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Abstract

Background/Objective: Hormone receptor (HR) status is one of the key factors in determining the treatment of breast cancer. Previous studies suggested that HR status may change in metastatic tissue. However, available studies focused mainly on primary biopsies and there are only few trials comparing HR status in the primary tumour and the metastasis using material from complete resection. The aim of the study was to determine the frequency of HR alterations in metastatic breast cancer.

Materials and methods: The study retrospectively examines a total of 50 patients who underwent brain, lung, or liver metastasectomy for metastatic breast cancer between January 2000 and January 2019.

Results: HR conversion was observed in a total of 30 cases (60.0%), while HER-2/neu (human epidermal growth factor receptor 2) discrepancy surprisingly occurred only in one case (2.0%). A change in immunophenotype occurred in 28% of cases. Triple-negativity was more frequent in brain metastases ($p = 0.039$).

Conclusions: We have confirmed that HR conversion between the primary tumour and its metastases occurs in a significant number of cases, which has important implications for further treatment decisions.

Key words: breast cancer metastases; hormone receptor status; receptor status discrepancy

Introduction

The prognosis of patients with metastatic breast cancer (BC) is generally poor. Treatment decisions for primary and metastatic BC are based not only, but quite fundamentally, on the status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2/neu) status.

The National Comprehensive Cancer Network (NCCN) guidelines recommend a biopsy of the first recurrence site for recurrent or stage IV disease along with the measurement of the ER, PR and HER-2/neu status [1]. The European School of Oncology International Consensus Guidelines for advanced BC also recommend a biopsy of a metastatic lesion to confirm the diagnosis, particularly if the metastasis is diagnosed for the first time [2]. However, routine immunohistochemical examination of metastatic breast lesions is still not a part of the standard workflow. Therefore, the indication for hormone therapy (HT) or HER2-targeted therapies is mainly determined by the biomarker status of the primary tumour.

Several studies noted a discrepancy of the hormone receptors (HR) and HER-2/neu expression status in the primary tumour and metastases [3–11]. However, the available studies

are highly heterogeneous — using different immunohistochemical staining protocols and different cut-off values for positivity (1% vs. 10% for ER and PR), evaluating the influence of different systematic therapies, and they differ also in the quality of available samples. The intratumoral heterogeneity of HR expression is well characterised in breast cancer [8]. This is the reason why the receptor studies may give false-negative HR status based on the type of the specimen submitted to histological examination and IHC analysis of either primary or metastatic lesions (different results of HR expression may be seen in the specimen from surgical resection, and core biopsy/fine-needle aspiration biopsy).

The aim of this study was to compare the receptor expression profiles between primary BC lesions and their metastases in the brain, lung and liver. The association between receptor conversion and prognostic outcomes was also analysed in these patients. We present here the first study of its kind in the Czech population and it is highly objective due to the use of a consistent methodology within a single centre.

Materials and methods

The study cohort included 50 patients with a median age of 52 years (at the time of diagnosis of the primary tumour) who underwent surgical treatment for BC metastasectomy at the Department of Surgery or the Department of Neurosurgery, University Hospital Pilsen, between January 2000 and January 2019.

The material obtained by fine-needle aspiration or core cut biopsy was excluded. To make the study as unbiased as possible, the study cohort is strictly based on tissue samples obtained by mastectomy/partial breast resection (for the primary disease) and by metastasectomy of the liver/lung/brain (for the metastasis). If the primary tumour tissue or metastases was not available for histologic revision and re-examination, the patient was excluded from the study.

Clinical-pathological characteristics (i.e. pathological stage of the disease, immunohistochemical status, phenotype, time to progression/TTP, oncological treatment details and follow-up data) were revised and collected.

Immunohistochemical analyses

All immunohistochemical (IHC) staining was performed in a single laboratory (University Hospital Pilsen), using a Ventana Benchmark XT automated stainer (Ventana Medical System, Inc., Tucson, AZ, USA). The following primary antibodies were used: estrogen receptor/ER (monoclonal, clone Sp1, Ventana, RTU), progesterone/PR (monoclonal,

clone IE2, Ventana, RTU), Ki-67 (monoclonal, clone MIB1, Ventana, RTU), HER-2/neu (monoclonal, clone 4B5, Ventana, RTU). Primary antibodies were visualised using a supersensitive streptavidin-biotin-peroxidase complex (BioGenex). Internal biotin was blocked using the standard protocol for the Ventana Benchmark XT automated stainer (hydrogen peroxide-based). Appropriate positive and negative controls were used. The percentage of positive cells was estimated. For ER, PR and Ki-67, only nuclear positivity was considered as a positive staining. For HER-2/neu, only membranous positivity was considered a positive result. Staining intensity was compared to positive internal (if available) and external controls.

