ISSN: 2476-2377

Research Article

International Journal of Cancer Research & Therapy

Breast Cancer Recurrence and Study of Factors Associated with Survival after Recurrence

Madiha Liaqat[1]*, Shahid Kamal[1] and Waqas Fazil[2]

[1]*College of Statistical and Actuarial Sciences (CSAS), University of the Punjab, Lahore, Pakistan.*

[2]*Institue of Nuclear Medicine & Oncology Lahore (INMOL)*

***Corresponding author**
Madiha Liaqat, College of Statistical and Actuarial Sciences (CSAS), University of the Punjab, Lahore, Pakistan, E-mail: madiha.phd.stat@pu.edu.pk

Submitted: 03 Oct 2019; **Accepted**: 12 Oct 2019; **Published**: 23 Oct 2019

Abstract

Background: *Breast cancer is the most occurring threat for women across world, survival of this deadly disease is effected by recurrence after primary treatment. This study was aimed to understand survival times, hazard ratios and prognostic factors of breast cancer after recurrence.*

Methods: *This study was conducted on 1028 Pakistani women through retrospective design from February, 2011 to February, 2018 at Punjab, Pakistan. Factors were analyzed using statistical tools and techniques to find out rate of mortality after recurrence. Descriptive statistics, univariate and multivariate hazard ratios were calculated, which are helpful for clinicians to make therapeutic strategies for breast cancer patients.*

Results: *From the total of 1028 patients 447 observed mortality due to breast cancer with in follow-up time after recurrence, while 581 were still alive or had expired due to other reasons. Median survival time after recurrence was 3 years. Survival of breast cancer patients depends upon many factors. Multivariate model was used to find out predictors of death. Significant factors included post- menopausal women who were diagnosed breast cancer of grade 11 and 111 at the age ≤ 45 and/or ≥ 56, recurrence age ≤ 45, estrogen receptor positive, progesterone receptor negative and Her2.neu positive with tumor size ≥ 4 & involved lymph nodes ≥ 6.*

Conclusions: *At younger age survival of patients had decreased after recurrence. Chemotherapy as a primary treatment had statistically significant effect on lower mortality for women recurred. Progesterone receptor negative have greater chances of mortality .Grade 11 & 111 tumor with, larger tumor size and greater number of lymph nodes had the highest hazards.*

Keywords: Breast Cancer; Recurrence; Hazard Ratio; Survival Analysis

Introduction

Breast cancer is the most frequently diagnosed cancer in Pakistani women, 1 out 9 women are suffered due to this disease in their life span [1]. Major risk factors in developing breast cancer are: age, race, family history, presence of a BRCA1 or BRCA2 genetic mutation, hormonal factors, history of benign breast disease, and certain lifestyle factors like obesity, weight gain after menopause, alcohol and tobacco consumption [2-6]. Early puberty and late menopause, contraceptive and/or prevention of miscarriage pills, no pregnancy and no breastfeeding are associated with higher rate of breast cancer cases [7-10]. It takes time to diagnose breast cancer due to lack of awareness and availability of health facilities in Pakistan. After diagnosis availability of doctors and time slot to give primary treatment like radiotherapy and chemotherapy have effect on patients' survival [11, 12].

Breast cancer patients usually experience local, regional and distant recurrence after primary treatment [8,13,14]. Literature showed mortality rate of breast cancer was greater for those women who faced recurrence than those without recurrence. Researchers have dealt recurrence as a second primary event after diagnosis [15]. Radiotherapy and chemotherapy are used as systematic treatment, sometimes chemotherapy is given before radiotherapy but there is no set standard for given chemotherapy [16,17]. Although due to advancement in technologies diagnosis and treatment of breast cancer have increased survival time of patients. Still breast cancer is deadly threat for women across world due to molecular heterogeneity. Molecular subtypes of breast cancer have varying survival rates in the clinical context when estrogen and progesterone receptors are not equal in status, estrogen receptor (ER) and progesterone receptor (PR) have proved their importance in treatment decision [18-20]. In some cases chemotherapy has increased survival time for estrogen receptor negative women [21]. Many researchers reported survival after local recurrence was much inferior for patients with triple-

negative breast cancer than for other patients [22,23]. In published researches 15% to 30% breast cancer cases fall in Her2 positive subtype which has worst survival rate, Her2 (epidermal growth factor gene is located on the long arm of chromosome [24-26]. The tumor size and number of involved nodes exert a powerful influence on recurrence and mortality [27]. Probability of breast cancer is high in families where any blood relation has cancer history or females' relatives have ovarian or breast cancer history [28]. For therapy decision making purpose it is important not only to study prognosis but also tumors' subtypes and recurrence [29].

Although many researches are available on overall survival and disease free survival of breast cancer patients, but very few have emphasized on survival time after recurrence [2,30] in cancer studies, recurrence plays an important role to find out survival time of patients [15]. Survival analysis techniques make it easy to interpret highly correlated risk factors of any disease, when censoring occur. Mostly censoring occurred in disease data if at the end of follow up understudy patients are still alive and do not experience event of interest [31].

In the present study recurrence is considered as an important event which may play a role in study of breast cancer progression. This study was undertaken with the following objectives: to find out effect of recurrence on breast cancer patients' mortality after observing different factors at time of primary diagnosis breast cancer, and to identify discordant factors to get in depth details of breast cancer progression.

Methods

Patients

We retrospectively reviewed the data of 1028 breast cancer women who have observed recurrence after primary treatment from February, 2011 to February, 2018 in Punjab, Pakistan. Data were obtained from medical record of hospitals and phone call interviews. Pathological, clinical and demographic factors were collected from patients' medical record. Phone calls were made to ask about end point which was death due to breast cancer, censored event was still alive or death due to other reasons.

Factors Analyzed

Only those patients were considered who observed recurrence after diagnosis breast cancer as a primary disease. Data was recorded about, age as diagnosis, age at recurrence, menopause status, family history of breast cancer, estrogen and progesterone receptor, Her2. neu status, initial tumor size and involved nodes. Tumor was graded on the scale of 1-111. Initial treatment, chemotherapy and radiotherapy were performed in accordance with clinical guidelines; information about endpoint (death) was collected via phone calls.

Therefore, 1028 patients and 12 factors were included in the model, which were: age of patients at diagnosis time (≤ 45, 46-55, ≥ 56 Years), age at recurrence time (≤ 45, 46-55, ≥ 56 Years), family history of breast cancer (No, Yes), initial menopause status (Pre-Menopause, Post-Menopause), estrogen receptor (Negative, Positive), progesterone receptor (Negative, Positive), her2. neu (Negative, Positive), initial chemotherapy (No, Yes), initial radiotherapy (No, Yes), initial tumor size (0-3, 4-7, ≥ 8), initial number of involved nodes (≤ 5, 6-15, ≥16) , and initial tumor grade (1,11,111). To analyze effect of recurrence on survival of breast cancer patients, time was considered from the first recurrence to death. We had discarded Information about treatments and other factors recorded after the first recurrence. All statistical analyses were carried out using R version 3.5.1.

