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Pietro Sanpaolo, Viviana Barbieri, Domenico Genovesi. Prognostic value of breast cancer subtypes on breast cancer specific survival, distant metastases and local relapse rates in conservatively managed early stage breast cancer: a retrospective clinical study. *EJSO - European Journal of Surgical Oncology*, 2011, 37 (10), pp.876. 10.1016/j.ejso.2011.07.001 . hal-00732668

HAL Id: hal-00732668

<https://hal.science/hal-00732668>

Submitted on 16 Sep 2012

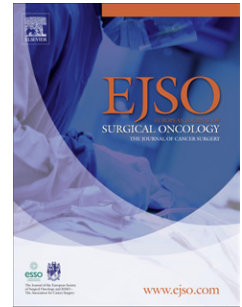
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Accepted Manuscript

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PII: S0748-7983(11)00385-4

DOI: [10.1016/j.ejso.2011.07.001](https://doi.org/10.1016/j.ejso.2011.07.001)

Reference: YEJSO 3193

To appear in: *European Journal of Surgical Oncology*

Accepted Date: 14 July 2011

Please cite this article as: Sanpaolo P, Barbieri V, Genovesi D. Prognostic value of breast cancer subtypes on breast cancer specific survival, distant metastases and local relapse rates in conservatively managed early stage breast cancer: a retrospective clinical study, *European Journal of Surgical Oncology* (2011), doi: 10.1016/j.ejso.2011.07.001

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Prognostic value of breast cancer subtypes on breast cancer specific survival, distant metastases and local relapse rates in conservatively managed early stage breast cancer: a retrospective clinical study

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Summary

Aim: To ascertain if breast cancer subtypes had prognostic effect on breast cancer specific survival, distant metastases and local relapse rates in women affected by early stage breast cancer.

Patients and Methods: Data of 774 patients affected by early stage breast cancer and treated with breast-conserving therapy were reviewed. Patients were grouped, based on steroid receptor status and HER2 status as: Luminal A (ER+/PR+/HER2-), Luminal B (ER+/PR+/HER2+), Basal-like (ER-/PR-/HER2-) and HER2 (ER-/PR-/HER2+). Distribution of variables among subtypes was evaluated with Pearson’s test. Survival rates were calculated with life tables; Cox regression stepwise method was used to identify predictive variables of survival.

Results: Median age was 55.0 years old (range 27-80) and median follow up time of 59.0 months (range 13.6-109.7). Breast cancer specific survival and distant metastases rates were different among breast cancer subtypes (both outcomes $P=0.00001$) but there was no difference regarding local relapse rates ($P=0.07$). Axillary nodes status ($P=0.00001$), adjuvant therapy ($P=0.03$) and breast cancer subtypes ($P=0.03$) resulted prognostic factors of breast cancer specific survival; axillary node status ($P=0.00001$) and breast cancer subtypes ($P=0.00001$) had an impact on distant metastases. Age ($P=0.003$), tumor size ($P=0.0001$),

positive or close surgical margin ($P=0.00001$) and tumor grade 3 ($P=0.049$) resulted prognostic factors of local relapse.

Conclusions: In our study, breast cancer subtype seems a prognostic factor of breast cancer specific survival and distant metastases rates, but not of local relapse rate. Patients could be submitted to conservative surgery, if feasible, but considering the differences in survivals, patients with worse prognosis should receive more aggressive adjuvant treatments.

Keywords: breast cancer subtypes; breast-conserving surgery; adjuvant radiotherapy; estrogen receptor; progesterone receptor; HER-2.

Introduction

Over the past few years, with the advent of modern diagnostic molecular technologies, breast cancer has not been considered a single disease, but a “wide range” of diseases¹. Gene profiling has determined a new classification of breast cancers^{2 3} which correlates with breast cancer behaviours and different clinical outcomes^{4 5}. Gene profiling, however, does not seem to be used in all facilities. An alternative way could be evaluate known biomarkers and to combine them to obtain an approximate sub-classification of breast cancers^{6 7}, useful to clinicians for treatment decisions. The aim of this retrospective study is to determine if the classification of breast cancer as subtypes correlates with clinical outcomes as breast cancer specific survival rates (BCSS), distant metastases rates (DM) and local relapse rates (LR). This is based on known biological markers as estrogen and progesterone receptors (ER and PR respectively) and HER-2 status.

