# Predictive and prognostic factors in solid tumors - prediction of pathological response based on routine diagnostics and the prognostic impact of complete remission

Physician thesis

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# 1.INTRODUCTION

For the last two decades, oncological diagnostics and therapies have been rapidly improving. This is especially true for breast cancer, as next to the regular diagnostic and medical treatments, practicing physicians must learn newer and more up to date methods. During my own work, I have experienced that we begin to learn more about the biological behavior of breast cancer in the last decades. The goal is to give specialized and more personalized treatments for every patient, if it is possible. Meanwhile applying traditional pathologic and diagnostic imaging, novel imaging modalities are also becoming more widely available. Modern chemotherapeutic and biological therapies have also been routinely used and made the treatments more personalized. The order of the treatments has also been changing in the last decades: in locally advanced disease surgical treatment is not the primary care, but pharmaceutical therapy could also be a first choice in these cases. Nowadays we are living in the so-called age of precision medicine.

The number of patients who are receiving the primary systemic therapy (PST) is constantly increasing. Earlier PST treatments were restricted to inflammatory and/or locally advanced breast cancer, the primary goal was to stabilize the disease and - if it was possible - to achieve operability. Today even those patients can receive PST whose tumors are initially operable, however pharmaceutical pre-treatment is recommended due to the unfavorable biological behavior of the tumors. Chemotherapy and/or biological therapies can also be applied during the primary systemic treatment. Endocrine therapy is enabled for older patients, with poor performance status.

Nowadays there is an ongoing argument of how PST helps reaching pathologic complete remission (pCR) and its prognostic value to favorable survival.

During the PST, the tumor response should be monitored. Probably the most effective tool for response evaluation would be the repeating of the core biopsy sampling, but this approach did not become a part of the daily routine for numerous reasons. Hereby it would be crucial to specify those breast cancer patient groups, who would benefit from drug pretreatment. Our research group aimed to clarify the role of current and to define novel predictive and prognostic markers. Besides conventional imaging modalities and complex

breast diagnostics, novel imaging modalities, hybrid imaging are also supporting the daily practice. However, in everyday routine it is necessary to apply simple, not too expensive but reproducible methods that can be routinely applied in each treatment cycle. Considering all ten above mentioned my research objective was to evaluate whether physical examination performed by a skilled oncologist and breast ultrasound could reliably monitor the effect of PST. We investigated whether the knowledge of the biological behavior of the tumor and adequate therapeutic response monitoring can predict the pathological response. Although, any several studies confirmed that achieving pCR predicts a favorable long-term outcome, novel publications contradicts this hypothesis suggesting that in different breast cancer subtypes pCR has got different prognostic value. Therefore, during my studies I have also analyzed the correlation between pCR and survival.

## 2.OBJECTIVES

There could be significant differences between the same stages of breast cancers both in response to therapy and survival rates. As a clinician, we strive to provide the most accurate predictive and prognostic markers as a basis to our decisions, therefore forming an individualized therapeutic plan for every patient. These markers must be capable of reliable response monitoring and to provide accurate information about long-term prognosis.

1. My objective was to examine that in a heterogenous breast cancer patient group (in terms of molecular subtype) could physical examination and breast ultrasound be able to predict pathological complete response in the early course of PST.

2. I have examined the response of certain molecular subtypes for the PST. Also, I have investigated the correlation between survival rates and pathological tumor response.

3. I have examined the rate of pCR in Her2 positive patient groups treated with biological therapy compared to those who treated with chemotherapy alone. By analyzing the data collected I sought to find out the role of added biological therapy to standard chemotherapy in the clinical outcome. Special attention was given to the response of Luminalis B / Her2 and purely Her2 positive breast cancer therapies.

4. I have been inspecting the precision of breast ultrasound (US) and physical examination (PE) done by skilled clinicians during PST in predicting the pathological response of Her2 positive breast cancer. I have also examined the correlation of PE and US with the pathological response and analysed whether this response evaluation tools are suitable for following the tumor response to biological treatment.

