POINT/COUNTERPOINT

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In the future, emission-guided radiation therapy will play a critical role in clinical radiation oncology

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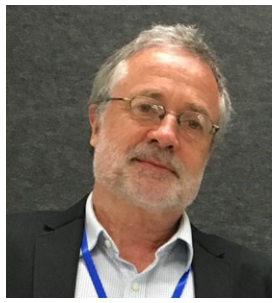
OVERVIEW

Emission-guided radiation therapy entails the use of radiation emitted by molecular imaging probes (SPECT for PET) to guide delivery directly, thus avoiding the need to wait for long acquisition times to collect sufficient count statistics. The potential of biological targeting in radiation treatment planning, taking advantage of advanced molecular imaging techniques in the form of hybrid SPECT/CT, PET/CT, or PET/MRI systems, is well established. The last three decades have witnessed abundant contributions indicative of the advantages of multiparametric molecular imaging in this framework. Ultimately, molecular imaging-guided radiation therapy planning holds the promise of improved delineation of target volumes even in the presence of significant motion. Yet, despite significant advances to date, challenges remain limiting exploitation of the potential of this technology in the clinic to academic facilities with advanced technical support. Fortunately, these limitations are not preventing novel exciting developments to emerge with the aim to further boost the incorporation of multimodality imaging in the process of radiation therapy planning for various indications. In this regard, the conceptual basis of using on-board PET to guide the radiation treatment process has been around since 2010. A small company based in the US (RefleXion Medical, Hayward, CA) pioneered the development of a device enabling commercial implementation of one approach to biologically guided radiation therapy. The product was displayed for the first time at the last ASTRO 2018 annual meeting. While some think that this is relevant technology that should soon be adopted for use in the clinic, others think that the concept is still in its infancy and not mature enough for clinical adoption. This is the topic addressed in this month's Point/Counterpoint debate.

Arguing for the proposition is Paul Keall, PhD. Dr. Keall is a National Health & Medical Research Council Senior Principal Research Fellow and Director of the ACRF Image X Institute at the University of Sydney. His team of scientists and clinical partners develop and apply novel cancer imaging and targeted radiotherapy methods. One of Dr. Keall's research interests is motion management in radiotherapy. He chaired the AAPM TG264 — *Safe Clinical Implementation of MLC tracking* and is currently chairing the update to TG76: *The management of respiratory motion in radiation oncology* (TG324). Dr. Keall has published over 300 papers and has 18 awarded patents. He is a Fellow of AAPM and a member of the *Medical Physics* Editorial Board.



Arguing against the Proposition is Tomas Kron, PhD. Dr. Kron was born and educated in Germany. After completing his PhD, he migrated to Australia in 1989 where he commenced his career in radiotherapy physics. From 2001 to 2005, he lived in Canada where he worked at the London Regional Cancer Centre and commissioned one of the first tomotherapy units. In 2005, Tomas became principal research physicist at Peter

MacCallum Cancer Centre in Melbourne, Australia where he now is Director of Physical Sciences. Tomas holds academic honorary appointments on a professorial level at Wollongong, RMIT, and Monash Universities. He has an interest in dosimetry of ionizing radiation, image-guided radiotherapy, and clinical trials as a tool for introducing new technology. This is demonstrated by more than 80 invited conference presentations and 260 papers in refereed journals. In 2014, he was awarded an Order of Australia Medal (OAM) for services to medicine, research, and education.

FOR THE PROPOSITION: PAUL KEALL, PH.D

Opening statement

It is an exciting time to be working in radiation therapy. Cancer patient survival is increasing with stereotactic ablative body radiotherapy. One- to two-year survival benefits are demonstrated for patients treated with limited metastatic disease. The use of radiotherapy for new conditions, particularly cardiac disease, shows extremely promising results.[1] The interaction of radiotherapy and immunotherapy presents major clinical opportunities. The adoption of MRI-Linacs opens new capabilities for treatment conformality. All these innovations are underpinned by major advances in imaging and targeted radiotherapy technology.

Emission-guided radiotherapy is another emerging technology that will also play a critical role in clinical radiation oncology. In this context, emission-guided radiotherapy is defined as in-treatment room PET (or SPECT) systems. PET is arguably the most sensitive molecular imaging modality. In addition to the widely used FDG radiotracer that measures tumor metabolic activity, there are agents that image tumor hypoxia, proliferation, antigen levels, and many other biological processes. It is a natural evolution to marry the anatomic and physiologic targeting capability of PET with rapidly advancing radiotherapy technology to yield emission-guided radiotherapy. It is currently the norm rather than the exception to treat tumors as functionally homogeneous — we prescribe the same dose to the entire planning target volume. With all the imaging information at hand, it seems medieval for uniform prescriptions to heterogeneous tumors to be the standard of practice. Emission-guided radiotherapy will give the treatment team both the information and the confidence to target radiation most where it is needed most, and least where it is needed least, achieving the combined goals of improved tumor control, reduced metastatic potential and normal tissue dose reduction.

