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THERANOSTICS AND PRECISION MEDICINE SPECIAL FEATURE: REVIEW ARTICLE

An introduction to the clinical practice of theranostics in oncology

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ABSTRACT

"Those who cannot remember the past are condemned to repeat it."
George Santayana 1905

"If men could learn from history, what lessons it might teach us! But passion and party blind our eyes, and the light which experience gives is a lantern on the stern, which shines only on the waves behind us!"
Samuel Taylor Coleridge 1835

The medical speciality of theranostic nuclear oncology has taken three-quarters of a century to move the stern light cast retrospectively by single-centre clinical reports, to the forepeak in the bow of our theranostic craft, where prospective randomised controlled multicentre clinical trials now illuminate the way forward. This recent reorientation of nuclear medicine clinical research practice to align with that of standard medical and radiation oncology protocols, reflects the paradigm shift toward individualised molecular oncology and precision medicine. Theranostics is the epitome of personalised medicine. The specific tumour biomarker is quantitatively imaged on positron emission tomography (PET)/CT or single photon emission computed tomography (SPECT)/CT. If it is clearly demonstrated that a tumoricidal radiation absorbed dose can be delivered, the theranostic beta or alpha-emitting radionuclide pair, coupled to the same targeted molecule, is then administered, to control advanced metastatic cancer in that individual patient. This prior selection of patients who may benefit from theranostic treatment is in direct contrast to the evolving oncological indirect treatments using immune-check point inhibitors, where there is an urgent need to define biomarkers which can reliably predict response, and thus avoid the high cost and toxicity of these agents in patients who are unlikely to benefit. The immune and molecular treatment approaches of oncology are a recent phenomenon and the efficacy and safety of immune-check point blockade and chimeric antigen receptor T-cell therapies are currently under evaluation in multicentre randomised controlled trials. Such objective evaluation is compromised by the inadequacy of conventional response evaluation criteria in solid tumour (RECIST) CT/MR anatomical/functional imaging to define tumour response, in both immune-oncology and theranostic nuclear oncology. This introduction to the clinical practice of theranostics explores ways in which nuclear physicians can learn from the lessons of history, and join with their medical, surgical and radiation oncology colleagues to establish a symbiotic collaboration to realise the potential of personalised molecular medicine to control advanced cancer and actually enhance quality of life whilst prolonging survival.

In the beginning…was radioiodine. The gamma emission of iodine-131, detectable by scanners, allows diagnostic localisation *in vivo*, and its beta emission provides concomitant radio-therapeutic capability within the same molecular platform. This is the essence of radionuclide theranostics, and gave birth to nuclear medicine, 75 years ago, with the diagnosis and treatment of thyroid cancer. Well-differentiated papillary and follicular cancers of the thyroid are common, and adjuvant radioiodine therapy improves overall survival (OS) and progression-free survival (PFS) in advanced disease. However, there appears to be little or no benefit in low-risk and intermediate-risk tumours,[1] where 5-year recurrence-free survival is already greater than 97% without iodine-131 treatment.[2]

Whilst radioiodine therapy of well-differentiated thyroid cancer is generally regarded as the exemplar of theranostic nuclear oncology, it has not been subjected to controlled prospective clinical trial scrutiny. From an oncologist's perspective, efficacy and toxicity have not been rigorously evaluated. There has been no formal Phase 1–2 dose-finding study, and maximum tolerated dose has not been defined. Indeed, there is no consistency in clinical practice with respect to administration of an empiric activity measured in gigabequerel (GBq), or a prescribed radiation-absorbed dose in gray (Gy). The manifest deficiencies of retrospective studies of "high-dose", "low-dose" and "no-dose" radioactive iodine therapy of well-differentiated thyroid cancer have been elegantly critiqued editorially in the *Journal of Nuclear Medicine*.[3] It is recommended that a more refined radionuclide approach incorporate lesional and critical organ dosimetry with PET/CT studies of iodine-124, as a theranostic pair, to ultimately improve outcomes and minimise myelotoxicity.