Samples with 1% or greater reactivity were defined as positive (for both ER and PR receptors). HER-2/neu overexpression was defined as a membrane staining score of 3+.

All patients were also classified according to their immunohistochemical profile into the following phenotypes: Luminal A (ER+, PR+, HER-2/neu-, MIB1 ˂ 14%), Luminal B (ER+, PR+/–, HER-2/neu+/–, MIB1 ˃ 14%), basal-like (triple-negative/i.e ER–, PR–, HER–2/neu–) and HER2-enriched (ER–, PR–, HER-2/neu+) tumours [12].

Statistical analysis

HR receptor expression status was analysed both quantitatively (staining percentage) and according to the staining status (i.e. positive/negative). Time to progression (TTP), progression-free survival (PFS) after metastasectomy and overall survival (OS) primary surgery were selected as treatment outcome indicators and analysed in relation to the clinical characteristics. TTP was defined from the time of surgery for the primary tumour to the diagnosis of the metastatic disease. PFS was defined from the time of metastasectomy to the time of the first diagnosis of recurrence or death. OS was defined from the time of the surgical treatment of the primary tumour to the time of death. As TTP had no censored observations (due to the sample definition), it was analysed as a regular continuous variable using non-parametric methods. Associations between continuous variables and PFS/OS were analysed using the univariable Cox proportional hazards model. Categorical survival factors were analysed using the Kaplan-Meier method with the Gehan-Wilcoxon test. 1- and 3-year survival and median survival were calculated by linear interpolation of the corresponding Kaplan-Meier survival curve estimate, and median follow-up was determined by the inverse Kaplan-Meier method of OS data. Mutual relationships of continuous variables were analysed using Kendall’s tau, associations of continuous and categorical variables were examined using Mann-Whitney U test and Kruskal-Wallis ANOVA, and interdependencies of categorical

variables were tested using Fisher's exact test. Statistical analysis was performed in STATISTICA (version 11Cz, TIBCO Software Inc., Palo Alto, CA, USA) and Matlab (version 2019b, The MathWorks, Inc., Natick, MA, USA). All reported p values are 2-tailed and the level of statistical significance was set at $\alpha = 0.05$. False discovery rate (FDR) was controlled using the Benjamini-Hochberg procedure, giving an FDR estimate of 30% at the set $\alpha = 0.05$. To achieve a conservative overall FDR of 5%, α would have to be reduced to 0.0013.

Results

A total of 50 patients were included in the study. Thirty patients (60%) underwent brain metastasectomy, ten patients (20%) underwent liver resection, and ten patients (20%) underwent lung surgery for histologically proven breast cancer metastases. The basic characteristics of the patients are summarized in Table 1.

Fifteen patients (30%) received neoadjuvant chemotherapy. None of the patients received any other neoadjuvant treatment. Adjuvant chemotherapy, radiotherapy, hormone therapy (HT) and targeted therapy were given to 33 (66%), 37 (74%), 12 (24%) and 7 (14%) patients, respectively.

We observed conversion of PR receptor status between the primary tumour and metastases in 26 cases (52.0%), of which 15 cases (30.0% overall) converted from positive to negative results and 11 cases (22.0%) changed the IHC status from negativity to positivity. ER conversion was found in 13 cases (26.0%), of which 11 (22.0%) were from positivity to negativity, and 2 cases (4.0%) from negativity to positivity. In total, 30 cases (60.0%) showed a change in their HR expression status in at least one of the receptors. Nine cases showed conversion of both receptors (18.0%). The likelihood of conversion was not significantly influenced by the location of the metastases. We found that HT reduced ER and PR positivity in metastatic tissue ($p = 0.023$ and $p = 0.009$, respectively) — Figure 1. A comparison of the receptor expression between the primary tumour and metastases is shown in Table 2.

