Journal of BUON **17:** 277-283, 2012

ORIGINAL ARTICLE

Discordant expression of hormone receptors and HER2 in breast cancer. A retrospective comparison of primary tumors with paired metachronous recurrences or metastases

P. Arapantoni-Dadioti, C. Valavanis, T. Gavressea, O. Tzaida, H. Trihia, I. Lekka

Department of Pathology, Metaxa Cancer Hospital, Piraeus, Greece

Summary

Purpose: *Expression of biomarkers in breast cancer, such as the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), can impact therapeutic decisions; however, it has been reported that their expression may change with disease progression. The aim of this retrospective study was to investigate the expression of these biomarkers in primary breast cancer and in its metachronous recurrences or metastases, and to estimate the percentage of cases with discordant expression.*

Methods: *Paired primary and metastatic tumor samples were collected from patients with primary breast cancer and subsequent metachronous distant metastases, diagnosed at the Metaxa Cancer Hospital, Piraeus, Greece, from 1988 to 2008. Two cases of local recurrence were also included. ER, PR and HER2 expression were assessed by immunohistochemistry (IHC) according to ASCO-CAP 2007 guidelines. Statistical comparisons were made using McNemar's exact test and Bowker's test for symmetry.*

Results: *Tumor samples from 110 patients were analysed. In the primary tumor, ER, PR and HER2 were positively expressed in 64.5%, 58.2% and 32.7% of cases, respectively, and expression of these biomarkers was lost in 18.2%, 21.8% and 10.9% of the corresponding metastases, respectively. Overall, a change of ER, PR and HER2 expression from positive to negative and vice versa occurred in 27.3% ($p = 0.0987$), 25.5% ($p < 0.001$) and 18.2% ($p = 0.5034$) of the cases, respectively.*

Conclusion: *The expression of ER, PR and HER2 in metachronous recurrences or metastases can be discordant from that observed in the primary tumor. As such changes can occur during disease progression, the evaluation of biomarkers in metastatic sites should be mandatory, whenever possible, to ensure that patients are receiving the most effective treatment at all times.*

Key words: breast cancer, estrogen receptor, HER2, metastases, progesterone receptor

Introduction

Breast cancer is the most common cancer in women, with an estimated 1,383,500 cases and 458,400 deaths worldwide in 2008 [1]. The prognosis and response to treatment of patients with breast cancer is variable, with expression of several biomarkers believed to be associated with this variability. These biomarkers include the ER and PR [2,3], which are expressed in approximately 80% of invasive breast cancers [4], and the overexpression and/or gene amplification of human epidermal HER2 [5], which occurs in 18-25% of breast cancers [6-8]. Expression of ER and/or PR is generally associated with a good prognosis, with ER-positive tumors often exhibiting slow tumor growth [9] and high levels of PR correlating with small tumor size and low histologic grade [9]. In contrast, HER2-positive breast cancer is considered to be more aggressive than HER2-negative breast cancer and is associated with increased cell proliferation and tumor invasiveness [10,11] and reduced overall survival [8].

Knowledge of receptor status (ER, PR and HER2) can have an impact on decision-making for breast cancer therapy, and strategies specifically aimed at patient populations that express different receptors have allowed a more targeted approach to treatment. For ex-

Correspondence to: Petroula Arapantoni-Dadioti, MD. Department of Pathology, Metaxa Cancer Hospital, 51, Botassi street, Piraeus 18537, Greece. Tel: +30 210 4285430, Fax: +30 210 4285450, E-mail: dadiotis@hol.gr

Received 30-01-2012; Accepted 24-02-2012

ample, as endocrine responsiveness improves with increasing expression of both ER and PR [12,13], hormone receptor-positive tumors are typically treated with endocrine therapy [14]. Furthermore, HER2-targeted agents (i.e. trastuzumab and lapatinib) are recommended for patients with metastatic HER2-positive breast cancer, and trastuzumab is the standard of care in the adjuvant setting for patients with early HER2-positive breast cancer [14,15]. Use of these agents in combination with chemotherapy has improved the prognosis for many patients in terms of response rates and survival [16-26]. For example, higher overall survival was observed in women with HER2-positive metastatic breast cancer who received trastuzumab, compared with those who did not receive trastuzumab (25.1 vs. 20.3 months; $p = 0.046$) [24]. Understanding of the role of receptors in breast cancer is still evolving.

