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EDITORIAL

Superfluous, controversial and luxury issues in nuclear medicine

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Many recent developments in Nuclear Medicine are being implemented in clinical practice today, but at the same time raise a lot of fundamental questions. Do we really need all these new techniques and radiopharmaceuticals, and what are their indications, challenges and drawbacks? What are the financial consequences, and do we have to reconsider the composition of the staff? Are these techniques mature enough yet to be implemented in patient care, only in academic settings or also in smaller nuclear medicine practices?

In the shadow of this context, we discussed and shared research, creativity, collaborations and remarkable developments during the last congress of EANM held in Barcelona. The title of the final plenary session of the Congress was 'Superfluous, Controversial and Luxury issues', which was initiated by congress president Stefano Fanti and moderated by Özgül Ekmekcioglu and Fred Verzijlbergen. This Editorial summarises the ideas that were discussed with the audience by six professional speakers with a focus on drawbacks and challenges.

This article is part of the Topical Collection on Editorial.

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Really, more new radiolabelled tracers?

Samantha YA Terry

Research and academia are experienced by many as a rat race, with success measured by the number of papers or patents, citations, impact factor of a journal, or how much grant funding is brought in. However, the pandemic has taught us, if anything, that there are different ways of working, not just in terms of working from home versus the office but also in redefining our personal and professional priorities. This rather provocative talk sought people to dig deep and ask themselves the following question ***'Does our current approach in radionuclide imaging appropriately impact the clinic or is it self-serving?'***. We, too, are guilty of churning variants of imaging tracers, but as the field has grown, it is now of importance for us as an imaging community to ask ourselves and others this question without judgment or facetiousness.

There has been a record growth in the development of radionuclide tracers in the last decade; a plethora of chelators, linkers and radionuclides can now be paired with targeting compounds, which themselves come in many different flavours, e.g. whole antibodies, fragments, peptides, and nanoparticles. This has come from several directions, such as an unmet diagnostic need for certain cancers or immune cells, but equally from our wish to find the next big thing and trump, or find an alternative, to [^{18}F]FDG. Also, society and business as a whole are based on choice; think about how many different coffee types exist. Despite the existing choice, there remains a continuing growth in radionuclide tracer synthesis, yet the actual impact on the clinic is disappointing.

Controversially, one might even state that the current system has detrimental consequences. For example, developing many novel radionuclide imaging tracers dilutes the funding pot available for the potential few key ones that perhaps the community should fully get behind. It can also, in some cases, be seen as a tremendous 'waste of time and effort'. Perhaps, if we take it one step further, this glut of tracers can be harmful; it causes confusion about which tracer to use

when, and a lack of in-depth analysis beyond target specificity and stability, could push forward the 'wrong tracer'. Finally, it is becoming more and more challenging to stay on top of the literature, meaning that most people are unable to sit back and have that 'aha' moment. Perhaps this is leading to a lack of high-impact innovation due to brain fog or a feeling that our 'brains are full'.

So, how do we now move on? We propose to choose a small handful of targets and tracers with which to collectively perform in-depth analysis and comparative studies (with other tracers of a similar ilk) and initiate and advocate standardisation and the production of clinical guidelines. In short, work as a team, not just across the clinical pipeline, but between basic scientists too. The first question, though, clearly, is which targets and tracers? Well, that will require the input of many, not just ourselves, so perhaps a better question is, 'When and how shall we meet up to discuss the priorities in radionuclide imaging'?

Nuclear neurology: clinical reality or eternal promise?

