Sequential steroid hormone receptor measurements in primary breast cancer with and without intervening primary chemotherapy

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Abstract

The objective of this analysis was to determine the accuracy of steroid receptor measurement in large core needle biopsies compared with surgically removed specimens and the influence of preoperative chemotherapy on hormone receptor status. We consecutively performed 722 large core needle biopsies in palpable lesions of the breast. The diagnosis of breast cancer was confirmed upon biopsy in 450 patients; 236 women underwent immediate surgery, and 214 patients received preoperative chemotherapy. We assessed estrogen (ER) and progesterone receptor (PR) in biopsy tissue and surgically removed specimens and calculated accuracy, sensitivity, specificity, the weighted κ value and Spearman's rank correlation. The modulation of steroid receptor status in preoperatively treated patients was tested by Cochran–Mantel–Haenszel statistics. The accuracy of ER evaluation in the biopsy material of patients without intervening chemotherapy was 91%, sensitivity and specificity were 94% and 80% respectively. Accuracy, sensitivity and specificity were 86% in patients treated preoperatively. In terms of PR assessment, we obtained slightly inferior results: accuracy, sensitivity and specificity were 80%, 73% and 85% respectively in patients without preoperative treatment, and 79%, 48% and 92% respectively in patients undergoing preoperative therapy. Following preoperative chemotherapy, patients showed a significant increase in ER-negative ($P = 0.02$) and PR-negative ($P = 0.0005$) measurements. We have concluded from our results that ER and PR receptor measurement in core needle biopsy is a reliable basis in clinical practice for selecting patients for neoadjuvant endocrine treatment. Preoperative cytotoxic chemotherapy induced a significant extent of variation in the steroid receptor expression of breast cancer cells.

Endocrine-Related Cancer (2003) **10** 91–98

Introduction

Estrogen (ER) and progesterone receptor (PR) determinations are established procedures in the routine management of patients with breast cancer, chiefly as predictive factors for response to adjuvant and palliative endocrine therapy (Clark 1996, Allred *et al*. 1998, Harvey *et al*. 1999). In addition, the selection for preoperative treatment modalities needs to be directed by molecular markers such as steroid hormone receptor status. Mouridsen *et al*. (1978), Allegra *et al*. (1980) and Chang *et al*. (1999) have shown that pretreatment ER and PR values significantly predict the response to preoperative administration of tamoxifen.

The selection for preoperative chemotherapy is currently based on such clinical factors as tumor size more so than on molecular markers. Preoperative chemotherapy has shown to increase the percentage of breast conservation, but does not positively correlate with overall survival (Fisher *et al*. 1998, Wolmark *et al*. 2001). In addition to the absence of c-erbB-2, lack of ER has recently been demonstrated to significantly predict for subsequent good clinical response. Lack of ER expression was additionally predictive for increased risk of death (Chang *et al*. 1999).

Studies from our own group in predictive factors indicating response to primary chemotherapy have shown that Her2/neu overexpression is predictive for achieving a pathological

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complete response after a preoperative taxane-containing cytotoxic chemotherapy regimen (Steger *et al*. 2000).

Together with clinical characteristics, assessment of biological and molecular markers pretherapy should allow physicians to focus therapeutic considerations on a given patient's individual tumor factors. Quality assurance of these measurements is the main framework for these considerations. A nationwide external quality assurance project has been conducted to assess the quality of immunohistochemical steroid receptor evaluation (Regitnig *et al*. 2002). The results of this quality program showed an excellent concordance of hormone receptor assessments in terms of ER ($\kappa = 0.57$) and slightly inferior results with regard to PR ($\kappa = 0.53$).

The primary objective of this analysis was to determine the accuracy of steroid receptor measurement in large core needle biopsies (CNB) compared with surgically removed specimens. Large core biopsy is a valid tool for the preoperative management of breast lesions (Di Loreto *et al*. 1996). The concordance of ER and PR status in biopsy and final specimen in a preoperatively untreated group allows for perfect quality assurance to assess ER and PR in CNB. The response of the primary tumor and lymph node metastasis to preoperative cytotoxic treatment is the most important parameter for overall outcome. Therefore, knowledge of factors predicting tumor response can avoid administration of treatment to patients who are not likely to respond. The second aim of this analysis was to determine the influence of preoperative chemotherapy on steroid receptor status. The changes in biological markers induced by chemotherapy may lead to a better understanding of breast cancer biology.