The importance of receptor status in the prognosis and response to therapy is reflected by the stringent guidelines available for accurate IHC testing of ER, PR and HER2 in breast cancer [27,28]. Despite the existence of guidelines supporting the retesting of metastases for ER and PR [27], guidelines for HER2 are less clear, and retesting of metastases for HER2 receptor status is not common practice everywhere. However, some studies have shown that there can be discordance between ER, PR and HER2 expression in primary breast tumors compared with metastases in the same patient [29-36]. As changes in receptor status can influence the therapeutic choices, it is important to understand the frequency with which these changes occur and to raise awareness of the importance of retesting metastases to allow for optimal treatment for all patients.

The aim of this retrospective study was to compare the expression of the ER, PR and HER2 proteins, analysed by IHC, in primary breast cancer with that in its metachronous recurrences or metastases, in order to estimate discordant cases.

Methods

Patients

This retrospective study considered all consecutive metachronous breast cancer metastases and local recurrences along with their primary tumors diagnosed in the "Metaxa" Cancer Hospital, Piraeus, Greece, from 1988 to 2008. This study was approved by the Metaxa Cancer Hospital Bioethics committee.

Tissue collection and handling

Samples from resections of the primary breast tumors and from biopsies of local metachronous recurrences or metastases were fixed in 10% buffered formalin for a maximum of 48h and then embedded in paraffin blocks. Time from sample collection to fixation was less than 2h.

Immunohistochemistry

IHC was used to assess protein expression of ER, PR and HER2 in all primary tumors and their corresponding metastases/local recurrences. ER was detected using monoclonal mouse anti-human ERα (clone 1D5) (Dako, Glostrup, Denmark) and PR was detected using monoclonal mouse anti-human PR (clone PgR 636, Dako). Sections (3 μm thick) were cut from paraffin-embedded tissue samples and were dry-heated (58° C, 1h). Subsequently, sections were deparaffinized and rehydrated in xylene (three times, 5 min each), 100% ethanol (twice, 2 min each), 95% ethanol (twice, 2 min each), followed by 50% ethanol (once for 2 min) and finally immersed in distilled water. Antigens were decloaked by heat-induced epitope retrieval using the Dako target retrieval solution pH 9 (3 in 1) and incubated for 40 min at room temperature in an antibody solution (1:50 in Dako REAL™ diluent). Primary antibodies were visualized using the Dako Envision HRP/DAB polymer system. Cells labeled by the ER or PR antibody displayed a nuclear staining pattern. The intensity of staining was categorized as weak, moderate or strong and the percentage of positive neoplastic cells was evaluated.

HER2 was detected using the HercepTest™ kit (Dako). Paraffin-embedded tissue samples were cut into sections (3 μm thick) and then dry-heated (58° C, 1h). Subsequently, sections were deparaffinized and rehydrated, as described above. Antigens were decloaked by heat-induced epitope retrieval for 20 min at 98° C in a preheated citrate buffer (10 mmol/l, pH 6.0) and then incubated for 30 min at room temperature in a prediluted ready-to-use antibody solution (polyclonal rabbit anti-human HER2 oncoprotein). The anti-HER2 antibody was visualized using HRP/DAB provided in the HercepTest™ kit. Cells labeled by the HER2 antibody displayed a staining confined to the cell membrane. Samples were classified as negative, IHC2+ or positive (IHC3+).