# 3.METHODS

## 3.1. Patient groups

**Selection of heterogenous breast cancer group**: Data from breast cancer patients undergoing primary systemic treatment between 1998 and 2009 were collected prospectively from a single center database. The type of study was retrospective; however, patients were prospectively selected, considering inclusion and exclusion criteria. I analyzed the data of 116 patients after excluding inflammatory breast cancer, metastatic disease, hormone therapy or if surgery and radiotherapy had occurred before. The presence of pre-treatment biopsy and immunohistochemistry was a condition for inclusion in the study. Patients received at least two cycles of systemic treatment, and the physical examinations were performed by a single group of specialists in the same center. The radiological diagnosis is based on mammography and US. Only those patients got accepted in this analysis who underwent surgery after PST, so histologic diagnosis was available. The choice of chemotherapy corresponded to the current guidelines.

**Selection of Her2 positive breast cancer patient group**: Data for patients undergoing PST between 2008 and 2013 were also selected prospectively from a single center database. Out of 188 patients, I selected patients whose cancer showed Her 2 overexpression, n=43. The Her2 status in core biopsies was confirmed by immunohistochemistry and / or FISH, and staging diagnostic imaging technics demonstrated the absence of metastases. Only those patients who had agreed to surgical therapy after completing PST were selected. Patients were divided into two groups: on one hand I was analyzing the Her2 overexpressing breast cancer patients receiving neoadjuvant chemotherapy and also biological treatment, which was the 1st treatment group. In the second treatment group, patients received biological therapy only as part of adjuvant treatment after surgery.

The histological evaluation was performed on formalin-fixed, paraffin-embedded tissue samples from the 2nd Department of Pathology at Semmelweis University.

Physical examination was performed by an experienced team, of the same oncologists within a center, similarly the UH studies were performed on the same university radiology

by skilled radiologists.

### 3.2. Histopathological analysis

The histology was performed both on core-biopsy samples prior to PST and on surgical specimens after PST. In the case of core biopsy, hematoxylin-eosin stained slides were reviewed for histological type, nuclear grade, tubule formation, mitosis index, inflammatory and lymphoid cell infiltration, as well as in situ components and lymphovascular infiltration. The hormone receptor status, Her2, Ki-67 labeling index assessed on core biopsies were done by routine IHC. The ER and PR positivity was considered proven in case of 3 or higher Allred scores. The Her2 overexpression was confirmed with IHC 3+ or FISH assay in case of IHC 2+. IHC 1+ and 0 tumors were considered Her2 negative. When determining the status of Her2, the recommendations in the current ASCO / CAP guideline diagnosis were applied. Biological subtype was assigned based on the 2013 St. Gallen consensus.

I identified the pCR according to the recommendations of the 2009 Kecskemet consensus. The definition of pCR for the primary tumor was ypT0/ypTis, i.e. the presence of DCIS in the sample was allowed. I also investigated the involvement and the degree of tumor response in the lymph nodes removed, where remission was considered complete if ypN0.

The pathological response was stratified by the Chevallier and Sataloff classification systems.

### 3.3. Physical examination and Ultrasound

Physical examination was performed before the first PST, with the assistance of an experienced professional oncologist. I considered the larger diameter of the tumor size recorded in the medical system, as well as the description about mobility, skin involvement etc. for determining the stage. I have recorded the status of lymph nodes (side, mobility, size). Similarly, I consider the result of the physical examination recorded at the last primary systemic treatment as well. In the present study, I did not consider the other examinations between the applied cycles. I defined a complete remission when the oncologist reported normal palpation finding. In the heterogeneous patient groups, I have analyzed the reported US examinations, done by experienced radiologists, beforehand the actual treatment and surgery, avg. 1-3 weeks. The same radiologist team, performed the

imaging before and after the treatment in Her2+ cases to decrease inter-observer variability. To declare complete remission, at the location of the original tumor must have been no residual or US detected lesion.

### 3.4. Statistical analysis

Each applied statistical test was two-sided, and the results of the tests were statistically significant at $p < 0.05$. The data was given as mean ± standard deviation or median (interquartile range). Patients were divided into pCR and non-pCR patient's groups for pathological response. The two groups were compared to the Mann-Whitney test (the sample was not normal). To compare data before and after the treatment Wilcoxon sign-rank test was applied. For binomial categoric data Chi-square probe was used depending on sample number, and Fisher exact test was utilized. Sensitivity, specificity, positive predictive value and negative predictive value was assessed.

Progression-free survival (PFS) and overall survival (OS) was assessed from the time of first histologically confirmed diagnosis to the date of the first progression or the last date of follow-up in months. Survival analyses were performed with Kaplan-Meier analysis and log-rank test depending on the complete remission, the subtypes and the treatment methods.

