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The Evolution of PET/MR is Hindered by our Field's Reluctance to Provide Critical Evaluation

Short title: Balanced PET/MR consideration

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Over the last 10 years our field has been able to review and develop opportunities for integrating commercially available PET/MR into clinical practice. We have done so with a coalition of industry, academia, and healthcare providers. Although the intention to deliver better technology to patients through dissemination of PET/MR is laudable, the delineation between academic and clinical utility is often omitted from the literature; this impedes the field in finding the proper context for the technology. In this circumstance, I am writing to follow-up on a recent article published in JNM: "PET/MRI Versus PET/CT for Whole-Body Staging: Results from a Single-Center Observational Study on 1,003 Sequential Examinations" by Martin and colleagues (*1*). The work described in this publication portrays a benchmark comparison of new and classic technologies relative to the classic domain of oncology in PET, but there are notable biases in the study design worthy of comment. Furthermore, the publication presents an opportunity to remark on many of the practical differences between PET/MR and PET/CT, which when presented alongside the authors' analysis, could portray a case for arriving at an opposite conclusion. Ultimately, 10 years into the commercial PET era, the field has yet to contextualize PET/MR in academic and clinical value equations, which promotes exclusivity and hinders opportunities to identify and address the barriers that incumber clinical impact.

The work performed by Martin and colleagues compares the diagnostic capacities between an implementation of a PET/CT system and an implementation for a PET/MR, for a given population. However, study design differences across cameras were numerous and uniformly biased favoring perceived superior performance of the PET/MR. The largest bias stems from the differences in PET hardware on the systems being compared, i.e., a Siemens Biograph mCT PET/CT and a Siemens mMR PET/MR. The specifications and performance comparison of these same, or similar, model systems have recently been reported (*2*). The two scanners have differences in bore size, transaxial coverage, crystal-to-detector encoding ratio, and different photon amplifier technologies (avalanche photo diode vs. photomultiplier tubes). All these design differences favor the PET scanner associated with the mMR model (better sensitivity, better resolution, better noise discrimination) and are unrelated to the MR component of the instrument. It is therefore no surprise that the authors see improved diagnostic image quality on the mMR instrument. With respect to the study design: although not all details have been provided, we can deduce that PET image quality was biased towards PET/MR because the acquisition time-per-bed was twice as long as the PET/CT while being acquired less than one isotope half-life later, i.e., the PET imaging in the PET/MR acquisitions were generated with more count statistics and less random coincidence detections. This compounds the fact that different post reconstruction filters were used between the scanners, and physiological differences favor increased sensitivity in the later PET/MR images (as noted

by the authors). Also worth noting, the mCT system performance appears “dummed down” by not using the time of flight reconstruction capacity of the system, which is readily available to users and has been shown to offer notable image quality enhancement (*2*) on the PET/CT.

Ultimately, it is not clear if the “improved lesion detectability” reported by Martin and colleagues stemmed from having readily accessible simultaneously acquired MR images available to clinicians, or better PET data from incrementally superior PET hardware in the mMR machine. The distinction is quite important to many readers because it directly impacts the answer to a principle question: is PET/MR worth the additional costs and complexity of operation when compared alongside a PET/CT?

An objective comparison of the two technologies with different overhead and workflows is challenging. It is a reasonable contention that such comparison research is laying the groundwork of benchmarking the technology to support further developments, and this fits within an academic context aligned with a vision of continued expansion. This sentiment is portrayed in the authors concluding their work will “…hopefully further pave the way toward a widespread introduction of PET/MRI into clinical patient care”. However, this analysis is at odds with the clinical value context. Clinically speaking, consideration of the large gap of approximately 5% of PET/CT patients for whom the authors were not able to obtain PET/MR images because they were “aborted by patient” or negated by “technical problems of PET/MRI” is perplexingly omitted from analysis, and at odds with the authors conclusions on the equivalence of the devices. Furthermore, from an operational perspective, comparable performance, relative to complexities and the cost of PET/MR technology, portray a case of its limited capacity and removal from the market as a PET/CT alternative, i.e., the antithesis of the authors’ concluding statement. These discrepancies reveal a discordance of PET/MR academic and clinical paradigms that is prevalent in the field.