Materials and methods

Between 1994 and 2000, we evaluated 722 patients with a palpable mass in the breast in an attempt to determine the histology of the lesion and – in the case of breast cancer – to compare several prognostic markers in tumor tissue obtained preoperatively from CNB and surgical specimens within a prospective evaluation. Pretherapeutic mammography was present and CNB was performed under local anesthesia using a 15-gauge needle (ASAP Detachable Biopsy System, Boston Scientific Corporation, Vienna, Austria) in all patients.

Of these patients, 450 (62.3%) presented with an epithelial malignancy of the breast upon biopsy. No false-positive results were seen. Immediate surgery was administered to 236 patients (52.4%) and sufficient material to compare hormone receptor status in the biopsy tissue and in the surgically removed specimen was obtained in 180 patients (76.3%). In order to facilitate breast-conserving surgery, 214 patients (47.6%) received preoperative chemotherapy. Excellent responses to primary treatment and complete pathological remission were observed in 23 women (10.7%), 191 patients were thus remaining in this analysis of sequential hormone receptor assessment in biopsy and surgically removed tissue. The two patient groups were analyzed separately.

CNB specimens were transferred to 24–h fixation in neutral-buffered formalin, and paraffin-embedded tissue sections of 3 μm thickness were processed. ER and PR determinations were performed by immunohistochemistry as described earlier (Reiner *et al*. 1990). In brief, tissue sections stained with a cut-off of less than 10% and low intensity of staining were recorded as hormone receptor negative, those showing more than 10% stained tissue were considered as receptor positive, showing three qualities discriminated as follows: weakly positive (1 +), 10–50% showed stained tumor tissue (medium positive (2 +), 50–80%; strongly positive (3 +)) and those with more than 80% staining. Intensity of staining was also recorded, influencing the results according to a distinct scoring scale (Reiner score) (Reiner *et al*. 1990). All tissue samples were scored by a single pathologist (M R), blinded to the intervention with chemotherapy. The methods of the whole procedure were not changed over the observation period.

Patients suitable for breast conservation without metastases shown by X-ray, ultrasound and scintigraphy were treated with primary surgery. Patients with T3 or T4 lesions, those primarily not suited for breast conservation, and those presenting with clinical signs of lymph node metastasis received preoperative chemotherapy. All women treated with breast-conserving surgery received postoperative irradiation, unless the patient was involved in a prospective randomized trial evaluating the importance of postoperative irradiation in a certain patient selection with very low risk for local relapse. In patients undergoing modified radical mastectomy, postoperative radiotherapy was left to the discretion of the responsible physician based on consultation within the interdisciplinary team.

The characteristics of the patients without preoperative treatment are shown in Table 1. The median age was 62 years, patients were predominantly postmenopausal (81.7%), 40% had a tumor smaller than 2 cm in diameter, and 47.2% had no lymph node involvement. Breast conservation was the predominant surgical procedure and was performed in 55%.

The characteristics of patients receiving preoperative chemotherapy are described in Table 2. Fluorouracil, epirubicin and cyclophosphamide (CMF) therapy was used primarily as it was part of a clinical study, the Austrian Breast and Colorectal Cancer Study Group Trial 7 (Jakesz 2001). An anthracycline-containing regimen CMF was subsequently introduced for preoperative treatment. Several patients (41.8%) received the combination of anthracycline and taxotere. Response to chemotherapy was assessed according to the International Union Against Cancer guidelines (Hayward *et al*. 1977). Complete pathological remission was defined as complete disappearance of invasive tumor cells, irrespective of a possibly residual, yet exclusively intraductal component. Reduction of tumor size of at least 50% was defined as

Table 1 Patient characteristics (without preoperative treatment) ($n = 180$)

Characteristics	Numbers	Percentage
Age (years)		
Median	62	
Range	23–88	
< 50	33	18.3
> 50	147	81.7
Clinical tumor size (cm)		
< 2	72	40.0
2–5	98	54.4
> 5	10	5.6
Surgical procedure		
Breast conservation	99	55.0
Mastectomy	81	45.0
Pathological tumor stage		
pT1	72	40.0
pT2	73	40.6
pT3	12	6.7
pT4	15	8.3
pTx	8	4.4
Pathological nodal stage		
pN0	85	47.2
pN1	77	42.8
pNx	18	10.0

pT1–x, pNO–x, according to UICC criteria (International Union against Cancer).