The phenotype also changed in up to 26% of cases. The highest number of changes was observed for conversions from Luminal B to basal-like in 6 cases (12%), then from Luminal B to HER2-enriched in 4 cases (8.0%), and from Luminal A to Luminal B in 1 case (2.0%). Surprisingly, there was also a change in phenotype from basal-like to Luminal B in 2 cases (4.0%) — see Table 3. Surprisingly, HER-2/neu discrepancy was identified only in one case (2.0%).

The group with consistent positive ER status showed a low level of the E3 ubiquitin-protein ligase MIB1 (MIB1), whereas the group with consistent negative ER showed high rate

of MIB1 count in the primary tumour. High MIB1 levels were also significantly associated with younger age at the time of metastasectomy ($p = 0.015$), with lower PR and ER expression in the primary tumour ($p = 0.019$ and $p = 0.025$, respectively), and with lower ER expression in the metastases ($p < 0.001$).

TTP was not associated with the site of the metastases, but was significantly associated with PR staining intensity in metastases ($p = 0.027$) and with ER expression in both the primary tumour and metastases ($p = 0.028$ and $p = 0.017$, respectively). A higher percentage of hormone receptor positivity was always associated with longer TTP.

PFS after metastasectomy was shorter in patients with HER2-positive primary tumours ($p = 0.023$) and metastases ($p = 0.013$) versus HER2-negative cases. PFS after metastasectomy was significantly influenced by the triple-negativity of the primary tumour, with longer PFS in the case of triple-negativity of the primary tumour — Figure 2.

OS after surgical treatment of the primary tumour was 54.6 months, with a median follow-up of 235.0 months. One-year OS was 96.1% [95% confidence interval (CI): 90.8–NA %] and three-year OS was 69.8% (95% CI: 57.0–82.6%). OS and PFS were strongly dependent on TTP ($p = 0.000$ and $p = 0.008$, respectively), with longer TTP leading to longer OS and PFS. Each month of TTP prolongation decreased the risk of progression or death after metastasectomy (prolonged PFS) by 1.1%. PFS was also significantly longer in patients with a higher age at the time of the metastasectomy ($p = 0.020$). Moreover, liver metastases were found in significantly younger patients than lung metastases ($p = 0.029$), and brain metastases had the poorest OS ($p = 0.007$) with the most frequent occurrence of triple-negativity in the metastatic tissue ($p = 0.039$). OS was not significantly affected by the conversion of the ER or PR — Figure 2.

Discussion

The prescription of HT or HER2-targeted therapy for metastatic BC is still mainly determined by the biomarker status in the primary tumour, although previous studies have shown that receptor conversion is a relatively common phenomenon (Tab. 4) [3, 5–11]. These observations could be explained by technical limitations of the method (rather than representing true changes in the tissue phenotype) and have mostly been ignored. However, the limited accuracy and reproducibility of receptor assays does not explain cases where receptor expression changes from 0 to 100% and vice-versa. It seems that the whole issue is much more complicated with a possible role of intratumoral heterogeneity [13]. Receptor

conversion is thought to be the result of clonal selection or selective pressure of therapy [14]. Examples of possible IHC staining results are shown in Figure 3.

The rate of discrepancy for HR status reported in the literature is 6–18% for ER, 25–42% for PR and 4–17% for HER-2/neu [3, 5–9, 11]. However, the studies are heterogeneous, particularly with regard to the tissue samples examined and the processing technology used. The fact that some authors included only core biopsies (limited material), which may not be sufficiently objective, may also lead to slightly different results. In contrast, we only included complete resections.

Most studies are in agreement that the discordance is significantly higher in PR status (when compared to ER and HER-2/neu), and that the conversions mostly occurred as a switch from positive to negative receptor status when compared to that from negative to positive [3–9]. While most studies consistently show that among the cases with HER-2/neu expression discordance, more patients gain HER-2/neu expression in the metastasis than lose it [3, 5, 6, 8–10].

As in other studies, positivity in the primary lesion and negativity in the recurrence site (for ER and PR) was a more common pattern than the opposite one in our study. We observed only one case of HER-2/neu receptor conversion in our cohort (conversion from negativity to positivity) and this finding is inconsistent with the results described in the literature — see Table 4.

Schrijver et al. performed meta-analysis of 39 studies [15]. They found that ER discordance was statistically significantly higher in brain and bone metastases compared to liver metastases, and PR discordance was higher in bone and liver metastases compared to brain metastases. PR conversion from positivity to negativity was statistically significantly more frequent than the conversion from negativity to positivity.

