Imaging of Cancer: Beyond Anatomy & Morphology

Focus on Arterial Spin Labeling in Cancer

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Highlights:

- ASL can provide quantitative assessment of blood flow in high flow tumors.
- ASL can be used to monitor anti-angiogenic therapies.
- ASL blood flow imaging is largely unaffected by vascular permeability changes.
- Insensitivity to lower flows will likely limit the use of ASL to particular tumor types.

Introduction:

Research over the last two decades has emphasized the crucial role of angiogenesis in supporting the growth of tumors. Blocking of blood supply growth has proven a highly successful approach in models that has led to approved therapies in a number of cancers. Imaging methods to monitor the response and eventual resistance of such therapies are of great potential value for clinical trials and clinical management(1-3).

Arterial Spin Labeling (ASL) blood flow MRI(4) is a totally noninvasive technique that employs magnetic fields to invert the magnetization (or spins) of water protons before they flow into tissue. Subtracting images with and without labeling provides a measure of blood flow into the tissue. Unlike dynamic contrast enhancement (DCE) studies, where contrast agents with limited transport across vessel walls are used, ASL employs a tracer that readily diffuses across the vasculature, the naturally occurring water of arterial blood. ASL has only recently become available for clinical use and its use has been primarily restricted to brain, but new techniques of labeling, motion correction, and fast imaging are showing promise for some cancer applications outside the brain.

Overview of Methods

Labeling

Labeling is the key to achieving blood flow sensitivity. In almost ASL studies, labeling of arterial blood is performed with spatially selective inversion shortly before imaging, typically in the range of 1 to 3 seconds. Inversion changes the sign of the longitudinal magnetization of blood water from positive to negative. After a delay to allow blood to move from the labeling location to the tissue of interest, the negative magnetization mixes with the tissue magnetization and decreases the total signal.

Labeling can be achieved either by a single pulse, known as pulsed ASL, or by repeatedly applying fields or pulses to achieve a continuous inversion of blood as it flows past a labeling plane. One particular variant of pulsed ASL, known as Flow Alternating Inversion Recovery (FAIR)(5), has been particularly widely used. This technique applies a non selective inversion recovery to invert all blood (and the tissue of interest). A control image where the inversion is made spatially selective to a slab containing the tissue of interest, but where all the blood outside the slab is not inverted, is also acquired. A particular characteristic of this approach is that all blood flow, whether from above or below the slice, is inverted. This can lead to undesirable venous contamination in some cases, but makes the ASL labeling effective regardless of the source and direction of arterial flow.

Continuous labeling (or CASL) can provide greater signal and signal-to-noise ratio than pulsed ASL(6). CASL uses special strategies to achieve adiabatic inversion of blood as it flows past a particular plane. First achieved by applying constant RF and gradient fields, it is more typically performed today with pseudocontinuous labeling(7), a strategy that uses pulsed RF and gradients to achieve continuous labeling. The higher signal from CASL is a distinct advantage but in some cancer applications, especially when the supplying arteries have very slow velocity or their direction of flow is unknown, pulsed ASL can be preferable.

Image Acquisition

Since ASL sensitivity is most analogous to proton density measurement, any high sensitivity method for proton density imaging is an option. The ASL signal change is small, approximately 1% of the proton density signal, so lower spatial resolution acquisitions must be used to preserve signal-to-noise ratio. Initial work on ASL made extensive use of echoplanar imaging because of its sensitivity and speed. Single shot echoplanar was particularly attractive for the reduction of motion artifacts that could otherwise obscure the small ASL signal. More recently, RARE (turbo spin echo or fast spin echo)(8), balanced SSFP(9), spiral(10) and even 3D hybrids of these techniques such as GRASE(11) have been employed. Background suppression to minimize motion artifacts is particularly critical for slower 3D techniques.

Motion Artifact and Background Suppression

Even when single-shot imaging is used, ASL requires the subtraction of a label and control image to generate a blood flow sensitive image. Subtraction imaging is notoriously motion sensitive and the small signal change associated with ASL only accentuates the problem. A number of different strategies to reduce motion artifacts have been employed. Some, such as cardiac and respiratory sorting or triggering or retrospective image realignment(8,12), are not unique to ASL and have achieved moderate success. More dramatic improvements can be achieved with background suppression(10,13). Background suppression uses additional inversion pulses at optimal times to decrease the signal from static tissue in the image to near zero. Motion errors are greatly reduced with such suppression. Suppression does cause a loss of labeled signal, a maximum of 25% for very high suppression, but the advantage for imaging robustness is typically worth this signal loss.

