

Reader-Independent Classification of Malignant and Benign Breast Lesions Based on Delayed ICG Washout Kinetics

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Abstract: Based on high frame-rate absorption changes after ICG bolus administration in suspicious lesion bearing breasts, a reader-independent, linear discrimination model is derived for discriminating between malignant and benign lesions.

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1. Introduction

We conducted a contrast-enhanced optical mammography study using ICG as a blood pool agent and demonstrated the benefit of high-frame rate absorption tomography [1]. With some post processing effort we were able to demonstrate a significant difference between malignant and benign lesion bearing breast based on the non-invasively measured and reconstructed early ICG bolus kinetics [1]. In this report, we utilize machine learning methods as know from online data classification such as Brain-Computer-Interfaces [2] and use the raw detector readings instead of the reconstructed tomographic datasets to automatically differentiate malignant from benign lesions bearing breast. This approach focuses on temporal absorption changes throughout the whole breast without demanding any a priori information on the spatial distribution of lesions.

2. Methods

Optical Mammography scans were carried out with a DYNOT 232 optical tomography system (NIRx Medical Technologies LLC, NY, USA) customized for mammography studies as described in detail in [6]. Subjects were scanned in the prone position on a modified patient bed with an opening and an adjustable gantry below holding a rigid plastic cup with 31 co-located source and detector fibers. Varying the protrusion of the fibers into the cup allowed accommodation to different breast sizes and assured good contact between the breast tissue and fiber sensors. The imager performs sequential illumination with 760 nm and 830 nm at each fiber position while simultaneously acquiring detector readings for each illumination site, resulting in a total of 961 measurements at a rate of approx. 2 Hz. Total recording time was over 2000 frames corresponding to about 20 minutes. Following an initial 5 min resting phase, a single bolus of 25 mg ICG (Pulsion AG, Munich, Germany) dissolved in 15 ml *aqua ad injectionem* was injected (injection time: 5 sec), followed by a 15 ml saline solution.

The study was approved by the hospital's ethics committee and all patients gave written informed consent. We recruited 30 patients of the radiology clinics who had a high probability for breast occupying lesions and who were scheduled for needle biopsy. Furthermore, we measured 4 healthy controls. Due to bad signal quality, 7 datasets had to be excluded from any further processing. Overall 16 breasts bearing a malignant lesion, 8 breasts bearing a benign lesion and 3 healthy controls were analyzed. Healthy controls were also labelled "benign" in the classification process.

All processing was done with customized routines using MATLAB (The Mathworks, Inc., Natick, MA). For each subject, we used the mean over all 961 raw detector readings of the 760 nm wavelength illumination channel, which is more sensitive to ICG than 820 nm illumination channel. To rule out differences in overall blood circulation between subjects the reference timepoint ($t_0=0$) was set to bolus onset in the breast, selected manually in the raw data. We extracted the time interval from 25 sec before to 600 sec after bolus onset, corresponding to 1250 acquisition frames. All channels were band-pass filtered (0.001 - 0.075 Hz), baseline subtracted (20 sec before bolus onset) and then normalized to the minimum of the mean time course, which corresponds to the maximum signal change due to ICG administration.

The median time courses over all benign and malignant cases are shown in Fig.1. Furthermore, we calculated the standardized mean difference (SMD) between both groups at each time-point. SMD is defined as the difference of the means for two different groups divided by the pooled standard deviation [1] and is commonly used in

practical meta-analysis. The greatest difference in ICG absorption between the two groups is reached when the absolute value of the SMD is maximal.

For the main analysis, the time information was windowed with a window size of 25 seconds, 50% overlap, and starting 12.5 sec before t_0 . The non-parametric Mann-Whitney U-test was applied to test whether the distributions of mean signal amplitude in each window for all malignant and benign datasets come from distributions with equal medians. This was tested in all 51 time windows. A Bonferroni corrected p-value of $p < 0.05/51$ was considered significant to reject the null hypothesis of equal medians. For each subject, the mean time course over all measurement channels within each time window was taken as features for cross-validation. The classifier used was a linear discriminant analysis (LDA) with shrinkage (RLDAshrink). Shrinkage is a common remedy for compensating the systematic bias [3, 4]. The loss function used was the area under the ROC curve [5]. The cross-validation splits were set such, that in each of the folds the training set consisted of all subjects, except the one to be tested. This procedure is generally called 'leave-one-subject-out' cross-validation. The errors of each fold (i.e. each subject) are then averaged and displayed in the lower part of Figure 1. By estimating and testing this model for each subject individually it is ensured that only data of other subjects is used. The shown results therefore generalize to unseen subjects. Finally, sensitivity and specificity were derived for all classification outcomes.

3. Results and discussion

Fig. 1 summarizes the results. Although the median time courses of relative signal changes after ICG bolus administration seem quite similar over all malignant and benign subjects, the standardized mean difference and furthermore the Mann-Whitney-U test reveal a clear difference between malignant and benign breasts in the late washout phase 200-400 sec after bolus onset in the breast, which is largest and significant at about 300 sec. Crossvalidating the mean time courses in each 25 sec time window results in a mean test loss that follows the same trend over time, with a minimum of 6.8% at 300 – 325 sec after bolus onset. Within this time window, 14 out of 16 malignant cases and 10 out of 11 benign cases are classified correctly, corresponding to a sensitivity and specificity of 87.5% and 90.9% respectively.