Completely different results were reported by Woo et al. [11]. Although they showed (like others) that conversion from positive to negative was more common than negative to positive in HR, they found no changes in ER, PR, or HER-2/neu status in brain metastases. No changes in ER status were observed in lung metastases. All primary triple-negative (basal-like) BC in their cohort remained triple-negative in the metastatic lesion. In contrast, Jung et al. [16] described discordance in ER, PR, and HER-2/neu between the primary tumour and resected brain metastases in more than 50% of 37 Korean patients included in their study.

We observed most conversions in brain metastases in our study. The transition to triple-negativity was also significantly more frequent in our cases. We did not demonstrate the likelihood of variation in conversion by the location of the metastases.

Our study also confirms that HT reduces ER and PR positivity in metastatic tissue (compared to their original appearance in the primary lesion). Equally, Chen et al. (8) reported the majority of conversions from positive to negative status in their study. They argued that this may be largely due to the selective killing of ER- and HER2-overexpressing BC cells by endocrine or HER2-targeted therapy.

Hoefnagel et al. [4] hypothesised that decreased survival in patients with acquired HR negativity (in metastases) may be caused by the initiation of HT (in stage IV disease) based on the immunohistochemical profile of the primary tumour (whereas the HR-negative cells, that actually forms the metastases, are known to be completely resistant to HT). Therefore, it would be important to know in advance which HR-positive patients are likely to develop HR-negative metastases. This would allow, for example, their adjuvant HT (to control their receptor-positive metastatic cells) to be supplemented with adjuvant chemotherapy. In their cohort, the OS of patients who converted from positive to negative ER or PR, or from negative to positive ER or PR, or who remained HR-negative, was comparable and significantly worse than that of patients who remained HR-positive. ER or PR receptor conversion from positive in the primary BC to negative in distant metastases has a negative prognostic value [4].

As IHC staining is not always routinely performed after metastasectomy in our institutions, some patients were treated based on the HR status in the primary tumour. In a retrospective review of HR status in metastases, we found that a total of 6 patients (12%) were treated with HT despite having an HR-negative metastatic disease. On the other hand, 3 patients (6%) should have received HT after metastasectomy (based on the HR-positive status in metastasectomy specimen), but they did not.

The results of a recent study by Chen et al. [8] showed that a positive ER status, whether in primary or metastatic BC, was associated with longer metastasis-free survival when compared with ER-negative primary tumours without conversion. Furthermore, a positive ER status in metastatic breast cancer disease (irrespective of the primary tumour HR status) was associated with a superior OS when compared to an ER-negative tumour without conversion. Shin et al. [10] reported that patients with concordant ER or PR positivity or discordant ER or PR status had significantly longer survival after recurrence than those with respective concordant negativity between the primary lesion and the recurrence site.

Similarly, survival analyses by Woo et al. [11] indicated that ER positive-to-negative conversion of ER was an independent poor prognostic factor in patients with primary ER-positive BC. Also, Dieci et al. [9] reported that patients with ER loss at recurrence had poor

OS, whereas those with PR loss did not. Bachmann et al. [17] found that PR and HER2 discordance correlated with shorter interval to metastasis. Aurilio et al. [18] reported that the time interval had no statistically significant effect on the discordance rate for ER, PR, or HER2. According to our results, the higher the percentage of HR positivity in the metastatic tumour, the longer the time to progression. However, PFS after mastectomy was shorter in the case of HER2-positive metastatic tissue, which is entirely consistent with our previous results [19].

Loss of HR or high level of MIB1 also appeared to be associated with a poor prognosis [20]. High levels of MIB1 in the primary lesion are associated with BC growth and invasion. The study by Ibrahim et al. [6] showed that patients with MIB1 ≥ 20% had a significantly worse median PFS than those with MIB1 < 20%. According to our study, the higher the MIB1, the lower the expression of HR. However, we did not observe a significant effect of MIB1 on OS.

We would like to point out that this study includes only tissue samples obtained by mastectomy/partial breast resection and samples obtained by metastasectomy. We believe this is an advantage, as a simple needle biopsy is a limited material and we don´t consider it objective enough for HR evaluation due to the well-known intratumoral heterogeneity and possible false-negativity of the IHC staining. Furthermore, by presenting a single-institution analysis, we were able to provide more detailed and specific data due to a strictly uniform processing technique, which is usually not possible when performing a large pooled literature review.