Applications in Cancer

Brain:

Since ASL has been most widely applied in the brain, it is not a surprise that much of the initial experience with ASL has been in the brain. Because the blood brain barrier is not an obstacle to water, ASL readily measures flow in the normal brain. Much like FDG PET, the high flow of normal gray matter can serve as a source of background confusion for detecting tumors. However, high grade glioma typically has ASL measured blood flow well above the gray matter background. In glioma, ASL blood flow correlates with tumor grade(14-16) and may serve as a marker of recurrent tumor in serial studies. Metastases are typically less prominent, though flow is measurable, and ASL has been used as a measure of radiation response(17). Meningioma is hyperintense on ASL(18). Studies comparing ASL perfusion with tumor vascular density have demonstrated reasonable correlation(19). Initial experience with reliability has been variable but has been improving with more robust techniques.

Renal Cancer

Like the brain, the kidney is a highly perfused organ and the most common primary tumor, clear cell renal carcinoma, is highly vascular. ASL has been used to characterize the response of

renal cancer metastases to antiangiogenic therapy(20,21) and to assess renal masses for indication of aggressiveness or progression(22,23). ASL is particularly attractive relative to contrast studies in those with reduced renal function. Though respiratory motion poses more challenges in the kidney than in the brain, the challenges are addressable with combinations of background suppression and other respiratory motion reduction techniques(8). Lung and mediastinal metastases of renal cancer can be more challenging to image with ASL, but they have been imaged.

Other Cancers

Success with ASL in brain tumors and renal cancer is partially a result of the intrinsically high vascularity and flow of these lesions. Application to hepatocellular carcinoma, for example, has shown a more mixed appearance with some cases hyperperfused but others undetectable despite strong enhancement on contrast studies. In some organs, such as the lung, the complexity of the vascular supply makes labeling challenging and other labeling strategies, such as velocity selective labeling(24), may be desirable.

Future Directions

Experience with ASL in cancer is still in the early stages. Over the next several years, the wider distribution of ASL and the incorporation of more robust techniques and protocols should lead to a broader experience with ASL in a variety of cancers. Increased education and standardization of methods and terminology will help clinicians better appreciate how ASL might best be incorporated into clinical assessments. Finally, improved techniques for motion reduction, and potentially labeling, for organs outside the brain may help to increase the utility of ASL in additional cancer applications.

References

1. Pedrosa I, Alsop DC, Rofsky NM. Magnetic resonance imaging as a biomarker in renal cell carcinoma. Cancer 2009;115(10 Suppl):2334-2345.
2. Wong ET, Brem S. Antiangiogenesis treatment for glioblastoma multiforme: challenges and opportunities. J Natl Compr Canc Netw 2008;6(5):515-522.
3. Folkman J, Browder T, Palmblad J. Angiogenesis research: guidelines for translation to clinical application. Thromb Haemost 2001;86(1):23-33.
4. Detre JA, Leigh JS, Williams DS, Koretsky AP. Perfusion imaging. Magn Reson Med 1992;23(1):37-45.
5. Kwong KK, Chesler DA, Weisskoff RM, Donahue MD, Davis TL, Ostergaard L, Campbell TA, Rosen BR. MR Perfusion Studies with T1-weighted Echo Planar Imaging. Magn Reson Med 1995;34:878-887.
6. Williams DS, Detre JA, Leigh JS, Koretsky AP. Magnetic Resonance Imaging of Perfusion Using Spin Inversion of Arterial Water. Proceedings of the National Academy of Sciences USA 1992;89:212-216.
7. Dai W, Garcia D, de Bazelaire C, Alsop DC. Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. Magn Reson Med 2008;60(6):1488-1497.
8. Robson PM, Madhuranthakam AJ, Dai W, Pedrosa I, Rofsky NM, Alsop DC. Strategies for reducing respiratory motion artifacts in renal perfusion imaging with arterial spin labeling. Magn Reson Med 2009;61(6):1374-1387.
9. Martirosian P, Klose U, Mader I, Schick F. FAIR true-FISP perfusion imaging of the kidneys. Magn Reson Med 2004;51(2):353-361.

