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A software prototype for the Assessment of Tumor Treatment Response using diffusion and perfusion MR imaging*

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Abstract—**Advanced MRI techniques including diffusion and perfusion weighted imaging, has the potential to provide early surrogate biomarkers to detect, characterize and assess treatment response of tumors. However, the widely accepted Response Evaluation Criteria in Solid Tumors (RECIST) are still considered as the gold standard for the evaluation of treatment response in solid tumors, even if according to recent studies RECIST seem to disregard the extent of necrosis, which is the target of all effective locoregional therapies. This is partly due to the fact that measurements of tumor size aren't the best criterion for assessing actual early response. On the other hand, more sophisticated techniques such as the Apparent Diffusion Coefficient (ADC) and perfusion parameters are usually processed manually and evaluated independently using commercial CAD software, not widely available. In this paper we present an open access extensible software platform providing both diffusion and perfusion analysis in a single, user friendly environment that allows the radiologist to easily and objectively evaluate tumor response to therapy.**

I. Introduction

Cancer is a remarkable disease that involves intractable neoplastic growth, invasion of surrounding tissue and metastasis mechanisms. The widely accepted response Evaluation Criteria in Solid Tumors (RECIST) criteria [1][2] have been introduced to unify therapy response assessment criteria with the goal to assist the definition of evaluable lesions and to enable the use of new imaging technologies (multi-slice CT and MRI). The RECIST documentation also makes specific recommendations on the usage of imaging techniques and protocols (particularly CT) are detailed. It is important to note however that the RECIST criteria largely rely on changes of lesion size to make response assessments despite many recognized limitations of using the size as a tumor response variable. Besides being a laborious process for the clinicians to measure e.g. the % change of the longest diameter of target lesions over time, this process is prone to error while it doesn't take into consideration the underlying change of the tumor composition (e.g. liquefaction due to response to treatment without apparent change in tumor size). This paper presents a multi-modality image analysis environment that can also handle new modalities, such as diffusion weighted imaging (DWI) and perfusion weighted imaging (PWI), in order to assist the clinician to extract more objective information for assessing the early response of the patient. Quantitative Analysis of Diffusion Weighted Images (DWI) using different b values is possible by calculating the apparent diffusion coefficient (ADC)." b values" notation is used in clinical MR scanners to map to different settings of gradient amplitude that actually vary the sensitivity of the DWI sequence to water motion. The ADC is calculated mathematically by fitting a decaying exponential function of the form $S_i = S_o\ e^{-bD}$ to the signal intensity on the y-axis against the b values on the x-axis, where S_i is the signal intensity of a given pixel; S_o is the signal intensity of a given pixel without diffusion sensitization; e is the base of the natural logarithm; b is the attenuation coefficient (mm^2/s); and D is the diffusion rate constant for the given pixel (s/mm^2). One of the most intriguing findings associated with the use of DWI in cancer patients has been that ADC measurements appear to be able to predict tumor response to chemotherapy and radiation treatment. Studies in breast carcinoma [3] have also shown that an early increase in the ADC after commencing treatment was predictive of better treatment outcome. In [3] it was shown that an increase in the ADC within 1 week of initiating treatment was predictive of at least a partial response, with response being defined by tumor size reduction at the end of therapy. The increase in the ADC preceded any reduction in tumor size. The use of ADC to evaluate and predict response has also been assessed in a number of animal studies [4].

The ultimate goal of perfusion weighted imaging is to measure or assess a number of heamodynamic parameters including blood flow (usually in the brain), expressed in milliliters per 100 gram of tissue per minute. This flow corresponds to microcirculatory tissue perfusion rather than the main vascular axes. To perform a PWI study a bolus injection of gadolinium is performed simultaneously with the acquisition of dynamic data sets. There are two different types of perfusion experiments: i) T2 or T2* perfusion and ii) T1 perfusion. The pulse sequences that are utilized for dynamic acquisitions should be fast to permit high temporal resolution. Gadolinium is known for its magnetic susceptibility effect at high concentration which leads to a decrease in the measured T2 and T2* due to the induced magnetic field inhomogeneities. The measured signal reduction during the first pass of the contrast agent depends on its vessel concentration, the number and diameter of vessels per volume unit, and the type of signal weighting. Usually the microvascular elements are more concerned and to this end T2-weighted sequences are used instead of T2* which also take into account larger vessels. Based on the

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measurements critical cancer imaging parameters such as the regional cerebral blood volume (RCBV) and blood flow (RCBF) can be estimated [5].

