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The future of MRI in radiation therapy belongs to integrated MRI-linac systems, not the standalone MRI-Sim

Vladimir Feygelman, Ph.D.,

Department of Radiation Oncology,

H. Lee Moffitt Cancer Center,

Tampa, Florida 33612

(Tel: 813-745-2757, E-mail: Vladimir.Feygelman@moffitt.org)

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Frank Lohr, M.D.,

Dipartimento die Oncologia,

Ospedaliero-Universitaria di Modena,

Modena 41110, Italy.

(Tel: 39 059 422 2300, E-mail: lohr.frank@policlinico.mo.it)

Colin G. Orton, Ph.D., Moderator

OVERVIEW

The use of MRI in radiotherapy planning and simulation is increasing rapidly and is beginning to be integrated into the external beam radiation therapy (EBRT) treatment process. Some have suggested that integrated MRI-linac systems, not the standalone MRI-Sim, represents the future of MRI in radiotherapy, and this is the claim debated in this month's Point/Counterpoint.

Arguing for the Proposition is Vladimir Feygelman, Ph.D. Dr. Feygelman received his 5-year (M.S.-equivalent) degree in Laser Physics in 1982 and his Ph.D. in Physical Chemistry in 1985, both from the Rostov State University in the former USSR. Upon landing in the US, he discovered the profession of Medical Physics and, after on the job training, became ABR-certified in Therapeutic Radiological Physics in 1995. Since then, he has held both purely clinical and research-oriented positions and, currently, is an Associate Member faculty physicist at Moffitt Cancer Center in Tampa, Florida. He is a member of the team charged with evaluating and implementing new technologies for the Radiation Oncology Department. Dr. Feygelman's current research interests center primarily around quality assurance equipment and procedures for advanced treatments, and he has over 60 peer-reviewed publications. He serves on several AAPM committees and task groups and is an Associate Editor of both *Medical Physics* and the *JACMP*.

Arguing against the Proposition is Frank Lohr, M.D. Dr. Lohr received his medical degree from Heidelberg University, Germany, followed by a residency in the Department of Radiation Oncology of Heidelberg University and the German Cancer Research Center, Heidelberg. During residency, he spent two years in radiobiological research on hyperthermia-induced gene therapy at Duke University, NC. Following his residency, he joined the team at the Department of Radiation Oncology at University Medical Center Mannheim, University of Heidelberg, as attending physician, where he became vice chairman in 2004 and associate adjunct professor in 2005. Recently, he moved to his current position as Director of Radiotherapy at the University Hospital, Modena, Italy. He is specially interested in precision radiotherapy techniques such as IMRT, VMAT (performed the second VMAT treatment in Germany), IGRT and SBRT. His main clinical and research interests are lung, gastric, H & N, CNS and prostate cancers, interdisciplinary optimization of surgery, systemic therapy (particularly immunotherapy) and radiotherapy, as well as the optimization of local radiotherapy based on optimal integration of imaging modalities such as MRI (e.g. iron-oxide nanoparticles) and PET. Dr. Lohr has contributed to more than 130 peer reviewed scientific articles, textbook chapters and textbooks and is co-editor of a German standard radiotherapy textbook.

FOR THE PROPOSITION: Vladimir Feygelman, Ph.D.

Opening Statement

There is no argument about the increasingly important role of MRI in radiation oncology.[1-3] We disagree only on what is the best approach to even tighter integration of MRI into the radiotherapy process.

In order to argue that the integrated MR-guided radiation therapy (IMGRT) system is, on balance, the optimal solution, all one has to do is to compare suitability and necessity of IMGRT *vs.* MR-Simulator (MRS) for the following list of tasks pertinent to radiation oncology.

