New challenges in complex breast cancer diagnostics: - the role of pathologic prognostics, the correlation of breast density and hormone replacement therapy

Abstracts of the Ph. D.thesis

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Introduction

Breast cancer (in both sexes) accounts for 10.5% of all cancers which puts it former into 2nd place behind bronchial cancer nowadays into 3nd place behind clorectal cancer regarding both incidence and as a cause of death. 502,000 people have died due to breast cancer worldwide in 2005, which accounts for 7% of tumor mortality and almost 1% of overall mortality. In Hungary mammography service screening is available countrywide since 2001 organized by the National Public Health and Medical Officer Service. Modern pathology describes the tumors with 3rd generation prognostic factors, which brings the issue of the validity of the complex diagnosis – synthesized from several imaging modalities and the preoperative cytopathology result versus the postoperative histology findings – enhanced with these novel prognostic factors.

A 2002 WHO study which proved significant increase in the risk of hormone related breast cancer caused a decrease in the spread of peri- and postmenopausal combined hormone replacement therapy which has started 50 years ago. While theoretical pathology, endocrine research and epidemiologic annals of breast cancer diagnostics are dealing with fragments

of the problem of hormone replacement therapy related breast density increase, breast radiologists have to answer these patients' questions regarding breast cancer and hormone replacement therapy routinely.

Goals

This study deals with the validity of complex breast examination to diagnose and to comprehensively describe breast cancer in view of the pathologic, prognostic factor driven classification and discusses some novel issues in relation to perimenopausal hormone replacement therapy.

1. Statistic evaluation of individual and combined preoperative diagnostics. Comparative evaluation of the sensitivity, specificity, PPV and NPV of mammography, ultrasound, palpation and cytology at two diagnostic significance levels.

2.Pathologic prognosis and diagnosis. Can the different tumors of the pathology classification be separated by the current preoperative diagnostic methods?

2.1 Are there any differences in overall diagnostic score, mammography, breast density, radiomorphology, ultrasound, and palpation and cytology results of tumors with good, medium and bad NPI prognosis?

2.2The possible differences of overall diagnostic score, mammography, breast density, radiomorphology, ultrasound, palpation and cytology results of Ki-67 positive (increased proliferation rate) tumors vs. Ki-67 negative tumors.

2.3Evaluation of any overlap between the NPI and the Ki67 classification.

2.4Are there any differences in overall diagnostic score, mammography, breast density, radiomorphology, ultrasound, palpation and cytology results of the triple negative and the basal-like breast tumours?

3.The correlation of hormone replacement therapy, breast density increase and cancer diagnostics. Can increased density be considered as an independent risk factor or it only makes diagnosis more difficult?

3.1Is there any difference between the density distributions (overall or in 10 year age groups) between normal, benign or malignant breasts?

3.2Is there a correlation between density and the rate of misdiagnosed and occult tumors?

3.3Is there a density related discrepancy of mammography vs. histology size and focality determination?

3.4Any possible differences in size, radiomorphologic classification, axillary nodal status, histology grade and steroid

receptor positivity between the tumors of the population of prolonged perimenopausal combined hormone replacement therapy vs. age related untreated ones?

Materials and methods

2028 breast change, verified by postoperative histology – which were diagnosed between 1996 and 2006 at the breast clinic of MaMMa Healthcare Co. – were reviewed. 85 patients (4.2%) had bilateral tumor, the followup of 95 patients (4.7%) revealed recurrence of malignancy. The final histology was benign in 434 cases (21.4%), in 1594 cases (78.6%) malignant disease was diagnosed. Out of these 1415 (88.77%) were invasive and 179 (11.23%) were in situ.

Diagnostic algorithm

Mammographic images were obtained, followed by examination consisting of focused history taking, physical examination and ultrasound and intervention if needed. Cytology or core biopsy sampling was carried out with preferably ultrasound guidance or – if the tumor was not visible on ultrasound – with the use of 2D mammography guidance.