Patients and Methods

All medical records of women treated between January 2000 and December 2008 were reviewed and 774 out of 1034 patients (74.8%) with early breast (pT1-2 N0-2) cancer resulted eligible for this study. Information was collected about age, tumor histology, tumor size,

surgical margins, axillary node status, tumor grade, adjuvant therapy, estrogen and progesterone receptor status and HER-2 status. Patients submitted to mastectomy, lost to follow up or with incomplete data were excluded (260 pts, 25.2%). Surgery consisted in quadrantectomy; axillary nodal dissection was performed on the basis of the result of sentinel node. Axillary node status resulted as follows: negative for 534 patients (69%), 1 to 3 positive nodes for 156 patients (20%) and more than 3 positive nodes for 84 patients (11%). As patients underwent surgery in several regional hospitals, a re-excision of primary tumor was not always performed and margin status resulted positive or close (≤ 2 mm) for 70 patients (9.0%). Clips to identify tumor bed were not always used. The histology of primary tumor was classified as invasive ductal carcinoma (652; 84.2%) or other (122; 15.8%), including lobular, medullary and tubular cancers. These last cases were included as a single group, because of the small number of patients with these histotypes. Estrogen and progesterone receptor status was determined with immunohistochemical analysis with a standard procedure, using 4 μ m sections of paraffin-embedded tissues stained with monoclonal antibodies for estrogen and progesterone receptors. Nuclear staining $\geq 1\%$ was considered a positive result. HER-2/neu status was determined with hercept test, but in case of a result 2+, a fluorescence in situ hybridization was performed.

Radiation treatment and systemic treatment

Adjuvant radiation therapy (RT) was administered to a total dose of 50 Gy, with 6-MV photons, always after the end of chemotherapy (CT) (in cases of systemic therapy). Two tangential fields with wedges to give a more homogeneous dose to the breast were used. A sequential boost dose of 10 Gy (16 Gy in all cases of positive or close margins) was added on tumor bed with a variable electron energy dose (9-12 MeV). In cases of four or more positive axillary nodes, a supraclavicular irradiation (total dose 50 Gy) was added.

Fifty-two patients (6.7%) did not receive systemic treatment, but only RT; hormone therapy alone (HT) was prescribed to 186 patients (24.0%); 536 patients (69.3%) received CT [328 patients (42.4%) CT alone and 208 (26.9%) both CT and HT]. CT consisted of CMF schedule

(cyclophosphamide, methotrexate and 5-fluorouracil) for 370 (69%) patients and doxorubicine-based schedules for 166 (31%) patients. Trastuzumab was administered to 85.4% of luminal B patients and to 87.3% of HER2 patients. Hormonal therapy administration started after surgery or, in case of systemic treatment, after completion of chemotherapy.

End points and statistical analysis

Breast cancer specific survival was defined as the interval between the date of surgery and the date of death for breast cancer. Distant metastasis was defined as the diagnosis of a clinically and/or radiographically documented distant relapse, while local relapse was intended as a clinically and histologically documented relapse in the ipsilateral breast. Patients entered follow up six weeks after completion of radiation therapy and then were controlled every four months for the first two years and every six months thereafter. On the basis of receptor status and HER-2 status, patients were grouped, as: Luminal A (ER+/PR+/HER2-), Luminal B (ER+/PR+/HER2+), Basal-like (ER-/PR-/HER2-) and HER2 (ER-/PR-/HER2+) (Table 1). Distribution of variables among subtypes were evaluated with cross-tables with Pearson's test. BCSS, DM and LR rates were evaluated with life tables and validated with Wilcoxon's test. Cox regression stepwise method was used to identify significant variables of outcome: age (<50 vs 50-64 vs >65-years), tumor histology (ductal vs other), tumor size (0.1-1 cm vs 1.1-2 cm vs >2 cm), margin status (negative vs positive or close), axillary nodal status (negative vs 1-3 positive nodes vs >3 positive nodes), tumor grade (1 vs 2 vs 3), adjuvant therapy (no therapy vs HT vs CT vs CT/HT), hormone therapy (yes vs no), chemotherapy (yes vs no), breast cancer subtypes (luminal A vs luminal B vs basal-like vs HER2). In a first phase, each variable was evaluated; then variables resulted significant at univariate analysis entered a stepwise model. At 5% significance level, the analysis was stopped. In the analysis, cases of close margins were considered together with positive ones, because all received a 16 Gy boost. All tests were two-sided; a p-value ≤ 0.05 confirmed a statistical significance.