Statistical Analysis

Kaplan-Meier estimator have been used to derive the survival curve for each variable to get survival probability with respect to time, while cumulative curves used to estimate hazard probability of each factor and log rank tests showed statistical significance factors for survival after recurrence [32,33]. Censored event was women still alive at the end of seven years or have died due to other reasons except breast cancer. To evaluate which factors have statically significant effect on survival of breast cancer women after recurrence, survival and cumulative curves have been used [34]. As at the end of follow-up some women were still alive or died due to any other reason, this event marked as right censoring. Multivariate analysis showed combine effects of understudy factors in seven years survival after recurrence, Survival after recurrence depends upon prognostic factors, multivariate hazard ratios were determined, ninety five percent confidence intervals, and P-values were calculated for hazard ratios of each variable.

Results

Different factors were considered to study progression of breast cancer, distribution of prognosis factors was as follows: age at diagnosis (≤ 45 (36.1%), 46-55 (58.7%), ≥ 56 (5.3%)), age at recurrence (≤ 45 (30.0%), 46-55 (61.9%), ≥ 56 (8.2%)), survival time after recurrence (0-2.99 (49.3%), 3-5.99 (45.8%), ≥ 6 (4.9%)), Family history of breast cancer (No (38.6%), Yes (61.4%)), initial menopause status (Pre-menopause (43.3%), post- menopause (56.7%)), estrogen receptor (Negative (54.1%), Positive (45.9%)), progesterone receptor (Negative (35.4%), Positive (64.6%)), Her2. neu (Negative (47.9%), Positive (52.9%), initial chemotherapy and radiotherapy (No (63.6%), Yes(36.4%) & No (12.6%), Yes (87.4%)), initial tumor size (0-3 (63.4%), 4-7 (35.4%), ≥ 8 (1.2%)), initial lymph nodes involved (≤ 5 (69.3%), 6-15 (25.9%), ≥ 16 (4.9%)) and initial tumor grade (1 (20.1%), 11 (36.6%) , 111 (43.3%).

447 women who were diagnosed breast cancer have been died after recurrence in seven years. Age at diagnosis ranged from 18 to 59 and 253 (56.6 %) were lied in age group 46-55. 62..2% women belonged 46 to 55 years of age at recurrence. 78.5 % were died due to breast cancer within 3 years after recurrence . Furthermore 68.0 % had family history of breast cancer, and 58.8 % were post-menopausal women. The molecular subtype distribution of death patients were estrogen receptor positive 263 (59.3 %), progesterone receptor negative 298 (66.7 %) and Her2.neu positive 293 (65.5 %). 144 (32.2%) while 416 (93.1%) received radiotherapy before recurrence and had died due to breast cancer. Mostly patients who were died due to breast cancer had larger tumor size, greater number of involved lymph nodes and higher grade of tumor.

Univariate Analysis

Univariate analysis showed age at diagnosis ≤45 and age at recurrence ≤45 less survival time after recurrence of breast cancer. There was higher rate of mortality for post-menopausal women than pre-menopausal (HR: 1.07, (95%CI: 0.89; 1.29), P= 0.479) [35]. Women who had family history of breast cancer have higher hazard ratio than those who did not have (HR: 1.51, (95%CI: 1.23; 1.84), P= <0.001). Estrogen receptor positive (HR:1.67,(95%CI: 1.38;2.02),P=<0.001), progesterone receptor negative (HR:0.17, (95%CI: 0.14;0.21),P=

<0.001) and HER2.neu positive (HR:2.37,(95%CI: 1.94;2.91), *P*= <0.001) had effected survival after recurrence a lot. Women underwent to Initial chemotherapy had lower rate of mortality (HR: 0.74, (95% CI: 0.60; 0.90), *P*=0.00248) while radiotherapy had no effect on mortality after recurrence (HR: 2.43 (95%CI: (1.69; 3.50), *P*= <0.001). Tumor sizes greater than (4-7 cm) had poor prognosis to those with tumor sizes (0-3 cm), (HR: 2.61 (95%CI: (2.16; 3.16), *P*= <0.001), the worst prognosis was for tumor size ≥ 8 (HR: 4.73 (95% CI: (2.57; 8.70), *P*= <0. 001). Additionally, the risk of death in women were diagnosed breast cancer as a primary disease who had less than two involved nodes was higher in comparison women with ≤5 initial lymph nodes involved (6-15, (HR: 3.41. 95%CI: (2.80; 4.16), *P*= <0.001) & (≥16, (HR: 7.08, 95%CI: 5.13; 9.79), *P*= <0.001). Deaths due to breast cancer were higher for women had tumor grade 11 and 111 as compared to grade 1 (HR=6.98 (95%CI: 3.85; 12.67) & 28.32 (95%CI: 15.83; 50.65), *P*<0.001).

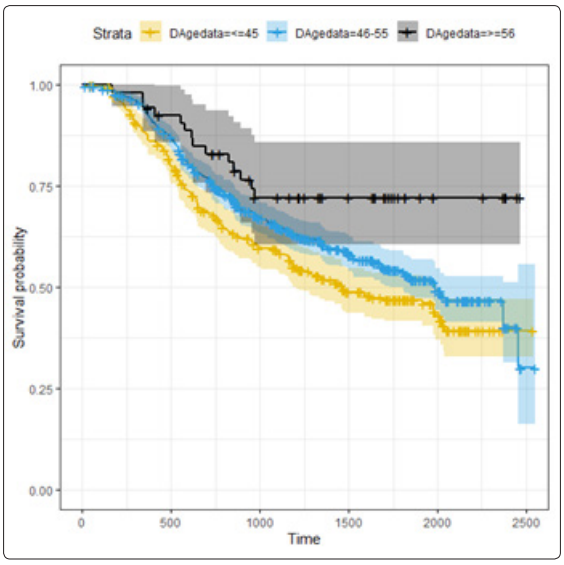
Table 1: Characteristics of Breast Cancer Patients (n=1028)

