2 subgroup, use of trastuzumab reduced the locoregional recurrences from 35 to 15 in the NSABP N-31 trial and also in from 22 to 12 in the North Central Cancer Treatment Group (NCCTG) N9831 trial, the use of adjuvant trastuzumab increases the disease free survival from 46 to 52 percent.[29] On the other hand, TNBC-tumor patients were not found to be isolated risk factor of local recurrence in other study at 5 years. This finding is also showed similarity with Freedman's study considering age, margin positivity and pathological factors which were taken as predictive factors in the past.[31]

There was a clean observation that early Ipsilateral Breast Tumor Recurrence (IBTR) is a significant predictor for distant metastases. But it is not clear whether early breast tumor relapse is a marker for or cause of distant metastases, this matter is still an unsolved issue raised by Bruce G. Haffty.[32]

In our study, nearly forty percent were TNBC and in total nearly 60 percent were HR negative patients, there is significant association of recurrence with larger tumors also.

It is evident that in developing countries the incidence of breast cancers are increasing, in total more than half cases exist there now.[1] In the present day, it is the leading cause of cancer related death in the underdeveloped world. Reports from India revealed that breast cancer remains the single largest cause for cancer deaths in Indian women.[33] Reports from different states reveal that 5-year survival remains 42.3%, 48%, 57% for stage III and 22% for stage IV patients.[33,34,.35]

Though there are limited study on post-recurrence survival, it is almost clear that survival status is poor in this scenario. Fisher et al experienced 60-70% survival in NSABP B06 trial.[18] Dent et al. in another study among the risk factors it was seen that 10 year survival was 35.7% in PR+ve cancer and 66.1% in PR -ve cancers.[10] Women with early onset of disease are prone to succumb early.[36] Overall 5 year survival was 44% when recurrence occurred within three years of primary treatment

described in another report.[14] Frequency of distal metastasis was 92% after recurrence when the interval from primary treatment was less than two yearsand 53% for intervals of 2–5 years.[37] In our series one third of death was before two years after recurrence, 31% survived more than five years. Death was more seen among the HR -ve group of patients.

The figure swings as high as 78% in black women in South Africa. In contrast, in the United States the majority of cases are detected in localized stages of the disease (Stages I and II).[25] The lowersocioeconomic status has been linked to decline use of optimal breast cancer care. Disparity also includes lifestyle, reproductive experiences, environmental exposure, diet and nutritional factors.[38]

In Bangladesh, mastectomy still prevails more than BCS like other developing countries.

The study brought to light the picture of incomplete adjuvant therapy. Over 70% patients failed to receive systemic therapy or radiotherapy completely or partially in the current series. On the other hand, though incidence of breast cancer increases in developed world, mortality declining over the years as there is enhancing facilities for early diagnosis and wide dimensions of cancer controlling activities.[39]

Limitations

There were few limitations in this study. We could not include all the attended cases in the study period because of shortages of proper documents. All patients couldn't be followed up for total period as some were lost. We had to summarize with a smaller sample size. Among the reported cases, since patients had to bear expenses of many of the investigations, complete investigations could not be possible for all. Finally, since it represents a section of the community, this report does not reflect the picture of whole nation.

Conclusion

Young age was exposed as important risk factor of recurrence in breast cancer. Recurrence was found also a determining factor of increased mortality. Apart from tumor biology and pathological factors, lower socioeconomic status and treatment facilities were also explored as an index. Besides these, knowledge and skill of the care giver delineated as a hidden associate factor for treatment failure. So attention to cancer care particularly to the deprived community at national level is important. It includes rendering proper diagnostic and treatment facilities and timely follow up, that might improve the overall treatment outcome including recurrence and survival in future. Setting up separate breast unit with trained manpower will be another milestone for the improved cancer care for the under privileged community of the country.

Recommendation

- To evaluate the factors related to the recurrence and post recurrent mortality after primary treatment among breast cancer patient, further study with large sample and longer period is recommended.

- Good clinical knowledge and specialized training required.

- Multidisciplinary approachand longtimefollow-up is recommended.

Contribution of authors

AKMI-Conception, design, acquisition of data, data analysis, data interpretation, manuscript writing & final approval.

NA-Analysis, drafting, critical revision & final approval.

MJK-Analysis, data interpretation, critical revision & final approval.

MR-Acquisition of data, interpretation of data, drafting & final approval.

AKMMUB-Conception, design, Analysis, drafting & final approval.

MUM-Data interpretation, analysis, critical revision & final approval.

MYHC-Analysis, critical revision & final approval.

MMR-Design, Analysis, critical revision & final approval.

Disclosure

The authors declared no competing interest.

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