Evaluation

The written report of all four examinations was coded according to the EU Breast Imaging 5 grade scale: 1 – normal, 2 – benign, 3 – indeterminate/borderline, 4 – probably

malignant, 5 – malignant. The all-score value (the sum of the scores as known from the literature) was also evaluated. Breast pattern or density was coded according to Tabár. Altogether 37 different data were recorded and coded – including detailed diagnosis, histology, operative data and history – into MS Excel worksheets for statistic comparison and multiple combined subgrouping and filtering.

Statistical methods

The programme Statistica was used for the statistical evaluation. Significance was measured by chi^2 test using $p<0.05$ as significance level. Fischer's test was used in cases with low patient numbers. The efficacy of mammography and ultrasound was evaluated by the mean, SD and median of the numeric values as tumor size and multifocality Sensitivity, specificity, PPV and NPV of all four diagnostic methods was calculated for the different diagnostic cut-off levels, which provided valuable data to evaluate the false negativity and positivity of the indeterminate lesions added to the baseline evaluation of the methods. ROC graphic analysis was performed on the subgroups of different breast patterns and radiomorphologic appearances to evaluation the sum score of the four diagnostic methods.

Results

1.Statistic evaluation of individual and combined preoperative diagnostics

1.1Comparative evaluation of the sensitivity, specificity, PPV and NPV of mammography, ultrasound, palpation and cytology at two diagnostic significance levels.

Sensitivity – NPV:

The sensitivity of mammography, cytology, ultrasound and physical examination was 93.1% - 91.5% - 88.3% and 69.1% respectively at lower positive-negative cut-off level. The relatively bad result of physical examination was due to its inferiority to imaging plus the 16.5% proportion of non-palpable tumors. At a higher cut-off level the sensitivity has decreased to 80.4% for cytology, 78.9% for mammography, 71.8% for ultrasound and 35.7% for physical examination and the order of the methods has also changed.

PPV – specificity:

The highest PPV is (0.9440) of physical examination, due to the very few false positive palpation results. Obviously this method has the highest false negative ratio for the <10 mm lesions and for the deeply located tumors in bigger breasts. Among the imaging modalities ultrasound overperforms

mammography, but their values (0.86 and 0.89 respectively) are quite similar in concordance with cytology

The results of the statistic outcome measures of mammography at two diagnostics cut-off levels normalized to breast pattern code.

Regardless of having the malignant limit below or above 3 each and every outcome measure was better in the low density breast group. Depiction and classification in dense breast is more difficult. Sensitivity is 94.6% and 85.2% in low and high density breast respectively, which drops further to 81.1% and 70.4% with increasing the malignant limit.

Result of mammography in correlation with radiomorphologic appearance.

Using low cut-off limit all four base radiomorphologic forms have very good sensitivity – above 90%. Stellate lesions have 99.8%, followed by microcalcifications and structural distortion with minimally lower scores, then the sensitivity of round lesions (91.3%). Raising the diagnostic limit minimally deteriorates the sensitivity of stellate lesions (to 97%) proving the very few false negative decisions in this subgroup. The value for microcalcifications has dropped to 78.5% and a furthermore decrease could have been noticed in the case of circumscribed lesions – 62.3% sensitivity at higher cut-off

level – and of structural distortion – 61.3%. These data prove that there is a relatively greater fraction of these lesions with indeterminate, non-specific radiomorphologic appearance, which finally turned out to be malignant. Stellate lesions have the highest PPV with only minimal increase on raising the cut-off level, showing that there was hardly any false positive stellate lesion. The lowest PPV value of microcalcifications (0.6157) can only be improved to 0.7260 when increasing the limit, showing the detrimental effect of too many false positive decisions.

Very interesting results could be seen if the sum score results were compared to that of mammographic diagnostics divided into groups based on breast pattern and the above mentioned radiomorphologic types.