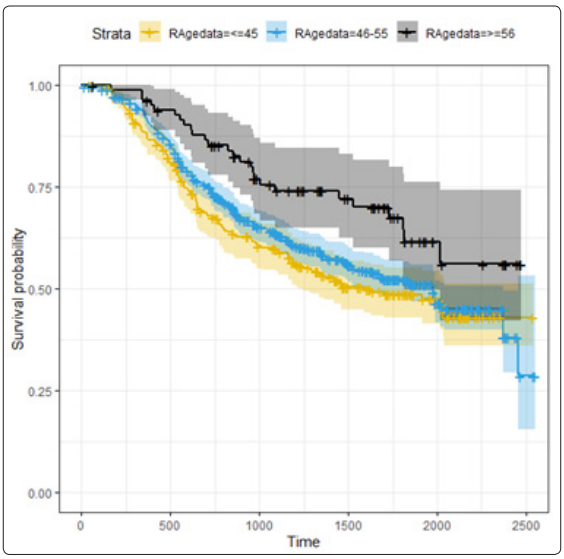
	Death (n=447)	Alive/Death other than Breast Cancer (n=581)	Total (n=1028)
Age at Diagnosis (Years)			
≤ 45	180 (40.3%)	191 (32.9%)	371 (36.1%)
46-55	253 (56.6%)	350 (60.2%)	603 (58.7%)
≥ 56	14 (3.1%)	40 (6.9%)	54 (5.3%)
Age at Recurrence (Years)			
≤ 45	143 (32.0%)	165 (28.4%)	308 (30.0%)
46-55	278 (62.2%)	358 (61.6%)	636 (61.9%)
≥ 56	26 (5.8%)	58 (10.0%)	84 (8.2%)
Survival Time after Recurrence (Years)			
0-2.99	351 (78.5%)	156 (26.9%)	507 (49.3%)
3-5.99	93 (20.8%)	378 (65.1%)	471 (45.8%)
≥ 6	3 (0.7%)	47 (8.1%)	50 (4.9%)
Breast Cancer Family History			
No	143 (32.0%)	254 (43.7%)	397 (38.6%)
Yes	304 (68.0%)	327 (56.3%)	631 (61.4%)
Initial Menopause Status			
Pre-Menopause	184 (41.2%)	261 (44.9%)	445 (43.3%)
Post-Menopause	263 (58.8%)	320 (55.1%)	583 (56.7%)
Estrogen receptor (ER)			
Negative	182 (40.7%)	374 (64.4%)	556 (54.1%)
Positive	265 (59.3%)	207 (35.6%)	472 (45.9%)
Progesterone receptor (PR)			
Negative	298 (66.7%)	66 (11.4%)	364 (35.4%)
Positive	149 (33.3%)	515 (88.6%)	664 (64.6%)
Her2.neu			
Negative	154 (34.5%)	330 (56.8%)	484 (47.1%)
Positive	293 (65.5%)	251 (43.2%)	544 (52.9%)
Initial Chemotheraphy			
No	303 (67.8%)	351 (60.4%)	654 (63.6%)
Yes	144 (32.2%)	230 (39.6%)	374 (36.4%)
Initial Radiotheraphy			
No	31 (6.9%)	99 (17.0%)	130 (12.6%)
Yes	416 (93.1%)	482 (83.0%)	898 (87.4%)
Initial Tumor Size (cm)			
0-3	206 (46.1%)	446 (76.8%)	652 (63.4%)
4-7	230 (51.5%)	134 (23.1%)	364 (35.4%)
≥8	11 (2.5%)	1 (0.2%)	12 (1.2%)
Initial Nodes Involved (n)			
≤ 5	216 (48.3%)	496 (85.4%)	712 (69.3%)
6-15	185 (41.4%)	81 (13.9%)	266 (25.9%)
≥ 16	46 (10.3%)	4 (0.7%)	50 (4.9%)
Initial Tumor Grade			
1	12 (2.7%)	195 (33.6%)	207 (20.1%)
11	121 (27.1%)	255 (43.9%)	376 (36.6%)
111	314 (70.2%)	131 (22.5%)	445 (43.3%)

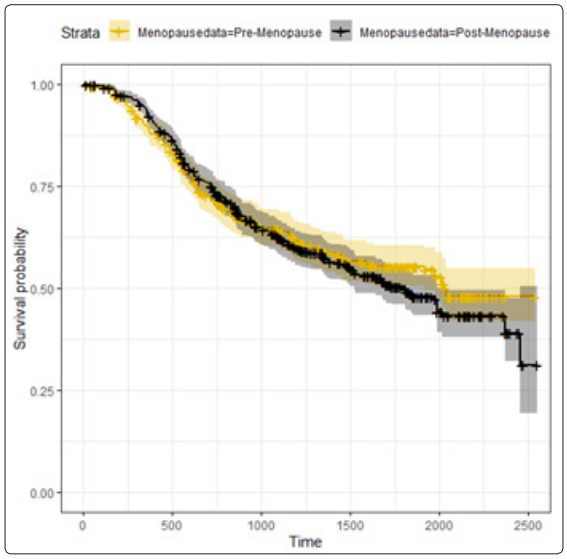
Table 2: Factors to predict mortality due to breast cancer

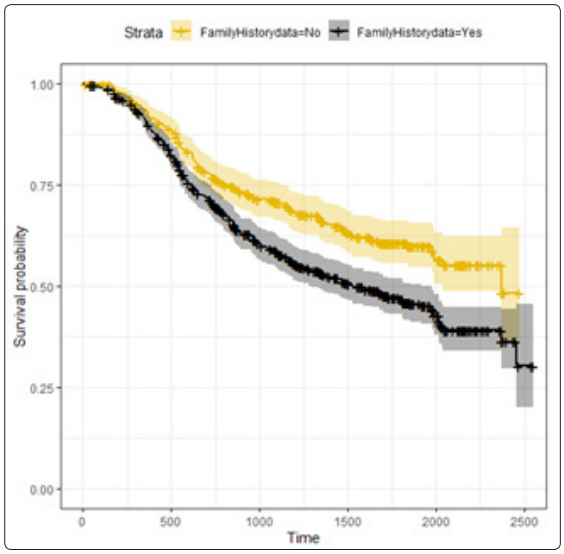
Factor	Univariate Analysis			Multivariate Analysis		
	HR	*95% CI*	*p Value*	*HR*	*95% CI*	*p Value*
Age at Diagnosis (Years)						
≤ 45	Reference			Reference		
46- 55	0.78 [0.65;0.95]		0.01297	0.76 [0.50;1.15]		0.19527
≥ 56	0.43 [0.25;0.75]		0.00263	1.62 [0.66;3.95]		0.29195
Age at Recurrence (Years)						
≤ 45	Reference			Reference		
46-55	0.88 [0.72; 1.08]		0.2111	0.78	[0.52; 1.16]	0.1221
≥ 55	0.53 [0.35; 0.81]		0.0032	0.48	[[0.23; 0.98]	0.0432
Initial Menopause Status						
Pre-Menopause	Reference			Reference		
Menopause	1.07 [0.89; 1.29]		0.479	1.44 [1.01; 2.05]		0.04421
Family History						
No	Reference			Reference		
Yes	1.51 [1.23;1.84]		<0.001	0.97 [0.78;1.20]		0.75882
Estrogen receptor						
Negative	Reference			Reference		
Positive	1.67 [1.38; 2.02]		<0.001	1.09 [0.89; 1.34]		0.39540
Progesterone receptor						
Negative	Reference			Reference		
Positive	0.17 [0.14; 0.21]		<0.001	0.36 [0.29; 0.46]		< 0.001
Her2.neu						
Negative	Reference			Reference		
Positive	2.37 [1.94; 2.91]		<0.001	1.98 [1.58; 2.47]		< 0.001
Initial Chemotherapy						
No	Reference			Reference		
Yes	0.74 [0.60; 0.90]		0.00248	0.75 [0.60; 0.93]		0.00745
Initial Radiotherapy						