Results

BCSS, DM and LR rates based on patient characteristics

Median age was 55.0 years old (range 27-80) and median follow up time of 59.0 months (range 13.6-109.7). Association between biological subtypes and other patient characteristics varied with age ($P=0.005$), with tumor grade ($P<0.0001$) and with adjuvant therapy ($P<0.0001$). During follow up we registered 125 distant metastases, 93 deaths and 26 breast relapses. Taking into account all patients, mean 5-year BCSS, DM and LR rates were 82.9%, 18.7% and 4.4% respectively. 5-year BCSS rates, stratified for each subtype, were: 93.4% for luminal A, 84.7% for luminal B, 71.7% for basal-like and 71.9% for HER-2 ($P=0.00001$). 5-year DM rates were: 11.4% for luminal A, 16.1% for luminal B, 24.3% for basal-like and 31.0% for HER-2 ($P=0.0001$). 5-year LR rates were: 3.6% for luminal A, 9.1% for luminal B, 4.8% for basal-like and 2.2% for HER-2 ($P=0.07$).

Patients with >3 positive axillary nodes, submitted to supraclavicular irradiation, had lower 5-year BCSS rates (53.1% vs 83.9%; $P=0.00001$) and higher 5-year DM rates (41.6% vs 16.2%; $P=0.00001$) compared to patients who did not receive such treatment (patients with 0 to 3 positive nodes). No difference in 5-year LR rates has been evidenced (5.9% vs 4.4%; $P=0.89$). Patients with positive or close surgical margins had higher 5-year LR rates (34.6% vs 1.3%; $P=0.00001$) compared to patients with negative margins.

Patients were also evaluated for age (<50 and ≥ 50 years old) and estrogen receptor status. 5-year BCSS rates were 69.7% for <50 years old ER negative patients and 84.9% for <50 years old ER positive patients ($P=0.00001$); 5-year BCSS rate was 66.9% for ≥ 50 years old ER negative patients vs 92.0% for ≥ 50 years old ER positive patients ($P=0.00001$). 5-year DM rate was 27.5% for <50 years old ER negative patients vs 22% for <50 years old ER positive patients ($P=0.004$), while 5-year DM rate was 28.9% for ≥ 50 years old ER negative patients vs 11.3% for ≥ 50 years old ER positive patients ($P=0.00001$). No difference was evidenced in 5-year LR rate between ER negative and ER positive receptors patients aged <50 years old

(10.8% vs 3.6%; $P=0.17$), while between patients ≥ 50 years old there was a slight significant difference (0% vs 4.9% for ER negative and ER positive patients, respectively; $P=0.04$).

Results of univariate analysis

At univariate analysis, axillary nodal status [>3 positive nodes HR 4.09 (95% C.I. 2.51-6.32); $P=0.00001$], adjuvant therapy ($P=0.0001$), hormone therapy alone [no HT HR 3.43 (95% C.I. 2.09-5.63; $P=0.00001$], chemotherapy alone [no CT 0.18 (95% C.I. 0.07-0.41); $P=0.00001$] and subtypes ($P=0.00001$) resulted statistically significant variables of BCSS. Axillary nodal status resulted to have an impact also on DM rates [>3 positive nodes HR 3.47 (95% C.I. 2.26-5.33); $P=0.00001$], together with age >50 years old ($P=0.03$), histology [other HR 0.41 (0.20-0.81); $P=0.01$], adjuvant therapy ($P=0.00001$), hormone therapy ($P=0.00001$), chemotherapy ($P=0.0004$) and subtypes ($P=0.00001$). Age ($P=0.03$), tumor size ($P=0.00001$), positive or close margins ($P=0.00001$) and tumor grade ($P=0.001$), resulted statistically significant for LR rates (Table 2).

Results of multivariate analysis

Multivariate analysis (Table 3) confirmed axillary nodal status as an independent prognostic factor of BCSS ($P=0.00001$) and DM rates ($P=0.00001$). Chemotherapy, as adjuvant therapy, was a predictive factor of BCSS rate ($P=0.01$), while subtypes were both prognostic factors of BCSS ($P=0.03$) and DM rates ($P=0.00001$). Age ($P=0.03$), tumor size ($P=0.0001$), positive or close margins ($P=0.00001$), and tumor grade ($P=0.049$) were all confirmed as prognostic variables of LR rates.

