Epidemiological and Clinical Factors Affecting Survival in Breast Cancer Patients

By

Jignasa Sathwara

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Tata Memorial Centre
Mumbai

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Date: 20/8/18

Place: Mumbai

(Dr B Ganesh)
Guide

Dr. B. Ganesh
Prof. & Head
Department of Medical Records
Biostatistics & Epidemiology
Tata Memorial Hospital
Dr. Ernest Borges Marg,
Parel, Mumbai-400 012.

STATEMENT BY AUTHOR

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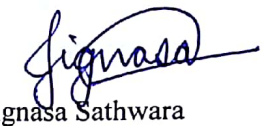
Jignasa Sathwara

DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University



Jignasa Sathwara

CERTIFICATE

I certify that the thesis titled "**Epidemiological and clinical factors affecting survival in breast cancer patients**" submitted for the degree of Doctor of Philosophy by **Jignasa Sathwara** is a record of the research carried out by her under my supervision. This work has not formed the basis for the award of any degree, diploma, associateship or fellowship at this or any other institute or university.

Dr B Ganesh

Mumbai

Date: 20 August 18

Dr. B. Ganesh
Prof. & Head
Department of Medical Records
Biostatistics & Epidemiology
Tata Memorial Hospital
Dr. Ernest Borges Marg,
Parel, Mumbai-400 012.

List of Publications arising from the thesis

- **Sathwara J**, Bobdey S, Ganesh B, Jain A**.** Socio-demographic factors and late stage presentation of breast cancer in tertiary care hospital. Indian J Med Paediatr Oncol 2015;36:154-60.
- **Sathwara J**, Bobdey S, Ganesh B. Nomogram for predicting survival in local advanced breast cancer patients. International Journal of Current advanced research. Published online Aug 2016 DOI: http://dx.doi.org/10.24327/ijcar.2017.4203.0462
- **Sathwara J**, Bobdey S, Ganesh B. Breast cancer survival studies in India: a review. Int J Res Med Sci 2016;4:3102-8. Print ISSN: 2320-6071 Online ISSN: 2320-6012 DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20162266

Paper Presentations

- Presented "Impact of Socio-Demographic Factors on Late-stage Presentation in Patients with Breast Cancer" in International Cancer Congress conference themed "Changing Paradigm in Cancer Management" between 9th & 10th July 2016 at Nagpur.
- Presented "Breast cancer survival studies in India: A review" in 37th Annual Scientific Meeting of the International Association of Cancer Registries between 8th to 10th October 2015 at Mumbai.

Conferences attended

- Participated as a Delegate in the Scientific Symposium "Frontiers in Epidemiology" held at Tata Memorial Centre, Mumbai from 6th to 7th March, 2017.
- Participated in the awareness program "Current Ethical & Regulatory Requirements for members of Institutional Ethics Committee" held on Feb 17-18, 2016 at Tata memorial hospital, Mumbai organized by Clinical Development Services Agency (CDSA), an extramural unit of Translational Health Science & Technology Institute, an autonomous organization of Dept. of Biotechnology, Ministry of Science & Technology, Govt. of India.
- Participated in the awareness program "Good Clinical Practice" held on Feb 16, 2016 at Tata memorial hospital, Mumbai organized by Clinical Development Services Agency (CDSA), an extramural unit of Translational Health Science & Technology Institute, an autonomous organization of Dept. of Biotechnology, Ministry of Science & Technology, Govt. of India.

Jignasa Sathwara
Date: 04 Sep 2018

DEDICATION

I dedicate this dissertation to my loving family: my parents, who have always supported me in whatever I chose to do and have been my number one fan; my sister (Tejal) and brother (Hardik), who are my sources of strength and inspiration and to my husband (Avdhesh), for his patience, love and understanding over the past 7 years.

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"At times our own light goes out and is rekindled by a spark from another person. Each of us has cause to think with deep gratitude of those who have lighted the flame within us."

-Albert Schweitzer

Philosopher, Physician, Nobel Peace Prize Winner

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No research is possible without the Library-The centre of learning resources. I take this time to express my gratitude to all the library staff for their services.

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Jignasa Sathwara.....

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HOMI BHABHA NATIONAL INSTITUTE

SYNOPSIS OF Ph. D. THESIS

1. Name of the Student: Jignasa Sathwara

2. Name of the Constituent Institution: Tata Memorial Hospital, Mumbai

3. Enrolment No. : HLTH09201304002

4. Title of the Thesis: Epidemiological and clinical factors affecting survival in breast cancer patients

5. Board of Studies: Health Sciences

SYNOPSIS

Epidemiological and clinical factors affecting survival in breast cancer patients

Introduction

Breast cancer (BC) is a major public health problem. It is one of the most commonly diagnosed malignancies and the leading cause of cancer death in women over the world. (1) According to 2012 GLOBOCAN statistics, nearly 1.7 million women were diagnosed with breast cancer with 522,000 related deaths-an increase in breast cancer incidence and related mortality by nearly 18 % from 2008. (2)

Breast cancer is considered as a heterogeneous condition and so requires evaluation of as many clinical and pathological features as possible to allow for best prediction of survival. (3) Cancer survival is a key index of the overall effectiveness of health services in the management of patients with cancer. Survival refers to the occurrence of a specific event of interest, starting from an initial time until a final time, for example, from the diagnosis of breast cancer to the death.(4) The study of cause and effect relationships is a basis of research and measurement of survival time is necessary for evaluation of chronic diseases. (5) Patterns of cancer incidence and survival vary around the globe and demographic, ecologic, environmental, cultural, and genetic variables may all contribute to this heterogeneity. (6)

The survival of breast cancer patients depends on factors such as genetic, age at diagnosis, access to care, stage of cancer, weight, physical activity status, alcohol consumption, social, economic, environmental factors and ethnicity (7). Identifying prognostic factors in patients with breast cancer plays an important role in treatment and care

of patients. Although several studies have been conducted to determine those factors affecting survival and disease-free survival rates in patients with breast cancer, patients of the country participated in the studies had different features from patients of other countries; an issue that has paid little attention. Thus, knowledge of prognostic factors in breast cancer mortality risk can play an important role in the treatment and care of patients. The survival rate after diagnosis and treatment of cancer is one of the most important indicators used in the treatment and assessment procedures. Although there have been several studies to determine influencing factors on the survival of patients and to estimate the survival duration in patients suffering from breast cancer, studies on Indian patients have created different results at different points. A recent Lancet publication with global data showed age standardized net survival with breast cancer of 80% or more in 34 countries and an increase worldwide but had no data on factors influencing it. (8) Population-based studies on breast cancer in India have showed five-year survival rates ranged from 42-48%, whereas hospital based studies across India shows 5 year relative survival rate ranged from 40-45 %. (9-13)

Tata Memorial Hospital (TMH), Mumbai, is a pioneer cancer centre in India and provides comprehensive cancer care to one and all through excellence in service, education and research. On an average 4000 patients attend the hospital daily for various cancer related investigation, treatment and follow-up. It has a well organized digital medical record system which provides sufficient opportunity for research. Therefore, this study was planned to comprehensively study and to evaluate the impact of demographic factors, patient characteristics and tumor related factors on overall and disease-free survival in patients with breast cancer.

Hypothesis

Patient characteristics and tumor related factors impact survival of breast cancer patients.

Aim

To study the impact of epidemiological and clinical factors on survival in breast cancer patients.

Primary Objective

To compute overall survival and disease free survival for epidemiological and clinical factors affecting survival in breast cancer patients.

Secondary Objectives

1. To identify time lines between registration and diagnosis, & diagnosis and commencement of treatment and to further evaluate its effect on overall survival.
2. To study patterns and factors which contribute to loss to follow-up and to compute loss adjusted follow-up rate for the associated factors.

Material and methods:

Study Design: The study was a retrospective analysis of hospital records of breast cancer patients from the Tata Memorial Hospital (TMH) Cancer Registry. All female breast cancer patients who were registered in TMH from 01st January 2008 to 31st December 2008 and had completed at least one modality of cancer directed treatment at TMH were included in the study.

Inclusion Criteria:

- All female cases newly diagnosed unilateral breast cancer patient registered in TMH between 01st January 2008 to 31st December 2008.
- All female cases who have completed at least one modality of cancer directed treatment at TMH.

Exclusion Criteria:

- All female cases who have received any form of cancer directed therapy before registering in TMH.

Sample Size:

Total 2,019 female breast cancer cases registered in TMH between 01st Jan 2008 to 31st Dec 2008, 761 cases were excluded (692 were prior treated cases, 25 cases were of bilateral breast cancer and 44 cases were excluded due to incomplete treatment). A total of 1258 female breast cancer patients were included in the study and their medical records were analyzed retrospectively.

Data Collection

Details regarding demographic characteristics, disease (tumor) related factors (including histological characteristic of the tumor), treatment received, co-morbid conditions, dates of important evolutions during treatment in the hospital (date of registration, diagnosis, treatment start date, etc) and vital status of the patient on the last date of follow-up, for each case was retrieved from the patient medical case file and hospital based electronic medical record (EMR) system.

Statistical Analysis:

- There were two main outcomes of interest, Overall Survival (OS) and Disease Free Survival (DFS). OS was defined as the time interval between the date of diagnosis and the date of death or the date of the last follow-up. DFS was defined as the time from diagnosis until any recurrence of breast cancer or date of death whichever is earlier. The closing date for recording the last follow-up was taken as 31st December 2014. The OS

and DFS was calculated by using actuarial method (14) and the difference in survival rates with regards to various factors were studied by Kaplan-Meier method (15) and compared using log-rank test. (16) The Cox-regression model (17) was used to investigate the effect of these factors simultaneously on OS and DFS in a multifactorial setting. All statistical analyses were performed using the Statistical Package for Social Science program (SPSS for Windows, version 20, SPSS, Chicago, IL). A probability, p value < 0.05 was considered to be statistically significant.

- **Statistical Analysis for timelines:** Time periods in days were calculated from date of registration to diagnosis and diagnosis to treatment commencement. These periods have been described in median, minimum and maximum period. The median time was taken as cut-off for categorization of time period and for analysis of its effect on overall survival.
- **Computation of Loss-adjusted survival (LAR):** Loss-Adjusted Survival Rate (LAR) a method proposed by Ganesh (18) was applied to obtain the corrected survival rates for various groups. Loss-adjusted survival is estimated under the assumption that survival of patients lost to follow-up is the same as that for patients with known follow-up time and have similar characteristics of different prognostic factors at first entry. Thus, using this method the estimated deaths in those with complete follow-up were calculated and then subsequently, these estimates were applied to those with incomplete follow-up to get expected deaths. A standard framework, such as the actuarial one, was then applied with the sum of observed and expected outcome events. The above methods along with mathematical derivations are described in detail elsewhere. (19)

Results:

Descriptive statistics: Of the 1258 women included in our final study population, 536 (42.6%) were early breast cancer, 597 (47.5%) were locally advanced breast cancer and 125 (9.9%) were metastatic breast cancer. The median age of the 1258 patients were 48 years (range: 22-89 years) and 53.7% of the patients were younger than 50 years. The majority of the patients (51.9%) were postmenopausal. 75.5% were non-residents i.e. from outside Mumbai city and 24.5% of patients were resident of Mumbai. 81.1% of patients were found to be literate and only 18.9% patients were found to be illiterates. 83% of the patients were Hinduism followers and 17% of the patients followed other religion. Majority of the patients (82.7%) were married and only 3.1% were found to be unmarried. Majority of the patients (84.7%) were multiparous. 6.4% patients had a positive family history of cancer and 21% of the patients presented with comorbid conditions. Infiltrating ductal carcinoma was the most common histologic type (94.9%), followed by infiltrating lobular carcinoma (1.2%). 1043 (82.9%) cases were found to be Grade III followed by 208 (16.5%) cases were found Grade II. Only 7 cases (0.6%) with Grade I was found. All the 1258 patients were staged according to the seventh edition of the American Joint committee on cancer (AJCC) staging manual on TNM classification system. 42.7% were found in stage II followed by 40.6 % in stage III, 9.9% of cases in stage IV and 6.8% of cases in stage I. The axillary node involvement was present in 199 (80.2%) patients. Of 1258 patients, 52.5% were estrogen receptor (ER) positive and 47.2% were progesterone receptor (PR) positive. Of the 1258 patients treated at TMH, 553 (82%) patients had surgery, 346 (51%) patients had radiotherapy and 307 (66%) had chemotherapy.

The observed 5 yr DFS for the non-metastatic breast cancer patients was found to be 76% (Table 1). The observed 5 yr OS rate of the entire cohort was found to be 72% (Table 2). The 5 yr OS rate was 91.5% for patients with Stage I disease, decreasing to 13% for Stage IV disease. The 5 yr DFS for early breast cancer and locally advanced breast cancer was found to be 89% and 65% respectively, whereas the 5 yr OS for early breast cancer and locally advanced breast cancer was found to be 90% and 69%.

Table 1: Disease-free Survival

Factor	Total Number	Survival in percentage				
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs
All cases*	1133	96	87	81	78	76
Early breast cancer	536	98	96	91	90	89
Locally advanced breast cancer	597	93	79	72	67	65

*excluding 125 cases of Stage IV

Table 2: Overall Survival

Factor	Total Number	Survival in percentage				
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs
All cases	1258	94	85	78	74	72
All cases*	1133	99	90	85	81	79
Early breast cancer	536	99	96	94	91	90
Locally advanced breast cancer	597	97	85	76	72	69
Metastatic breast cancer	125	66	37	24	15	13

*excluding 125 cases of Stage IV

Early Breast Cancer: In univariate analysis, the effects of age, residence, education status, religion, marital status, menopausal status, parity, family history of cancer, co-morbidity status, quadrant location, tumor grade, pathological tumor size, hormonal receptor status, number of involved axillary lymph nodes, status of extensive intraductal component, status of

lymphovascular invasion on DFS and OS were evaluated. The significant prognostic factors for disease free and overall survival are shown in Table 3.

Table 3: The results of the univariate analysis of the prognostic factors for disease free and overall survival for Early Breast Cancer patients

Survival	Prognostic factors	p value
Disease free survival	Tumor grade (High grade>low grade)	0.004
	ER and PR (-) > ER and/or PR (+) tumor	0.003
	EIC (positive>negative)	0.043
	LVI (positive>negative)	<0.001
	Nodes involved (+4>1-3>0)	<0.001
Overall survival	Education status (Illiterate >Literate)	0.015
	Tumor grade (High grade>low grade)	0.052
	ER and PR (-) > ER and/or PR (+) tumor	0.012
	EIC (positive>negative)	0.035
	LVI (positive>negative)	0.009
	Nodes involved (+4>1-3>0)	<0.001
	Pathological T stage (T3>T2>T1)	0.003

ER: Estrogen Receptor, PR: Progesterone Receptor, EIC: Extensive intraductal component, LVI: Lymphovascular invasion >: The group on the left side has a worse survival

In multivariate analysis the prognostic factors that were statistically significant in univariate analysis, were tested and the independent predictors of DFS and OS were found (Table 4). In multivariate analysis, tumor grade, hormonal receptor status, absence of lymphovascular invasion and pathological lymph node negative were found to be independent predictors of DFS, while education status, hormonal receptor status and pathological lymph node negative were

found to be independent predictors of OS. The number of pathological axillary lymph nodes and hormonal status was found to be the most important prognostic factor both for DFS and OS.

Table 4: Summary of independent predictors of survival of breast cancer

Early Breast Cancer (n=536)		**Locally Advanced Breast Cancer (n=597)**		**Metastatic Breast cancer (n=125)**
Disease-free survival	**Overall survival**	**Disease-free survival**	**Overall survival**	**Overall survival**
• Tumor grade • Hormonal status • LVI • Pathological axillary lymph nodes	• Education status • Hormonal status • Pathological axillary lymph nodes	• Tumor grade • Hormonal status • EIC • LVI • Pathological axillary lymph nodes	• Education status • Tumor grade • Hormonal status • EIC • LVI	• Hormonal status • Number of metastases • Site of metastases

Abbreviations-EIC: Extensive intraductal component, LVI: Lymphovascular invasion

Locally Advanced Breast Cancer: In univariate analysis, the effects of age, residence, education status, religion, marital status, menopausal status, parity, family history of cancer, co-morbidity status, quadrant location, tumor grade, number of involved axillary lymph nodes, hormonal receptor status, status of extensive intraductal component, status of lymphovascular

invasion on DFS and OS were evaluated. The significant prognostic factors for disease free and overall survival are shown in Table 5.

Table 5: The results of the univariate analysis of the prognostic factors for disease free and overall survival for Locally Advanced Breast Cancer patients

Survival	Prognostic factors	p value
Disease free survival	Education status (Illiterate >Literate)	0.009
	Tumor grade (High grade>low grade)	0.001
	ER and PR (-) > ER and/or PR (+) tumor	0.027
	EIC (positive>negative)	0.001
	LVI (positive>negative)	<0.001
	Nodes involved (+4>1-3>0)	<0.001
Overall survival	Education status (Illiterate >Literate)	0.002
	Tumor grade (High grade>low grade)	0.003
	ER and PR (-) > ER and/or PR (+) tumor	0.002
	EIC (positive>negative)	<0.001
	LVI (positive>negative)	<0.001
	Nodes involved (+4>1-3>0	<0.001

ER: Estrogen Receptor, PR: Progesterone Receptor, EIC: Extensive intraductal component, LVI: Lymphovascular invasion >: The group on the left side has a worse survival

In multivariate analysis, tumor grade, hormonal receptor status, absence of extensive intraductal component, absence of lymphovascular invasion and pathological lymph node negative were found to be independent predictors of DFS, while education status, tumor grade, hormonal receptor status, absence of extensive intraductal component, absence of lymphovascular invasion and pathological lymph node negative were found to be independent predictors of OS. The tumor

grade, hormonal receptor status, absence of extensive intraductal component, absence of lymphovascular invasion and pathological lymph node negative was found to be the most important prognostic factor both for DFS and OS (Table 4).

Metastatic Breast Cancer: In univariate analysis, the effects of age, residence, education status, religion, marital status, menopausal status, parity, family history of cancer, co-morbidity status, quadrant location, tumor grade, hormonal receptor status, number of metastatic sites and site of metastases on OS were evaluated. The significant prognostic factors for overall survival are shown in Table 6.

Table 6: The results of the univariate analysis of the prognostic factors for overall survival for Metastatic Breast Cancer patients

Survival	Prognostic factors	p value
Overall survival	Education status (Illiterate >Literate)	0.046
	Tumor grade (High grade>low grade)	0.033
	ER and PR (-) > ER and/or PR (+) tumor	<0.001
	Number of metastases (Multiple>Single)	0.022
	Site of Metastases (Visceral>Bone)	0.011

ER: Estrogen Receptor, PR: Progesterone Receptor, >: The group on the left side has a worse survival

In multivariate analysis, hormonal receptor status, number of metastases and site of metastases were found to be the most important independent predictors of OS (Table 4).

Timelines: In the present study, the median time from diagnosis to initiation of treatment was found to be 10 days and it was found to be associated with overall survival ($p< 0.001$). This study showed that a delay of treatment initiation at any cut-off point within 30 days after biopsy confirmation had an impact on OS in breast cancer.

Loss adjusted survival rate (LAR): In our study overall 5yr survival for all cases by actuarial method was found to be 72% and Loss adjusted survival rate was found to be 70%. Similarly, in subset analysis for early and locally advanced diseases the 5yr survival by actuarial and LAR method was found to be 90% & 89.1%, and 69% & 65.7% respectively.

Discussion:

Breast cancer is the most common female cancer in India, in common with many Western countries. This thesis aimed to study the various factors that affect the survival of breast cancer patients in India. This study was concentrated on epidemiological research, with data derived from hospital based cancer registry. Breast cancer is the most frequently detected cancer among women. Early diagnosis leads to long term survival when the patients are treated with surgery, radiotherapy, chemotherapy, and hormone therapy. Unfortunately, advanced disease could still be encountered in some patients resulting in a poorer prognosis.

In current study we found 5 year overall survival rate of 72% which is in agreement with literature. Sankaranarayanan R et al. (2010) in his study of 25 population-based cancer registries in 12 countries in sub-Saharan Africa, Central America and Asia, found India to have the lowest survival rate in Asian countries and this difference was attributed to lack of established screening and early detection programmes, which in turn results in majority of cases presenting with advanced stage disease and lower survival. (20) There are few studies on breast cancer survival from India, on a retrospective basis. A large breast cancer study was undertaken at Tata Memorial hospital by Dinshaw et al (2006) to study the various factors among those treated with breast conserving therapy (BCT). During 1980-2000, 1,022 pathological Stage I/II breast cancer patients (median age 43 years) underwent BCT were studied. The study showed an overall 5-year and 10-year actuarial survival of 87% and 77% respectively in this series. (21) A

population-based study of 1514 breast cancer patients published (Nandakumar et al, 1995) showed that the observed 5 year survival was 42.3%. (22) In another study from India, analysis from 487 early breast cancer patients seen by Raina et al (1995) reported 5 year DFS and OS to be 73% and 78%, respectively. (23) A total of 2080 cases of invasive female breast cancer registered in MMTR, Chennai, (Gajalakshmi et al 1997) with a follow-up rate of 84% reported that observed survival rates at 1, 3 and 5 years were 80%, 58% and 48% respectively; the corresponding figures for relative survival were 81%, 61% and 51. (24) In another study of 449 patients with breast carcinoma (Krishnan Nair et al 1993) showed that the 5-year overall survival rate was 40%. (25) Two-thirds of patients with advanced-stage disease on presentation accounted for the poor overall survival in this study.

Stage at diagnosis is one of the important determinants of survival. The present study showed an inverse relationship of stage-of disease with survival which has been shown in earlier studies (22-27). The 5-year overall survival rates were 85% for patients with T1, 63% for T2, 32% for T3, and 21% for T4 lesions. Those with N0 disease had a 68% 5-year survival rate. The survival rates were 90% for patients with Stage I, 65% for Stage II, 33% for Stage III, and 6% for Stage IV disease (25). In a report published by the American Cancer Society (2015), the five-year relative survival rate among US Whites was 99% for localized disease, 86% for regional and 27% for distant metastases patients. The interpretation of international differences in cancer patient survival has been simplified by examining survival according to each disease stage at diagnosis which in the present study has been studied in terms of clinical stage at diagnosis.

The impact of age at diagnosis on breast cancer survival has been long debated. This study found no evidence of a relationship between age at diagnosis and survival. These findings

accord with some studies (28,29) but not others (30,31) although in the latter studies the age categorization and settings were different.

Of all demographic factors assessed, only education status was related to breast cancer prognosis in this study. Literacy showed an advantage in survival over illiterate patients. This is in agreement with literature. (5,9) This study found no evidence for a relationship between family history of breast cancer and survival. This is consistent with the results of several other studies (31-33).

Our findings revealed that tumour size, histological grade, hormonal receptor status, status of lymphovascular invasion, status of extensive intraductal component and pathological lymph node status were associated with breast cancer survival after mutual adjustment. This result is consistent with some other studies (34-35).

Timelines: Detection and treatment of cancer at an early stage improves the prospects for long-term survival. In many types of cancer, the outlook for patients with small, localized tumours is much better than that of patients with advanced or metastatic disease. (36,37) Earlier treatment is generally accepted to improve the prognosis in a woman with breast cancer, and so a prompt response by both patient and doctor to the finding of a breast lump is desirable and even worth the considerable expense of public and professional educational campaigns. Hence in order to assess the influence of time on breast cancer survival we estimated two broad timelines in our study. Majority, of the patients were diagnosed within 7 days and the median period of diagnosis was found to 4 days. On survival analysis time required for diagnosis was not found to be associated with survival. Toring et al. in his study showed the waiting time paradox in their analyses, longer intervals being associated with poorer outcomes, particularly mortality. (38)

This is important and begins to provide more robust evidence about the relationship between time to diagnosis.

In the present study, the median time from diagnosis to initiation of treatment was found to be 10 days and it was found to be associated with overall survival ($p< 0.001$). This study showed that a delay of treatment initiation at any cut-off point within 30 days after biopsy confirmation had an impact on OS in breast cancer. Two population-based cohort studies from Korea reported that longer intervals between diagnosis and treatment initiation are related to worse OS in breast cancer (39-40).

Loss adjusted survival rate (LAR): In our study overall 5yr survival for all cases by actuarial method was found to be 72% and Loss adjusted survival rate was found to be 70%. Similarly, in subset analysis for early and locally advanced diseases the 5yr survival by actuarial and LAR method was found to be 90% & 89.1%, and 69% & 65.7% respectively. Thus, adjustment for loss of follow-up gave an estimated 0.9 – 3.3 % units less 5 years survival than the observed (actuarial) survival. The small difference between the absolute (actuarial) survival and the loss-adjusted survival observed in this study is much less than in other studies. (5,41) This can be because our study had only 14.1% loss to follow up as compared to much higher loss to follow-up reported by other quoted studies i.e Ganesh et al. (5) loss to follow-up of 35-43%; Sriamporn et al. (41) loss to follow-up of 26.7%. This observation of small difference between the absolute (actuarial) survival and the loss-adjusted survival is not confined to cancer of the breast; differences for other sites also and have also been reported of similar (small) size. (42)

Summary and Conclusion

Summary:

- **Disease-free Survival:** The 5-year disease-free survival of breast cancer (excluding metastatic breast cancer cases) was found to be 76%. The 5-year disease-free survival for Early breast cancer and Locally Advanced breast cancer was found to be 89% and 65% respectively.
- **Overall Survival:** The 5-year overall survival of breast cancer (all cases) was found to be 72%. The 5-year overall survival for Early breast cancer, Locally Advanced breast cancer and Metastatic breast cancer was found to be 90%, 69% and 13% respectively.
- In Early breast cancer the independent predictors of prognosis for disease-free survival were tumor grade, hormonal status, LVI and pathological axillary lymph nodes.
- In Early breast cancer the independent predictors of prognosis for overall survival were education status, hormonal status and pathological axillary lymph nodes.
- In Locally advanced breast cancer the independent predictors of prognosis for disease-free survival were tumor grade, hormonal status, EIC, LVI and pathological axillary lymph nodes.
- In Locally advanced breast cancer the independent predictors of prognosis for overall survival were education status, tumor grade, hormonal status, EIC, LVI and pathological axillary lymph nodes.

- In Metastatic breast cancer the independent predictors of prognosis for overall survival were hormonal status, number of metastases and site of metastases.
- The median time period from registration to pathological confirmation of diagnosis was 4 days, from diagnosis to commencement of treatment was 10 days. The time period between registration and diagnosis was not found to be associated with survival, whereas time period between diagnosis and to start of treatment was found to be associated with survival.
- Overall 5 year survival rate and loss-adjusted survival rate were found to be 72% and 70% respectively.

Conclusion:

Breast cancer is a global public health problem and studies that help to understand the disease, its progression and associated factors are extremely important. The analysis of OS and DFS at 5 years performed in this study enabled us to have a better understanding of the profile of patients treated at the oncology service, the natural history of the disease and the factors involved in prognosis within a national context. The 5-year survival rates were better in patients with the early stages of breast cancer patient than in those with the advanced stages. The screening aimed at an early diagnosis of breast cancer represents an important strategy to achieve better overall survival and disease-free survival, associated with ensuring access by women to suitable treatment. These conditions are particularly important in the population examined. The multivariate survival analysis showed that some demographic factors are important and independent prognostic factors in mixed cohort of breast cancers, particularly in locally advanced breast cancer patients. Demographic factors should therefore be included when biological prognostic variables in breast cancer are analyzed, particularly in retrospective

cohorts. The present study showed factors affecting survival of breast cancer are consistent with those described in the literature. Better survival rates are associated to lower tumor grade, absence of lymphovascular invasion, absence of extensive intraductal component, node negative and positive hormone receptors. By combining morphologic, clinical and hormonal determinants, the prognosis of the individual breast cancer will become predictable with increasing accuracy and permit judicious selection of the most effective therapeutic protocol. Knowledge of the main characteristics and the factors associated with disease progression strengthens the need for new studies at Indian cancer treatment centers in order to obtain control of breast cancer in the country.

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LIST OF ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
ASR	Age Standardized Incidence Rate
BC	Breast Cancer
BCS	Breast Conservation Surgery
CDT	Cancer Directed Treatment
CI	Confidence Interval
CT	Chemotherapy
DALY	Disability-adjusted life year
DFS	Disease-free Survival
EBC	Early Breast Cancer
EIC	Extensive Intraductal Component
ER	Estrogen Receptor
FISH	Fluorescence in situ hybridization
HER2	Human Epidermal Growth Factor Receptor 2
HICs	High-income countries
HR	Hazard Ratio
LABC	Locally Advanced Breast Cancer
LMICs	Low-middle income countries
LVI	Lymphovascular Invasion
M	Distant metastasis
MBC	Metastatic Breast Cancer
N	Lymph nodes
OR	Odds Ratio
OS	Overall Survival
PR	Progesterone Receptor
RCT	Randomized controlled trial
RT	Radiotherapy
SD	Standard Deviation
SEER	Surveillance, Epidemiology and End Results
SES	Socioeconomic status
SPSS	Statistical Package for Social Sciences
Sx	Surgery
T	Primary Tumor
TMH	Tata Memorial Hospital
TNM	Tumor Node Metastases
USA	United States of America
WHO	World Health Organization

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INTRODUCTION

CHAPTER 1

INTRODUCTION

Sarasvati namastubhyam
Varade KAmarUpiNi
VidyArambham Karishyami
Siddhir Bhavatu Me SadA

"O Goddess Saraswathi; salutations to you, the giver of boons, the one who fulfills desires. I shall begin my studies. May there always be accomplishment for me."

1.1 Background: In general, cancer is a type of disease which makes the cells divide, grow and multiply uncontrollably. (1) The cancer is named after the part of the body which it starts from. Breast Cancer (BC) means the unregulated growth of the cells which arise in the breast tissues and its multiplication and spread. Infected cells which divide and multiply rapidly may form a mass of extra tissues. These mass tissues are called tumors. The tumours are either cancerous (malignant) or (benign). The malignant tumors multiply and invade the intact tissues of the body. (2) If the spread is not controlled, it can result in death.

1.2 Most kinds of breast cancer start from the inner lining of milk ducts and therefore are known as ductal carcinomas, whereas so called lobular carcinomas appear in the lobules. When breast cancer starts to spread outside the breast, the cancer cells reach the lymph nodes under the armpit. In this case, the cancer starts to spread to all body lymph nodes. (2) In order to be successful in the treatment of cancer, early diagnosis, before the tumor spreads to the surrounding tissues or distant organs, is mandatory.

1.3 Cancer is a leading cause of premature death and disability worldwide, especially in women. (3) Based on the GLOBOCAN 2012 estimates, about 14.1 million cancer cases and 8.2 million cancer deaths are estimated to have occurred in 2012; of these, 57% of the new cancer cases and 65% of the deaths occurred in the economically developing world. (4) Furthermore, it is estimated that between 1990 and 2013, absolute disability-adjusted life year (DALYs) due to all cancers for both sexes increased by 29% globally, by 10% in developed countries, and by 40% in developing countries. (3)

1.4 Breast cancer is a disease which affects people worldwide, contributing to a substantial public health burden. Every year, 1.7 million women are diagnosed with breast cancer, making it the most common cancer in women worldwide. (4) With an estimated 522 000 deaths in 2012, breast cancer is the leading cause of cancer death in women (accounting for 15% of all cancer deaths), ahead of lung cancer (491 000 deaths). (4)

1.5 The major known risk factors for breast cancer include female sex, age, and family history, and reproductive factors, including early age at menarche, later menopause, nulliparity, and first childbirth after age 30 years, all of which are independent risk factors. (5) Breastfeeding is independently associated with a reduced risk, with longer duration associated with a greater reduction in risk of developing breast cancer. (6) Overweight and obesity are associated with an increased risk for post-menopausal breast cancer, whereas the effect of these factors on pre-menopausal breast cancer is less clear and remains an area of active study. (7)

1.6 Cancer survival is a key index of the overall effectiveness of health services in the management of patients with cancer. Survival refers to the occurrence of a specific event of interest, starting from an initial time until a final time, for example, from the diagnosis of breast cancer to the death. (8) The study of cause and effect relationships is a basis of research and measurement of survival time is necessary for evaluation of chronic diseases. (9) Patterns of cancer incidence and survival vary around the globe and demographic, ecologic, environmental, cultural, and genetic variables may all contribute to this heterogeneity. (10)

1.7 Breast cancer is no longer seen as a single disease but rather a multifaceted disease comprised of distinct biological subtypes with diverse natural history, presenting a varied spectrum of clinical, pathologic and molecular features with different prognostic and therapeutic implications. (11) Management of breast cancer relies on the availability of robust clinical and pathological prognostic and predictive factors to guide patient decision making and the selection of treatment options.

1.8 Breast cancer survival data are skewed and consist of complications in the pattern of early events and in the end stage. A recent Lancet publication with global data showed age standardized net survival with breast cancer of 80% or more in 34 countries and an increase worldwide but had no data on factors influencing it. (12) Population-based studies on breast cancer in India have showed five-year survival rates ranged from 42-48%, whereas hospital based studies across India shows 5 year relative survival rate ranged from 40-45 %. (13–17)

1.9 Patterns in cancer incidence can provide important insight into the impact of lifestyle upon cancer development whereas patterns in survival can provide information about the burden and severity of cancer. In the epidemiology of a disease, which is multifactorial to such an extent as we believe breast cancer to be, attention should be paid even to "weak '' factors and an attempt should be made to assign a place to them in an etiologic system which is biologically sound. Knowing the factors that influence survival rates among women with breast cancer may help define early detection actions, and improve treatment and care proposals in all the areas of health. Therefore, this study was planned to comprehensively study and to evaluate the impact of demographic factors, patient characteristics and tumor related factors on overall survival and disease free survival in patients with breast cancer.

Review of Literature

CHAPTER 2

REVIEW OF LITERATURE

2.1 Descriptive Epidemiology

Breast cancer is the most common malignancy among women worldwide and in 140 of 184 countries, with an estimated 1.67 million estimated incident cases. The number of women with incident breast cancer in Asia was estimated at 651,000 in 2012, comprising 38.8% of all cases globally, followed by Europe (27.7% of all cases) and North America (15.3% of all cases). (18)

2.1.1 Burden of disease

Worldwide 1,676,633 women were diagnosed with BC. The burden of BC is higher in less developed regions with 882, 949 cases than in more developed regions with 793, 684 cases estimated by Globocan, 2012. India itself has burden 144,937 BC cases. This implies that, though, the percentage of total women affected seems less, the BC burden in India has almost reached about 2/3rds of some of the developed nations and is steadily rising. (19)

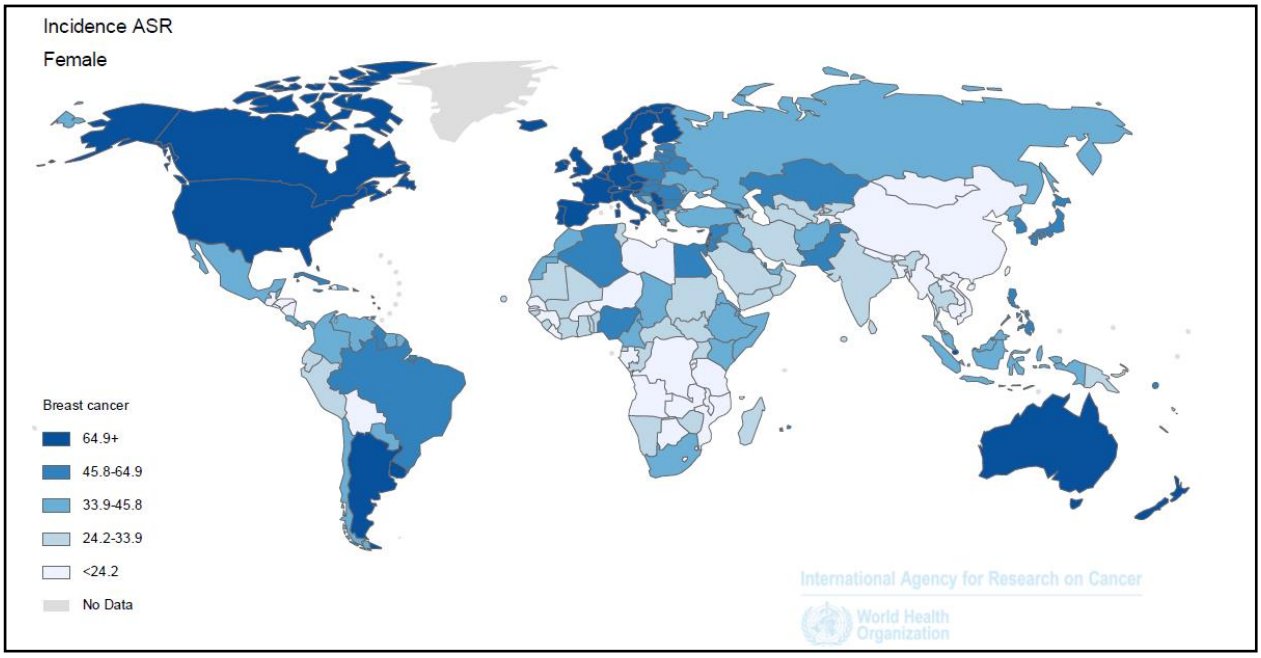
2.1.2 Incidence of Breast cancer

With urbanization and changes in life style, there is increasing incidence of breast cancer. Breast cancer incidence has been highest in Northern America, Western and Northern Europe, and Australia/New Zealand, with rates ranging from 85.8 to 96.0 (Figure 2.1).

Breast cancer incidence rates in Asian countries are estimated at one-fourth to one-third of the rates in the traditionally high-risk countries, with an Asian average rate of 29.1. (4)

In India the incidence of breast cancer is significantly lower than western countries. Breast cancer in India varies from as low as 5 per 100,000 female populations per year in rural areas to 30 per 100,000 female populations per year in urban areas. (20)

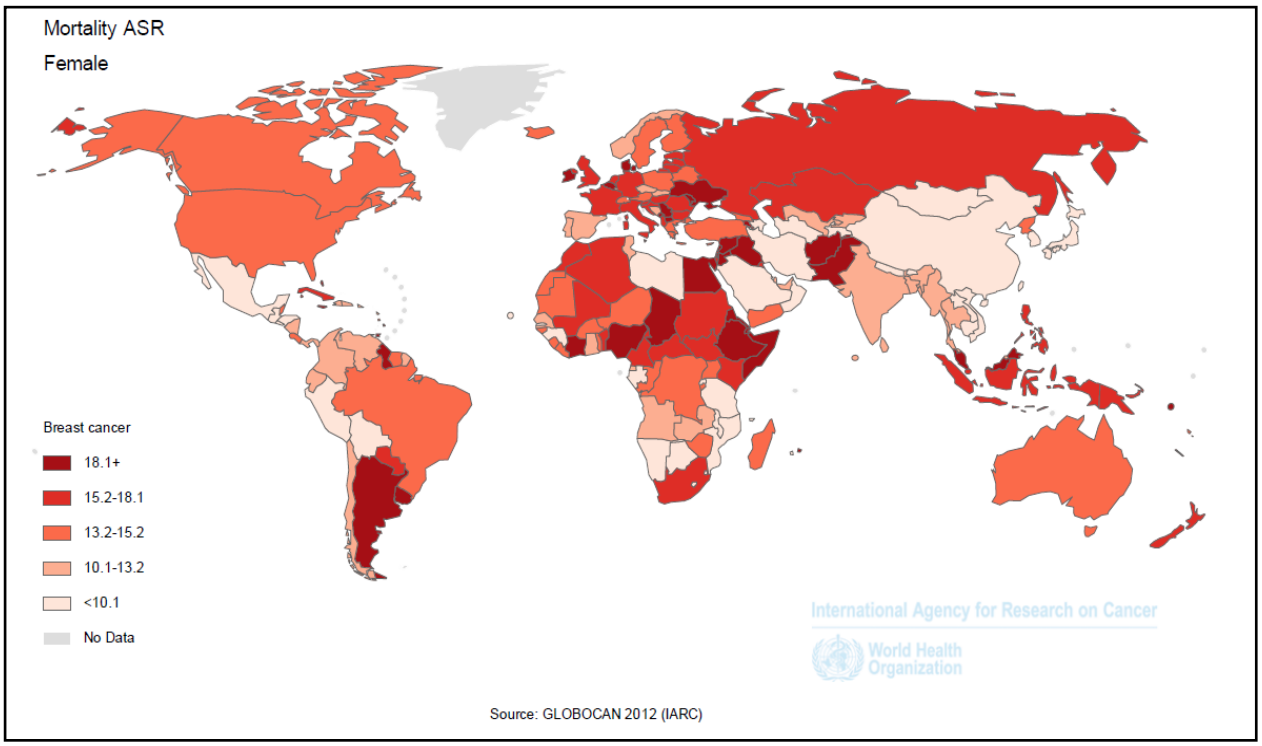
Figure 2.1: Age standardized (world) Incidence rate (per 100,000) of Female Breast Cancer (All ages).



2.1.3 Mortality of Breast cancer

The World Health Organization (WHO) has estimated that female BC resulted in a total of 5,884,000 years of life lost globally during 2004. This represented just over 1% of all premature mortality amongst females, but there was a large amount of variation in this proportion between regions, ranging from around 8% in parts of Europe to less than 0.5% in Africa. (21) The age-standardized mortality rate (ASMR) for breast cancer is 12.9 worldwide, with an average ASMR for breast cancer in Asia of 10.2. Similar to breast cancer incidence, there is substantial heterogeneity in breast cancer mortality by region, with the highest mortality in western Asia [15.1], followed by south-eastern Asia [14.1], south-central Asia [13.5], and eastern Asia [6.1] (Figure 2.2). (18)

Figure 2.2: Age Standardized (world) Mortality Rate (per 100,000) of Female Breast Cancer (All ages).



2.2 Breast Cancer Survival

Breast cancer survival in most LMICs is lower than in high-income countries and mortality rates vary more widely than does incidence. Global surveillance of cancer survival trends was recently initiated by the CONCORD-2 study, 24 which analyzed individual data from 279 population-based registries in 67 countries for more than 25 million adults (aged 15–99 years) diagnosed with one of ten common cancers during the 15-year period 1995–2009. Net survival up to 5 years after diagnosis was estimated after correction for death from other causes. Data were available from 59 countries for almost 5·5 million women diagnosed with breast cancer. For women diagnosed during 2005–09, 5-year net survival was 80% or higher in 34 countries, but much lower in India (60%), Mongolia (57%), and South Africa (53%). (12)

A large international study followed up patients with cancer diagnosed in 1990–2001 in 12 countries undergoing major socioeconomic transition and noted similarly wide variations in cancer survival. Survival for women with localized disease was reported to be around 90% for countries with highly developed health services (Singapore and Turkey), compared with 76% in countries where they were less developed (Thailand, India, and Costa Rica), with a greater disparity for women with regional disease (75·4% for more developed health services vs 47·4% for less developed health services). (22)

In India itself there is wide variation in breast cancer survival with highest 5 year relative survival reported in Barshi and lowest in Bhopal (Table 2.1). The observed differences in survival between countries and different regions seems to be largely a result of differences in screening programmes, early detection services, and cancer treatment facilities in these regions which have probably contributed to variation in survival observed. (13-17)

Table No.2.1: 5 year absolute and relative survival of different sites in India (22)

S.no	Place (Registry)	Female Breast Cancer						
		No.	% 5-year		% 5-year absolute survival by extent of			
			Abs	Rel	Localized	Regional	Dist. met.	Unknown
1.	**Barshi** (1993-2000)	121	49.6	55.4	-	-	-	
2.	**Bhopal** (1991–95)	258	30.2	32.3	41.1	22.6	0.0	42.1
3.	**Chennai** (1993-99)	3067	43.7	48.6	70.8	48.9	12.3	46.6
4.	**Karungappally**(1991–97)	192	47.1	51.5	78.6	43.1	7.8	53.4
5.	**Mumbai** (1992–94)	7294	46.0	51.4	74.2	32.8	3.8	48.1

Abbreviations: Abs-Absolute, Rel-Relative, Dist. met.-distant metastasis

2.2.1 Survival statistics

Survival statistics are derived from three types of sources: the randomised controlled clinical trial, which represents the 'gold standard' for the evaluation of different methods of treatment; the hospital-based study, which gives information about the outcome of treatment in particular settings; and population-based survival from cancer registries, which reflects on an average, the result of the whole range of cancer control activities, including screening and the organisation of treatment services. (23)

Cancer survival reported from above settings may have different perspectives, but estimation of survival rates is routinely done using standard life table approaches such as the

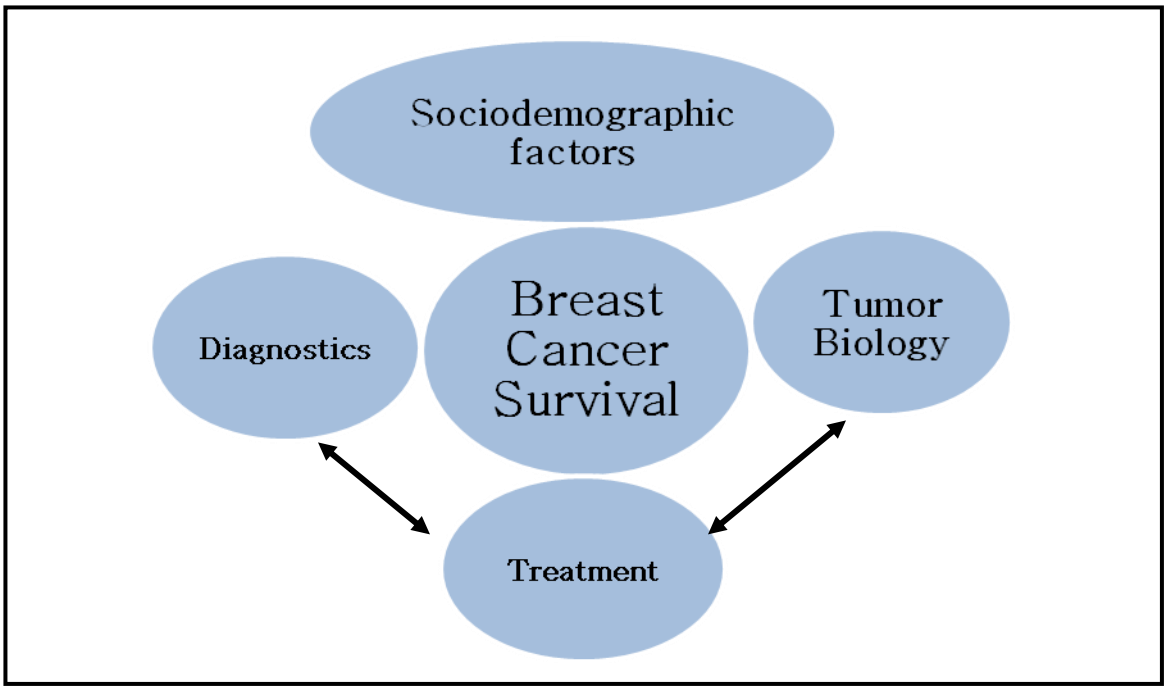
actuarial (24) or Kaplan-Meier (25) methods. The life table, one of the basic tools in the description of mortality experience of a population, was first developed as early as 1693 by E. Halley in England. It forms the basis for calculation of the life table estimate of the survivor function, which is still widely used today in the analysis of data from epidemiological studies.