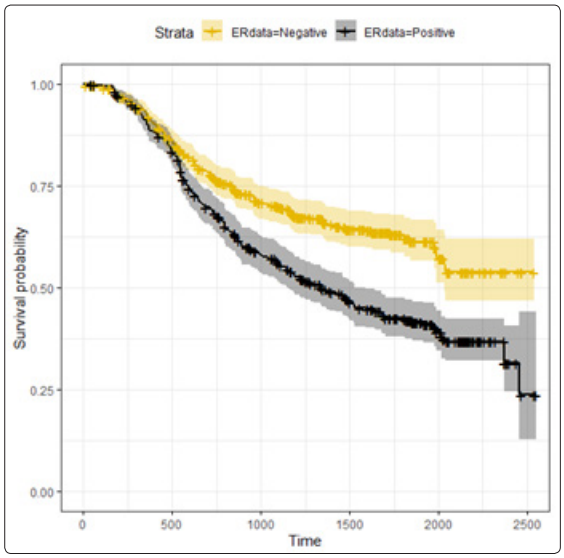
No	Reference	Reference
Yes	2.43 [1.69; 3.50] <0.001	1.53 [1.05; 2.24] 0.02577
Initial Tumor Size (cm)		
0-3	Reference	Reference
4-7	2.61 [2.16; 3.16] <0.001	1.39 [1.14;1.71] 0.00140
≥ 8	4.73 [2.57; 8.70] <0. 001	1.06 [0.55;2.07] 0.85640
Initial Nodes Involved (n)		
≤ 5	Reference	Reference
6-15	3.41 [2.80; 4.16] <0.001	2.22 [1.79; 2.75] < 0.001
≥ 16	7.08 [5.13; 9.79] <0.001	4.30 [2.93;6.31] < 0.001
Initial Tumor Grade		
1	Reference	Reference
11	6.98 [3.85; 12.67] <0.001	6.47 [3.54; 11.81] < 0.001
	28.32 [15.83; 50.65] <0.001	16.51 [9.10;29.95] < 0.001

