Original Study

Outcome of HER2 positive luminal operable breast cancer in comparison with outcome of other operable luminal breast cancer patients: Long follow–up of single center randomized study

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Abstract

Introduction

In clinical practice, there is increasing recognition that HER2–positive breast cancer patients are not a homogeneous group. Especially patients with luminal B breast cancers which are now subdivided to more than two groups.(12)

Aim of the study

The aim of this study is to know the effect of HER2 positivity on luminal breast cancer patients by comparing disease free survival DFS luminal of HER2 positive breast cancer patients with other luminal cases with HER2 negative disease. Also we explored the effect of HER2 positivity on different risk factors for breast cancer.

Patients and methods

We compared the outcome of 25 HER2 positive luminal breast cancer patients with a control group of other luminal operable breast cancer at the same period of time with the same eligibility and exclusive criteria.

Results

Total of 59 operable luminal breast cancer patients were eligible for the study, 25 of them were luminal HER2 positive and the 34 were control group of luminal HER2 negative. We found that HER2 positive luminal breast cancer patients were having more unfavorable risk factors and have more incidence of relapse mainly after 48 months follow–up than other luminal patients: after 24 months follow–up period HER2 positive luminal patients have cumulative DFS of 91% compared with 93% in luminal HER2 negative patients but after 48 months follow–up the difference between the two groups became more obvious as it was 66% for luminal HER2 positive group and 90 % for the control group. High risk patients for luminal HER2 positive breast cancer patients have higher risk of relapse (60% compared with 86%), and this appeared also in other subgroups.

Conclusion

HER2 positive luminal breast cancer patients have a higher incidence of relapse compared with other luminal breast cancer, and this difference appear mainly after 48 months of follow–up. High risk patients for luminal HER2 positive breast cancer have higher risk of relapse than high risk patients of other luminal patients.

Keywords

HER2 positive, luminal breast cancer, DFS 48 months, breast cancer risk factors

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Introduction

Amplification and/or overexpression of the human epidermal growth factor 2 (HER2) oncogene, which belongs to the epidermal growth factor receptor (EGFR/HER) family, occurs in about 15% of invasive breast cancers, and enables constitutive activation of growth factor signaling and triggering breast cancer cell survival, proliferation, and invasion.[1] Most of studies concluded that in the clinical practice, there is increasing recognition that HER2–positive breast cancer patients are not a homogeneous group. In particular, the hormone receptor HR status is emerging as a relevant stratification factor with practical clinical implications.[1,2,3] Also, that other risk factors should be used to define the optimum adjuvant therapy for these patients who have both hormone receptor positive and HER2 positive tumor[5]

The association between estrogen receptor ER status and mortality is known to be time dependent, with hazard ratios for ER–positive versus ER negative tumors being lower than one in the first years after diagnosis and becoming higher than one after 7–10 y. Mortality in women with ER–positive tumors remains fairly constant over time, whereas the mortality in women with ER–negative tumors is initially higher than that in women with ER–positive disease and then falls to a lower rate after 7–10 y.[10, 11]

The response of HER2 overexpressing breast cancer cells to endocrine therapy has been of concern due to the major role of endocrine therapy in early stages of breast cancer, some clinical data have indicated that patients with HER–2/neu–positive (i.e., overexpressed) tumors may not benefit from this treatment.[2, 3] Other studies were showing a benefit from endocrine therapy in HER2 positive hormone positive breast cancer patients.[4] Chemotherapy is one of the most important back bone of adjuvant therapy for high risk breast cancer patients, some studies showed that a significant benefit from taxanes containing adjuvant chemotherapy in patients with luminal B HER2 positive tumors [6,7] while others showed that there is limited benefit from chemotherapy in luminal A breast cancer.[7]

In this study we compared the long time outcome of operable luminal B HER2 positive breast cancer patient with other luminal operable breast cancer cases, after adjuvant chemotherapy and hormonal therapy and we will compare the effect of risk factors and treatment in both groups.

Materials and methods:

We followed 25 luminal B HER2 positive breast cancer patients during the period from 2009 to 2012 after their surgery, chemotherapy and hormonal therapy, and compared their outcome with the outcome of other operable luminal breast cancer patients during the same period of time. The control group was selected under the same eligibility and exclusion criteria of the first group. Information about patients and their outcome and follow–up were obtained from the archive of Nasser Institute Cancer Center NICC. Figure 1 shows patient randomization.