Discussion

ER and PR status and BCSS and DM rates

Our results show that breast cancer subtypes distribution varies significantly with age ($P=0.005$), with tumor grade ($P<0.0001$) and with adjuvant therapy ($P<0.0001$), but not in

terms of axillary node status ($P=0.54$), which has also been described by other authors⁸, maybe due to an equally pattern of dissemination to lymphatics of the four subtypes⁹. There was no difference in the distribution of subtypes in terms of tumor size, as reported by some authors⁹. This study seems to evidence a significant difference of BCSS and DM rates among the four subtypes (both $P=0.00001$). We underline that luminal A and luminal B subtypes have similar better BCSS and DM rates compared to basal-like and HER2 subtypes that have similar, but worse, BCSS and DM rates. The evident difference is due to ER and PR status, as luminal A and luminal B subtypes are both ER and PR positive, while basal-like and HER2 are ER and PR negative. Comparable results have been reported by other authors^{4 10}. The decreasing BCSS and the increasing DM rates (from luminal A to HER2) reflect a higher risk of distant metastases showed by univariate analysis (both $P=0.00001$) and confirmed by multivariate analysis ($P=0.03$ and $P=0.00001$ respectively). These results could be explained with the fact that basal-like and HER2 tumours recur both more frequently and also earlier when compared with luminal tumours. Moreover ER and PR positive breast cancers (luminal A and luminal B) respond to adjuvant therapies (chemotherapy and hormone therapy), leading to better survivals, while ER and PR negative breast cancers (basal-like and HER2) seem resistant to adjuvant therapies. Though there is no evidence regarding this issue, a “surrogate” explanation is furnished by differences in pathologic response to neoadjuvant chemotherapy reported by some authors¹¹.

HER-2 status and BCSS and DM rates

Breast cancers expressing HER2 are resistant to chemotherapy schedule (CMF) and patients treated with anthracycline schedules have better survivals compared to patients treated with CMF schedule¹².

These results seem to be confirmed by a subgroup analysis we made, in which patients affected by HER2 positive breast cancer and submitted to CMF had a 5-year BCSS rate of 69.3%. compared to 77.9% of patients submitted to anthracyclines ($P=0.003$). The same

patients had a DM rate of 34.8% compared to 22.8 % of patients submitted to anthracyclines ($P=0.03$).

Table 1 shows that grade 3 tumor is more frequently basal like and HER2 (48.4% and 23.2%, respectively; $P<0.0001$): this result could be explained with the fact that well or moderately differentiated tumors express steroid receptors. Regarding this issue, we made a subgroup analysis, comparing patients affected by luminal A and luminal B breast cancer who received hormone therapy. Luminal A patients had 5-year BCSS rate of 94.6% vs 81.5% of luminal B ($P=0.09$) and a 5-year DM rate of 9.2% vs 16.8% ($P=0.04$). This last result confirms that tumours expressing HER-2 (luminal B) are less sensitive to hormone therapy when compared with the luminal A tumours.

ER and PR prognostic values in local recurrence

Our results show that there is no difference in local relapse rates among the four subtypes, independently from steroid receptor status. In the NSABP B 14 trial (node negative patients randomized to tamoxifen for 5-years vs observation) was reported a significant decrease in the risk of breast recurrence at 5-years (2.2% vs 5.5%; $P=0.002$). Horiguchi et al.¹³ reported in their single institution experience that positive estrogen receptor status was a favourable prognostic factor for local control after breast conservative therapy. Similar results were published by other authors^{14 15 16 17}. On the other hand, Rutqvist et al. in the Stockholm trial reported a 7-years local recurrence rate of 5% for patients observed vs a 2% rate for patients treated with tamoxifen, but the difference was not statistically significant. In the NSABP B 16 trial¹⁸ (node positive patients randomised to tamoxifen alone vs tamoxifen + doxorubicin and cyclophosphamide) a 5-year local recurrence rate was found of 2.6% vs 0.9%, respectively, but this result did not reach statistical significance. Haffty et al.¹⁹ did not find an association between ER negative status and higher risk of local recurrence (2% rate of local recurrence for women treated with tamoxifen vs 5% rate for ER- patients; $P=ns$) and Fisher et al.²⁰ in their study for the National Surgical Adjuvant Breast and Bowel Project reported a lower incidence

of ipsilateral breast relapses (2.8% at 8 years) in the radiotherapy + tamoxifen arm vs tamoxifen alone vs radiotherapy + placebo, regardless of estrogen receptor status.