PET/MR vs. PET/CT technologies in oncological imaging - the clinical value equation:

Current “outperformance” applications of PET/MR vs. PET/CT have not yet made their way into the clinic. Having soft tissue anatomical imaging and the myriad of potential MR supported functions available alongside PET may provide quantifiable benefits such as those presented by Martin and colleagues. However, it is unclear whether those same benefits could be achieved with more cost-effective separate PET/CT and MR machines, and more aggressive lower dose PET/CT protocols (i.e., improved image reconstruction or extending PET/CT scan times to those encountered in PET/MR), or simply supernumerary imaging orders.

A complete comparison of PET/MR and PET/CT in oncological imaging should include economic and practical considerations involved in owning and operating the technologies – relevant for virtually all potential users. PET/MR scanners have considerably higher purchase and maintenance costs (approximately 2-3-fold), which do not currently translate into a commensurate improvement in diagnostic quality. There are additional higher costs associated with PET/MR scanner resources, maintenance, facility safety, and technologist staff and training. PET/MR generally has lower throughput than PET/CT – paradoxically, generally speaking, the more the advantages of MR on the PET/MR system are utilized in existing or potential protocols, the longer the required scan acquisition times are – this further stresses economics, patient comfort, and ultimate feasibility at the patient level. Exasperating the issue of long scan times affecting patient comfort, the PET/MR patient experience imposes loud noises that PET/CT does not as well as an increased incidence of claustrophobia from smaller bores.

From an operational perspective, the MR portion of PET/MR is more complex than CT and more difficult to standardize across patients/centers/vendors (*3*). PET/MR is capable of a large abundance of image acquisition techniques and protocols. However, it is more complex to operate, whereas the contrasting CT portion of a PET/CT machine is almost a "one click" operation. Furthermore, replacing the traditional CT technology with MR is not a one to one equivalent substitution, but comes with technological tradeoffs. The most immediate required function of having a coregistered modality acquired with PET, attenuation correction, is performed most elegantly and robustly with transmission photon imaging, i.e., CT. Although the PET/MR field has largely addressed this issue, simple tasks, such as imaging research phantoms, remain challenging on contemporary commercial systems. A robust review of clinical considerations, alongside a discussion of PET/MR avenues for innovation can be found in the literature (*4*).

The PET/MR research tool/clinical tool duality:

Ultimately, assessing the value of PET/MR requires consideration across two paradigms: PET/MR as a research tool, and PET/MR as a clinical support instrument in 21st century medicine. Efforts to delineate the two are challenging because they overlap by design/nature – uniquely this regulatory approved tool was brought to the market before its indications. The two enterprises have different motivations, resources, and barometers of success that we need to contextualize if we are to deliver the technology to its most appropriate utilization. For example, we don't want to stifle the ambitious or improbable aims of research with day-to-day practical limitations that can be addressed later, nor alternatively do we want to push *Cadillac* technology into hospitals and healthcare systems where it does not fit.

We can perhaps understand the relationship of PET/MR technology in our field from the perspective of innovation science. The label “early adopters” has aptly been used to self-describe current users of PET/MR technology (*3*). This term is derived from “diffusion of innovation” theory, work that is seminal in the field by Everett Rogers. It describes a role that early customers play in the potential transition of innovation from invention to widespread adoption (*5*). Notably, the work, and its derivatives, identify how the relationship between industry and early adopters can be synergistic with often overlapping interests – early adopters may be less sensitive to product limitations, less sensitive to price, and prone to confirmation bias. It is also worth mentioning that early adopters exist in both successful and unsuccessful innovation paradigms.

Our field has the opportunity to evaluate an innovative technology, PET/MR, and usher it into its ideal role. Through their vision of PET/MR relevance and expansion, vendors and early adopters continue to play an essential role in directing resources and energy towards cultivating potential into value. In this case, PET/MR pioneers are, by means of ownership, self-selectively less equipped to consider challenges of scalable and cost-efficient delivery of medicine. The greater academic field must partner and play an essential role providing robust perspective and evaluation, including due critical analysis. In between the vision for innovation and its impact lie the shortcomings of the vision that need to be addressed. Patients, healthcare providers, vendors, and academic communities all stand to benefit from finding a pathway for the expansion of PET/MR beyond small academic clusters to larger communities and/or to understand if there is not a reasonable one.

We are 10 years into the age of commercial PET/MR, and the role of the technology remains indeterminant. Academic scientists, physicians, and journals, such as JNM, play roles of supporting development of both research and clinical standards. Ultimately, the closer we can align research and community needs in PET/MR, the more efficiently we can reveal and move the field toward its ideal destination.

References

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