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GUEST EDITORIAL

From the inside out: radionuclide radiation therapy

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Introduction

External beam radiation therapy—for me, it conjures an image of a gleaming steel-and-chrome City of the Future, with every beam and rebate machined exactly and a myriad moving parts, swift and precise. But *radionuclide* radiation therapy. Well, that's more a thatched cottage, with hand-made tools, and a scroll of cantrips distilled from ancient lore.

Why this great gulf between the industrial and the domestic? The two forms of therapy have the same range of patient outcomes, from true therapeutic intent (e.g. ^{131}Iodine for thyroid cancer) to improvement in quality of life (e.g. ^{153}Sm-EDTMP for palliation of painful boney metastases). But there is a crucial difference and it is this: precision.

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External beam radiation therapy seeks to deliver an exact, prescribed dose to the target cells, while keeping the collateral dose to normal cells below specified limits. By contrast, in traditional radionuclide therapy, the administered activity is prescribed but the dose that is in fact delivered, to either target or normal organs, is unknown.

The good news is that this is now changing. Radionuclide therapy is moving towards the norm of external beam, of quantitative individual patient dosimetry. But, of course, it takes a while to turn a spinning wheel into a supercomputer. Below I discuss the current state of progress, and some of the challenges that remain.

Metabolism

The essence of radionuclide therapy is metabolism. Where is the radiopharmaceutical taken up? How quickly? How much? Is it bound or does it wash out again?

The first step, then, is to measure uptake (i.e. Bequerels per gram through-out the whole body) as the radiopharmaceutical is metabolised, over the course of several days. Avid uptake in the tumour is obviously important, but retention is equally important: if the activity washes out quickly the total dose delivered will be low.

Traditionally, imaging in nuclear medicine has been essentially qualitative. Quantitative results were relative: cardiac ejection as a fraction of the maximum; renal function as a percentage of the total. This changed with the advent of PET which was always designed to be quantitative. But even more importantly for radionuclide therapy, quantitative SPECT is now becoming common.

To generate a quantitative image, it is necessary to correct for attenuation, scatter and the point spread function (PSF) of the imaging system. Correcting for

attenuation was made easy with the incorporation of CT into the nuclear medicine scanner. A crude correction for scatter could be done based on measured photons below the peak energy window (and PET systems have improved significantly on this). Finally, with the implementation of iterative reconstruction, it became much simpler to incorporate the imaging system PSF in the reconstruction.

This last is still a work in progress. SPECT camera vendors have naturally concentrated on ^{99m}Tc, and do not yet provide PSF information for all therapy isotopes. For example, quantitative imaging of ^{131}I would currently require in-house modelling of the collimator and system response.

Anatomy

While metabolism is crucial, anatomy is also important. Quantitative imaging gives the location of the radioactive atoms, at a series of time points. But there is another step after this: where will the radiation from those atoms be absorbed?

For particulate radiation, with a short travel distance, this can be addressed using a dose kernel. That is, each uptake image is convolved with the distribution of dose about a point source for the relevant isotope. The practical importance of applying such kernels depends on the isotope (alpha or beta emitter) and the anatomy. A classic example is dose to normal liver cells from metastases within the liver.

Of course, almost all isotopes also emit gammas, and calculating the gamma cross-dose is much more difficult. In theory, the path of the radiation from each voxel should be modelled, using the patient's specific anatomy. This is a Monte Carlo problem which is time-consuming to set up (with manual organ segmentation) and even more time-consuming to run. In the future, this process should be increasingly automated and optimised. But dose modelling based on individual patient anatomy is currently restricted to research applications, and to isotopes where the impact can be important. In the clinic, standard geometric phantoms are used (for adult females and males, and for children).

Planning process

External beam therapy uses CT images to develop a plan for the individual patient. In radionuclide therapy, ideally the patient is injected with a very low activity of the radiopharmaceutical, to provide dosimetry images. This is the protocol, for example, for ^{131}I-MIBG therapy for pheochromocytomas. However, it is not always possible. In ^{131}I therapy for thyroid cancer, there has been on-going concern that a small initial administration may 'stun' the thyroid cancer cells and reduce uptake of the therapy administration. An even more complex problem arises with ^{177}Lu-DOTA TATE (a.k.a. Lu-TATE) therapy.