1) *The interrelated processes of initial target delineation, tissue segmentation, simulation, and planning*. Neither IMGRT nor MRS is truly needed. The concept of MR-only simulation was introduced over a decade ago.[4] However the publication list since then is much more persuasive in terms of *technical feasibility* of the approach, rather than the measurable *benefits*. Over the last 10 years, deformable image registration algorithms have gained greatly in quality, availability, and acceptance. Diagnostic MRI scans are easily and routinely incorporated in the treatment planning process through registration with the planning CT. Interestingly, the Utrecht group, which has a great deal of experience in, and knowledge of, MRI, still chose to use CT to define the geometry for treatment planning and fuse MR images to it.[1]

2) *Patient positioning*. IMGRT is suitable for the task while the MRS is not. An intermediate solution, in-room MR on rails registered to the treatment isocenter, [5] is theoretically usable but cumbersome, particularly for repeated intra-fraction imaging.

3) *Adaptive re-planning*. An integrated system is clearly advantageous, allowing for both off-line and on-line geometrically adaptive re-planning, including the "dose of the day" re-

optimization and treatment to the isotoxicity of organs-at-risk (OARs). Only off-line re-planning is possible with the typical stationary MRS.

4) *Motion management*. IMGRT, and IMGRT only, is capable of directly tracking/gating the target and surrounding tissues in real time, anywhere in the body, with MRI-quality contrast and no external surrogates, invasive fiducials, or ionizing radiation.

5) *Functional imaging biomarkers*. While the long-standing, but yet to be fulfilled, promise of using functional MR imaging to individualize radiation therapy is great, so are the challenges,[6] one of the most insidious being reproducibility.[7] Whether reliable and practical functional MRI biomarkers are ever found (and that is, statistically speaking, not an easy feat [8]), both systems have advantages and disadvantages for discovering and exploiting them. Potentially better image quality and more sophisticated scanning protocols in MRS may or may not balance out the value of high frequency (daily) IMGRT scans.

To summarize, in every conceivable clinical or research category, IMGRT capabilities are either superior to, or on par with the MRS. Right now and in the foreseeable future, it is an ultimate SBRT tool, "*making radiotherapy more of an interventional radiology process*", as was elegantly stated by Lagendijk et al.[1] IMGRT combines immediately available, neatly integrated motion management and daily dose adaptation capabilities with future research experience in functional imaging, which is way more than can be plausibly speculated about the MRS standalone system.

AGAINST THE PROPOSITION: Frank Lohr, M.D.

Opening Statement

There is no doubt that the ideal situation for radiotherapy would be a treatment under more or less static conditions in an ideal dosimetric situation with permanent on-line image-based control of the position of tumor, OARs, and patient surface. On-line MR-guidance is therefore an appealing concept and it has already been applied to brachytherapy.[9] However, to provide clinical results beyond what current image guidance strategies in external beam radiotherapy can achieve, several requirements must be fulfilled on the way, and the allocation of a large amount of resources has to be justified.

We have already come very close to the objective of treating a quasi-static geometric situation if advanced image guidance strategies already available at moderate cost are fully used. Several such strategies are now available but are underutilized, typically for lack of funding or perceived complexity. Recent developments such as Flattening-Filter-Free (FFF)-delivery and fast collimators have, however, dramatically shortened treatment time and thus rendered advanced imaging strategies more feasible. Considerable expertise is needed, as it is also for MR-guidance. Continuous 2D-tracking based on fiducials placed by minimally invasive procedures has entered the clinical routine for the ablation of small lesions without complex interference of OARs and achieved precision is near-perfect.[10]

3D-imaging with CBCT, particularly in conjunction with breath-hold strategies,[11] still has considerable potential. Accuracies in the range of 3 mm can be consistently achieved across treatment targets using deep inspiration breath-hold, resulting in favorable dose distributions and straightforward dose accumulation. 4D-approaches are available, and ultrafast "snapshot" volume imaging is ready to be deployed clinically.[12] Ultrasound, where applicable, allows not only for positioning but for tracking in 2D and 3D.[13] Surface scanning as a complementary positioning and gating tool not using ionizing radiation may simultaneously provide patient surveillance and gating signals during a therapy session, further improving overall precision of a treatment.[14]

The integration of functional MR-data into the treatment process is desirable, but the possibilities at the currently available field strengths in integrated machines are limited. Another aspect is that non-coplanar treatment strategies have recently gained renewed interest outside the cranial area [15] and high-LET radiation, too, may have further potential to improve clinical results independent of imaging strategy. Both strategies are currently not feasible in conjunction with in-room MR-guidance. Finally, local control of small, mobile lesions is already excellent. For larger lesions, overcoming integral dose limits by using particle strategies may be more important than minimally further improving geometric precision.