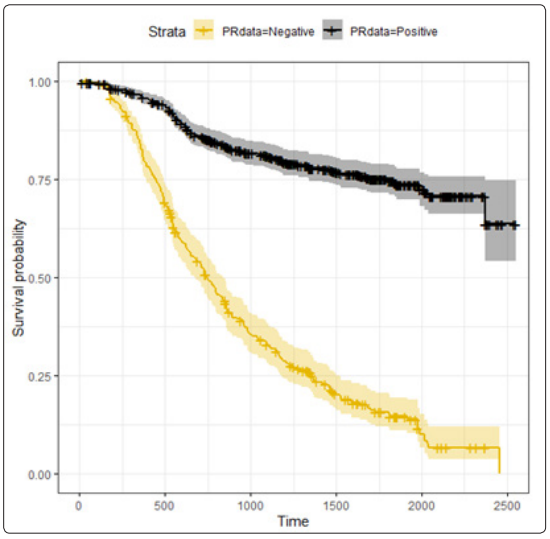


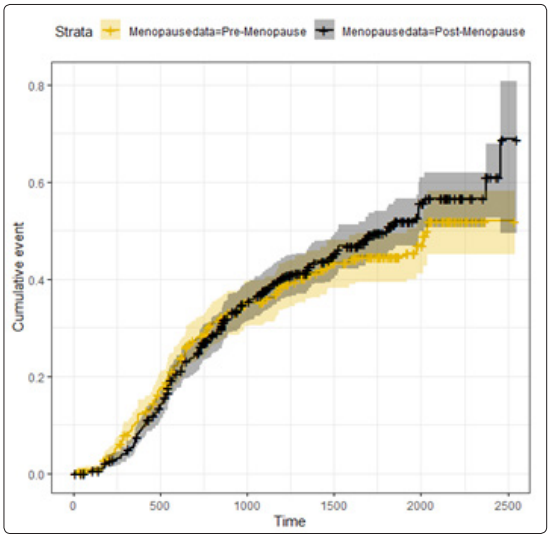


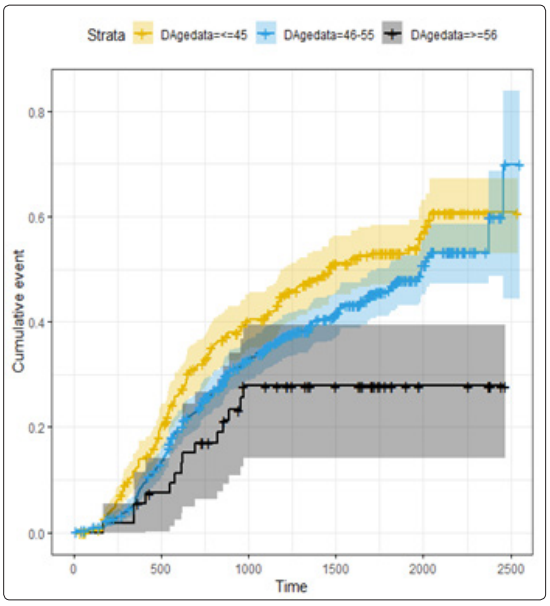


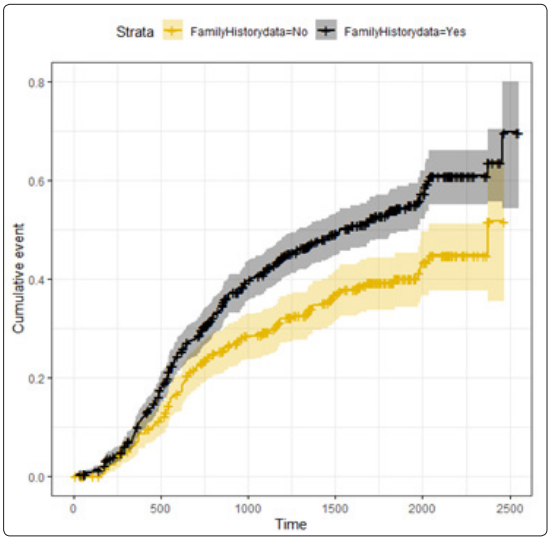


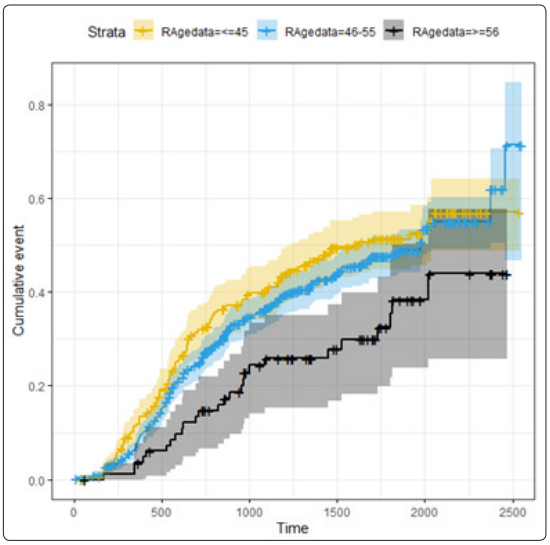


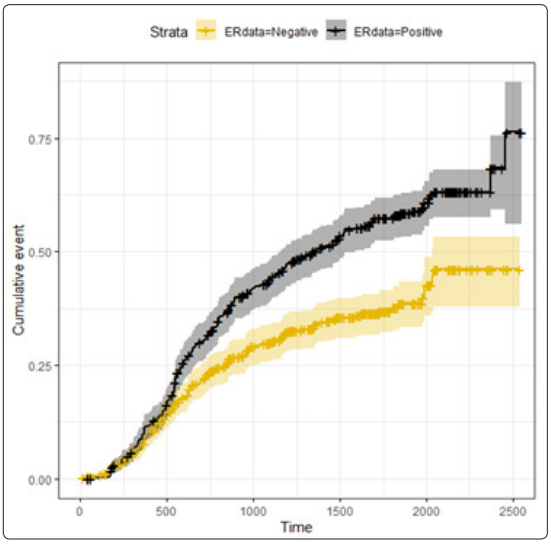

Strata
PRdata=Negative
PRdata=Positive
Survival probability
Time

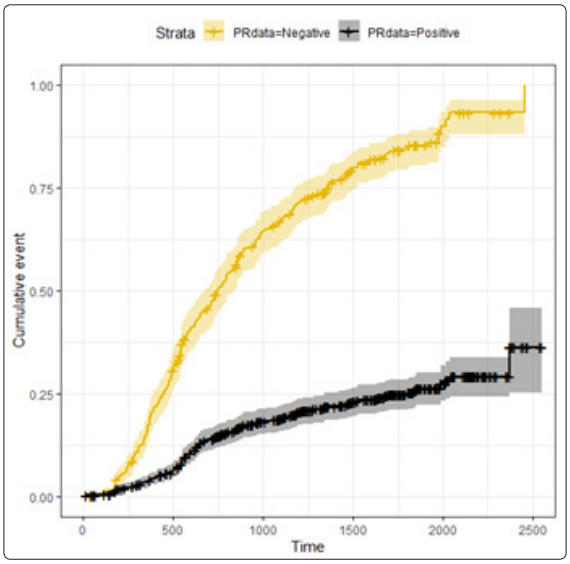

Strata
Menopausedata=Pre-Menopause
Menopausedata=Post-Menopause
Cumulative event
Time