Manual delineations of suspicious lesions is routinely used as the gold standard (e.g. in the RECIST criteria) but it is time consuming, observer dependent and in some difficult cases prone to error (e.g. distributed timorous areas with low image contrast). Also, early response to therapy may involve change in tumor composition (necrosis, liquefaction) without apparent tumor size change. This paper presents an integrated tool that can analyze multi-modality data including MR diffusion or perfusion data, in order to assist the radiologist/clinician in diminishing the time consuming and highly subjective process of manually assessing tumor response based on the RECIST, as well as allow him/ her to take into consideration quantitative information from ADC/ perfusion data in assessing patient response. This integrated tool has the potential of examining cancer under a global prism that consolidates crucial information also from diffusion and perfusion techniques.

This paper focuses on the platform architecture and the proposed response assessment workflow (Section II) that deals with image handling, tumor delineation and treatment evaluation. Assessment of therapy response and tumor progression in some indicative real clinical cases is described in section III.

II. DR EYE PLATFORM

A. System architecture

The presented platform is built on three fundamental modules (the "Core Module", the "Plug-in Module" and the "3D Visualization Module" [6]). The Core Module represents the basic functionality of the platform which includes the intuitive graphical user interface, the multi-modal DICOM image handling and processing tools, the tools for creating and controlling of multilayered annotations and a variety of build in methods (necessary for the platform's functionality). The Plug-in Module supports platforms‘ unique extensibility features, rendering it as the solid foundation for both in house (Core available plugins) and third party (third party plugins) algorithm development. Finally, the 3D Visualization module is based on the Visualization Toolkit (VTK), which provides 3D reconstruction and visualization of the annotations and simulations provided by the aforementioned modules.

The main advantage of the proposed architecture is that the clinician can perform a number of diverse tasks that would require transferring intermediate results/data, in a single platform. The user quickly and accurately delineates cancer related regions of interest from multi-modal imaging data and adds multiple labels to annotate and manage many different areas of interest in each selected slide. The close collaboration with clinicians in designing the platform has ensured that it has the potential to be used in the clinical setting [8] or as an “in-silico oncology” research tool [9][10]. Based on this architecture, the different technologies concerning cancer image analysis and modeling developed by our group are currently being integrated in a platform called Dr. Eye (available at http://biomodeling.ics.forth.gr/) [6][7][8], a novel, open access and easy to use platform, for intuitive annotation and/ or segmentation, visualization and growth simulation of tumors. Its development is clinically driven and adopts a modular structure with an open architecture allowing the deployment of plug-in modules from third developers. This is achieved by the use of the reflection feature of the Microsoft .NET framework. Each plug-in is an "assembly", a special type of dynamic-link library (DLL) with the ability to describe itself and the types that are defined in it, due to the fact that all the necessary information are contained internally as metadata. The reflection feature allows the developer to get information from the assemblies about the contained types, their members, their accessibility, attributes and so more. Thus one can use the platform as the primary step, and main interface, in order to create a new plug-in. That way the developer takes advantage the rich and user-friendly capabilities of the platform while simultaneously the platform gains a new feature.

Both Diffusion and Perfusion analysis modules have been implemented as separate plug-in modules to enable assisted therapy decision-making.

B. Workflow

The DrEye software can assist the decision support regarding patient response through a semi-automatic strategy that involves well know procedures such as 3D image registration, segmentation, as well as more specific ones tailored for the needs of diffusion/perfusion data.

The patient response assessment workflow starts with multi-modal images within and between two treatment studies being aligned with a deformable registration and tumor being delineated with an interactive technique [7]. Annotations can be compared, subtracted or unified between different modalities annotations regarding the same patient examination in order to optimize tumor delineation (e.g. exclude edematous, necrotic tissue). The user can then compute tumor volumetric data including tumor volume, surface, RECIST diameter, 3D longest diameter, as well as to assess ADC and perfusion changes in the tumorous area.

Dr Eye offers several services that allow the comparison of pre and post therapy patient data including 1D/2D histogram plots of annotated tumor regions (in the 2D case one can observe e.g. the joint distribution of pre and post therapy ADC tumor values), fusion services (e.g. color CE maps overlaid in T1), statistical comparison of annotated regions (median, mean, skewness, kurtosis, sensitivity/ specificity, mismatch statistics etc.) and 3D visualization of multi-modally annotated tumors.

Some of the most important patient response assessment workflow Dr. Eye elements are now described:

1) Data Import

Patient DICOM data is imported into the platform either manually as files or via a DICOM server connection. DICOM headers are used to correctly identify and utilize the perfusion sequence images.