The data has been stored in Microsoft Excel 2010 (Microsoft Corp., Redmond Washington, USA). Statistica 64 11 (Statsoft Inc., Tulsa, Oklahoma, USA) software was used for calculations.

Ethical approval was obtained, number 76/2007.

# 4.RESULTS

## 4.1. The role of physical examination and ultrasound in predicting the pathological response to PST in the heterogeneous breast cancer patient group

I have collected the clinical and pathological characteristics of 116 patients and tumors. The patients mean age at the time of diagnosis was 49.9 years (IQR 38-59). The mean pretreatment tumor size assessed by PE was 40 mm (IQR 30-50) and if assessed by breast US it was mean 27 mm (IQR 22-36). The majority of patients had invasive ductal carcinoma (83.62%) and most patients had T2 tumors (56.9%), 16.4% had T3, 12% had T4 tumors and only 9.5% had T1 tumors. Among 116 patients there were 67 node-positive cases (57.8%). About hormone receptor status, 52.6 % of the tumors were ER positive and 34.5 % were PR positive.

The composition of the primary systemic treatment corresponds to the guideline valid for the period under review: 24 patients had received taxane-based treatment, 48 had received combined taxane-antracycline treatment, and only 8 patients of 116 were treated at that time with trastuzumab-containing therapies, not having routine part of the study period the neoadjuvant trastuzumab. Twenty-one patients received anthracycline-based treatment without taxanes and a total of 15 other therapies.

PE and US measurements were compared with the residual pathologic tumor size. Measured with PE, 27.6% of the patients achieved a clinical complete regression. However, the pathological complete response rate was lower, 21.5%. According to the results obtained by US, the clinical CR rate was 15.5 %.

Of the 25 patients who achieved a pCR, 9 were clinically described as partial responders by PE, the remaining were described as complete responders. US indicated complete response in 5 cases, and partial response in 9 cases. After neoadjuvant treatment, both PE and US measurements showed significant correlation with pathological remission ($p < 0.001$ and $p = 0.004$, respectively).

I also analyzed whether in pCR cases US added an additional value to PE evaluation. I found that in cases when the PE correctly identified pCR, only 50% of US examinations showed complete remission - the false positivity rate was high. If the PE was false positive

only one US examination contradicted the result of PE. Thus, US did not add any additional diagnostic value to PE.

### 4.2. I have examined the subtypes expected to respond to PST and the correlation between pathological response and survival

I have examined the complete pathological remission rates related to the different treatment options, with the following results: the rate was 30% in the taxane-based group, 25% in the taxane-antracycline group, 9.5% in the anthracycline group, and 37.5% in the trastuzumab-treated group. Upon pathological review of tumor and nodal status, pathological complete or near-complete remission (pCR= Chevallier I and II) was observed in 25 of 116 cases (21.5%), 44 % of whom had triple negative histology and 76% had high-grade tumor. Only 10 Luminal A patients were enrolled in this study, and all of them failed to achieve pCR. The same was true for the majority of Luminal B tumors (83.4%).

I have studied the effect of clinical and pathological features on the response to neoadjuvant therapy by univariate regression analysis. Negative ER and PR status and Her2 positivity were the factors associated with an increased percentage of pCR. The menopausal status was not associated with the likelihood of achieving pCR, no significant correlation was found (Chi square test 4.76, df = 2, p = 0.093). However, we emphasize that the mean age was significantly lower in the pCR group than the non-pCR group (44.4 + -12.3 vs. 50.8 + -11.8, p = 0.017).

The median follow-up was 56.1 months (IQR 36.3-77.1). Concerning DFS, pCR was not associated with better outcome. Likewise, overall survival was not significantly better in the group of patients achieving pathological complete remission, p = 0.237. The difference was still not significant when the four Chevallier groups were compared for overall survival (p = 0.079), although subgroup analysis revealed a difference between Chevallier III and IV in OS time (p = 0.031). Although, triple negative breast tumors are more likely to achieve pathological complete remission due to primary systemic therapy, this subtype has the shortest disease-free survival.

### 4.3. Impact of targeted therapy on pCR ratio in Her2 positive tumors

I have analyzed data from 43 patients treated between 2008 and 2013 who received

biological, i.e. trastuzumab treatment due to Her2 overexpressing tumor and underwent surgery.