2.2.2 Conceptual Framework

The conceptual framework below shows the various factors that will be conceptualized to independently affect the breast cancer survival (Figure 2.3). These factors were broadly categorized into socio-demographic and clinical factors. Many factors influence the survival of patients with breast cancer; they include patient factors, stage of disease, tumor biology, and cancer treatment. However, there is much variability as individuals with the same stage and similar pathological diagnoses can experience different clinical courses. Tumor biology is likely the most important; secondly, the treatment options and the response to the treatment. Breast cancer survival is driven by the variability of the patients and their tumours.

Breast cancer is commonly treated by various combinations of surgery, chemotherapy, radiation therapy, hormone therapy and targeted therapy via a multimodality approach. Selection of therapy is influenced by clinical and pathologic features that could predict their response to these therapies.

Figure 2.3: Overview of the factors that affect breast cancer survival



2.3 Factors affecting Breast Cancer Survival

2.3.1 Epidemiological factors

2.3.1.1 Age at diagnosis

A person's age is correlated with their health status as well as with most determinants of health. It has been suggested that age at diagnosis is related to breast cancer survival, but the data regarding this issue are conflicting. Some studies (26–29) have indicated a poorer prognosis for young patients, while others (30,31) have reported that younger women fare better than older. Others have shown that age is not correlated with disease-free or overall survival after adjustment for other prognostic variables. (32–34) These conflicting results may possibly be

explained by [1] the small number of patients included in some of the studies; [2] differences in the selection of patients, as most of the series studied consist of cases referred to special hospitals; or [3] differences in the age grouping used in the analysis, since in many studies, all patients younger than age 50 years have been grouped together.

2.3.1.2 Place of Residence

Access to high-quality care is key to ensuring optimal survival, and access may be influenced by where a woman lives. Women living in rural areas of a given country are less likely to access optimal and timely care, and may therefore have a disadvantage compared to women living in more urban areas. Socioeconomic status (SES) is best described as a combination of highly correlated yet distinct factors, including income, education, occupation, and place of residence. (35) Data from these factors are commonly used as proxy variables to indicate overall SES. (36)

2.3.1.3 Level of Education

Impact of education on the cancer survival has been studied by many investigators. Education is a key factor of the socio-economic status, influences lifestyles, behavioral patterns, reproductive factors like parity and even stage at presentation. (37) The association between education level and survival rate of breast cancer was inconsistent across studies around the world. (38–40)

2.3.1.4 Religion

India is a vast country with widely varying social, cultural, religious and dietary practices, and each of these factors differs depending on the religion. The major religion is Hinduism followed by Islam, Christianity and others (among them Jains, Buddhists, Sindhis, Sikhs, Neobuddhists, Parsi etc). Such kinds of religions probably cannot be found in any other countries of the world. Religion is one of the psychosocial factors thought to influence health outcomes. (41) Few studies have looked at whether religiousness influences cancer survival; and those that have, generally did not adequately control for biomedical factors. (42,43)

2.3.1.5 Marital Status

Marriage has been theorized to have protective effects for longevity through the social pathways of social integration, social support, social control, and social role attainment as well as the material pathways of financial resources and economies of scale. (44) Understanding how marriage influences survival will shed light on the importance of social support mechanisms in management of various diseases, including cancers. Studies assessing the impact of marital status on survival among patients with cancer have yielded conflicting results ranging from, with protective, (45–48) mixed, (49,50) and non-significant. (51–53)

2.3.1.6 Menopausal status

A large number of epidemiologic studies have suggested that age at menopause is an important determinant of breast cancer. Breast cancer survival has been shown to be different for

premenopausal and postmenopausal patients. (54) Postmenopausal breast cancer women generally do better as compared to premenopausal patients. (55) Menstrual status also did not affect survival. (56)

2.3.1.7 Parity

Many epidemiological studies have established that low parity is associated with an increased risk of breast cancer. (57) There are, however, relatively few studies that have examined parity in relation to survival following breast cancer diagnosis. One study has reported a positive association between low parity and poor survival, (58) others have reported a positive association between high parity and poor survival, (59–61) yet a few have found no convincing relation. (62,63)

2.3.1.8 Family history of cancer

A family history of breast cancer is a known risk factor for the onset of disease, with an increased risk depending on the degree of family history. (64) Family history is a well established etiologic risk factor for breast cancer (65), its relationship with survival remains unclear. A number of studies have observed improved survival for women with a positive family history while others (66–68) report little or no difference (69–72) or worse survival. (73–76)

2.3.1.9 Comorbidity

Coexisting diseases at BC diagnosis are highly correlated with prognosis. (77–80) Previous studies of breast cancer patients have found that the presence of comorbid conditions is statistically significantly associated with overall survival and all-cause mortality. (81–85) The presence of comorbidities in patients with cancer has been negatively associated with patients' health outcomes. Several studies have shown poorer survival among cancer patients with comorbidity, but the underlying mechanisms remain unclear. (86,87)

2.3.2 Clinical factors

2.3.2.1 Disease staging (TNM Staging)

Stage at diagnosis is the most important determinant of breast cancer survival. (88) Staging is an important issue for all types of cancers and it enables us to group the patients according to almost equal survival probabilities. Staging of breast cancer takes into consideration the size of the tumor (T), the number and location of metastatic lymph nodes (N), and distant organ metastasis (M). The most accepted classification is the TNM staging system developed by the American Joint Committee on Cancer (AJCC). (89) Another staging classification that is sometimes used is that proposed by the United States National Cancer Institute of Surveillance, Epidemiology, and End Results (SEER) Program. This system considers three stages: (1) localized, for tumors confined to the breast with no extension to the lymph nodes (equivalent to TNM stages I and IIA); (2) regional, when breast cancer has disseminated to the regional lymph nodes (equivalent to stages IIB, IIIA, IIIB and IIIC); and (3) distant, when cancer has spread to distant organs (TNM stage IV). (90)

2.3.2.2 Tumor size

Tumor size has been recognized as the strongest predictor of outcome for patients with invasive breast carcinoma. (91) Tumor size is as an independent prognostic factor and larger tumors have been found to have negative effects on breast cancer-specific survival. (88) Tumor size predicts both relapse and distant relapse in non-operable stage. (92) Patients had a relapse-free survival rate of 91% at 10 years and 87% at 20 years for tumors <1 cm compared to 73% and 68% for tumors greater than 1cm. (93) Variation in tumor size predicts 10-year distant metastasis risk ranging from below 10% for tumors less than 10 mm to 90% for tumors larger 30 mm. (94) An increased mortality rate was associated with larger tumor size (11-20 mm tumors vs. 1-10 mm tumors, standard morality ratios =1.42) in hormone receptor-positive breast cancer patients. (95) The prognostic impact of tumor size is partly related to the fact that tumor size is capable of predicting incidence of axillary lymph node metastasis, 10% in tumors less than 1 cm and 35% for a tumor diameter of 1.6-2cm. (96) An increase in tumor size has been associated with a significant risk of lymph node metastasis in stage I. (97,98) Tumor size is still an apparent independent factor for long-term survival and patients with larger tumors had lower survival rate. (99,100)

2.3.2.3 Axillary Nodal status

The absence or presence of metastases to the regional lymph nodes is also of prognostic importance with regard to disease free and overall survival. While regional metastasis is partially a function of time (invasive breast cancers are more likely to become node-positive the longer

they exist in the preclinical phase), nodal involvement is also considered to indicate a more biologically aggressive breast cancer phenotype. (101,102) Axillary lymph node status is one of the most important prognostic factors in women with early stage breast cancer. (94,103) Lymph node metastasis has been assessed as a strong independent factor for both overall survival (OS) and disease free survival (DFS). (104) One previous study found average 10-year survival for patients with node-negative breast cancers was 75%, but only 25-30% for patients with node-positive disease. (105) A similar trend is apparent with regard to disease recurrence; one previous study found that while only 20-30% of node-negative patients experienced recurrence of their breast cancer within 10 years, recurrence occurred for approximately 70% of patients with node-positive breast cancers. (106) Rates of survival have also been found to be poorer with increasing numbers of affected lymph nodes. For example, previous studies have demonstrated that cases with four or more positive nodes have poorer rates of 5-year (101,106) and 10-year (107) survival compared with patients with 3 or fewer positive nodes.

2.3.2.4 Histologic Type

Histological examination of cancer cell morphology and architectural patterns are of importance in defining tumor subtype. Invasive ductal carcinoma is the most frequent subtype and presents two thirds of all breast cancers. This cancer is aggressive and typically metastasizes to bone, lung and liver. The lobular subtype is found in approximately 10% of patients and a better survival is expected if patients receive endocrine therapy as compared with patients with invasive ductal carcinoma. (108) Lobular carcinomas are more often low grade and patients have

a better prognosis than those with ductal carcinomas. (109) The medullary type is typically hormone receptor-negative, HER2(-) and p53(+) positive with an aggressive clinical behavior. (110) It is reported that about 5-7% of all breast cancers are of this type. Mucinous carcinoma is found in 3% of patients and tends to have a rather good prognosis. Papillary carcinoma represents 1-2% of all breast cancers and is in a majority of cases ER(+) and has a good prognosis. However, patients with a ductal or lobular infiltrating histological type had a poor prognosis compared with those with other subtypes. (111)

2.3.2.5 Tumor location

Tumour location within the breast has been proposed as an independent prognostic factor. (112) Tumours in the upper outer quadrant (UOQ), which is the most frequent site of tumour location, have been associated with improved survival compared to other quadrants (113,114); survival data for non-UOQ tumours have been mixed with findings demonstrating decreased survival for the lower inner quadrant (LIQ), and lower, medial or periareolar regions. (115–120) In contrast, other studies have found no association between tumour location and outcome. (121–123) The prognostic significance of tumor location in breast cancer remains unclear.

2.3.2.6 Histological Grade

Tumor grade is defined as prognostic factor in breast cancer. (124) Invasive carcinomas are today graded according to Scarff-Bloom-Richardson (SBR) or Elston-Ellis system; they are strongly correlated to overall and recurrent free survival. (125–127) The grading is based on the

sum of scores assigned three histological features: degree of ductal differentiation, pleomorphism, and mitotic index. A comparative report from France showed that both these two histological grade systems were strongly predictive for overall and disease-free survival. Assessment of 1,831 patients with operable breast cancer showed that patients with grade I tumors had a significantly better survival than those with grade II and III tumors. (128) Patients with low grade tumors had survival higher than high grade tumors, 9% and 20% in disease stage I and II, respectively. (109) Tumor grading was found to be the strongest independent prognostic factor for both OS and DFS in Malaysian (129) or breast cancer-specific survival in both Caucasian and African-American population sampled. (88) Postmenopausal women with high grade tumors have eight times higher mortality as compared to those with low grade tumors. (98) A similar correlation was also seen for 10-year disease free survival in untreated young patients. (130) The tumor grade was also confirmed as an independent marker of long-term survival in patients with lymph node negative disease. (99) High tumor grade was likely to predict regional metastasis and a 2.69 times increased risk of node metastasis was observed for high-grade tumors as compared with low-grade tumors. (97) In operable breast cancer, histologic grade was an independent predictor of both BCSS and DFS. (131)

2.3.2.7 Extensive Intraductal Component (EIC)

EIC was defined as ductal carcinoma in situ (DCIS) occupying 25% or more of the area encompassed by the infiltrating tumor and DCIS present in grossly normal adjacent breast tissue. (132,133) The precise contribution of EIC to local recurrence rates is not clear. Kurtz et al. (134)

reported that the presence of an extensive intraductal component (EIC) is an independent risk factor for local failure after breast conserving treatment in premenopausal women. On the other hand Hurd et al. (135) found no influence of EIC on overall survival. Conversely, others have reported no association between EIC and increased local recurrence rates. (136,137)

2.3.2.8 Lymphovascular invasion (LVI)

LVI has been reported as an additional prognostic factor in patients with breast cancer. (138–140) Lee et al. (141) found LVI to be an independent prognostic factor for DFS in their study. LVI is a widely recognized prognostic factor in lymph node-negative breast cancers. (142) However, there are controversial data about its prognostic significance in lymph node-positive patients. (143–146) LVI should be considered in the therapeutic strategy as a decision making tool in the adjuvant chemotherapy setting. (147)

2.3.2.9 Molecular Features

2.3.2.9.1 Estrogen receptor and progesterone receptor

There are two kinds of hormone receptors, estrogen receptor (ER) and progesterone receptor (PR), which are members of a nuclear hormone receptors super family that is located in the cytosol for operation of ligand-dependent transcription factors. There are two types of ER, (ERα and ERβ) of which ERβ is more widely distributed in the body than ERα , which is expressed mostly in the uterus and mammary gland. (148) The role of ERα- and ERβ-driven pathways might change during breast tumorigenesis. (149)

Immunohistochemistry (IHC) has rapidly become the predominant method for measuring ER and PR in clinical practice and it can be performed on a variety of samples including fine needle aspirates, core biopsies, fresh or frozen tissue and paraffin-embedded archival tissue. In long-term follow-up, hormone receptor status has been identified as an independent prognosticator of outcome (100,150–152) and an independent prognostic factor for both OS and DFS in Asia patients. (129) However, another cohort study from Sweden failed to demonstrate a significantly prognostic value of ER at 5 years after diagnosis, in spite of lower survival in patients with ER negative tumors (103) or at 10-years post-diagnosis in untreated young patients. (130) Patients with double hormone receptor positive tumors had the best breast cancer-specific survival with a 50% of risk reduction of breast cancer death compared to those with ER/PR(-) tumors. Hormone receptor status was identified therefore as an independent prognostic factor of outcome (150), which was also observed for postmenopausal women. (98) Although patients with hormone receptor-negative tumors received greater benefit from neoadjuvant chemotherapy in terms of pathologic response, they have worse outcomes in terms of recurrence and survival as compared to hormone receptor-positive patients. (153)

2.3.2.9.2 HER2 status

The HER2 oncogene is located in chromosome 17 that encodes for a 185 KD transmembrane glycoprotein receptor belonging to the epidermal growth factor receptor (EGFR) family including HER1/EGFR, HER2, HER3 and HER4 (154), which are crucial in the activation of sub cellular signal transduction pathways controlling epithelial cell growth, regulation of cell proliferation, differentiation and survival.

Women with *HER2* gene amplification have poor prognosis. *HER2* amplification has been identified as an independent prognostic factor in breast cancer with lymph node metastasis and is also associated with other poor prognostic factors. (155,156)It also predicted shorter disease free and cancer-specific survival in ER(+) patients but not in ER(-) cases. (130,157) Overexpression of HER2 protein also influences in outcome of treatment in patient with ER(+) tumors treated with adjuvant endocrine therapy (157), which was also a negative prognostic factor in untreated patients with ER(+) tumors. Amplification of *HER2* oncogene in tumors and metastatic lymph nodes may be a useful independent marker of poor prognosis and correlated with tumor recurrence and shorter survival in early stage. (100,158) The *HER2* oncogene was an independent prognostic factor for DFS in premenopausal women with node negative disease. (159) However, HER2 over expression did not adversely influence response to adjuvant oophorectomy plus tamoxifen treatment in patients with estrogen receptor-positive tumors (160) and notably, in a population from Asia. (129)

2.3.2.10 Metastatic sites and number of sites

One of the most important of these factors is tumor burden, which considers the number of metastatic lesions and the specific anatomical location of the metastases. Patients presenting with solitary (oligo) lesions survive longer than patients with multiple lesions. (161) In addition, a significantly superior prognosis has been observed amongst patients with loco-regional and bone metastases compared to patients with metastases in visceral organs. (161–164) According to the literature, the site of metastasis is an important prognostic factor in breast

cancer. Visceral metastases, such as those affecting lungs, are predictive of a poor prognosis and shorter survival. (161,165)

2.3.3 Treatment of Breast Cancer

Treatment of breast cancer mainly consists of local and systemic therapies. Surgery and radiotherapy are the treatment modalities used for local control of the disease where as chemotherapy and hormone therapies are used for systemic control of the disease. The properties of the patient and tumor determine the choice of treatment. Although the indications to use them differ due to histopathologic characteristics of the tumor, the best results are obtained when these treatment methods are applied in combination. (166)

2.3.3.1 Early-stage disease

- Treatment is with curative intent
- Surgery is the single most important intervention
- Breast conserving surgery (BCS) followed by radiation therapy (RT) is equivalent to mastectomy
- Adjuvant loco-regional RT improves local control and survival for node-positive women after mastectomy or BCS
- Most of the patients benefits from adjuvant systemic therapy
- Choice of adjuvant systemic therapy is based on the extent of disease, patient age, oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status, and a limited number of other prognostic factors

2.3.3.2 Locally advanced disease

- Treatment is with curative intent
- Usually starts with systemic therapy (chemotherapy and/or hormone therapy depending on ER,PR,Her2, age and comorbidities):
    - ⇨ >75% of patients have stable disease or respond to systemic therapy but <40% achieve a pathological complete response
- Both mastectomy and loco-regional RT should follow systemic therapy

2.3.3.3 Metastatic disease at first presentation or at relapse

- Treatment is with palliative intent
- Initial treatment frequently achieves symptoms improvement and sometimes there is prolongation of survival but cure is not currently achievable
- If ER positive, treatment is sequential use of hormone therapy, chemotherapy and intermittent, symptom-directed RT or surgery
- If ER negative, or there is symptomatic visceral disease, or if the disease was initially ER positive but becomes hormone resistant, chemotherapy should be tried
- HER2-positive cancers benefits from the addition of anti-HER2 therapy to chemotherapy
- Surgery and RT are useful in selected patients with symptoms for local masses or infiltrative lesions which are amenable to resection or stabilization (chest wall, brain, bone, etc.)

2.4 Timelines

Delay in diagnosis and initiation of treatment are among the reasons considered for widening gap in survival rates for breast cancer. Studies have shown mixed results in treatment delay and breast cancer outcome. A meta-analysis by Richards *et al.* (167) found that prolonged time of greater than 3 months from symptom recognition to initial treatment (surgery or neo-adjuvant chemotherapy) is associated with lower survival rates. However, Brazda *et al.* (168) found that treatment delay of greater than three months did not have an effect on overall breast cancer survival. Research has shown that it is vital that patients receive breast cancer diagnosis and treatment in a timely manner which can impact their survival, especially when greater than 90 days are taken before treatment is received. Future efforts should focus on elucidating and eliminating the multitude of barriers which may contribute to this disparity. (169) A literature review by Unger-Saldaña *et al.* (170) reported that prolonged delay in diagnosis and treatment impacted the patient's survival, their clinical stage at diagnosis, lymph node involvement, tumor size, and their quality of life. Two population-based cohort studies from Korea reported that longer intervals between diagnosis and treatment initiation are related to worse OS in breast cancer. (171)

2.5 Loss-adjusted survival of cancer patients

Cancer survival data is a key indicator for monitoring progress against cancer. There are several publications on breast cancer survival from all over the world, but in spite of it being a major public health problem studies from Indian subcontinent are sparse which is essentially due lack of adequate follow-up. The same is true for many developing countries, where health information systems are not well developed. Sufficient follow-up is the key for estimating survival because if the proportion of cases lost to follow-up is substantial and if the loss to follow-up is correlated with the probability of death (prognosis) of the patient after he or she was lost the survival estimates likely to be biased. (172) Socio-demographic and clinical characteristics of patients may help to predict loss to follow-up as the losses are also likely to be related to the patient's prognosis: low social status is related to lack of continuous patient surveillance; extent of disease is related to the motivation of follow-up, etc. Thus, Information on the association between prognostic factors and loss to follow-up can be used to reduce the bias in estimates of survival. (173) Ganesh et al. in 1995 (174) proposed a method to reduce this bias by computation of loss-adjusted survival. This method takes into consideration differential losses, by assuming that patients lost to follow-up within strata defined by certain variables have the same probability of death as those still remaining under observation and belonging to the same stratum. It is reasonable to expect survival experience in patients lost to follow-up and with complete follow-up to be more similar within a prognostic group, than when all patients are considered together. The difference between the crude actuarial survival and the loss adjusted value thus indicates the magnitude of the effect of differential loss to follow-up. (173)

AIMS & OBJECTIVES

CHAPTER 3

AIMS AND OBJECTIVES

3.1 Aim

To study the impact of epidemiological and clinical factors on survival in breast cancer patients.

3.2 Primary Objective

3.2.1 To compute overall survival and disease free survival for epidemiological and clinical factors affecting survival in breast cancer patient.

3.3. Secondary Objectives

3.3.1 To identify time lines between registration and diagnosis, diagnosis & commencement of treatment and to further evaluate its effect on overall survival.

3.3.2 To study patterns and factors which contribute to loss to follow-up and to compute loss adjusted follow-up rate for the associated factors.

MATERIAL & METHODS

CHAPTER 4

MATERIAL AND METHODS

4.1 Study Design:

- The study was a retrospective analysis of hospital records of breast cancer patients from the Tata memorial hospital (TMH) cancer registry.
- All female breast cancer patients who were registered in TMH from 01 January 2008 to 31 December 2008 were included in the study.

4.2 Inclusion Criteria:

- All female cases newly diagnosed unilateral breast cancer patient registered in TMH between 01st January 2008 to 31st December 2008.
- All female cases who have completed at least one modality of cancer directed treatment at TMH.

4.3 Exclusion Criteria:

- All female cases who have received any form of cancer directed therapy before registering in Tata Memorial Hospital

4.4 Attributes of the study cohort:

4.4.1 Breast cancer cases: Patients with cancer of Breast with ICD codes C50.1-C50.9 were included in the study.

4.4.2 Newly Diagnosed Breast cancer Cases: Patients with no prior history of taking any form of cancer directed treatments, who have come for the first time to TMH without a confirmed diagnosis of malignancy and whose malignancy was pathologically confirmed at TMH.

4.4.3 Unilateral: Having to do with one side of the body i.e (left or right side of breast)

4.4.4 Prior Treated Cases: Those patients who have received some or complete cancer directed treatment before registration at TMH.

4.4.5 Completed cancer directed treatment: Patients who had received atleast one modality of cancer directed treatment i.e surgery, radiotherapy, chemotherapy, hormonal therapy either alone or in combination as per treatment planned in TMH.

4.4.6 No/ Incomplete cancer directed treatment: Patient who had not received or not accepted treatment, those patients who had incomplete treatment at TMH or patients in whom treatment status was unknown as per the hospital records.

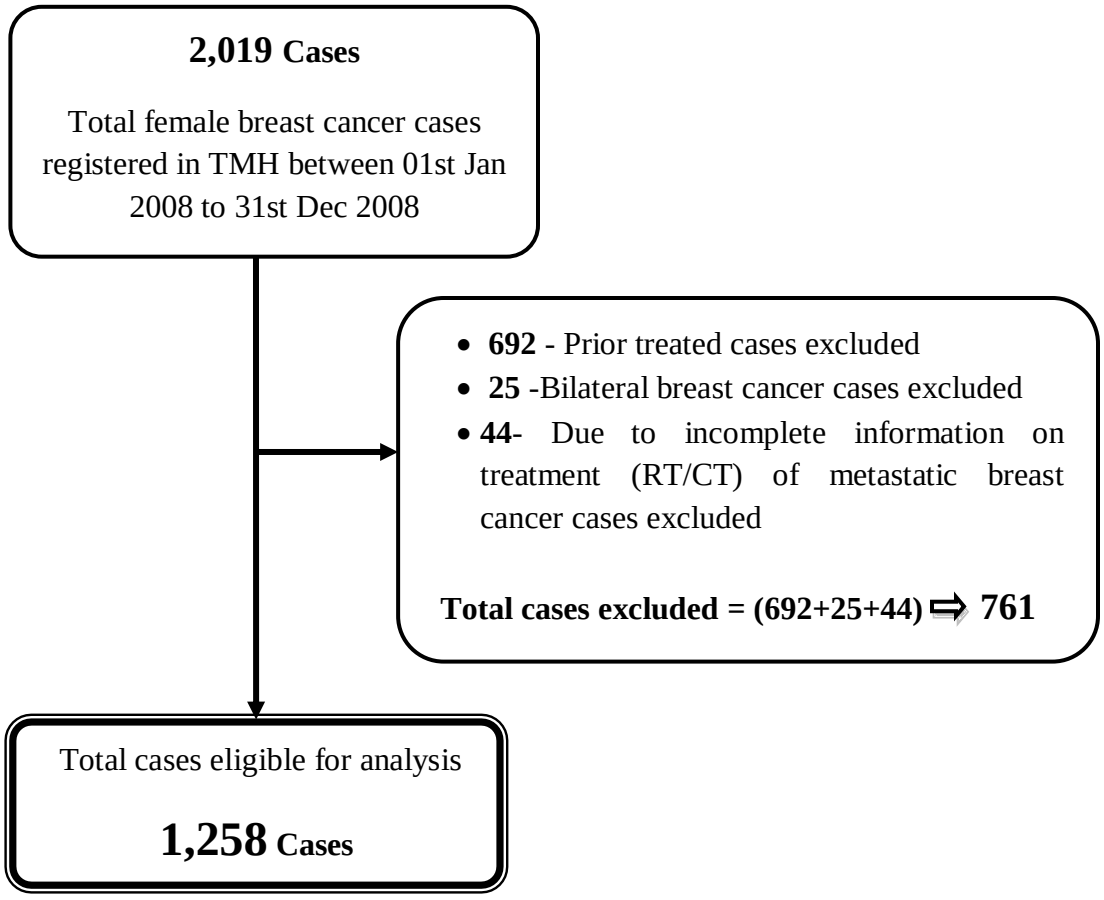
4.5 Period of enrolment:

All female breast cancer patients registered in TMH between 01st January 2008 to 31st December 2008.

4.6 Sample Size:

Records of 1258 female breast cancer patients were selected as per the inclusion and exclusion criteria (Fig 4.1) and retrospectively analyzed.

Fig 4.1. Flowchart for selection of cases



4.7 Data Collection:

All the information concerning demographic variables, diagnosis, staging, surgery, chemotherapy, radiotherapy, hormonal status and follow-up status were retrieved by patient files and computerized archives hospital based electronic medical record system (EMR).

4.7.1 Demographic variables

4.7.1.1 Age at Diagnosis: This refers to the age in completed years on the date of registration in TMH. The date was calculated from the date of birth of the patient mentioned in the hospital records till the date of registration. Age-groups were classified according to the decade of age.

4.7.1.2 Residence: The Patient's address postal pin code was taken into consideration for residence coding. Mumbai (who have been residing in Mumbai for more than 1 yr) and Outside Mumbai.

4.7.1.3 Education Status: Educational status at the time of registration was recorded Illiterate/ school level (Primary, Middle or Higher secondary)/ college and above. Women with formal education were grouped together as Literate and Illiterate women were considered in a separate group.

4.7.1.4 Marital Status: Marital status at the time of registration was recorded as Unmarried/ Married/ Widow/ Widower/Separated/Divorced.

4.7.1.5 Religion: Religion was recorded at the time of registration as Hindu/Muslim/Christian/Jain/Parsi/Neo-buddhist/Others.

4.7.2 Menstrual and Reproductive factors

4.7.2.1 Menopausal status at presentation: Menopausal status at the time of registration was recorded as Perimenopausal/Premenopausal/Postmenopausal.

4.7.2.2 Parity: Information on reproductive history was limited to parity only and was collected from medical records. Parity was defined as the number of full term pregnancies. A woman was only considered as nullipara when explicitly stated. Parity was categorized as: nullipara, one, two, three, and four or more children. Information on parity was missing for some women.

4.7.2.3 Family History of cancer: Information on family history of cancer was recorded at the time of registration. A positive family history was considered to be at least one first-degree female relative (mother or sister) diagnosed with breast or ovarian cancer.

4.7.2.4 Comorbidity: Presence of following co-morbid conditions was obtained from medical records. Hypertension, Diabetes Mellitus, Ischemic heart disease, Asthma and Human immunodeficiency virus positivity was recorded.

4.7.3 Disease (tumor) related factors

4.7.3.1 Laterality: Left side or right sided

4.7.3.2 Primary Histology: Primary histological type of the tumor was obtained from the biopsy reports (Infiltrating Ductal Carcinoma/ Infiltrating Lobular Carcinoma/ others).

4.7.3.3 Quadrant location: Tumor location was collected from medical records. The primary tumor site was divided into the upper-outer quadrant (UOQ), upper-inner quadrant (UIQ), lower-outer quadrant (LOQ), lower-inner quadrant (LIQ), and central location including the nipple and areola complex (central).

4.7.3.4 TNM Staging: Details of TNM staging was obtained from the clinical notes in the medical records. All patients were staged according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging manual on TNM classification system.

4.7.3.5 Clinical classification: Patients were broadly divided into three categories, early breast cancer (EBC), locally advanced breast cancer (LABC), and metastatic breast cancer (MBC). EBC has been defined as tumors of not more than 5 cm diameter, with either impalpable or palpable but not fixed lymph nodes and with no evidence of distant metastases. This corresponds to tumors that are T1-2, N0-1, and M0 according to AJCC (Seventh

edition). LABC was defined as T stage ≥T3 and/or N stage ≥ N2 without any evidence of distant metastasis. MBC was defined as any breast cancer with evidence of distant metastasis.

4.7.3.6 Histological characteristic of the tumor: Details of the histological characteristics of the tumor such as tumor grade, tumor size, Lymphovascular invasion (LVI), Extensive intraductal component (EIC) and histological axillary lymph node involvement was obtained histopathological reports of the surgical specimen.

4.7.3.7 Hormonal receptor status: Information on status of estrogen receptor (ER), progesterone receptor (PR) and epidermal growth factor receptor type 2 (HER2) were determined by immunohistochemistry (IHC). The cutoff value to determine if ER and PR were positive was ≥1% of tumor cells with nuclear staining. Tumors with HER2 score of 3+ were considered positive. If the HER2 grading was reported as 2+, fluorescence in situ hybridization (FISH) study was done in the majority of cases.

4.7.3.8 Molecular subtype classification: Based on the hormonal receptor status the molecular subtype classified into three groups as follows: **HR positive** (estrogen receptor [ER] or progesterone receptor [PR] positive, HER2 negative), **HER2 positive** (HER2 amplification or overexpression and any ER or PR status), and **Triple negative** (ER and PR negative, HER2 negative).

4.7.4 Treatment Given: Details of the cancer directed treatment i.e surgery, radiotherapy, chemotherapy, hormonal therapy either alone or in combination provided was obtained from the patient's medical records and the hospital based electronic medical record system (EMR).

4.7.5 Timelines:

Following time periods for each patient was calculated for each patient.

4.7.5.1 Time between registration and diagnosis Time between registration to diagnosis was calculated as time from date of registration to the date of pathological reporting of malignancy.

4.7.5.2 Time between diagnosis and commencement of treatment: Time between diagnosis and treatment commencement was calculated as time from date of pathological reporting of malignancy to the date of initiation of whichever modality of treatment given first to the patient.

4.8 Statistical Analysis:

There were two main outcomes of interest, Overall Survival (OS) and Disease Free Survival (DFS). OS was defined as the time interval between the date of diagnosis and the date of death or the date of the last follow-up which ever was earlier. DFS was defined as the time from diagnosis until any recurrence of breast cancer or date of death whichever is earlier. The closing date for recording the last follow-up was taken as 31st December 2014. The overall and disease-free survival was calculated by using actuarial method and the difference in

survival rates with regards to various factors were studied univariately by Kaplan-Meier curves and the log-rank test. The Cox-regression model was used to investigate the effect of these factors simultaneously on overall and disease-free survival in a multifactorial setting. All statistical analyses were performed using the Statistical Package for Social Science (SPSS for Windows, version 20, SPSS, Chicago, IL) program. A p value < 0 .05 was considered to be statistically significant.

4.8.1 Statistical Analysis for timelines:

Time periods in days were calculated from date of registration to diagnosis, diagnosis to treatment commencement and treatment commencement to treatment completion. These periods have been described in median, minimum and maximum period. The median time was taken as cut-off for categorization of time period and for analysis of its effect on overall survival using Kaplan-Meier curves and the log-rank test.

4.8.2 Computation of Loss-adjusted survival:

Loss-Adjusted Survival Rate (LAR) a method proposed by Ganesh (1995) was applied to obtain the corrected survival rates for various groups. Loss-adjusted survival is estimated under the assumption that survival of patients lost to follow-up is the same as that for patients with known follow-up time and similar characteristics of different prognostic factors at first entry. Thus using this method the estimated deaths were obtained by logistic regression in those with complete follow-up and then subsequently these estimates were applied to those with incomplete follow-up. A standard method, such as the actuarial one, was then applied with the sum of

observed and expected outcome events. The above methods along with mathematical derivations are described in detail elsewhere. (Ganesh,1995) (Survcan)

RESULTS

CHAPTER 5

RESULTS

Following factors were analyzed for accessing their prognostic significance:

- **Epidemiological factors**
    - Age at diagnosis
    - Place of residence
    - Education level
    - Religion
    - Marital status
    - Menopausal status at presentation
    - Parity
    - Family history of cancer
    - Comorbid conditions

- **Clinical factors**
    - Laterality
    - Tumor location
    - Tumor histology
    - Tumor grade
    - Clinical TNM staging
    - Histopathological parameters
        - Presence of Extensive Intraductal Component (EIC)
        - Presence of Lymphovascular Invasion (LVI)
        - Pathological axillary lymph nodes
    - Hormonal receptor status (Positive/Negative)
    - Treatment

5.1 Descriptive Analysis: Medical records of 1258 pathologically proven breast cancer patients were retrospectively analyzed. The entire cohort was then divided into three parts based on stage of the disease 1) Early Breast Cancer (EBC) 2) Locally Advanced Breast Cancer (LABC) and 3) Metastatic Breast Cancer (MBC). 42.6% cases were EBC, 47.5% were LABC and 9.9% cases were MBC (Table 5.1). Distribution of these patients as per patient characteristics and tumor related factors is presented in succeeding paragraphs.

Table 5.1: Distribution as per Clinical classification

Clinical classification	**Number (%)**
Early Breast Cancer (EBC)	536 (42.6)
Locally Advanced Cancer (LABC)	597 (47.5)
Metastatic Breast Cancer (MBC)	125 (9.9)
All Cases	1258 (100)

5.1.1 Age at diagnosis: The age distribution of the entire cohort ranged between 2nd and 8th decade, the youngest being 22 years old and the oldest being 89 years old. Maximum numbers of patients were seen in 4th decade (34.1%), followed by 5th decade (26%). 19.6% of patients were below the age of 40 years and 20.3% of patients were above the age of 60 years. Table 5.1.1 shows the distribution of cases according to age and number of patients in the respective groups.

Table 5.1.1: Distribution as per Age at diagnosis of patients

Age at diagnosis (years)	All Cases Number (%)	EBC Number (%)	LABC Number (%)	MBC Number (%)
22 to 29	31 (2.5)	11 (2.1)	19 (3.2)	1 (0.8)
30 to 39	215 (17.1)	81 (15.1)	112 (18.8)	22 (17.6)
40 to 49	429 (34.1)	171 (31.9)	221 (37.0)	37 (29.6)
50 to 59	327 (26.0)	145 (27.1)	144 (24.1)	38 (30.4)
60 to 69	203 (16.1)	95 (17.7)	86 (14.4)	22 (17.6)
70 to 79	44 (3.5)	30 (5.6)	11 (1.8)	3 (2.4)
80 to 89	9 (0.7)	3 (0.6)	4 (0.7)	2 (1.6)
Total	1258 (100)	536 (100)	597 (100)	125 (100)
Median Age (years)	**48**	**50**	**47**	**50**
Range (years)	**22-89**	**22-85**	**23-89**	**28-85**

5.1.2 Place of Residence: 75.5% were non-residents i.e. from outside Mumbai city and 24.5% of patients were resident of Mumbai. Table 5.1.2 shows the distribution of the patients as per place of residence in the different groups.

Table 5.1.2: Distribution as per Place of Residence of patients

Place of Residence	All Cases Number (%)	EBC Number (%)	LABC Number (%)	MBC Number (%)
Mumbai	308 (24.5)	161 (30.0)	115 (19.3)	32 (25.6)
Non-Mumbai	950 (75.5)	375 (70.0)	482 (80.7)	93 (74.4)
Total	1258 (100)	536 (100)	597 (100)	125 (100)

5.1.3 Education Status: 81.1% of patients were found to be literate and only 18.9% patients were found to be illiterates (Table 5.1.3). There was a significant relationship between patient's educational level and stage at diagnosis of breast cancer ($p < 0.001$). In other words, those patients with lower educational level were diagnosed at more advanced level of disease.

Table 5.1.3: Distribution as per Education status of patients

Education status	All Cases Number (%)	EBC Number (%)	LABC Number (%)	MBC Number (%)	*p value**
Illiterate	238 (18.9)	61 (11.4)	147 (24.6)	30 (24.0)	< 0.001
Literate	1020 (81.1)	475 (88.6)	450 (75.4)	95 (76.0)	
Total	1258 (100)	536 (100)	597 (100)	125 (100)	

*** Calculated using Chi square test*

5.1.4 Religion: Distribution of patients as per religion is presented in Table 5.1.4. As shown, 83% of the patients were Hinduism followers and 17% of the patients followed other religion.

Table 5.1.4: Distribution as per Religion of patients

Religion	All Cases Number (%)	EBC Number (%)	LABC Number (%)	MBC Number (%)
Hindu	1044 (83.0)	441 (82.3)	494 (82.7)	109 (87.2)
Non-Hindu	214 (17.0)	95 (17.7)	103 (17.3)	16 (12.8)
Total	1258 (100)	536 (100)	597 (100)	125 (100)

5.1.5 Marital Status: Majority of the patients (82.8%) were married and only 3.1% were found to be unmarried (Table 5.1.5). Distribution of patients as per marital status in different groups is presented in Table 5.1.5.

Table 5.1.5: Distribution as per Marital Status of patients

Marital Status	All Cases Number (%)	EBC Number (%)	LABC Number (%)	MBC Number (%)
Married	1042 (82.8)	454 (84.7)	486 (81.4)	102 (81.6)
Widow/divorced/separated	177 (14.1)	68 (12.7)	90 (15.1)	19 (15.2)
Single (Unmarried)	39 (3.1)	14 (2.6)	21 (3.5)	4 (3.2)
Total	1258 (100)	536 (100)	597 (100)	125 (100)

5.1.6 Menopausal Status at presentation: In present study there is slight preponderance of carcinoma breast in post menopausal women (51.9%). Table 5.1.6 shows the distribution as per the menopausal status at presentation of patients in the different groups.

Table 5.1.6: Distribution as per Menopausal Status at presentation of patients

Menopausal Status at presentation	All Cases Number (%)	EBC Number (%)	LABC Number (%)	MBC Number (%)
Pre-menopausal	605 (48.1)	248 (46.3)	297 (49.7)	60 (48.0)
Post-menopausal	653 (51.9)	288 (53.7)	300 (50.3)	65 (52.0)
Total	1258 (100)	536 (100)	597 (100)	125 (100)

5.1.6 Parity: Majority of the patients (84.7%) were multiparous and only 6.4% were found to be Nulliparous. In 8.9% of cases whose parity status was unknown. Table 5.1.6 shows the distribution of patients as per parity in different groups.

Table 5.1.7: Distribution as Parity of patients

Parity	All Cases Number (%)	EBC Number (%)	LABC Number (%)	MBC Number (%)
Nulliparous	81 (6.4)	31 (5.8)	40 (6.7)	10 (8.0)
Multiparous	1065 (84.7)	455 (84.9)	507 (84.9)	103 (82.4)
Unknown	112 (8.9)	50 (9.3)	50 (8.4)	12 (9.6)
Total	1258 (100)	536 (100)	597 (100)	125 (100)

5.1.7 Family history of cancer: In this study only 80 (6.4%) patients gave history of her mother/sister suffering from carcinoma of breast. Table 5.1.7 shows the distribution as per the Family history of cancer of patients in the different groups.

Table 5.1.8: Distribution as per Family history of cancer of patients

Family history of cancer	All Cases Number (%)	EBC Number (%)	LABC Number (%)	MBC Number (%)
Yes	80 (6.4)	47 (8.8)	27 (4.5)	6 (4.8)
No	1178 (93.6)	489 (91.2)	570 (95.5)	119 (95.2)
Total	1258 (100)	536 (100)	597 (100)	125 (100)

5.1.8 Presence of co-morbidity: 21% of the patient had comorbidity present and 79% of the patients were without comorbidity. Table 5.1.8 shows the distribution as per the presence of the comorbidity in patients in the different groups. Record of five main comorbidities namely Hypertension, Diabetes mellitus, Heart Disease, Asthma and Human Immunodeficiency Virus (HIV) infection was obtained from the medical records of the patients and their distribution is given in Table 5.1.9.

Table 5.1.9: Distribution as per Presence of co-morbidity of patients

Presence of co-morbidity	All Cases Number (%)	EBC Number (%)	LABC Number (%)	MBC Number (%)
Present	264 (21.0)	125 (23.3)	116 (19.4)	23 (18.4)
Absent	994 (79.0)	411 (76.7)	481 (80.6)	102 (81.6)
Total	1258 (100)	536 (100)	597 (100)	125 (100)

Table 5.1.10: Distribution as per types of comorbidities

Co-morbidities	Number (%)
Hypertension	130 (10.3)
Diabetes mellitus	52 (4.1)
Heart Disease	5 (0.4)
Others (Asthma and HIV)	22 (1.7)
Hypertension and Diabetes	30 (2.5)
Any combination of above	25 (2.0)
Co-morbidity present (any of the above mentioned)	**264 (21)**

5.1.8 Laterality: 653 patients out of 1258 presented with lump in left breast and 605 patients presented with lump in right breast (Table 5.1.10).

Table 5.1.11: Distribution as per Laterality

Laterality	Number (%)
Left	655 (51.9)
Right	605 (48.1)
Total	1258 (100)

5.1.9 Tumor Location: Tumors were found in all quadrants with highest frequency 33.1% of cases being in upper outer quadrant, next in frequency, cases were found in breast NOS, 31.5 %. This was closely followed by cases in upper inner quadrant, central region, lower outer and lower inner quadrant. Least number of cases was found in the aerola and the axillary tail. Table 5.1.11 shows the distribution of cases according to quadrants.

