Detecting tumor response to therapy with automated analysis of contrast-enhanced ultrasound

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To grow beyond 3 mm, a tumor requires the development of new blood vessels (angiogenesis) to sustain their accelerated proliferation and metabolic rates. Tumor cells release vascular endothelial growth factor (VEGF) to stimulate angiogenesis, but the excessive levels of VEGF released cause the new vasculature to develop irregularly in both structure and functionality. Tumor vasculature has become a popular target for chemotherapeutics, particularly in combinatorial therapy. Their effect on tumor vessels, which occurs within hours to days, is difficult to detect with CT or MRI. Contrast-enhanced ultrasound (CEUS) has the ability to image functional capillaries because it can detect intravenously injected micron-sized bubbles contrast agents that remain intravascular and have a nonlinear response to ultrasound, allowing contrast specific imaging. CEUS has the added advantage of being inexpensive, safe, and can be done repeatedly at the bedside. Since the imaging signal received from CEUS is proportional to the concentration of microbubbles, real time imaging with CEUS produces a time-intensity curve (TIC) which can be analyzed to measure parameters associated with perfusion kinetics, e.g., blood flow rate and volume. The scientific literature shows that quantitative analysis of CEUS can be employed to monitor tumor response to therapy. The goal of this project is to develop computational algorithms that analyze CEUS videos to characterize and quantify tumor perfusion in order to detect the time of peak tumor response to treatment to enable optimized and personalized treatment regimen. Patients enrolled in an ongoing therapeutic trial at UC San Diego were imaged with simultaneous B-mode and contrast specific imaging using the GE Logiq E9 ultrasound system. Patients were imaged pre- and several times during 7 days post-treatment. A 0.2ml bolus injection of Definity, a commercial microbubble-based agent approved for cardiac imaging, was injected intravenously followed by 5ml saline flush as the tumor was being imaged in real-time. The video captured the arrival, equilibration, and washout of the agent over three minutes. Sophisticated software-based image processing and quantitative analysis techniques were implemented to measure several intensity-based and time-based perfusion parameters on a pixel-by-pixel basis and display them as a color heatmap for easy interpretation, as described below. In comparison to pre-clinical animal studies, motion is a major limiting factor for quantitative analysis of clinical CEUS cines. To reduce the impact of motion on pixel-based measurements, an affine image registration technique was applied to correct in-plane motion throughout each CEUS video. Rather than registering all frames sequentially or arbitrarily choosing a single reference frame as is common in literature, a unique image registration system was developed that optimally chose reference frames and hierarchically performed the image registration steps. These additional steps ensured a reference frame with maximal correspondence to the entire cine and minimized error propagation. Since CEUS is a 2D imaging modality and image registration techniques can only correct motion within the imaging plane, through-plane motion can still distort results. Following motion correction, an optimal reference frame was selected again, and its correlation with all other frames were calculated. After high-pass filtering the correlation curve to remove low frequency baseline shifts (motion) while maintaining high frequency fluctuations (breathing), a global threshold was applied to adaptively maintain the in-phase frames of each respiratory cycle. A region of interest (ROI) was manually drawn around the viable perimeter of the tumor. The contrast specific image was linearized to the echo power of the ultrasound signal, the signal within the tumor ROI was averaged for each frame, and the signal was low-pass filtered over time to eliminate noise spikes, producing the ROI TIC. Several
measurements were made from the ROI TIC for use in the pixel-based analysis, including baseline intensity (I0), baseline time (T0), peak intensity (Ipeak), and peak time (Tpeak). The videos were then processed on a pixel-by-pixel basis to produce color heatmaps and intensity profile plots. Two sets of heatmaps show time of arrival (TOA) of the contrast agent: the time it took for the first microbubbles to reach each pixel within the image relative to T0. These images showed how fast blood was delivered to localized areas within the tumor. One TOA heatmap was measured as the time when each pixel crossed 80% of the peak intensity of the ROI TIC, and in the other, it was when each pixel crossed 80% of the peak intensity of its own pixel TIC. In another pair of heatmaps, the wash out time (WOT) of the contrast agent was displayed, that is, the time it took for the last microbubbles to leave each pixel within the image relative to Tpeak. These images showed how fast blood was cleared from localized areas within the tumor. These two heatmaps measured the WOT as the time point when each pixel dropped below either 50% of the ROI peak intensity or 50% of its own peak intensity. The last pair of heatmaps showed full-width at half-max (FWHM) information -- a measure of the total amount of time each pixel stayed enhanced. The FWHM was measured as the total amount of time each pixel remained above either the half max of either the ROI TIC or 50% of its own peak intensity. The colormaps of each image type were held constant across study time points. The intensity profile plots showed the mean intensity across the long axis of the tumor at multiple time points within each cine, including wash-in, peak enhancement, and wash-out. These plots allow observers to easily identify differences in tumor behavior between the edge and center of the tumor. Our analysis detected that this therapeutic agent induced a faster contrast arrival time and slower washout time at 3 and 6 hours compared to baseline, and this effect was different at the tumor center as compared to the edge (Fig. 2). The pixel-by-pixel heatmap display allowed the detection of geographical changes that would be missed by global time-intensity analyses as is currently done.