ER-positive and PR-positive normal breast tissue samples from each patient and HER2-positive paraffin-embedded breast carcinomas from the archive of the Pathology Department in the "Metaxa" Cancer Hospital were used as positive controls. Negative control tissue slides from verified negative breast cancer samples were also included.

Statistical analysis

The McNemar exact test or Bowker's test for symmetry were performed to compare expression levels for each receptor in the primary tumors with those in metachronous recurrences or metastases. A p-value below 0.05 was considered to be statistically significant.

Results

From 1988 to 2008, samples were collected from 110 patients with primary breast cancer who were subsequently treated for metastatic breast cancer at the same hospital. In addition to the primary tumor, there were 89 metachronous distant metastases, 19 metachronous lymph node metastases, and two local recurrences. Clinical and pathologic features of the primary tumors are given in Table 1. In Table 2 the sites of the metastases are shown.

Table 1. Patient age and primary tumor characteristics

Characteristics	*Patients, N (%)*
Mean age, years (range)	55.4 (30-94)
Tumor size	
T1a	0 (0.0)
T1b	6 (5.4)
T1c	29 (26.4)
T2	44 (40.0)
T3	12 (10.9)
T4	0 (0.0)
Not determined	19 (17.3)
Histologic type	
Invasive ductal carcinoma	92 (83.6)
Invasive lobular carcinoma	18 (16.3)
Histologic grade	
G1	2 (1.8)
G2	31 (28.2)
G3	60 (54.5)
Not determined	17 (15.5)

Table 2. Sites of the metastases

Metastatic sites	*Patients, N (%)*
Metachronous lymph node metastases	19 (17.3)
Local recurrence	2 (1.8)
Distant metastases	89 (80.9)
Skin	23 (20.9)
Stomach	6 (5.4)
Small bowel	8 (7.3)
Large bowel	2 (1.8)
Liver	17 (15.4)
Thyroid gland	2 (1.8)
Soft tissues	2 (1.8)
Bone marrow	7 (6.4)
Omentum	2 (1.8)
Bones	7 (6.4)
Lung	9 (8.2)
Ovary	4 (3.6)
Total	110 (100)

ER expression

An example of the staining pattern for ER in primary and metastatic tumor samples is presented in Figure 1a. ER was positively expressed in 64.5% of primary tumors (Table 3). Overall discordance for ER between the primary tumor and the corresponding metastases was 27.3%. Twenty (18.2%) cases that had ER expression in the primary tumor lost ER expression in the corresponding metastases, while 10 (9.1%) cases that did not have ER expression in the primary tumor gained ER expression (Table 3; Figure 2). The number of patients who changed from ER-positive to ER-negative was not significantly different from the number of patients who changed from ER-negative to ER-positive ($p = 0.0987$). In some ER-positive cases, the percentage of cells stained positively for ER receptors changed considerably. A relevant increase in the percentage of positive cells was observed in 3 (2.7%) cases and a relevant decrease in the percentage of positive cells was observed also in 3 (2.7%) cases.