The assumed dose relationship of iodine-131 to myelotoxicity has yet to be defined, and the traditional blood clearance methodology is too imprecise. Direct measurement of bone marrow and tumour radiation absorbed dose by PET/CT imaging of iodine-124 is now being explored, in order to optimise efficacy and obviate myelosuppression and prevent haematological malignancy in thyroid cancer patients treated with iodine-131.

The absence of prospective controlled trials of radioiodine therapy (RAI) of low-to-intermediate risk thyroid cancer has given rise to extravagant and erroneous claims of causation of acute myeloid leukaemia and chronic myeloid leukaemia by statistical analysis of incomplete Surveillance, Epidemiology, and End Results Program of the National Cancer Institute Registry data.[4] No administered dose information or accurate staging is recorded in the Surveillance, Epidemiology, and End Results Program of the National Cancer InstituteR registries, and the conclusion of this recently published flawed retrospective analysis which appeared in the *Journal of Clinical Oncology*,[4] that "Our results demonstrate the importance of avoiding treatment with RAI in patients with low-risk or intermediate-risk disease, in whom RAI has shown no or questionable benefit", is not justified by the presented data. Furthermore, response data were not reported. The conclusion was refuted in a storm of letters to the editor.[5–13] Correspondents from all over the world presented evidence of significant improvement in survival, and decreased mortality from subsequent solid malignancies after RAI, and accorded the minimal risk of haematological malignancy its correct perspective.[14]

The major lesson to be learnt by nuclear medicine specialists in confronting controversial oncology literature is to change our training and practice in a way which enables greater involvement in clinical decision making in the practice of theranostics.[15] We must also embrace the ethos of prospective controlled trials.

To date there is no prospective randomised controlled clinical trial (RCT) of radioiodine therapy of low-risk or intermediate-risk well-differentiated thyroid cancer and there is no formally established evidence base for objective response rate (ORR), PFS or OS, nor has the long-term toxicity profile been adequately characterised. It is probably too late to rectify historical shortcomings, but they behove us to learn from them, particularly in our relationships with our oncologist colleagues.

Prospective individual prescription of radiation absorbed dose of radioiodine, in the form of iodine-131-anti-CD20 monoclonal antibody radioimmunotherapy (RIT) of indolent non-Hodgkin lymphoma (NHL), has been in routine clinical use for 20 years.[16] Iodine-131-tositumomab (Bexxar, GSK, Brentford, UK) RIT of NHL was predicated upon a measured whole-body radiation absorbed dose of 0.75 Gy and this prescribed dose was also adopted in prospective clinical trials of iodine-131-rituximab RIT, which was demonstrated to expose haemopoietic marrow to doses of less than the myelotoxic threshold of 2 Gy.[17] Long-term follow-up of 10 years in patients with advanced follicular NHL has demonstrated no significant myelotoxicity, and the incidence of myelo-dysplastic syndrome/acute myeloid leukaemia after first-line RIT was zero.[18] In this INITIAL study (ACTRN 1260 7000153415), as well as minimal toxicity, the efficacy was greater than conventional R-CHOP chemotherapy with PFS 77% *vs* 42–48% at 8 years.[18–20]

The failure of iodine-131 RIT of indolent NHL to enter mainstream clinical haemato-oncological practice is a direct consequence of the inability of the nuclear medicine community to engage, and collaborate with, medical haemato-oncologists to resolve issues of logistics, politics and regulatory concerns regarding radiation safety and reimbursement. The manifestly superior efficacy and lower toxicity profile in comparison with standard R-CHOP chemotherapy of NHL, even when supported by the clinical trial resources of a major pharmaceutical company, was insufficient to convince oncologists, and Bexxar was withdrawn from the market in 2014.

