High-Resolution Metabolic Imaging of Human Breast Cancer

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Introduction: The use of the tracer pharmacokinetic paradigm for DCE-MRI is incorrect. All tracer expressions presume the signal has no information on tracer compartmentalization. In DCE-MRI, however, the contrast agent [CA] is the tracer molecule but water is the signal molecule: CA compartmentalizations are intrinsic to the DCE H2O signal time-course. This requires the shutter-speed [SS] pharmacokinetic paradigm (1). ROI-averaged SS DCE-MRI parameters allow better specificity in breast (2) and prostate (1.3) cancer detection and in breast therapy prediction (4). However, recent findings of intra-tumor phyllogenetic heterogeneity (5) and its metabolic consequences (6) provide challenges for: blood tests, point biopsies, ex vivo tissue homogenization, and for ROI- and population-averaged imaging biomarkers. A premium is placed on individualized in vivo metabolic imaging, with intra-tumor resolution generally unattainable. Since SS DCE-MRI yields the metabolic biomarker τi [the mean intracellular water lifetime], it allows metabolic imaging with 1H2O MR spatial resolution. For in-depth analyses, we take two representative human breast cancer [neoadjuvant chemotherapy] NACT case studies from a larger population. The subjects are their own controls.

Methods: The patients [grade 2 IDC, HER2-pos, BRCA1/BRCA2-neg] consented to research DCE-MRI at [therapy point] TP0 - before NACT and TPi - after first 3 week NACT cycle, as well as other points during and after the NACT course, usually 6 cycles. Axial bilateral DCE-MRI with fat-saturation and full breast coverage was acquired [3D GE-based TWIST (7)] at 3T [Siemens]. The parameters included 10° flip angle, 2.9/6.2 ms TE/TR, a parallel imaging acceleration factor of 2, 30-34 cm FOV, 320x320 matrix size, and 1.4 mm slice thickness. The total acquisition time was ~ 10 min for 32-34 image volume sets with 18-20 s temporal resolution. CA (Prohance®) IV injection (0.1 mmol/kg at 2 mL/s) was timed to start following acquisitions of two baseline image volumes. Inclusive tumor ROIs were drawn by experienced radiologists. The pixel-by-pixel DCE time-course data were subjected to SS pharmacokinetic analyses to extract Ktrans, τi, and τ. Ktrans is mainly a rate constant for capillary CA extravasation/tissue arrival, and vj the CA distribution volume (interstitium) fraction. Response to NACT and residual cancer burden [RCB] for each patient were determined by pathology analysis of post-therapy resection specimens and comparison with pre-therapy core biopsy specimens.

Results: Figure 1 shows axial images and 12 zoomed SS tumor parametric maps. Panels a and h display whole [one] breast image slices: 2 cm scale bars. Panel a and the upper 6 maps [b-g] are from a patient subsequently determined a non-complete responder by pathology [Non-pCR] after 18 weeks of NACT. Panel h and the lower 6 maps [i-n] are from a patient similarly judged a complete responder [pCR], RCB = 0. The top row [b-d, i-k] for each patient was obtained at TP0, the bottom row [g-l, n] at TPi, after only one 3 week NACT cycle [best estimates for image slice equivalence]. Thus, a comparison of a patient’s TP0 map with that at TPi shows the effect of the first NACT cycle. The Non-pCR patient [1a] is ER- and PR-negative, but with family history: her NACT comprised a Trastuzumab, Docetaxel, and Carboplatin cocktail, once/cycle. The pCR patient [1h] is ER- and PR-positive: her NACT comprised a Trastuzumab, Paclitaxel cocktail. The Ktrans decrease [1i,l] for the pCR patient is dramatic. At the same time, τi increase and Ktrans decrease after 3 weeks NACT predict very well the RCB to be surgically found after 15 more weeks of therapy. This prediction bears up in ROI- and population-averaged results (4).

The maps exhibit significant intra-tumor heterogeneity that appears anatomic. For example, the TP0 Ktrans maps [1b, 1i] display elevated values in the tumor rim relative to the core: the variation exceeds 10X. Furthermore, there are often spatial correlations between imaging biomarkers. A premium is placed on individualized pre-therapy resection specimens and comparison with pre-therapy core biopsy specimens.

Discussion: The large τi value, 544 ms, in Fig. 1h obtains while vj is also very large, 0.84 [2m]. If vj is large, then vi [1 – vi] is small. As it should not [and contrary to what one might intuit], τi does not decrease with vi; it reflects Pn. The Pn (passive) component [Figure 2] includes simple diffusion, passage through aquaporin channels, leakage through membrane proteins, etc... However, the active trans-membrane water cycling, Pn(active), flux [108 H2O molecules/sec] dominates Pn(passive) (9). This is H2O co-transport, via membrane substrate symporters, paced by the driving membrane ATPase pump; Na+/K+ATPase [NKA] for mammalian cells. The τi magnitude is sensitive to the ATP, and K+ substrates for, and specific inhibitors of, the driving ATPase transporters (9,12,13). Thus, τi is a reciprocal measure of on-going NKA activity. Before therapy, the responsive tumor has a rim that is relatively well perfused [large Ktrans (1i)] and has relatively high NKA activity [small τi (1k)]. After 1 NACT cycle, the perfusion is drastically reduced [1j] and the activity concomitantly decreased, particularly in the residual core [large τi (1n)]. This is sensible, and seems provide a direct high-resolution view of the spatial, microenvironmental, and metabolic consequences of therapy.

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