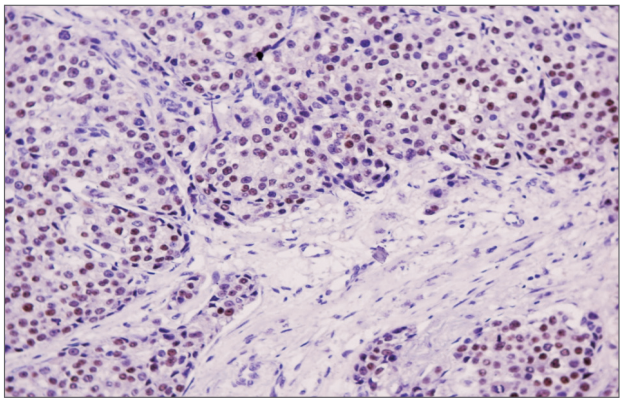
PR expression

Examples of PR staining patterns in primary and metastatic tumor samples are given in Figure 1b. PR was positively expressed in 58.2% of primary tumors (Table 3). Overall discordance for PR expression between the primary tumor and the corresponding metastases was 25.5%. Twenty-four (21.8%) cases that showed PR expression in the primary tumor lost PR expression in the corresponding metastases, while 4 (3.6%) cases that were negative for PR expression in the primary tumor gained PR expression (Table 3; Figure 2). The number of patients who changed from PR-positive to PR-negative was significantly different from the number of patients who changed from PR-negative to PR-positive ($p < 0.001$). In some PR-positive tumors, the percentage of cells stained positively for PR changed considerably. A relevant increase in the percentage of positive cells was detected in 1 (0.9%) case and a relevant decrease in the percentage of PR-positive cells was observed in 2 (1.8%) cases.

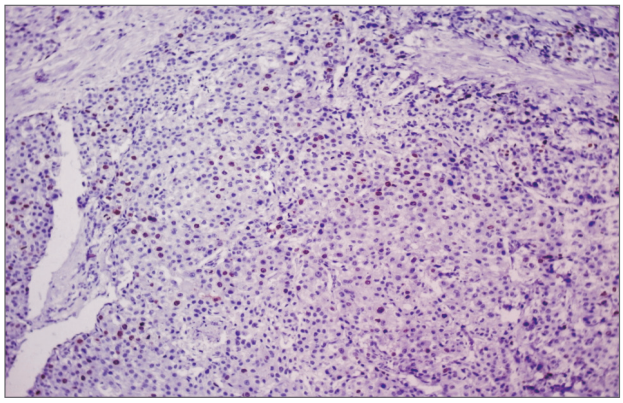
HER2 expression

An example of a HER2 staining pattern from a primary tumor sample (IHC2+) and a metastatic tumor sample (IHC3+) is shown in Figure 1c. HER2 was positively expressed (defined as IHC3+) in 32.7% of the primary tumors (Table 4). Overall discordance of HER2 between the primary tumor and the corresponding metastases was 18.2% ($p = 0.5034$). Twelve (10.9%) cases that were positive for HER2 expression in the primary tumor were negative for HER2 expression in the corresponding metastases, while 8 (7.3%) cases that were negative for HER2 expression in the primary tumor became positive in the metastases (Table 4; Figure 2). In addition, 6 (5.5%) cases that were negative in the primary tumor became IHC2+ in the metastases, while 2 (1.8%) cases that were IHC2+ in the primary tumor were negative in the metastases. Furthermore, 5 (4.5%) cases that were IHC2+ in the primary tumor were positive (IHC3+) in the metastases and 5 (4.5%) cases that were positive (IHC3+) in the primary tumor were IHC2+ in the metastases (Table 4). The change of HER2 expression status (negative, IHC2+ or positive [IHC3+]) was not statistically significant (Bowker's test, overall p-value = 0.4235).

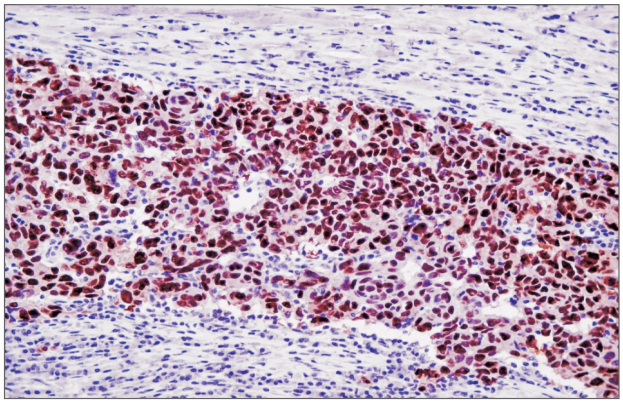
Aa. Primary tumor (×200).