Moreover, in this study, the use of hormone therapy was not a predictive factor of local recurrence at univariate and multivariate analyses: maybe, the “protective” effect of hormone therapy on steroid receptor positive patients (luminal A and luminal B) has been evidenced during our follow up of nearly 5-years. Notwithstanding, a longer follow up could have revealed no difference between steroid receptor positive and steroid receptor negative patients, as reported by Fowble et al.²¹ who suggested that hormone therapy delays the interval to local recurrence and with longer follow up the improvement in local control brought by hormone therapy could disappear.

HER-2 prognostic value in local recurrence

In the current study HER-2 status did not affect local relapse rate and there was no statistically significant difference regarding local recurrence between HER-2 negative (luminal A and basal-like) and HER-2 positive (luminal B and HER2) patients. Other studies report similar results. Harris et al.²² in their retrospective study, compared 266 HER-2 negative and 86 HER-2 positive patients: no difference in local recurrence rate was reported ($P=0.15$). In a study from MD Anderson Cancer Center 32 HER-2 positive and 76 HER-2 negative patients were compared: no difference in local relapse-free survival at 5 and 10 years was found²³.

Margin status

In this study, patients with positive or close surgical margins received a boost dose of 16 Gy. A higher radiation dose can not compensate for positive surgical margins²⁴, but literature reports conflicting results due to different definitions of negative margins²⁵ or to different delivered doses^{16 26}, so a definitive conclusion on boost dose has not been reached yet.

Positive axillary nodes

Results of this study show that patients with >3 positive axillary nodes were nearly five times likely to develop distant metastases. Our results agree with the ones reported in some studies^{27 28}, though other studies reported conflicting results²⁹.

Conclusions

In this retrospective study, we demonstrated a variability in BCSS and DM rates among the four subtypes. New technologies allow, nowadays, gene profiling of breast cancer: nevertheless, clinicians, in their daily practice, have to make decisions on how to treat patients based on classic prognostic factors. An important question is whether a “surrogate” classification, instead of gene profiling, is corrected to classify breast tumors: the answer should come out from randomized trials that could lead to new guidelines of breast cancer treatment. Local control rate is not different among subgroups in our study, but, considering the retrospective nature of this study, breast cancer subtypes classification should not be used to choice surgery management.

Conflict of Interest Statement

All Authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) this work.

Funding Source

All Authors participated in the study design, in the collection, analysis and interpretation of data, in the writing of the manuscript; and in the decision to submit the manuscript for publication. Any study sponsors had involvement in this manuscript.

Acknowledgments

The authors thank Dr. Michela Fabrocini and Dr. Loreta Sanpaolo for reviewing the whole manuscript and Reviewers for their helpful comments.

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Table 1. Patient and tumour characteristics by subtype (N=774)

	Luminal A	Luminal B	Basal-like	HER2	
	361 (46.7)	124 (16.0)	155 (20.0)	134 (17.3)	<i>P</i>
Age	No/%	No/%	No/%	No/%	0.005
< 50	106 (29.4)	43 (34.7)	62 (40.0)	39 (29.1)	
50-64	161 (44.6)	47 (37.9)	73 (47.1)	53 (39.6)	
> 65	94 (26.0)	34 (27.4)	20 (12.9)	42 (31.3)	
Histology					0.36
Ductal	296 (82.0)	107 (86.3)	136 (87.7)	113 (84.3)	
Other	65 (18.0)	17 (13.7)	19 (12.3)	21 (15.7)	
Tumor size					0.38
0.1-1 cm	169 (46.8)	56 (45.2)	72 (46.5)	55 (41.0)	
1.1-2 cm	166 (46.0)	54 (43.5)	63 (40.6)	65 (48.5)	
> 2 cm	26 (7.2)	14 (11.3)	20 (12.9)	14 (10.5)	
Margins					0.60
Negative	326 (90.3)	112 (90.3)	140 (90.3)	126 (94.0)	
Positive/close	35 (9.7)	12 (9.7)	15 (9.7)	8 (6.0)	
Axillary node status					0.54
Negative	242 (67.0)	81 (65.3)	113 (72.9)	98 (73.1)	
1-3	79 (21.9)	30 (24.2)	26 (16.8)	21 (15.7)	
> 3	40 (11.1)	13 (10.5)	16 (10.3)	15 (11.2)	
Tumor grade					< 0.0001
1	108 (29.9)	35 (28.2)	29 (18.7)	48 (35.8)	
2	174 (48.2)	66 (53.2)	51 (32.9)	55 (41.0)	
3	79 (21.9)	23 (18.5)	75 (48.4)	31 (23.2)	
Adjuvant therapy					< 0.0001
No	18 (5.0)	8 (6.5)	17 (11.0)	9 (6.7)	
Hormone therapy	144 (39.9)	42 (33.9)	-	-	
Chemotherapy	51 (14.1)	14 (11.3)	138 (89.0)	125 (93.3)	
Chemotherapy+hormone therapy	148 (41.0)	60 (48.4)	-	-	
Hormone therapy					< 0.0001
yes	292 (80.9)	102 (82.3)	-	-	
no	69 (19.1)	22 (17.7)	155 (100.0)	134 (100.0)	
Chemotherapy					< 0.0001
yes	199 (55.1)	74 (59.7)	138 (89.0)	125 (93.3)	
no	162 (44.9)	50 (40.3)	17 (11.0)	9 (6.7)	