As we stand on the threshold of a revolutionary era of theranostic nuclear oncology it is imperative that the nuclear medicine community adopts rigorous evaluation criteria for our novel tumour-targeted molecular therapies. We are obliged to establish a credible evidence base which will lead to regulatory approval, oncologist acceptance and eventual reimbursement and incorporation into sustainable mainstream clinical practice worldwide. The consequences of not performing prospective randomised controlled clinical trials of novel theranostics have already been seen in the 15-year delay in the introduction of gallium-68 imaging and lutetium-177-octreotate peptide receptor radionuclide therapy (PRRT) of gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs) to patients in North America, and many European countries. The landmark NETTER-1 Phase 2 RCT of lutetium-177-octreotate PRRT of progressive enteric NETs, published in 2017, established level 1b evidence of efficacy.[21] This led to incorporation, for the first time, apart from last-line salvage, into European Neuroendocrine Tumor Society guidelines, and to regulatory approval by Food and Drug Administration and European Medicines Agency, albeit a very long time after the first clinical use at the start of the century. Even now, it should be remarked, there has been no formal Phase 1 dose-escalation study of lutetium-177-octreotate PRRT of GEP-NETs.

All patients are treated empirically with an arbitrary administered activity, 7.4 GBq lutetium-177, for four cycles, at 6–10 week intervals. Dosimetry is not performed in clinical practice and the radiation absorbed dose in each treated individual is conjectural.

Theranostic nuclear oncologists would be well-advised to learn from their radiation oncologist colleagues to prescribe a specified, personalised radiation absorbed dose in Gy to the tumour, or, at least, to the critical normal organ, and then verify that the dose has indeed been delivered. Such radiation dosimetry is now mandated in the European Union by the European Council Directive 2013/59 which states that "for all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified".[22]

Formal dosimetry studies require quantitative SPECT/CT imaging using the same acquisition geometry at several time points, and they are impractical in routine clinical practice. However, a single 96 h SPECT/CT 3D map of radiation absorbed dose to tumour, kidney, liver and spleen, following therapeutic administration of lutetium-177-octreotate for PRRT of GEP-NETs, has been recently validated.[23] Although retrospective, this simplified measurement of delivered dose after each cycle will allow personalised, optimised and justifiable theranostic treatment in the individual patient. It is only by obtaining such clinical dosimetric data that we can address dose-response and dose-related toxicity in our evaluation of efficacy and safety in real-world patient populations.

Prospective dosimetry demands a longer half-life than the 1 hour of gallium-68, and the use of fluorine-18 radioligands is being explored. However, the theranostic paradigm, when strictly applied, demands the same molecule for diagnosis and treatment. Copper-64, a positron emitter with half-life 12.7 h is an attractive dosimetric proposition, given its favourable chemistry for radiolabelling small molecules. The recent advent of a reliable supply of its theranostic pair, copper-67, from a linear accelerator (Idaho Accelerator Center, Pocatello, ID), promises worldwide availability of this efficacious theranostic treatment radionuclide. Copper-64-SARTATE is in clinical trial in paediatric neuroblastoma (ACTRN12617001259336). In adults, a Phase1/2a prospective clinical trial of copper-64/67 for theranostic management of meningioma is being conducted at Royal North Shore Hospital, Sydney (ACTRN12618000309280). sarcophagine-prostate-specific membrane antigen (PSMA) for prostate cancer is moving to clinical development in first half 2019.

Control of the actual radiation absorbed dose to tumour and critical organs, particularly haemopoietic marrow, is essential for the safe use of theranostic radionuclides in combination with chemotherapeutic or immunomodulatory agents to improve objective response rates, whilst avoiding additive toxicity. The addition of capecitabine and temozolomide to the standard regimen of lutetium-177-octreotate PRRT monotherapy of gallium-68-octreotate-avid GEP-NETs appears to significantly improve both ORR and PFS,[24,25] and this combination is currently under evaluation in the CONTROL-NETS RCT in a formal nuclear physician-medical oncologist multicentre collaboration (CTC 0120/AGO14NET).

