RESEARCH ARTICLE

Reconsideration of Clinical and Histopathological Prognostic Factors in Breast Cancer Patients: A Single Center Experience

Ozgur Tanriverdi*, Nezih Meydan, Sabri Barutca

Abstract

**Background:** The clinical course of the neoplasm may vary due to both patient and tumor cell characteristics. **Aim:** The aim of this study was to research the influence of certain clinical and pathological features on the prognosis of early stage breast cancer. **Materials and Methods:** This study included 117 women that were treated and followed-up in between the years 2001-2011. The demographic, clinical and histopathological features of the cases were reviewed retrospectively. **Statistical analysis:** In categorical comparisons between groups, cross-tab statistics were provided and significance levels were estimated using chi-square test. Cox regression analysis, Pearson and Spearman correlation tests, and the Kaplan-Meier test were also used. **Results:** With an average of 35-months follow-up, the mean disease-free survival of patients was 91 months and the mean overall survival time was 132 months. In the whole study group, the disease-free survival rates were 88, 84, 83 and 52%, while the overall survival rates 95, 94, 83, and 83% within the first, third, fifth and tenth years, respectively. The disease-free and overall survival rates were decreased with increasing tumor grades, though this was not statistically significant. The presence of lymphovascular invasion, positive staining with Ki67 and postmenopausal status were associated with shorter disease-free and overall survival times. In multivariate analysis, only age and Her2/neu receptor status influenced the prognosis significantly. **Conclusions:** In parallel to clinical, histopathological, and immunohistochemical prognostic features in breast cancer, in this study positive Her2/neu receptor status, a previously accepted poor prognostic factor, was found to have positive influence after trastuzumab treatment.

Keywords: Breast cancer - prognosis - receptor - Her2/neu - biological markers

Asian Pac J Cancer Prev, 15 (2), 807-812

Introduction

Breast cancer is the most common malignant disease in women and second most common cancer related cause of death. It remains as an important health problem because of high mortality and morbidity rates (Taneja et al., 2010; Weigel et al., 2010; Drukker et al., 2013; Siegel et al., 2013). Therefore, clinical, histopathological, and immunohistochemical characteristics that are thought to be related to survival rates of this disease are the main subjects of many current studies.

In parallel with new information on tumor biology, clinical studies focusing on determining predictive and prognostic factors in breast cancer increased in number. Today, it is accepted that tumor cells have different biological behaviors in each breast cancer case. So, because of the presence of different subgroups without homogeneity in receptor status, it is known that disease course and treatment benefits differ for each case (Taneja et al., 2010). In many clinical studies, apart from hormone receptor and Her2/neu status, some immunohistochemical characteristics of the tumor are reported to be separate prognostic factors for both survival and relapse.

While many molecules and genetic mutations in different stages of carcinogenesis such as tumor cell proliferation, cell adhesion, inhibition of apoptosis, angiogenesis are accepted as predictive and/or prognostic factors, some have not yet taken a place in guidelines (Weigel et al., 2010; Drukker et al., 2013).

In this study, we aimed to assess in the early-stage breast cancer cases which applied to our department following surgical treatment, in the light of current information, clinical and histopathological characteristics which have positive or negative effect on breast cancer progress and their relationship with each other.

Materials and Methods

Among the early stage breast cancer patients treated and followed-up in Adnan Menderes University Medical School by Medical Oncology Department from 2001 to 2011, 117 who had available information and who could be reached are enrolled in this study. Patients were referred to our department with pathology results after curative surgery.

Demographic characteristics of patients such as
age, height, weight, menopause status and histological characteristics of tumor such as tumor type, lymph node status, tumor size, and lymphovascular invasion were recorded. Information from patients’ files were recorded including date of diagnosis, operation date, which breast the tumor is located and its localization, type of surgery, adjuvant chemotherapy initiation date and administered regimens in this therapy, adjuvant radiotherapy initiation date, information about hormonotherapy and trastuzumab if they were administered, relapse localizations, and time till the relapse, and whether if the patient was alive or not.

Immu­no- histochemical staining of tumor cells with estrogen and/or progesterone receptor with a rate of >1% was considered as positive for hormone receptor status. Similarly, immuno- histochemical detection of human epidermal growth factor receptor-2/neu (Her2/neu) expression with a value of +3 or positive results with fluorescent in situ hybridization out of whose immuno-histochemical staining are +2, were considered as Her2/ neu over-ex­pression.

