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The Holy Grail and the Quest for the Gold Standard

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The Holy Grail and the Quest for the Gold Standard

In this issue of the *American Journal of Neuroradiology*, Jaremko et al¹ report that apparent diffusion coefficient (ADC) values are not always reliable to discriminate medulloblastomas from pilocytic astrocytomas (PAs according to the 2007 WHO classification of brain tumors², instead of previously used juvenile pilocytic astrocytomas JPAs). This article raises a number of important issues.

Let's Face It—The Holy Grail is a Myth. Diffusion MR imaging is exquisitely sensitive for acute brain infarctions and has been extensively used in clinical practice and research projects. Brain infarcts are one of the most frequent diagnoses on neuroimaging studies. Thus, finding an intracranial focal area with reduced diffusion should raise the suspicion of infarction. However, claiming all brain lesions that are bright on diffusion-weighted MR images (DWI) and dark on ADC maps are acute infarcts is, nevertheless, clearly incorrect. Pediatric cerebellar tumors (and all other lesions) are also not diagnosed by a single pulse sequence, as is confirmed by Jaremko et al.¹ They refer to an often-quoted study, of which I happen to be the first author, in which we stated: "ADC values and ratios could prove reliable for distinction of other intracranial tumors, if used in a selective manner to answer specific questions, combined with patient age, tumor location, and other imaging findings. Isolated analysis of diffusion properties does not provide universally reliable identification of different brain tumor types and grade; however, this may not be clinically relevant, because diagnosis is never based on a single sequence but rather on careful analysis of the entire brain MR imaging study."³ For instance, an atypical teratoid-rhabdoid tumor cannot be distinguished from medulloblastoma by its diffusion properties, but it is significantly more likely to be hemorrhagic and involve the cerebellopontine angle, in addition to being found in younger patients.⁴ Another quote from the same article read: "In addition to JPAs, hemangioblastomas and schwannomas are other posterior fossa tumors that have been found to have similar high ADC values. These 3 neoplasms may therefore not be distinguished solely on the basis of their diffusion properties; however, extra-axial location of schwannomas and presence of prominent flow voids within hemangioblastomas should allow for correct diagnosis in most cases."³

Diffusion MR imaging is very helpful in differentiating pediatric cerebellar tumors. That is not just my personal experience, but also that of colleagues around the world, who keep telling me how, "They wouldn't believe me it was a medulloblastoma, but I saw it was really dark on ADC!" It beats the classic teaching of a "cyst with a nodule" for PA (true in only about half of cases and not uncommon in other tumors, as was also shown in the present study) any day of the week. Jaremko et al found an "outlier" PA with "clear diffusion restriction within the nodular component".¹ It could be that the low diffusion signal actually represents an area of hemorrhage, calcification, or even necrosis, which do occur in PAs. Regardless of

its nature, it is still just a single focus within a much larger enhancing mass that is bright on ADC. I have not seen or heard of a PA that was truly dark on ADC. As a matter of fact, we have seen PAs in adults (even in their 70s) that were still bright on ADC maps.

Another "outlier" in the article by Jaremko et al was a medulloblastoma "that presented with diffuse metastasis ... in which each individual lesion was small and difficult to assess quantitatively".¹ Region of interest (ROI) positioning can be at times quite challenging and these lesions were probably not discernible from the underlying brain. Our initial proposal (and the one we still follow) was that enhancing/solid portions of medulloblastomas have lower to similar diffusion compared to the normal brain. So, I believe that we can probably ignore the 2 outliers mentioned above (I would need to review the images to form a definite opinion). In ependymomas, one does see some overlap in ADC values with other tumors; however, their very heterogeneous appearance on other sequences is usually highly suggestive of the diagnosis. Additionally, this heterogeneity is also commonly present on ADC maps, unlike PAs and medulloblastomas (another reason why measurements are commonly inferior to "eyeballing"). Also, lower ADC values tend to be present in anaplastic ependymomas, suggesting a higher grade. We have seen rare cases of desmoplastic medulloblastoma with higher ADC values (the only one that I believe truly shows overlap in this article). Could this perhaps portray a better prognosis?

Gold Standard or Fool's Gold? Whenever a new diagnostic test of any kind becomes available, its accuracy is compared with that of the existing gold standard, be it catheter angiograms or histologic grading. . . or pneumoencephalograms. However, the only true gold standard is the patient's outcome. Discrepancy between tests may frequently be due to the superiority of a new diagnostic technique (though it is usually, at least initially, considered a proof of its limited accuracy). It has recently been shown that contrast-enhanced perfusion MR imaging may be a better prognosticator than histology for patients with astrocytomas and grade 2 gliomas.⁵⁻⁷ Thus, using histology as the gold standard may not always be golden. As I speculated, ependymomas with low ADC may carry a worse prognosis, whereas desmoplastic medulloblastomas with high ADC may indicate less aggressive tumors. We need to investigate further.

The Magic Words. First-year radiology residents readily start mentioning restricted diffusion while looking at the second or third brain MR imaging study in their careers, usually as something bright on DWI. When asked, "Restricted in reference to what?" or "What is the opposite of restricted?" they usually do not know (though some actually do mention the term that is even more magical—facilitated). The question of terminology may not be as important as these other issues, but unclear terms may be quite confusing and misleading. Diffusion MR imaging is like any other imaging we evaluate—the lesion can be brighter, darker, or about the same signal as the tissue of origin, whether we use fancy words or not. Take epidermoid as an example: extra-axial, very bright on DWI, similar to brain on ADC—diffusion is restricted compared with the CSF but not restricted compared with the brain. Is it restricted or not? It gets a bit confusing, doesn't it? I propose, as a number of people already do, using simple standard terms

for ADC and DWI, such as “increased” and “reduced,” “high” and “low,” “bright” and “dark.” I like to think that our expertise and knowledge of neuroradiology are truly valuable and that conveying the findings in the clearest possible way is the best we can do for our patients, without using obscure terms that are not well understood by other physicians.

Terminator: Neuroradiologists versus Computers. Finally, I believe years of dedicated training and clinical experience in reviewing imaging studies allow us to perform detailed analysis and search for clues in all available images (and clinical data when/if available and pertinent). This experience provides better diagnostic accuracy than measurements of any sort. Quantification is clearly an important and increasing component of neuroradiology, however it needs to be used appropriately. For example, in follow-up studies of various lesions, there is no way size measurements could replace direct visual comparison of the imaging studies. Measurements are really pseudo-objective (and potentially pseudoscientific): Calipers may be placed in a slightly different manner, the imaging plane and windowing can be different, and so forth. If this is the case with simple 2D values, errors can only multiply with ROI positioning, for which detailed descriptions and definitions are necessary (number, size, shape, location, mean, minimum, maximum), as with ADC values. At the same time, this complicates and prolongs our reads and is, therefore, unlikely to be truly accepted and widely implemented in clinical practice. Jaremko et al also found that “the visual technique” provided identical results to those of quantitative ADC measurement.¹ That is why ADC maps are so helpful in differentiating PAs and medulloblastomas—just bright versus dark.

It is for this same reason that the use of instant algorithms and/or processing of all the collected imaging data by compli-

cated computer programs does not provide perfect diagnostic accuracy. Our expertise is better (and more efficient). There may come a day when this statement will not be true, but this is not the day. We cannot always be right, but we should strive to make the call whenever possible. Extensive differential diagnosis lists may be good for training purposes but not in real life. It is better (and more useful) to be wrong occasionally than to be essentially useless most of the time.

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