Inclusion criteria

1. Patients with non–advanced operable (M0) breast cancer, with pathology showing infiltrating duct carcinoma IDC grade II
2. Age more than 18ys
3. HER2 positive +3 by IHC or SISH if HER2 = +2
4. Estrogen receptor ER positive by IHC.
5. Did not have anti HER2 treatment as an adjuvant therapy
6. Patient did not have any chemotherapy or targeted therapy during her life before adjuvant therapy for cancer patient.

Exclusion criteria

1. Patient with advanced breast cancer
2. Patients who had neo adjuvant therapy for breast cancer
3. Patients who relapsed within first 3 months of diagnosis and before adjuvant therapy
4. Patients without radical surgery before adjuvant chemotherapy
5. Patients with inadequate adjuvant chemotherapy or hormonal therapy during follow–up period
6. Patients who missed follow–up before 24 months of HER post treatment follow–up period
7. Patients with incomplete medical records or data file
8. Patients with unknown results for IHC : ER, PR, or HER2
9. Pathology of DCIS, invasive lobular carcinoma,

mucinous carcinoma, or other rare types
10. Patients who have ER negative tumor
11. HER2 negative luminal patients are included in control group only

Immune–Histo–Chemistry (IHC) examination

Pathologic results were obtained by IHC in the same center or at the MOH certified center in Egypt, and all pathologic results were done by at least two expert pathologists. Tumors from all patients were assessed or reassessed (if the initial results were already available) for ER, PR, HER2 status by two experienced pathologists. With respect to HR determined by IHC, the percentage of neoplastic cells expressing either ER or PR was recorded. Fewer than 5% of neoplastic cells were considered as negative for HR expression. HER2 was determined initially by IHC and graded from 0 to 3+. HER2 negative was defined as HER2 graded 0 or 1+, positive defined as 3+. Scores of HER2 2+ were confirmed either as HER2 negative or HER2 positive according to the SISH analysis

Character N (%)	HER2 positive	Control arm (B)	Whole group
Number (%)	25(42)	34(57)	59(100)
Age			
< 50	20(80)	23(67.6)	43(72)
≥50	05(20)	11(32.4)	16(27)
LN			
<3	11(44)	15(44)	26(44)
≥3	14(66)	19(66)	33(55)
T1, T2	16(64)	27(79.4)	43(72)
T3, T4	09(30)	07(20)	16(27)
Menopausal status	22(88)	27(79.4)	49(83)
Pre	03(12)	07(22)	10(16)
Post			
Risk assessment	19(76)	16(47)	24(40.7)
High risk	06(24)	18(52.9)	35(59.3)
Moderate risk			

Table 1. Patient characteristics in whole group and in each subgroup

Staging and risk assessment

All patients were staged according to the American Joint Committee on Cancer (AJCC 2010, 7th edition) TNM Staging System for Breast Cancer. [13]

Initial treatment

Surgery and adjuvant chemotherapy and hormonal therapy, Radiation therapy

All patients have surgery followed by anthracyclines based chemotherapy with or without taxanes. With at least the median number of anthracyclines cycles is 4 and taxanes is three. Indications of chemotherapy and hormonal therapy were confirmed by ST gallen recommendation for breast cancer 2013 [12]

Radiation therapy

All patients have external beam radiation therapy EBRT 50 Gy 25 fractions in five weeks with energy 6 to 15 MEV by linear accelerator. Supra clave area was irradiated in case of lymph node LN positive more than three. Indications of radiotherapy included any LN positive patient or size of tumor more than 5 cm or T4 tumors.

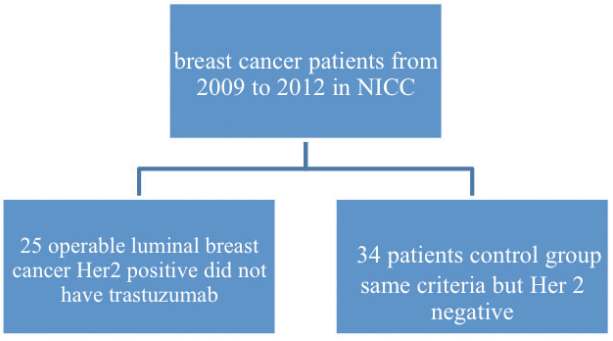

Figure 1. Patient randomization

Results

Patients

59 patients with luminal breast cancer were enrolled in the study, 25 patients from the luminal

HER2 positive who have operable breast cancer, and were treated with surgery followed by post–operative chemotherapy with or without taxanes followed by radiation therapy if indicated and all of these patients have endocrinal therapy in the form of tamoxifen, or none of these patients had the chance to take adjuvant trastuzumab during this period of time.