Silvia Morbelli

Molecular imaging in neurology allows investigating, in the clinical setting, several physiological and pathological processes such as perfusion, metabolism, neurotransmission, transport mechanisms, and pathological protein deposition. Molecular neuroimaging tools have already shown great potential to serve as biomarkers for neurodegenerative diseases, thus deepening our understanding of disease development and improving the prediction and diagnosis also at a single patient-level. In several clinical scenarios, these tools have demonstrated greater sensitivity and specificity with respect to morphological imaging. However, given the lack of effective disease-modifying drugs, structural MRI is considered mandatory in the workup of neurodegenerative disorders, while the use of brain PET and SPECT in nuclear neurology is still a matter of debate due to the supposed lack of cost-effectiveness. While, very recently, at least in the field of Alzheimer's disease (AD), the availability of effective drugs is no longer a mirage, it is crucial for the Nuclear Medicine (NM) community to discuss nuclear neurology as a clinical reality today (even in the absence of disease-modifying drugs) [1].

In this framework, it is essential to ease the awareness of the community with respect to the recent availability of diagnostic flow charts already including molecular imaging biomarkers and developed in collaboration with clinical societies. In recent years, some national and international initiatives based on the Delphi methodology developed intersocietal consensus algorithms to guide the choice of biomarkers for the etiological diagnosis of dementing disorders. In this regard, the "European consensus for etiological diagnosis of neurocognitive disorders" has involved all the competent European scientific societies, including the European Association of Nuclear Medicine [2]. This initiative further supported the present role of our tools to support the differential diagnosis, especially in complex clinical scenarios such as the spectrum of frontotemporal degeneration and atypical parkinsonian syndromes. Differential diagnosis of neurodegenerative diseases is crucial not only for prognostic reasons but also given the potential different side effects of medication often used as supporting treatments in patients with dementing disorders. In fact, cholinergic drugs (currently used in AD patients) may significantly worsen behavioural symptoms in frontotemporal dementia. Similarly, patients with dementia with Lewy Bodies can be vulnerable to the potentially fatal neuroleptic malignant syndrome.

On the other side when coming to the suspect of AD, currently available flow-chart tend to support the use of cerebrospinal fluid (CSF) as the first biomarker and amyloid or [18F]FDG PET is more often considered as a second biomarker. This choice is mainly due to economic reasons as well as the further information on TAU pathology and neurodegeneration provided by CSF biomarkers. Such a scenario would result in the use of PET when CSF results are inconclusive or when lumbar puncture is contraindicated or refused by the patients. Overall, these situations are likely to occur in up to 30% of cases based on published meta-analyses still making absolute numbers potentially huge. Currently, more than 55 million people live with dementia worldwide, and there are nearly 10 million new cases every year. Accordingly, the cornerstone of the entire dementia workflow will be profoundly affected by the registration of new drugs for clinical use. In this framework, it is also essential to discuss the responsibilities of the NM Community.

The community need to work, today on the publications of high quality well-designed prospective trials comparing different biomarkers thus building the evidence for the use of our tools. Similarly, it is crucial to strengthen the relationship with our clinical partners to gain their trust by improving the harmonization and standardization of our procedures in the clinical routine. Finally, the NM community has to be aware that WE have the possibility to make a difference in supporting the final validation of new disease-modifying drugs. In fact, molecular imaging biomarkers are crucial to step up effective interventional clinical trials. The availability of both amyloid and tau imaging biomarkers can further refine patients' eligibility for next-generation clinical trials [3]. In fact, thanks to these biomarkers, patients' recruitment and stratification can be performed not only in terms of their correct diagnosis but also with regard to the staging of the disease following a process that the NM community has been successfully following in the field of oncology for several years.

Theranostics, is it a treat or trick?

Juliano J. Cerci

Theranostics refers to the diagnostic pairing with a therapeutic agent that shares a specific target in diseased cells or tissues. Nuclear medicine (NM) is currently one of the greatest components of the theranostic concept in clinical and research scenarios, especially in oncology.

From 1941 with the first use of iodine-131, to the publication of the VISION trial [4] last year, so many things happened in the theranostic field, including MIBG therapy, [177Lu]Lu-DOTATATE therapy and prostate radionuclide therapy. The PET/CT era in theranostics started with [177Lu]Lu-DOTATATE. The publication of the NETTER trial changed the game in neuroendocrine tumours.