Table 5.1.12: Distribution as per Topographic description of Breast cancer cases with ICD Codes (distribution of location of tumor in relation to quadrant)

Topographic description	Number (%)
C50.0 (Aerola, nipple)	3 (0.2)
C50.1 (Central Portion of Breast)	110 (8.7)
C50.2 (Breast Upper Inner Quadrant)	197 (15.7)
C50.3 (Breast Lower Inner Quadrant)	51 (4.1)
C50.4 (Breast Upper Outer Quadrant)	416 (33.1)
C50.5 (Breast Lower Outer Quadrant)	79 (6.3)
C50.6 (Breast Axillary tail)	6 (0.5)
C50.9 (Breast, NOS)	396 (31.5)
Total	**1258 (100)**

5.1.10 Primary Tumor Histology: Of the 1258 cases studied, 1194 (94.9%) were classified as infiltrating duct carcinoma without special features or not otherwise specified designated as NOS type, 15 (1.2 %) cases were found to be infiltrating lobular carcinoma and 49 (3.9%) were found to be into others category which includes special sub-types of invasive carcinoma and mixed infiltrating ductal and lobular carcinoma. A detailed list of the various histologic type of tumors is given in Table 5.1.12.

Table 5.1.13: Distribution as per Primary Tumor Histology

Tumor Histology	Number (%)
Ductal carcinoma	1194 (94.9)
Lobular carcinoma	15 (1.2)
***Others**	49 (3.9)

*Others includes special sub-types of invasive carcinoma and mixed infiltrating ductal and lobular carcinoma

5.1.11 Tumor Grade: Table 5.1.13 shows that 1043 (82.9%) cases were found to be grade III followed by 208 (16.5%) cases were found in grade II. Only 7 cases (0.6%) with grade I was found. For analysis we grouped grade I and grade II as Low grade and grade III as high grade. The distribution of tumor grade according to clinical classification is shown in Table 5.1.14. Statistically significant correlation was observed between tumor grade and clinical classification of breast cancer i.e EBC, LABC and MBC (P= 0.007).

Table 5.1.14: Distribution as per Tumor Grade

Tumor Grade	Number (%)
Grade I	7 (0.6)
Grade II	208 (16.5)
Grade III	1043 (82.9)
Total	**1258 (100)**

Table 5.1.15: Distribution of Tumor Grade according to clinical classification

Tumor Grade	All Cases Number (%)	EBC Number (%)	LABC Number (%)	MBC Number (%)	*p Value* *
Low grade (I+II)	211 (16.8)	110 (20.5)	86 (14.4)	15 (12.0)	0.007
High grade (III)	1047 (83.2)	426 (79.7)	511 (85.6)	110 (88.0)	

** Calculated using Chi square test*

5.1.12 TNM Staging: All the 1258 patients were staged according to the seventh edition of the American Joint committee on cancer (AJCC) staging manual on TNM classification system. 42.7% were found in stage II followed by 40.6 % in stage III, 9.9% of cases in stage IV and 6.8% of cases in stage I (Table 5.1.15).

Table 5.1.16: Distribution as per Clinical TNM Stage

Clinical TNM Stage	Number (%)
Stage I	85 (6.8)
Stage II	537 (42.7)
Stage III	511 (40.6)
Stage IV	125 (9.9)
Total	1258 (100)

5.1.13 Treatment taken: 92.1% of the patients had undergone surgery, 64.7% had taken radiotherapy, 82% of the patients had taken neoadjuvant or adjuvant chemotherapy and 50.3% of the patients had taken hormonal therapy or targeted therapy. (Table 5.1.16)

Table 5.1.17: Distribution as per Treatment taken

Type of Treatment	Number (%)
Surgery	
Yes	1158 (92.1)
No	100 (7.9)
Radiotherapy	
Yes	814 (64.7)
No	444 (35.3)
Chemotherapy	
Yes	1032 (82.0)
No	226 (18.0)
Hormonal therapy/Targeted therapy	
Yes	633 (50.3)
No	625 (49.7)

5.1.14 Histopathological Features: Histological characteristics of the tumor were obtained from histopathological reports of 1158 cases that had undergone surgical intervention. The distribution of these histological features is as shown in Table 5.1.17.

Table 5.1.18: Distribution as per Histological parameters in surgically treated cases (n=1158)

Histological Parameters	EBC Number (%)	LABC Number (%)	MBC Number (%)
Extensive Intraductal Component (EIC)			
Negative	468 (87.3)	525 (89.6)	24 (82.8)
Positive	68 (12.7)	61 (10.4)	5 (17.2)
Lymphovascular Invasion (LVI)			
Negative	419 (78.2)	447 (76.3)	29 (80.6)
Positive	117 (21.8)	139 (23.7)	7 (19.4)
Pathologically Axillary Lymph Node removed			
Node-negative	263 (49.1)	204 (34.8)	19 (52.8)
1 to 3 nodes positive	148 (27.6)	170 (29.0)	9 (25.0)
≥ 4 nodes positive	125 (23.3)	212 (36.2)	8 (22.2)

5.1.15 Hormonal receptor status: Table 5.1.18 shows the distribution of hormonal receptor.

Table 5.1.19: Distribution as per Hormonal Receptor status

Hormonal Receptor status	Number (%)
Estrogen Receptor (ER) status*	
Positive	660 (52.5)
Negative	594 (47.2)
Progesterone receptor (PR) status*	
Positive	579 (46.0)
Negative	675 (53.7)
Her-2 status*	
Positive	226 (18.0)
Negative	1028 (81.7)

** Unknown for 4 (0.3%) cases.*

5.1.16 Hormonal status: 52.5% of the cases were hormonal receptor positive and 47.2% of the cases were hormonal receptor negative (Table 5.1.19).

Table 5.1.20: Distribution as per Hormonal status

Hormonal status	All Cases* Number (%)	EBC Number (%)	LABC Number (%)	MBC Number (%)
HR positive	660 (52.5)	309 (57.6)	283 (47.4)	68 (54.4)
HR negative	594 (47.2)	227 (42.4)	310 (51.9)	57 (45.6)
Total	1254 (99.7)	536 (100)	593 (100)	125 (100)

***** *Unknown for 4 (0.3%) cases.*

5.2 Survival Analysis of Breast cancer

5.2.1 Disease-Free Survival (n=1133): Patients' disease-free survival (DFS) was calculated as the time interval between the date of diagnosis and the date of first recurrence or date of death whichever was earlier. At a median follow-up of 70 months, 248 (21.9%) patients had relapsed. 40 patients (3.5%) had local recurrence; 31 patients (2.7%) had recurrence in regional lymph nodes and 177 (15.6%) in distant organs. Bone was the commonest site of first metastatic recurrence in 55 patients followed by lung-54, liver-42, brain-21, contralateral breast-3 and pericardium-2. At last follow-up, 916 (80.8%) patients were alive and disease-free and 217 (19.1%) had died; 192 out of 217 (88.7%) had died due to disease progression and 25 deaths were unrelated to breast cancer. The 5 year disease-free survival of the cohort calculated by using actuarial method was found to be 76% (Table 5.2.1).

Table 5.2.1: Disease-free survival (n=1133) by Life table method

Total Number*	Disease-Free Survival (%)				
	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 Yrs
1133	96	87	81	78	76

*excluding 125 cases of Stage IV

5.2.2 Overall Survival (n=1258): Patients' overall survival (OS) was calculated as the time interval between the date of diagnosis and the date of death or the date of last follow-up. The data closure date was taken as 31st December 2014. Out of the 1258 patients, at the end of follow-up (31st Dec 2014), 326 (25.9%) patients had expired. The median follow-up period was 69.5 months (range, 1 to 84 months). The 5 year overall survival of the cohort calculated by using actuarial method was found to be 72% (Table 5.2.2).

Table 5.2.2: Overall survival by Life table method

Total Number	Overall Survival (%)				
	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 Yrs
1258	94	85	78	74	72
1133*	98	90	85	81	79

*excluding 125 cases of Stage IV

5.2.3 Survival according to Clinical TNM staging: Clinical TNM stage was found to significantly affecting both overall survival and disease-free survival ($p<0.001$) (Fig. 5.2.1). Stage III had the lowest 5yr disease-free survival and overall survival rate of 63.2% and 67.1% respectively and Stage I had the highest 5yr disease-free survival and overall survival rate of 92.7% and 91.5% respectively (Table 5.2.3). Thus, higher stages were found to have poorer prognosis as compared to lower stages.

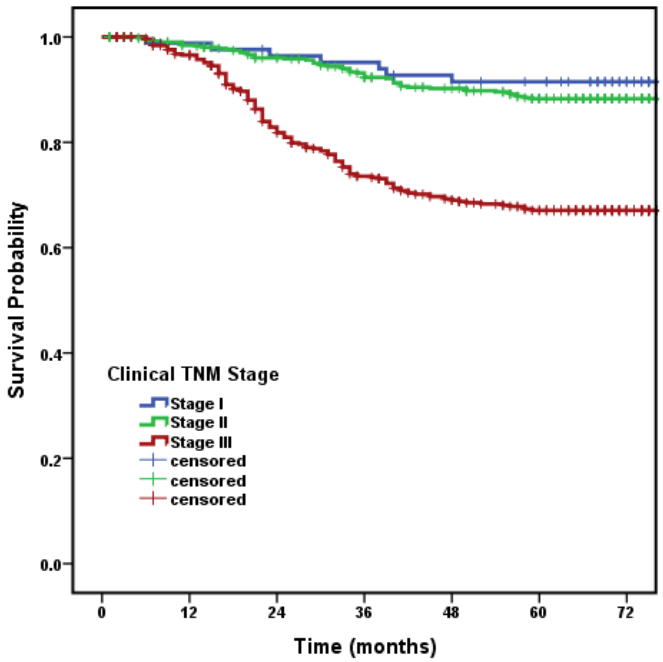
Table 5.2.3: Observed disease free survival and overall survival rate in (%) of breast cancer according to Clinical TNM stage

Clinical TNM Stage#	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 Yr	3 Yrs	5 Yrs		1 Yrs	3 Yrs	5 Yrs	
Stage I	85	98.8	92.7	92.7		98.8	95.2	91.5	
Stage II	537	97.3	89.2	85.3	<0.001	98.4	92.3	88.3	<0.001
Stage III	511	91.7	69.2	63.2		96.6	73.5	67.1	
Univariate Analysis									
		Hazard Ratio (95% CI)			***p value****	**Hazard Ratio (95% CI)**			***p value****
Stage I		1				1			
Stage II		2.01 (0.87 – 4.64)			0.099	1.38 (0.63 – 3.03)			0.418
Stage III		6.02 (2.66 – 13.60)			<0.001	4.53 (2.12 – 9.67)			<0.001

Abbreviations: CI=confidence interval
**Calculated using Log Rank Test #Stage IV was excluded.*

Figure 5.2.1: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 1133 patients with breast cancer, depending upon the clinical TNM stage

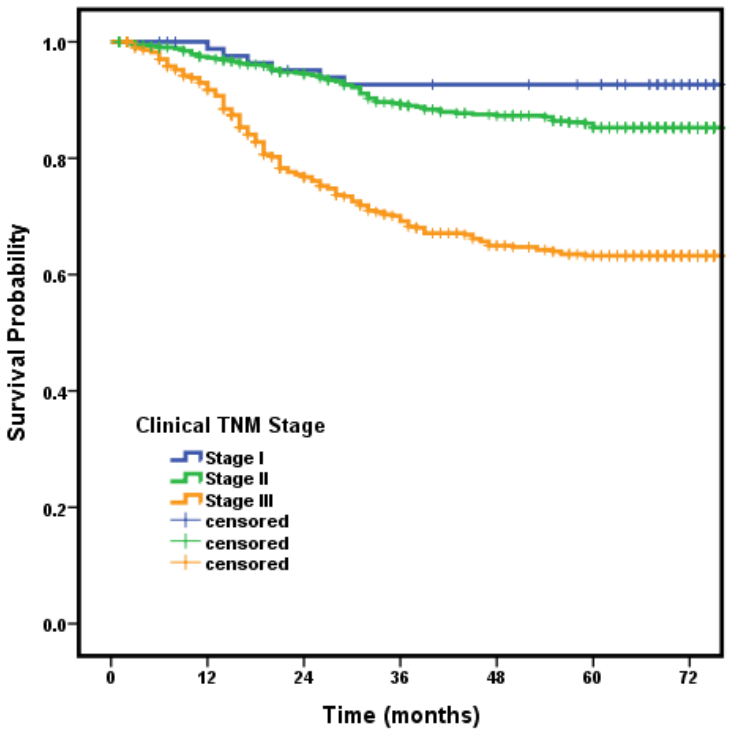
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Stage I	85	82	79	78	75	57	57
Stage II	537	499	474	449	424	395	318
Stage III	511	473	387	332	299	272	203

Figure 5.2.2: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 1133 patients with breast cancer, depending upon the clinical TNM stage

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Stage I	85	82	77	75	74	72	57
Stage II	537	492	461	425	402	372	301
Stage III	511	454	355	307	272	251	192

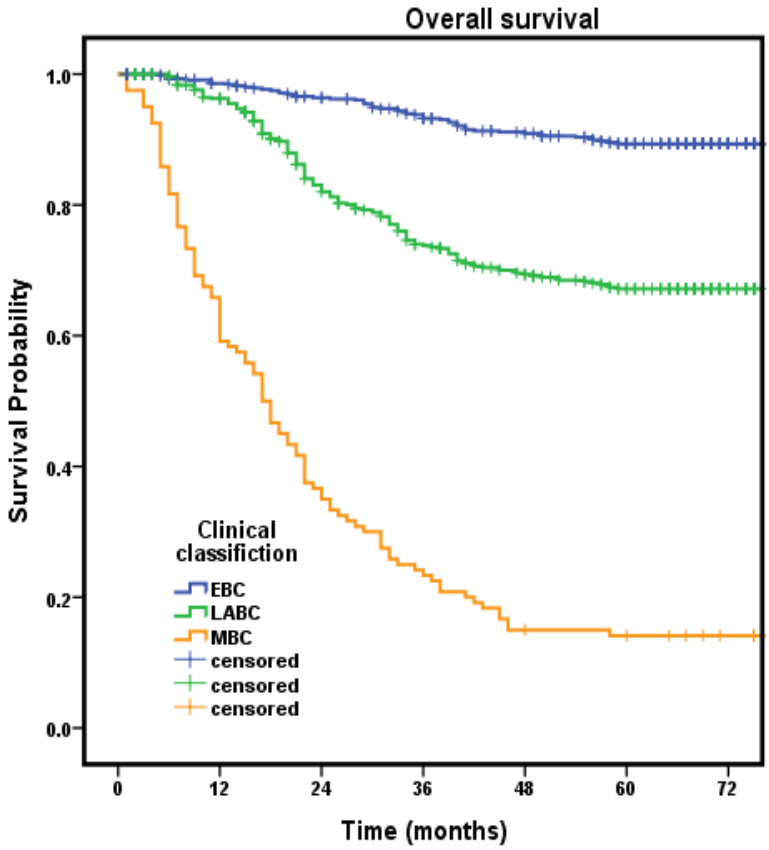
5.2.4 Survival according to Clinical classification: Clinical classification of breast cancer was found to be significantly affecting overall survival ($p<0.001$) (Fig. 5.2.3). Patients with metastatic breast cancer had the lowest 5yr overall survival rate of 13.5% and patients with early breast cancer had highest 5yr overall survival rate of 89.6 % (Table 5.2.4). Thus, higher stages were found to have poorer prognosis as compared to lower stages.

Table 5.2.4: Observed overall survival rate in (%) of breast cancer according to Clinical Classification

Clinical classification	Total Number	Overall Survival rate in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
EBC	536	98.6	96.3	93.4	90.9	89.6	< 0.001
LABC	597	96.9	83.7	75.7	71.6	69.4	
MBC	125	59.2	35.2	23.2	15.2	13.5	

**Calculated using Log Rank Test*

Figure 5.2.3: Observed overall survival rate (%) of breast cancer according to clinical classification



Number at risk	0	12	24	36	48	60	72
EBC	536	504	479	458	433	413	326
LABC	597	552	456	400	363	331	239
MBC	125	74	44	29	19	16	11

Early Breast Cancer (EBC)

5.3 Survival Analysis of Early Breast Cancer (n= 536)

5.3.1 Disease-Free Survival of EBC: The 5-year actuarial disease free survival for the EBC group is 89% (Table 5.3.2). At a median follow-up of 73 months, 59 (11.0%) patients had relapsed. 13 patients (2.4%) had local recurrence; 6 patients (1.1%) had recurrence in regional lymph nodes and 40 (7.5%) in distant organs. Lung was the commonest site of first metastatic recurrence in 15 patients followed by bone-12, brain-7, liver-5 and contralateral breast-1. At last follow-up, 485 (90.5%) patients were alive and disease-free and 51 (9.5%) had died; 39 out of 51(76.4%) had died due to disease progression and 12 deaths were unrelated to breast cancer.

5.3.2 Overall Survival of EBC: The median follow-up period was 74 months (range, 1 to 84 months). At the end of follow-up (31st Dec 2014) out of the 536 patients, 51 (9.5%) patients had expired (Table 5.3.1). The 5-year overall survival of the EBC cohort calculated by using actuarial method was found to be 90% (Table 5.3.2).

Table 5.3.1: Details of the early breast cancer cases

Details	**Number (%)**
Alive at closing date	**410 (76.5)**
Dead	**51 (9.5)**
Lost to follow up	**75 (14)**
• < 1year • 1-3 years • 3-5 years	27 21 27

Table 5.3.2: Observed disease-free survival and overall survival rate of Early Breast Cancer by Life table method

N=536	Survival in percentage (%)				
	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 Yrs
Disease-free Survival	98	96	91	90	89
Overall survival	99	96	94	91	90

5.3.3 Survival according to Age at Diagnosis: Patient's age at diagnosis were categorized into two categories less than or equal to 50 and greater than 50 and its effect on overall and disease-free survival was analyzed using Kaplan-Meier curves and the log-rank test. The five year disease-free survival rate (%) for the age groups ≤ 50 and >50 yrs was 85.4% and 90.6% respectively. This difference was not found to be statistically significant (p=0.066) (Table 5.3.3) (Fig 5.3.1). It was observed that patients with age less than or equal to 50 yrs had a 5yr overall survival rate of 90% and those of age 50 yrs and above had a 5yr overall survival rate of 89.2%, however this difference was not statistically significant (p=0.770) (Table.5.3.3) (Fig.5.3.1).

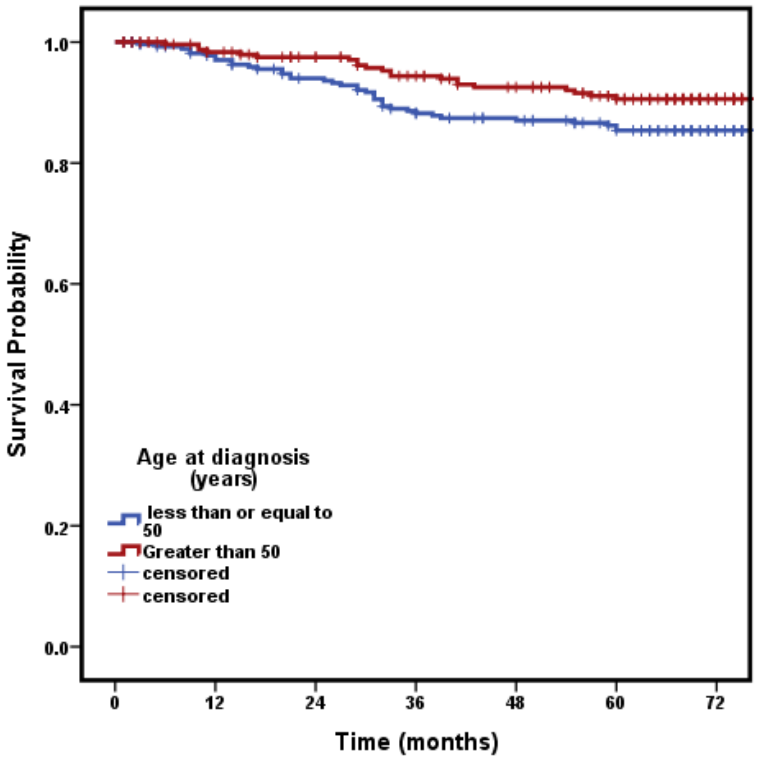
Table 5.3.3: Observed disease-free survival and overall survival rate (%) of early breast cancer according to age at diagnosis

Age at Diagnosis (Years)	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
≤ 50	281	97.0	88.2	85.4	0.066	98.9	93.6	90.0	0.770
> 50	255	98.3	94.4	90.6		98.4	93.2	89.2	

**Calculated using Log Rank Test*

Figure 5.3.1: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to age at diagnosis

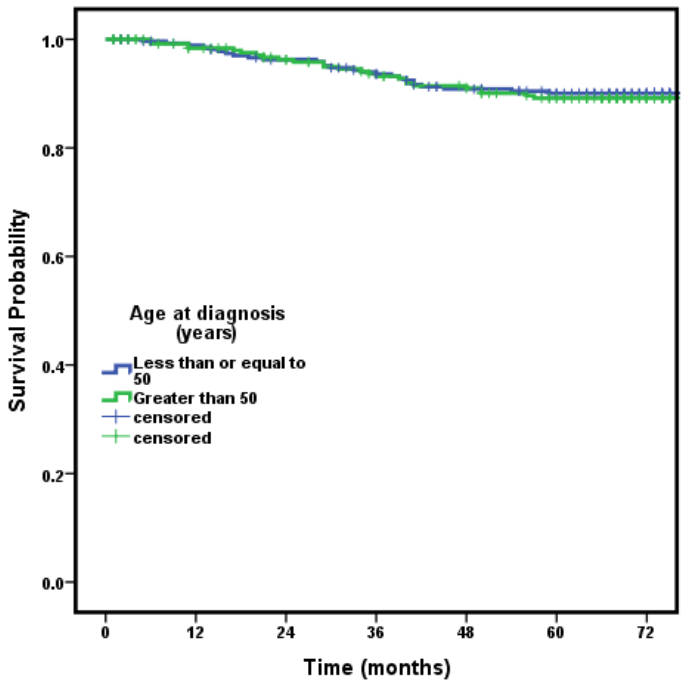
(a) Disease free survival



Number at risk	0	12	24	36	48	60	72
≤ 50	281	261	245	228	219	207	176
> 50	255	235	223	209	198	184	138

Figure 5.3.1: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to age at diagnosis

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
≤ 50	281	265	254	244	229	219	185
> 50	255	237	225	213	205	191	143

5.3.4 Survival according to Residence: Patients who came from different regions for diagnosis and treatment may have differences in biological behavior and response to treatment. To assess the residence factor, survival analysis was carried out and presented in Table 5.3.4. Patients who were non-Mumbai residents fared well compared to residents of Mumbai (Fig.5.3.2).

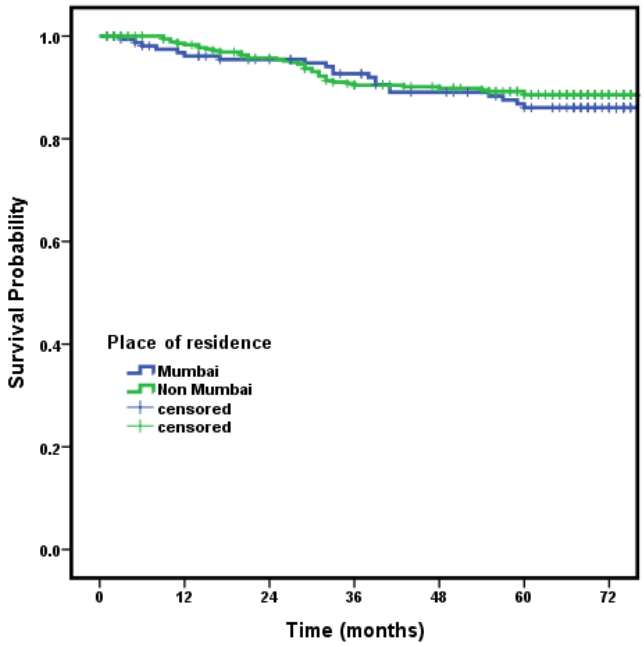
Table 5.3.4: Observed disease-free survival and overall survival rate (%) of early breast cancer according to residence

Residence	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Mumbai	161	96.1	92.7	86.1	0.490	97.4	93.4	88.4	0.557
Non-Mumbai	375	98.3	90.4	88.6		99.2	93.4	90.2	

**Calculated using Log Rank Test*

Figure 5.3.2: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Residence

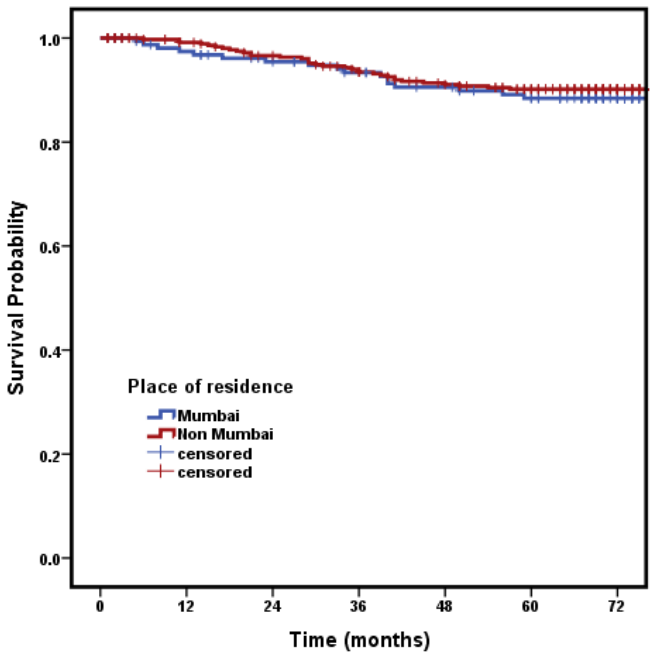
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Mumbai	161	148	140	132	122	115	92
Non-Mumbai	375	348	328	305	295	276	222

Figure 5.3.2: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Residence

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Mumbai	161	150	142	135	128	122	96
Non-Mumbai	375	352	337	322	306	288	232

5.3.5 Survival according to Education status: The five-year disease-free survival rate of literate and illiterate was found to be 88% and 86.6 % respectively, however this was not found to be statistically significant (Table 5.3.5). Education status was found to be significantly associated with overall survival. The five-year overall survival rate of literate and illiterate was found to be 90.6% and 81.2 % respectively. This difference was statistically significant (p=0.015) (Table 5.3.5) (Fig.5.3.3).

Table 5.3.5: Observed disease-free survival and overall survival rate (%) of early breast cancer according to education status

Education status	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Literate	475	98.0	91.4	88.0	0.592	99.3	94.6	90.6	0.015
Illiterate	61	94.5	88.6	86.6		92.9	83.2	81.2	

**Calculated using Log Rank Test*

Figure 5.3.3: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to education status

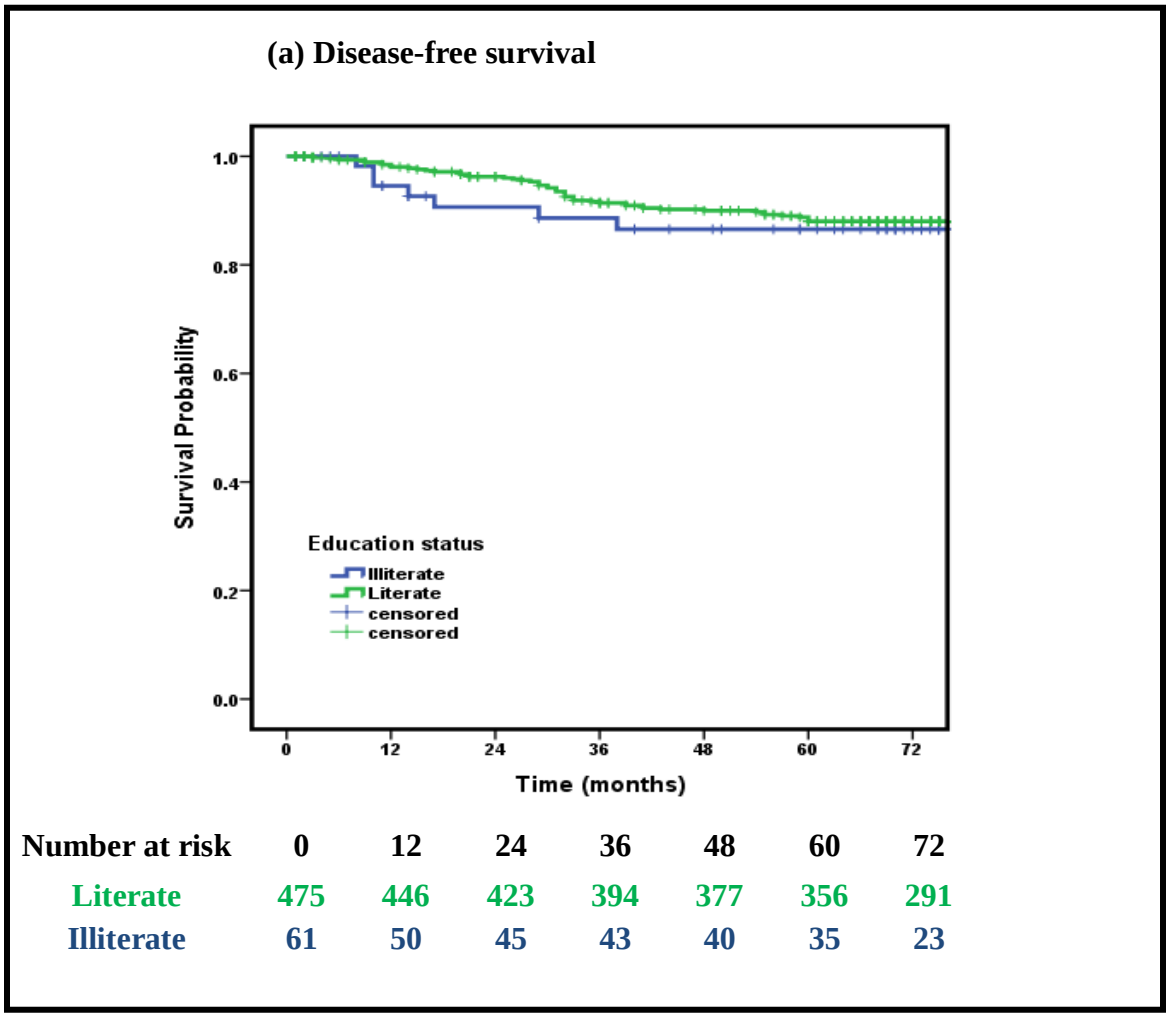
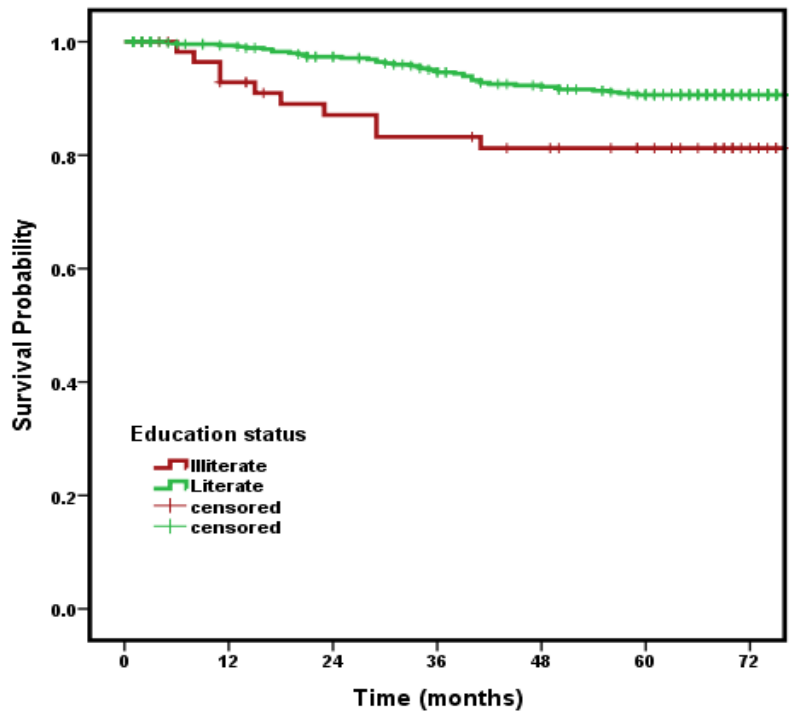


Figure 5.3.3: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to education status

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Literate	475	451	434	414	394	375	305
Illiterate	61	51	45	43	40	35	23

5.3.6 Survival according to Religion: Patients were categorized as per their religion at the time of registration and their effect on survival was analyzed. There was no significant (p=0.518, p= 0.342) difference in both disease-free survival and overall survival between Hindu patients and Non-Hindu patients (Table 5.3.6) (Fig. 5.3.4).

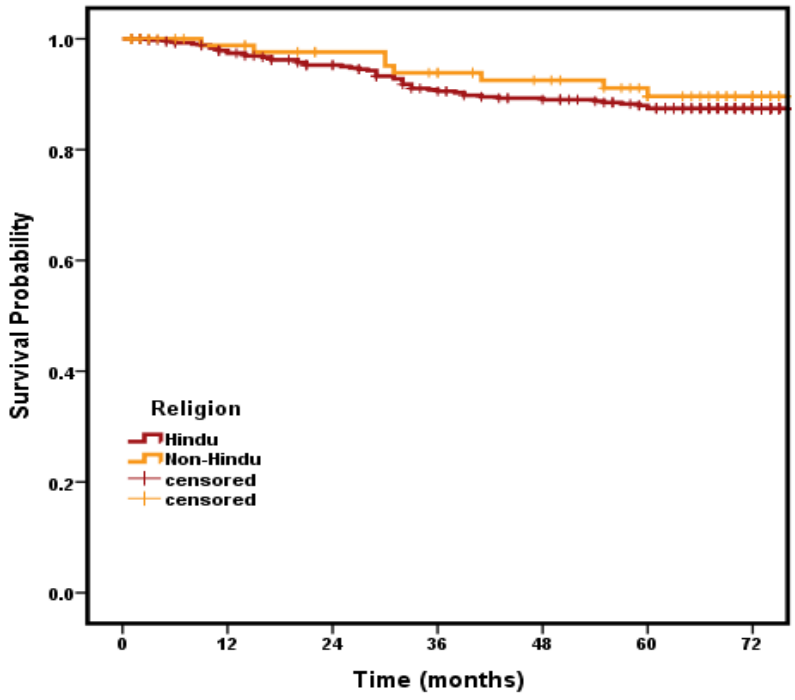
Table 5.3.6: Observed disease-free survival and overall survival rate (%) of early breast cancer according to religion

Religion	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Hindu	441	97.4	90.5	87.4	0.518	98.6	92.8	89.1	0.342
Non-Hindu	95	98.8	93.9	89.6		98.9	96.4	92.3	

**Calculated using Log Rank Test*

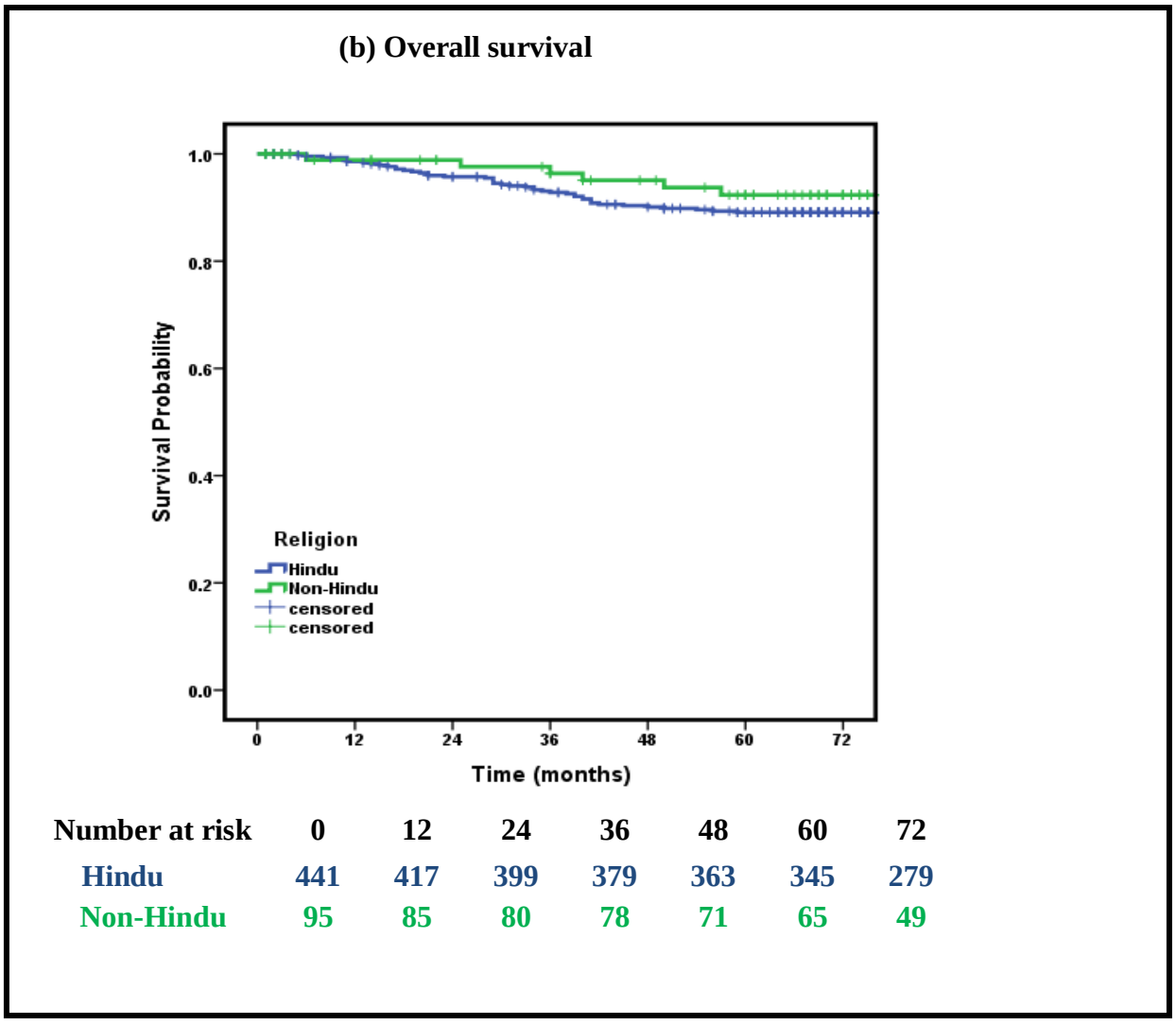
Figure 5.3.4: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Religion

(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Hindu	441	412	390	363	349	330	267
Non-Hindu	95	84	78	74	68	61	47

Figure 5.3.4: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Religion



Number at risk	0	12	24	36	48	60	72
Hindu	441	417	399	379	363	345	279
Non-Hindu	95	85	80	78	71	65	49

5.3.7 Survival according to marital status: Patients were categorized as per their marital status at the time of registration. No significant difference was seen in 5 yr disease-free and overall survival of patients based on marital status (Table 5.3.7) (Fig.5.3.5).

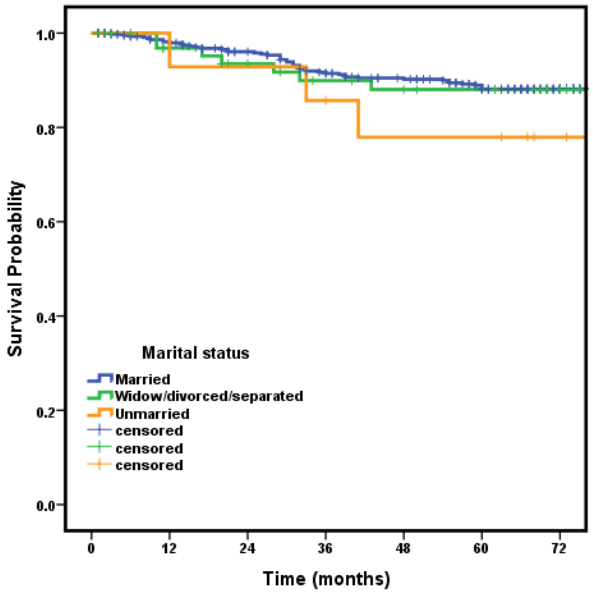
Table 5.3.7: Observed disease-free survival and overall survival rate (%) for early breast cancer according to marital status

Marital status	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Married	454	99.8	91.5	88.1	0.531	99.1	95.1	91.3	0.071
Widow/divorced/separated	68	96.8	89.9	88.1		95.3	83.7	80.3	
Single (Unmarried)	14	92.9	85.7	77.9		100	85.7	78.6	

**Calculated using Log Rank Test*

Figure 5.3.5: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to marital status

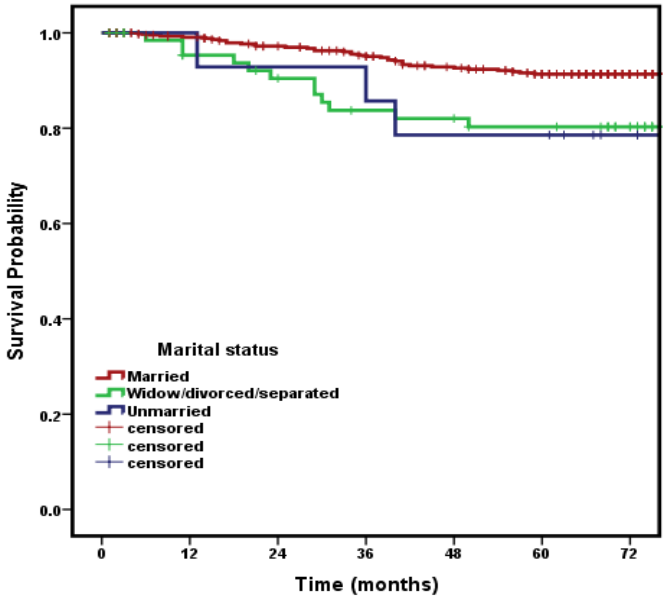
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Married	454	424	401	376	360	336	270
Widow/divorced/seperated	68	58	54	49	47	45	37
Unmarried	14	14	13	12	10	10	7

Figure 5.3.5: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to marital status

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Married	454	429	411	395	375	354	284
Widow/divorced/seperated	68	59	55	49	48	45	37
Unmarried	14	14	13	13	11	11	7

5.3.8 Survival according to Menopausal status: The five-year disease-free survival rate for Premenopausal and Postmenopausal patients was found to be 85.3% and 90.1% respectively (Table 5.3.8), but this difference was not statistically significant (p=0.096) (Fig.5.3.6). A 5 yr overall survival rate for Premenopausal and Postmenopausal patients was found to be 91.7% and 87.8% respectively (Table 5.3.8), but this difference was not statistically significant (p=0.142) (Fig.5.3.6).

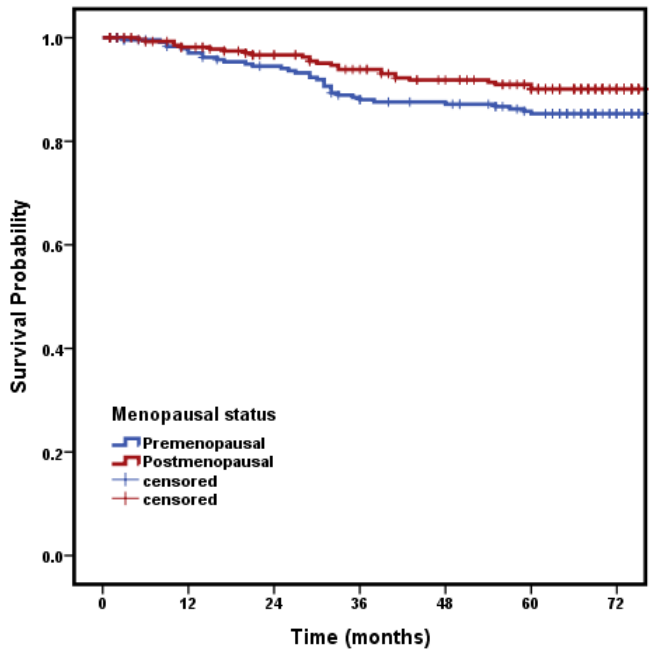
Table 5.3.8: Observed disease-free survival and overall survival rate (%) of early breast cancer according to menopausal status

Menopausal Status	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Pre-menopausal	248	97.0	88.0	85.3	0.096	99.6	95.3	91.7	0.142
Post-menopausal	288	98.2	93.9	90.1		97.8	91.8	87.8	

**Calculated using Log Rank Test*

Figure 5.3.6: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Menopausal status

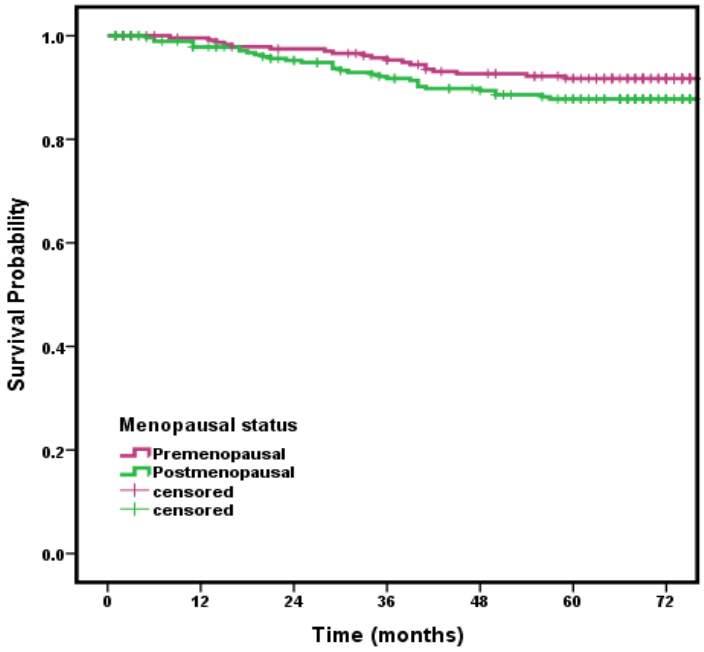
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Premenopausal	248	231	220	204	198	185	156
Postmenopausal	288	265	248	233	219	206	158

Figure 5.3.6: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Menopausal status

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Premenopausal	248	235	227	220	208	198	165
Postmenopausal	288	267	252	237	226	212	163

5.3.9 Survival according to Parity: Patient parity status was taken at the time of registration. Parity was classified as nulliparous and multiparous. A 5 yr disease-free survival rate for nulliparous and multiparous patients was found to be 89.9% and 87.8% and 5 yr overall survival rate for nulliparous and multiparous patients was found to be 90% and 89.2% respectively (Table 5.3.9), but this difference was not statistically significant (Fig.5.3.7).