10. Ye F, Frank J, Weinberger D, McLaughlin A. Noise reduction in 3D perfusion imaging by attenuating the static signal in arterial spin tagging (ASSIST). Magn Reson Med 2000;44(1):92-100.
11. Fernandez-Seara MA, Edlow BL, Hoang A, Wang J, Feinberg DA, Detre JA. Minimizing acquisition time of arterial spin labeling at 3T. Magn Reson Med 2008;59(6):1467-1471.
12. Gardener AG, Francis ST. Multislice perfusion of the kidneys using parallel imaging: image acquisition and analysis strategies. Magn Reson Med 2010;63(6):1627-1636.
13. Maleki N, Dai W, Alsop DC. Optimization of background suppression for arterial spin labeling perfusion imaging. Magma 2012;25(2):127-133.
14. Warmuth C, Gunther M, Zimmer C. Quantification of blood flow in brain tumors: comparison of arterial spin labeling and dynamic susceptibility-weighted contrast-enhanced MR imaging. Radiology 2003;228(2):523-532.
15. Weber MA, Gunther M, Lichy MP, Delorme S, Bongers A, Thilmann C, Essig M, Zuna I, Schad LR, Debus J, Schlemmer HP. Comparison of arterial spin-labeling techniques and dynamic susceptibility-weighted contrast-enhanced MRI in perfusion imaging of normal brain tissue. Invest Radiol 2003;38(11):712-718.
16. Wolf RL, Wang J, Wang S, Melhem ER, O'Rourke DM, Judy KD, Detre JA. Grading of CNS neoplasms using continuous arterial spin labeled perfusion MR imaging at 3 Tesla. J Magn Reson Imaging 2005;22(4):475-482.
17. Weber MA, Thilmann C, Lichy MP, Gunther M, Delorme S, Zuna I, Bongers A, Schad LR, Debus J, Kauczor HU, Essig M, Schlemmer HP. Assessment of irradiated brain metastases by means of arterial spin-labeling and dynamic susceptibility-weighted contrast-enhanced perfusion MRI: initial results. Invest Radiol 2004;39(5):277-287.
18. Kimura H, Takeuchi H, Koshimoto Y, Arishima H, Uematsu H, Kawamura Y, Kubota T, Itoh H. Perfusion imaging of meningioma by using continuous arterial spin-labeling: comparison with dynamic susceptibility-weighted contrast-enhanced MR images and histopathologic features. AJNR Am J Neuroradiol 2006;27(1):85-93.
19. Noguchi T, Yoshiura T, Hiwatashi A, Togao O, Yamashita K, Nagao E, Shono T, Mizoguchi M, Nagata S, Sasaki T, Suzuki SO, Iwaki T, Kobayashi K, Mihara F, Honda H. Perfusion imaging of brain tumors using arterial spin-labeling: correlation with histopathologic vascular density. AJNR Am J Neuroradiol 2008;29(4):688-693.
20. de Bazelaire C, Alsop DC, George D, Pedrosa I, Wang Y, Michaelson MD, Rofsky NM. Magnetic resonance imaging-measured blood flow change after antiangiogenic therapy with PTK787/ZK 222584 correlates with clinical outcome in metastatic renal cell carcinoma. Clin Cancer Res 2008;14(17):5548-5554.
21. De Bazelaire C, Rofsky NM, Duhamel G, Michaelson MD, George D, Alsop DC. Arterial spin labeling blood flow magnetic resonance imaging for the characterization of metastatic renal cell carcinoma(1). Acad Radiol 2005;12(3):347-357.
22. Lanzman RS, Robson PM, Sun MR, Patel AD, Mentore K, Wagner AA, Genega EM, Rofsky NM, Alsop DC, Pedrosa I. Arterial spin-labeling MR imaging of renal masses: correlation with histopathologic findings. Radiology 2012;265(3):799-808.
23. Pedrosa I, Rafatzand K, Robson P, Wagner AA, Atkins MB, Rofsky NM, Alsop DC. Arterial spin labeling MR imaging for characterisation of renal masses in patients with impaired renal function: initial experience. Eur Radiol 2012;22(2):484-492.
24. Wong EC, Cronin M, Wu WC, Inglis B, Frank LR, Liu TT. Velocity-selective arterial spin labeling. Magn Reson Med 2006;55(6):1334-1341.