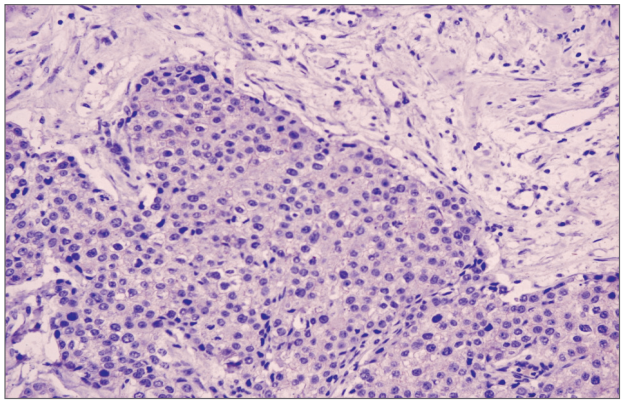
Ab. Metastatic tumor (×100).



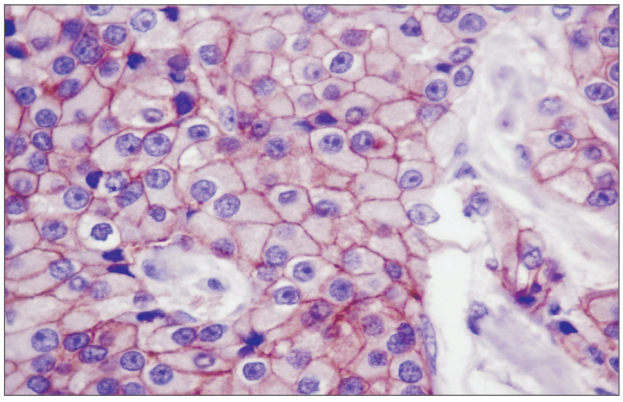
Ba. Primary tumor (×200).



Bb. Metastatic tumor (×200).



Ca. Primary tumor (IHC2+) (×400).



Cb. Metastatic tumor (IHC3+) (×200).

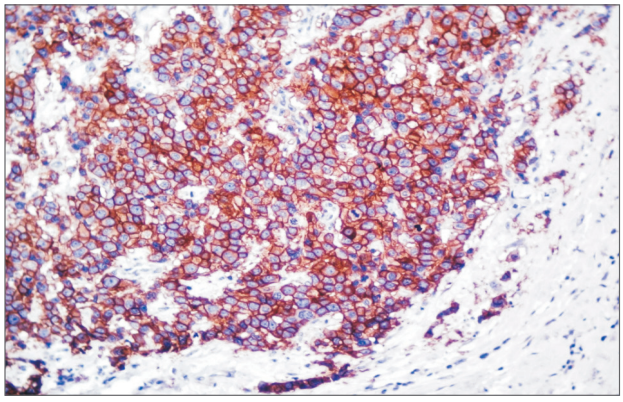


Figure 1. Receptor expression in primary and metastatic tumor samples. Tumor samples stained for **(A)** ER, **(B)** PR and **(C)** HER2. **Aa:** Primary tumor (×200); **Ab:** Metastatic tumor (×100). **Ba:** Primary tumor (×200); **Bb:** Metastatic tumor (×200). **Ca:** Primary tumor (IHC2+) (×400); **Cb:** Metastatic tumor (IHC3+) (×200). ER was detected using monoclonal mouse anti-human ERα (clone 1D5) (Dako, Glostrup, Denmark). PR was detected using monoclonal mouse anti-human PR (clone PgR 636) (Dako) and primary antibodies were visualized using the Dako Envision HRP/DAB polymer system. HER2 was detected using the HercepTest™ kit (Dako) and the anti-HER2 antibody was visualized using HRP/DAB provided in the HercepTest™ kit.