2) Co-registration

Although image registration is a built-in feature in Dr. Eye, it was not used in the presented case. Actually, there is a wide consensus regarding the validity of the results after applying co-registration in case only quantitative analysis is

needed especially in the non-rigid case where image volume can change. The differential histogram analysis is independent from the spatial registration of the pre and post-therapy ADC maps. In addition, perfusion MR sequence images were nearly free from motion artifacts and no further post-processing was necessary.

3) Tumor delineation:

Tumor segmentation may be performed using various different algorithms implemented in the platform (e.g. user adaptive Magic Wand, active contours, etc. [7]). In our case we used the Magic Wand algorithm [7] that is based on finding and selecting all the pixels around a pre-specified user-selected initial point that are similar in gray intensity. A tolerance value can be specified by the user to determine how closely to match colors (higher tolerance ends up in a larger selection). All the points selected by the algorithm are automatically stored in an image mask of the same size as the original image. To improve segmentation accuracy the B1000 diffusion image was used as a reference and the semi-automatic segmentation results were manually corrected form an expert radiologist. The selected ROIs were automatically copied to the actual ADC maps. Subsequent segmentation was performed in both pre and post treatment images.

4) ADC histogram analysis

Once the images are registered and segmented, histogram calculations are performed on the ADC maps of pre- and post-treatment studies. Specifically, histogram distribution of ADC values are generated for both studies after tumor volume segmentation and the results are displayed in a superimposed way for easiness in assessing any volume changes (Fig. 1). Quantitative analysis is also provided including several statistical measures (mean, standard deviation, skewness, kurtosis, etc.).

5) Angiomap-based analysis

Depending on the shape of the contrast enhancement (CE) curve calculated from the perfusion images, an angiomap can be reconstructed. In this parametric color map the percentage difference between the arterial peak dynamic scan and the last dynamic scan (in terms of in signal intensities) is calculated and illustrated using three different colors corresponding to the three different contrast enhancement curve types. Type I or progressive enhancement is rendered with blue color, type II or plateau enhancement with green color and type III or wash out with red color. Since wash out is typical for malignant lesions, the radiologist can easily identify the suspicious areas.

6) Visualization

Three dimensional models of various classifications can be reconstructed while the volume of each individual classification is calculated together with the total lesion volume. Type I, II and III volume types are represented as a percent of the total volume to indicate different pathological components.

III. Assessment of Response and Progression

A. Patient history information

A 40-years-old patient with high suspicion of malignant lesion from conventional mammography underwent MR mammography and an infiltrative ductal carcinoma was

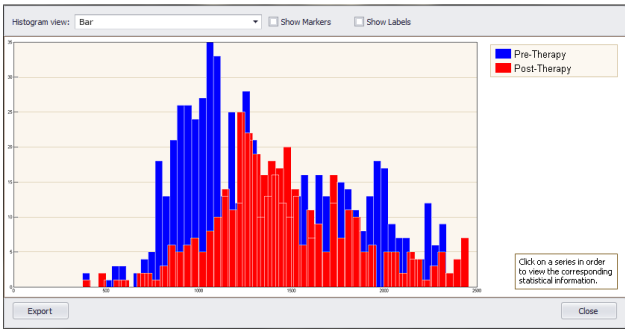

Figure 1. Overlay histogram distributions depict ADC changes that reflect tumor response. Different colors are used to label Pre (blue) and Post-Therapy (red) histograms.

detected. The patient received chemotherapy and a follow up MR Mammography study was conducted two months later. The study was HIPAA compliant with all patient identifiers removed before data interpretation and informed consent was waived.

B. Breast imaging protocol

All imaging experiments were conducted on a 1.5T MR scanner (MAGNETOM Avanto, Siemens Healthcare), equipped with strong gradients (gradient amplitude 40 mT/m and slew rate 200 mT/m/s). A dedicated 4 channels breast matrix coil was used while the examination protocol comprised of diffusion weighted spin echo - echo planar imaging sequence with 4 b values (0, 200, 600 and 1000), a dynamic FLASH sequence with fat suppression and 6 dynamic scans with a temporal resolution of 68 secs. In addition T2 weighted TSE and STIR sequences were applied.

IV. Results & Discussion

A retrospective assessment was performed on one indicative clinical case (described in III-A) using both perfusion (IV-A) and diffusion (IV-B) imaging data under the proposed unified analysis environment.