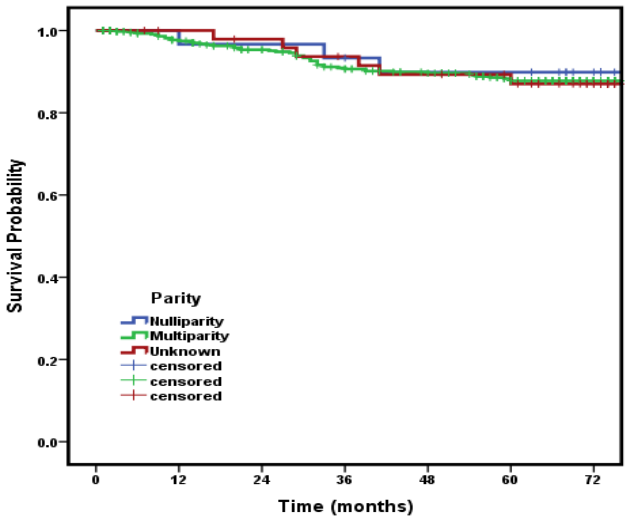
Table 5.3.9: Observed disease-free survival and overall survival rate (%) of early breast cancer according to parity

Parity	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Nulliparous	31	96.7	93.3	89.9		100.0	93.3	90.0	
Multiparous	455	97.5	90.6	87.8	0.933	98.4	92.7	89.2	0.615
Unknown	50	100.0	93.7	87.0		100.0	100.0	93.5	

**Calculated using Log Rank Test*

Figure 5.3.7: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to parity

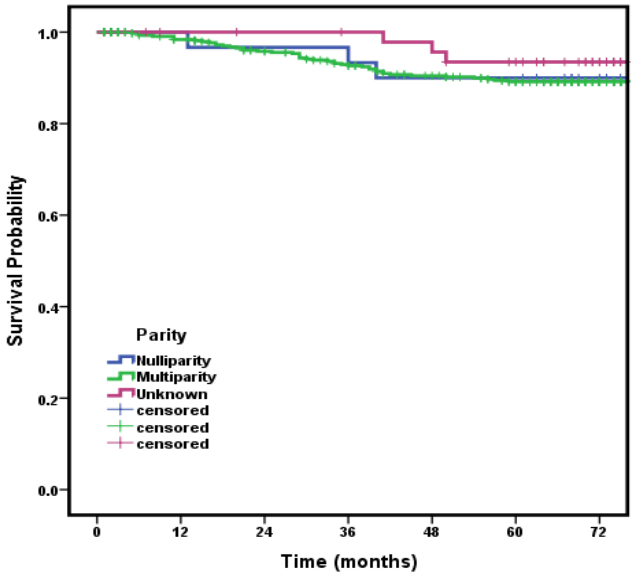
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Nulliparity	31	30	29	28	26	26	21
Multiparity	455	418	393	366	350	326	264
Unknown	50	48	46	43	41	39	29

Figure 5.3.7: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to parity

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Nulliparity	31	30	29	29	27	27	21
Multiparity	455	424	403	382	362	342	277
Unknown	50	48	47	46	45	41	30

5.3.10 Survival according to Family history of cancer: Patients were categorized as per presence of family history of cancer. No significant difference was seen in 5 yr disease-free survival and overall survival of patients based on family history of cancer (Table 5.3.10) (Fig.5.3.8).

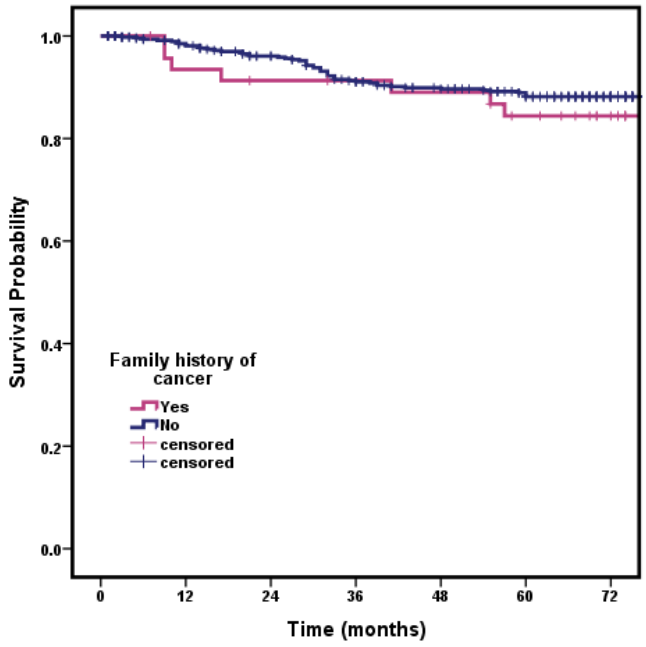
Table 5.3.10: Observed disease-free survival and overall survival rate (%) of early breast cancer according to family history of cancer

Family history of cancer	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Yes	48	93.5	91.3	84.4	0.444	97.0	93.5	93.5	0.408
No	489	98.1	91.1	88.2		98.7	93.4	89.2	

**Calculated using Log Rank Test*

Figure 5.3.8: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to family history of cancer

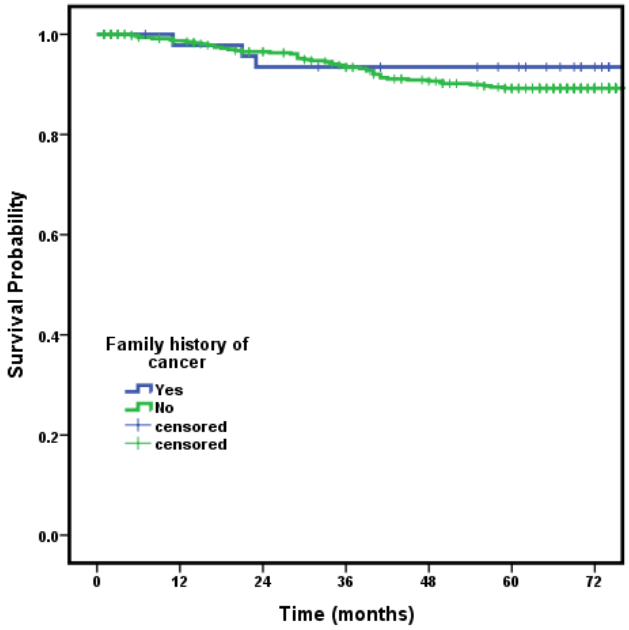
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Yes	47	43	41	40	39	35	29
No	489	453	427	397	378	356	285

Figure 5.3.8: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to family history of cancer

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Yes	47	45	43	42	41	39	32
No	489	457	436	415	393	371	296

5.3.11 Survival according to Presence of comorbidity: The 5 yr disease-free survival rate in patient with comorbidity was 89.8% and patient without comorbidity was 87.3% (Table 5.3.11) (Fig. 5.3.9). Early breast cancer patients having a concomitant comorbidity (Hypertension, Diabetes mellitus, Heart Disease, Asthma and HIV) were found to have 5yr overall survival of 86.4% as compared to 90.6% in patients without any comorbidity (Fig.5.3.9), but this difference did not achieve statistical significance (p=0.201) (Table 5.3.11).

Table 5.3.11: Observed disease-free survival and overall survival rate (%) of early breast cancer according to presence of co morbidity

Comorbidity	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Present	125	97.4	92.8	89.8	0.482	97.5	92.1	86.4	0.201
Absent	411	97.7	90.6	87.3		99.0	93.8	90.6	

**Calculated using Log Rank Test*

Figure 5.3.9: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Presence of comorbidity

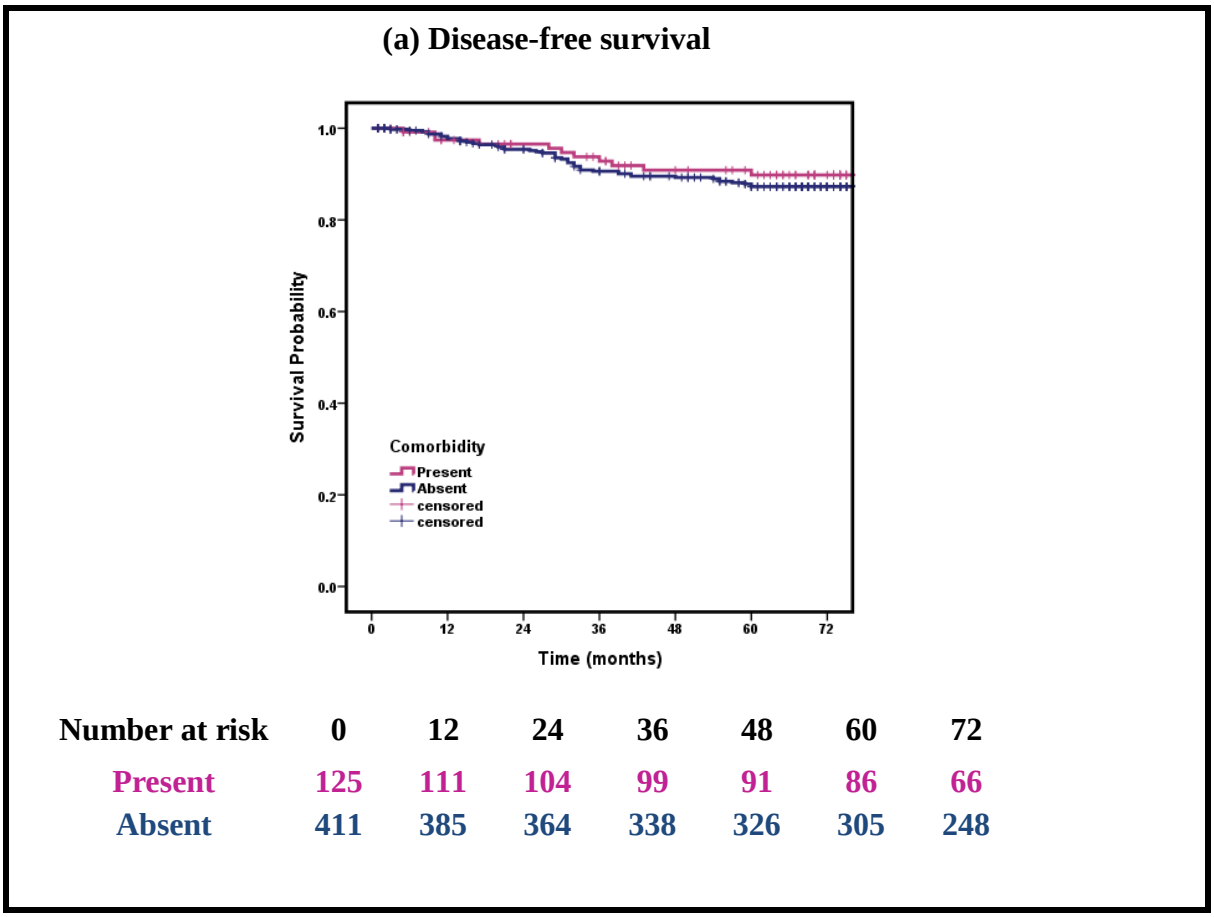
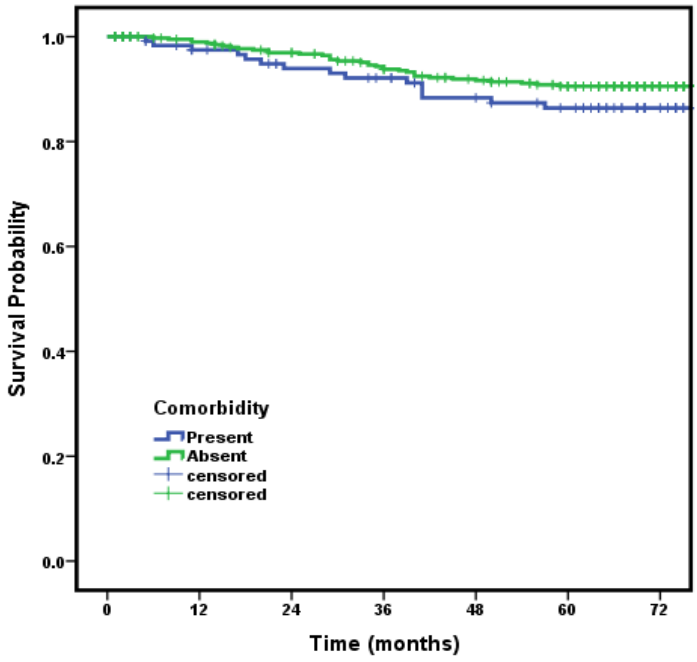


Figure 5.3.9: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Presence of comorbidity

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Present	125	112	104	100	93	87	67
Absent	411	390	375	357	341	323	261

5.3.12 Survival according to Quadrant location: A 5 yr disease-free survival rate for patient with Outer and Inner+Central quadrant location was found to be 85.8% and 89.5% respectively (Table 5.3.11). However, this difference was not statistically significant (Fig. 5.3.10). A 5 yr overall survival rate for patient with Outer and Inner+Central quadrant location was found to be 89.7% and 89.5% respectively (Table 5.3.11). However, this difference was not statistically significant (Fig. 5.3.10).

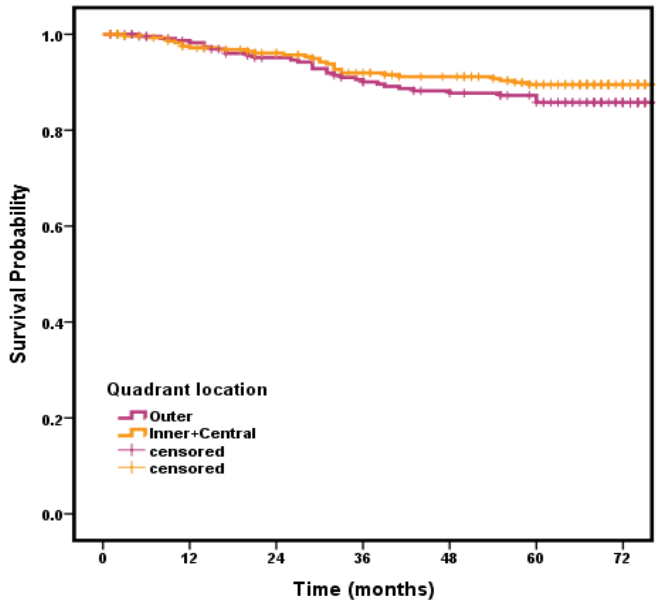
Table 5.3.12: Observed disease-free survival and overall survival rate (%) of early breast cancer according to quadrant location

Quadrant location	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Outer	241	98.2	90.1	85.8	0.235	97.8	92.0	89.7	0.949
Inner + Central	295	97.2	91.9	89.5		99.3	94.5	89.5	

**Calculated using Log Rank Test*

Figure 5.3.10: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Quadrant location

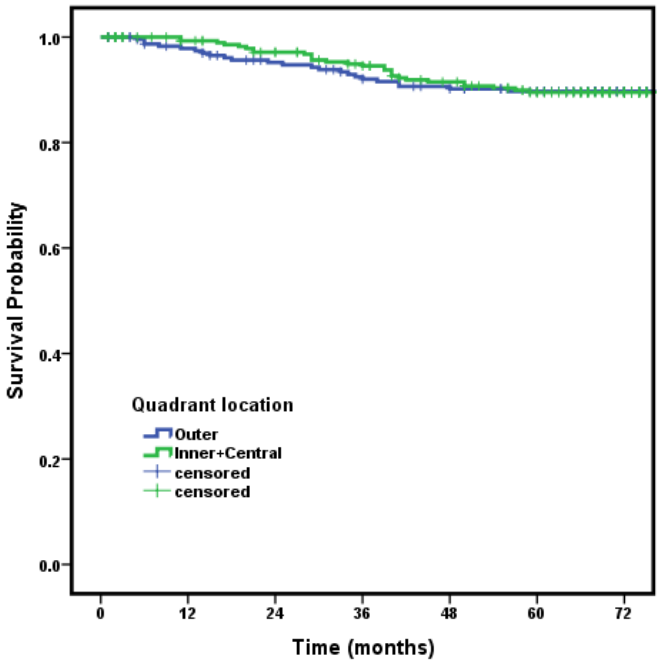
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Outer	241	223	208	196	187	179	145
Inner + Central	295	273	260	241	230	212	169

Figure 5.3.10: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Quadrant location

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Outer	241	224	212	203	196	188	151
Inner + Central	295	278	267	254	238	222	177

5.3.13 Survival according to Tumor grade: Patients with grade I and grade II had the 5 years disease-free survival rates of 98.0% in comparison to 85.2% for grade III patients (P<0.05; Table 5.3.13; Fig. 5.3.11). Patients having high grade (III) tumor were found to have the worst 5yr overall survival of 88.3%, whereas patients with low grade tumors had 95.0% 5yr overall survival (Table 5.3.13; Fig.5.3.12).

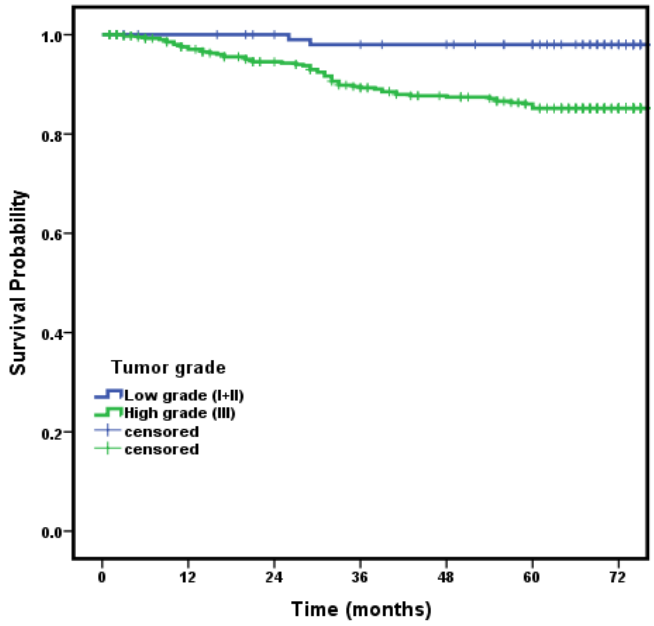
Table 5.3.13: Observed disease-free survival and overall survival rate (%) of early breast cancer according to tumor grade

Tumor grade	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Low grade (I+II)	110	100.0	98.0	98.0	0.001	100.0	99.0	95.0	0.044
High grade (III)	426	97.1	89.3	85.2		98.3	92.0	88.3	

**Calculated using Log Rank Test*

Figure 5.3.11: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Tumor grade

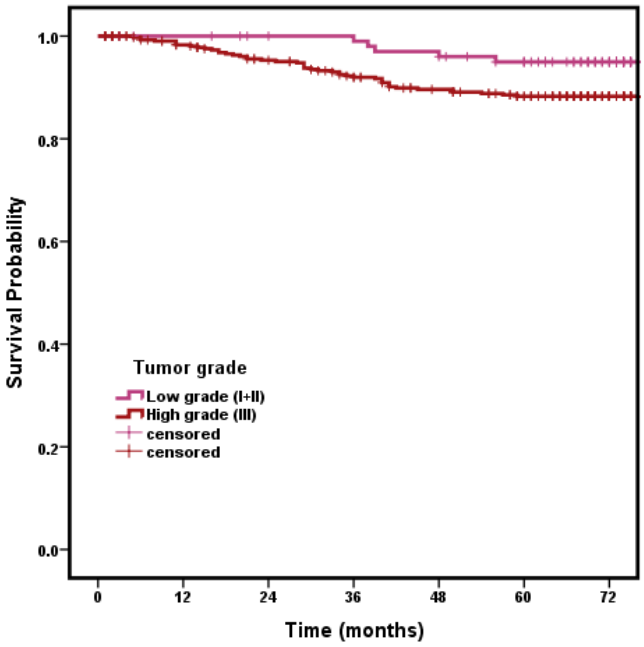
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Low grade (I+II)	110	104	101	98	96	91	69
High grade (III)	426	392	367	339	321	300	245

Figure 5.3.11: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Tumor grade

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Low grade (I+II)	110	104	101	98	96	91	69
High grade (III)	426	392	367	339	321	300	245

5.3.14 Survival according to Hormonal status: The survival probabilities by hormonal status are presented in Table 5.3.14, highlighting significant survival differences between the hormonal receptor positive and hormonal receptor negative (p value <0.05) (Fig. 5.3.12).

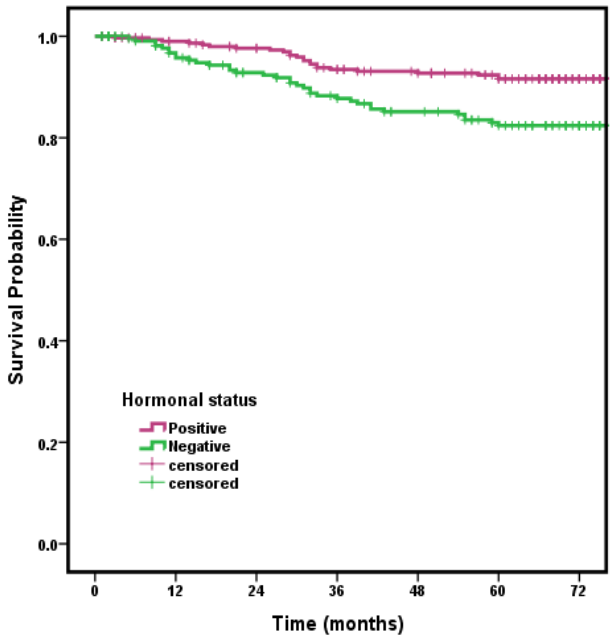
Table 5.3.14: Observed disease-free survival and overall survival rate (%) of early breast cancer according to hormonal status

Hormonal status	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
HR Positive	309	99.0	93.5	91.6	0.002	98.7	95.3	92.1	0.031
HR Negative	227	95.8	87.7	82.4		98.6	90.7	86.1	

**Calculated using Log Rank Test*

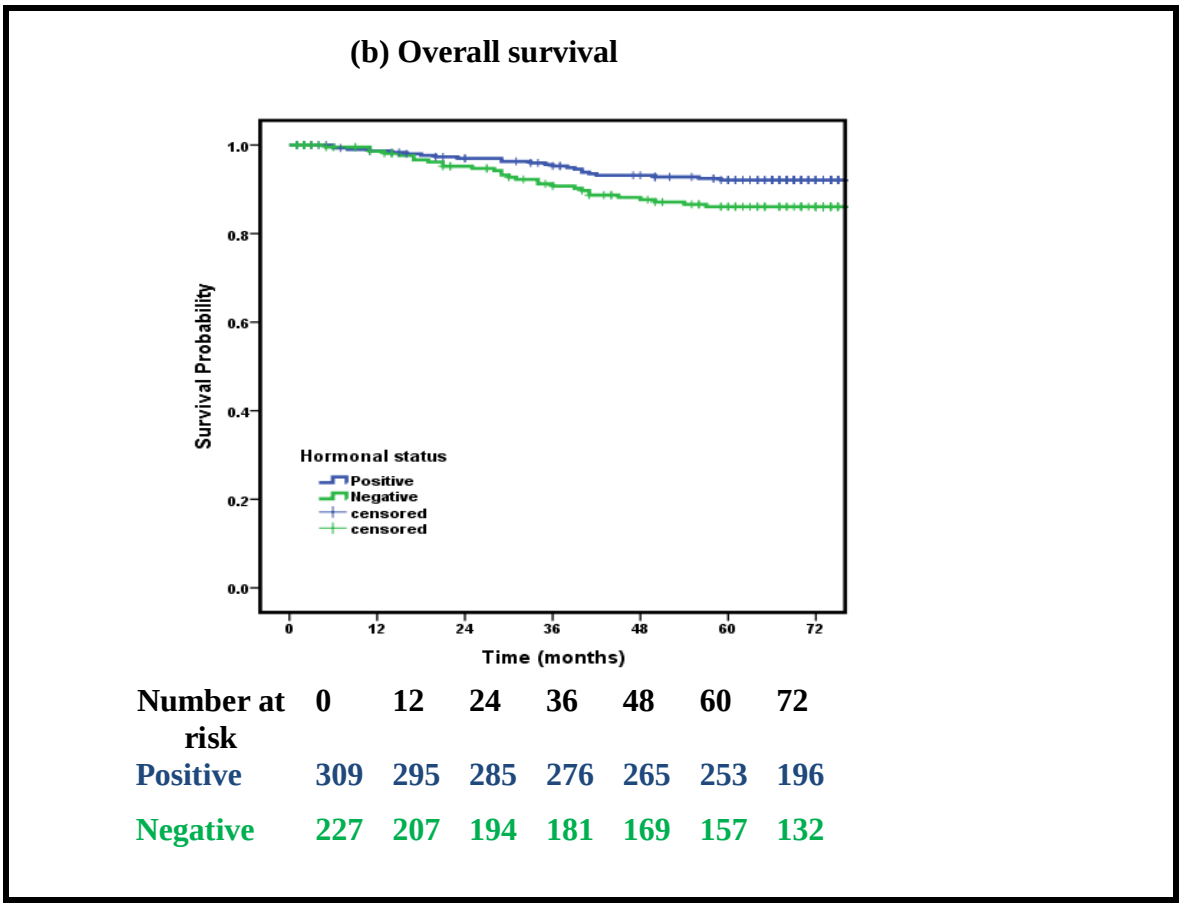
Figure 5.3.12: Kaplan-Meier curves of overall survival (a) and disease-free survival (b) for 536 patients with early breast cancer, according to Hormonal status

(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Positive	309	293	283	266	257	244	189
Negative	227	203	185	171	160	147	125

Figure 5.3.12: Kaplan-Meier curves of overall survival (a) and disease-free survival (b) for 536 patients with early breast cancer, according to Hormonal status



Number at risk	0	12	24	36	48	60	72
Positive	309	295	285	276	265	253	196
Negative	227	207	194	181	169	157	132

5.3.15 Survival according to Extensive Intraductal Component (EIC): Presence of EIC on histology was found to be significantly affecting both disease-free and overall survival adversely. Patients with EIC had 5 yr disease-free survival of only 80% as compared to 88.9% in those patients without EIC (Table 5.3.15) (Fig. 5.3.13). Patients with EIC had 5 yr overall survival of only 82.1% as compared to 90.7% in those patients without EIC (Table 5.3.15) (Fig. 5.3.13).

Table 5.3.15: Observed disease-free survival and overall survival rate (%) of early breast cancer according to Extensive Intraductal Component

Extensive Intraductal Component	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Negative	468	97.5	92.2	88.9	0.039	98.7	94.5	90.7	0.031
Positive	68	98.5	83.6	80.0		98.5	85.6	82.1	

**Calculated using Log Rank Test*

Figure 5.3.13: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Extensive Intraductal Component

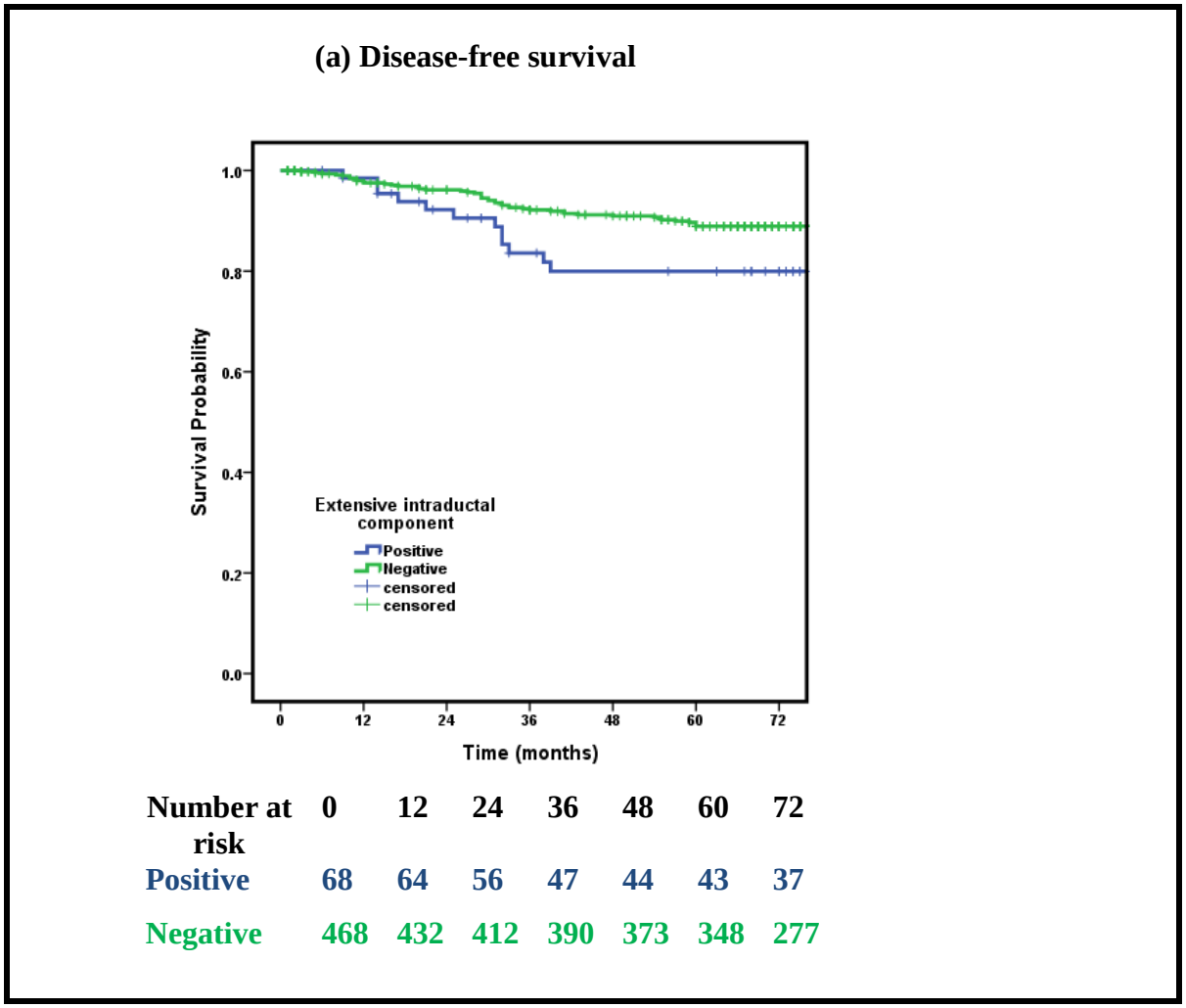
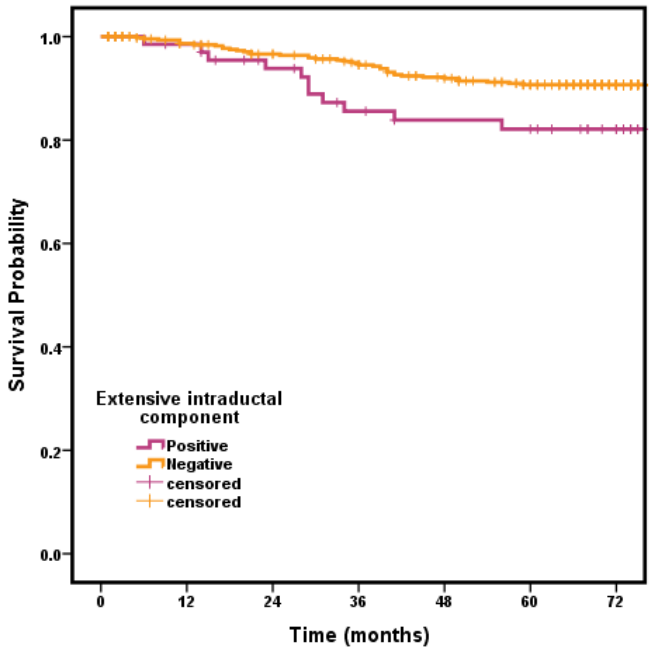


Figure 5.3.13: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Extensive Intraductal Component

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Positive	68	65	58	51	48	47	39
Negative	468	437	421	406	386	363	289

5.3.16 Survival according to Lymphovascular invasion (LVI): Presence of LVI on histology was found to be significantly affecting both disease-free and overall survival adversely. Patients with LVI had 5 yr disease-free survival of only 77.1% as compared to 90.7% in those patients without LVI (Table 5.3.16) (Fig. 5.3.14). Patients with LVI had 5 yr overall survival of only 83% as compared to 91.4% in those patients without LVI (Table 5.3.16) (Fig. 5.3.14).

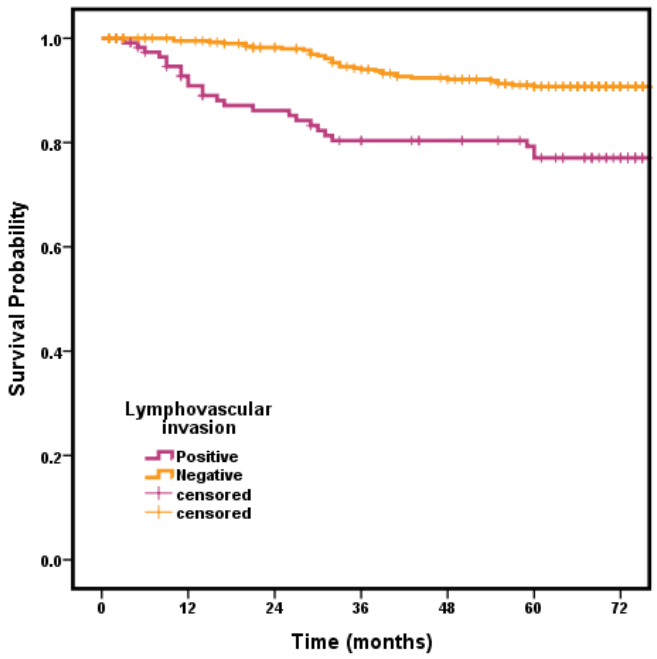
Table 5.3.16: Observed disease-free survival and overall survival rate (%) of early breast cancer according to Lymphovascular invasion

Lymphovascular invasion	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Negative	419	99.5	94.0	90.7	<0.001	99.5	94.9	91.4	0.007
Positive	117	90.9	80.4	77.1		95.5	88.0	83.0	

**Calculated using Log Rank Test*

Figure 5.3.14: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Lymphovascular invasion

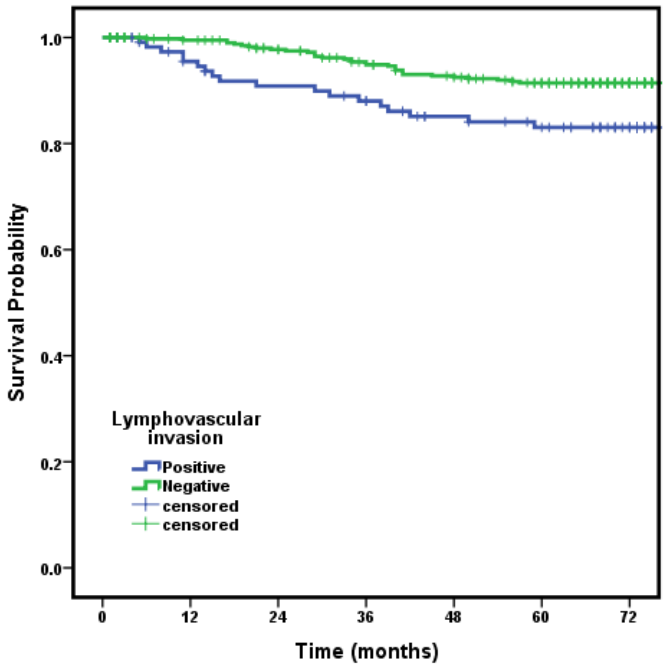
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Positive	117	99	90	82	77	72	57
Negative	419	397	378	355	340	319	257

Figure 5.3.14: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Lymphovascular invasion

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Positive	117	104	97	93	84	79	64
Negative	419	398	382	364	350	331	264

5.3.17 Survival according to Pathological Axillary lymph nodes: The 3 and 5 years disease-free survival for patients with 1–3 positive axillary nodes were 90.1% and 88.6% respectively in comparison to 81.1% and 73.2% for patients with equal to or more than four positive axillary nodes. For node negative patients the 3 and 5 years disease-free survival were 95.7% and 93.3% respectively (Fig. 5.3.15). This difference proved to be statistically significant (p<0.001). The 3 and 5 years overall survival for patients with 1–3 positive axillary nodes were 95.5% and 91.5% respectively in comparison to 79.1% and 75.1% for patients with equal to or more than four positive axillary nodes. For node negative patients the 3 and 5 years overall survival was 98.4% and 94.9% respectively (Table 5.3.16). This difference proved to be statistically significant (p<0.001). Presence of positive nodes on histopathology was found to significantly affect the survival adversely (p=0.00) (Fig. 5.3.15).

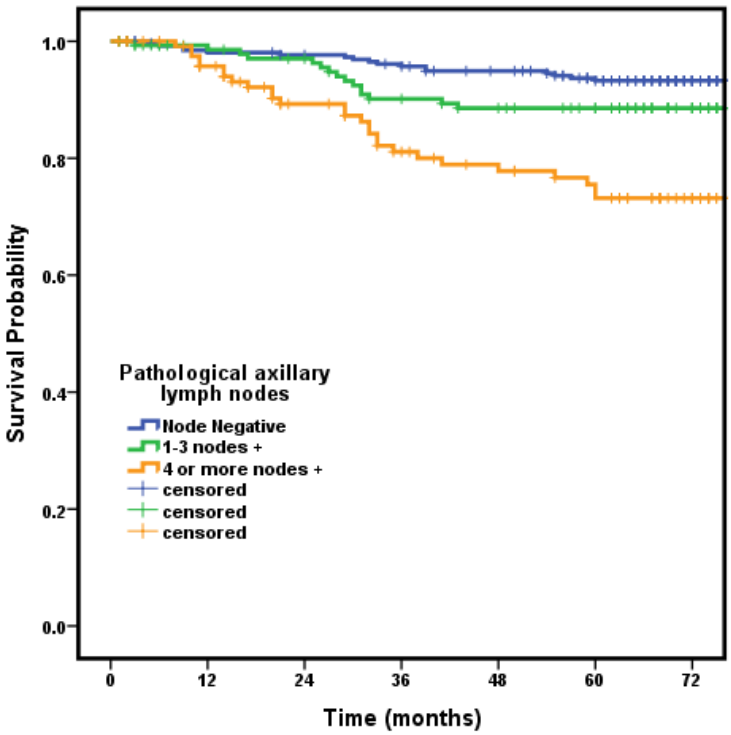
Table 5.3.16: Observed disease-free survival and overall survival rate (%) of early breast cancer according to Pathological Axillary lymph nodes

Pathological Axillary lymph nodes	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Node Negative	263	98.1	95.7	93.3	<0.001	99.6	98.4	94.9	<0.001
1-3 Positive nodes	148	98.5	90.1	88.6		99.3	95.5	91.5	
≥4 Positive nodes	125	95.7	81.1	73.2		95.8	79.1	75.1	

**Calculated using Log Rank Test*

Figure 5.3.15: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Pathological Axillary lymph nodes

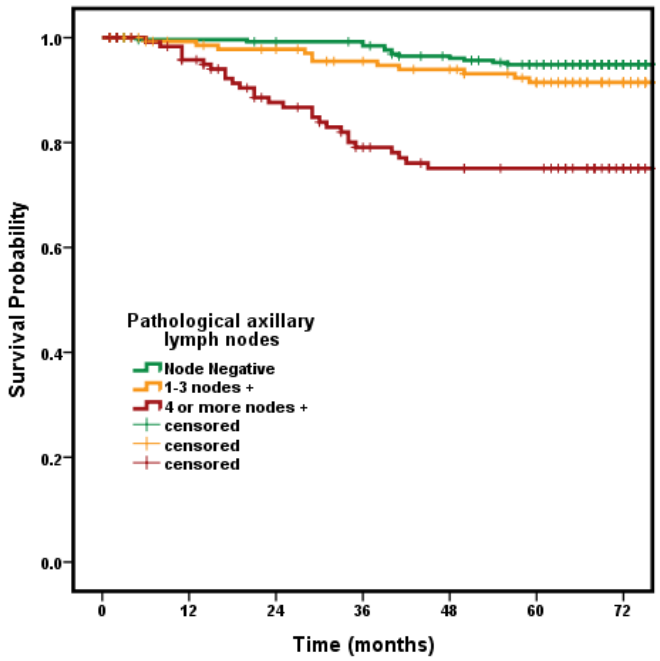
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Node Negative	263	254	250	244	235	221	179
1-3 nodes positive	148	133	128	116	111	105	85
4 or more nodes positive	125	109	90	77	71	65	50

Figure 5.3.15: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Pathological Axillary lymph nodes

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Node Negative	263	257	255	253	241	229	187
1-3 nodes positive	148	134	130	123	119	110	87
4 or more nodes positive	125	111	94	81	74	71	54

5.3.18 Survival according to Pathological Tumor size: 5 yr disease-free survival and overall survival rate of breast cancer patients was found to be significantly associated with size of the primary tumor (Fig. 5.3.16). Patients with tumor size of more than 5 cm had poorer prognosis as compared to patients with smaller size tumors (Table 5.3.18).