Of 43 cases (mean age 51.47 ± 11.07 years), 15 were Her2-positive subtypes and 28 were luminal B / Her2-positive tumors. 26 patients initially received taxane-based PST treatment, they received trastuzumab only as adjuvant therapy (treatment group 1). In the remaining 17 cases, patients received trastuzumab as part of PST (treatment group 2) prior to surgery. After PST treatment, all patients agreed to surgical removal of the tumor as follows: 25 (58.1%) mastectomy, 18 (41.9%) breast conserving surgery, 40 axillary block dissection (ABD) (93%) and 3 sentinel node removal (7%).

Both groups of patients showed a favorable tumor response to PST treatment. Of the 1st treatment group, 10 patients (38.5%) achieved pCR, from the 2nd treatment group 8 (47%). For better clarity and data analysis I divided patients into pCR and non-pCR,

pCR was significantly more common in both treatment groups for tumors of the purely Her2-positive subtype than in Luminal B / Her2-positive tumors ($p = 0.043$ in Group 1, $p = 0.029$ in Group 2). Only 7 pCR was achieved out of 28 Luminal B / Her2-positive tumors.

### 4.4. Accuracy of physical examination and ultrasound in predicting pathological response in the HER2 positive breast cancer group

I have analyzed the two methods in the Her2 positive patient group treated with and without trastuzumab in the neoadjuvant setting.

In 46 patients, the tumor size by PE and UH were correlated with pathological response, i.e. Chevallier classification. I have collected data recorded before and after PST, prior to surgery. As in the heterogeneous patient group the physical examination better predicted the pathological response than the UH. When we separately analyzed, the patient group treated with biological agent in the neoadjuvant setting compared with the chemotherapy alone treated group, it was found that this benefit was further enhanced by physical examination. In case of US, the number of false positive cases was very high (six out of 1 while seven in 2nd patient group). In addition, the number of false negative cases was low, only two in treatment group 1, while zero in the 2nd.

## 5.CONCLUSIONS

**The role of physical examination and ultrasound in predicting the pathological response to PST in the heterogeneous breast cancer patient group**

• In the daily routine procedure, physical examination and ultrasound can predict the pathological response, but in our study the physical examination showed a slightly better correlation with the pathological tumor response.

• Physical examination is an inescapable and essential diagnostic step during PST, reliably indicates residual tumor, so even with the up-to-date, modern diagnostic procedures it is not permissible to abandon the PE. PE should be recorded in each treatment cycle.

• Standardization is needed, however an expert guideline is crucial. The condition of reliability is the definition of oncological breast centers, stable team, consisting of well-trained oncologist, radiologist, surgeon and pathologist.

**We investigated the subtypes expected to respond to PST and the correlation between pathological response and survival**

• In this study, I have verified that even under routine conditions following the guidelines our results do not deviate from international literature. PST treatment of triple-negative and Her2 positive tumors is clearly recommended, while in the case of luminal B-like tumors, it is not yet clear upon existing predictive and prognostic markers which patient benefit from neoadjuvant treatment.

• In this real-life observational study, the pathological complete response was not associated with better survival rates compared to non-responder tumors. My results concluded that the use of pCR as a survival substitution endpoint is questionable, and probably depends on breast cancer subtypes

• By studying breast cancer subtypes, I found that although triple negative tumors achieved a higher rate of pathological complete response, survival rate still failed to

improve

• In the heterogeneous patient group, there was a significant difference in disease-free survival among the Chevallier III and IV groups, which is otherwise consistent with international practice.

**Impact of targeted therapy on pCR ratio in Her2 positive tumors**

• In this study, I found that in the Her2 overexpressing breast cancer group, as part of the PST treatment, trastuzumab was achieved with a more favorable pCR ratio than the results found in the randomized clinical trials.

• The biological behavior of Luminal B / Her2-positive tumors with endocrine sensitivity is different: pCR is rarer and its prognostic value is lower. In the case of Luminal B / Her2-positive tumors, it may be justified to segregate further subgroups, narrowing the PST range of indications. At present, there's no suitable marker for this purpose, the combined consideration of all predictive and prognostic markers can give an indication of the choice of primary therapy. Further investigation, typing and searching for markers of Luminal B immunophenotypic breast tumors will be an exciting chapter in oncology.

**The accuracy of physical examination and ultrasound in predicting the pathological response in the HER2 positive breast cancer group**

• PE correlated better than US with pathological response both in standard chemotherapy and combined monoclonal antibody therapy, but due to the low sample size, further validation of this result is necessary.

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