Outcome of this group of patient was compared with a control group of 34 patients with luminal breast cancer who were HER2 negative and were treated during the same period of time in the same center. The control group was selected under the same eligibility and exclusion criteria of the first group, but these patients were HER2 negative, some of them were postmenopausal and have aromatase inhibitor as adjuvant endocrine therapy after chemotherapy.

Luminal B HER2 positive patients have patients (80%) with age less than 50 years old and more premenopausal patients (88%) than the control group, which had more number of patients with tumor size T1, and T2 (79%) compared with HER2 positive patients who have 64% only with T1, T2 tumor size.

Percentages of LN positive patients were similar in both groups but in general, HER2 positive patients have more high risk patients (76%) than the control group who only had 47% of the patients with high risk features. Table 1 is a list showing patient characteristics.

Treatment

About 50% of the whole patients were treated with adjuvant anthracyclines and the other half had anthracyclines and taxanes; there were no significant difference between the number of patients who have either type of adjuvant therapy in each group

All patients have adjuvant radiation therapy, and also have adjuvant endocrine therapy, but the number of patients who have aromatase inhibitors as the first line is more in control group (17%) compared to zero % due to the presence of more postmenopausal patients. (see Table 2)

Results of follow–up

We investigated the results of follow–up of patients for 48 months, and noted that cumulative survival for HER2 positive group was 90% and 62% in 24 and 48 months respectively, compared with HER2 negative group which had 92% and 87% in 24 and 48 months respectively. Although this difference in DFS was not significant, it is still in favor of HER2 negative patients. (see Figure 2).

Subgroup analysis was done for each risk factor that can affect DFS for these patients and we noted that there were no significant differences but likewise DFS was still in favor of HER2 negative patients as shown in Table 3 and Figure 2.

Follow–up of all patients for 48 months shows that cumulative DFS was significantly shorter in patients with HER2 positive tumor (66.2 for HER2 positive vs. 90 for luminal HER2 negative), and that was also

Treatment n(%)	HER2 positive	HER2 negative	Whole group
Adjuvant chemotherapy			
Anthracyclines	12(48)	18(53)	30(50.8)
Anthracyclines and taxanes	13(52)	16(47)	29(49.2)
Hormonal therapy			
Tamoxifen	25(100)	28(82.3)	53(89.8)
Aromatase inhibitor	00	06(17.6)	06(10.2)

Table 2. Treatment results

noticed in patients with high risk cases (60 for HER2 positive vs 86.7 for HER2 negative). Please refer to Table 3 and Figures 3, 4, 5, 6 and 7 for details.

Follow–up of high risk patients in each group shows that the difference between HER2 positive luminal patients and HER2 negative luminal cases in DFS began to appear after 36 months follow–up (Figure 7) and not on 48 months like other risk factors shown in Figures 3, 4, 5, 6.

Sub analysis of DFS in each risk factor like age < 50 years, premenopausal status, T3, T4 tumor size and Lymph nodes more than 3 is shown in Table 3 and Figures 3, 4, 5, 6 and 7 and data shows that HER2 positive luminal breast cancer patients have unfavorable DFS in cases which harboring any risk factor.

Treatment results

Although there is difference between the number of patients who have taxanes as an adjuvant therapy for operable breast cancer, difference in DFS between each group was not showing significant difference in P value however changes in DFS was in favor of HER negative control group after 24 months follow–up. (See Table 4 and Figure 8).

Factor	HER2 positive cumulative DFS survival %	HER2 negative cumulative DFS survival %	P value
Whole groups:			
24 months	91	93	0.128
48 months	66.2	90	
Pre–menopausal			
24 months	83	92	0.232
48 months	65	87	
Age < 50 years			
24 months	89	90	0.393
48 months	65.5	85	
Lymph nodes >3			
24 months	85	88.9	0.150
48 months	51	66.4	
T3, T4			
24 months	85	62	0.876
48 months	34	62	
High risk patients			
24 months	89%	86.7%	0.178
48 months	60%	86.7%	