We are aware of the limitations of our study, which include its retrospective design and the limited cohort size. Larger cohorts with longer follow-up and multivariable assessment are needed to further evaluate the true prognostic value of HR conversion in distant BC metastases.

Conclusion

We confirmed that HR conversion between the primary tumour and its metastases occurs in a significant number of cases. HR conversion occurs in more than half of the cases of breast cancer metastases, whereas HER2 discrepancy is rare. We proved that the tumour phenotype changes in more than a quarter of the cases in the metastatic disease, which has important implications for further treatment decisions and patient prognosis. HR status should always be assessed in the metastatic disease before deciding for further treatment as IHC evaluation of metastasis for HR status may alter treatment decisions in patients with

metastatic BC. In cases of positive-to-negative conversion, HT should be discontinued to avoid unnecessary treatment side effects. Resistance to treatment may develop due to a change in phenotype. Knowledge that the phenotype of the tumour (and therefore the status of the HR), can change in time is important, especially in situations where metastasectomy cannot be performed and further systemic treatment is chosen “blindly”. If possible, at least an attempt should be made to take a biopsy sample from the metastasis before indication of further HT in patient.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author contributions

Conceptualization: K.P., O.H. and V.T.; methodology K.P., J.V., P.H., V.T. and O.H.; investigation: K.P., R.V., K.P., J.V., J.D., M.S., J.Š., I.Z. and O.H.; writing — original draft preparation: K.P., R.V., and P.H.; writing — review and editing: V.P., O.H., V.T. and J.M.

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Table 1. Basic characteristics of the patients

Characteristic	**n (%)**
Patient	
Female	50 (100.0)
Age (years) — breast surgery Median [min–max]	52 [26–78]
Histology of primary tumour	
DIC	39 (78.0)
LIC	2 (4.0)
Other	7 (14.0)
Size of the primary tumour [mm] Median [min–max]	20 [4.0–90.0]
TNM stage at diagnosis	
Tis	2 (4.0)
T1a	0 (0)
T1b	2 (4.0)
T1c	18 (36.0)
T2	24 (48.0
T3	1 (2.0)
T4	3 (6.0)
N0	26 (52.0)
N1	15 (30.0)
N2	5 (10.0)
N3	4 (8.0)
N4	0 (0)
M0	49 (98.0)
M1	1 (2.0)
TTP (months) Median [min–max]	31.0 [5.4–224.9]
Age (years) — metastasectomy Median [min–max]	56 [28–78]
PFS (months)	
Median (95% CI)	10.2 [3.3–15.7]
OS (months) Median (95% CI)	54.6 [42.6–93.0]

DIC — ductal invasive carcinoma/invasive carcinoma not otherwise specified; LIC — lobular invasive carcinoma; RFA — radiofrequency ablation; TTP — time to progression; PFS — progression-free survival; OS — overall survival; CI — confidence interval

Table 2. Rate of discrepancy according to the direction of conversion (%)

Rate of discrepancy according to the direction of conversion n(%)						
	ER (+/–)	**ER (–/+)**	**PR (+/–)**	**PR (–/+)**	**HER 2 (+/–)**	**HER2 (–/ +)**
Liver metastases (n = 10)	2	0	4	2	0	0
Pulmonary metastases (n = 10)	2	0	1	3	0	0
Brain metastases (n = 30)	7	2	10	6	0	1
Total (n = 50)	**11 (22%)**	**2 (4%)**	**15 (30%)**	**11 (22%)**	**0 (0%)**	**1 (2%)**
p-value, localization difference	0.890	NA	0.307	0.890	NA	NA

ER — estrogen receptor; PR — progesterone receptor; HER2 — human epidermal growth factor receptor 2; NA — not available

Table 3. Rate of phenotype and its changes

	Phenotype (primary tumour) n (%)	**Phenotype (metastasis) n (%)**	**Change of phenotype n (%)**
Liver metastasectomy (n = 10)	Luminal A — 0 (0%)	Luminal A — 0 (0%)	2 (20%)
	Luminal B — 7 (70%)	Luminal B — 5 (50%)	
	HER2 enriched — 3 (30%)	HER2 enriched — 4 (40%)	
	Basal-like — 0 (0%)	Basal-like — 1 (10%)	