Emission-guided radiotherapy has many forms — I will highlight three here.

1. *PET-guided external beam radiotherapy.* A variety of systems have been used to determine the tumor position in real-time during radiotherapy. However, using PET imaging for this task enables both anatomic and physiologic targeting opportunities. For example, the feasibility of PET-guided external beam radiotherapy has been demonstrated by several groups.[2–4] One approach to PET-guided external beam radiotherapy is being commercially pioneered by RefleXion Medical who raised $100M in 2018 alone to develop a product and have assembled a consortium of early adopters. PET-guided external beam radiotherapy becomes increasingly useful as the number of cancer targets increases, for example, for treating metastatic disease. Multiple targets also pose a motion management challenge as different targets can be moving independently of each other — PET imaging will naturally be able to show the motion of individual lesions. Another intriguing potential of PET-guided external beam radiotherapy is to tailor the total dose delivered based on the quantitative biological changes during treatment as opposed to having the same dose and fraction size for all patients.
2. *PET-guided patient dose measurements during particle therapy.* Particle therapy is promising, but to date, randomized trial evidence has not demonstrated its benefit.[5] One obvious hypothesis is that the motion and range uncertainties during treatment mask the benefit observed from planning studies. To unlock the clinical potential of particle therapy, PET is a feasible method for the non-invasive monitoring of particle therapy treatments.[6,7] PET monitoring, coupled with beam adaptation, will reduce motion and range uncertainties. PET-guided particle therapy is being developed and investigated in many centers to enable the routine use of emission-guided radiotherapy during particle therapy.
3. *Emission-guided radionuclide therapy.* Using a combined SPECT and PET approach, patients for liver cancer radioembolization can be imaged pretreatment with, for example, ^{99m}Tc to predict the therapeutic dose and measured posttreatment, for example, from the small proportion of positrons emitted from ^{90}Y resin microspheres.[8] In this context, pretreatment imaging can be used for planning, and posttreatment imaging can be used to evaluate if adjuvant treatment options are needed.

The three emission-guided radiotherapy examples given here are a subset of the ongoing development in this broader space linking emission guidance with radiation therapy. The future technological developments, clinical applications, and concomitant improvements in emission-guided radiotherapy patient outcomes are exciting. Watch this space!

AGAINST THE PROPOSITION: TOMAS KRON, PH.D

Opening statement

There is no doubt that emission imaging (or nuclear medicine/molecular imaging) has made a huge difference to the practice of radiation oncology.[9,10] PET scanning and to some degree SPECT have had a tremendous impact on staging and patient selection for curative and palliative radiotherapy. There is no doubt that emission imaging impacts the way we delineate and characterize targets (and even critical structures) profoundly.[11,12] "Anatomy follows function," and

therefore, tumor response to therapy can be predicted earlier with emission imaging than with anatomic imaging. But as image guidance aims to help us directing radiation to a physical target every time we treat the patient,[13] do we really want this "glimpse into the future of anatomy," in particular toward the end of treatment after having inflicted several logs of cell kill?

In fact, there are many fundamental problems when trying to take emission imaging into the treatment room for image guidance:

1. We talk of PET, but we mean PET/CT.[10] Without anatomical correlation and attenuation correction, emission-based imaging technologies have limited value in target definition let alone image guidance. As such, it is not sufficient to integrate emission detectors in the treatment unit, but one also has to combine it with CT or MRI — the technical complexity and cost make this not a very convincing option.
2. Related to the previous point is the time required for imaging. Unless very high activities are administered, the efficiency of Linac-based emission detectors will be smaller than dedicated diagnostic systems and as such, acquisition time will be long — too long for motion management or repeat acquisitions during delivery.
3. FDG-PET is the most likely candidate for image guidance. However, the very success of radiotherapy in achieving several logs of cell kill already half way through the treatment course may wipe out the very signal to be used for image guidance just when we most need it. The inflammation which is a result of radiation injury complicates matters as it is nonspecific to the target.[14]
4. Many imaging protocols require the patient to wait a well-defined time after a tracer is injected to ensure the desired activity distribution is established. Can we expect patients to come hours before treatment and can we be sure that there are no delays in bringing the patient into the treatment room?
5. Whatever the approach, the spatial resolution of emission imaging is significantly worse that anatomical imaging.[15] The (sub) millimeter accuracy desirable for modern radiotherapy approaches, such as SBRT, will always rely on anatomical imaging.
6. Finally, operators would require a completely new set of skills interpreting and quickly making decisions based on PET or SPECT images, let alone perform the injections and supervise the required waiting period.

In summary, emission-guided target identification is the future, but emission-guided image guidance is less likely to be part of it. Let us not let our desire for the most fancy imaging technology use a laser where a torch is needed.