Table 3. Subgroup analysis for DFS of high risk patients in each group

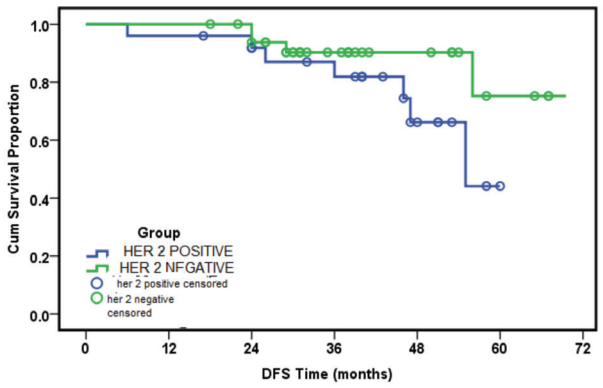

Figure 2. DFS curve of luminal HER2 positive group (blue) compared with DFS of luminal HER2 negative green. The two curves begin to separate after follow–up of 48 months

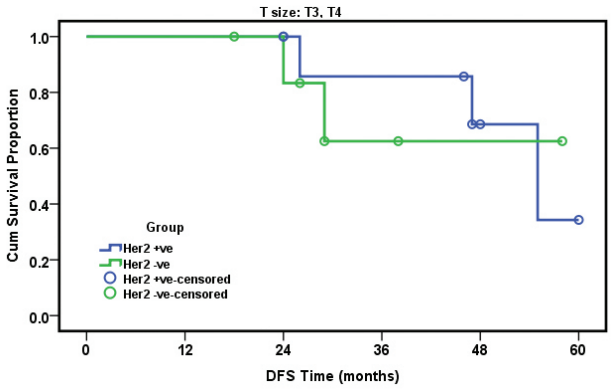

Figure 5. Curves of DFS for T3, T4 risk groups begin to separate after 24 months follow–up

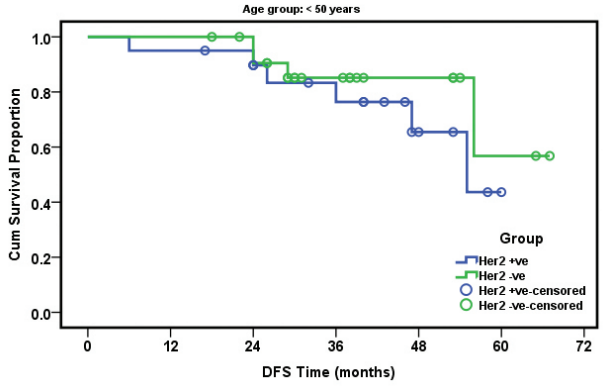

Figure 3. DFS for age <50 years risk groups show that although there is no significant P value, curves begin to separate after 48 months follow–up for both groups

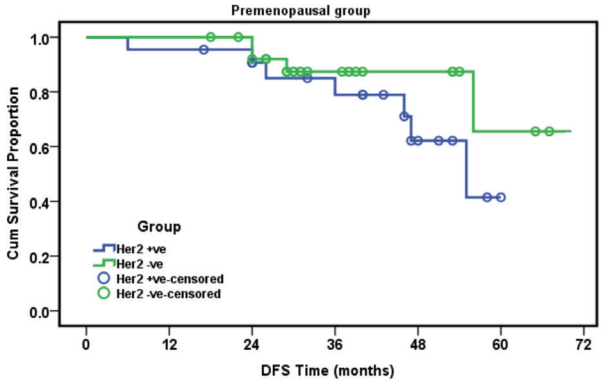

Figure 6. DFS of the premenopausal patients in the two groups begin to separate at 48 months

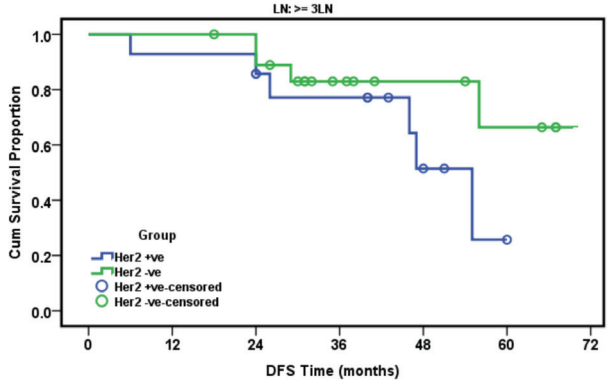

Figure 4. Curves for Lymph nodes more than or equal 3 risk groups. Curves begin to separate after follow–up of 48 months making significant difference.