Table 2. Univariate analysis of variables for breast cancer specific survival (BCSS), distant metastases rates (DM) and local relapse rates (LR)

	BCCS			DM			LR		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	P
Age			0.20			0.03			0.03
< 50	1.00	-		1.00	-		1.00	-	
50-64	0.67	0.42-1.07		0.86	0.58-1.27		0.29	0.11-0.77	
>65	0.70	0.41-1.19		0.51	0.30-0.85		0.49	0.19-1.30	
Histology			0.24			0.01			0.27
Ductal	1.00	-		1.00	-		1.00	-	
Other	1.47	0.76-2.84		0.41	0.20-0.81		0.44	0.10-1.88	
Tumor size			0.23			0.06			0.00001
0.1-1 cm	1.00	-		1.00	-		1.00	-	
1.1-2 cm	1.24	0.78-1.97		1.55	1.04-2.30		1.07	0.37-3.11	
> 2 cm	1.75	0.90-3.37		1.69	0.91-3.13		9.34	3.49-24.96	
Margins			0.12			0.42			0.00001
Negative	1.00	-		1.00	-		1.00	-	
Positive/close	2.39	0.75-7.58		0.71	0.31-1.63		24.15	10.23-56.97	
Axillary node status			0.00001			0.00001			0.68
Negative	1.00	-		1.00	-		1.00	-	
1-3	0.57	0.30-1.11		0.97	0.60-1.55		0.61	0.20-1.83	
> 3	4.02	2.51-6.32		3.47	2.26-5.33		0.91	0.21-3.92	
Tumor grade			0.47			0.68			0.001
1	1.00	-		1.00	-		1.00	-	
2	1.06	0.63-1.78		1.12	0.72-1.73		2.35	0.50-11.12	
3	1.35	0.79-2.32		1.23	0.76-1.99		8.16	1.87-35.54	
Adjuvant therapy			0.00001			0.00001			0.98
No	1.00	-		1.00	-		1.00	-	
Hormone therapy	0.86	0.15-4.71		0.56	0.21-1.45		0.92	0.17-4.77	
Chemotherapy	6.79	1.66-27.72		2.12	0.98-4.61		1.08	0.24-4.84	
Chemotherapy+hormone therapy	2.26	0.52-9.83		0.94	0.40-2.16		0.94	0.19-4.58	
Hormone therapy			0.00001			0.00001			0.74
Yes	1.00	-		1.00	-		1.00	-	
No	3.43	2.09-5.63		2.48	1.68-3.65		1.13	0.52-2.47	
Chemotherapy			0.00001			0.0004			0.84
Yes	1.00	-		1.00	-		1.00	-	
No	0.18	0.07-0.41		0.41	0.25-0.69		0.91	0.38-2.18	
Subtypes			0.00001			0.00001			0.16
Luminal A	1.00	-		1.00	-		1.00	-	
Luminal B	2.40	1.11-5.19		1.57	0.86-2.90		2.71	1.01-7.31	
Basal-like	5.21	2.89-9.38		2.89	1.81-4.59		1.84	0.68-4.96	
HER 2	4.81	2.61-8.86		3.15	1.97-5.04		0.86	0.23-3.18	