There are many publications about theranostics and especially high-quality data, but phase 3 randomized trials are required to build up a path in oncology, where there are so many pharma competitors.

A few years later, the same story happened in a new indication, in a disease much more prevalent and a lot of commercial interest. The TheraP trial [5] an Australian phase 2 trial, presented in the ASCO plenary and published in *Lancet* and later the VISION trial, published in the *New England Journal* again put NM theranostics on the spot.

Especially the publication of the VISION trial, a phase 3 randomized trial with more than 800 patients, proving a better overall survival in prostate cancer patients submitted to [177Lu]Lu-PSMA is a game changer. This and other studies exemplify how important partnerships with the industry are to enter this world of oncology treatment.

Looking at the prostate cancer therapeutic landscape since 2004, there have been many new agents approved for advanced prostate cancer, particularly within the last 10 years. This expansion in the therapeutic landscape, which is suitable for patients, presents a challenge for physicians and raises questions: (1) How is the treatment chosen? (2) How is the sequence of therapies defined? There is so much information, opportunities, and bias in this decision!

Trial publications are essential, but also the assessment, availability and costs of the treatment are as much important. We need investment in the first step of those things: we need phase 3 randomized trials to build up a path in oncology, where there are so many pharma competitors. But NM needs to work on all those steps. Finally, most of these challenges are not solved by us nuclear medicine physicians. It relies on the work of nuclear medicine national associations, government decisions and many other actors.

But what can we nuclear medicine physicians on a daily basis do to grow in theranostic nuclear medicine? We can work on our department organization for the treatment, we can develop administrative tools, we need to take an active part in the multidisciplinary board meetings and in the oncology team, and finally, we need to work on the attention to care and patient experience.

So, what is the trick to treat?

- Perform high-quality research and clinical trials
- Support NM societies
- Work on our NM departments

Personalized medicine: every man has his own PSMA!

Helle D Zacho

Since the first clinical introduction of PSMA PET/CT in 2012, it has become a clinical reality and a cornerstone in what we know as personalized medicine. In the context of nuclear medicine, the term personalized medicine means the use of molecular imaging to provide a precise diagnosis (or disease stage) and thus enables a tailored treatment plan — preferably delivering a more effective treatment with fewer side effects.

In less than a decade, PSMA PET/CT has become the first imaging choice in patients with biochemical recurrence of prostate cancer. Moreover, PSMA PET/CT has proven to possess a higher diagnostic accuracy than conventional imaging in the primary setting and is the most accurate method for disease staging of prostate cancer currently available. In addition to the excellent diagnostic features, the use of PSMA radioligand therapy, as shown in the VISION trial, improved survival in patients treated with [177Lu]Lu-PSMA compared to the standard of care. Despite the numerous achievements by PSMA PET/CT in terms of diagnostic accuracy, we are still facing challenges, as our colleagues in urology and/or oncology request evidence that we are not only providing new and fancy images but that our imaging in fact improves patient-related outcome and such data are not available yet.

Much effort has been put into the development of evidence of the diagnostic accuracy pf PSMA PET, and most trials have been conducted using the 68 Ga-labelled ligand PSMA-11 ligand. The Ga-labelling poses several challenges, such as the need for a Ga-generator and a short half-life of gallium-68 compared to fluoride-18. In addition, the PSMA-11 ligand undergoes urinary excretion which may impair the visibility of small lesions near the bladder. For these and many other reasons, the pursuit for new PSMA ligands is continuously growing. Consequently, considerable effort,

time and a lot of money have been put into the search for the new and perhaps *perfect* PSMA-ligand.

Currently, we know of more than 50 different PSMA-ligands, many of which are only used in a lab, they were developed, and several ligands have only been used in cell lines or animal models. Few PSMA ligands — 10 or less — are in fact in clinical use across the world. On top of the money and time spent in the race for the *perfect* PSMA ligand, there is a striking lack of standardization between studies, very few comparative studies and hardly any with a relevant number of patients to detect a potential difference or at least evaluate new tracers in non-inferiority studies compared to some of the well-characterized ligands.