While staining of tumor cells with a rate of 20% or more was considered as ki67 positive, for p53 expression staining of cells with a rate of 11% or more is considered as positive criterion.

 Ethics

The protocol for this retrospective study was compatible with the local ethical guidelines. The study was approved by the Academic Committees in our center and written informed consents were obtained from all participants.

Statistical analyses

The data are expressed as the mean±standard deviation or the median and inter­quartile range (25-75%). The distribution of variables was analyzed with the Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, independent Student’s t test. Nonparametric variables were analyzed with the Mann-Whitney U test. However, qualitative parameters were analyzed with the Chi-square test and Fisher’s test. The Kruskal-Wallis test was used for comparisons between clinical and demographic variables.

In categorical comparisons between groups, cross-tab statistics were provided and significance levels were estimated using chi-square test. Prognostic values of demographic and tumor characteristics were assessed with Cox regression analysis according to forward model. For relationships of same characteristics with survival and with each other, Pearson and Spearman correlation tests were used. Disease-free survival is estimated as time between diagnosis and first relapse and overall survival is estimated as time between diagnosis and death. Their impacts on life were evaluated with Kaplan-Meier test.

A value of p<0.05 was accepted as statistically significant. All analyses were performed using Statistical Program for Social Sciences version 15.0 for Windows.

Results

Mean age of 117 female patients in this study was

| Features                          | n, % mean±std.dev. |
|-----------------------------------|--------------------|
| Age (years): n, (mean±std.dev)    | 117, (55±12)       |
| Age at diagnosis (years): n, (mean±std.dev) | 117, (52±12)       |
| Family history for breast cancer  |                    |
| Absence                          | 104 (89)           |
| Presence                         | 13 (11)            |
| Menopausal status                |                    |
| Postmenopausal                   | 66 (56)            |
| Premenopausal                    | 51 (44)            |
| Time of the menopause: n, (mean±std.dev) | 66, (48±4)         |
| Body mass index                  |                    |
| Obesity (>30 kg/m²)              | 27 (26)            |
| (kg/m²)                          | 37 (37)            |
| Normally (<25 kg/m²)             | 37 (37)            |
| Histological type                |                    |
| Invasive ductal carcinoma        | 94 (80)            |
| Invasive lobular carcinoma       | 9 (8)              |
| Inflammatory carcinoma           | 7 (6)              |
| Atypical medullary, tubular and other | 7 (6)             |
| Localization of tumour in the breast |                |
| Upper outer quadrant             | 52 (50)            |
| Lower outer quadrant             | 5 (5)              |
| Upper inner quadrant             | 3 (3)              |
| Lower inner quadrant             | 12 (11)            |
| Unknown                          | 16 (15)            |
| Multifocality or multicentricity |                    |
| Absence                          | 16 (14)            |
| Presence                         | 101 (86)           |
| Operation type                   |                    |
| Radically mastectomy             | 76 (65)            |
| Breast-conservation surgery      | 41 (35)            |
| Axillary approaches              |                    |
| Axillary dissection              | 97 (83)            |
| Sentinel lymph node sampling     | 27 (21)            |
| Tumour grade                     |                    |
| 1                                | 7 (6)              |
| 2                                | 73 (62)            |
| 3                                | 21 (18)            |
| Unknown                          | 16 (14)            |
| Tumour size (mean±std.dev: 2.2±0.9 (cm)) |                |
| <2 cm                            | 19 (16)            |
| 2-5 cm                           | 58 (50)            |
| >5 cm                            | 39 (33)            |
| Nodal status                     |                    |
| N0                               | 55 (47)            |
| N1                               | 26 (23)            |
| N2                               | 18 (15)            |
| N3                               | 18 (15)            |
| Lymphovascular invasion          |                    |
| Absence                          | 29 (25)            |
| Presence                         | 70 (60)            |
| Unknown                          | 18 (15)            |
| Stage (TNM)                      |                    |
| I                                | 21 (18)            |
| II                               | 84 (72)            |
| III                              | 12 (10)            |
| Estrogen receptor status         |                    |
| Positive                         | 69 (59)            |
| Negative                         | 48 (41)            |
| Progesterone receptor status     |                    |
| Positive                         | 68 (58)            |
| Negative                         | 49 (42)            |
| Her2/neu status                  |                    |
| Positive*                        | 41 (35)            |
| Negative                         | 76 (65)            |
| Main molecular subtype of tumor  |                    |
| Luminal A                        | 50 (43)            |
| Luminal B                        | 29 (25)            |
| Her2- positive                   | 18 (15)            |
| Triple negative                  | 19 (16)            |
| Ki67 staining                    |                    |
| Absence                          | 67 (58)            |
| Presence                         | 39 (33)            |
| p53 status                       |                    |
| Absence                          | 73 (62)            |
| Presence                         | 37 (32)            |
| Unknown                          | 7 (6)              |
| Ki67 scoring                     |                    |
| <20%                             | 67 (58)            |
| 20-50%                           | 20 (17)            |
| >50%                             | 19 (16)            |
| Unknown                          | 11 (9)             |
| p53 scoring                      |                    |
| Negative                         | 73 (62)            |
| Score 1                          | 9 (8)              |
| Score 2                          | 16 (14)            |
| Score 3                          | 12 (10)            |
| Unknown                          | 7 (6)              |