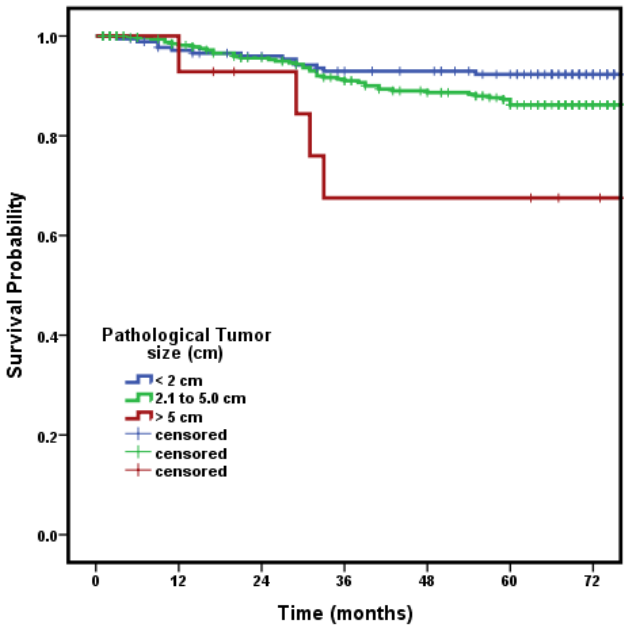
Table 5.3.18: Observed disease-free survival and overall survival rate (%) of early breast cancer according to Pathological Tumor size

Pathological Tumor size (cm)	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
< 2.0 cm	180	97.1	93.0	92.3		100	97.7	93.3	
2.1 to 5.0 cm	342	98.1	91.0	86.2	0.015	97.8	92.1	88.5	0.006
> 5 cm	14	92.9	67.5	67.5		100	70.1	70.1	

**Calculated using Log Rank Test*

Figure 5.3.16: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Pathological Tumor size

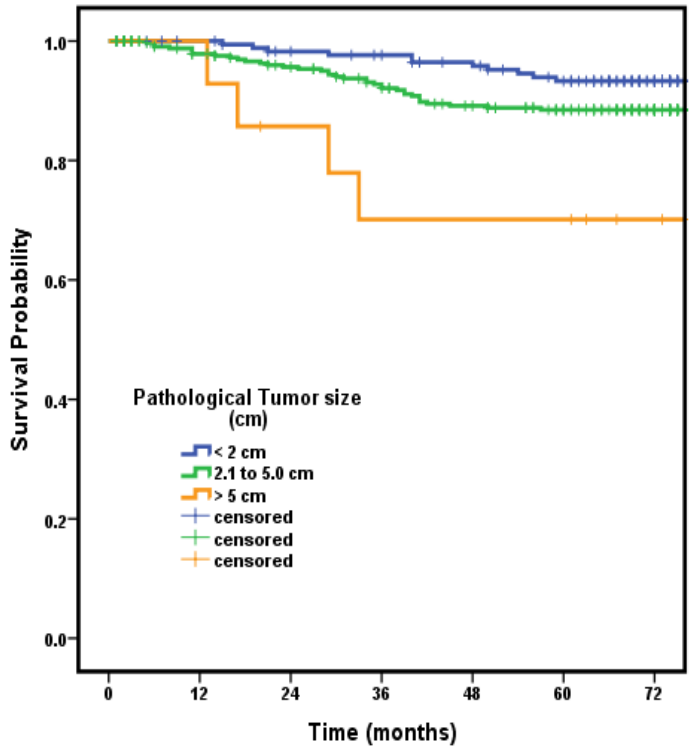
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
< 2cm	180	168	161	152	148	140	108
2.1 to 5 cm	342	314	296	277	261	243	200
> 5 cm	14	14	11	8	8	8	6

Figure 5.3.16: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 536 patients with early breast cancer, according to Pathological Tumor size

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
< 2cm	180	173	166	162	156	147	113
2.1 to 5 cm	342	315	302	286	269	254	209
> 5 cm	14	14	11	9	9	9	6

5.3.19 Multivariate analysis for determining independent prognostic factors for disease-free survival: All the factors which were found to influence disease-free survival in univariate analysis, such education status, tumor grade, hormonal status, histological lymphovascular involvement, extensive intraductal component, pathological axillary lymph nodes and pathological tumor size were considered for further multivariate analysis. In addition, age was added to adjust their effect in multivariate model. Thus, using, multivariate Cox proportional step down reduction method we found, high tumor grade (HR = 5.58, 95% CI = 1.33 – 23.34; p=0.018), hormonal status negative (HR = 1.76, 95% CI = 1.04 – 2.99; p=0.034), presence of lymphovascular involvement (HR = 1.87, 95% CI = 1.08 – 3.23; p=0.024) and more than or equal to four positive pathological lymph nodes (HR = 3.58, 95% CI = 1.89 – 6.79; p<0.001) as independent predictors for poor disease-free survival in early breast cancer patients (Table 5.3.20).

5.3.20 Multivariate analysis for determining independent prognostic factors for overall survival: All the factors which were found to influence overall survival in univariate analysis, such education status, tumor grade, hormonal status, histological lymphovascular involvement, presence of extensive intraductal component, pathological axillary lymph nodes and pathological tumor size were considered for further multivariate analysis. In addition, age was also added to adjust the effect in multivariate model. Thus, using, multivariate Cox proportional step down reduction method we found, literate patients (HR= 0.36, 95% CI=0.18-0.73; p=0.005), hormonal status negative (HR = 1.94, 95% CI = 1.11 – 3.38; p=0.019 and more than or equal to four positive pathological lymph nodes (HR = 6.24, 95% CI = 3.20 – 12.16; p<0.001) as independent predictors for poor overall survival in early breast cancer patients (Table 5.3.19).

Table 5.3.19: Univariate and multivariate analysis of prognostic factors for disease-free survival in patients with early breast cancer

Parameter	No. of cases	Univariate		Multivariate	
		HR (95% CI)	p value	HR (95% CI)	p value
Age at diagnosis (years)					
≤ 50	281	1			
> 50	255	0.61 (0.35-1.03)	0.069	--	0.236
Education status					
Illiterate	61	1			
Literate	475	0.80 (0.36-1.77)	0.594	--	0.347
Tumor grade					
Low grade (I+II)	110	1		1	
High grade (III)	426	7.91 (1.93 – 32.42)	0.004	**5.58 (1.33-23.34)**	**0.018****
Hormonal status					
Positive	309	1		1	
Negative	227	2.22 (1.32– 3.73)	0.003	**1.76 (1.04-2.99)**	**0.034****
EIC					
Negative	468	1			
Positive	68	1.92 (1.02– 3.62)	0.043	--	0.121
LVI					
Negative	419	1		1	
Positive	117	2.87 (1.71- 4.83)	<0.001	**1.87 (1.08-3.23)**	**0.024****
Pathological Axillary lymph					
Node Negative	263	1		1	
1-3 Positive nodes	148	1.78 (0.89-3.57)	0.102	1.80 (0.89-3.63)	0.098
≥4 Positive nodes	125	4.41 (2.40-8.10)	<0.001	**3.58 (1.89-6.79)**	**<0.001****
Pathological Tumor size					
< 2cm	180	1		--	0.528
2.1 to 5.0 cm	342	1.76 (0.94-3.29)	0.073		0.586
> 5.1 cm	14	4.62 (1.50-14.18)	0.007		0.455

§ Abbreviations: HR, hazard ratio; CI, confidence interval

** Significant (p value <0.05)

Table 5.3.20: Univariate and multivariate analysis of prognostic factors for overall survival in patients with early breast cancer

Parameter	No. of cases	Univariate		Multivariate	
		HR (95% CI)	p value	HR (95% CI)	p value
Age at diagnosis (years)					
≤ 50	281	1	0.770	--	0.615
> 50	255	1.08 (0.62-1.87)			
Education status					
Illiterate	61	1		1	
Literate	475	0.43 (0.21-0.87)	0.019	**0.36 (0.18-0.73)**	**0.005****
Tumor grade					
Low grade (I+II)	110	1			
High grade (III)	426	2.49 (0.99 – 6.28)	0.052	--	0.167
Hormonal status					
Positive	309	1		1	
Negative	227	2.20 (1.19– 4.10)	0.012	**1.94 (1.11-3.38)**	**0.019****
EIC					
Negative	468	1			
Positive	68	2.04 (1.05– 3.99)	0.035	--	0.192
LVI					
Negative	419	1			
Positive	117	2.15 (1.21-3.81)	0.009	--	0.270
Pathological Axillary lymph					
Node Negative	263	1		1	
1-3 Positive nodes	148	1.69 (0.75-3.78)	0.198	1.78 (0.79-3.98)	0.160
≥4 Positive nodes	125	5.78 (2.98-11.23)	<0.001	**6.24 (3.20-12.16)**	**<0.001****
Pathological T stage					
< 2cm	180	1		--	0.343
2.1 to 5.0 cm	342	1.83 (0.93-3.60)	0.079		0.339
> 5.1 cm	14	5.59 (1.77-17.56)	0.003		0.470

§ Abbreviations: HR, hazard ratio; CI, confidence interval

**Significant (p value<0.05)

Locally Advanced Breast Cancer (LABC)

5.4 Survival Analysis of Locally Advanced Breast Cancer (n= 597)

5.4.1 Disease-Free Survival of LABC: The 5-year actuarial disease free survival for the LABC group is 65% (Table 5.4.1). At a median follow-up of 62 months, 188 (33.9%) patients had relapsed. 27 patients (4.5%) had local recurrence; 25 patients (4.2%) had recurrence in regional lymph nodes and 137 (22.9%) in distant organs. Bone was the commonest site of first metastatic recurrence in 42 patients followed by liver-39, lung-38, brain-14 and contralateral breast-two. At last follow-up, 388 (70%) patients were alive and disease-free and 166 (30%) had died; 152 (27.4%) had died due to disease progression and fourteen deaths were unrelated to breast cancer.

Table 5.4.1: Overall survival and Disease-free survival of Locally Advanced Breast Cancer by Life table method

N=597	Survival in percentage (%)				
	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 Yrs
Disease-free Survival	93	79	72	67	65
Overall survival	97	85	76	72	69

5.4.2 Overall Survival of LABC: The median follow-up period was 65 months (range, 2 to 84 months). At the end of follow-up (31st Dec 2014) out of the 597 patients, 166 (27.8%) patients had expired, and 431 (72.2%) were censored (Table 5.4.2). The 5-year overall survival of the LABC cohort calculated by using actuarial method was found to be 69% (Table 5.4.1).

Table 5.4.2: Details of the locally advanced breast cancer cases

Details	Number (%)
Alive at closing date	**329 (55.2)**
Dead	**166 (27.8)**
Lost to follow up	**102 (17.0)**
• < 1year • 1-3 years • 3-5 years	26 37 39

5.4.3 Survival according to Age at Diagnosis: Patient's age at diagnosis were categorized into two categories less than or equal to 50 and greater than 50 and its effect on overall and disease-free survival was analyzed using Kaplan-Meier curves and the log-rank test. The five year disease-free survival rate (%) for the age groups ≤ 50 and >50 yrs was 64.2% and 67.3% respectively. This difference was not found to be statistically significant (p=0.496) (Table 5.4.3) (Fig 5.4.1). It was observed that patients with age less than or equal to 50 yrs had a 5yr overall survival of 70.3% and those of age 50 yrs and above had a 5yr overall survival of 67.7%, however this difference was not statistically significant (p=0.649) (Table.5.4.3) (Fig.5.4.1).

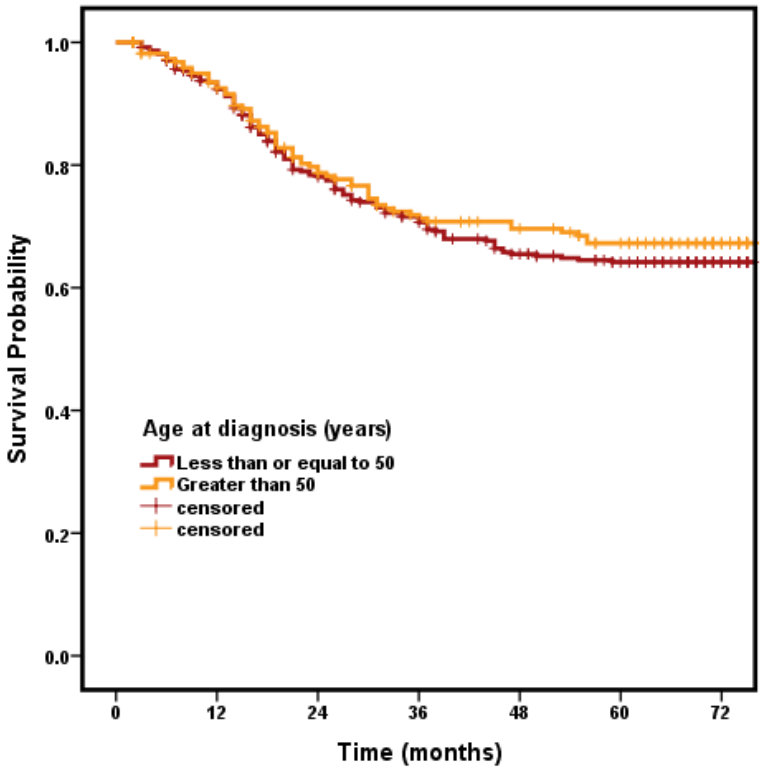
Table 5.4.3: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to age at diagnosis

Age at Diagnosis (Years)	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
≤50	372	92.3	70.7	64.2	0.496	96.2	76.2	70.3	0.649
>50	225	92.5	71.3	67.3		97.6	74.8	67.7	

**Calculated using Log Rank Test*

Figure 5.4.1: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to age at diagnosis

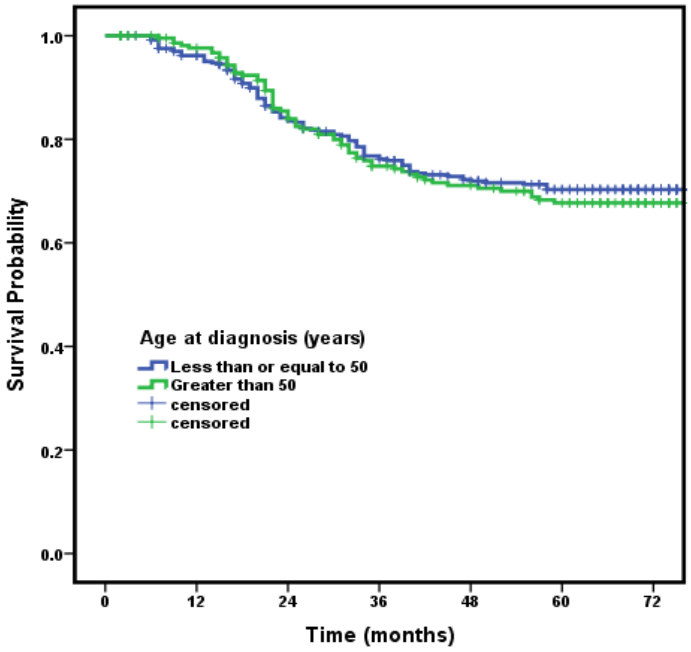
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
≤ 50	372	336	269	238	209	193	156
> 50	225	196	156	132	122	111	80

Figure 5.4.1: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to age at diagnosis

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
≤ 50	372	346	289	259	233	211	168
> 50	225	206	172	143	131	118	82

5.4.4 Survival according to Residence: A 5 yr Disease-free survival rate for Mumbai residents and Non-Mumbai residents was found to be 70.1% and 64.1% respectively (Table 5.4.3), but this difference was not statistically significant (p=0.441) (Fig.5.4.2). A 5 yr overall survival rate for Mumbai residents and Non-Mumbai residents was found to be 71.1% and 68.9% respectively (Table 5.4.3), but this difference was not statistically significant (p=0.833) (Fig.5.4.2).

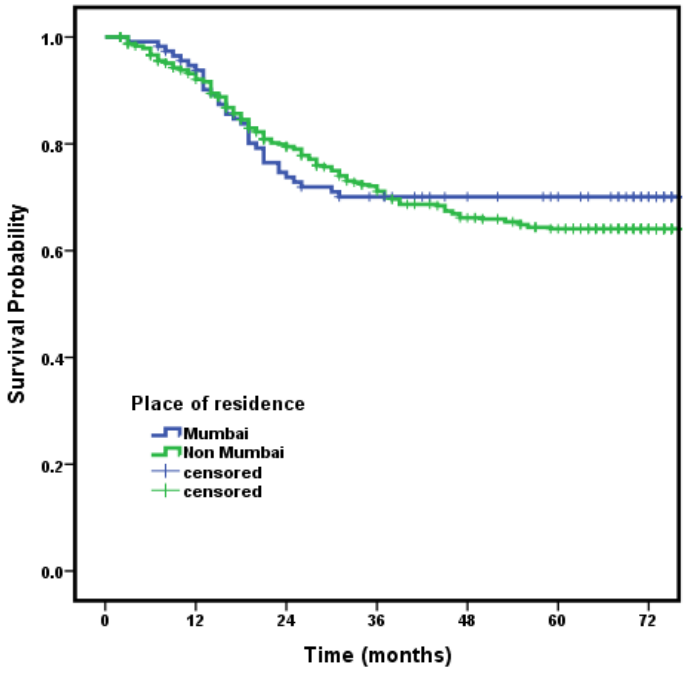
Table 5.4.3: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to residence

Residence	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Mumbai	115	93.8	70.1	70.1	0.441	95.6	74.1	71.1	0.833
Non-Mumbai	482	92.1	71.1	64.1		97.0	76.1	68.9	

**Calculated using Log Rank Test*

Figure 5.4.2: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to residence

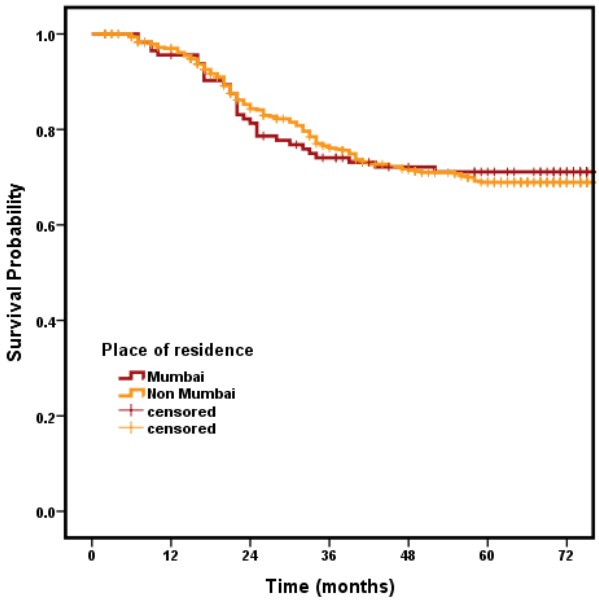
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Mumbai	115	105	82	74	67	63	51
Non-Mumbai	482	427	343	296	264	241	185

Figure 5.4.2: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to residence

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Mumbai	115	108	92	80	72	67	54
Non-Mumbai	482	444	369	322	292	262	196

5.4.5 Survival according to Education: Patients were categorized as per their educational status at the time of registration. 5 year disease-free survival rate of literate and illiterate was found to be 67.7% and 57.9 % respectively. This difference was statistically significant (p=0.014) (Table 5.4.4) (Fig.5.4.3). 5 year overall survival rate of literate and illiterate was found to be 72.6% and 58.5 % respectively. This difference was statistically significant (p=0.001) (Table 5.4.5) (Fig.5.4.3).

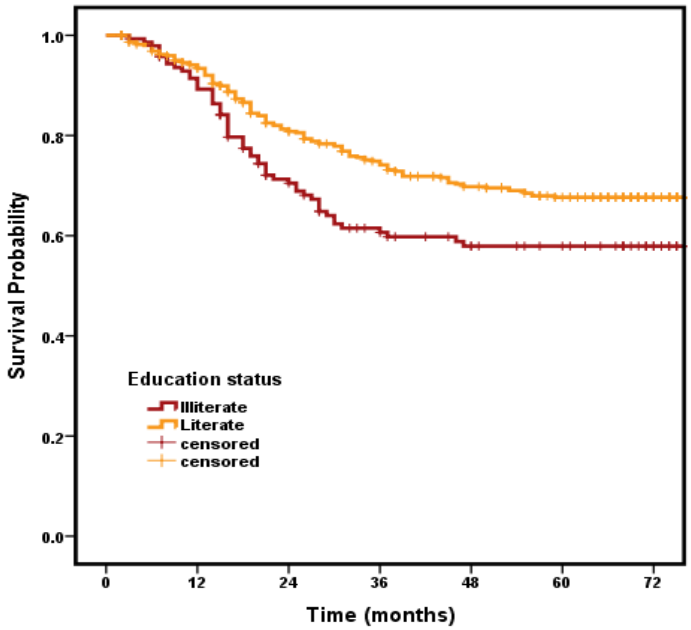
Table 5.4.5: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to education status

Education status	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Literate	450	93.4	74.1	67.7	0.014	96.6	78.4	72.6	0.001
Illiterate	147	89.2	60.6	57.9		97.2	66.6	58.5	

**Calculated using Log Rank Test*

Figure 5.4.3: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to education status

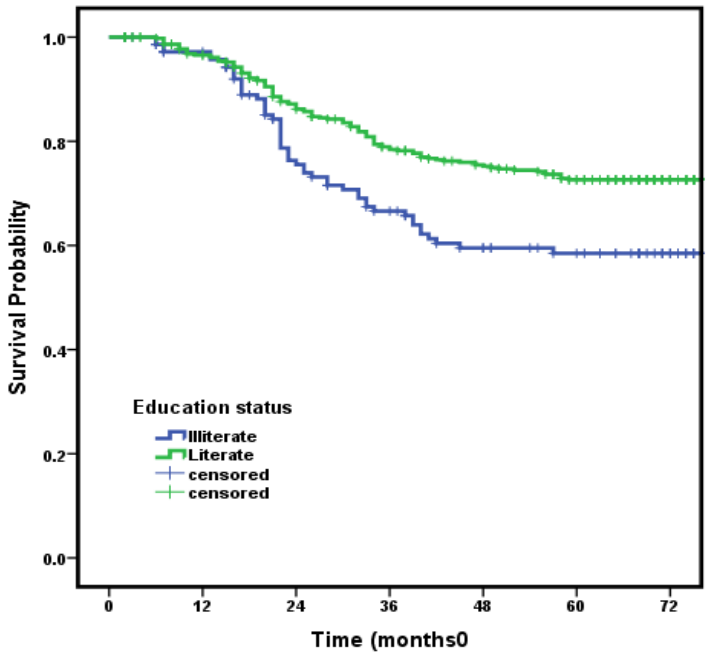
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Literate	450	406	335	299	269	248	195
Illiterate	147	126	90	71	62	56	41

Figure 5.4.3: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to education status

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Literate	450	419	365	323	299	272	209
Illiterate	147	133	96	79	65	57	41

5.4.6 Survival according to Religion: Patients were categorized as per their religion at the time of registration and their effect on survival was analyzed. There was no significant (p= 0.210, p=0.141) difference in disease-free and overall survival rate between Hindu patients and Non-Hindu patients (Table 5.4.6) (Fig. 5.4.4).

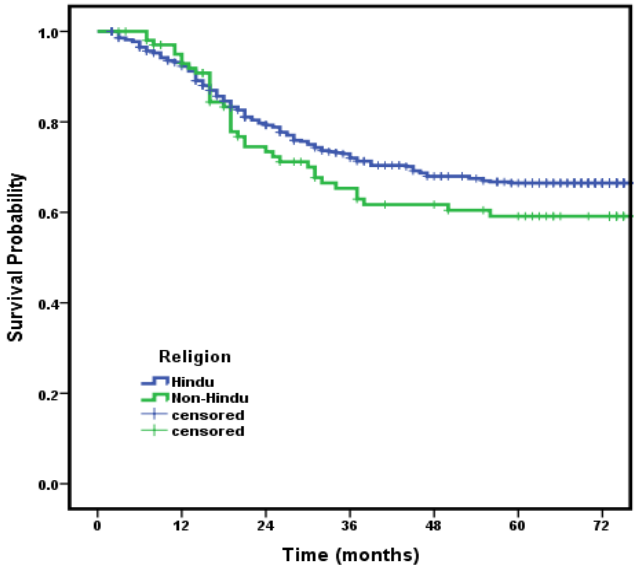
Table 5.4.6: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to religion

Religion	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Hindu	494	92.3	72.0	66.5	0.210	96.2	77.2	70.6	0.141
Non-Hindu	103	92.9	65.3	59.1		99.0	67.9	62.9	

**Calculated using Log Rank Test*

Figure 5.4.4: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to religion

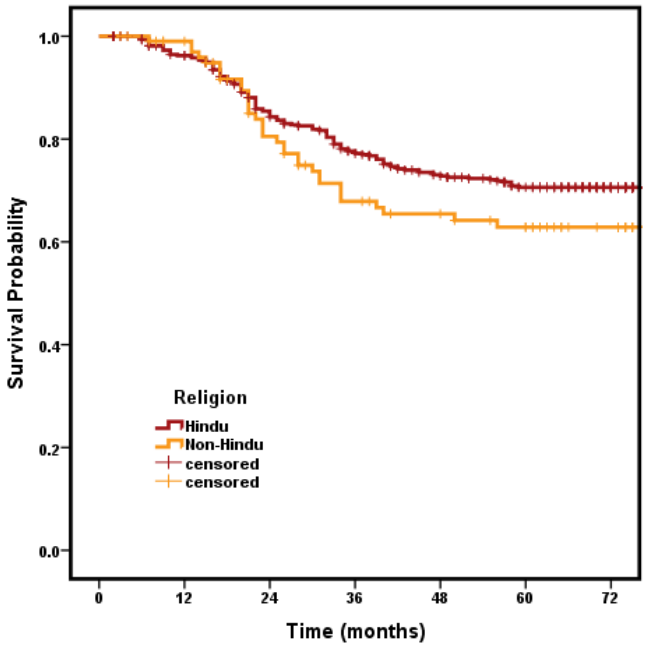
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Hindu	494	440	358	315	281	259	200
Non-Hindu	103	92	67	55	50	45	36

Figure 5.4.4: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to religion

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Hindu	494	456	389	344	311	281	213
Non-Hindu	103	96	72	58	53	48	37

5.4.7 Survival according to Marital status: Patients were categorized as per their marital status at the time of registration. No significant difference was seen in 5 yr disease-free survival and overall survival of patients based on marital status (Table 5.4.7) (Fig.5.4.5).

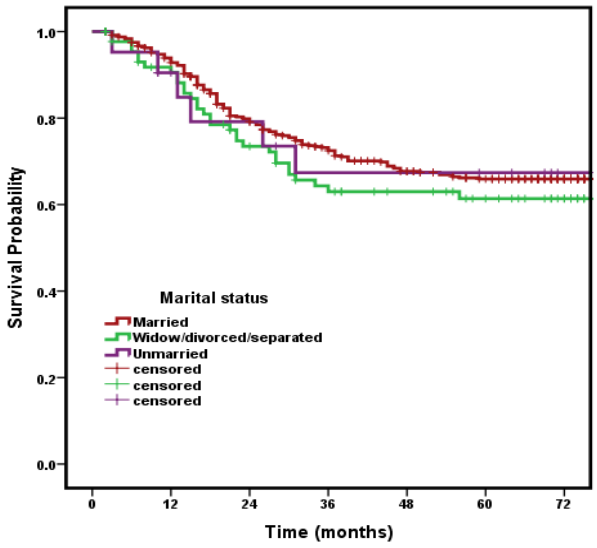
Table 5.4.7: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to marital status

Marital status	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Single (Unmarried)	21	90.5	67.4	67.4		95.2	73.7	73.7	
Married	486	92.8	72.5	65.9	0.578	97.0	76.7	70.5	0.289
Widow/divorced/ separated	90	90.6	63.0	61.4		95.3	70.4	61.5	

**Calculated using Log Rank Test*

Figure 5.4.5: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to marital status

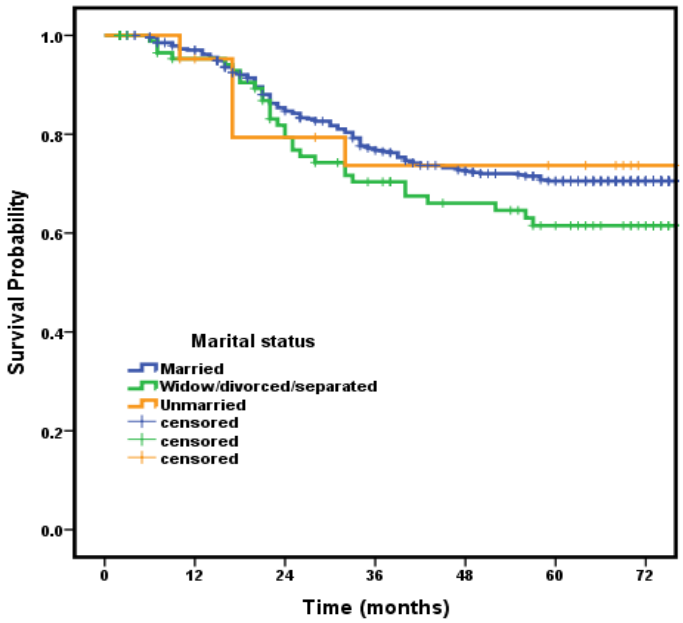
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Married	486	439	353	311	278	258	203
Widow/divorced/seperated	90	76	58	48	42	36	27
Unmarried	21	17	14	11	11	10	6

Figure 5.4.5: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to marital status

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Married	486	454	381	336	306	279	215
Widow/divorced/seperated	90	79	65	53	45	38	28
Unmarried	21	19	15	13	13	12	7

5.4.8 Survival according to Menopausal status: A 5 yr disease-free survival and overall survival rate for premenopausal and postmenopausal patients was found to be 65.5% and 65% and 72.5% and 66%, respectively (Table 5.4.8), but this difference was not statistically significant (Fig.5.4.6).

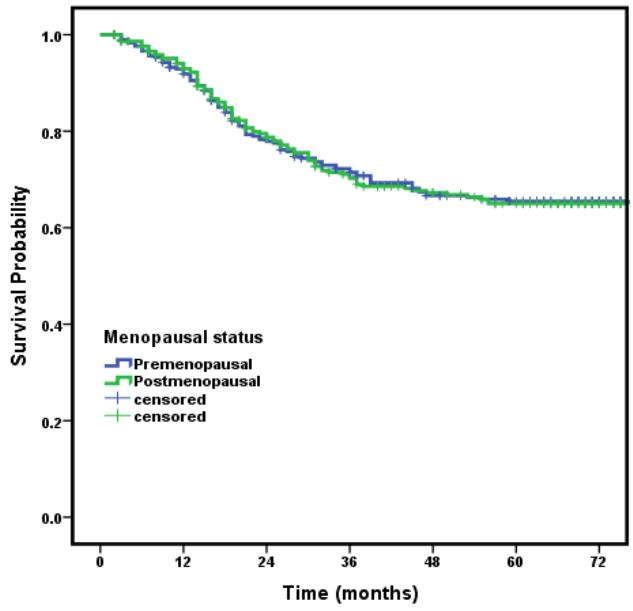
Table 5.4.8: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to Menopausal status

Menopausal Status	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Pre-menopausal	297	91.9	71.5	65.5	0.964	96.3	77.8	72.5	0.111
Post-menopausal	300	93.0	70.2	65.0		97.2	73.4	66.0	

**Calculated using Log Rank Test*

Figure 5.4.6: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to menopausal status

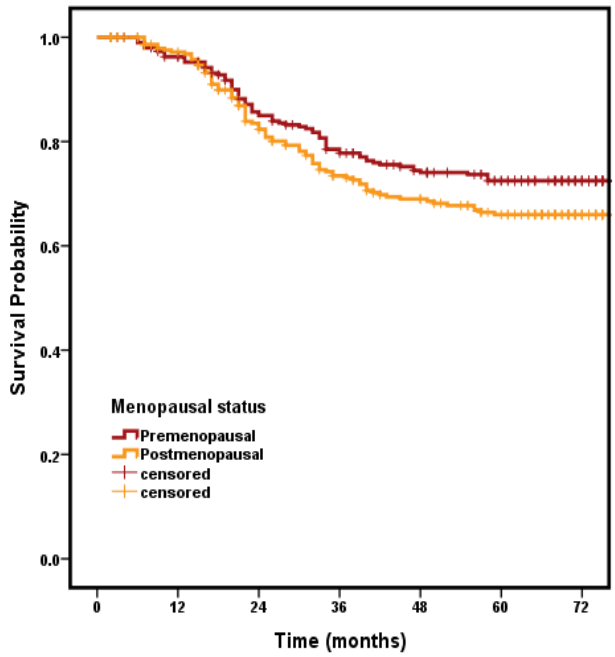
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Premenopausal	297	271	222	199	176	164	136
Postmenopausal	300	261	203	171	155	140	100

Figure 5.4.6: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to menopausal status

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Premenopausal	297	281	241	217	197	179	145
Postmenopausal	300	271	220	185	167	150	105

5.4.9 Survival according to Parity: Patient parity status was taken at the time of registration. Parity was classified as Nulliparous and Multiparous. A 5 yr disease-free survival rate for Nulliparous and Multiparous patients was found to be 57.2% and 66.2% respectively (Table 5.4.9), but this difference was not statistically significant (p=0.566) (Fig.5.4.7). A 5 yr overall survival rate for Nulliparous and Multiparous patients was found to be 59.5% and 70.3% respectively (Table 5.4.9), but this difference was not statistically significant (p=0.356) (Fig.5.4.7).

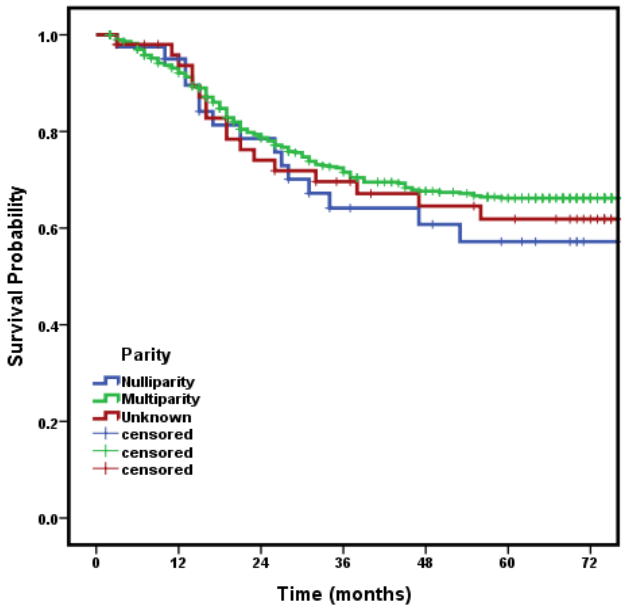
Table 5.4.9: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to parity

Parity	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Nulliparous	40	95.0	64.1	57.2		97.5	62.8	59.5	
Multiparous	507	92.1	71.6	66.2	0.566	96.3	77.2	70.3	0.356
Unknown	50	93.6	69.6	61.9		100.0	71.0	68.5	

**Calculated using Log Rank Test*

Figure 5.4.7: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to parity

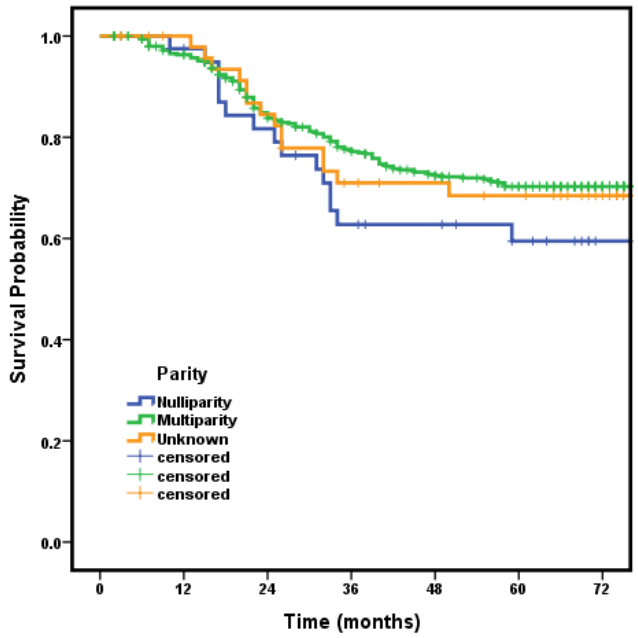
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Nulliparity	40	36	28	20	18	15	9
Multiparity	507	452	363	321	288	266	209
Unknown	50	44	34	29	25	23	18

Figure 5.4.7: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to parity

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Nulliparity	40	38	31	23	21	17	10
Multiparity	507	468	392	349	315	286	221
Unknown	50	46	38	30	28	26	19

5.4.10 Survival according to Family history of cancer: Patients were categorized as per presence of family history of cancer. No significant difference was seen in 5 yr disease-free survival and overall survival of patients based on family history of cancer (Table 5.4.10) (Fig.5.4.8).

Table 5.4.10: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to family history of cancer

Family history of cancer	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Yes	27	92.3	75.2	70.8	0.550	96.2	76.2	71.4	0.922
No	570	92.4	70.7	65.0		96.7	75.7	69.3	

**Calculated using Log Rank Test*

Figure 5.4.8: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to family history of cancer

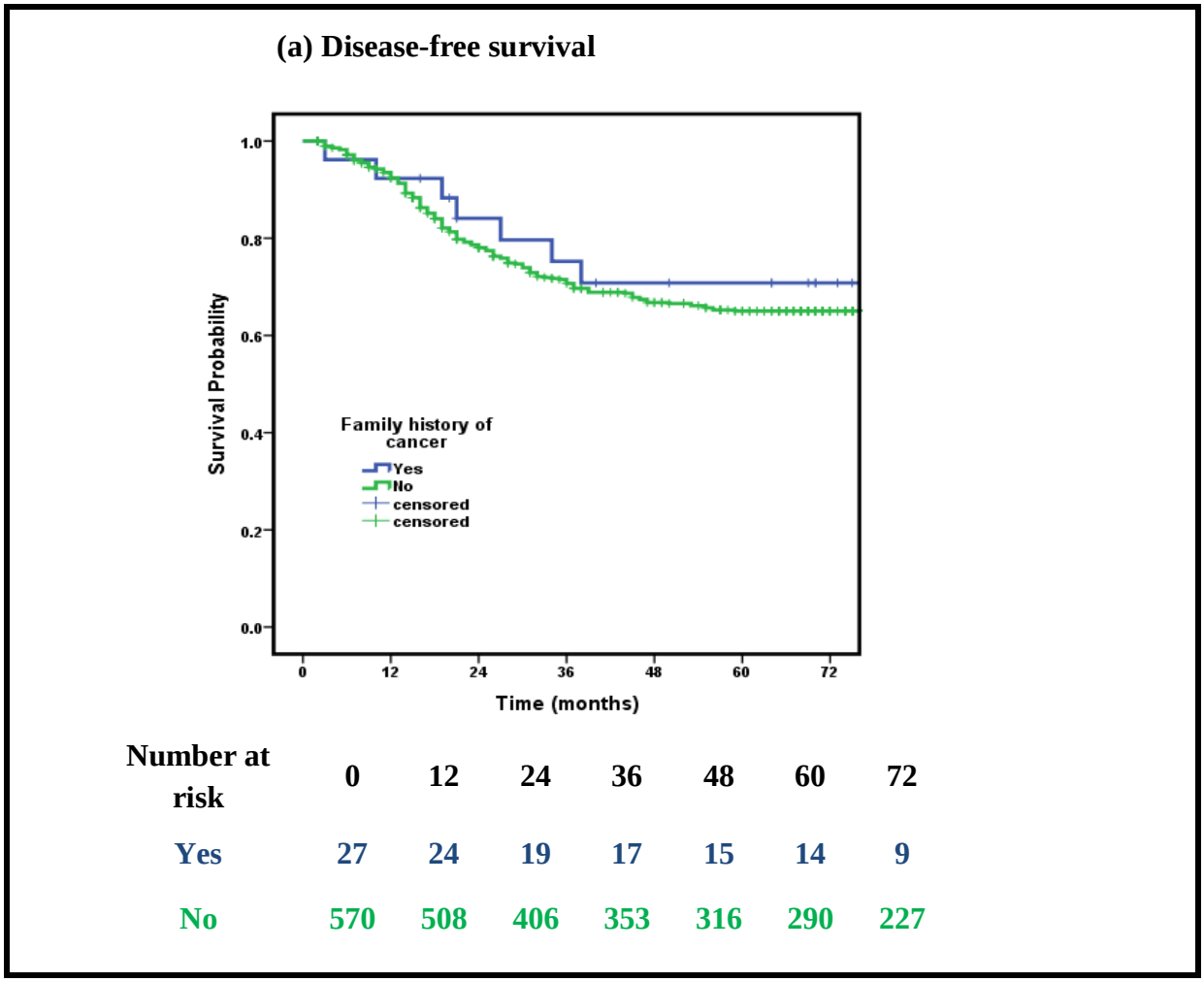
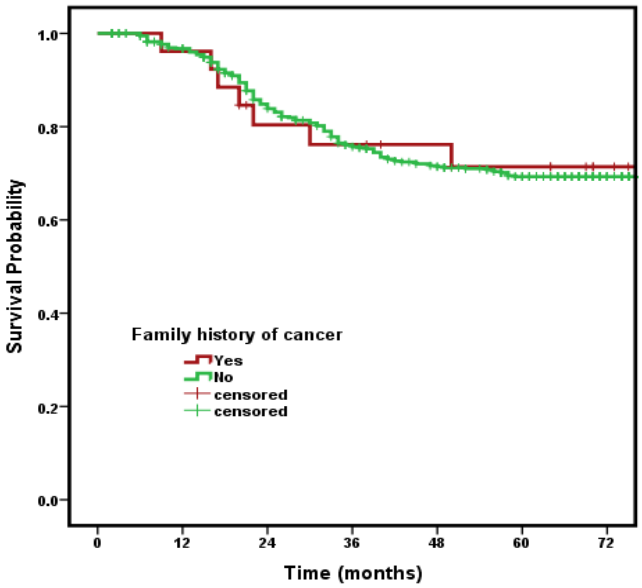


Figure 5.4.8: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to family history of cancer

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Yes	27	25	19	18	16	14	9
No	570	527	442	384	348	315	241

5.4.11 Survival according to Presence of comorbidity: The 5yr disease-free survival of patient with presence of comorbidity was 63.2% as compared to 65.7% in patients without any comorbidity (Fig. 5.4.9), but this difference did not achieve statistical significance (p= 0.912) (Table 5.4.11). Locally advanced breast cancer patients having a concomitant comorbidities (Hypertension, Diabetes mellitus, Heart Disease, Asthma and HIV) were found to have 5yr overall survival of 65.1% as compared to 70.4% in patients without any comorbidity (Fig. 5.4.9), but this difference did not achieve statistical significance (p= 0.291) (Table 5.4.11).

Table 5.4.11: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to presence of comorbidity

Comorbidity	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Present	116	95.5	70.8	63.2	0.912	98.2	71.2	65.1	0.291
Absent	481	91.6	70.9	65.7		96.3	76.8	70.4	

**Calculated using Log Rank Test*

Figure 5.4.9: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to presence of comorbidity

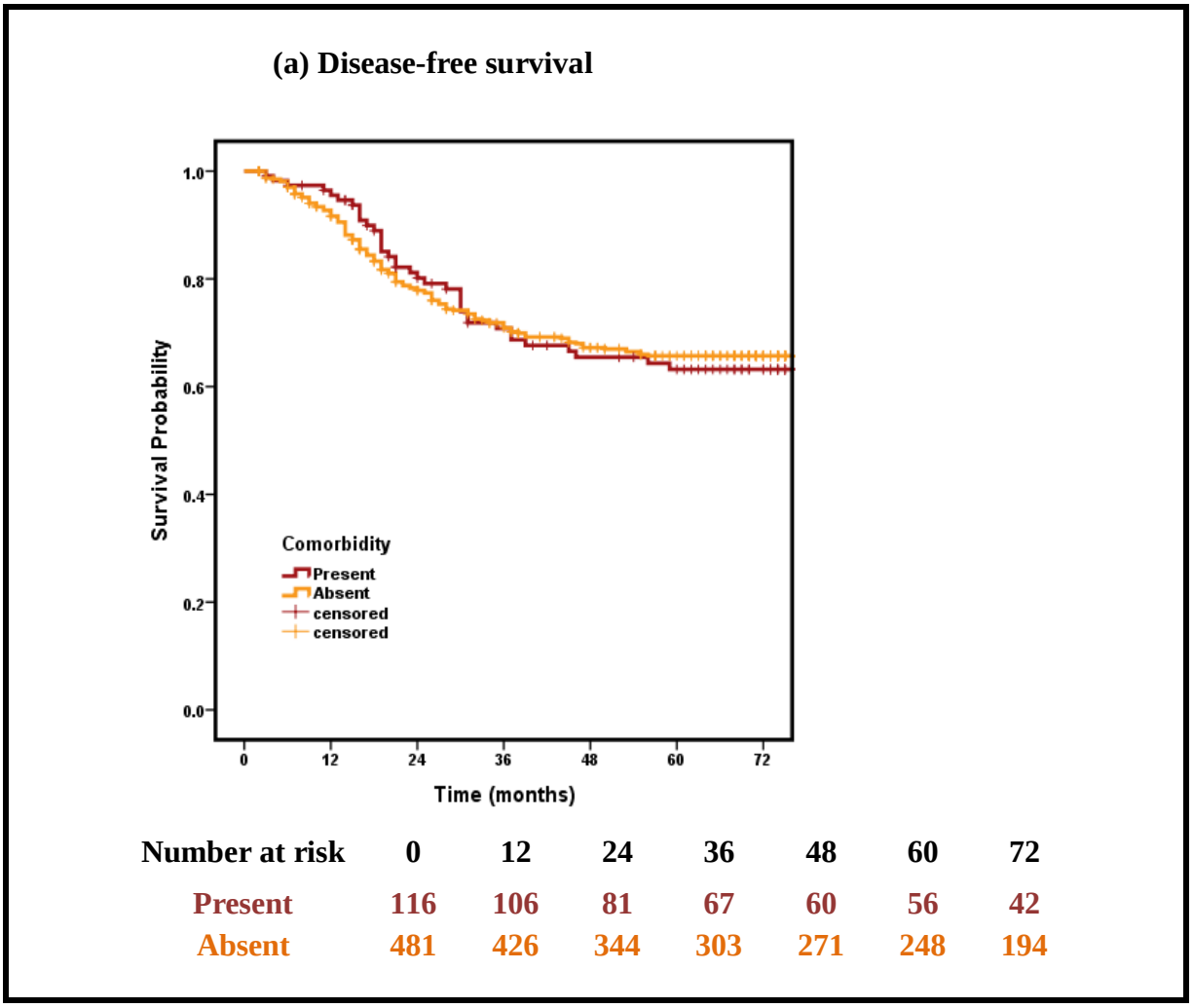
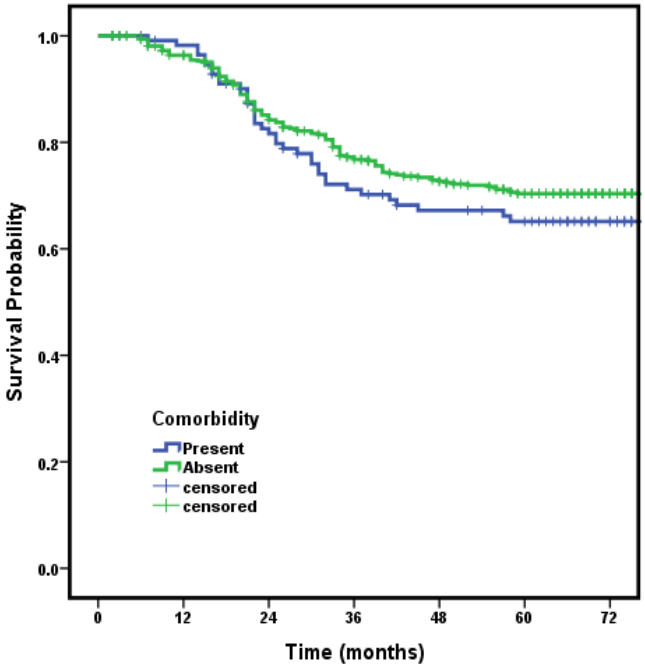


Figure 5.4.9: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to presence of comorbidity

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Present	116	109	88	74	67	63	46
Absent	481	443	373	328	297	266	204

5.4.12 Survival according to Quadrant location: A 5 yr Disease-free survival rate for patient with Outer and Inner+Central quadrant location was found to be 68.7% and 63.2% respectively (Table 5.4.12). However, this difference was not statistically significant (Fig. 5.4.10). A 5 yr overall survival rate for patient with Outer and Inner+Central quadrant location was found to be 71.1% and 68.3% respectively (Table 5.4.12). However, this difference was not statistically significant (Fig. 5.4.10).