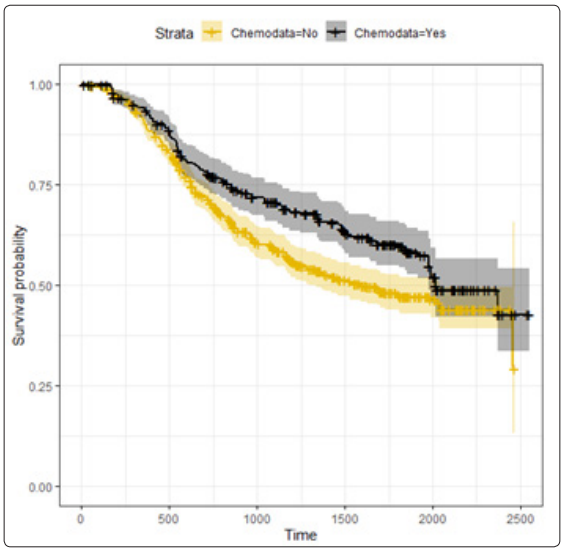

Strata
DAgedata=<=45
DAgedata=46-55
DAgedata=>=56
Cumulative event
Time

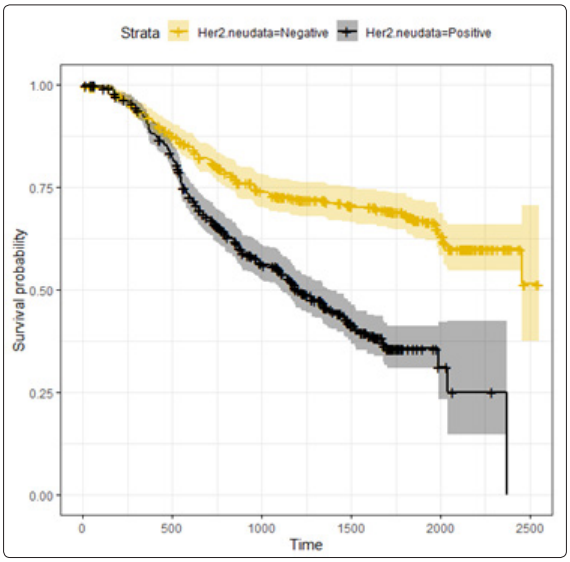

Strata
FamilyHistorydata=No
FamilyHistorydata=Yes
Cumulative event
Time

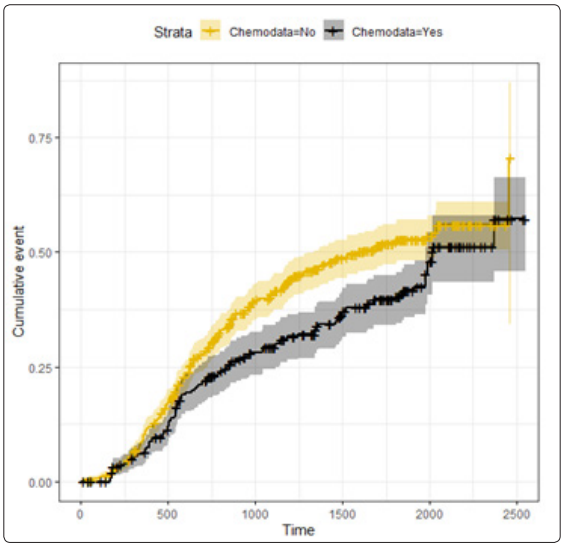

Strata
RAgedata=<=45
RAgedata=46-55
RAgedata=>=56
Cumulative event
Time

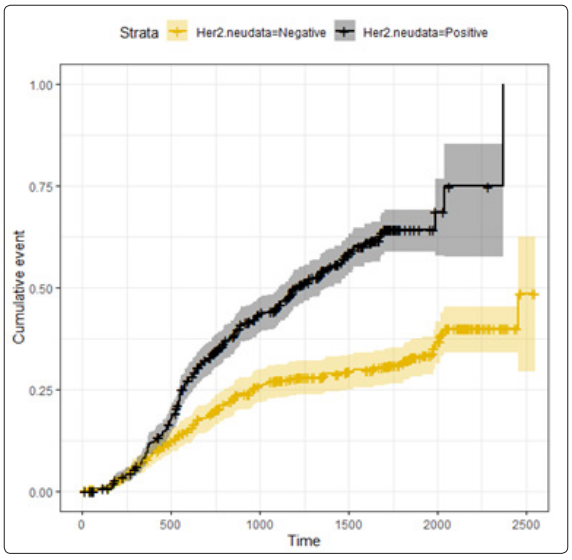

Strata
ERdata=Negative
ERdata=Positive
Cumulative event
Time

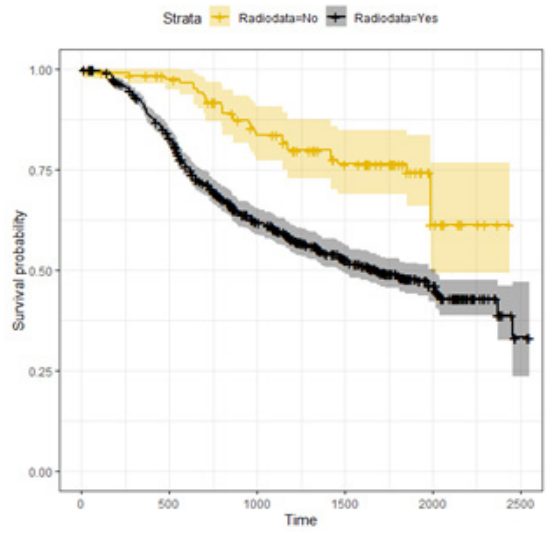

Strata
PRdata=Negative
PRdata=Positive
Cumulative event
Time

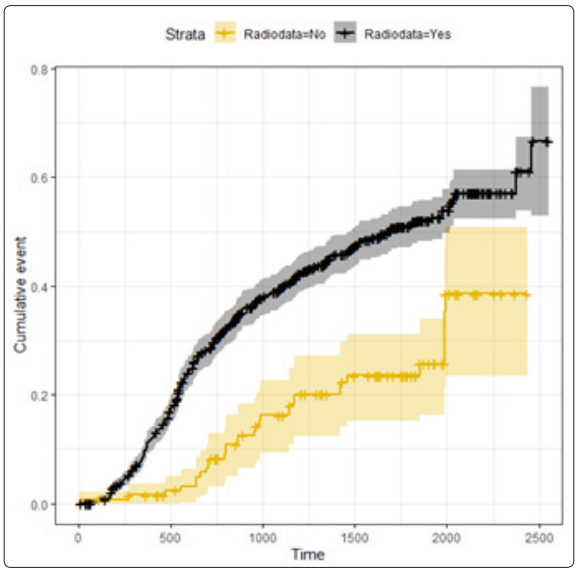

Strata
Chemodata=No
Chemodata=Yes
Survival probability
Time

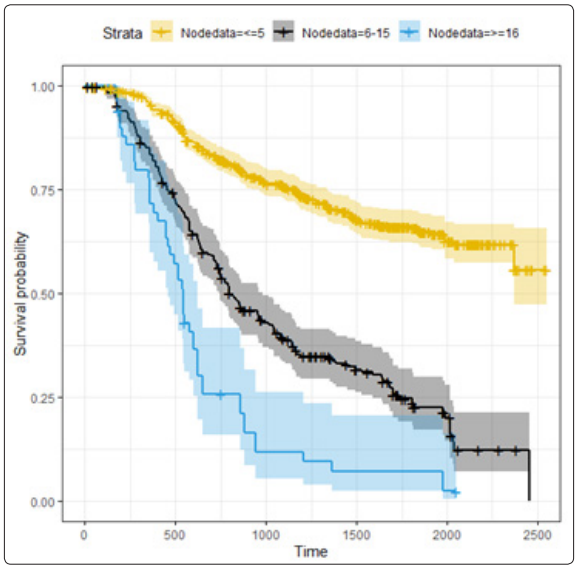

Strata
Her2.neudata=Negative
Her2.neudata=Positive
Survival probability
Time

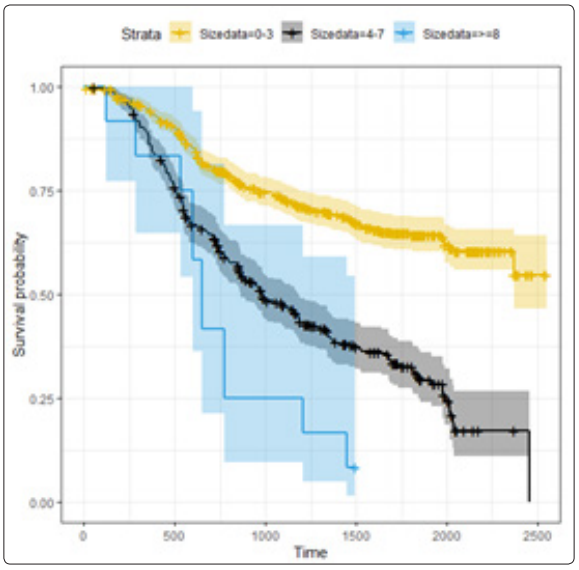

Strata
Chemodata=No
Chemodata=Yes
Cumulative event
Time

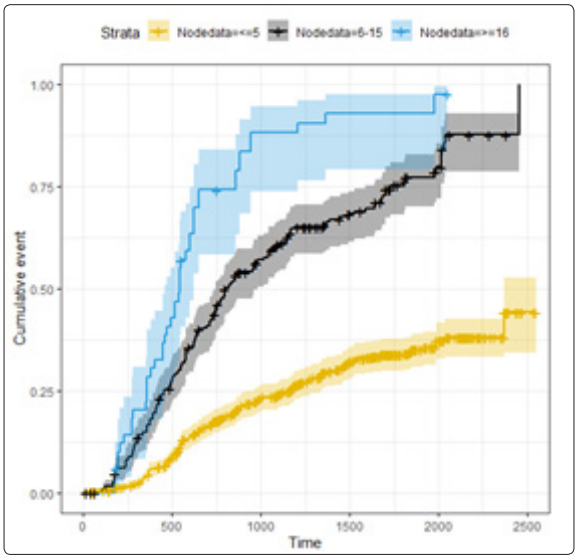

Strata
Her2.neudata=Negative
Her2.neudata=Positive
Cumulative event
Time

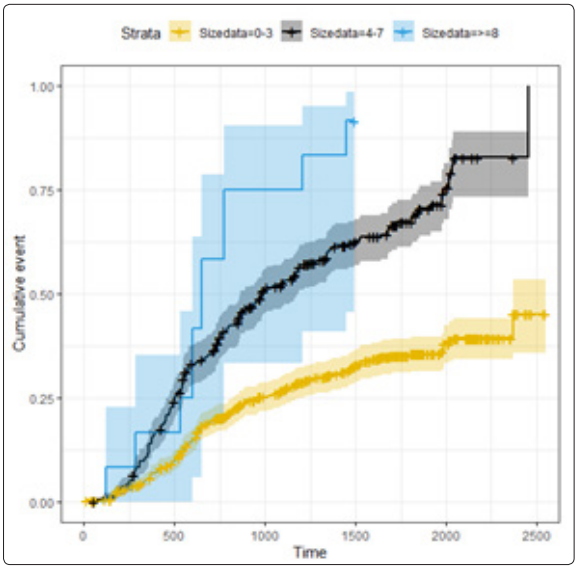

Strata
Radiodata=No
Radiodata=Yes
Survival probability
Time

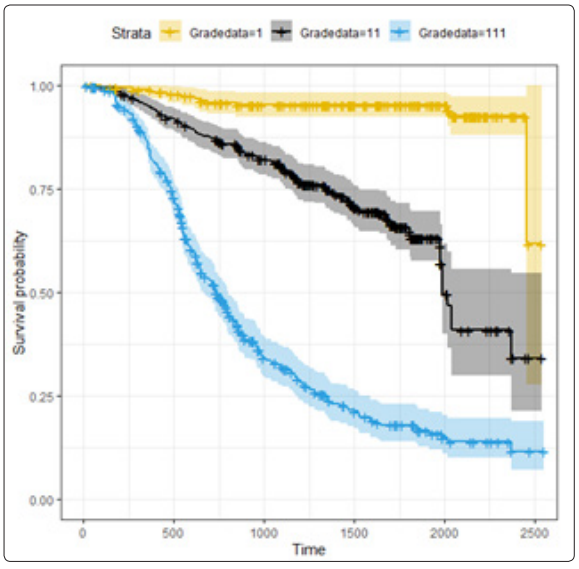

Strata
Radiodata=No
Radiodata=Yes
Cumulative event
Time

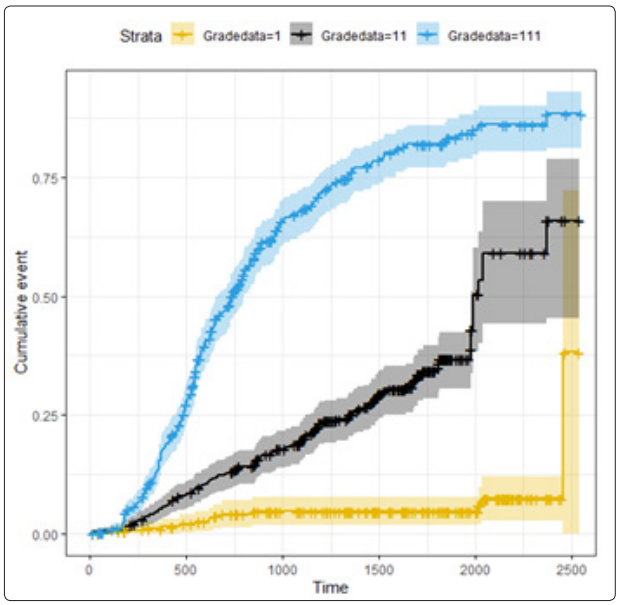

Strata
Nodedata=<=5
Nodedata=6-15
Nodedata=>=16
Survival probability
Time


Strata
Sizedata=0-3
Sizedata=4-7
Sizedata=>=8
Survival probability
Time


Strata
Nodedata=<=5
Nodedata=6-15
Nodedata=>=16
Cumulative event
Time


Strata
Sizedata=0-3
Sizedata=4-7
Sizedata=>=8
Cumulative event
Time


Strata
Gradedata=1
Gradedata=11
Gradedata=111
Survival probability
Time



Figures: Survival and cummulative curve by all factors

Multivariate Analysis

To identify significant prognostic factors, a multivariate Cox regression analysis was conducted assuming a proportional hazard rate (13). The considered death due to breast cancer after recurrence statistically significant factors were : age at diagnosis ≥ 56 , post-menopause, estrogen receptor positive, progesterone receptor negative, Her2.neu positive, no chemotherapy , tumor size ≥ 6 , lymph nodes ≥ 8 and high grade of tumor (11&111). Our multivariate model showed two strongest predictors of breast cancer mortality among women who experienced recurrence after primary treatment are lymph nodes and grade. Estrogen receptor and Her2.neu positive while progesterone receptor negative women had more deaths within 7 years after recurrence than women progesterone receptor positive. (Table 2)

Discussion and Conclusions