Table 2 Patient characteristics (with preoperative treatment) ($n = 191$)

Characteristics	Numbers	Percentage
Age (years)		
Median	51	
Range	33–74	
Premenopausal	73	38.2
Postmenopausal	118	61.8
Clinical tumor size		
T1	5	2.6
T2	110	57.6
T3	42	22
T4	34	17.8
Preoperative therapy		
CMF	58	30.4
FEC	59	30.9
Taxane-containing regimen	74	38.7
Response to chemotherapy		
pPR	113	59.2
pNC	74	38.7
pPD	4	2.1
Surgical procedure		
Breast conservation	126	66
Mastectomy	65	34
Pathological tumor stage		
pT1	96	50.3
pT2	57	29.8
pT3	20	10.5
pT4	18	9.4
Pathological nodal stage		
pN0	76	39.8
pN1	111	58.1
pNx	4	2.1

FEC, fluorouracil, epirubicin and cyclophosphamide; pPR, pathological partial remission; pNC, pathologically no change; pPD, pathologically progressive disease.

partial remission, reduction of tumor size of less than 50% was considered as stable disease, any increase in tumor size in the course of preoperative therapy was determined as progressive disease.

Within 7 years, a total of 214 patients was treated preoperatively at our institution. It is noteworthy that these patients were generally 10 years younger (mean = 51.3 years) than those not given primary chemotherapy, only 60% in this group were postmenopausal. A tumor of less than 2 cm in diameter was present only in 2.8%, and 17% had a T4 lesion. Sixty-two patients were treated with CMF as a part of the above-mentioned Austrian Trial 7 (Jakesz 2001). Since 1996, when increasing evidence was presented that an anthracycline-containing chemotherapeutic regimen showed higher response rates, this kind of chemotherapy was mainly employed. Eighty-eight patients were part of two clinical trials, one with preoperative Taxol and the other with a combination of epirubicin and taxotere. The overall response to primary chemotherapy was 63.4%, the pathological complete response rate was 10.7%. Breast-conserving surgery was given to 67.6% of all patients given primary chemotherapy.

Statistical analysis

We calculated the accuracy, sensitivity, specificity and κ coefficient of ER and PR results and correlated positive tumors (1 +, 2 + and 3 +) versus negative (0). Accuracy refers to the degree of concordance between the percentage of ER- or PR-positive and -negative results in biopsy and the ER or PR results in the final histology of surgically removed tissue. Test sensitivity was calculated as the percentage of ER- and PR-positive biopsies in surgically removed specimens (percentage true positive). Test specificity was calculated as the percentage of ER- and PR-negative biopsies in surgically removed tissue (percentage true negative). Patients with or without preoperative treatment were analyzed separately.

κ is the proportion of agreements after chance agreement has been excluded. Its upper limit is +1.00 (total agreement). The value of κ is near to zero if agreement between two different variables is just by chance. Weighted κ was used to dichotomize between different categories of steroid receptor (0, 1 +, 2 +, 3 +) (Cohen 1960).

Spearman's rank correlation is a distribution-free analog of Pearson's correlation coefficient. Spearman's rho coefficient (r) indicates agreement. A value of r approximating one indicates good agreement; a value near zero poor agreement. We calculated the correlation of ER and PR results

discriminating four different qualities, negative, 1 +, 2 + and 3 + positive.

The influence of primary chemotherapy on steroid receptor status in the final specimen was tested by Cochran–Mantel–Haenszel statistics. This statistic assumes a common odds ratio; in short, the purpose of the Cochran–Mantel–Haenszel statistic is to test whether the response is conditionally independent of the hormone receptor status when adjusting for the hormone status at biopsy (Landis *et al.* 1978).

Results

Patients without intervening preoperative therapy

Results of ER assessment are shown in Table 3. ER was negative in the biopsy in 50 (27.8%) out of 180 patients given neither chemotherapy nor any other cytotoxic treatment preoperatively, and negative in surgical specimen in 47 patients (26.1%); 123 patients were regarded to be positive in both the biopsy and surgical procedure. Concordant results between ER in the biopsy and surgically removed specimens were obtained in 163 out of 180 patients, giving an accuracy of 91%. Sensitivity and specificity of ER assessment in CNB were 94% and 80% respectively. The weighted κ was 0.69. A significant Spearman's correlation of sequential ER status was found with $r = 0.76$ ($P = 0.01$).