Abbreviations: HR= hazard ratio

Table 3. Results of multivariate analysis

	Breast cancer specific survival		
	HR	95% CI	P
Axillary node status			0.00001
Negative	1.00	-	
1-3	0.49	0.25-0.95	
> 3	4.62	2.92-7.30	
Adjuvant therapy			0.03
No	1.00	-	
Hormone therapy	1.65	0.27-9.79	
Chemotherapy	5.71	1.37-23.80	
Chemotherapy+hormone therapy	2.97	0.60-14.53	
Subtypes			0.03
Luminal A	1.00	-	
Luminal B	2.50	1.15-5.41	
Basal-like	3.09	1.27-7.53	
HER 2	2.57	1.04-6.38	
Distant metastases			
Axillary node status			0.00001
Negative	1.00	-	
1-3	0.98	0.61-1.58	
> 3	3.63	2.36-5.60	
Subtypes			0.00001
Luminal A	1.00	-	
Luminal B	1.65	0.89-3.04	
Basal-like	2.97	1.87-4.73	
HER 2	3.23	2.03-5.15	
Local relapses			
Age			0.003
< 50	1.00	-	
50-64	0.18	0.06-0.48	
>65	0.77	0.27-2.15	
Tumor size			0.0001
0.1-1 cm	1.00	-	
1.1-2 cm	0.84	0.27-2.63	
> 2 cm	5.44	1.94-15.23	
Margins			0.00001
Negative	1.00	-	
Positive/close	26.00	10.28-65.73	
Grading			0.049
1	1.00	-	
2	1.74	0.35-8.47	
3	4.62	1.01-21.11	