And the question is to whom is this ever-increasing number of new PSMA ligands relevant? Patients? Doctors? Radiochemists? Or perhaps the industry? Frankly, in our opinion, patients have gained little — if any — benefit from the increasing number of PSMA ligands as evidence of improvements in patient-related outcomes are still lacking. We as doctors, radiochemists, physicists and alike might benefit in terms of publications of new interesting PSMA ligands, how-to-studies on synthesis, dosimetry studies, animal studies and perhaps "first-in-man" studies.

There might be several other explanations for wanting alternative ligands, but at the end of the day, we spend much time, not least money to develop new tracers potentially at the cost of not moving a small selection of our well-known PSMA ligands forward to evaluate their impact of patient-related outcome. As a nuclear medicine society, we suggest that we get together to plan the future of PSMA PET focusing on the patient-related outcome and expand our focus to include non-prostatic targets (such as glioblastoma, hepatocellular carcinoma and other cancer entities) using PSMA-ligands already available in the clinical setting. Even though PSMA PET is a cornerstone in personalized medicine for prostate cancer — it does not mean that every man should have his own PSMA ligand!

Dosimetry: necessary or redundant?

Steffie Peters

In molecular radiotherapy (MRT), electron or alpha emitting radionuclides are used to cause radiation-induced tissue effects in cancer patients. In recent years, the variety and number of different MRTs and their applications have increased, bringing to attention a very long–held discussion on the added value of performing dosimetry when applying this type of therapy.

Dosimetry is the calculation of the absorbed dose in tissues at risk and/or target tissue. This could potentially help to design an MRT in such a way that the therapeutic window is optimally exploited, meaning the target tissue gets an absorbed dose as high as possible while at the same time preventing toxic side effects in tissues at risk. This concept is well known and obligatory in external beam radiotherapy (EBRT), but it is far less common in MRT (where it is actually also obligatory according to the Council Directive 2013/59/Euratom). Why is this?

Critics of dosimetry might feel that dosimetry for MRT is complicated since many factors have to be taken into account and assumptions to be made in the calculation of the absorbed dose. This means that dosimetry is not easily performed and is therefore not accessible for all centres performing MRT. In other words: it is a luxury product that should not be obligatory since this might hamper the application of MRT in many centres, preventing patients from getting a treatment that would be potentially very beneficial. What's more, the uncertainty in absorbed dose calculations is in the order of 20 to 30%, compared to 3% in EBRT, so how clinically relevant would these calculations be? In addition, performing dosimetry requires many resources (scanners, personnel, software) and is considered patient-unfriendly since the patient will have to return to the hospital on multiple occasions to get scanned. And then, all of these factors combined of course mean that dosimetry is an expensive exercise. So this means that for it to be worth it, the added benefit of dosimetry needs to be noticeable.

Actually, it is! Dosimetry can help to personalize cancer treatment. Correct selection of treatment for a specific patient or even specific lesion might be challenging for most cancer treatments, but the perk of MRT is that we can see what we treat by performing pre- and post-treatment scanning. And then, we can treat what we see (and more, since MRT also targets unseen sub-clinical tumour cell clusters). So the idea of applying fixed activities for all patients is very old-fashioned because by using dosimetry, we have a tool at hand to optimize patient-specific treatment. This is especially important since we know that the same injected activity might lead to very different absorbed doses between patients. Even the same absorbed doses might lead to different radiobiological effects. So, we should not refrain from using dosimetry because it is not perfect since not performing dosimetry holds an even greater risk of undertreatment, leading to recurrence and/or radioresistance, which in turn leads to very expensive healthcare. So it is better to invest in the optimal treatment from the beginning by performing dosimetry.