Lung metastasectomy (n = 10)	Luminal A — 0 (0%)	Luminal A — 0 (0%)	2 (20%)
	Luminal B — 4 (40%)	Luminal B — 2 (20%)	
	HER2 enriched — 1 (10%)	HER2 enriched — 2 (20%)	
	Basal-like — 5 (50%)	Basal-like — 6 (60%)	
Brain matastasectomy (n = 30)	Luminal A — 1 (3.3%)	Luminal A — 0 (0%)	9 (30%)
	Luminal B — 10 (33.3%)	Luminal B — 6 (20%)	
	HER2 enriched — 6 (20%)	HER2 enriched — 8 (26.7%)	
	Basal-like — 13 (43.3%)	Basal-like — 16 (53.3%)	
Total (n = 50)	Luminal A — 1 (2.0%)	Luminal A — 0 (0%)	**13 (26%)** **Luminal B to Basal-like (6x)** **Luminal B to HER2 enriched (4x)** **Basal-like to Luminal B (2x)** **Luminal A to Luminal B (1x)**
	Luminal B — 21 (42%)	Luminal B — 13 (26%)	
	HER2 enriched — 10 (20%)	HER2 enriched — 14 (28%)	
	Basal-like — 18 (36%)	Basal-like — 23 (46%)	

HER-2/neu — human epidermal growth factor receptor 2.

Table 4. Reported rates for discordance of hormone receptor (HR) between primary and metastatic breast cancer [3, 5–11]

	Rate of discrepancy (%)			Rate of discrepancy according to the direction of conversion (%)						
	ER	**PR**	**HER 2**	**ER (+/-)**	**ER (-/+)**	**PR (+/-)**	**PR (-/+)**	**HER 2 (+/-)**	**HER 2 (-/+)**	**Total n**
Nishimura (2011)	10.3	25.8	14.4	8.2	2.1	19.6	6.2	3.1	11.3	97
Amir (2012)	16.0	40.0	10.0	11.7	4.3	36.2	4.3	2.1	6.4	94
Ibrahim (2012)	16.4	41.7	17.5	9.5	6.9	33.0	8.7	5.0	12.5	120
Curtit (2013)	17.0	29.0	4.0	12.3	4.7	22.1	7.2	2.6	0.9	235
Dieci (2013)	13.4	39.0	11.8	10.9	2.5	30.3	8.4	3.4	8.4	119
Shin (2016)	18.1	25.0	10.3	11.1	6.9	17.4	7.6	2.8	7.5	114
Woo (2019)	6.0	40.0	12.0	5.3	24.3	5.9	0.7	2.0	2.0	152
Chen (2020)	18.3	40.3	13.7	15.8	2.6	31.0	9.3	7.8	5.9	387

ER — estrogen receptor; PR — progesterone receptor; HER-2/neu — human epidermal growth factor receptor 2

Figure 1. The development of hormone receptor (HR) staining intensity between the primary tumour and the metastasis compared according to adjuvant hormone therapy (HT). It shows

that both estrogen receptor (ER) (**A**) and progesterone receptor (PR) (**A**) abundance is more likely to decrease in the metastasis if the patient has obtained HT for the primary tumour. Only patients with primary tumours positive for the respective HT were included in the comparison