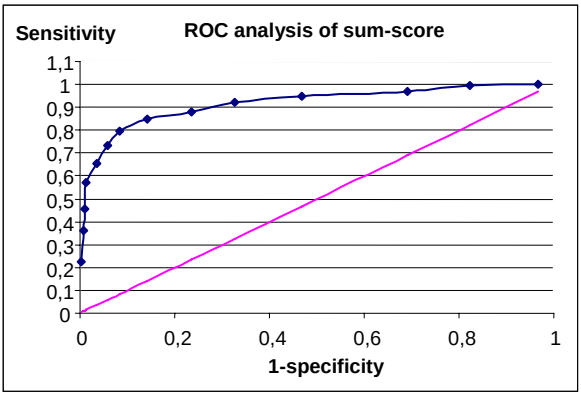

Fig. 1. Sum score ROC analysis

The sum score ROC curve shows that the combined result of the four diagnostic methods is quite good, the mathematical integral of the graph – which is the area under the curve (AUC) – is relatively big, which means good correlation between the preoperative diagnosis and the final histology.

Comparison of the sum score and mammographic results in the different breast pattern subgroups.

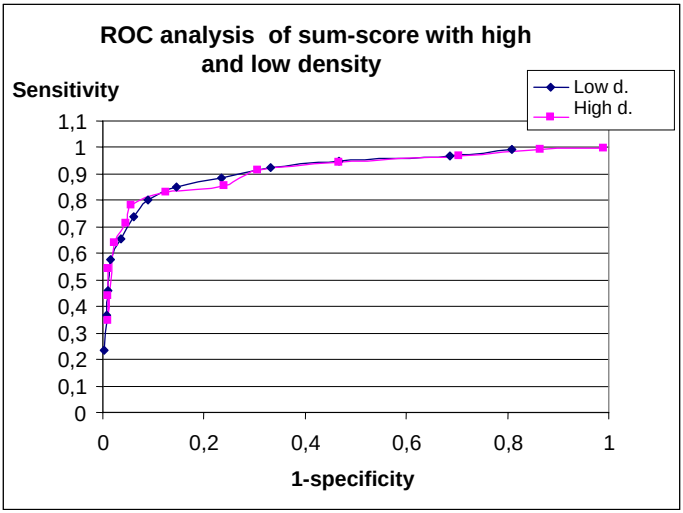

Fig. 2. Sum score ROC analysis grouped by breast pattern

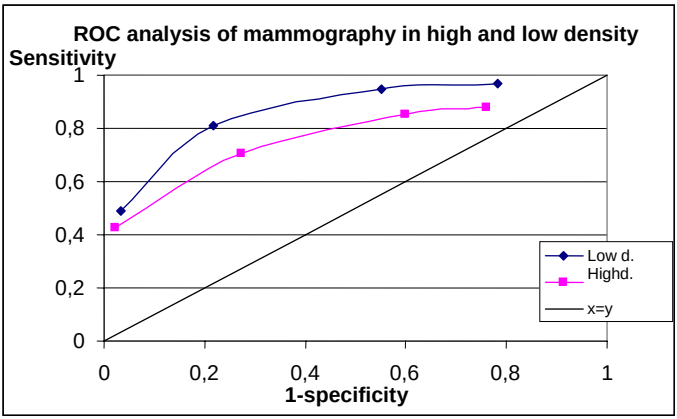

Fig. 3. R code ROC analysis grouped by breast pattern

Combining the two curves makes the difference between the ROC curves of mammography in the cases of low and high density breast patterns well noticeable, which was also proven by the numerical values. The marked difference in diagnostic efficacy is shown by the significantly smaller AUC of dense breasts compared to the low density curves, but the sum score curves lack the same kind of difference. So in the mammographically challenging, difficult to evaluate dense breast cases the other methods help to complete the complex decision.