In conclusion, if on line MR-guidance is necessary, then there is a general necessity for broad use of advanced image guidance strategies, particularly as successful screening programs such as those for lung cancer and, potentially, even pancreatic cancer, are established, as this potentially leads to more localized disease being treated. These opportunities should be exploited immediately with available technology while, in parallel, on-line MR-guidance is scientifically developed to provide added value in applications such as intratumoral dose painting, conformal treatment of individual lymph nodes identified as positive by novel markers, or other situations not yet identified that go beyond just providing geographic precision.

Rebuttal: Vladimir Feygelman, Ph.D.

My distinguished opponent has chosen to shift the debate away from the relative merits of IMGRT vs. MRS. It is understandable, given the paucity of reported clinical accomplishments of MRS in the last 15 years. Instead, the strategy of the opposing Opening Statement is to enumerate different existing IGRT approaches, with the aim of convincing the reader that IMGRT is an unnecessary luxury. In reality, each one of those techniques comes with a sizable disclaimer. Some only work for certain disease sites. Others require implanted fiducials or rely on external surrogates, and/or provide no information beyond (hopefully) tumor location. My opponent and his co-authors seems to advocate that breath-hold is the ultimate answer to the problem of motion in radiotherapy and is willing to resort to extraordinary measures to induce prolonged breath-holds beyond normal physiology.[1] However, in the same breath the authors "*emphasize the urgent need for more research on the position changes of both tumors and healthy tissue throughout breath-holding*." This in itself contradicts my opponent's main postulate that the current image guidance strategies have already achieved the saturation point of clinical impact. To further dispel that assertion, early reports from the clinical IMGRT sites, admittedly anecdotal so far, indicate that there may be a subgroup of patients, previously considered untreatable, that can now be offered beneficial radiotherapy.

Unlike the other IGRT techniques, IMGRT is universally applicable to any disease site and provides direct visualization, with best image quality currently available, of the tumor and surrounding OARs, for both adaptive re-planning and real-time motion management. While the cost of an MR-guided system currently is roughly double that of the nicely equipped accelerator, once one adds up the costs of separate IGRT systems best suited for every clinical situation, the cost gap narrows appreciably, yet without matching the image quality and seamless workflow of IMGRT.

Rebuttal: Frank Lohr, M.D.

There is no doubt that online MR-guidance will further simplify current IGRT workflows, and this may already be a value in itself, as was the transition from 2D to 3D x-ray based imaging that has made precision treatments easier than before. If the clinical advent of MR-guidance raises the awareness that 3D imaging should be used in most instances, this would be another positive, as the need for CBCT and advanced motion management is still not commonly agreed upon within the community. The systems being placed now should be systematically used to clarify issues that are open, some of which were also highlighted by my opponent:

- To what extent is there an added value (useful functioning imaging) of MR over pure geometric accuracy at relatively low field strengths?
- Can functional data from higher field strengths be easier/better integrated into the daily image datasets when MR-base datasets are matched?
- What are the relative merits of tracking in different clinical situations (with potentially suboptimal cumulative dose distributions in OARs for larger targets) vs. inspiration breath-hold gating (with potentially better dosimetric characteristics and easier dose cumulation)?
- Do adaptive strategies really have merit in H&N and lung cancer, where conclusive data is still elusive?

- And, finally, can the concept of online MR-guidance be transferred to particle therapy, where dose distributions depend more on anatomical geometry than for photon therapy and the case for online MR-guidance is therefore stronger?

Disclosure of Conflicts of Interest

The authors have no relevant conflicts of interest to disclose.

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