Discussion

The results of this study show discordance between receptor expression in primary breast tumors and patient-matched metastases for ER, PR and HER2, with statistical significance reached for PR. Several studies report similar findings for ER, PR and HER2 [31,32,35], including that of statistical significance for PR only [31]. Idirisinghe et al. reported that among women with distant metastases, discordance for ER, PR and HER2 was 18, 42 and 7%, respectively, while among women with local recurrence discordance was 13, 33 and 2%, respectively [31]. In a separate study with distant metastases reported in 70.5% of metastatic cases, discordance was

Table 3. Estrogen and progesterone receptor expression levels in the primary tumor and corresponding metastases

	Metastases, N (%)			
	Negative	*Positive*	*Total*	*p-value*
Estrogen receptor				
Primary lesion				
Negative	29 (26.4)	10 (9.1)	39 (35.5)	0.0987
Positive	20 (18.2)	51 (46.4)	71 (64.5)	
Total	49 (44.5)	61 (55.5)	110	
Progesterone receptor				
Primary lesion				
Negative	42 (38.2)	4 (3.6)	46 (41.8)	< 0.001
Positive	24 (21.8)	40 (36.4)	64 (58.2)	
Total	66 (60.0)	44 (40)	110	

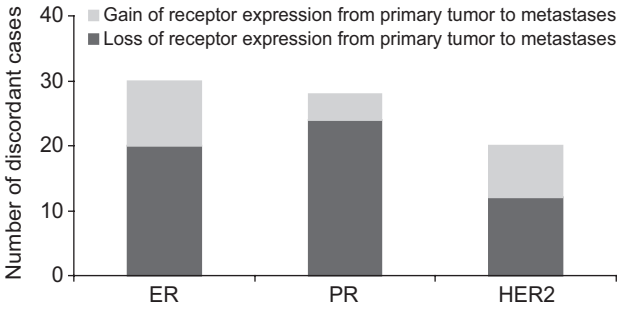


Figure 2. Discordant cases for ER, PR and HER2. Shown is the number of discordant cases for which a change (loss or gain) in receptor status was observed from the primary tumor to the corresponding metastases for ER, PR and HER2. ER: estrogen receptor, HER2: human epidermal growth factor receptor 2, PR: progesterone receptor. HER2 data are shown for positive (IHC3+) to negative and negative to positive (IHC3+) conversion only and do not include conversions to or from IHC2+.

observed in 36, 54 and 15% of the cases for ER, PR and HER2, respectively [35], while a further study reported a discordance of 10% for HER2 among women with metachronous metastases [32]. A recent study reported discordance for HER2 expression in only 3.7% of the cases (by IHC) and for ER and PR expression in 6.4% and 21.4% of the cases, respectively [37]. In the majority of the cases, a change in ER expression status was correlated with a change in PR expression status [37]. The change in PR expression was affected by adjuvant cytotoxic plus hormonal therapy [37].

Discrepancies between different studies do exist, with some studies having reported significant discordance for ER (ERβ 20%; $p < 0.002$) [36] and HER2 (21.5%; $p < 0.001$) [30], whereas another study concluded that ER, PR and HER2 expression were generally concordant between primary tumors and metastases [38]. These discrepancies may be a consequence of differences in the type of metastases, as significant ER discordance was reported in a population with only lymph node metastases, and significant HER2 discordance was reported in a population with few (29.4%) distant metastases. However, a study examining ER discordance reported that discordance was not associated with metastatic site (local vs. distant) [39]. Although inaccuracies in testing procedures do occur, as can discrepancies due to sampling procedures, it is generally accepted that change of receptor status during disease progression is a biologic phenomenon [33]. Bogina et al. discussed that intratumoral heterogeneity and clonal selection for hormone receptors and HER2 during progression, and also that antitumor therapy may contribute to discordant expression of these biomarkers in the primary tumor and its corresponding metastases [37].