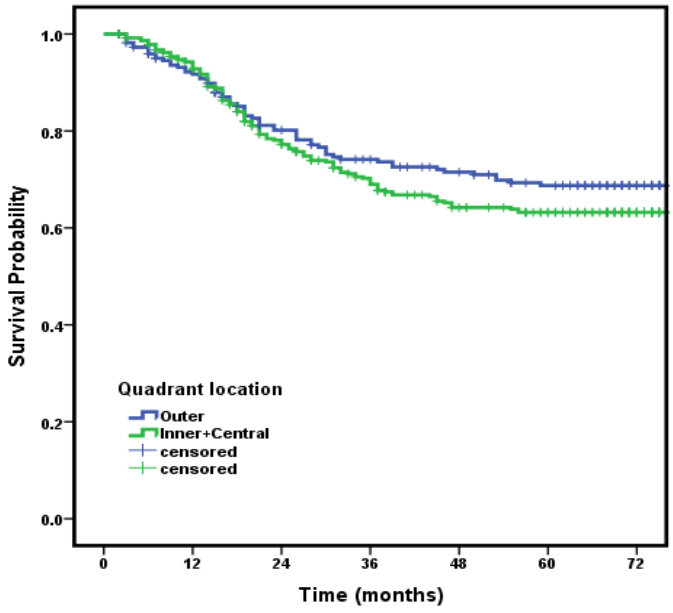
Table 5.4.12: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to quadrant location

Quadrant location	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Outer	225	91.7	74.1	68.7	0.241	96.3	75.8	71.1	0.547
Inner + Central	372	92.8	69.0	63.2		97.0	75.6	68.3	

**Calculated using Log Rank Test*

Figure 5.4.10: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to quadrant location

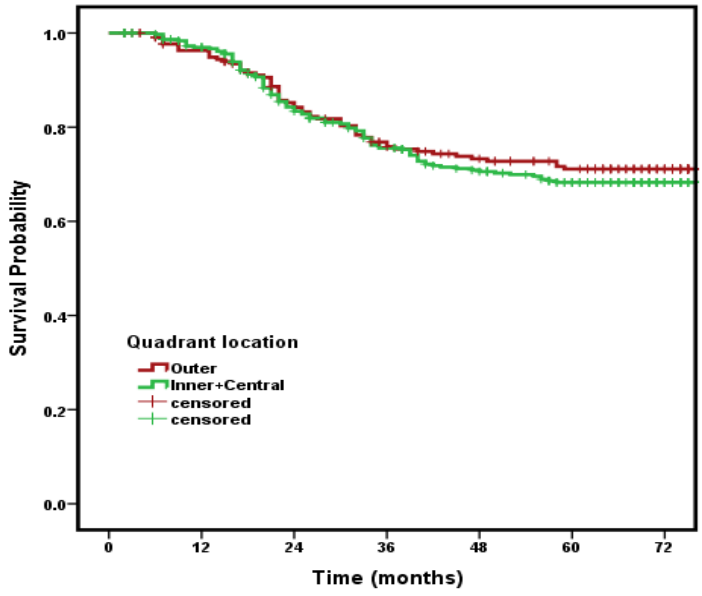
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Outer	225	197	161	144	134	121	92
Inner + Central	372	335	264	226	197	183	144

Figure 5.4.10: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to quadrant location

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Outer	225	205	174	153	141	129	98
Inner + Central	372	347	287	249	223	200	152

5.4.13 Survival according to Tumor grade: Patients having high grade (III) tumor were found to have the worst 5yr disease-free survival of 62.2%, whereas patients with low grade tumors had 82.8 % 5yr disease-free survival rate (Table 5.4.12) (Fig. 5.4.11). Patients having high grade (III) tumor were found to have the worst 5yr overall survival of 66.7%, whereas patients with low grade tumors had 84.0 % 5yr overall survival (Table 5.4.12) (Fig. 5.4.11.

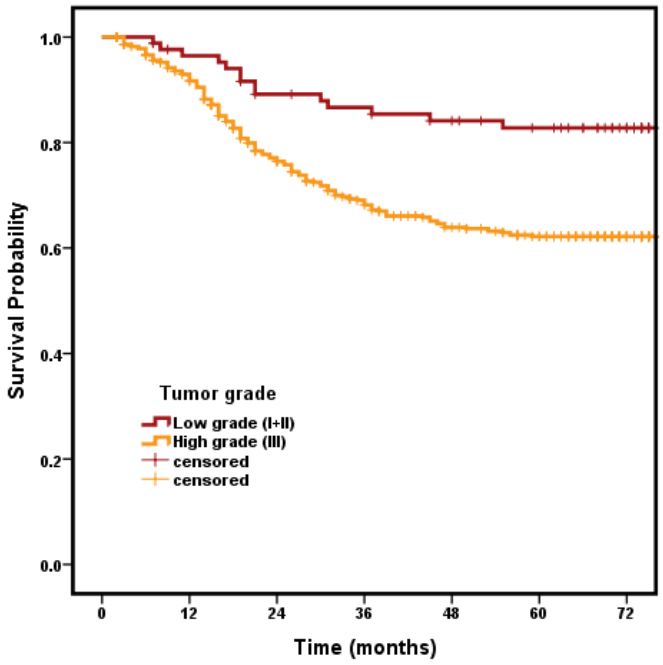
Table 5.4.12: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to tumor grade

Tumor grade	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Low grade (I+II)	86	96.4	86.7	82.8	0.001	98.8	87.9	84.0	0.002
High grade (III)	511	91.7	68.2	62.2		96.3	73.5	66.7	

**Calculated using Log Rank Test*

Figure 5.4.11: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to tumor grade

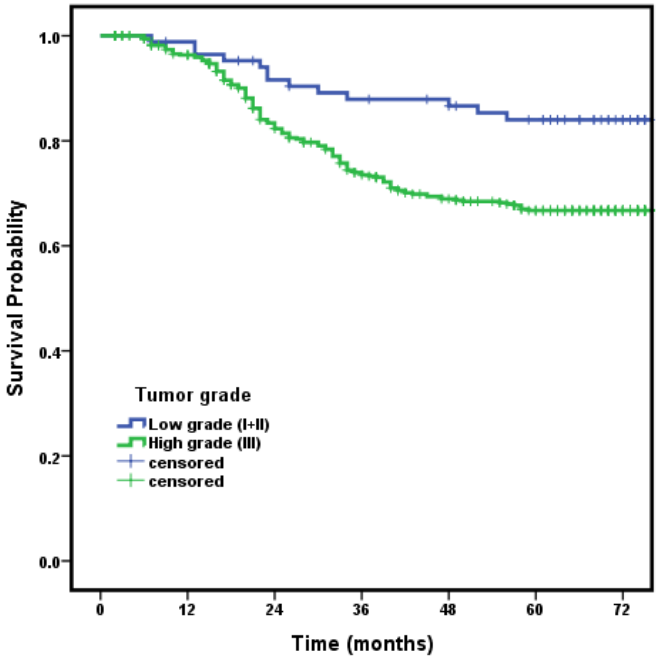
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Low grade (I+II)	86	80	72	69	65	60	49
High grade (III)	511	452	353	301	266	244	187

Figure 5.4.11: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to tumor grade

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Low grade (I+II)	86	83	75	71	69	63	49
High grade (III)	511	469	386	331	295	266	201

5.4.14 Survival according to Hormonal status: The survival probabilities by hormonal status are presented in Table 5.4.14, highlighting significant survival differences between the hormonal receptor positive and hormonal receptor negative (p value <0.05) (Fig. 5.3.12).

Table 5.4.14: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to hormonal status

Hormonal status	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
HR Positive	283	94.5	76.7	68.1	0.043	98.5	83.6	74.7	0.002
HR Negative	310	90.4	65.6	62.8		95.0	68.4	64.4	

**Calculated using Log Rank Test*

Figure 5.4.12: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to hormonal status

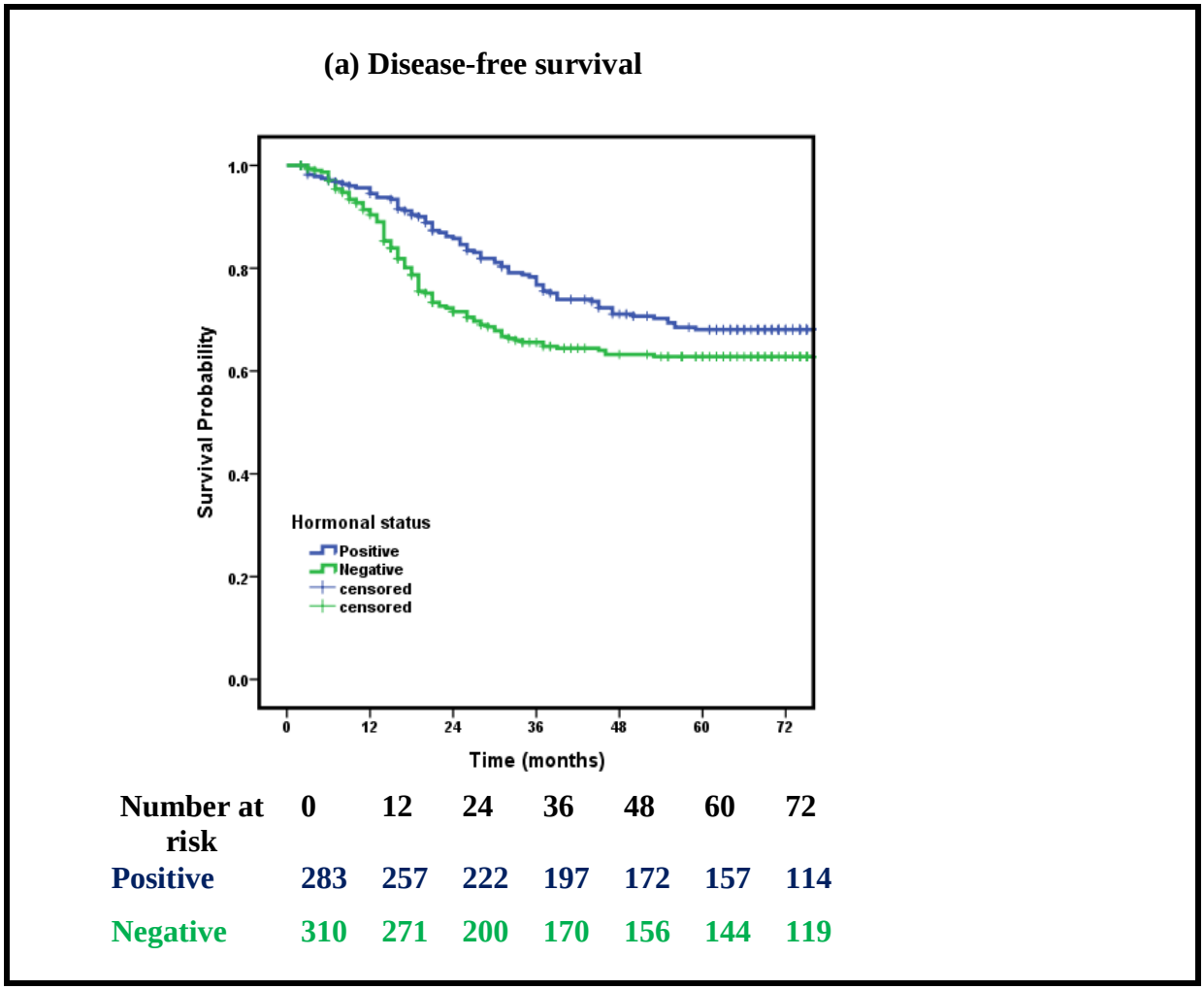
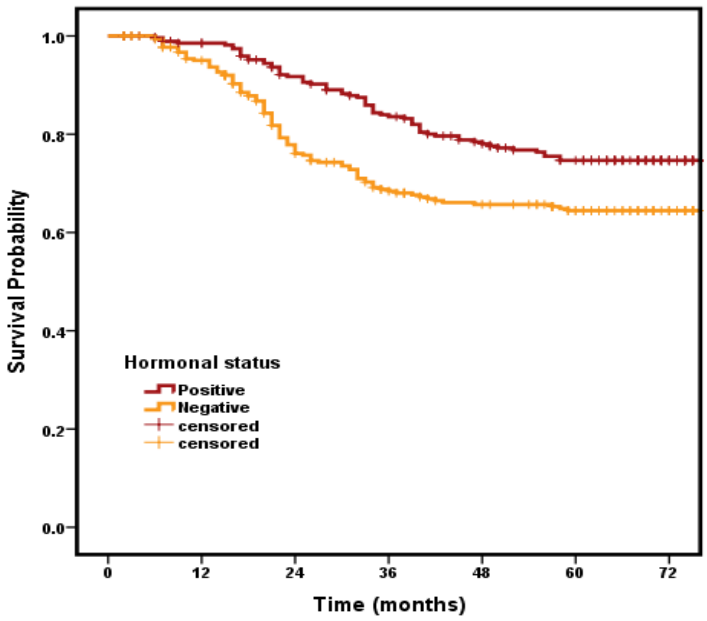


Figure 5.4.12: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to hormonal status

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Positive	283	265	239	215	194	175	123
Negative	310	283	218	184	167	151	124

5.4.15 Survival according to Extensive Intraductal Component (EIC): Presence of EIC on histology was found to significantly affect both overall and disease-free survival adversely. Patients with EIC had 5 yr disease-free survival of only 45.2% as compared to 68.1% in those patients without EIC (Table 5.4.15) (Fig. 5.4.13). Patients with EIC had 5 yr overall survival of only 46.1% as compared to 72.8% in those patients without EIC (Table 5.4.15) (Fig. 5.4.13).

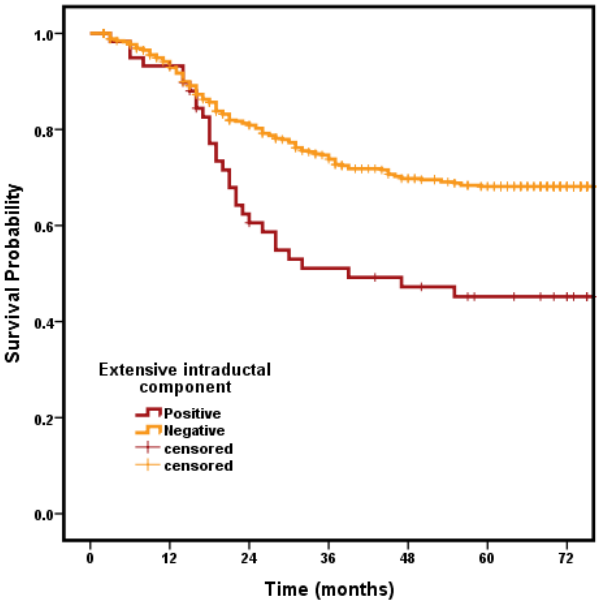
Table 5.4.15: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to Extensive Intraductal Component

Extensive Intraductal Component	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Negative	480	92.9	73.8	68.1	<0.001	97.2	78.6	72.8	<0.001
Positive	61	93.2	51.1	45.2		94.9	56.1	46.1	

**Calculated using Log Rank Test*

Figure 5.4.13: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to extensive intraductal component

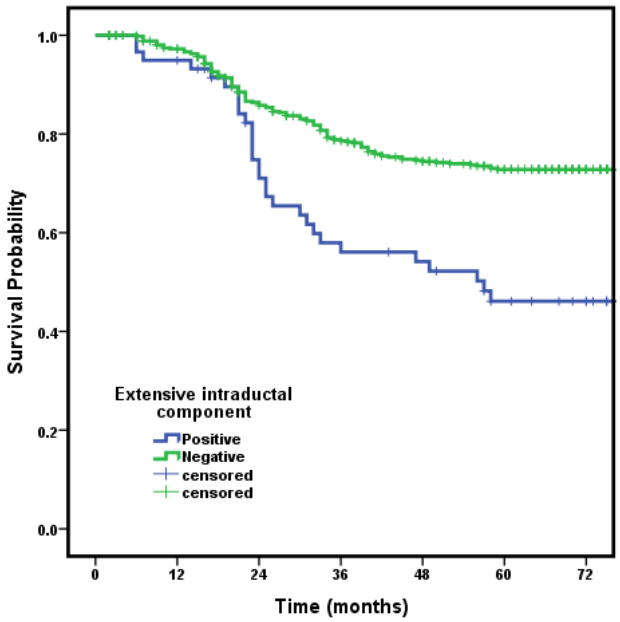
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Positive	61	55	34	27	24	20	17
Negative	525	471	387	341	305	282	218

Figure 5.4.13: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to extensive intraductal component

(b) Overall Survival



Number at risk	0	12	24	36	48	60	72
Positive	61	56	40	31	28	21	17
Negative	525	488	416	368	334	306	232

5.4.16 Survival according to Lymphovascular invasion (LVI): Presence of LVI on histology was found to significantly affect both overall and disease-free survival adversely. Patients with LVI had 5 yr disease-free survival of only 42.2% as compared to 73% in those patients without LVI (Table 5.4.16) (Fig. 5.4.14). Patients with LVI had 5 yr overall survival of only 49.2% as compared to 76.4% in those patients without LVI (Table 5.4.16) (Fig. 5.4.14).

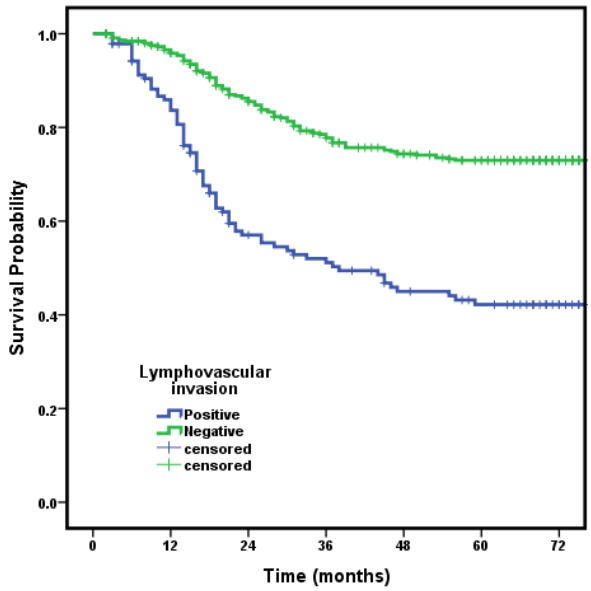
Table 5.4.16: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to lymphovascular invasion

Lymphovascular Invasion	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 Yr	3 Yr	5 Yr		1 Yr	3 Yr	5 Yr	
Negative	447	96.5	77.8	73.0	<0.001	98.4	81.6	76.4	<0.001
Positive	139	83.6	51.1	42.2		92.5	58.9	49.2	

**Calculated using Log Rank Test*

Figure 5.4.14: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to Lymphovascular invasion

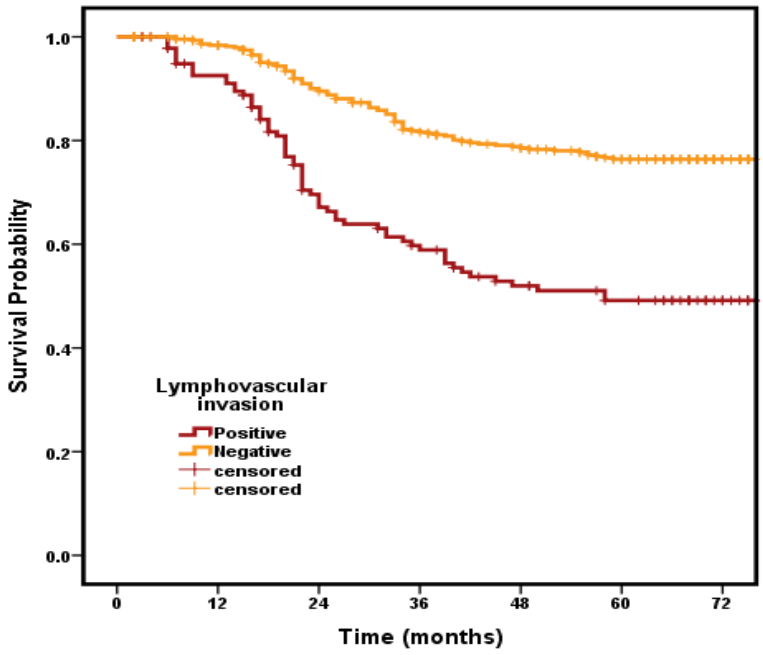
(a) Disease-free survival



Number at risk	0	12	24	36	48	60	72
Positive	139	114	69	61	50	44	31
Negative	447	412	352	307	279	258	204

Figure 5.4.14: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to Lymphovascular invasion

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Positive	139	122	85	71	58	51	35
Negative	447	422	371	328	304	276	214

5.4.17 Survival according to Pathological Axillary lymph nodes: 5yr Disease-free survival for node negative, 1-3 nodes and more than or equal to 4 nodes positive patients was found to be 80.1% , 73.5% and 45.9% respectively (Table 5.4.17). 5yr overall survival for node negative, 1-3 nodes and more than or equal to four nodes positive patients was found to be 85.9% , 72.3% and 53% respectively (Table 5.4.17). Presence of positive nodes on histopathology was found to significantly affect both disease-free and overall survival adversely ($p<0.001$) (Fig. 5.4.15).

Table 5.4.17: Observed disease-free and overall survival rate (%) of locally advanced breast cancer according to Pathological Axillary lymph nodes

Pathological Axillary lymph nodes	Total Number	Disease Free Survival (%)			*p value**	Overall Survival (%)			*p value**
		1 yr	3 yrs	5 yrs		1 yr	3 yrs	5 yrs	
Node Negative	204	98.0	83.5	80.1	<0.001	99.0	88.8	85.9	<0.001
1-3 Positive nodes	170	93.9	78.7	73.5		97.6	80.8	72.3	
≥4 Positive nodes	212	87.5	55.3	45.9		94.7	60.8	53.0	

**Calculated using Log Rank Test*

Figure 5.4.15: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to pathological axillary lymph nodes

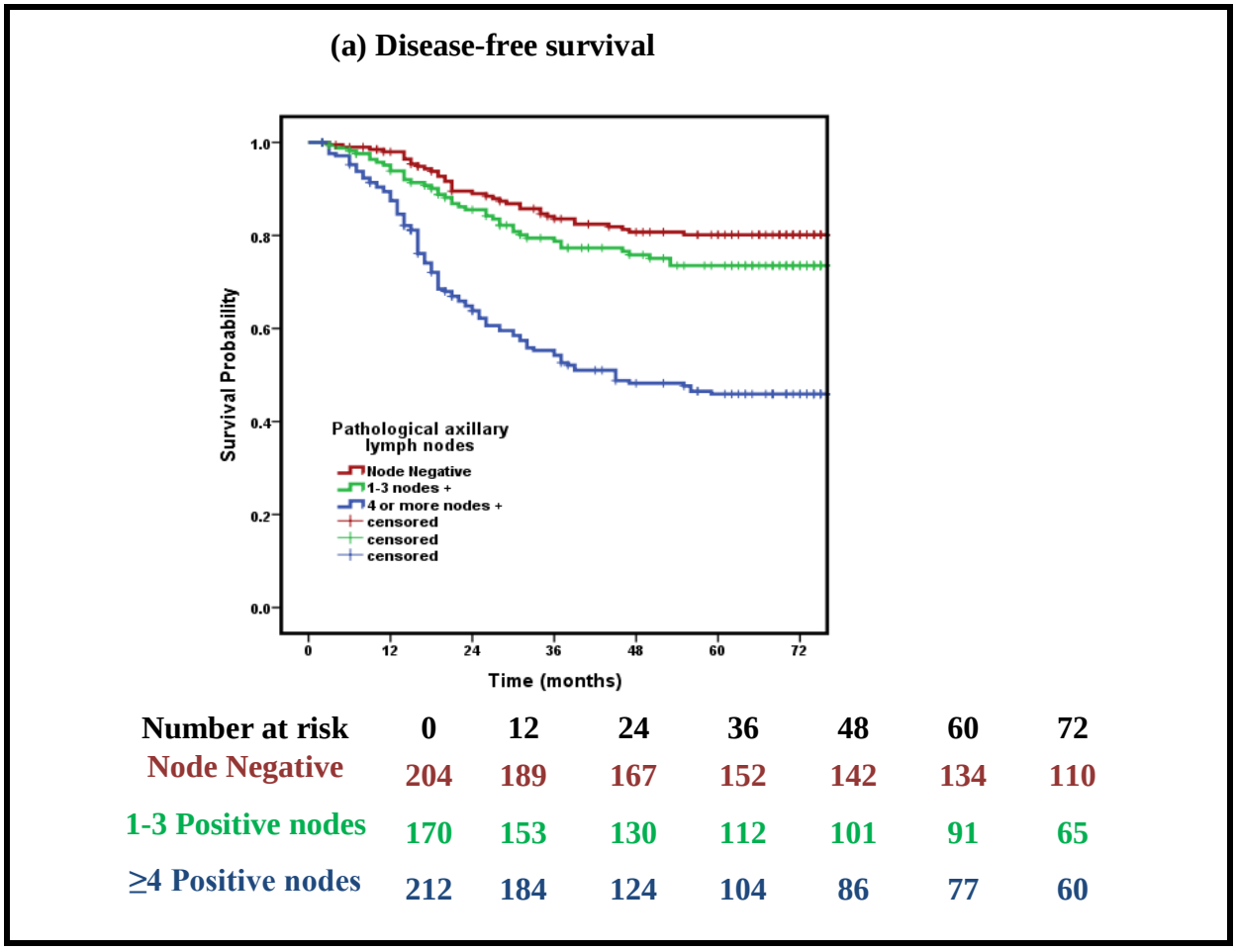
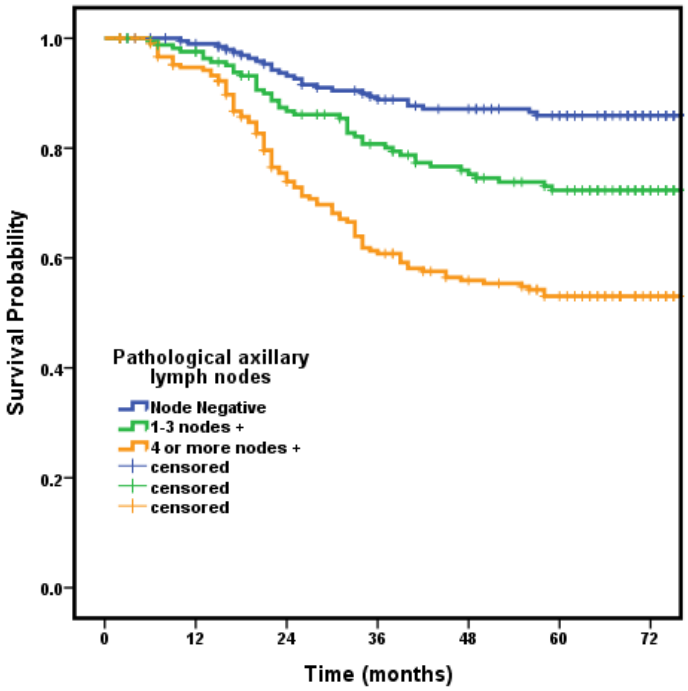


Figure 5.4.15: Kaplan-Meier curves of disease-free survival (a) and overall survival (b) for 597 patients with locally advanced breast cancer, according to pathological axillary lymph nodes

(b) Overall survival



Number at risk	0	12	24	36	48	60	72
Node Negative	204	193	175	162	153	142	115
1-3 Positive nodes	170	158	136	120	108	96	69
≥4 Positive nodes	212	193	145	117	101	89	65

5.4.18 Multivariate analysis for determining independent prognostic factors for disease-free survival: All the factors which were found to influence disease-free survival in univariate analysis, such education status, tumor grade, hormonal status, histological lymphovascular involvement, extensive intraductal component and pathological axillary lymph nodes were considered for further multivariate analysis. In addition, age was added to adjust their effect in multivariate model. Thus, using, multivariate Cox proportional step down reduction method we found, high grade tumor (HR = 2.10, 95% CI = 1.16 – 3.81; p=0.014), hormonal status negative (HR = 1.53, 95% CI = 1.12 – 2.09; p=0.006), presence of EIC (HR = 1.73, 95% CI = 1.16 – 2.58; p=0.006), lymphovascular involvement (HR = 1.85, 95% CI = 1.34 – 2.56; p=0.001) and more than or equal to four positive pathological lymph nodes (HR = 3.18, 95% CI = 2.09 – 4.83; p<0.001) as independent predictors for poor disease-free survival in locally advanced breast cancer patients (Table 5.4.19).

5.4.19 Multivariate analysis for determining independent prognostic factors for overall survival: All the factors which were found to influence overall survival in univariate analysis, such as education status, tumor grade, hormonal status, histological lymphovascular involvement, extensive intraductal component and pathological axillary lymph nodes were considered for further multivariate analysis. In addition, age was added to adjust their effect in multivariate model. Thus, using, multivariate Cox proportional step down reduction method we found, literate patient (HR = 0.63, 95% CI = 0.45 – 0.89; p=0.009), high grade tumor (HR = 1.94, 95% CI = 1.01 – 3.71; p=0.045), Hormone receptor negative (HR = 2.01, 95% CI = 1.44 – 2.81; p<0.001), presence of EIC (HR = 2.09, 95% CI = 1.39 – 3.15; p<0.001), lymphovascular

involvement (HR = 1.64, 95% CI = 1.16 – 2.32; p=0.005) and more than or equal to four positive pathological lymph nodes (HR = 4.32, 95% CI = 2.67 – 6.99; p<0.001) as independent predictors for poor overall survival in locally advanced breast cancer patients (Table 5.4.18).

Table 5.4.18: Univariate and multivariate analysis of prognostic factors for disease-free survival in patients with locally advanced breast cancer

Parameter	No. of cases	Univariate		Multivariate	
		HR (95% CI)	p value	HR (95% CI)	p value
Age at diagnosis (years)					
≤ 50	336	1	0.283	--	0.336
> 50	217	0.84 (0.62-1.14)			
Education status					
Illiterate	142	1		1	
Literate	412	0.66 (0.48-0.90)	0.009	0.75 (0.54-1.04)	0.092
Tumor grade					
Low grade (I+II)	77	1		1	
High grade (III)	477	2.62 (1.49 – 4.61)	0.001	**2.10 (1.16-3.81)**	**0.014****
Hormonal status					
Positive	322	1		1	
Negative	100	1.38 (1.03– 1.85)	0.027	**1.53 (1.12-2.09)**	**0.006****
EIC					
Negative	513	1		1	
Positive	74	2.00 (1.33– 3.00)	0.001	**1.73 (1.16-2.58)**	**0.006****
LVI					
Negative	125	1		1	
Positive	462	2.64 (1.94- 3.57)	<0.001	**1.85 (1.34-2.56)**	**0.001****
Pathological Axillary lymph					
Node Negative	291	1		1	
1-3 Positive nodes	157	1.36 (0.86-2.14)	0.178	1.50 (0.94-2.38)	0.084
≥4 Positive nodes	141	3.23 (2.19-4.75)	<0.001	**3.18 (2.09-4.83)**	**<0.001****

§ Abbreviations: HR, hazard ratio; CI, confidence interval

** Significant (p value <0.05)

Table 5.4.19: Univariate and multivariate analysis of prognostic factors for overall survival in patients with locally advanced breast cancer

Parameter	No. of cases	Univariate		Multivariate	
		HR (95% CI)	p value	HR (95% CI)	p value
Age at diagnosis (years)					
≤ 50	372	1	0.651	--	0.980
> 50	225	1.07 (0.78-1.46)			
Education status					
Illiterate	147	1		1	
Literate	450	0.59 (0.42-0.82)	0.002	**0.63 (0.45-0.89)**	**0.009****
Tumor grade					
Low grade (I+II)	86	1		1	
High grade (III)	511	2.32 (1.32 – 4.10)	0.003	**1.94 (1.01-3.71)**	**0.045****
Hormonal status					
Positive	283	1		1	
Negative	310	1.63 (1.19– 2.24)	0.002	**2.01 (1.44-2.81)**	**<0.001****
EIC					
Negative	525	1		1	
Positive	61	2.27 (1.52– 3.40)	<0.001	**2.09 (1.39-3.15)**	**0.001****
LVI					
Negative	447	1		1	
Positive	139	2.74 (1.99- 3.76)	<0.001	**1.64 (1.16-2.32)**	**0.005****
Pathological Axillary lymph					
Node Negative	204	1		1	
1-3 Positive nodes	170	2.09 (1.28-3.42)	0.003	**2.48 (1.49-4.11)**	**<0.001****
≥4 Positive nodes	212	4.19 (2.71-6.49)	<0.001	**4.32 (2.67-6.99)**	**<0.001****

§ Abbreviations: HR, hazard ratio; CI, confidence interval

**Significant(p-value<0.05)

Survival Analysis of Metastatic Breast Cancer (MBC)

5.5 Overall Survival Analysis of Metastatic Breast Cancer (n= 125)

5.5.1 Overall Survival: Patients' overall survival (OS) was calculated as the time interval between the date of diagnosis and the date of death or the date of the last follow-up. The closing date for recording the last follow-up was taken as 31st December 2014. Out of the 125 patients, at the end of follow-up (31st Dec 2014), 109 (87.2%) patients had expired, and 16 (12.8%) were censored. The median follow-up period was 17.0 months (range, 1 to 82 months). The 5-year overall survival of the cohort calculated by using actuarial method was found to be 13% (table 5.5.1).

Table 5.5.1: Overall survival of Metastatic Breast Cancer by Life table method

Total Number	Survival in percentage (%)				
	1 Yr	2 Yrs	3 Yrs	4 Yrs	5 Yrs
125	66	37	24	15	13

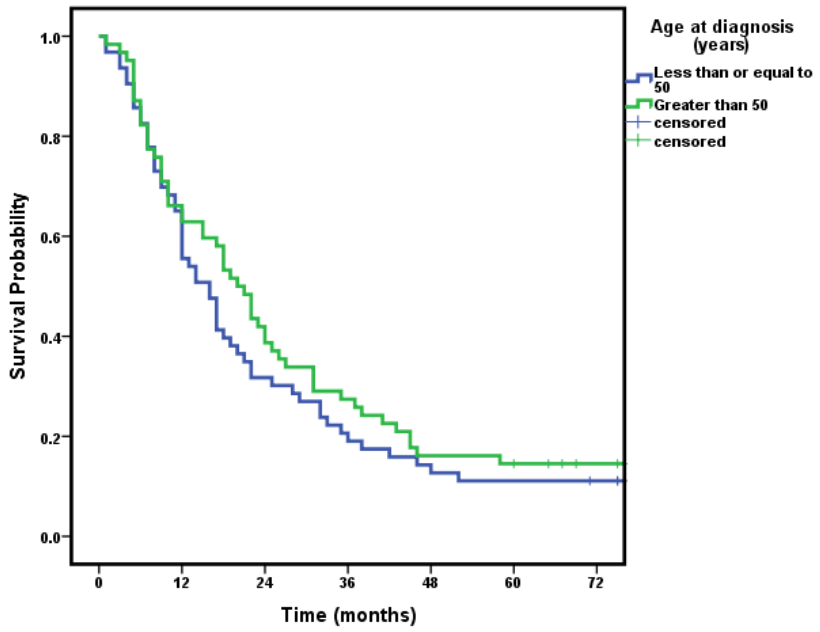
5.5.2. Overall survival according to Age at Diagnosis: Patients were categorized according to cut-offs based on age at diagnosis and its effect on survival was analyzed using Kaplan-Meier curves and the log-rank test. The difference in 5 yrs overall survival rate between age group less than or equal to 50 yrs and more than or equal to 50 yrs was found to be statistically significant (Table 5.5.2). It was observed that patients with age less than or 50 yrs had a 5yr overall survival of 11.1% and those of age 50 yrs and above had a 5yr Overall survival of 14.5%, however this difference was not found to be statistically significant (p=0.342) (Fig.5.5.1).

Table 5.5.2: Observed overall survival rate (%) of metastatic breast cancer according to age at diagnosis

Age at Diagnosis (Years)	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
≤ 50	63	55.6	31.7	19.0	12.7	11.1	0.342
> 50	62	62.9	38.7	27.4	16.1	14.5	

**Calculated using Log Rank Test*

Figure 5.5.1: Observed overall survival rate (%) of metastatic breast cancer according to age at diagnosis



Number at risk	0	12	24	36	48	60	72
≤ 50	**63**	**41**	**20**	**13**	**9**	**7**	**6**
> 50	**62**	**41**	**26**	**17**	**10**	**9**	**5**

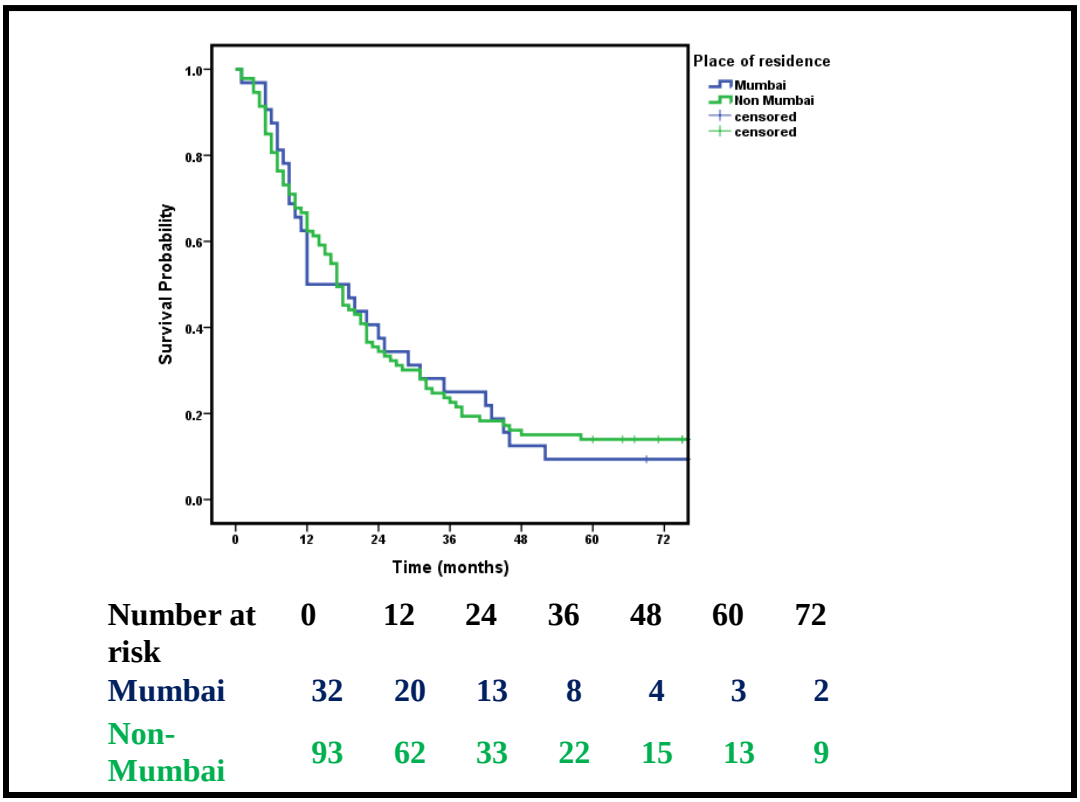
5.5.3 Overall survival according to Residence: A 5 yr overall survival rate for Mumbai residents and Non-Mumbai residents was found to be 9.4% and 14.0% respectively (Table 5.5.3), but this difference was not statistically significant (p=0.875) (Fig.5.5.2).

Table 5.5.3: Observed overall survival rate (%) of metastatic breast cancer according to Residence

Residence	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Mumbai	32	50.0	37.5	25.0	12.5	9.4	0.875
Non-Mumbai	93	62.4	34.4	22.6	15.1	14.0	

**Calculated using Log Rank Test*

Figure 5.5.2: Observed overall survival rate (%) of metastatic breast cancer according to residence



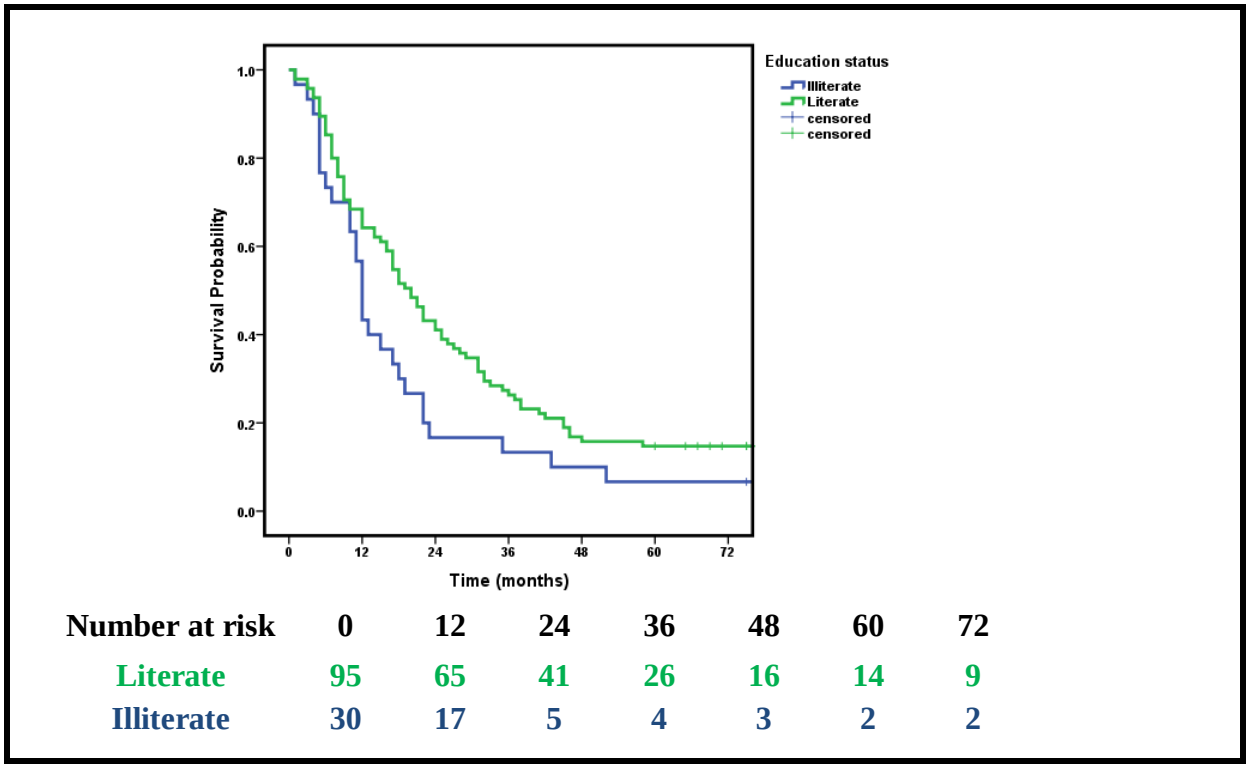
5.5.4 Overall survival according to Education: Patients were categorized as per their educational status at the time of registration. 5 year overall survival rate of literate and illiterate was found to be 14.7% and 6.7 % respectively. This difference was statistically significant ($p<0.05$) (Table 5.5.4) (Fig.5.5.3).