Abbreviations: HR= hazard ratio

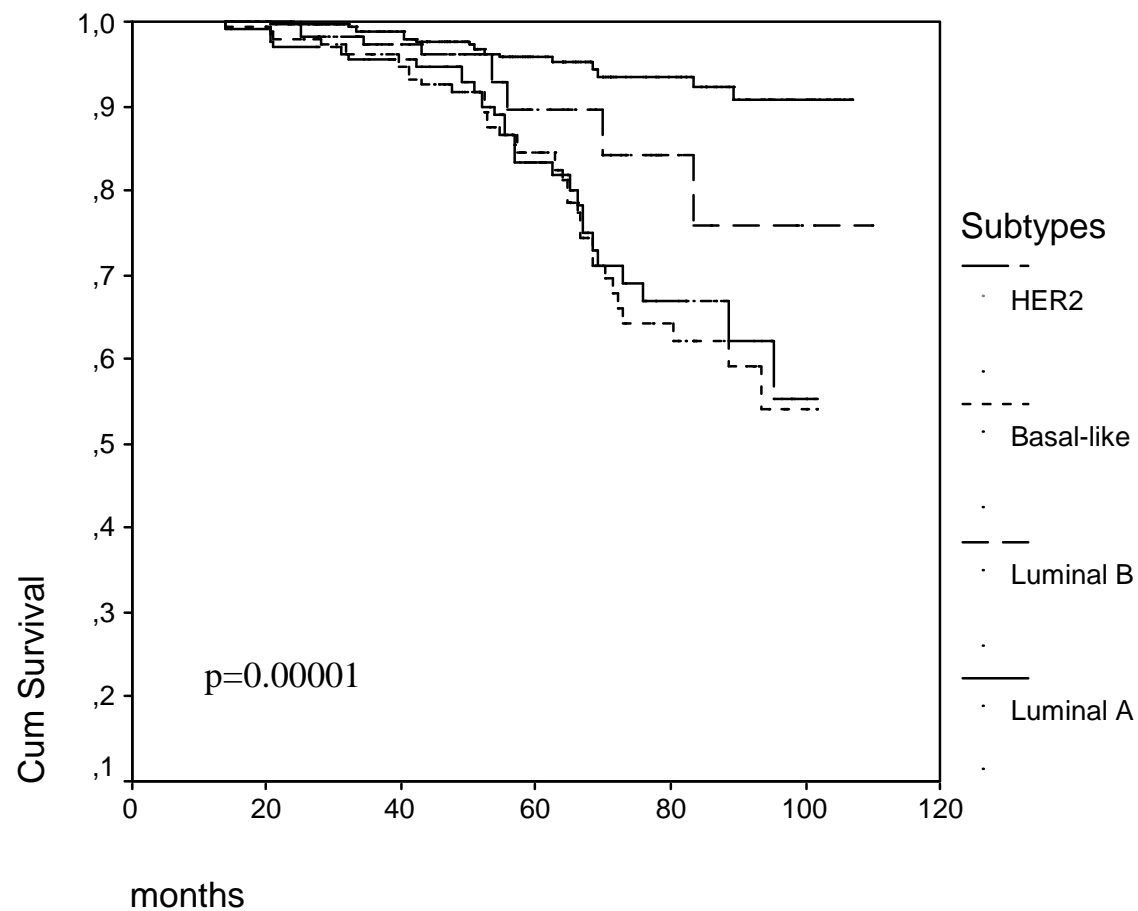


Fig. 1 Breast cancer specific survival based on breast cancer subtypes

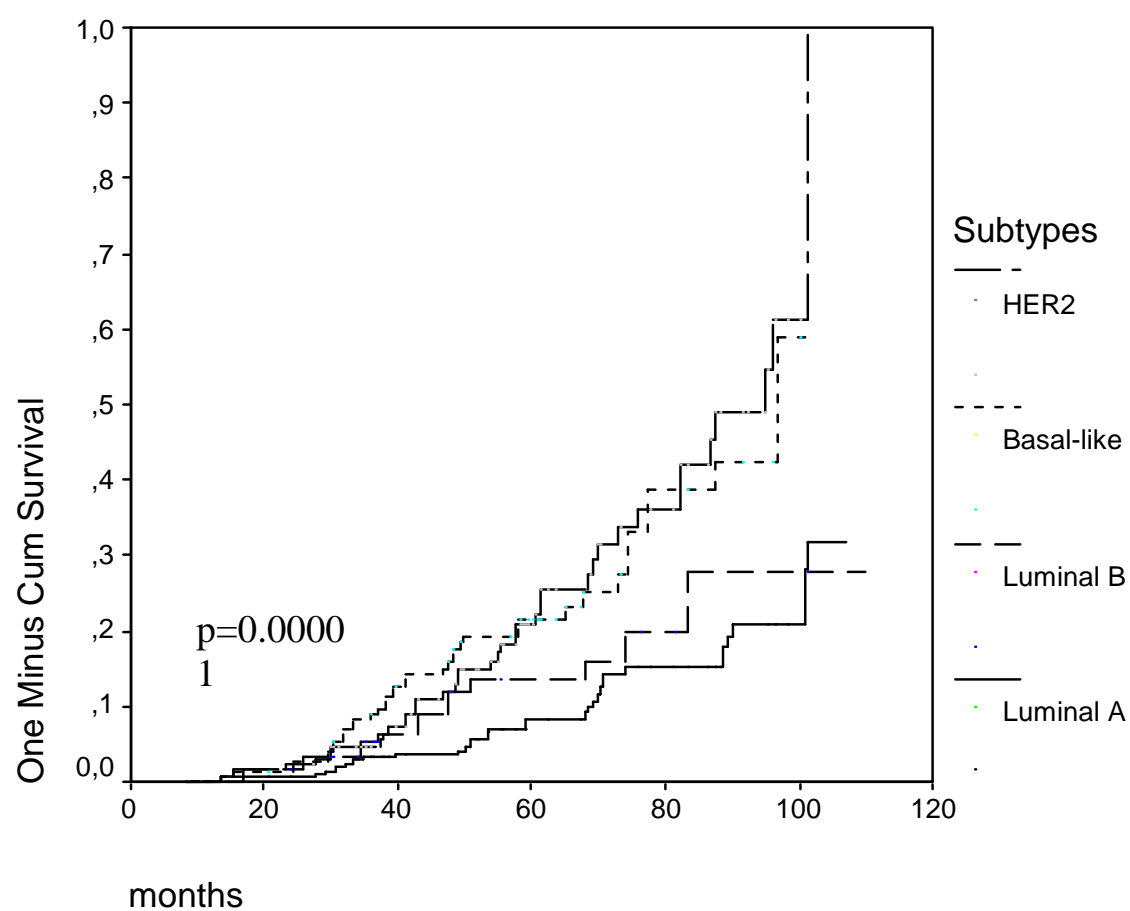


Fig. 2 Distant metastases rates based on breast cancer subtypes