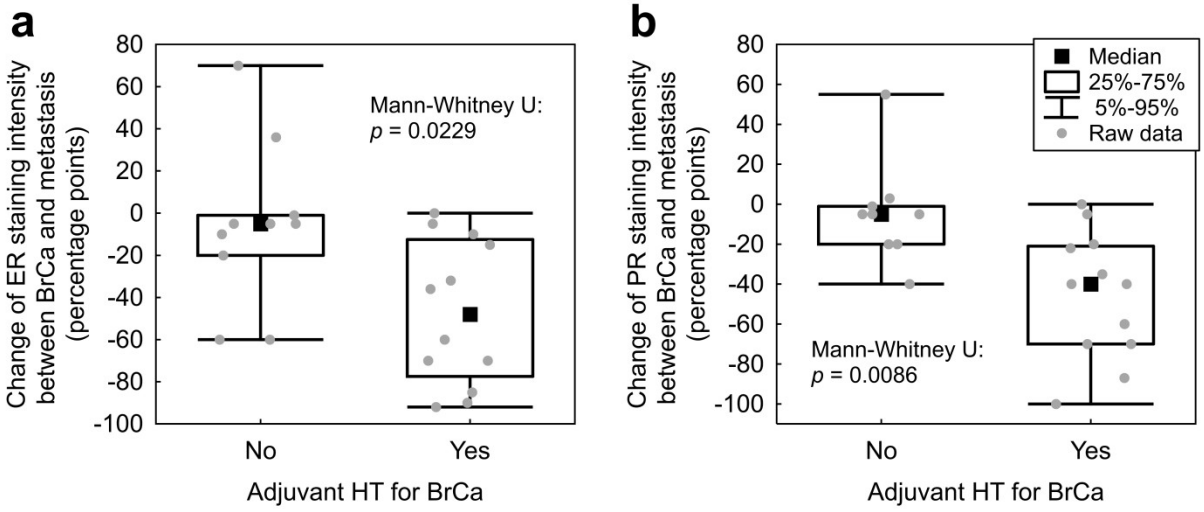

Figure 2. Kaplan-Meier plots of overall survival (OS) after patient stratification according to the location of the metastasis: Brain metastases had significantly the poorest OS (**A**); according to receptor conversion: OS was not significantly affected by the conversion of the estrogen receptor (ER) or progesterone receptor (PR) (**B–C**). Progression-free survival (PFS) after metastasectomy was shorter in patients with human epidermal growth factor receptor 2 (HER2) expression in the primary tumour (**D**) as well as in metastases (**E**). PFS after metastasectomy was significantly affected by triple negativity of the primary tumour, with longer PFS in case of triple negativity of the primary tumour

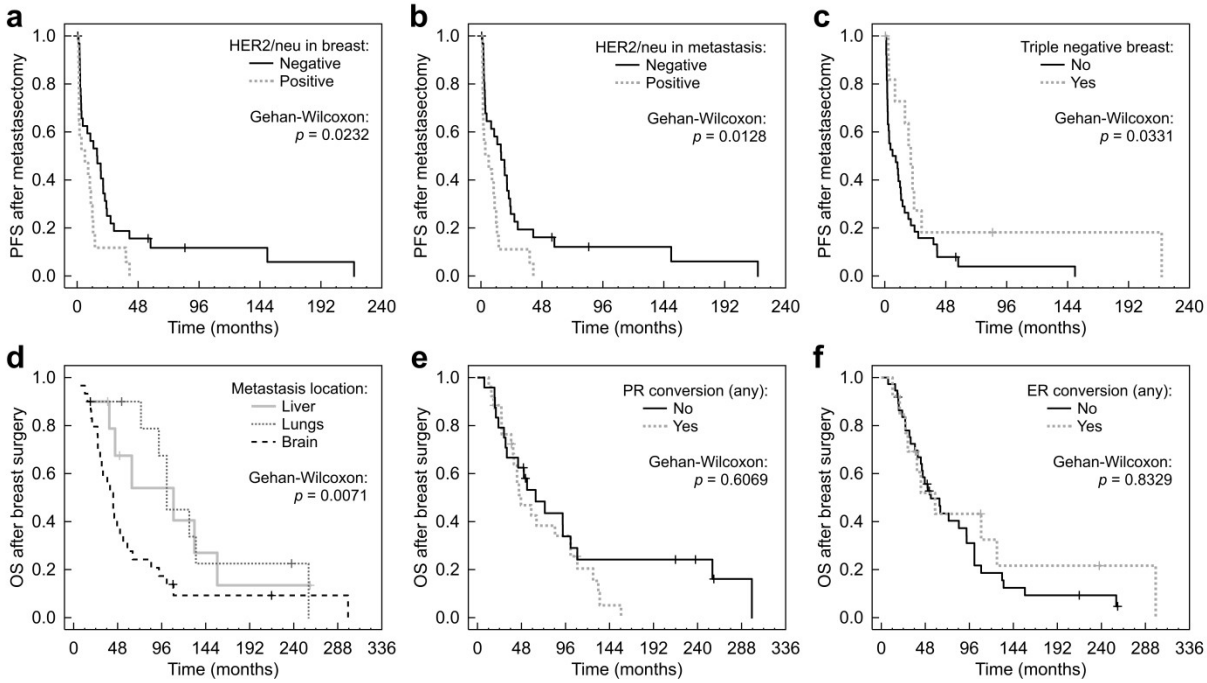

Figure 3. Examples of possible immunohistochemical (IHC) staining results: Primary breast cancer in estrogen receptor (ER) (**A**) and progesterone receptor (PR) (**B**) staining. Brain metastases in ER (**C**) and PR (**D**) staining