Table 5.5.4: Observed overall survival rate (%) of metastatic breast cancer according to Education status

Education Status	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Literate	95	64.2	41.1	26.3	15.8	14.7	0.040
Illiterate	30	43.3	16.7	13.3	10.0	6.7	

**Calculated using Log Rank Test*

Figure 5.5.3: Observed overall survival rate (%) of metastatic breast cancer according to education status



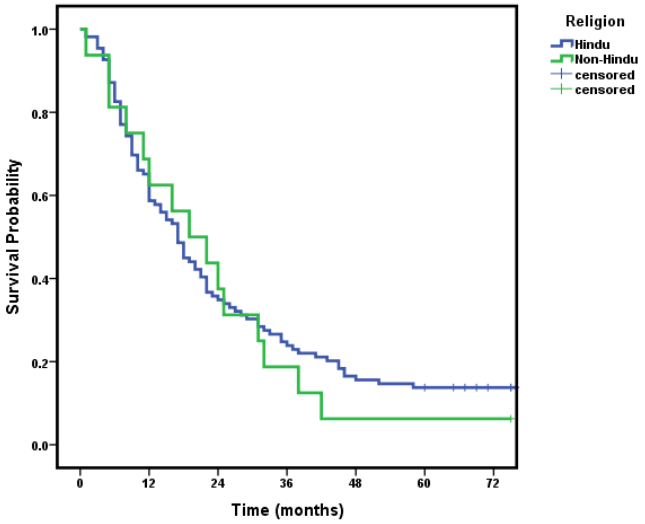
5.5.5 Overall survival according to Religion: Patients were categorized as per their religion at the time of registration and their effect on survival was analyzed. There was no significant (p= 0.676) difference in survival between Hindu patients and Non-Hindu patients (Table 5.5.5) (Fig. 5.5.4).

Table 5.5.5: Observed overall survival rate (%) of metastatic breast cancer according to religion

Religion	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Hindu	109	58.7	34.9	23.9	15.6	13.8	0.676
Non-Hindu	16	62.5	37.5	18.8	6.3	6.3	

**Calculated using Log Rank Test*

Figure 5.5.4: Observed overall survival rate (%) of metastatic breast cancer according to according to Religion



Number at risk	0	12	24	36	48	60	72
Hindu	109	71	39	27	18	15	10
Non-Hindu	16	11	7	3	1	1	1

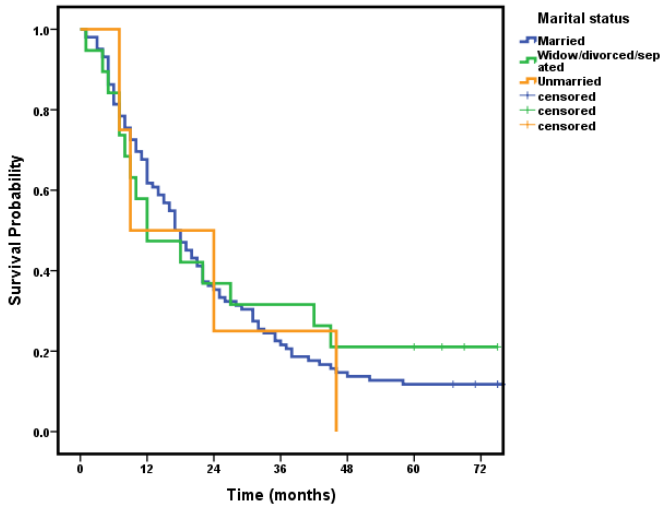
5.5.6 Overall survival according to Marital status: Patients were categorized as per their marital status at the time of registration. No significant difference was seen in 5 yr overall survival of patients based on marital status (Table 5.5.6) (Fig.5.5.5).

Table 5.5.6: Observed overall survival rate (%) of metastatic breast cancer according to marital status

Marital status	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Single (Unmarried)	4	50.0	25.0	0	0	0	0.843
Married	102	61.8	35.3	21.6	13.7	11.8	
Widow/divorced/separated	19	47.4	36.8	31.6	21.1	21.1	

**Calculated using Log Rank Test*

Figure 5.5.5: Observed overall survival rate (%) of metastatic breast cancer according to marital status



Number at risk	0	12	24	36	48	60	72
Married	102	69	37	23	15	12	10
Widow/divorced/seperated	19	11	7	6	4	4	1
Unmarried	4	2	2	1	0	0	0

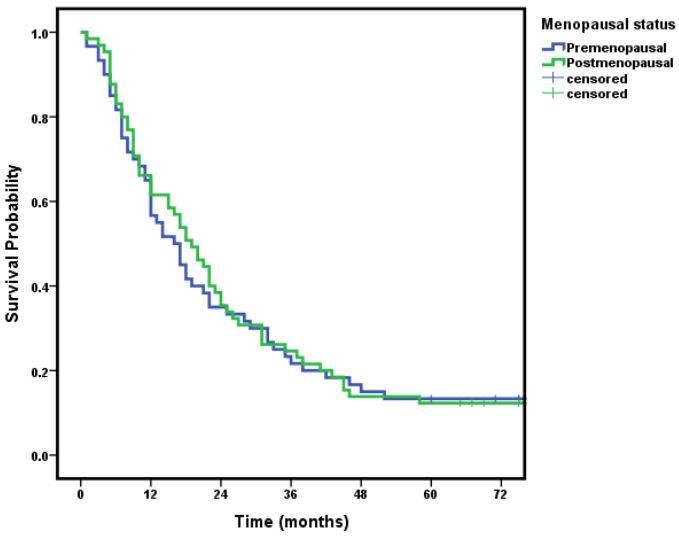
5.5.7 Overall survival according to Menopausal status: A 5 yr overall survival rate for Premenopausal and Postmenopausal patients was found to be 13.3% and 12.3% respectively (Table 5.5.7), but this difference was not statistically significant (p=0.828) (Fig.5.5.6).

Table 5.5.7: Observed overall survival rate (%) of metastatic breast cancer according to Menopausal status

Menopausal Status	Total Number	Overall Survival in percentage (%)					p Value*
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Pre-menopausal	60	56.7	35.0	21.7	15.0	13.3	0.828
Post-menopausal	65	61.5	35.4	24.6	13.8	12.3	

**Calculated using Log Rank Test*

Figure 5.5.6: Observed overall survival rate (%) of metastatic breast cancer according to menopausal status



Number at risk	0	12	24	36	48	60	72
Premenopausal	60	39	21	14	10	8	6
Postmenopausal	65	43	25	16	9	8	5

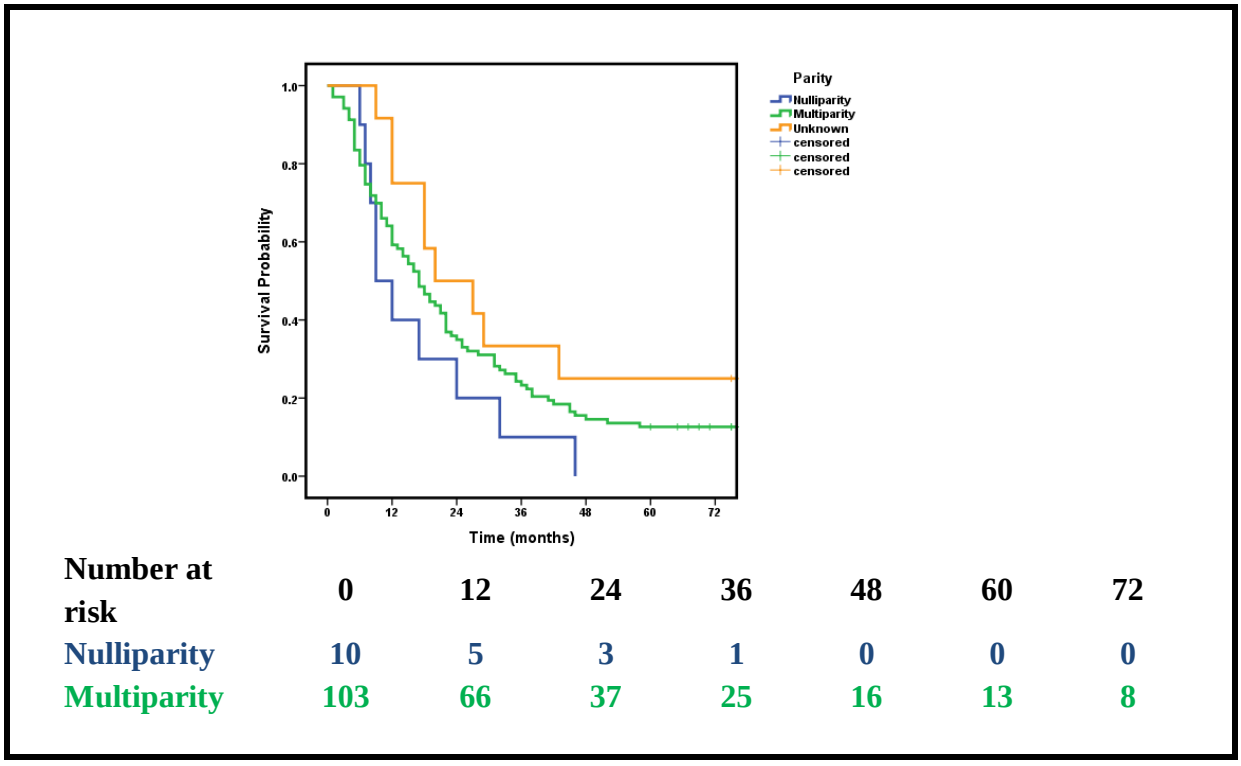
5.5.8 Overall survival according to Parity: Patient parity status was taken at the time of registration. Parity was classified as Nulliparity and Multiparity. A 5 yr overall survival rate for Multiparity patients was found to be 12.6% (Table 5.5.8) (Fig.5.5.7).

Table 5.5.8: Observed overall survival rate (%) of metastatic breast cancer according to parity

Parity	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Nulliparity	10	40.0	20.0	10.0	00.0	0.00	0.194
Multiparity	103	59.2	35.0	23.3	14.6	12.6	
Unknown	12	75.0	50.0	33.3	25.0	25.0	

**Calculated using Log Rank Test*

Figure 5.5.7: Observed overall survival rate (%) of metastatic breast cancer according to parity



Number at risk	0	12	24	36	48	60	72
Nulliparity	10	5	3	1	0	0	0
Multiparity	103	66	37	25	16	13	8

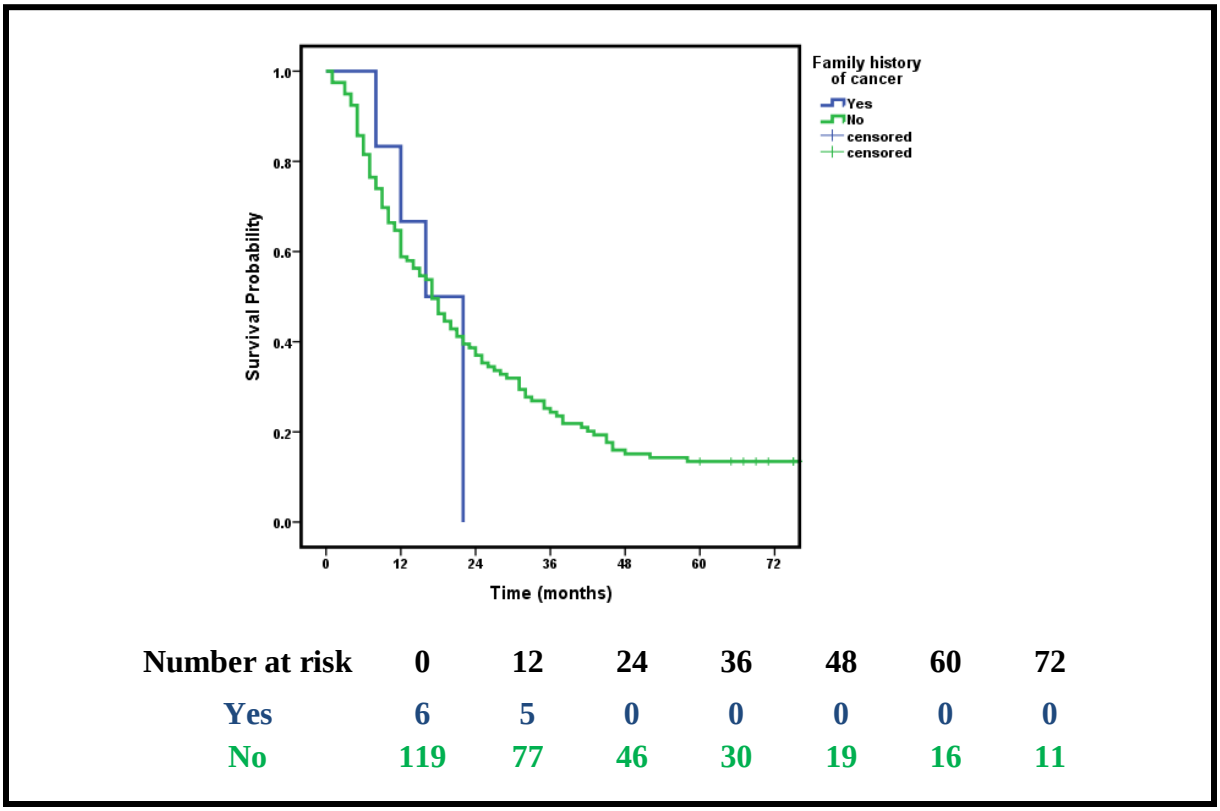
5.5.9 Overall survival according to Family history of cancer: Patients were categorized as per presence of family history of cancer. No significant difference was seen in 5 yr overall survival of patients based on family history of cancer (Table 5.5.9) (Fig.5.5.8).

Table 5.5.9: Observed overall survival rate (%) of metastatic breast cancer according to family history of cancer

Family history of cancer	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Yes	6	66.7	0.00	0.00	0.00	0.00	0.373
No	119	58.8	37.0	24.4	15.1	13.4	

**Calculated using Log Rank Test*

Figure 5.5.8: Observed overall survival rate (%) of metastatic breast cancer according to family history of cancer



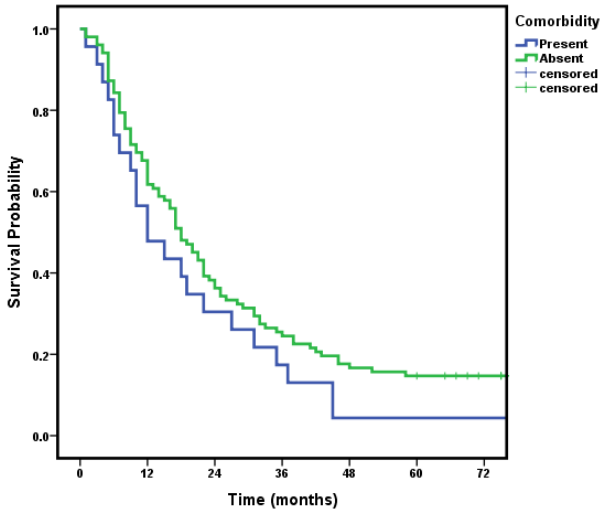
5.5.10 Overall survival according to Presence of comorbidity: Metastatic breast cancer patients having a concomitant comorbidity (Hypertension, Diabetes mellitus, Heart Disease, Asthma and HIV) were found to have 5yr overall survival of 4.3% as compared to 14.7% in patients without any comorbiditiy (Fig. 5.5.9), but this difference did not achieve statistical significance (p= 0.155) (Table 5.5.10).

Table 5.5.10: Observed overall survival rate (%) of metastatic breast cancer according to Presence of comorbidity

Comorbidity	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Present	23	47.8	30.4	17.4	4.3	4.3	0.155
Absent	102	61.8	36.3	24.5	16.7	14.7	

**Calculated using Log Rank Test*

Figure 5.5.9: Observed overall survival rate (%) of metastatic breast cancer according to Presence of comorbidity



Number at risk	0	12	24	36	48	60	72
Present	23	13	7	4	1	1	1
Absent	102	69	39	26	18	15	10

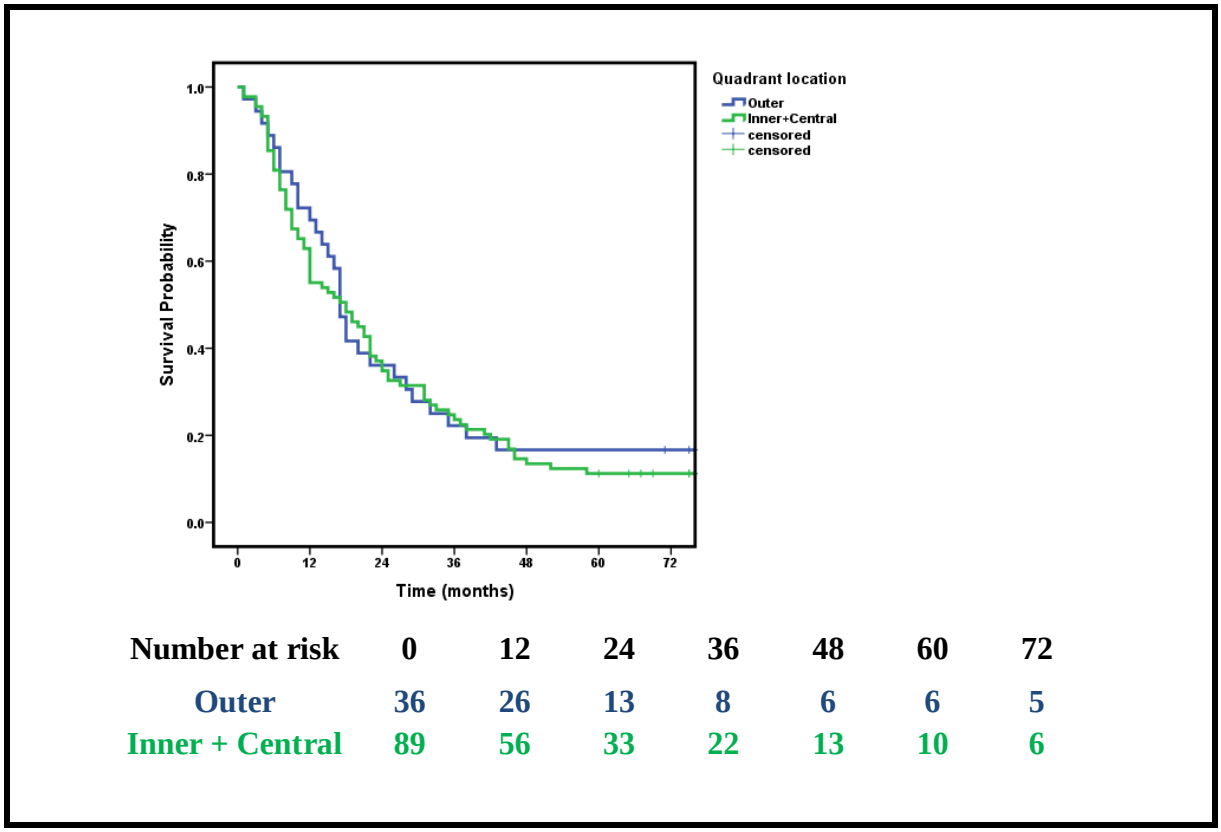
5.5.11 Overall survival according to Quadrant location: A 5 yr overall survival rate for patient with Outer and Inner+Central quadrant location was found to be 16.7% and 11.2% respectively (Table 5.5.11). However, this difference was not statistically significant (Fig. 5.5.10).

Table 5.5.11: Observed overall survival rate (%) of metastatic breast cancer according to Quadrant location

Quadrant location	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Outer	36	69.4	36.1	22.2	16.7	16.7	0.660
Inner + Central	89	55.1	34.8	23.6	13.5	11.2	

**Calculated using Log Rank Test*

Figure 5.5.10: Observed overall survival rate (%) of metastatic breast cancer according to Quadrant location



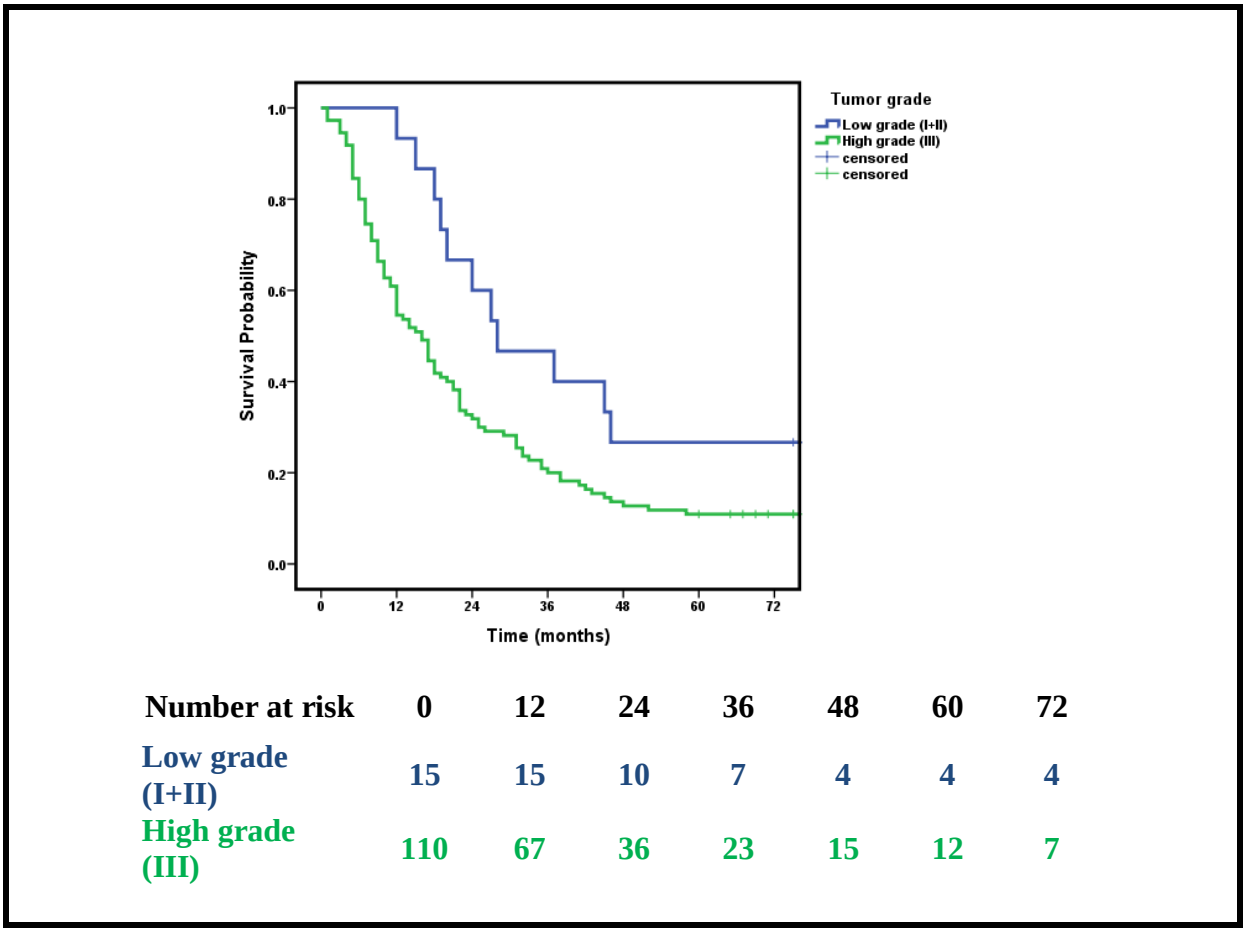
5.5.12 Overall survival according to Tumor grade: Patients having high grade (III) tumor were found to have the worst 5yr overall survival of 10.9%, whereas patients with low grade tumors had 26.7 % 5yr overall survival (Table 5.5.12) (Fig. 5.5.11).

Table 5.5.12: Observed overall survival rate (%) of metastatic breast cancer according to Tumor grade

Tumor grade	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Low grade	15	93.3	60.0	46.7	26.7	26.7	0.027
High grade	110	54.5	31.8	20.0	12.7	10.9	

**Calculated using Log Rank Test*

Figure 5.5.11: Observed overall survival rate (%) of metastatic breast cancer according to Tumor grade



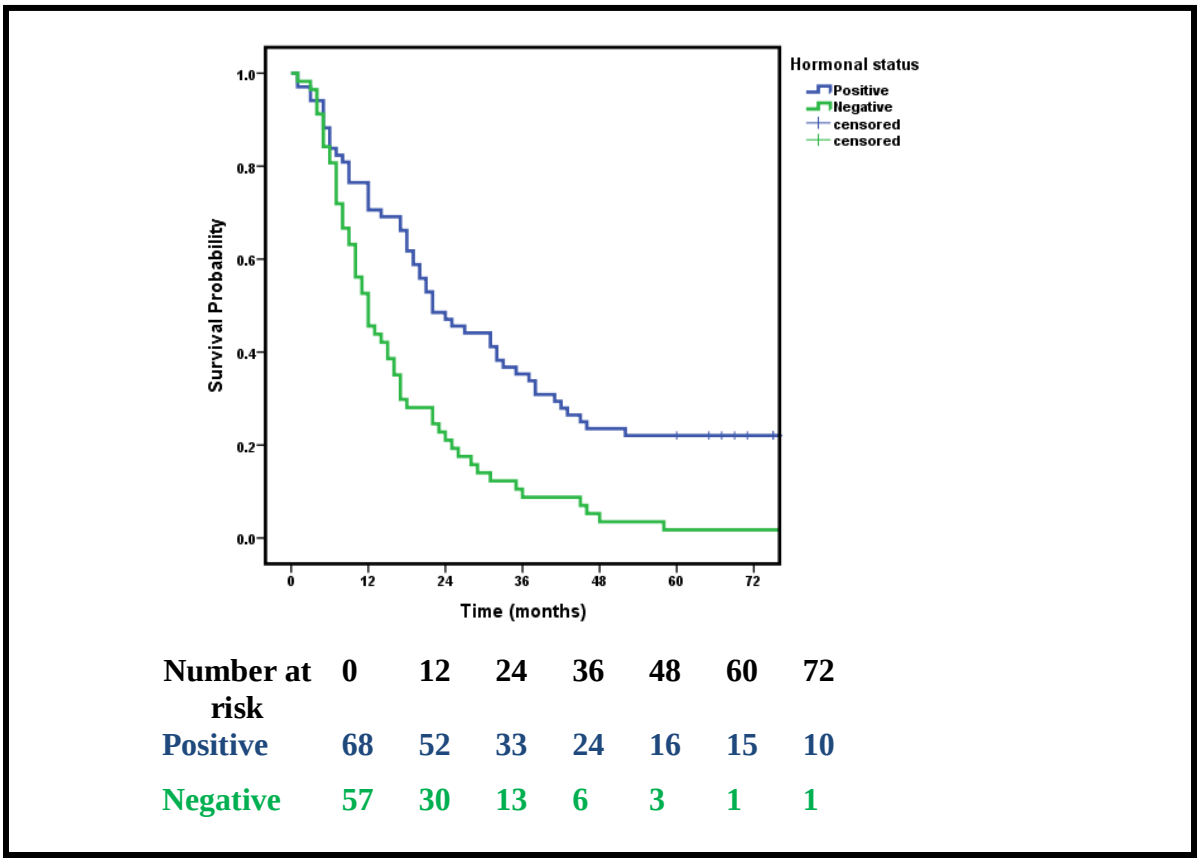
5.5.13 Overall survival according to hormonal status: 5 yr overall survival rate of HR positive and HR negative patients is 22.1% and 1.8% respectively (Table 5.5.13) (Fig.5.5.14)

Table 5.5.13: Observed overall survival rate (%) of metastatic breast cancer according to hormonal status

Hormonal status	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
HR Positive	68	70.6	47.1	35.3	23.5	22.1	<0.001
HR Negative	57	45.6	21.1	8.8	3.5	1.8	

**Calculated using Log Rank Test*

Figure 5.5.12: Observed overall survival rate (%) of metastatic breast cancer according to hormonal status



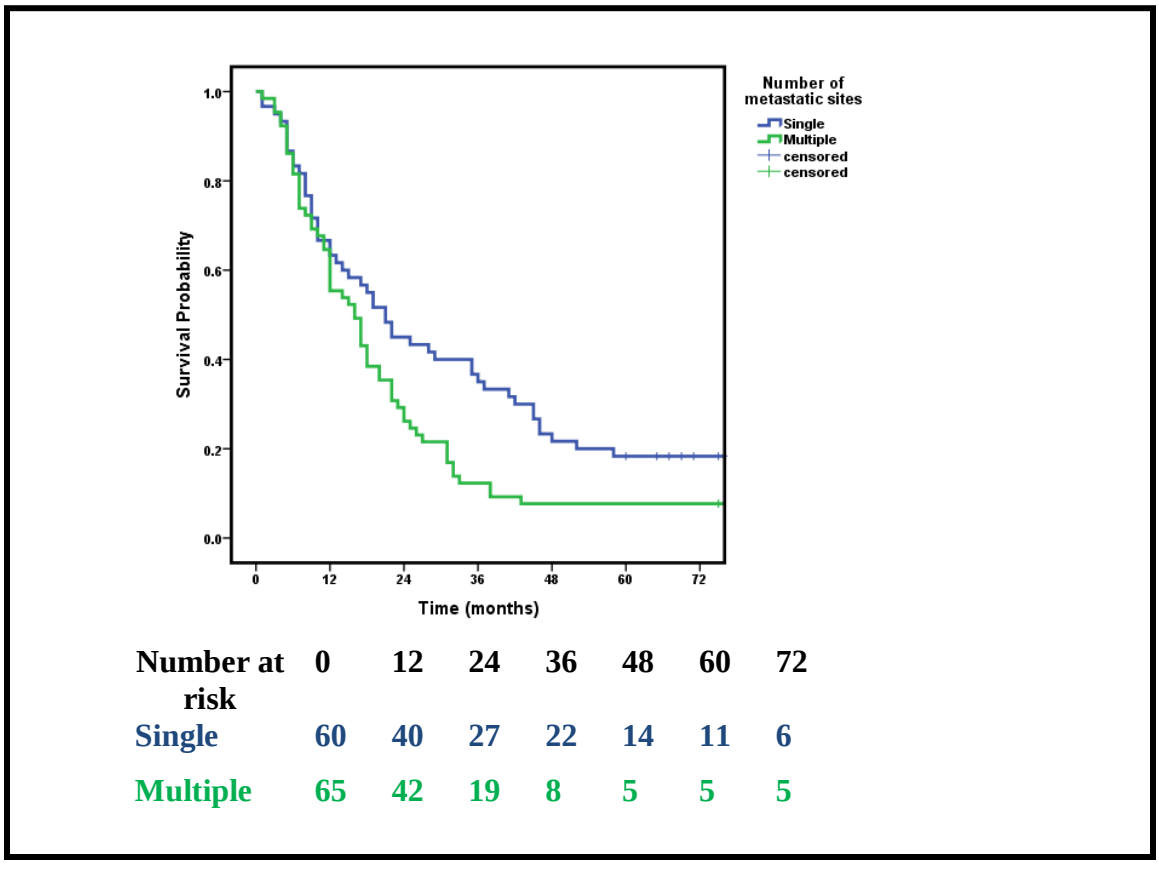
5.5.14 Overall survival according to Number of metastases: Presence of number of metastases on histology was found to significantly affect the survival adversely. Patients with single mets had 5 yr overall survival of only 18.3% as compared to 7.7% in those patients with multiple mets (Table 5.5.14) (Fig. 5.5.13).

Table 5.5.14: Observed overall survival rate (%) of metastatic breast cancer according to Number of metastases

Number of metastases	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Single	60	63.3	45.0	35.0	21.7	18.3	0.018
Multiple	65	55.4	26.2	12.3	9.2	7.7	

**Calculated using Log Rank Test*

Figure 5.5.13: Observed overall survival rate (%) of metastatic breast cancer according to Number of metastases



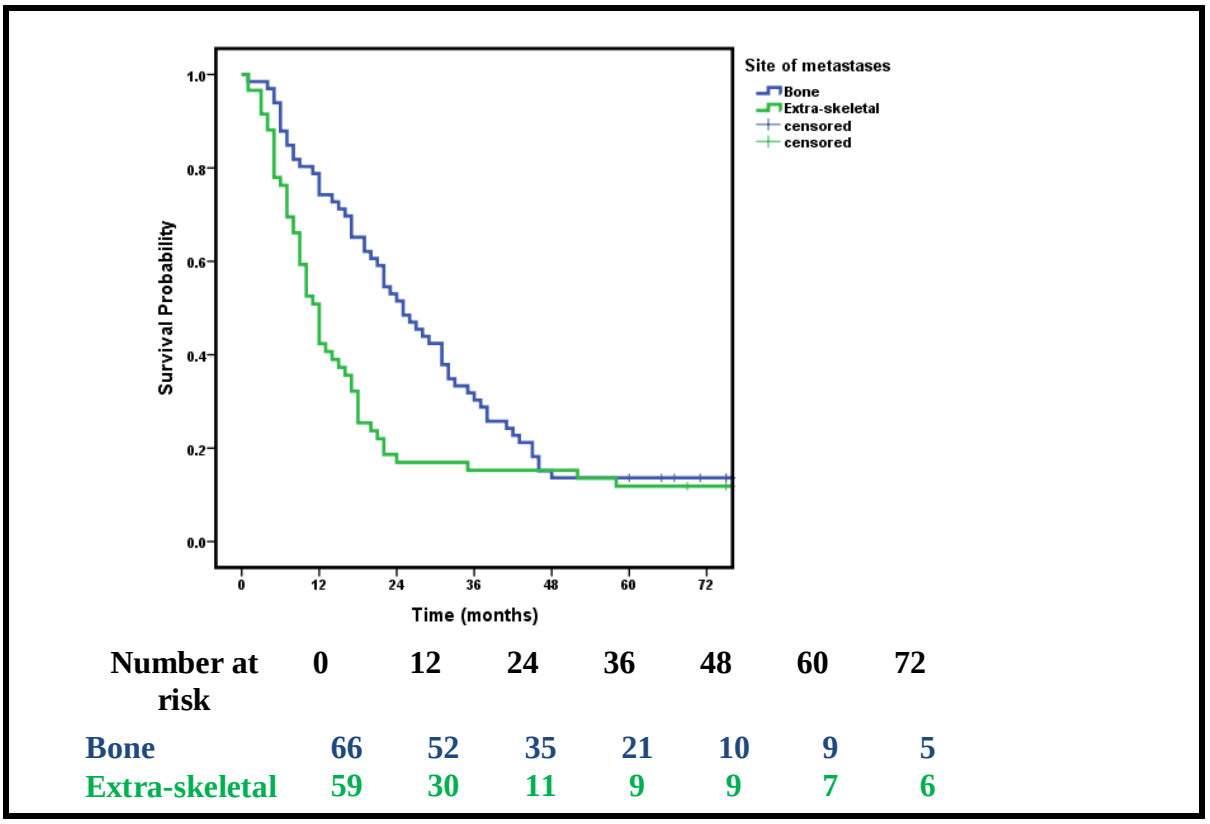
5.5.15 Overall survival according to Site of metastases: Site of metastases was found to significantly affect the survival adversely. Patients with Bone mets had 5 yr overall survival of only 13.6% as compared to 11.9% in those patients with Extraskeletal (Table 5.5.15) (Fig. 5.5.14).

Table 5.5.15: Observed overall survival rate (%) of metastatic breast cancer according to Site of metastases

Site of metastases	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Bone mets	66	74.2	51.5	30.3	13.6	13.6	0.009
Extraskeletal	54	42.4	16.9	15.3	15.3	11.9	

**Calculated using Log Rank Test*

Figure 5.5.14: Observed overall survival rate (%) of metastatic breast cancer according to Site of metastases



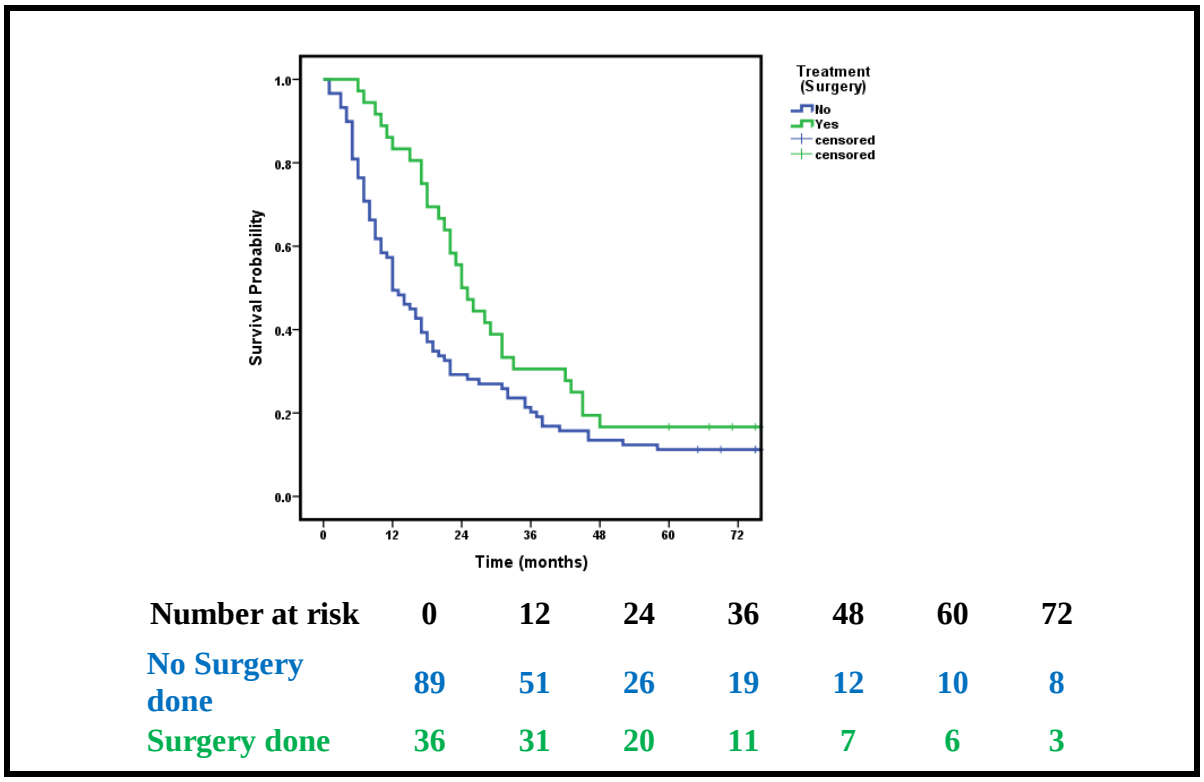
5.5.16 Overall survival according to Treatment: 5yr overall survival rate of the patient who has undergone surgery has 16.7% as compared to 11.9% patient who has not taken surgery, this difference was statistically significant (p=0.027) (Table 5.5.16) (Fig.5.5.15).

Table 5.5.16: Observed overall survival rate (%) of metastatic breast cancer according to Treatment

Treatment	Total Number	Overall Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Sx done	36	83.3	50.0	30.6	16.7	16.7	0.027
No sx	89	49.4	29.2	20.2	13.5	11.2	

**Calculated using Log Rank Test*

Figure 5.5.15: Observed overall survival rate (%) of metastatic breast cancer according to Treatment



5.5.17 Multivariate analysis for determining independent prognostic factors for Overall survival:

All the factors which were found to influence overall survival in univariate analysis, such as education status, tumor grade, hormonal status, site of metastases and number of metastases were considered for further multivariate analysis. In addition, age was to adjust their effect in multivariate model. Thus, using, multivariate Cox proportional step down reduction method we found, hormonal status negative (HR = 2.04, 95% CI = 1.37 – 3.04; p <0.001), presence of number of mets (HR = 1.66, 95% CI = 1.13 – 2.45; p=0.010) and site of mets (HR = 1.48, 95% CI = 0.99 – 2.19; p=0.051) as independent predictors for poor overall survival in metastatic breast cancer patients (Table 5.5.17).

Table 5.5.17: Univariate and multivariate analysis of prognostic factors for overall survival in patients with metastatic breast cancer

Parameter	No. of cases	Univariate		Multivariate	
		HR (95% CI)	*p value*	HR (95% CI)	*p value*
Age at diagnosis[+] (years)					
≤ 50	79	1			
> 50	66	0.69 (0.46 – 1.03)	0.075	--	0.536
Education status					
Illiterate	30	1			
Literate	95	0.64 (0.41 – 0.99)	0.046	**--**	0.267
Tumor grade					
Low grade (I+II)	15	1			
High grade (III)	110	1.97 (1.05 – 3.68)	0.033	**--**	0.121
Hormonal status					
HR Positive	68	1		**1**	
HR Negative	57	2.18 (1.48 – 3.20)	<0.001	**2.04 (1.37- 3.04)**	**<0.001****
Number of metastases					
Single	60	1		**1**	
Multiple	55	1.56 (1.06 – 2.30)	0.022	**1.66 (1.13-2.45)**	**0.010****
Site of Metastases					
Bone	66	1		**1**	
Visceral	59	1.63 (1.11 – 2.40)	0.011	**1.48 (0.99-2.19)**	**0.051****

§ Abbreviations: HR, hazard ratio; CI, confidence interval

** Significant (p value <0.05)

Treatment timelines

5.6.1 Time taken for diagnosis: Time period from registration of patient at Tata memorial Hospital to pathological confirmation of malignancy was taken as time to diagnosis. The median duration for diagnosis was 04 days (Table 5.6.1). Majority of cases (98%) were diagnosed within 15 days and only 25 cases (2%) required more than 16 days for diagnosis (Table 5.6.2). The duration taken for diagnosis was divided into three categories for analyzing its effect on overall survival of patients (Table 5.6.3). No significant difference in 5 yr survival rates was observed as per the time taken for diagnosis (Fig. 5.6.1).

Table 5.6.1: Time taken for diagnosis

Sl. No.	Time period from date of registration to date to diagnosis	Duration (days)
1.	**Median**	04
2.	**Minimum**	01
3.	**Maximum**	26

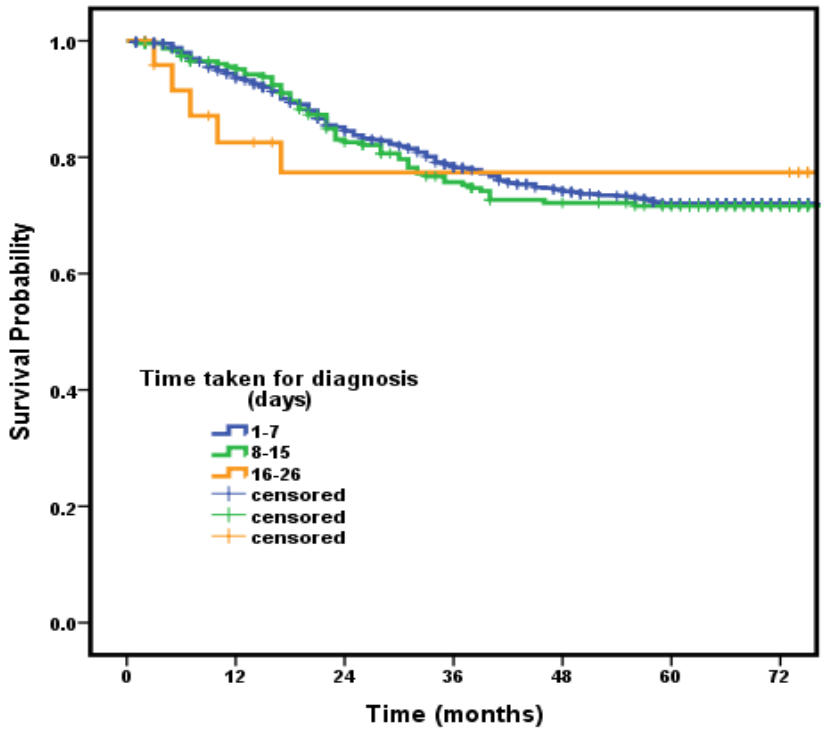
Table 5.6.2: Distribution of patients as per time taken for diagnosis

Sl. No.	Time taken for Diagnosis (days)	No. of patients (%)	Cumulative total (%)
1.	**≤ 7 days**	999 (79.4)	999 (79.4)
2.	**8 to 15 days**	234 (18.6)	1233 (98.0)
3.	**16 to 30 days**	25 (2.0)	1258 (100.0)

Table 5.6.3: Observed survival rate (%) of breast cancer according to time taken for diagnosis

Factor	Total Number	Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Time taken for diagnosis (Days)							
≤ 7 days	999	93.6	84.5	78.2	74.1	72.1	0.962
8 to 15 days	234	95.1	82.6	75.7	72.1	71.6	
≥ 16 days	25	82.5	77.4	77.4	77.4	77.4	

Figure 5.6.1: Observed survival rate (%) of breast cancer according to time taken for diagnosis



Number at risk	0	12	24	36	48	60	72
1-7 days	999	907	796	722	663	609	481
8-15 days	234	211	175	152	139	131	93
16-30 days	25	18	15	15	15	15	15

5.6.2 Time between diagnosis and commencement of treatment: Time period between pathological confirmation of malignancy and initiation any type of cancer directed treatment (CDT) i.e surgery or radiotherapy or chemotherapy, was considered as time taken for treatment commencement. The median duration for treatment initiation was 10 days (Table 5.6.4). In majority of patients (98.7%) treatment was started within 90 days of pathological diagnosis of malignancy (Table 5.6.5). The duration taken for treatment initiation was divided into four categories for analyzing its effect on overall survival of patients (table 5.6.5). The 5 yr overall survival for taking treatment within 30 days was 74.2 % and patients taking treatment more than 90 days was 49.2 % . This was statistically significant ($p<0.001$) (figure 5.6.2). The hazard ratio was 2.3 fold more in the patients whose commencement of cancer directed treatment started more than 90 days as compared to the patients whose commencement of cancer directed treatment started within 30 days.