Table 3 ER in patients without intervening chemotherapy

ER – biopsy	ER – surgical specimen				Total number
	Negative	1 +	2 +	3 +	
Negative	40	5	3	2	50
1 +	4	14	6	1	25
2 +	3	4	53	10	70
3 +	0	5	7	23	35
Total number	47	28	69	36	180

Results of PR assessment are given in Table 4. In terms of PR, 98 patients (54.4%) showed negative results in the primary biopsy and 105 patients (58.3%) in the surgical specimen. Eighty-two (45.6%) were positive in the biopsy and 75 (41.6%) in the surgical specimen. Concordant PR status in CNB and the final specimen was found in 143 out of 180 patients, with an accuracy of 80%. The PR status upon biopsy was true positive in 60 patients and true negative in 83 patients, sensitivity and specificity were 73% and 85% respectively. The weighted κ for four PR receptor qualities was 0.52. The correlation of sequential PR status was also significant, although slightly inferior compared with the ER results, $r = 0.64$ ($P = 0.01$).

Table 4 PR in patients without intervening chemotherapy

PR – biopsy	PR – surgical specimen				Total number
	Negative	1 +	2 +	3 +	
Negative	83	8	7	0	98
1 +	14	12	6	1	33
2 +	7	9	16	5	37
3 +	1	2	5	4	12
Total number	105	31	34	10	180

Patients with preoperative treatment

Table 5 presents the results of ER assessment. Out of 191 patients given intervening chemotherapy, 91 (47.6%) were ER negative in the primary biopsy and 92 (48.2%) in the final surgical specimen. One hundred patients were ER positive in the biopsy and 99 patients in the final surgical material. Exactly concordant ER status was found in 164 patients, accuracy was 86%. Sensitivity and specificity of ER evaluation was 86% and 86% respectively. The weighted κ was 0.64. Spearman's coefficient was significant, $r = 0.75$ ($P = 0.01$).

Table 5 ER in patients with preoperative chemotherapy

ER – biopsy	ER – surgical specimen				Total number
	Negative	1 +	2 +	3 +	
Negative	78	7	2	4	91
1 +	9	7	8	2	26
2 +	5	8	30	12	55
3 +	0	3	3	13	191
Total number	92	25	43	31	191

Results of PR assessment are given in Table 6. One hundred and thirty-one patients (68.6%) showed PR-negative results in the biopsy and 152 women (79.6%) were finally identified as PR negative. PR was shown to be positive in both biopsy and surgically removed material in only 29 patients. The accuracy of PR measurement in needle biopsy was 79%. Only 29 out of 60 patients showed true-positive PR status in the biopsy, and sensitivity was rather low at 48%. The number of true-negative biopsies was 121 out of 131 with a specificity of 92%. Sequential PR assessment after

Table 6 PR in patients with preoperative chemotherapy

PR – biopsy	PR – surgical specimen				Total number
	Negative	1 +	2 +	3 +	
Negative	121	3	4	3	131
1 +	18	8	4	1	31
2 +	9	0	7	2	18
3 +	4	4	2	1	11
Total number	152	15	17	7	191

preoperative chemotherapy produced a rather low level of correlation, weighted κ was 0.37. However, the calculation of Spearman's coefficient did indicate a significant correlation, $r = 0.47$ ($P = 0.01$).

Modulation of ER status in patients with ER-positive results in CNB (Table 7)

Fourteen out of 100 ER-positive patients undergoing preoperative treatment showed a decrease in ER status and finally proved to be ER negative (14%), whereas only seven out of 130 ER-positive patients without preoperative chemotherapy were ER negative in the surgically removed specimen (5.4%). The calculation of Cochran–Mantel–Haenszel statistics demonstrated a statistically significant shift of ER-positive to ER-negative status due to primary chemotherapy ($P = 0.02$).

Table 7 Modulation of ER status in patients with ER-positive results in CNB

Preoperative chemotherapy	ER status in final specimen		Total ER positive in CNB
	ER negative	ER positive	
Without	7 (5.4%)	123 (94.6%)	130
With	14 (14.0%)	86 (86.0%)	100
Total	21 (9.1%)	209 (90.9%)	230

The endocrine effect of neoadjuvant chemotherapy inducing menopause in premenopausal patients may be a simple explanation of decreasing ER expression in these patients. In fact, seven out of fourteen (50%) patients showing a decrease of ER status were premenopausal at the time of diagnosis.