*immunohistochemical or FISH
53±12 years (age range 30-80) and their mean age at diagnosis was 52±12 years (age range 26-82). While only one of these patients were observed without treatment, systemic adjuvant therapies and/or radiotherapy were given to remaining 116 patients.

Demographic and clinical characteristics of patients and histological and immuno-histological characteristics of tumor are shown in Table 1.

Patients’ hormone receptor and Her2/neu status and stratification by receptors is pre-sented in Table 1. In follow-up period average of 35 months (range: 3-153 months), patients’ mean estimated disease-free survival was 91 months (range: 75-108 months), mean overall survival was 132 months (range: 119-145 months).

83 patients (71%) were disease-free and still in follow-up, 25 patients (21%) were being treated for metastatic disease. With one of them being co-morbid, a total of 9 (8%) patients had lost their lives.

Disease-free survivals in overall study group were 88% in first year, 84% in third year, 83% in fifth year, and 52% in 10th year. Same values were 95%, 84%, 83%, and 83% for overall survival, respectively.

Results of disease-free survival and overall survival are indicated in Table 2, 3, and 4.

Tumor size was in a linear relationship with pathological node status and number of nodes involved (r=0.22, p=0.017, r=0.245, p=0.008, respectively). Relapse risk in patients with lymphovascular invasion was increased 3.3 times (95% CI 1.4-7.5; p=0.006), and death risk was increased 2.2 times (95%CI 1.4-3.4; p=0.014). Also lympho-vascular invasion in our patients was in a moderate linear relationship with T stage (r=0.210, p=0.023), pathologic nodal stage (r=0.250, p=0.007), and number of nodes involved (r=0.260, p=0.005).

In postmenopausal patients, disease-free and overall survival times were worse compared to premenopausal patients. In both groups there was no significant difference
between hormone receptor status, tumor degree, Her2/neu status, disease stage, node involvement, ki67 and p53 staining characteristics (p>0.05). However, in postmenopausal women, there was a higher rate of lymphovascular invasion (46% vs 29%; p=0.47) and mostly T3 tumor (38% vs 28%; p=0.51) was present. There was no significant relationship between Her2/neu status and other study variables.

In 29% of patients (n=29) distant metastasis was observed, in 3% (n=4) local relapse in similar histological characteristics was observed and in 1% (n=1) a second cancer in similar histological type in opposite breast was observed. In 10% of patients (n=11) bone metastasis, in 5% (n=6) lung metastasis, in 3% (n=4) liver metastasis, in 1% (n=1) both bone and brain metastasis, and in 1% (n=1) isolated brain metastasis were observed.

Mean age of patients with metastasis was 64 years (age range 30-88) and it was statistically more than patients without metastasis (mean age 52, range 34-84) (p=0.001). In post-menopausal women, metastasis rate was 36% (n=24) and this rate was significantly higher compared to premenopausal women (18%, n=89) (p=0.038).

In multivariate analysis, age and Her2/neu status for disease-free survival were found as prognostically significant (OR 1.08 95%CI 1.05-1.14; p=0.001 and OR 0.135 94%CI 0.31-0.59; p=0.008, respectively). On overall survival, only age was significantly effective (OR 1.08, 95%CI 1.05-1.14; p=0.001).

