

Meeting Minutes: Proposed Joint AIUM TSC/QIBA Biomarkers Subcommittee Biomarker Recommendation, Discussion and Possible Selection

Tuesday, March 24, 2015, 10:30 am - 12:45 pm ET, Room: Europe 4

AIUM/WFUMB Meeting, Disney Swan and Dolphin Hotel

Minutes taken by Keith Wear

- Invited: TSC Members or Representatives, QIBA US Coordinating Committee, and invited content experts
- Purpose: To initiate selection of a quantitative imaging technology and the clinical target to recommend for a joint QIBA/AIUM effort to develop a quantitative ultrasound imaging biomarker profile.
- Chairs: Drs. Tim Hall, Chair, QIBA Ultrasound Coordinating Committee, and Brian Garra, Vice Chair, AIUM Technical Standards Committee and Vice Chair, QIBA Ultrasound Coordinating Committee

1. Participants were encouraged to attend the following meetings:

- Technical Standards Committee Meeting, Saturday, March 21st:
 - Disney Swan and Dolphin Hotel, Room Europe 1, Dolphin Lobby Level 3.
- Quantitative Ultrasound - Sunday, March 22nd, 1:00 – 3:00 PM:
 - Room Southern Hemisphere IV
- Quantitative Imaging Biomarker Development, Tuesday, March 24th, 8:15 – 10:15:
 - Room Northern Hemisphere E, 3-4.
 - These sessions are summarized in Addenda 1 and 2.
 - It was assumed most have attended these two sessions.

Score sheets were distributed to participants. They were asked to score all of the biomarker candidates prior to presentations.

2. Summary discussion of pros and cons of the various biomarker technologies and targets discussed in the above mentioned quantitative US sessions.

First topic: Liver Tumor Volume Estimation (Brian Garra). Clinically important. Examples: HCC, CRC. There are 1.2 million new cases of CRC per year (USA – 137 k/yr). There are 560k new HCC cases per year (USA – 36k/yr). Size estimates are needed to monitor tumor progression and response to therapy. The techniques developed here can be applied to other organs: kidney, cardiac, uterus, thyroid, IMT. Reliable US measurement would lower costs compared to CT and MRI. Ultrasound is the only option for resource-poor countries worldwide. Volume estimation is feasible because the methods are known and just need refining and standardization. Jon Rubin: we have trouble visualizing lesions with B-mode. Other organs might be better biomarker choices because of the difficulty of visualizing liver lesions. Jonathan Rubin believes that size criteria are not that important relative to other criteria such as flow.

Second topic: Contrast agents for using changes in sub harmonic amplitudes in order to measure blood pressure (Flemming Forsberg). SHAPE: Sub harmonic Aided Pressure Estimation. Pressure measurement has been studied at 4 institutions. Pressure waveforms measured with SHAPE and with catheters line up very well in large? animals. SHAPE is a useful

screening tool for portal hypertension. There are about 83 million Americans suffering from more than one type of cardiovascular disease, with 78 million Americans having high blood pressure and 15.4 million Americans having coronary heart diseases. About 500,000 new cases of heart failure are diagnosed each year in the USA and ten times that number of Americans is currently affected by heart failure.

There is more variability at normal blood pressures than with the four human cases of high blood pressures. (True in large animals?) The reason for this variability is unknown. Current methods for diagnosing hypertension are limited – counting platelets, measuring spleen size. Jonathan Rubin believes that SHAPE could be the “magic bullet” for ultrasound contrast agents. Biomarker would be difference between hepatic vein (HV) and portal vein (PV) pressures. There is a paper in *Ultrasonics* (2012) that describes the method. There is some variation among different contrast agents, but (according to Forsberg) they all work well.

A downside is trouble getting contrast agents approved for non-cardiac indications by the FDA. Forsberg currently has FDA-approved IND for SHAPE using Sonazoid. IND's can be amended if protocols are modified. This method could be applied to all patients with cirrhosis. Cirrhosis by itself won't kill you, but cirrhosis plus portal hypertension is far more dangerous. This would have a huge constituency including radiologists, hepatologists, and gastroenterologists. Forsberg argues that there would be little dependence on contrast agents because of the relative calibration measurement (HV vs. PV).

Third topic: “Sub-resolution Structure” High frequency ultrasound (Jonathan Mamou). High frequency ultrasound can be used to detect cancer in lymph nodes. Clinical results indicate good results in colorectal, gastric, and breast. 301 lymph nodes from 171 patients have been classified. Detection of colorectal and gastric cancer metastases is almost perfect. Detection of breast cancer metastases is quite good. The most important parameter for classification is scatterer size. This method produces images of cancer probability. This method uses multi-feature classifiers. This method can guide pathologists to suspicious regions. Pathologists don't have time to scan an entire tissue sample, so an imaging method to guide them to suspicious regions would be helpful.

Richard Barr questioned the clinical utility in breast because patients get radiation treatment even when pathology is negative, in breast. However, breast is only one potential application. The next step is to move to lower frequencies to use for gross surgical specimens. One potential problem is the effects of phase aberration. Backscatter coefficient analysis has been used to measure glomerular size *in vivo*, and backscatter coefficient measurements correlated well with pathologist score.

Fourth topic: Blood Volume Flow (Jonathan Rubin). Flow measurements are based on velocity or some parameter based on velocity. However, volume flow is more important than velocity. However velocity is what is available. Velocity measurements are ubiquitous. The proposed biomarker is a direct volume flow measurement in ml per minute. You need 3D acquisition method to measure the surface of a cross section of a vessel. The advantage of this measurement is that it is angle-independent and makes no assumptions about shape of vessel or about type of flow (e.g. laminar). With modern technology, this could be done in real time. There would be no errors due to angle effects. Ultrasound measurements of volume flow correlate well with MRI measurements. Every manufacturer that does 3D sampling can do this. The application might be umbilical vein flow. You need at least 4 voxels across the vessel to get a reliable measurement. The larger the vessel, the less of a problem partial volume effects would be.

Fifth topic: Contrast (Brian Fowlkes). DCE-US has been used for many years and evaluated in phantoms, animal models and human. Guidelines for the use of DCE-US have been established. Phantoms would be available to characterize system performance. A variety of contrast agents could be assessed as well as imaging systems. It is done around the world, particularly in liver.

CT is a competitor, but CT does not have the same flow dynamics; this is a disadvantage for CT. Some might argue that cardiac applications would be more promising.

Challenges include:

- Selection of specific application. Likely candidates would include liver, breast, thyroid, prostate, and heart.
- It would take both agent manufacturers and system manufacturers working together.
- FDA approval of contrast agents for non-cardiac indications. One candidate would be myocardial perfusion.
- There might be political problems with getting cardiologists to work with QIBA, which is connected with RSNA, a radiological organization. Robert Eckersley said that methods to improve quantitative measures of microbubble contrast can benefit from attenuation correction and nonlinear artifact correction. Nonlinear propagation can induce artifacts, which can be corrected to some degree. Applications could be tumor management and drug response. In serial studies, it is difficult to find the same location again. However, 3D data would ameliorate this problem and improve the statistics.

After the presentations and during discussions, the attendees edited their score sheets, and submitted them.

The meeting was adjourned at ~12:45 pm.