Modulation of PR status in patients with PR-positive results in CNB (Table 8)

Fifty-eight patients were primarily PR positive in the core biopsy, 30 out of 58 (51.7%) presented with PR negativity in the final surgical specimen following preoperative treatment. In patients not given preoperative therapy, only 22 out of 82 PR-positive women (26.8%) finally appeared to be PR negative. The increase in PR negativity induced by preoperative chemotherapy was statistically significant ($P = 0.0005$) tested again by the Cochran–Mantel–Haenszel statistics. Menopausal status offers no explanation of the decrease in PR status, only eight (26%) of the primarily PR-positive patients were premenopausal at the time of diagnosis and developed PR-negative disease following chemotherapy.

Table 8 Modulation of PR status in primarily PR-positive patients

Preoperative chemotherapy	PR status in final specimen		Total PR positive in CNB
	PR negative	PR positive	
Without	22 (26.8%)	60 (73.2%)	82
With	30 (51.7%)	28 (48.3%)	58
Total	52 (37.1%)	88 (62.9%)	140

Discussion

The results of sequential steroid hormone receptor assessment upon immunohistochemistry in CNB and a definite surgical specimen, without intervening treatment performed at a time interval of 7–14 days, failed to show any marked difference. Disconcordance between measurements at these different time-points was less than 10% for ER and approximately 20% for PR determinations. In terms of ER negativity in surgical specimens, correct prediction from biopsy was possible in 40 out of 47 (85.1%), and for positivity in 123 out of 133 patients (92.5%). As to PR negativity, the correct prediction from CNB was 83 (79.0%) out of 105 in surgically removed material, and in 59 (79.7%) out of 74 patients for PR positivity. It can therefore be stated that receptor measurements in CNB are, in a high percentage, representative of the receptor quality shown by the entire tumor.

Steroid hormone receptors have proven to be the most important predictive markers for selection of systemic treatment. This has been shown clearly in the selection of postoperative endocrine treatment for premenopausal as well as postmenopausal patients (Early Breast Cancer Trialists' Collaborative Group 1998*a*, Jakesz *et al.* 2002). Data from the overview concerning the effect of dependence on tamoxifen on receptor status indicated a risk reduction in the annual odds of recurrence of 34% and 10% for ER-positive and ER-poor patients respectively. The reduction in the annual odds of death was 20% and only 6% at 10 years for the two different receptor qualities (Early Breast Cancer Trialists' Collaborative Group 1998*a*).

Whether or not receptor status plays an important role as a predictive marker for response to chemotherapy is still an open question. In metastatic breast cancer, Lippman & Allegra (1980) have argued that patients with ER-negative tumors show a much better response rate than those with ER-positive tumors, although this result was not confirmed by other authors. In the adjuvant situation, the overview data can be interpreted such that chemotherapy appears more beneficial in receptor-negative patients (risk ratio of annual odds of recurrence was 36% compared with only 20% in ER-positive patients), yet the formal test for heterogeneity was not significant in that meta-analysis.

A retrospective analysis presented at the National Institutes of Health (NIH) Consensus Conference in 2000 indicated that only patients with ER-negative tumors drew a significant benefit from adjuvant taxane administration (NIH 2001). It should therefore be strongly recommended that future adjuvant trials be based on the quality of steroid hormone receptor

status in order to prospectively evaluate their predictive importance for response to adjuvant chemotherapy. Knowledge of receptor status is essential to conduct trials applying preoperative endocrine treatment.

Another goal of our study was to investigate whether or not primary chemotherapy induces some selective change in the hormone receptor distribution of the primary tumor. Breast cancer is a heterogeneous disease in terms of the quality of different cell clones present within the same tumor. This applies to many molecular and biological properties indicated by hormone receptors and other measurable markers. As discussed earlier, we hypothesized that primary chemotherapy preferentially kills undifferentiated ER- and PR-negative tumor cells and largely tends to leave ER-positive and PR-positive tumor cells behind. This assumption is supported by results from the Early Breast Cancer Trialists' Collaborative Group (1998*b*) investigating recurrence and death rates in patients treated with adjuvant chemotherapy and stratified by ER content of the primary tumor. The data indicate that the reduction in the annual odds of recurrence is 30% in ER-poor patients and 18% in ER-positive patients respectively. The reduction in the annual odds of death in ER-negative patients amounts to 17%, while there is no significant improvement in overall survival for ER-positive patients.