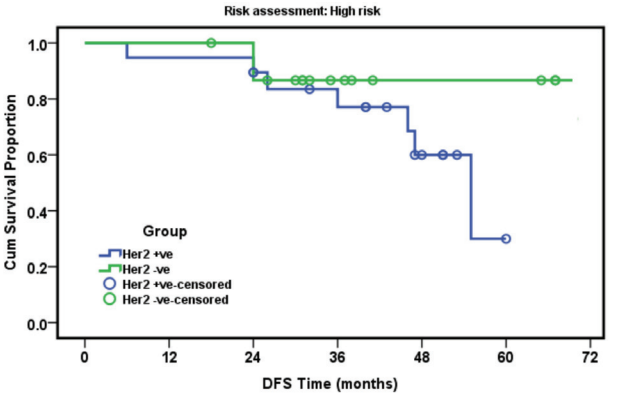

Figure 7. DFS curves of high risk patients in the two groups begin to separate after 36 months follow–up.

Follow–up of patients for 48 months after adjuvant chemotherapy and during endocrine therapy showed that cumulative DFS was significantly less in patients with HER2 positive after 48 months specially in patients who have taxanes–containing therapy, (61% for HER2 positive vs. 86% for HER2 negative luminal type) which was explained that taxanes was given to patients with high risk factors including HER2 positivity. (see Table 4)

All patients have adjuvant endocrine therapy in the form of tamoxifen or aromatase inhibitor; because

Treatment	HER2 positive luminal group	HER2 negative control group	P value
No taxanes			
24 months	91%	94%	0.146
48 months	70%	94%	
Taxanes			
24 months	91%	93%	0.482
48 months	61%	86%	

Table 4. Results of treatment comparison between each group

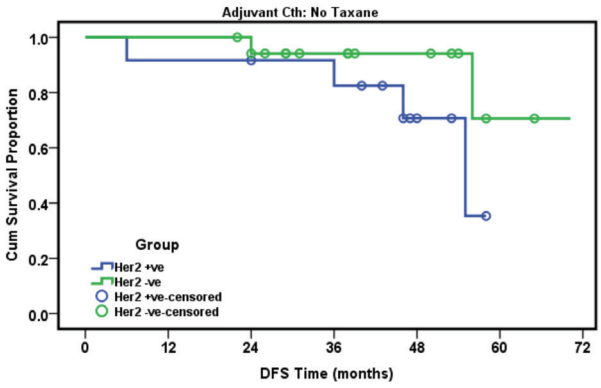

Figure 8. Comparison between DFS of each subgroup group who have anthracyclines only as an adjuvant therapy

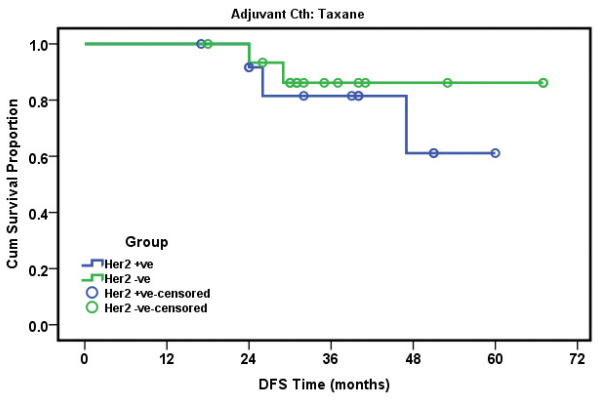

Figure 9. The difference in DFS in the two groups in patients who have taxanes and anthracyclines as adjuvant therapy

the number of patients who have adjuvant aromatase inhibitors is small, comparison between the two different endocrine therapies was not possible.

Statistical Methods

Data was analyzed using IBM SPSS advanced statistics version 22 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi–square test or Fisher's exact test was used to examine the relation between qualitative variables. For normally distributed quantitative data, comparison between two groups was done using Student t–test. Survival analysis was done using Kaplan–Meier method and comparison between two survival curves was done using log–rank test. All tests were two–tailed. A p–value < 0.05 was considered significant.

Discussion

HER2 positive luminal breast cancer patients are harboring more risk factors than other luminal breast cancer cases; this fact affected their prognosis, mainly DFS. But sub analysis of this fact exposed that not only risk factors are affecting DFS but also HER2 positivity; the comparison between the 2 high risk subgroups (see Table 3 and Figure 7) shows that even high risk patients in HER2 positive luminal group have worse prognosis as an effect of HER2 positive which was not treated by anti HER2 treatment.