DOTA TATE (DT) is a somatostatin analogue and binds to receptors expressed by neuroendocrine tumour cells. But it is also taken up by the kidneys, so the radionuclide therapy has the potential for kidney damage. Consequently, patients receive an infusion of amino acids as part of the therapy protocol, to saturate the binding sites in the kidneys. With a low activity administration, which is adequate for dosimetry purposes, amino acids are not required for renal protection. But should they be given anyway so that the metabolic uptake mimics the situation for therapy? If so, a smaller infusion or the same amount?

In this case, it is common to perform dosimetry post-therapy; i.e. use the therapy administration for the dosimetry imaging. This may seem pointless but it is still useful for Lu-TATE because the standard protocol is a cycle of four doses, for each patient. The post-therapy dosimetry is used to determine the dose per activity (Gy per GBq) for that individual, to kidney, liver and tumour. This information can tailor future activity per cycle, and also the number of cycles.

Another problem for this model of individual dosimetry is that it is restricted to therapy isotopes which are gamma emitters. This is a problem, of course, because from a therapy point of view, the ideal isotope is a pure particle emitter. Consequently, many compounds are precluded from individual patient dosimetry. Unless—perhaps—a single pharmaceutical could be tagged with a gamma emitter for dosimetry and a particle emitter for therapy….

Theranostics and radiopharmaceuticals

If you have passed within a city block of a nuclear medicine department in the last year or so, you have probably heard the word "theranostics". The idea is simple: that a single radiopharmaceutical could be tagged with different isotopes, for imaging and for therapy applications. A very common example is tagging DOTA TATE with ^{68}Ga, a positron emitter, and ^{177}Lu, a beta emitter. Following recent advances in radiopharmaceutical manufacture, such pairings are now a practical reality.

Over the last decades, clinical PET has been synonymous with FDG. While there have always been more exotic tracers, these have been restricted to specialist research facilities. Now, several vendors sell synthesis modules, disposable kits and reagents for routine production of a range of tracers. In-house expertise is certainly still essential since the vendors' claims of a "turn-key solution"

are often exaggerated, and the product must be manufactured to the standard of a sterile injectable. However, manufacture and quality control can now be done by a skilled radiochemist, in a reasonably well-equipped hospital laboratory.

The new compounds include several different tumour tracers. The most common are probably ^{68}GaDT and ^{68}Ga-PSMA. ^{68}GaDT, as already discussed, is used in the imaging of neuroendocrine tumours and ^{68}Ga-PSMA is an imaging agent for prostate cancer. Other tracers are designed to be generic, and so useful in a wide range of tumours; an example is ^{68}Ga-CXCR4-2 which binds to chemokine receptors expressed in many tumour types.

All of these tracers can be labelled with ^{177}Lu for use in therapy. And the options are not limited to ^{177}Lu. Other isotopes which have been attached include ^{90}Y which is a pure beta emitter, and ^{213}Bi which is an alpha emitter.

External beam and radionuclide therapy

Our job is to offer as many treatment options as possible to each patient. New radionuclide therapies are emerging rapidly, as seen by recently published reports of patients who were treated on compassionate grounds [1, 2]. If results continue to support this early promise, radionuclide therapy will need to be integrated into the array of available therapies. This is already happening at some institutions. LuTATE therapy—originally offered only to patients who had exhausted all other options—is now moving forward in the therapy chain.

Integrating external beam and radionuclide therapy for an individual patient is not straight-forward, since radionuclide therapy is by necessity hyper-fractionated; in fact, it is continuous. However, the radionuclide dose can be expressed in terms of the Biological Equivalent Dose, or converted to the equivalent of 2 Gy fractions. This is a language which radiation oncologists are comfortable with, and which allows them to use both external beam and radionuclide therapy options, tailored for an individual patient.

Conclusion

We can expect to see the continued expansion of radionuclide therapy and its closer integration with external beam therapy, and chemotherapy, in the treatment options. The range of radiopharmaceuticals is expanding, the quantitation is improving and the clinical outcomes are very encouraging. The City of the Future awaits!

References

1. Kratochwil C et al (2016) PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with Lu-177 labeled PSMA-617. J Nucl Med. doi:10.2967/jnumed.115.171397
2. Baum RP, Kulkarni HR, Wester H-J (2015) Theranostics of prostate cancer using Lu-177-labeled PSMA small molecule for peptide radioligand therapy (PRLT). J Nucl Med 56(Suppl 2):p2. doi:10.2967/jnm565abs