If adjuvant chemotherapy were more effective in receptor-negative tumors, receptor status would change subsequent to primary chemotherapy. However, we failed to find a correlation to support this hypothesis. The number of tumors determined as ER negative increased significantly in patients undergoing preoperative chemotherapy. No exhaustive explanation is available as yet for these unexpected results. The fact that receptor content cannot logically be measured in a tumor after a complete pathological response is another problem of methodology. The numbers we report, however, make it unlikely that the results are significantly influenced by this potential source of bias.

Results similar to our own were reported in very small patient cohorts by Frassoldati *et al.* (1997) and Makris *et al.* (1999). Responders to primary chemotherapy presented a significant decrease in ER levels, and all patients showed significant increases in apoptotic index and p170 regardless of type of response (Frassoldati *et al.* 1997). Reduction in ER scores, but not in PR, was reported for responders to neoadjuvant chemotherapy assessed by sequential fine needle aspiration (Makris *et al.* 1999). However, several other studies investigating modulation of steroid receptor status by primary chemotherapy reported no significant changes of ER or PR (Hawkins *et al.* 1990, Bottini *et al.* 1996, Schneider *et al.* 2000).

The majority of studies investigating the biological mechanism of steroid receptor expression and regulation are initiated to clarify the development of resistance to endocrine treatment. Data are currently lacking as to hormone receptor alteration due to cytotoxic substances. Robertson (1996) has proposed that estrogen is a stable phenotype in breast cancer cells. While expression of ER in tumor cells is stable, the relative or absolute number of ER-positive or ER-negative cells may vary in the course of disease, depending on a variety of host–tumor interactions. Epidermal growth factor receptor (EGFR) expression is inversely related to ER expression, subdividing ER-negative tumors into two groups; ER-negative/EGFR-negative tumors are more likely to respond to endocrine treatment than ER-negative/EGFR-positive tumors (Nicholson 1993). The dual receptor phenotype may not be irreversibly fixed. Mutually exclusive staining for ER or EGFR on individual tumor cells raises the option that ER and EGFR expression either have a common regulating mechanism or that both pathways interact to cross-regulate their expressions (Sharma *et al.* 1994). The major controlling mechanism of EGFR overexpression in breast cancer cells is transcriptional regulation. Wilson & Chrysogelos (2002) have identified a region within the first intron of the EGFR gene that mediates transcriptional repression of EGFR gene expression in ER-positive/EGFR-low-expressing breast cancer cells.

An attractive hypothesis to explain the progression to steroid independence is that the tumor acquires the ability to constitutively express autocrine growth factors. There is evidence in some cancer models that particular fibroblast growth factors (FGF) may function as autocrine growth factors capable of conferring steroid independence. FGF overexpression in the estrogen-dependent breast cancer cell line MCF-7 induces an estrogen-independent phenotype as determined by tumor growth and metastasis in nude mice. Because this alteration is not due to changes in ER levels, it is likely that the FGF autocrine loop acts downstream from an estrogen signal (McLeskey *et al.* 1998).

Clinical data indicating the potential influence of chemotherapy upon ER status are outstanding as yet. *In vitro* observations using arsenic trioxide (AS203) as a cytotoxic agent, however, suggest that AS203 specifically inhibits the expression and signaling pathway of ERα (Chen *et al.* 2002). ERα is thought to function as a ligand-activated transcription factor and promotes growth of breast cancer cells by targeting expression of signaling components of the insulin-like growth factor system (Oesterreich *et al.* 2001).

We conclude from our results that the correct prediction of ER (91%) and PR (80%) measurement in CNB can indeed serve as a reliable basis in clinical practice for selecting patients for preoperative systemic treatment. The results are less concordant when discriminating the three levels of receptor positivity. Quality control for both ER and PR measurement is still an important undertaking for the basis of daily clinical practice. Surprisingly, primary chemotherapy induced a significant decrease in ER and PR levels. Further trials are to be designed to clarify the obviously important

interaction between receptor biology and cytotoxic chemotherapy.

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