Rebuttal: Paul Keall, Ph.D

We know that tumors and normal tissues are functionally heterogeneous. It seems backward that, in the 21st century, we are still treating tumors and healthy tissue as uniform structures. Emission-guided radiation therapy gives us the opportunity to move toward preferential targeting and sparing of the tissue that matters, accounting for changes with time and personalizing the dose and fractionation schedule based on individual responses.

In the opening statement against the proposition, six of the challenges that emission-guided radiation therapy faces on the journey to play a critical role in clinical radiation oncology were identified. To briefly address, these six challenges:

1. *Need for attenuation correction*. As volumetric pretreatment anatomic guidance is the current standard, pretreatment anatomic guidance should naturally continue for emission-guided radiation therapy treatments. The pretreatment image can be used for attenuation correction.
2. *Imaging time*. We currently accept the additional time for pretreatment imaging as worthwhile because patient outcomes are a higher priority than imaging times. With the patient interests first and foremost, time is not the priority, outcomes are. With immunotherapy costing $100,000 per patient per year in some cases, the time and cost of radiotherapy are negligible when viewed in the broad lens of cancer care costs.
3. *Signal/noise reduction as tumor cells decrease and inflammation increases during a course of therapy*. For single and few-fraction SABR treatments, we may not expect significant changes during the treatment. For prolonged fractionated treatments, the temporal changes in the tumor microenvironment represent an opportunity for understanding and optimizing the normal and cancer cellular kinetics on an individual basis.
4. *Increased time for tracer uptake*. We expect a large proportion of cancer patients to undergo brutal cycles of chemotherapy to improve their survival chances. Increasing the time spent in a radiotherapy department with a nontoxic radiotracer in the veins — as opposed to large doses of cytotoxic drugs — is a small inconvenience when weighted against the life expectancy of the patient.
5. *Spatial resolution*. The physiologic information from emission-guided radiation therapy augments the anatomic information from treatment planning, pretreatment, and real-time imaging. The additional functional information may be lower resolution than anatomic guidance methods; however, the additional information enables a new paradigm — selectively boosting the parts of the tumor most likely to be treatment resistant and/or cause metastases.
6. *Educational needs*. Any new technology requires reskilling and reeducation of staff. With other technology, such as knowledge-based planning, having dramatic implications for the workforce, we should embrace the opportunity to learn new skills and be the experts in the growing field of emission-guided radiation therapy.

To close, let us be bold. Dr von Eschenbach, when he was Director of the US National Cancer Institute, stated that we are at a strategic inflection in oncology, a point of unprecedented growth in knowledge, technology, and resources. The integration of these three key sectors provides an opportunity for exponential progress toward the goal of eliminating suffering and death due to cancer.[16] Emission-guided radiation therapy combines these three sectors opening opportunities for anatomic and functional targeting across cancer disease sites and disease stages. For all of the reasons mentioned, emission-guided radiation therapy will play a critical role in clinical radiation oncology.

Rebuttal: Tomas Kron, Ph.D

In his opening statement, Paul Keall provides an excellent summary of the excitement that surrounds modern radiotherapy and there is no doubt that functional imaging contributes significantly to this. However, of the three examples for emission guided radiotherapy given (external beam, particle, and radionuclide therapy), only the latter is a convincing application of what can be termed "emission-guided radiation therapy."

It is claimed that emission-guided RT will give "the confidence to target radiation most where it is needed most, and least where it is needed least." However, one of the limitations of PET is that one can only explore one metabolic pathway at a time. For treatment planning, it may be possible to assess hypoxia, metabolic activity, proliferation, and possibly EGFR status (or other factors) in sequence,[17] but only one tracer can be used at treatment time. Can we be certain as to what indicates where dose is needed throughout the whole treatment course?

Given the limited spatial resolution and the link of sensitivity to radionuclide dose, it is also unlikely that motion management will yield anything but an internal target volume (ITV). Clearly a step back from the exciting developments in motion adaptive radiotherapy that have just become available.[18]

It is granted that radionuclide therapy benefits significantly from emission imaging if personalized dose calculations are to be performed. However, this is either based on imaging with a test dose days prior to treatment or on assessment of the very activity distribution used for treatment (and of course not modifiable at this time).[19] None of this would qualify as "emission guidance" in the traditional sense.

It has been nearly 20 yr since Clifton Ling's seminal paper on biological targeting.[20] While cited and discussed by many, progress has been slow and clinical trials are just getting under way. Most of them are phase I/II studies with practice changing phase III trials in development.[21] We are just gaining confidence in PET/SPECT-based treatment planning. It looks like a lot of work is still needed before emission-guided radiation therapy can even be considered as a research tool for clinical radiation oncology.

CONFLICTS OF INTEREST

Dr. Keall and Dr. Kron have no relevant conflicts of interest.

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