The information in our study is relevant for women who have experienced recurrence after diagnosis breast cancer as a primary disease and have gone through initial treatment of chemo and/or radiotherapy or both. Age of patients at diagnosis time was the most important factor effecting survival. Relationship between breast cancer death rate and age has been controversial topic for many researchers [7,35,36]. We divided age into to three classes; the median age at diagnosis was 47 years while for recurrence it was 49 years which are similar to those found in other studies, age at diagnosis ≥ 56 and recurrence before ≤ 45 years have greater hazard [32]. Women with early-onset breast cancer are more likely to experience a recurrence and once they do, are more likely to succumb to their disease [8]. Analysis depicted, after recurrence age group ≤ 45 years old women have high risk for death than age groups 46-56 & ≥ 56. Our results are consistent with early age of onset being a risk factor for local recurrence [14,32]. Other important factors included tumor 4-7 size, lymph nodes ≥ 6. Estrogen and progesterone status were classified according to the examination of the primary tumor results, our study has emphasized prognostic factors at the time of diagnosis. It is not clear which factors contributed to the relatively poor prognosis in young women [36]. In one study, average survival time after recurrence occurred within 3 years, poor prognosis was ≥ 6 (4.9%) years survival rate after recurrence.

In the univariate analysis, prognosis was worst in women who recurred after receiving chemo and radiotherapy and had family history of breast cancer; however family history was not significant in multivariate model [37]. We did not include information of treatment after recurrence, as many studies reported that chemotherapy after recurrence was effective to increase survival time. Progesterone receptor negative and estrogen receptor positive high grade tumors have increased rate of mortality, our results supported this statement [38]. Her2.neu positive have greater hazard of mortality for breast cancer women [39]. Post-menopausal women have estrogen receptor and HER2.neu positive with progesterone receptor negative not gone through chemotherapy had increased risk of deaths after recurrence within seven years, which justify previous published results [8, 40-44].

In this research, the number of involved nodes, grater tumor size and tumor grade 11&111 were important factors to study the probability of deaths after recurrence in women diagnosed breast cancer. It is highly recommended to add hormone therapy and trastuzumab in systematic treatment to get in depth analysis. Our research finding has opened new avenues for clinicians to study breast cancer progression in Pakistan.