Pathologic prognosis and diagnosis

2.1 Nottingham Prognostic Index and diagnosis

The report distribution of good, medium and bad prognosis NPI groups is significantly differs from each other when **age**

and diagnostics sum score is evaluated. **Mammography code and breast density distribution** is identical in these NPI groups, but there is a difference in terms of **radiomorphologic distribution**. There is significant difference among the NPI categories when **ultrasound** and **cytology reports** are in the limelight. There is no well defined trend in the ultrasound cases, C5 cytology is the most frequent in the worst prognosis group.The strongest significance can be noted in the distribution of the **physical examination** results

2.2 Diagnostic differences based on Ki-67 proliferation activity

Ki-67 positive (increased proliferation activity) cases were compared with negatives. There was no difference between them based on neither the sum score, nor the code distribution of the diagnostic methods. The only difference was noted based in breast density.Glandular and fibroadipose breast pattern can more frequently be seen in K-i67 positive cases, adipose structure is relatively rare. A radiomorphologic difference can also be noted: the proportion and the absolute number of stellate lesions is decreased compared with the usually infrequent circumscribed forms.

2.3 The good and bad **NPI** prognosis groups are mostly overlapping with the **Ki-67** positives and negatives

2.4 The subgroup of triple negative and basal carcinomas

Analyzing the score distribution of **both imaging modalities and cytology** both in the triple negative and in the basal carcinoma group malignancy was overrepresented with more certain diagnosis compared to all of the invasive cancers. The **radiomorphologic distribution** is also altered in relation to the group of all malignants: in the case of triple negative and basal carcinomas the proportion of stellate forms decreased whereas the circumscribed forms are more frequent.

3. Relations of hormone therapy, increase of density and breast cancer diagnostics

3.1 Can increased density be considered as an independent risk factor or it only makes diagnosis more difficult?

The proportion of type 2 adipose breast pattern is in correlation with **aging**, along with a decrease of the proportion of glandular pattern in both healthy population and in breasts with benign or malignant pathology. The proportion of type 4 and 5 dense breasts is unchanged and not related to aging, but more often associated with pathologic changes.

3.2 The rate of **mammographically occult tumors** is fourfold in very dense breasts compared to the low density pattern

population (12 vs. 3%). The rate of false negative malignancies is similar in all density classes.

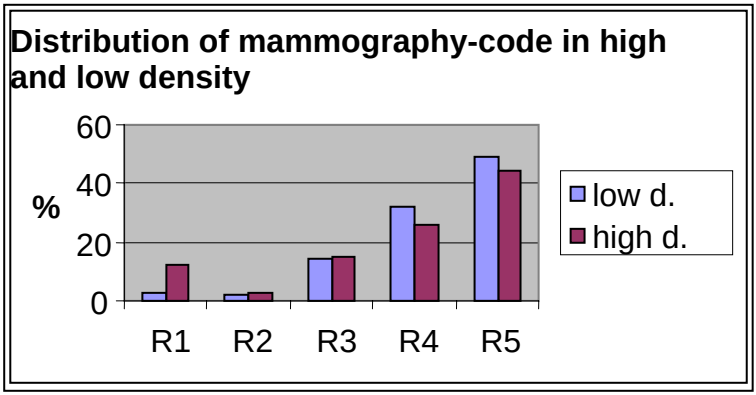

Fig. 9. Mammography description of malignancies in the different density groups

3.3 **Comparison of mammographic and histologic tumor size** showed that the mammographic underestimation of tumor size has the same likelihood both in the low (1,2,3) and in the high (4,5) density groups and even the classification into five separate groups would not change the results.

In the case of **multifocal tumors** the number of foci was correctly depicted by mammography in 80%, 82.4% in the low and 71.7% in the high density group.

While tumor size determination is independent of breast pattern, the number of foci can be set in low density breasts.