Discussion

Although it might seem like a repetition of previous studies, we aimed to compile data of our early stage breast cancer patients in our institute and determine aspects of it that is consistent with literature, approach our patients and their tumor cells from our own perspective and understand them better.

While in beginnings of last century, breast cancer patients had an average survival of 3 years, today these rates are for one year 98%, for three years 85%, and for five years 82% (Goldhirsch et al., 2007). In our study, our patients’ survival was in one year 95%, in three years 84%, and in five years 83%. These rates were generally consistent with literature data.

Many studies are conducted to understand the natural progression of breast cancer and to find better prognostic and predictive indicators of this disease. Until today, more than 150 prognostic factors are identified. However, in clinical practice very few of these factors are being used. Today, nodal metastasis, tumor size, histological type, tumor degree, presence of lymphovascular invasion, hormone receptor and Her2/neu status, and patient’s age at diagnosis are main prognosis related characteristics that are being used. Independent from all patient and tumor related characteristics; most important prognostic factor of breast cancer is axillary involvement (Kröger et al., 2006; Taneja et al., 2010; Weigel et al., 2010; Jung et al., 2013).

In previous studies, it was reported that in patients with 1 to 3 node involvement five year survival rate was 73%, with 4 to 12 it was 46%, and with more node involvement it was 28%. However, in node-negative breast cancer patients five year survival rate was reported as 83%. Overall, in patients with node involvement mortality rate was 20% (Carter et al., 1989; Rosen et al., 1992; Truong et al., 2008). We can explain the inconsistency of our study with the literature with our relatively short follow-up periods.

In patients without nodal involvement, most important prognostic factor is tumor size. While in tumors smaller than 1 cm, five year survival rate was reported by Carter et al. (1989) as 99%, this rate is 89% in tumors with a size of 1 to 3 cm, and 86% in tumors with a size of 3 to 5 cm. When it comes to disease-free survival rates, according to rates reported by Rosen et al. (1992); 20 year disease-free survival rate was 88% in tumors smaller than 1 cm, in tumors with a size of 1.1 to 3 cm it was 72 cm, and in tumors with a size of 3.1 to 5 cm it was 59%.

In current studies, it is stated that in tumors smaller than 1 cm, other prognostic factors should be considered for adjuvant therapy decision (Lai et al., 2011). In our study, we could not find any significant relationship between tumor size and disease-free/overall survival. Similarly, also in univariate and multivariate analyses, tumor size was not found as a prognostic factor. This situation may be related to relatively small number of patients.

In our study, we could not reach a distinct conclusion about tumor degree as an important prognostic factor. Inconsistent results may be related to relatively small number of patients.

In our study most important prognostic factor that is prominent is lymphovascular invasion. A significant relationship between lymphovascular invasion and risk of recurrence was shown by Rosen et al. (1989). In this study, while recurrence rate in stage 1 breast cancer patients with lymphovascular invasion was 38%, in patients without lymphovascular invasion this rate was 22% (Rosen et al., 1989). In current guidelines, presence of lymphovascular invasion is reported as an important prognosis indicator in node-negative breast cancer patients with borderline tumor size (Rakha et al., 2012).

In contrary to the literature, we have found that postmenopausal breast cancer patients had worse survival rates. This inconsistent result may be related to our use of only adjuvant endocrine therapy option on 12% of patients, beyond high lymphovascular invasion rate and large tumor size in postmenopausal women.

In breast cancer, endocrine approach is an important part of the treatment. Grann et al. (2005) showed in their study that estrogen and progesterone receptor status was an independent prognostic factor in breast cancer. In a study (EBCTCG) (1998), high rates of estrogen positivity reduced death risk related to cancer by 31%. However, another study (Dunnwald et al., 2007) reported that postmenopausal breast cancer patients with high estrogen receptor expression had that same bad prognosis of hormone receptor negative breast cancer patients.

But in ATAC (Dowsett et al., 2008) and BIG 1-98 (Viale et al., 2007) studies, it is found that breast cancer patients with different levels of estrogen receptor expression benefited from tamoxifen and aromatase inhibitors with a similar rate. In current guidelines based on current literature data, it is stated that hormone receptor
status has mainly a predictive value.