References

1. The Daily Times. (Online) 2009. Available from URL: http://www.dailytimes.com.pk/default.asp?page=200942story_2-4-2009_pg13_11.
2. Engmann NJ, Golmakani MK, Miglioretti DL, Sprague BL, Kerlikowske K, et al. (2017) Population-attributable risk proportion of clinical risk factors for breast cancer. JAMA Oncol 3: 1228-1236.
3. Jung S, Wang M, Anderson K, Baglietto L, Bergkvist L, et al. (2016) Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. International journal of epidemiology 45: 916-928.
4. Kispert S, McHowat J (2017) Recent insights into cigarette smoking as a lifestyle risk factor for breast cancer. Breast Cancer: Targets and Therapy 9: 127-132.
5. Lynch BM, Neilson HK, Friedenreich CM (2011) Physical activity and breast cancer prevention. Recent Results. Cancer Res 186: 13-42.
6. Majeed W, Aslam B, Javed I, Khaliq T, Muhammad F, et al. (2014) Breast cancer: major risk factors and recent developments in treatment. APJCP 15: 3353-3358.
7. Horn J, Asvold BO, Opdahl S, Tretli S, Vatten LJ (2013) Reproductive factors and the risk of breast cancer in old age: a Norwegian cohort study. Breast Cancer Res Treat 139: 237-243.
8. Killander F, Anderson H, Rydén S, Möller T, Hafström LO, et al. (2009) Efficient reduction of loco-regional recurrences but no effect on mortality twenty years after postmastectomy radiation in premenopausal women with stage ii breast cancer—a randomized trial from the South Sweden Breast Cancer Group. Breast 18: 309-315.
9. Rojas K, Stuckey A (2016) Breast Cancer Epidemiology and Risk Factors. Clinical obstetrics and gynecology 59: 651-672.
10. Washbrook E (2006) Risk factors and epidemiology of breast cancer. Women's Health Medicine 3: 8-14.
11. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, et al. (2005) Effects of radiotherapy and of differences in the extent

of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366: 2087-2106.
12. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, et al. (2013) Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 24: 2206-2223.
13. Arvold ND, Taghian AG, Niemierko A, Abi Raad RF, Sreedhara M, et al. (2011) Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. J Clin Oncol 29: 3885-3891.
14. Courdi A, Doyen J, Gal J, Chamorey E (2010) Local recurrence after breast cancer affects specific survival differently according of patient age. Oncology 79: 349-354.
15. Sirohi B, Leary A, Johnston SR (2009) Ipsilateral breast tumor recurrence: is there any evidence for benefit of further systemic therapy? Breast J 15: 268-278.
16. Bozovic SI, Azambuja E, McCaskill S W (2012) Chemoprevention for breast cancer. Cancer Treat Rev 38: 329-339.
17. Ng W, Delaney GP, Jacob S, Barton MB (2010) Estimation of an optimal chemotherapy utilization rate for breast cancer: setting an evidenced based benchmark for the best quality cancer care. Eur J Cancer 46: 703-712.
18. Roulot A, Héquet D, Guinebretière JM, Vincent-Salomon A, Lerebours F, et al. (2016) Tumoral heterogeneity of breast cancer. Ann Biol Clin (Paris) 74: 653-660.
19. Tamimi RM, Colditz GA, Hazra A, Baer HJ, Hankinson SE, et al. (2012) Traditional breast cancer risk factors in relation to molecular subtypes of breast cancer. Breast Cancer Res Treat 131: 159-167.
20. Yang XR, Chang CJ, Goode EL, Couch FJ, Nevanlinna H, el al. (2011) Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the breast cancer association consortium studies. J Natl Cancer Inst 103: 250-263.
21. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, et al. (2010) American society of clinical oncology/college of american pathologists guideline recommendations for immune histochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 28: 2784-2795.
22. Aysola K, Desai A, Welch C, Xu J, Qin Y, et al. (2013) Triple Negative Breast Cancer - An Overview. Hereditary genetics: current research 2013: 001.
23. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L, et al. (2016) Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol 13: 674-690.
24. Nahta R, Yu D, Hung MC, Hortobagyi GN, Esteva FJ, et al. (2006) Mechanisms of disease: understanding resistance to HER2 targeted therapy in human breast cancer. Nat Clin Practice 3: 269-280.
25. Verma S, Miles D, Gianni L, Ian E. Krop, Manfred Welslau, et al. Trastuzumab emtansine for Her2-positive advanced breast cancer. N Engl J Med 367: 1783-1791.
26. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, et al. (2013) Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 31: 3997-4013.
27. Carter CL, Allen C, Henson DE (1989) Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 631: 181-187.
28. Rosato V, Bosetti C, Negri E, Talamini R, Dal Maso L, et al. (2014) Reproductive and hormonal factors, family history, and breast cancer according to the hormonal receptor status. Eur J Cancer Prev 23: 412-417.
29. Bunderd NJ (2001) Prognostic and predictive factors in breast cancer. Cancer Treatment Review 27: 137-142.
30. Hooning MJ, Aleman BM, Van Rosmalen AJ, Kuenen MA, Klijn JG, et al. (2006) Cause-specific mortality in long-term survivors of breast cancer: a 25-year follow-up study. Int J Radiat Oncol Biol Phys 64: 1081-1091.
31. In J, Lee DK (2018) Survival analysis: Part I - analysis of time-to-event. Korean journal of anesthesiology 71: 182-191.
32. Narod SA (2012) Breast cancer in young women. Nat Rev Clin Oncol 9: 460-470.
33. Wu J (2015) Sample size calculation for the one-sample log-rank test. Pharmaceutical statistics 14: 26-33.
34. Zwiener I, Blettner M, Hommel G (2011) Survival analysis: part 15 of a series on evaluation of scientific publications. Dtsch Arztebl Int 108: 163-169.
35. Hartley MC, McKinley BP, Rogers EA, Kalbaugh CA, Messich HS, et al. (2006) Differential expression of prognostic factors and effect on survival in young (≤40) breast cancer patients: a case-control study. Am Surg 72: 1189-1194.
36. Brenner H, Hakulinen T (2004) Are patients diagnosed with breast cancer before age 50 years ever cured? J Clin Oncol 22: 432-438.
37. Brewer HR, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ (2017) Family history and risk of breast cancer: an analysis accounting for family structure. Breast Cancer Res Treat 165: 193-200.
38. Prat A, Cheang MCU, Martín M, Parker JS, Carrasco E, et al. (2013) Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal a breast cancer. J Clin Oncol 31: 203-209.
39. Piccart M, Hortobagyi GN, Campone M, Pritchard KI, Lebrun F,et al. (2014) Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Ann Oncol 25: 2357-2362.
40. Basse C, Arock M (2015) The increasing roles of epigenetics in breast cancer: Implications for pathogenicity, biomarkers, prevention and treatment. Int J Cancer 137: 2785-2794.
41. Collett D (1994) Modelling Survival Data in Medical Research. London: Chapman and Hall/CRC.
42. Cox DR (1972) Regression models and life tables (with discussion). J R Statist Soc B 34: 187-220.
43. Harbeck N, Gnant M (2017) Breast cancer. The Lancet 389: 1134-1150.
44. Zardavas D, Irrthum A, Swanton C, Piccart M (2015) Clinical management of breast cancer heterogeneity. Nat Rev Clin Oncol 12: 381-394.