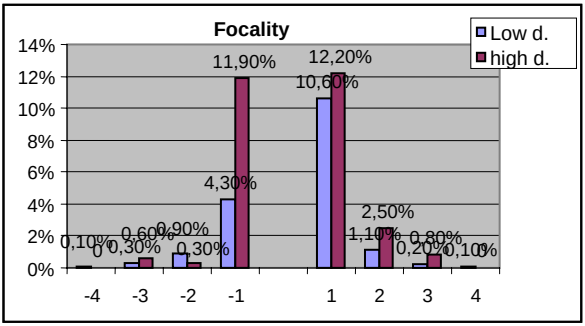

Fig 10. Different s in the numbers of pathologically and mammographically determined tumor foci according to density.

3.4 Comparison of the breast carcinomas of patients on prolonged peri- and postmenopausal combined hormone replacement therapy with age matched controls

The average tumor size in the treated group is minimally smaller, the proportion of <10 mm tumors is slightly higher.

Neither radiomorphologic distribution or nodal status, nor histology grade or steroid receptor positivity shows a trend towards treated patients. Though minimal differences can be noted, these are not significant and without fixed tendency.

Conclusions

-The results of all four diagnostics methods equal the figures known from the literature. Sensitivity slightly drops on raising the malignancy limit. In case of increased mammographic

density sensitivity, specificity, PPV and NPV values are inferior to that of low density breasts, but the combined sum score analysis of all four methods showed similar accuracy in the diagnosis of cancer in both high and low density breast, because the remaining modalities are completing the relatively bad results of the others. Based on radiomorphologic appearance the sensitivity of stellate lesions is the highest, round lesions have the lowest, but in this latter case the other modalities help, so sum score sensitivity is independent of morphology. Ultrasound, palpation and cytology are the least helpful in the cases of tumors appearing as microcalcifications.

Putting together the radiologic methods into the hands of one doctor and organizing them to a single occasion along with the close cooperation with the pathologist is crucial for this achievement.

New statements:

-The analysis of sum score and mammographic appearance proved significant results which are important for the evaluation of the connection of modern pathologic diagnostics and prognosis. -There are specific changes in the sum score and mammographic radiomorphologic distribution of the different prognostic groups according to NPI and the Ki-67 reaction.

-The triple negative and basal carcinomas which have the worst prognosis showed the most malignant signs in the case of all of our diagnostic tools and have appeared on mammography as indeterminate circumscribed lesions in increased density breast baseline pattern. The diagnostic results of these aggressive tumors are encouraging to look for further correlations between the preoperative diagnostics attributes, mammographic appearance and prognostic factors.

Breast cancers of patients on over 5 years of combined hormone replacement therapy were followed up for 10 years and were compared with patients with no medication to evaluate the connection of peri- and postmenopausal hormone replacement therapy and breast cancer, which became a controversial issue recently.

New statements:

- Hormone replacement therapy causes breast density increase, which decreases mammographic sensitivity, but this deficiency is made even by the other diagnostic methods.

-In these cases compared to low density breasts the probability of having a mammographically occult tumor is quadrupled.

-There is no significant difference in low or high density baseline breast parenchyma in the mammographic or histologic evaluation of tumor size, but exists in focality recognition.

-Increased density can more often be noticed – compared to normal population – in the case of either malignant or benign breast pathology. In the case of dense breasts it is worth completing the more difficult perception with adjuvant methods even in symptom and complaint free patients to diagnose the tumors.

-Within the scope of this study the diagnostics and clinicopathologic factors (radiomorphologic distribution, axillary node involvement, histologic grade, and hormone receptor positivity) were not significantly worse than that of hormone treated ones.

MRI is inherent part of modern breast diagnostics. It is used especially in the case of dense breasts to evaluate multifocality and tumor size. The kinetic studies and the even higher sensitivity and specificity of MR spectroscopy will complete the current methods.

These results encourage us to seek for further correlations between modern histologic prognostics and the routine breast diagnostics, especially in the case of specific subgroups of mammographic forms, like malignant microcalcifications.

List of own publications

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