Approximately 20-25% of breast cancers are HER2-positive [10]. The high rate of HER2-positive

Table 4. Human epidermal growth factor receptor 2 expression in the primary tumor and the corresponding metastases

Primary lesion	*Metastases, N (%)*			
	Negative	*IHC2+*	*Positive (IHC3+)*	*Total*
Negative	51 (46.4)	6 (5.5)	8 (7.3)	65 (59.1)
IHC2+	2 (1.8)	2 (1.8)	5 (4.5)	9 (8.2)
Positive (IHC3+)	12 (10.9)	5 (4.5)	19 (17.3)	36 (32.7)
Total	65 (59.1)	13 (11.8)	32 (29.1)	110

Overall p-value = 0.4235 (Bowker's test of symmetry); p-value negative vs. 2+ = 0.2891; p-value negative vs. positive = 0.5034; p-value 2+ vs. positive = 1.00

cases in our study (32.7%), may be due to the fact that the study included only patients who experienced disease progression.

Change of receptor status can have an impact on therapeutic decisions. Discordance rates in receptor status presented here, as well as in previous studies, support retesting of the tumor in the metastatic disease, because knowledge of a change in receptor expression would allow use of a more appropriate therapeutic approach.

There is substantial evidence for a change in HER2 and hormone receptor status during disease progression among women with breast cancer. As these changes may be of great clinical importance and influence therapeutic decisions, evaluation of biomarkers in the metastatic site might be considered mandatory.

Authors' contributions

PA-D designed the study, TG was responsible for sample collection and IHC and samples were evaluated by PA-D, CV, OT, HT and IL. CV was responsible for statistical analyses and CV and TG prepared the draft manuscript. All authors approved the final manuscript for submission.

Acknowledgements and funding

The authors would like to thank Chrisavgi Lekanidou and Thomas Karinos for their technical assistance in IHC and Aliki Migou for her technical assistance in sample preparation. The statistical analyses were funded by Roche Hellas. We also thank Becky Bradley who provided medical writing services on behalf of F. Hoffmann-La Roche Ltd.

References

1. Global Cancer Facts & Figures (2nd Edn): [http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-027766.pdf]
2. Dahlman-Wright K, Cavailles V, Fuqua SA et al. International Union of Pharmacology. LXIV. Estrogen receptors. Pharmacol Rev 2006; 58: 773-781.
3. Edwards DP, Wardell SE, Boonyaratanakornkit V. Progesterone receptor interacting coregulatory proteins and cross talk with cell signaling pathways. J Steroid Biochem Mol Biol 2002; 83: 173-186.
4. Onitilo AA, Engel JM, Greenlee RT, Mukesh BN. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival. Clin Med Res 2009; 7: 4-13.
5. Cho HS, Mason K, Ramyar KX et al. Structure of the extracellular region of HER2 alone and in complex with the Herceptin Fab. Nature 2003; 421: 756-760.
6. Owens MA, Horten BC, Da Silva MM. HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. Clin Breast Cancer 2004; 5: 63-69.
7. Sjögren S, Inganäs M, Lindgren A, Holmberg L, Bergh J. Prognostic and predictive value of c-erbB-2 overexpression in primary breast cancer, alone and in combination with other prognostic markers. J Clin Oncol 1998; 16: 462-469.
8. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987; 235: 177-182.
9. Taneja P, Maglic D, Kai F et al. Classical and novel prognostic markers for breast cancer and their clinical significance. Clin Med Insights Oncol 2010; 4: 15-34.
10. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009; 14: 320-368.
11. Ménard S, Tagliabue E, Campiglio M, Pupa SM. Role of HER2 gene overexpression in breast carcinoma. J Cell Physiol 2000; 182: 150-162.
12. Piccart-Gebhart MJ. New developments in hormone receptor-positive disease. Oncologist 2010; 15 (Suppl 5): 18-28.
13. Arpino G, Weiss H, Lee AV et al. Estrogen receptor-positive, progesterone receptor-negative breast cancer: association with growth factor receptor expression and tamoxifen resistance. J Natl Cancer Inst 2005; 97: 1254-1261.
14. NCCN clinical practice guidelines in oncology: Breast cancer. V 2 2011.
15. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 2007; 18: 1133-1144.
16. Blackwell KL, Pegram MD, Tan-Chiu E et al. Single-agent lapatinib for HER2-overexpressing advanced or metastatic breast cancer that progressed on first- or second-line trastuzumab-containing regimens. Ann Oncol 2009; 20: 1026-1031.
17. Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. J Clin Oncol 2010; 28: 92-98.
18. Di Leo A, Gomez HL, Aziz Z et al. Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. J Clin Oncol 2008; 26: 5544-5552.
19. Geyer CE, Forster J, Lindquist D et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355: 2733-2743.
20. Kroep JR, Linn SC, Boven E et al. Lapatinib: clinical benefit in patients with HER 2-positive advanced breast cancer. Neth J Med 2010; 68: 371-376.
21. Marty M, Cognetti F, Maraninchi D et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 2005; 23: 4265-4274.
22. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast

cancer. N Engl J Med 2005; 353: 1659-1672.
23. Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005; 353: 1673-1684.
24. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344: 783-792.
25. Smith I, Procter M, Gelber RD et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007; 369: 29-36.
26. Slamon D, Eiermann W, Robert N et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC -> T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC -> TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2/neu positive early breast cancer patients: BCIRG 006 Study. Cancer Res 2009; 69: 62 (abstr).
27. Hammond ME, Hayes DF, Dowsett M et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). Arch Pathol Lab Med 2010; 134: e48-e72.
28. Wolff AC, Hammond ME, Schwartz JN et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 2007; 25: 118-145.
29. Pectasides D, Gaglia A, Arapantoni-Dadioti P et al. HER-2/neu status of primary breast cancer and corresponding metastatic sites in patients with advanced breast cancer treated with trastuzumab-based therapy. Anticancer Res 2006; 26: 647-653.
30. Santinelli A, Pisa E, Stramazzotti D, Fabris G. HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. Int J Cancer 2008; 122: 999-1004.
31. Idirisinghe PK, Thike AA, Cheok PY et al. Hormone receptor and c-ERBB2 status in distant metastatic and locally recurrent breast cancer. Pathologic correlations and clinical significance. Am J Clin Pathol 2010; 133: 416-429.
32. Fabi A, Di Benedetto A, Metro G et al. HER2 protein and gene variation between primary and metastatic breast cancer: significance and impact on patient care. Clin Cancer Res 2011; 17: 2055-2064.
33. Arslan C, Sari E, Aksoy S, Altundag K. Variation in hormone receptor and HER-2 status between primary and metastatic breast cancer: review of the literature. Expert Opin Ther Targets 2011; 15: 21-30.
34. Gong Y, Han EY, Guo M, Pusztai L, Sneige N. Stability of estrogen receptor status in breast carcinoma: a comparison between primary and metastatic tumors with regard to disease course and intervening systemic therapy. Cancer 2011; 117: 705-713.
35. Sari E, Guler G, Hayran M, Gullu I, Altundag K, Ozisik Y. Comparative study of the immunohistochemical detection of hormone receptor status and HER-2 expression in primary and paired recurrent/metastatic lesions of patients with breast cancer. Med Oncol 2011; 28: 57-63.
36. Gschwantler-Kaulich D, Fink-Retter A, Czerwenka K et al. Differential expression pattern of estrogen receptors, aromatase, and sulfotransferase in breast cancer tissue and corresponding lymph node metastases. Tumour Biol 2011; 32: 501-508.
37. Bogina G, Bortesi L, Marconi M et al. Comparison of hormonal receptor and HER-2 status between breast primary tumours and relapsing tumours: clinical implications of progesterone receptor loss. Virchows Arch 2011; 459: 1-10.
38. Azam M, Qureshi A, Mansoor S. Comparison of estrogen receptors, progesterone receptors and HER-2/neu expression between primary and metastatic breast carcinoma. J Pak Med Assoc 2009; 59: 736-740.
39. Carreño G, Del Casar JM, Corte MD et al. Local recurrence after mastectomy for breast cancer: analysis of clinicopathological, biological and prognostic characteristics. Breast Cancer Res Treat 2007; 102: 61-73.