Hormone receptor positivity increases with age. In previous studies, hormone receptor positivity rate is reported as 55-65%. In our study, we found this rate as 68%. We found that this rate was 79% in patients above sixty years of age. Another result of our study that is in-consistent with literature is overall and disease-free survival rates in hormone-sensitive and non-hormone-sensitive patients. We explain this situation with our relatively small number of patients.

In 15 to 30% of breast cancer patients, Her2/neu over-expression and amplification is seen. In previous studies, it is reported that patients with nodal metastasis and Her2/neu over-expression had bad prognosis (Curigliiano et al., 2009; Gonzales-Angulo et al., 2009). However, in node-negative patients it is shown that their prognoses will be worse in case of presence of Her2/neu over-expression. In our study we saw that Her2/neu receptor status had a significant effect on survival, but this relationship did not reflect on overall survival.

In HERA (Smith et al., 2007) study involving 5102 node-positive and high risk node-negative breast cancer patients, in women with breast cancer with adjuvant trastuzumab therapy administration for one year, survival rates were positively affected compared to patients without trastuzumab administration over two years of follow-ups. However, in results of Fin-Her (Joensuu et al., 2009) study showing that trastuzumab therapy for nine weeks also provides an advantage on disease-free survival; it is shown that trastuzumab therapy concomitant with docetaxel for nine weeks is effective, economic, and safe in side-effect aspect. Today in international guidelines, extension of anti-Her2/neu therapy in adjuvant setting to 52 weeks suggestion is in the foreground. Also, in a study of Rodrigues et al. (2010), it is stated that adjuvant therapy with trastuzumab, and long term suppression of Her2/neu receptor have positive effects on disease-free survival.

Biological group identified as triple-negative, without estrogen receptor, progesterone receptor, and Her2/neu expression consists of 10 to 15% of all breast cancer patients. Most of breast cancers related to mutant BRCA1 are reported as triple-negative patients (Nishimura and Arima, 2008). Patients in this group are generally younger, with higher axillary nodal involvement rate and with tumors with larger sizes and higher degrees. Because of these char-acteristics, they are considered to have aggressive progression. In our study, insufficient detec-
tion of events due to relatively small number of patients and short follow-up period did not allow characteristics of triple-negative breast cancer patients to be identified.

Despite many studies, prognostic characteristics of ki67 and p53 expression in breast cancer have not been clarified, yet. Today, especially in node-negative patients with small sized tumors, it is thought that these should be considered during treatment decision (Nishimura and Arima, 2008). However, ki67 staining over 20% is shown by Nishumara and Arima (2008) to be in a linear and significant relationship with young age, nodal involvement, large tumor size, hormone receptor negativity, p53 expression and Her2/neu over-expression. In our study, we did not find ki67 staining characteristics to be in any statistically significant relationship with metastasis rate and disease-free survival. However, it is found that in patients with highly stained tumors overall survival was affected negatively.

In a similar way, studies on p53 expression are also controversial. However, it is reported in a frequency of 20 to 50% in hereditary breast cancer patients. After the study of Ferrero et al. (2000), p53 expressions and mutations are considered to affect disease-free and overall survival negatively. In our study, probably due to our relatively small number of patients, no significant effect of p53 expression on survival could be shown.

In conclusion, this study of ours in 2011 which has relatively short follow-up times and small in numbers of patients, although till then studies on some new treatment options and prognostic molecules have been published, when inconsistent results according to inform-ation of its time are considered, it lets us think that we deal with one of most heterogenic patient groups of clinical oncology and what we know as right for breast cancer patients can always change. Today, clinical progression of each case with breast cancer and which treatment will be administered to these patients are determined by dealing with specific characteristics of patient and tumor separately. Therefore, it is obvious that a lot of histological, molecular, and genetic factors apart from prognostic and predictive factors accepted in international guidelines will continue to be studied. Thus, we are in an opinion that each breast cancer treatment center should examine its own data, and achieved results and also literature-based information should guide them on their clinical experience.

References

Carter C, Allen C, Henson D (1989). Relation of tumor size, lymph node and survival in 24 740 breast cancer cases. Cancer, 63, 181-7.

Curigliano G, Viale G, Bagnari V, et al (2009). Clinical relevance of Her2 overexpression/amplification in patients with small tumour size and node-negative breast cancer. J Clin Oncol, 27, 5693-99.