It is time to stop asking whether dosimetry is necessary or redundant, instead we should be asking how we can implement dosimetry into daily clinical MRT practice. Nevertheless, there are many challenges to tackle. We should gain more knowledge on dose–effect relations, tracer kinetics and radiobiology, preferably patient-specific. We should provide standardized and simplified dosimetry protocols that balance clinical benefit with the complexity and accuracy of the absorbed dose calculations. We should make use of software developments to aid easy dosimetry calculations. And

we should invest in setting up the necessary resources and logistics needed for dosimetry.

If we are open to the idea of personalized treatment using dosimetry, we will enter a positive vicious circle: we will optimally exploit the potential of MRT, leading to improved treatment effect, in its turn motivating the use of MRT even more. The next big improvement in MRT will be personalized MRT.

Radiomics: way to the future or useless fancy name?

Xavier Boulvard Chollet

The quantitative analysis of an image is a concept that appeared more than 60 years ago. However, its use in the medical fields is more recent, starting in the 1980s and with an exponential increase in publications in the last few years. The term radiomics was first used in 2010 and can be divided into two main groups: first-order and higher-order features. The first ones include the analysis of the shape with the sphericity, the compacity and the volume (also known as metabolic tumour volume, MTV); histogram-based features (kurtosis, skewness, homogeneity and entropy), and finally, standardized uptake value (SUV) features like the maximum SUV, the mean SUV, the peak SUV and the total lesion glycolysis (TLG, the product of the mean SUV by the MTV). Nevertheless, all of those features are easily understandable. On the other hand, the higher-order section includes the texture features, which represent the relationship between the different voxels inside the volume of interest (VOI) in a greyscale: there is the grey-level co-occurrence matrix (the relationship between a given voxel and all its surrounding voxels, one at a time), the grey level run length matrix (the relationship between a given voxel and all the voxels confined in the same axis, repeating the procedure in every axis), the grey level zone length matrix (the relationship between a given voxel and all its surrounding voxels at the same time) and the neighbourhood grey level difference matrix (the differences between a given voxel and all its surrounding voxels) whereas all of these features have different subcategories based on mathematical formulas. We must keep in mind that it is required to set up the distance between the voxels and the surrounding ones and the resampling step for the grey scale (for example, 64 discrete values, between 0 and 20 SUV units).

It is important to remember that because radiomics study the relationship between the voxels including in a VOI, small changes in the acquisition or reconstruction protocols can interfere with their analysis. That is why studies about radiomics should use the same protocols and even the same equipment to ensure homogeneity: to obtain the best predictive values. Another option would be to use data obtained in equipment accredited by EARL.

Another point to keep in mind is that we obtain many different features in every VOI (nearly 50 with the LifeX software and more than 200 in some studies). To avoid getting results randomly, large cohorts of patients are needed, and it could be interesting to create groups on messaging platforms for anybody willing to study radiomics and unify protocols to obtain bigger cohorts. Nowadays, there are several different software to extract radiomics features from medical images. Personally, I would encourage scientists to use LifeX, first because it is free and secondly because it has a very intuitive and user-friendly interface.

Finally, analyzing the differences between, for example, the SUVmax in two different samples (patients with adenocarcinoma and patients with squamous cell carcinoma) is relatively easy using a *t*-test or a Wilcoxon test, but, in the case of radiomics, because we have many results, we need another test, which can be the Least Absolute Shrinkage and Selection Operator (LASSO). Right now, even if there are growing numbers of publications about radiomics, there is still a long way to go, and we can believe that in the future, with more sensitive equipment, and smaller size of voxels, we will use radiomics on a daily basis with promising results in diagnosis and prognosis.

In the light of these summaries of six presentations, "Superfluous, Controversial and Luxury issues' of Nuclear Medicine" engaged attention to the use of the most beneficial ones among the rapidly developing technologies. Nevertheless, this session presented one of the most intelligent topics to raise awareness for our daily practice in Nuclear Medicine. In conclusion, considering the great impact of the session on the audience, this topic will definitely continue to be discussed for a long time.

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