DFS of HER2 positive luminal patients decline more after 48 months, which could be the effect of HER2 positivity for these patients or the decrease on the effect of ER positivity. Our results were similar to the result of BLow [8] who studied the different prognosis for different tumor subtypes of breast cancer, which exposed the fact that luminal breast

cancer prognosis become worse after 5–10 years, and HER2 positive non luminal breast cancer has worse prognosis than HER2 positive luminal breast cancer. The study also showed that these two groups are extremely different subtypes.

We are not sure whether the decline in DFS curves for HER2 luminal breast cancer after 48 months is the effect of HER2 positivity or the loss of effect of ER positivity, but since these patients were having anti hormonal therapy but not having anti HER2 therapy, then we can assume that these patients have poorer prognosis due to untreated HER2 positive breast cancer.

The use of taxanes containing therapy showed no significant difference in DFS between both groups and that was similar to results of other studies (6) confirming that the main effective adjuvant treatment for this group of patient could be the anti HER2 therapy and endocrine therapy beside anthracycline with or without taxanes containing chemotherapy.

Our results confirming that adjuvant systemic treatment for luminal B HER2 positive breast cancer should include chemotherapy, anti HER2 therapy and hormonal therapy to overcome the decline of DFS that can occur after 48 months of follow up of these patients.

In conclusion, our results confirm that HER2 positive luminal breast cancer cases have unfavorable prognosis compared with other luminal breast cancer, and DFS of this group of patients declines after 48 months and it also declines with the presence of any risk factor for breast cancer like premenopausal status, age < 50 years, large tumor size or lymph node more than 3.

The limitations of our study include a small number of patients and follow–up is less than 10 years for luminal breast cancer.

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References

1. Citri A, Yarden Y. EGF–ERBB signaling: towards the systems level. Nat Rev Mol Cell Biol 2006; 7: 505–516.
2. Yamauchi H, Stearns V, Hayes DF: When is a tumor marker ready for prime time? A case study of c–erbB–2 as a predictive factor in breast cancer. J Clin Oncol 19:2334–2356, 2001.
3. Carlomagno C, Perrone F, Gallo C, et al: c–erb B2 overexpression decreases the benefit of adjuvant tamoxifen in early–stage breast cancer without axillary lymph node metastases. J Clin Oncol 14:2702–2708, 1996.
4. Love RR, Duc NB, Havighurst TC et al. Her–2/neu overexpression and response to oophorectomy plus tamoxifen adjuvant therapy in estrogen receptor–positive premenopausal women with operable breast cancer. J Clin Oncol 2003; 21: 453–457
5. Montemurro F, Di Cosimo S, Arpino G: Human epidermal growth factor receptor 2 (HER2)–positive and hormone receptor–positive breast cancer: new insights into molecular interactions and clinical implications. Annals of Oncology 24: 2715–2724, 2013
6. Fountzilas G, Dafni U, Bobos M, et al: differential response of immunohistochemistry defined breast cancer subtypes to anthracycline– based adjuvant chemotherapy with or without paclitaxel. PloS ONE, June 2012; 7, 6 e 37946. Www. Plosone.org.
7. Roche H, Fumoleau P, Spielmann M, Canon JL, Delozier T, et al(2006)Sequential adjuvant epirubicin–based and docetaxel chemotherapy for nodepositive breast cancer patients: the FNCLCC PACS 01 Trial. J Clin Oncol 24: 5664–5671
8. Blows FM, Driver KE, Schmidt MK, Broeks A, van Leeuwen FE, et al. (2010) Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. PLoS Med 7: e1000279
9. Part L, Carey L, Adamo B, Vidal M et al : Molicular features and survival out comes of intrinsic subtypes withen HER2 positive breast cancer: JNCI Vol. 106, Issue 8 | dju152 | August 13, 2014.
10. Jatoi I, Baum M (1995) Screening for breast cancer, time to think – and stop? Lancet 346: 436–437
11. Azzato EM, Greenberg D, Shah M, Blows F, Driver KE, et al. (2009)Prevalent cases in observational studies of cancer survival: do they bias hazard ratio estimates? Br J Cancer 100: 1806–1811.

12. Goldhirsch A, Winer EP, Coates AS 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: Annals of Oncology 24: 2206–2223, 2013 doi:10.1093/annonc/mdt303.

13. Edge SB, Byrd DR, Compton CC (eds). AJCC Cancer Staging Handbook, 7th ed. New York, NY.: Springer, 2010