Table 5.6.4: Time taken to start cancer directed treatment

Sl. No.	Time period from date of diagnosis to date of start of cancer directed treatment	Duration (days)
1.	**Median**	10
2.	**Minimum**	01
3.	**Maximum**	117

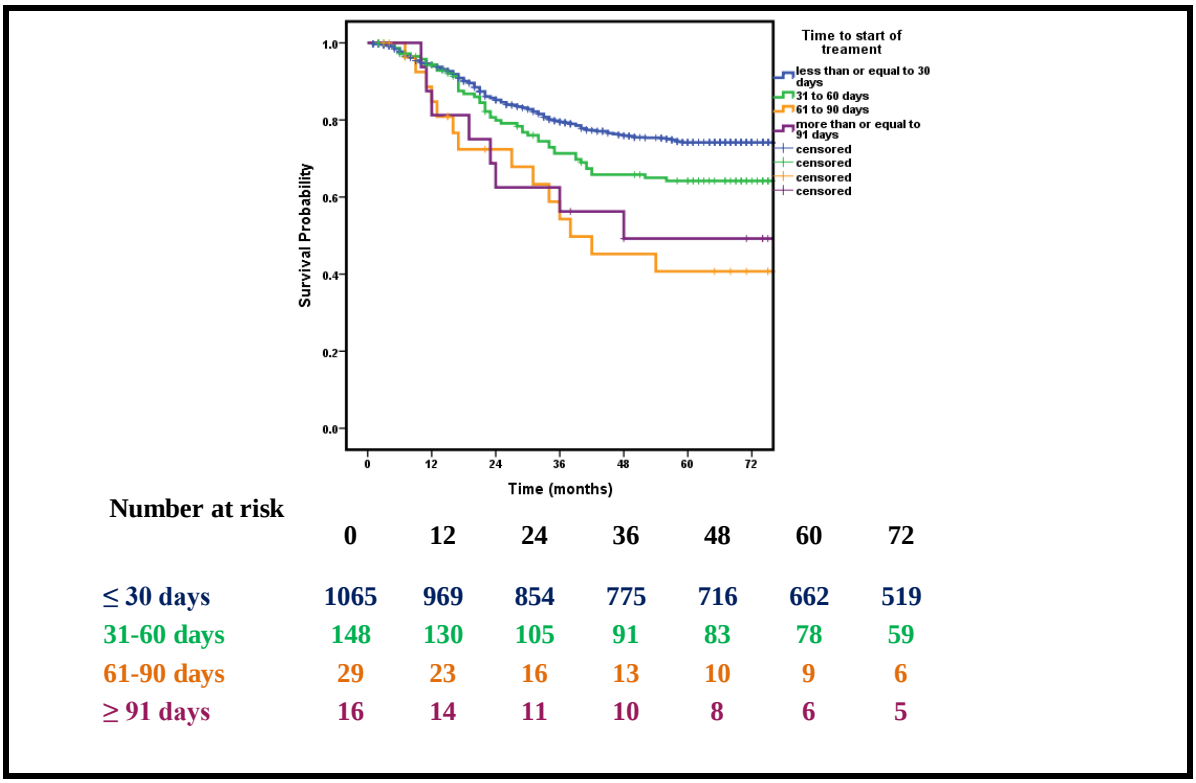
Table 5.6.5: Distribution of patients as per time taken to start cancer directed treatment

Sl. No.	Time taken for Diagnosis (days)	No. of patients (%)	Cumulative total (%)
1.	**≤ 30 days**	1065 (84.7)	1065 (84.7)
2.	**31 – 60 days**	148 (11.8)	1213 (96.4)
3.	**61 - 90 days**	29 (2.3)	1242 (98.7)
4.	**≥ 91 days**	16 (1.3)	1258 (100)

Table 5.6.6: Observed survival rate (%) of breast cancer according to time taken to start cancer directed treatment

Factor	Total Number	Survival in percentage (%)					*p Value**
		1 Yr	2 Yrs	3 Yrs	4Yrs	5Yrs	
Time taken to start Cancer Directed treatment (Days)							
≤ 30 days	1065	94.0	85.2	79.5	75.9	74.2	<0.001
31 – 60 days	148	94.3	79.9	71.3	65.8	64.2	
61 - 90 days	29	84.7	72.4	54.3	45.2	40.7	
≥ 91 days	16	81.3	62.5	56.3	49.2	49.2	
Cox proportional Hazard ratio							
		Hazard ratio					**P value**
≤ 30 days		1					
31 – 60 days		1.45 (1.06-1.97)					0.019
61 - 90 days		2.78 (1.162-4.76)					< 0.001
≥ 91 days		2.36 (1.17-4.78)					0.017

Figure 5.6.2: Observed Survival rate (%) of Breast cancer according to Time taken from diagnosis to start of Cancer Directed Treatment



Number at risk

	0	12	24	36	48	60	72
≤ 30 days	**1065**	**969**	**854**	**775**	**716**	**662**	**519**
31-60 days	**148**	**130**	**105**	**91**	**83**	**78**	**59**
61-90 days	**29**	**23**	**16**	**13**	**10**	**9**	**6**
≥ 91 days	**16**	**14**	**11**	**10**	**8**	**6**	**5**

5.7 Loss-adjusted survival (LAR): Loss adjusted survival rates were calculated by using method proposed by Ganesh (1995). The proportion and risk (hazard ratio) of death and loss to follow-up at 5 years from the index date, by prognostic factors, are presented in Table 5.7.1. The proportion of patients lost to follow-up during the 5-year period was 14.1 %, and of dying was 25.9 %. The risk of loss to follow-up varied from 0.43-fold by level of education and 1.4-fold by stage of disease. The risk of death increased 0.48 fold by level of education ($p<0.001$) and 3.3-fold with locally advanced and 20.2-fold in metastatic stage of disease ($p <0.001$). The observed (actuarial) survival at 5 years was 72.0% (Table 5.7.2). During this period, 14.1% of cases were lost to follow-up; 4.2% in the first year, 4.6% of those remaining in the second and third years, and 5.3% of the remainder in the fourth and fifth years (Table 5.7.2). Adjustment for loss of follow-up gave an estimated survival of 70 % at 5 years from index date, 2 % units less than the observed (actuarial) survival. This suggests that the patients who were lost to follow-up had a slightly higher mortality than assumed in the actuarial method of survival analysis, in which such deaths occur at the same rate as among those with complete follow-up. Table 5.7.2 also gives the estimate of loss-adjusted survival by stage, adjusted for differential loss to follow-up by age and education.

Table 5.7.1: Number of cases, proportion and risk (Hazard ratio, HR) of death and loss to follow-up at 5 years from the index date (date of registration) and 95% confidence interval (CI) by factors studied

		Proportion at 5 years from index date		Hazard Ratio (HR) and 95% CI, (*p value*)	
Factors studied	**Number of cases**	**Lost (%)**	**Dead (%)**	**Lost HR[a]**	**Dead[b] HR**
All Cases	1258	14.1	25.9	--	--
Age (≤ 50 yrs)	716	13.3	25.7	1	1
Age (> 50 yrs)	542	15.1	26.2	1.16 (0.86 – 1.56), (0.318)	1.03 (0.83 – 1.29), (0.742)
Education (Illiterate)	238	22.3	37.8	1	1
Education (Literate)	1020	12.2	23.1	0.43 (0.31 – 0.59), (<0.001)	0.48 (0.38 – 0.62), (<0.001)
EBC	536	14.0	9.5	1	1
LABC	597	17.1	27.8	1.40 (1.04 – 1.89), (0.026)	3.35 (2.45 – 4.59), (<0.001)
MBC	125	0.0	87.2	--	20.28(14.49– 28.40), (<0.001)

[a]ORs of each factor adjusted for all other factors in the table. [b]Estimated among those with complete follow-up only.

Table 5.7.2: Number of cases, proportion dead and lost to follow-up at varying intervals of time and 5-year cumulative absolute and loss-adjusted survival

	Survival in percentage (%)									
	1 Yr		2 Yrs		3 Yrs		4 Yrs		5 Yrs	
All Cases										
Total Number	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**
1258	5.5	4.2	9.1	2.8	5.9	1.8	3.7	2.1	1.7	3.2
Actuarial Method (%)	94		85		78		74		72	
Loss Adjusted Rate (%)**	94.0		83.2		76.3		72.0		70.0	
** Adjusted for Age, Education and Stage										
EBC										
Total Number	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**
536	1.3	5.0	2.2	2.1	2.2	1.9	2.4	1.9	1.3	3.2
Actuarial Method (%)	99		96		94		91		90	
Loss Adjusted Rate (%)**	98.5		96.0		93.4		90.6		89.1	
** Adjusted for age and education										
LABC										
Total Number	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**	**Dead (%)**	**Lost (%)**
597	3.2	4.4	11.2	4.0	7.7	2.2	3.7	2.7	2.0	3.9
Actuarial Method (%)	97		85		76		72		69	
Loss Adjusted Rate (%)**	96.0		82.3		72.7		68.2		65.7	
** Adjusted for age and education										

DISCUSSION

CHAPTER 6

DISCUSSION

Tata Memorial Hospital (TMH), Mumbai is a premier cancer centre for diagnosis and treatment in India. Survival rates among breast cancer patients have improved over the years, as a result of earlier diagnosis. The present study is a hospital-based retrospective study of histologically confirmed breast cancer patients, seen at TMH between 1st Jan 2008 to 31st Dec 2008. The total patients' eligible for study was 1258 cases. An attempt has been made to study the factors, demographic and clinical, that influence the survival. Additionally, the loss-adjusted rates (LAR) reported are adjusted for losses to follow-up.

6.1.1 Disease-free Survival: A total of 1133 cases of non-metastatic breast cancer (Table 5.1), were included in the study. The observed 5-year disease-free survival (DFS) rate for the cohort was found to be 76% (Table 5.2.1). Survival rates similar to our study were reported by Raina et al. who in their study of 487 early breast cancer patients found 5 yr DFS of 73%. (175)

6.1.2 Overall Survival: In the current study, the 5-year overall survival (OS) rate for the entire population was 72% (stages I-IV). (Table 5.2.2) Sankaranarayanan R et al. (2010) in his study of 25 population-based cancer registries in 12 countries in sub-Saharan Africa, Central America and Asia, found India to have the lowest survival rate (47.4%) in Asian countries and this difference was attributed to lack of established screening and early detection programmes, which in turn

results in majority of cases presenting with advanced stage disease and lower survival. (20) A large breast cancer study which was undertaken at Tata Memorial hospital by Dinshaw et al. to study the various factors among those treated with breast conserving therapy (BCT). During 1980-2000, 1,022 pathological Stage I/II breast cancer patients (median age 43 years) underwent BCT were studied. The study showed an overall 5-year and 10-year actuarial survival of 87% and 77% respectively in this series. (176) A population-based study of 1514 breast cancer patients published showed that the observed 5 year survival was 42.3% and the corresponding relative survival was 46.8%. (177) The observed survival was 57.4% for localized disease, 45.8% for direct extension, 37% for those with regional node involvement, 14.2% for distant metastasis and 38.3% for those with un-staged disease. A total of 2080 cases of invasive female breast cancer registered in MMTR, Chennai, with a follow-up rate of 84% reported that observed survival rates at 1, 3 and 5 years were 80%, 58% and 48% respectively; the corresponding figures for relative survival were 81%, 61% and 51. (38) In another study of 449 patients with breast carcinoma showed that the overall 5-year survival rate was 40%. (56)

6.2 Factors affecting survival:

6.2.1 Age at diagnosis: The median age at diagnosis of patients in our study was 48 years (Range: 22-85 years); significantly lower than the western figures, but similar to other Indian figures. (178–182) The median age at diagnosis for early breast cancer in our study was 50 years (range 22-85) which is similar to one of the Indian study (175), whereas the median age at diagnosis for locally advanced breast cancer in our study was 47 years (range 23-89), which was

in accordance to the some studies. (183,184) The median age at diagnosis for metastatic breast cancer cohort in our study was 50 years which was consistent with literature report. (185,186)

The prognostic value of age at diagnosis is particularly controversial due to the fact that there is no worldwide consensus on age boundaries for the definition of "young" age breast cancer. In the literature, the cut-off point of young age varies and has been set at age, 30, 35, 40, and 45. As a consequence, variation in disease management may occur in patients of similar age. In our study, we used cut-off of 50 years of age to evaluate its influence on both disease-free and overall survival. Kaplan-Meier survival analysis showed that early breast cancer patients aged ≤50 years exhibited significantly better OS than women aged >50 years (Table no 5.3.2). Similarly, locally advanced breast cancer patients aged ≤50 years also exhibited significantly better OS than women aged 51 years or more (Table no. 5.4.2). However, patients aged > 50 years exhibited better DFS than patients aged ≤50 years in both early and locally advanced breast cancer. We noted that metastatic breast cancer patients aged >50 years exhibited significantly better OS than women aged ≤50 years (Table no 5.5.2). Our finding on the absence of any impact of age at diagnosis on breast cancer survival is in agreement with the findings from some other studies especially those from Asian populations. (27,30,187) Other studies, however, mostly those conducted in western countries, found that age at presentation does influence the outcome of breast cancer and suggest that age should be taken into consideration for patient management. (188–190) They demonstrated that breast cancer in young women is less favourable because of advanced stage, tumour aggressiveness, and negative hormone-receptor status. However, this predictive role of age at diagnosis is not universally found and accepted.

(30,191,192) In a large cohort study conducted in Swedish women, the less favourable survival of young age breast cancer was more predominant in those diagnosed with early stage breast cancer. (188) One possible limitation of this study is that entire cohort was heterogeneous and contained a mixture of premenopausal and postmenopausal patients. Adami et al. showed complex pattern of survival as a function of age at diagnosis of breast cancer. (28) Various explanations have been given for these conflicting results, including small numbers of patients comprising the study population, differences in patient selection criteria and differences in the age groupings used in the analyses. Larranaga et al. concluded in his study in Spain that age, stage of the disease, and the level of cellular differentiation affect survival of breast cancer. (193) The consecutive studies conducted by Kim et al. stated in his study of Asian countries that clinical factors of breast cancer such as mean age of diagnosis, stage of the disease, and spread of estrogen and progesterone receptor in Asian countries are different, and the mean age at the time of diagnosis for breast cancer in Asian women is usually between 49.0 and 50.0 years. (18,194) The results of Fallahzadeh et al. study suggest that women whose age of diagnosis was less than 50 years survived more than women older than 50. (195)

6.2.2 Place of Residence

Majority of the patients in the study were non-resident of Mumbai 75.5% (Table 5.1.2). The effect of residence as a proxy for access to care may differentially affect stage at diagnosis and survival if access to screening services is different from access to follow-up and treatment services. Place of residence is considered mainly because the hospital registers a large proportion

of cases from outside the city of Mumbai and this is important for determining the follow-up rates. Place of residence did not however show any survival differences in our study (Table 5.3.3, 5.4.3 and5.5.3). This is in agreement with other Indian studies. (9)

6.2.3 Level of Education

Educational level can be taken as an indirect indicator of social class. In our study we found 81.1% literacy rate (Table 5.1.3). In our study we found level of education to be independent prognostic factor for overall survival in patients with early breast cancer (Table 5.3.20) as well as for locally advanced breast cancer patients (Table 5.4.19). However, level of education didn't emerge as an independent prognostic factor for disease-free survival in patients with early breast cancer neither for locally advanced breast cancer patients. In metastatic breast cancer (Table 5.5.4) we found higher survival rate with literate patients as compared to illiterate patient this difference was statistically significant, but failed to achieve independent predictor in multifactorial analysis. Our results were similar to one of the population-based study of survival from breast cancer conducted by Nandakumar et al. which showed educational status was one of the independent predictors of survival. (Nandakumar et al, 1995). This may be related to the knowledge, awareness, attitudes, patterns of use of health services, compliance to treatment and clinical follow-up.

6.2.4 Religion

Majority of the patients were following Hinduism 83% (Table 5.1.4). Breast cancer has figured prominently in research evaluating the impact of psychosocial factors on cancer morbidity and mortality. (41) Religion is one of the psychosocial factors thought to influence health outcomes. (196) Numerous articles, both medical and pastoral, have identified the extent to which various aspects of religiousness help women cope with breast cancer, experiencing, for instance, greater hope in stressful circumstances. (197,198) Few studies have looked at whether religiousness influences cancer survival; and those that have, generally did not adequately control for biomedical factors. (43,199) In our study we did not found any correlation of breast cancer with religion.

6.2.5 Marital Status:

Married persons enjoy overall better health and increased life expectancy compared with the unmarried (divorced, separated, never married). (46,200,201) Research also indicates a survival advantage for married persons living with a chronic disease such as cancer. (49,202,203) Married persons typically enjoy higher socioeconomic status than unmarried persons, which may translate into better access to healthcare. Marriage may also reflect a healthy selection bias, such that those with psychiatric or physical impairments may be less likely to marry. (200) Marriage may also influence lifestyle behaviors such as health screenings, diet, and exercise, all of which may be mediating factors of better health. (202) Additionally, marriage may offer a protective

benefit through increased social support networks. (204) Cassileth et al. and Neale et al. did not identify any significant association between marital status and the extent of disease, therapy, and overall survival. (205,206) In our cohort of patients 82.8% were married and 17.2% were either unmarried or widow/divorced/separated at the time of registration in the hospital (Table 5.1.5) and marital status was not found to have any influence on both disease-free and overall breast cancer survival. There can be a number of reasons for not finding any association between marital status and breast cancer survival, firstly, we have capture marital status at cancer diagnosis only; changes in marital status following diagnosis are not tracked. The changes in marital status may have an influence on outcomes. Secondly, we placed divorced, widows and separated women into a single category; however, studies have shown that while there may be some variation among groups of unmarried women (i.e. never married, divorced and widowed), they all fare worse than their married counterparts. Thirdly, most of the studies showing improved survival in married individuals are from western developed world, where better social support and companionship have been cited as the main reasons for improved survival. (207) India is culturally and socially very different from the western countries, and is socially very closely knit; particularly the concept of joint families may make up for the social and emotional support for the unmarried or widowed elders in the family.

6.2.7 Parity

Parity is an established risk factor for breast cancer. We did not find a significant difference between overall survival rates of nulliparous and multiparous women, but also showed that higher parity was associated with lower survival rates.

6.2.8 Menopausal status

Almost 51.9% of the patients in our study were postmenopausal (Table 5.1.6). We did not find any association of survival with menopausal status. A study on breast cancer survival in Hawaii also found no association for menopausal status. (208) Premenopausal women are believed to have a worse prognosis in terms of DFS and OS. (209) However, in the metaanalyses of EBCTCG, it was documented that when age was taken into account, menopausal status did not have an independent influence on the treatment outcome. (210) In our study, menopausal status was not an independent predictor of DFS and OS.

6.2.9 Family history of cancer

A positive family history of breast or ovarian cancer is a risk factor for breast cancer. (211,212) In our study, we did not find any association of a positive family history and breast cancer survival. (Table 5.3.10, Table 5.4.10 and Table 5.5.9) Previous studies on the impact of family history on survival after breast cancer have yielded ambiguous results, some indicating better, some similar, and some even worse survival rates for patients with a positive family

history. (71,73,213) Differences in definition of family history, study design, definition of outcome measures (overall survival versus disease specific or disease free survival), and adjustment for confounders, as well as limited sample size of studied populations, make results of the various studies difficult to compare.

6.2.10 Comorbidity:

Comorbidity is common among cancer patients, in our study 21% patients had one or more comorbidities (Hypertension, Diabetes mellitus, Heart Disease, Asthma and Human Immunodeficiency Virus (HIV) (table 5.1.8). Several studies investigated the impact of comorbidities on survival in breast cancer patients. (78,214,215) Breast cancer patients with comorbidities have poorer survival than breast cancer patients without comorbidity. (81,84,216) In our study we did not found the presence of comorbidity to be independent predictor of prognosis for patients with early breast cancer, locally advanced breast cancer and metastatic breast cancer. In early breast cancer (table 5.3.10) , locally advanced breast cancer (table 5.4.10) and metastatic breast cancer (table 5.5.10) analysis patients with comorbidity were found to have considerably lower 5 year overall survival rate as compared to patients without co morbidity, however this difference failed to achieve statistical significance ($p=0.201$,$p=0.291$ & $p=0.155$, respectively).

6.3.1 Staging

Literature shows that in India majority of new cases are advanced stage-locally advanced or higher stage at the time of diagnosis. (217,218) According to various studies majority of carcinoma breast cases in the west report in Stages I and II of disease, whereas in India 45.7% report in advanced stages. (181,219) sss

The clinical stage at breast cancer diagnosis remains one of the most important prognostic factors of survival. (220) The most accepted classification is the TNM staging system developed by the American Joint Committee on Cancer (AJCC). (89) In our study, clinical TNM staging was found to be significantly affecting both overall and disease-free survival in breast cancer cases (table 5.2.9). The 5 yr disease-free survival rates for stage I, II and III were found to 92.7%, 85.3% and 63.2% respectively, whereas 5yr overall survival rates for stage I, II and III were found to 91.5%, 88.3% and 67.1% respectively. (table 5.2.3) Similar, 5 yr disease-free survival rates of 75%, 65.6%, 49%, and 30% for stage I, II, III and IV respectively.

The reported 5-year survival rates for 252710 patients who were diagnosed between 2007 and 2013 in the United States SEER regions were 98.9% for localized stage cancer patients, 85.2% for regional stage patients and 26.9% for distant stage patients. (221) The overall 5 year survival rate in our study for EBC, LABC and MBC was found to be 90%, 69% and 13% respectively. In our study, we reported the 5 year disease-free survival of early breast cancer and locally advanced breast cancer of 89% and 65% respectively. There is an inverse correlation between the stage of the disease and survival and this study confirmed this finding.

6.3.2 Histological grade: Majority of patients (82.9%) were diagnosed with grade III tumours (Table 3.1.13). This is in accordance with other studies. (222) The tumor's histological grade is a well-known prognostic factor, and high histological grades were reported to have a negative impact on patient survival. (223–225) Similarly, in our study also high grade tumor was found to be an independent predictor of poor disease-free survival in early breast cancer patients as well as in locally advanced breast cancer patients.

6.3.3 Tumor location: Determination of whether tumour location can be used prognostically is important in optimising treatment. Tumour location is highest in the UOQ (50–58%) across multiple populations; include Chinese, Danish, the United Kingdom and women treated within the United States Department of Defence healthcare system. (226) Upper-outer quadrant breast cancers have a more favorable survival advantage when compared with tumors in other locations. (114) In our study, tumours in the UOQ showed a trend towards favourable prognosis although this did not reach the level of significance (P = 0.0754). In this study, the UOQ, which was the most common site for tumours within the human breast, was not significantly associated with improved survival. Reasons for discordant results are varied. For example, the manner in which tumour locations are grouped can affect survival results: when quadrants were evaluated individually or when tumour sites were combined into inner versus outer or lower versus upper, survival did not differ.

6.3.4 Lymphovascular Invasion (LVI)

In the majority of studies, the high rate of positive lymphovascular invasion (LVI) shows a close relationship with known markers of a poor prognosis. (227) The presence of LVI can predict a worse outcome for patients with invasive breast cancer. LVI may also be used as an indicator of aggressive behavior and the metastatic ability (nodal and systemic) of the primary malignancy (228–230) and also LVI is an adverse prognostic factor of both relapse and survival in node-negative patients treated with mastectomy and systemic therapy. (230) Freedman et al. reported that LVIs that are accompanied by other poor prognostic factors have been previously mentioned, but LVI alone is not an independent determinant in terms of local regional recurrence or survival in multivariate analysis. (231) LVI is well-documented in breast tumors; although it is a marker of a poor prognosis, there is no consensus in the literature on this subject. Upon univariate analysis, we found that LVI shortens the overall survival; however, LVI was also found to affect the overall survival and disease-free survival in multivariate analysis.

6.3.5 Extensive Intraductal component (EIC): EIC was defined as ductal carcinoma in situ (DCIS) occupying 25% or more of the area encompassed by the infiltrating tumor and DCIS present in grossly normal adjacent breast tissue.

6.3.6 Hormonal factors:

The prognostic role of hormone receptor status is similar to that in early stage disease, and positivity is associated with better outcome. (232) Dunnwald et al. looked at hormone receptor ER/PR status (positive or negative) and the relative risk of mortality according to demographic

or clinical variations. They examined data from 11 population-based cancer registries taking part in the Surveillance, Epidemiology, and End Results program and included in their study 155,175 women from the years 1990 to 2001, who were over 30 years old and had a primary diagnosis of invasive breast carcinoma. The goal of their study was to determine relations between joint hormone receptor status and breast cancer mortality risk and the Cox proportional hazards model was implemented to compare results within categories divided by diagnosis year, diagnosis age, ethnicity, histologic tumour type, stage at time of study, size and grade, and axillary lymph node status. Results showed that in comparison to women with ER+/PR+ tumours, women with ER+/PR-, ER-/PR+, or ER-/PR- tumours experienced higher risks of mortality, irrespective to a great extent of the various demographic and clinical tumour characteristics assessed. (233) Hormone receptor status is important not only as a prognostic factor but also as a predictor of response to endocrine therapy. (234) ER-positive patients have better DFS than ER-negative patients regardless of nodal involvement. (235) The longer DFS and OS in receptor-positive patients regardless of the hormonal therapy and chemotherapy used dictates that the receptor positivity of the primary tumor not only predicts the response to hormonal therapy but also is related to an inherent lack of biological aggressiveness. (209) Our data confirmed the positive and independent effect of receptor positivity on DFS and OS in multivariate analysis.

6.3.7 Axillary lymph nodal status

The distribution of patients with axillary lymph nodes involved was similar to data from other available studies. (11) As a matter of fact, patients without metastatic axillary lymph node

involvement have a better prognosis with regard to both OS and DFS. As lymph node involvement increases, survival decreases regardless of the tumor size. The patients with four or more positive lymph nodes have the poorest survival expectance. (236) In this study, similar to previous reports nodal involvement correlated with worse DFS and OS. (209,236) This unfavourable effect was more prominent when 4 or more lymph nodes were involved.

6.3.8 Treatment: Surgery is the frontline treatment for breast cancer. () In our study also 92.1% (1158) of cases were treated with surgery either alone or in combination with radiotherapy (RT) or chemotherapy (CT) (table 5.1.15). 64.7% had taken radiotherapy, 82% of the patients had taken neoadjuvant or adjuvant chemotherapy and 50.3% of the patients had taken hormonal therapy or targeted therapy.

6.3.9 Metastatic Breast Cancer: Almost all deaths in patients with diagnosis of breast cancer are due to metastatic disease, with metastases to bones, lung, liver, and brain among the most common sites [11]. Few studies with small number of patients have evaluated the prognostic significance of metastatic pattern in treatment naive patients. It is important to identify predictors of specific organ involvement in a large cohort of patients.

The median OS of 17 months seen in the overall patient population in our study is similar to the survival reported by previous authors that analyzed patients with de novo stage IV breast cancer [14–17]. Our study showed important differences in OS according to metastatic pattern. Patients with bone-only metastases had the longest OS, whereas those with visceral pattern had

the worse prognosis (table no 5.5). Ren et al. confirmed the worse prognosis of patients with multi-organ involvement among 194 women diagnosed with de novo stage IV breast cancer between 1997 and 2010; however, they reported no differences in OS between bone and visceral pattern [19]. An interesting study by Lobbezoo et al. compared outcomes of 815 patients with de novo or recurrent metastatic breast cancer and identified that patients with visceral metastases as well as those with multiple metastatic sites had worse OS, findings consistent with our results [17].

We observed that the number of affected organ sites had a significant impact on survival. When compared with patients with one metastatic site, patients with multiple affected sites had 1.6 times higher risk of death. In all, our study underscores the importance not only of metastatic pattern but also of specific metastatic sites in the prognosis of patients with stage IV breast cancer at initial diagnosis and provides specific risk estimates for each group.

Our results showed that the subtype with best prognosis was the HR-positive group. This finding differs from previous studies that have described the best outcomes in the HR-positive group [9, 20, 21]. An interesting finding that emerges from our study is that patients with HR negative had different OS compared with patients with HR-positive (hazard ratio 2.04; 95% CI 1.37–3.04) (Table 5.5.17).

6.3.3 Summary of Independent predictors of survival: Table 6.3.1 (given below) provides a summary of the identified independent predictors of disease-free survival and overall survival in all the three cohort analysis. In multivariate analysis for EBC cohort tumor grade, positive

hormonal receptor status, absence of lymphovascular invasion and pathological lymph node negative were found to be independent predictors of DFS, while education status, positive hormonal receptor status and pathological lymph node negative were found to be independent predictors of OS. The number of pathological axillary lymph nodes and hormonal status was found to be the most important prognostic factor both for DFS and OS for EBC. In multivariate analysis for LABC, tumor grade, hormonal receptor status, absence of extensive intraductal component, absence of lymphovascular invasion and pathological lymph node negative were found to be independent predictors of DFS, while education status, tumor grade, hormonal receptor status, absence of extensive intraductal component, absence of lymphovascular invasion and pathological lymph node negative were found to be independent predictors of OS. The tumor grade, hormonal receptor status, absence of extensive intraductal component, absence of lymphovascular invasion and pathological lymph node negative was found to be the most important prognostic factor both for DFS and OS for LABC. In multivariate analysis for MBC, hormonal receptor status, number of metastases and site of metastases were found to be the most important independent predictors of OS.

Table 6.3.1: Summary of independent predictors of survival of breast cancer

Early Breast Cancer (n=536)		Locally Advanced Breast Cancer (n=597)		Metastatic Breast cancer (n=125)
Disease-free survival	**Overall survival**	**Disease-free survival**	**Overall survival**	**Overall survival**
• Tumor grade • Hormonal status • LVI • Pathological axillary lymph nodes	• Education status • Hormonal status • Pathological axillary lymph nodes	• Tumor grade • Hormonal status • EIC • LVI • Pathological axillary lymph nodes	• Education status • Tumor grade • Hormonal status • EIC • LVI	• Hormonal status • Number of metastases • Site of metastases

Abbreviations-EIC: Extensive intraductal component, LVI: Lymphovascular invasion

6.4 Timelines:

The goal of early detection is to diagnose and treat breast cancer patients in an early stage when the prognosis for long-term survival is best. Prognosis is generally more favorable for women with early stage disease than for those with more advanced disease. Since early detection is associated with decreased mortality, one would think that it is important to minimize delays in

detection, diagnosis, and treatment. Longer waiting times prior to breast cancer diagnosis and the initiation of therapy are of prognostic concern if delay leads to stage progression, disease worsening, or treatment complications. There are two major types of delay. Patient delay is delay in seeking medical attention after self-discovering a potential breast cancer symptom or failure to keep appointments. System delay is delay within the health care system in getting appointments, scheduling diagnostic tests, receiving a definitive diagnosis, and initiating therapy. Both of these, by leading to delays in diagnosis and treatment, could result in a poorer prognosis for women with breast cancer. (237) Hence in order to assess the influence of time on breast cancer survival we estimated two broad timelines in our study namely time between registration in this hospital (TMH) and diagnosis and time between diagnosis and commencement of treatment.

6.4.1 Time between registration and diagnosis:

Diagnosis delay, the time between seeking medical advice and the date of final diagnosis based on pathological examination (i.e. biopsy), remains a serious problem. Studies have shown that diagnosis delay of over 3 months is associated with a bigger tumour size, positive lymph nodes, high incidence of late clinical stages, and metastatic disease. (237,238) Delay in diagnosis predicts worse clinical outcomes. (239) The delay may cause mortality of the patient. In our study, we estimated the time period required to pathologically confirm the diagnosis of tumor from the time of registration of the patient in this institute. Majority, of the patients were diagnosed within 7 days and the median period of diagnosis was found to 4 days (table 5.6.1). On survival analysis time required for diagnosis was not found to be associated with survival

(table 5.6.3). A meta-analysis containing 38 studies demonstrated that delays of 3–6 months are associated with poor survival. (167) One study has suggested that a delay of >6 months is associated with late tumor stage in breast cancer ($p<0.05$), although overall survival was not significantly different between delayed and non-delayed cases. (240) Interestingly, our results showed no significant difference between time for diagnosis and overall survival, which is in agreement with the study of Love et al. (240) However, we need to acknowledge the limitation that due to the retrospective nature of our study we could only analyze the effect of time required for diagnosis in the hospital but could not account for the time period from onset of symptoms to patient reporting to first health care centre, which is likely to be longer than the time spent in the hospital for diagnosis.

6.4.2 Time between diagnosis and commencement of treatment:

In the present study, the median time from diagnosis to initiation of treatment was found to be 10 days, and was found to be associated with overall survival ($p<0.001$) (table 5.6.6). Richards et al. conducted a study of 2,964 women who presented with any stage of breast cancer to Guy's Hospital in London between 1975 and 1990. (167) A total of 32% of the women had symptoms for at least 12 weeks prior to their first hospital visit. Among these women, 32% had locally advanced or metastatic disease, compared to 10% of those women with delays of <12 weeks. Women with delays of 12–26 weeks had significantly worse survival rates than those with <12 weeks of delay. In multivariate analyses, the adverse impact of delay on survival was attributable to an association between longer delays and more advanced stage, but this adverse

impact disappeared within individual stages of disease. Neale et al. demonstrated that even without adjustment for tumor grade, patients at Houston's M.D. Anderson Hospital with delay of more than 6 months had substantially lower cumulative survival after 10 years than patients with delay of 3–6 or <3 months. (241) Treatment delay (the number of weeks between the date of diagnosis and date of definitive treatment) was evaluated in a retrospective case-only study on 8,860 adolescent and young adult breast cancer cases diagnosed from 1997 to 2006 using the California Cancer Registry database. (242) The 5-year survival in women who were treated by surgery and had treatment delay of more than 6 weeks was 80% compared with 90% (P = 0.005) in those with treatment delay of <2 weeks. In multivariate analysis, longer treatment delay was a significant risk factor for shorter survival. McLaughlin et al. conducted a retrospective analysis of 1,786 low-income, adult female North Carolina Medicaid enrollees diagnosed with breast cancer from January 1, 2000 to December 31, 2002, in the linked North Carolina Central Cancer Registry Medicaid Claims database to study the impact of long delay between a biopsy-confirmed breast cancer diagnosis and treatment initiation on survival. (243) The median delay was 22 days. Adjusted Cox proportional hazards regression demonstrated that the delay interval did not affect survival among those diagnosed at an early stage, but among late-stage patients, intervals between diagnosis and first treatment ≥60 days were associated with significantly worse breast cancer-specific survival (HR = 1.85, 95% CI = 1.04–3.27; P = 0.04). Brazda et al. conducted a retrospective review of patients undergoing breast cancer treatment between August 2005 and December 2008 in a comprehensive, multidisciplinary breast oncology program in two hospital systems. (168) The patients were divided into three groups based on interval to

treatment (the time between date of pathological diagnosis, usually via core needle biopsy, and the date of initial therapy, either surgical or systemic): 0–45, 46–90, and >90 days, and there was no association between the interval to treatment and survival. Because previous studies had revealed decreased survival with delays >90 days, the authors separated patients into groups based on interval to treatment of 90 days, but there was no demonstrable difference in survival between these two groups. However, we need to acknowledge the limitation that we have analyzed the relationship between delay and survival time, without considering tumor stage.

6.5.1 Loss-adjusted survival rate (LAR):

The literature on survival analysis uses standard statistical methods such as actuarial (or life-table) method (24) and the product-limit method (25) for estimating survival rates. All these methods hold true only under certain assumptions. The main assumption of these methods is the independence of risk of death and withdrawal. Thus, survival estimates may be biased if the proportion of cases lost to follow-up is substantial (as in many developing countries, where health information systems are not well developed), and if the loss to follow-up is correlated with the probability of death (prognosis) of the patient after he or she was lost. In India, the withdrawals are most often non-technical withdrawals i.e. they are loss to follow-up. (174) Prognostic factors that may also predict loss to follow-up are related to the clinical characteristics of the disease, the patient and the social environment. For example, recurrence or relapse of the disease and serious comorbidity are prognostic factors that may cause the patient to move away (for treatment, or terminal care), making them impossible to trace. (172) Furthermore, the bias in

the estimation of survival probability is dependent on both the magnitude and nature of losses to follow-up, and may be in either direction. For example, the true probability of death of patients lost to follow-up may be greater than assumed if patients with poor prognosis are more likely to be lost. In these circumstances, the actuarial survival estimate is biased and too high. The first step in deciding whether bias in the actuarial estimate of survival is likely is to examine whether loss to follow-up varies according to prognostic variables such as age, stage, etc. Computation of loss-adjusted survival (174) then takes into consideration such differential losses, by assuming that patients lost to follow-up within strata defined by these variables have the same probability of death as those still remaining under observation and belonging to the same stratum. It is reasonable to expect survival experience in patients lost to follow-up and with complete follow-up to be more similar within a prognostic group, than when all patients are considered together. The difference between the crude actuarial survival and the loss-adjusted value indicates the magnitude of the effect of differential loss to follow-up.

6.5.2 In our study overall 5 yr survival for all cases by actuarial method was found to be 72% and Loss adjusted survival rate was found to be 70%. Similarly, in subset analysis for early and locally advanced breast cancer the 5 yr survival by actuarial and LAR method was found to be 90% & 89.1%, and 69% & 65.7% respectively. Thus, adjustment for loss of follow-up gave an estimated 2.0% units less 5 years survival than the observed (actuarial) survival. The small difference between the absolute (actuarial) survival and the loss-adjusted survival observed in this study is much less than in other studies. (9,172) This can be because our study had only

14.1% loss to follow up as compared to much higher loss to follow-up reported by other quoted studies i.e Ganesh et al. (9) loss to follow-up of 35-43%; Sriamporn et al. (172) loss to follow-up of 26.7%. The low loss to follow-up observed in our study was because our study cohort comprised of only those cases who were residents of Mumbai and it has been seen that in patients treated at TMH, the proportion of loss to follow-up is much lower among residents of Mumbai as compared to non-residents. (174) Furthermore, tracking of Mumbai cases is better because of integration of our data with Mumbai population based cancer registry and also due to sharing of mortality data by the local municipal vital registration system (Brihanmumbai Municipal Corporation). This method of calculating loss-adjusted survival rates has been shown to be useful where large numbers of patients are lost to follow-up. (173) However, this observation of small difference between the absolute (actuarial) survival and the loss-adjusted survival is not confined to cancer of the breast cancer; differences for other sites like oral cavity (data from six registries from developing countries) and larynx (data from Chennai and Mumbai cancer registries) have also been reported to be of similar (small) size. (244) Thus, the small correction of survival by loss-adjustment seen in our study is probably due to low proportion of loss to follow-up and larger correction are more likely to occur in datasets with higher loss to follow-up, due to patients coming from a wide geographic area.

6.6 Strengths and Limitations:

To the author's knowledge, this study is the first to provide a comprehensive examination of the impact of socio-demographic and clinical factors related to the stage at diagnosis, disease-

free survival and overall survival for women diagnosed with breast cancer in India. These factors include age at diagnosis, residence, religion, education level, family history of cancer, comorbidity, quadrant location, tumor grade, hormonal status, histopathological factors and treatment related factors. Further, all of the analyses presented in this dissertation also were stratified by stage at diagnosis providing a unique insight into the effects of socio-demographic and clinical factors within different stage at diagnosis.

The information for large number of variables was retrieved from all possible resources such as medical case records, electronic medical records, pathological reports and OPD data. One unique aspect about TMH is that it is comprised of a culturally diverse population to create a rich environment from which to conduct research. Additionally, due to its large proportion of patient, TMH is the premier cancer centre in India for the number of breast cancer cases diagnosed and treated a factor that has contributed to the large sample size of this study.

Additionally, it evaluates large no. of factors affecting both disease-free and overall survival, as well as timelines of different evolutions involved in patient care. In addition, loss adjusted survival rate to cater for patients lost in follow-up has also been computed and presented. This dissertation primarily used a retrospective study design, making it impossible to establish any causal relationship between the stage of diagnosis and socio-demographic factors, or between initial treatment selection and a patient's socio-demographic and clinical factors. For this research, it was limited to the data contained in the public file made available for research purposes by the TMH. Further, the TMH does not collect information related to a cancer

patient's comorbidities, income status and detailed information on reproductive and menstrual factors etc.

CHAPTER 7

SUMMARY AND CONCLUSION

7.1 Summary of findings: The summary of finding s is as follows

7.1.1 Disease-free Survival: The 5-year disease-free survival of breast cancer (excluding metastatic breast cancer cases) was found to be 76%. The 5-year disease-free survival for Early breast cancer and Locally Advanced breast cancer was found to be 89% and 65% respectively.

7.1.2 Overall Survival: The 5-year overall survival of breast cancer (all cases) was found to be 72%. The 5-year overall survival for Early breast cancer, Locally Advanced breast cancer and Metastatic breast cancer was found to be 90%, 69% and 13% respectively.

7.1.3 Early Breast cancer:

7.1.3.1 In Early breast cancer the independent predictors of prognosis for disease-free survival were tumor grade, hormonal status, LVI and pathological axillary lymph nodes.

7.1.3.2 In Early breast cancer the independent predictors of prognosis for overall survival were education status, hormonal status and pathological axillary lymph nodes.

7.1.4 Locally Advanced Breast cancer:

7.1.4.1 In Locally advanced breast cancer the independent predictors of prognosis for disease-free survival were tumor grade, hormonal status, EIC, LVI and pathological axillary lymph nodes.

7.1.4.2 In Locally advanced breast cancer the independent predictors of prognosis for overall survival were education status, tumor grade, hormonal status, EIC, LVI and pathological axillary lymph nodes.

7.1.5 Metastatic Breast cancer:

In metastatic breast cancer the independent predictors of prognosis for overall survival hormonal status, number of metastases and site of metastases.

7.1.6 Timelines: The median time period from registration to pathological confirmation of diagnosis was 4 days, from diagnosis to commencement of treatment was 10 days. The time period between registration and diagnosis was not found to be associated with survival, whereas time period between diagnosis and to start of treatment was found to be associated with survival.

7.1.7 LAR: Overall 5 year survival rate and loss-adjusted survival rate were found to be 72% and 70% respectively.

7.2 Conclusion

Breast cancer is a global public health problem and studies that help to understand the disease, its progression and associated factors are extremely important. The analysis of OS and DFS at 5 years performed in this study enabled us to have a better understanding of the profile of patients treated at the oncology service, the natural history of the disease and the factors involved in prognosis within a national context. The 5-year survival rates were better in patients with the early stages of breast cancer patient than in those with the advanced stages. The screening aimed at an early diagnosis of breast cancer represents an important strategy to achieve better overall survival and disease-free survival, associated with ensuring access by women to suitable treatment. These conditions are particularly important in the population examined. The multivariate survival analysis showed that some demographic factors are important and independent prognostic factors in mixed cohort of breast cancers, particularly in LABC patients. Demographic factors should therefore be included when biological prognostic variables in breast cancer are analyzed, particularly in retrospective cohorts. The present study showed factors affecting survival of breast cancer are consistent with those described in the literature. Better survival rates are associated to lower tumor grade, absence of lymphovascular invasion, extensive intraductal component, node negative and positive hormone receptors. By combining morphologic, clinical and hormonal determinants, the prognosis of the individual breast cancer will become predictable with increasing accuracy and permit judicious selection of the most effective therapeutic protocol. Knowledge of the main

characteristics and the factors associated with disease progression strengthens the need for new studies at Indian cancer treatment centers in order to obtain control of breast cancer in the country.

CHAPTER 8

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