A delayed washout of ICG might result from the abnormal vascular architecture of neoangiogenic vessels in malignant tumors which are disorganized, functionally abnormal, and hyperpermeable [6]. As ICG binds to macromolecules like albumin, α -1-lipoproteins and β -1-lipoproteins [7], it acts as a macromolecular contrast agent on different timescales. While during early enhancement, tissue concentration contrast is determined by intravascular contributions [8], increased capillary permeability in tumorous tissue also leads to extravasation of ICG which has been proven feasible for tumor detection and discrimination [9]. Furthermore, our results are in line with Schmitz et al. [10] who evaluated delayed return to baseline following a Valsalva breathing maneuver for identifying malignant breast lesions.

4. Conclusion

By measuring ICG enhancement following bolus injection with high-frame rate optical imaging, our approach allows a fast reader-independent differentiation between malignant and benign breast lesions. The algorithm is very promising especially because no reconstruction or time-consuming post-processing is required. The trained classifier could readily be used for online classification and thus be applied as a diagnostic tool adjunct to x-ray mammography or fMRI. To further investigate the robustness of the suggested approach more patient data would be desirable.

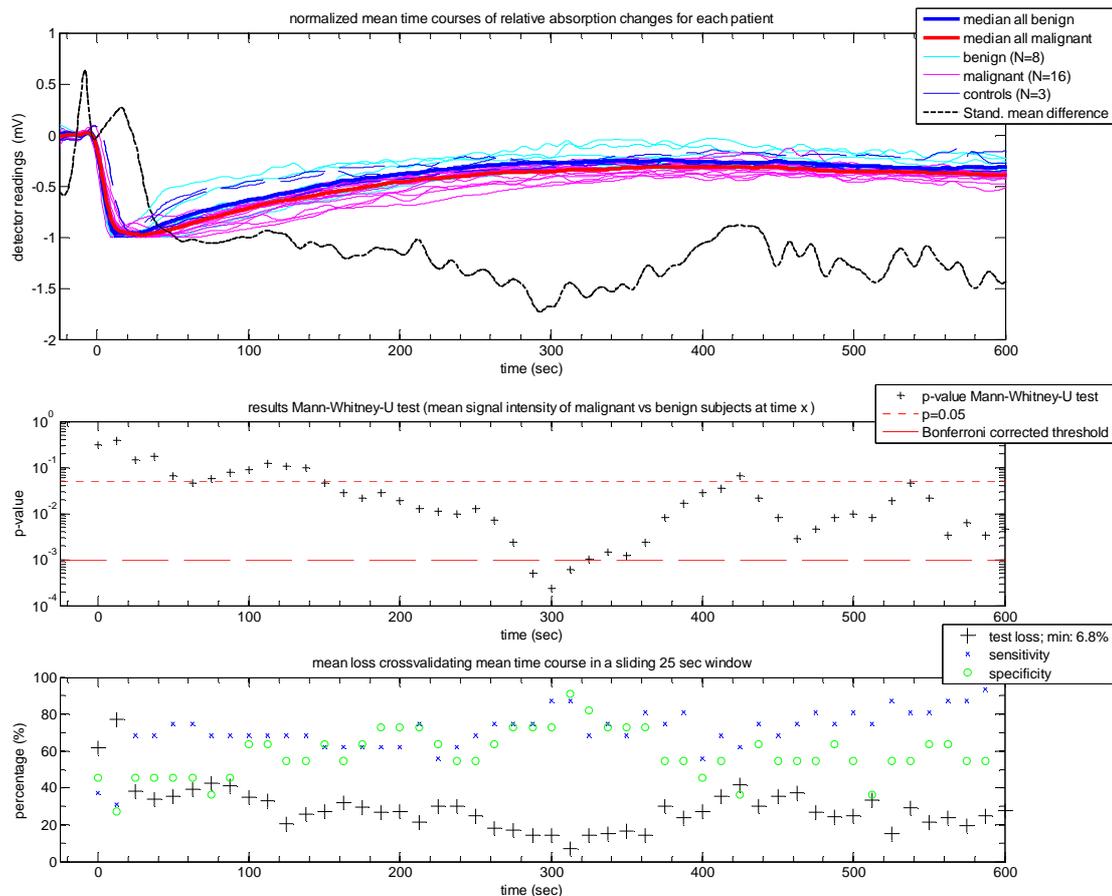


Fig.1 Results. Top row: Median and individual time courses of mean signal changes after ICG bolus administration. Middle row: p-values of the Mann-Whitney-U test, uncorrected and Bonferroni-corrected significance level. Here, for each time point, the mean signal over all 961 measurement channels of all malignant and all benign cases was tested for 1200 time points after bolus onset. Bottom row: mean test loss crossvalidating the mean time courses in each 25 sec time window centered around the given time point x and the corresponding sensitivity and specificity values.

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