Dowsett M, Allred C, Knox J, et al (2008). Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor-2 (Her2) status with recurrence in the aromidex, tamoxifen, alone or in combination trial. J Clin Oncol, 26, 1059-65.

Drukker CA, Bueno-de-Mesquita JM, Retel VP, et al (2013). A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. Int J Cancer, 133, 929-36.

Dunnwald LK, Rossing MA, Li CI (2007). Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res, 9, 6-9.

Early Breast Cancer Trialists’ Collaborative Group (1998). Tamoxifen for early breast cancer: an overview of the randomized trials. Lancet, 351, 1451-67.

Ferrero JM, Ramaioi A, Formento JL, et al (2000). p53 determination alongside classical prognostic factors in node-negative breast cancer: An evaluation at more than 10-year follow-up. Ann Oncol, 11, 393-7.

Goldhirsh A, Wood WC, Gelber RD, et al (2007). Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol,
Gonzales-Angulo AM, Litton JK, Broglio KR, et al (2009). High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol, 27, 5700-6.

Grann VR, Trowel AB, Zojualla NJ, et al (2005). Hormone receptor status and survival in a population-based cohort of patients with breast carcinoma. Cancer, 103, 2241-51.

Joensuu H, Bono P, Kataja V, et al (2009). Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, or with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer study. J Clin Oncol, 27, 5685-92.

Jung KW, Won YJ, Kong HJ, et al (2013). Survival of Korean adults patients by stage at diagnosis, 2006-2010; national cancer registry study. Cancer Res Treat, 45, 162-71.

Kröger N, Milde-Langosh K, Riethdorf S, et al (2006). Prognostic and predictive effects of immunohistochemical factors in high risk primary breast cancer patients. Clin Cancer Res, 12, 159-68.

Lai HW, Kuo SJ, Chen LS, et al (2011). Prognostic significance of triple negative breast cancer at tumor size 1 cm and smaller. Eur J Surg Oncol, 37, 18-24.

Nishimura R, Arima N (2008). Is triple negative a prognostic factor in breast cancer? Breast Cancer, 15, 303-8.

Rakha EA, Martin S, Lee AHS, et al (2012). The prognostic significance of lymphovascular invasion in invasive breast carcinoma. Cancer, 118, 3670-80.

Reinke T (2013). Poor risk assessment limits breast cancer survival. Manag Care, 22, 6-7.

Rodrigues MJ, Wassermann J, Albiger L, et al (2010). Trastuzumab treatment in T1ab, node-negative, human epidermal growth factor receptor 2-over-expressing breast carcinomas. J Clin Oncol, 28, 541-2.

Rosen PP, Groshen S, Saigo PE, Kinne DW, Hellman J (1989). Pathological prognostic factors in stage I (T1N0M0) and stage II (T1N1M0) breast carcinomas: a study of 644 patients with median follow-up of 18 years. J Clin Oncol, 7, 1239-51.

Rosen PP, Groshen S, Kinne DW (1992). Survival and prognostic factors in node-negative breast cancer: results of long-term follow-up studies. J Natl Cancer Inst Monogr, 11, 159-62.

Siegel R, Naishadham D, Jemal A (2013). Cancer statistics, 2013. CA Cancer J Clin, 63, 11-30.

Smith I, Practer M, Gelber RD, et al (2007). 2-year follow-up of trastuzumab after adjuvant chemotherapy in Her2 positive breast cancer: a randomized controlled trial. Lancet, 39, 39-29.

Taneja P, Maglic D, Kai F, et al (2010). Classical and novel prognostic markers for breast cancer and their clinical significance. Clin Med Insights: Oncol, 4, 135-34.

Truong PT, Vinh-Hung V, Cserni G, et al (2008). The number of positive nodes and the ratio of positive to excised nodes are significant predictors of survival in women with micrometastatic node-positive breast cancer. Eur J Cancer, 44, 1670-7.

Viale G, Regan MM, Maiorano E, et al (2007). Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early breast cancer: BIG-1-98. J Clin Oncol, 25, 3846-52.

Weigel MT, Dowsett M (2010). Current and emerging biomarkers in breast cancer: prognosis and prediction. Endocr Relat Cancer, 17, 245-62.