TABLE I
ADC-based Analysis Pre-/ Post Treatment Tumor Assessment (Absolute/ Relative Volume Change wrt Total Volume)

ADC range	Pre-Therapy Mean ± std Volume (cm^3)	Post-Therapy Mean ± std Volume (cm^3)	Change Volume (%)
Low (301-1000)	859±116 6.038cm^3	824±156 1.480cm^3	↓ 75.489%
Moderate (1001-1500)	1205±138 10.241cm^3	1287±129 7.440cm^3	↓ 27.351%
High (1501-4000)	1868±230 9.588cm^3	1871±274 5.680cm^3	↓ 40.759%
Total Volume	1370±441 25.867cm^3	1467±402 14.600cm^3	↓ 43.557%

A. ADC analysis results

ADC is able to yield ultrastructural information on cellular density and properties of the extracellular matrix, linked to lesion aggressiveness and tumor response [11]. In a large extracellular volume, which may be caused by fluid

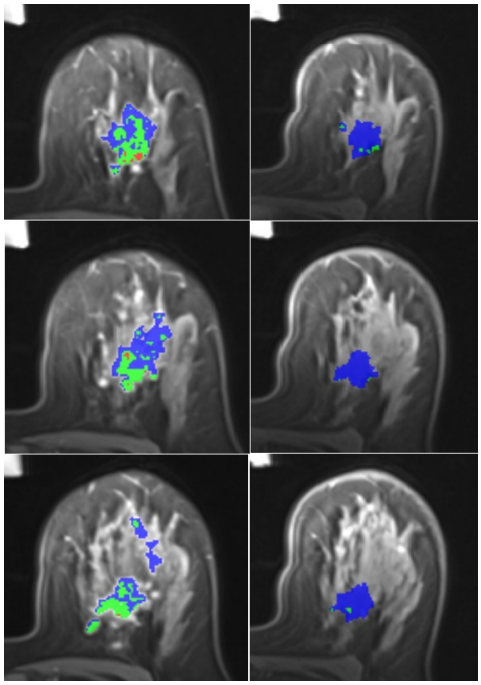

Figure 2. Angio-map of three representative slides depicting Pre-therapy (left side) and Post –therapy maps (right side). There is a significant transformation in terms of contrast enhancement curve types from Type II to Type I in the post therapeutic angiomap that is compatible with tumor response. (Type I is shown with blue color, type II with green and type III with red color.)

accumulation, as in a tumor edema, is high. In contrast, hypercellularity (compact tumor cells) restricts diffusion by decreasing the extracellular volume, thus, giving low ADC values. Figure 1 illustrates change in tumor histogram intensity values before and after treatment. As shown in Table I, there is a significant reduction (75.5%) of tumor areas exhibiting low ADC values that are compatible with hypercellular aggressive tumor areas. This is a strong sign of response to therapy. In addition, the total lesion volume was reduced approximately 43%. Hence, apart from the typical RECIST volume based measurements ADC histograms may be used as an early predictive biomarker for both vascular disruptive drugs and apoptosis-inducing therapies [12][13].

B. Angiomap-based analysis results

Figure 2 reflects a significant transformation in terms of contrast enhancement curve types from Type II (Plateau) to Type I (Persistent) in the post therapeutic Angiomap that is compatible with tumor response. Perfusion analysis revealed a significant increase (95.5%) in the number of tumor pixels that presented with persistent enhancement curve (type I) that is mostly indicative of benign tissues. The same analysis showed a significant reduction in the tumor pixels exhibiting plateau enhancement (type II) and complete elimination of areas with wash out effects (type III). All these findings support the conclusion of diffusion analysis that the tumor is responding to the chemotherapy scheme that was applied to this patient.

V. CONCLUSION

The presented open-access software provides integrated multimodal functionalities for assessment of treatment response based on both perfusion and diffusion MR image analysis. As the presented cases illustrate, ADC and perfusion based Angiomaps may well advance some of the drawbacks of current criteria for the assessment of response to treatment providing more quantitative indicators in a clinical setting and may well be used as early predictive biomarkers for assessing therapy response.

TABLE II
PRE-/ POST TREATMENT TUMOR ASSESSMENT
(ABSOLUTE/ RELATIVE VOLUME CHANGE WRT TOTAL VOLUME)

Type	Pre-Therapy Absolute (cm^3) Relative (%)	Post-Therapy Absolute (cm^3) Relative (%)	Change Absolute (cm^3) Relative (%)
Persistent (Type I)	2.610 cm^3 56.16 %	2.653 cm^3 96.42 %	↑ 0.043 cm^3 ↑ 95.42 %
Plateau (Type II)	1.969 cm^3 42.34 %	0.098 cm^3 3.58 %	↓ 1.871 cm^3 ↓ 91.54 %
Wash-Out (Type III)	0.069 cm^3 1.5 %	0.000 cm^3 0 %	↓ 0.069 cm^3 ↓ 100%
Total Volume	4.648 cm^3 100 %	2.751 cm^3 100 %	↓ 1.897 cm^3 ↓ 40.813 %

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