A pilot feasibility study, NETTLE, combining lutetium-177-octreotate PRRT with everolimus dramatically improved efficacy of the biological agent in pancreatic NET, attaining 80% ORR as against 6% for monotherapy with everolimus alone.[26] This may be contrasted with Pharma RCT of chemotherapeutic combinations with everolimus, such as COOPERATE-2 (NCT01374451), where pasireotide (Signifor LAR, Novartis Pharmaceuticals, East Hanover, NJ) failed to increase the PFS of 16 months. Combination BEZ235 P13K inhibitor treatment of pancreatic NET caused devastating toxicity such that the trial was abandoned.[27] It is regrettable that the opportunity to formally test the promising NETTLE results in a Pharma designed and sponsored Phase 3 multicentre, multinational RCT was eschewed in the current COMPETE study of everolimus *vs* lutetium-177-edotriotide (Solucin ITM Garching Germany) PRRT (NCT 03049189), without a combination arm to take advantage of potential synergism of oncology and theranostic approaches.

The standard current management of GEP-NETs comprises definitive diagnosis with gallium-68-octreotate PET/CT, biopsy to determine tumour differentiation by Ki-67 score and, for symptomatic disease, the institution of long-acting somatostatin-receptor blocking therapy. Upon inevitable relapse, given continued demonstrable tumour receptor avidity for gallium-68-octreotate on PET/CT, PRRT is given with the theranostic radionuclide pair, lutetium-177-octreotate. However, some patients with less-well-differentiated NET often show considerable heterogeneity in tumour uptake of gallium-68-octreotate, and in such grade 2–3 NET patients a fluorine-18-FDG PET/CT imaging study is correlated with the gallium-68-octreotate PET/CT. Discordant tumour uptake may then be appropriately treated with cisplatin/etoposide chemotherapy for control of aggressive disease, followed by lutetium-177-octreotate theranostic control of the ingravescent component of the NET. This sequential approach has been shown in Australian single-centre studies to improve outcomes (*Professor Michael Hofman, personal communication April 2018*), and has been adopted into routine clinical practice.

A new somatostatin-receptor (sst) antagonist is currently being evaluated in a Pharma open-label trial of satireotide (lutetium-177-OPS201) (Ipsen Pharma Berlin Germany) for PRRT of GEP-NETs, and also bronchial carcinoid, paraganglioma and phaeochromocytoma (NCT 02592707). Direct prospective comparative study of the gallium-68-OPS202 (gallium-68-NODAGA-JR11) sst receptor antagonist with sst receptor agonist gallium-68-DOTATOC PET/CT in well-differentiated GEP-NETs demonstrated higher tumour-to-background ratios with an increased detection rate of liver metastases and improved overall sensitivity 94 *vs* 59% in favour of the antagonist.[28] The higher tumour uptake of JR11 than of DOTATOC suggests that higher tumour radiation doses may be delivered by antagonists, because there is early clinical evidence that NET washout is slow.[29] However, formal dosimetry studies to measure this dose in Gy have not been performed. There may also be the potential

to treat tumours of other organs, such as carcinoma of head and neck, where individual tumour cells may over express the neuroendocrine receptor. Such molecular targeting, rather than organ-based tissue targeting is an analogue of the "tumour agnostic therapy",[30] approach of oncologists in immunotherapy, although it may perhaps be viewed more appropriately as ecumenical, or "broad-church", thus expressing some faith that it might work.

One of the great strengths of the theranostic paradigm is the accurate selection of patients who will predictably benefit from targeted molecular tumour-specific radionuclide therapy. The ability to image tumour uptake of novel radiopeptides with high sensitivity and specificity offers the opportunity to perform exploratory tracer feasibility studies in actual cancer patients thus circumventing reliance upon pre-clinical animal model studies which are frequently misleading. The mechanisms of receptor localisation of radiopeptides, and the physical and chemical attributes of the radionuclide ligands developed for PRRT have been comprehensively reviewed,[31] and are outside the scope of this introduction to theranostic molecular oncology clinical practice.

Our major objective is actually to introduce theranostics into mainstream oncology clinical practice. The current status of management of prostate cancer is outlined in the *Journal of Clinical Oncology* editorial of 10 April 2018[32] ; "Since 2004 six distinct therapies have been approved for the treatment of metastatic castrate-resistant prostate cancers on the basis of an overall survival benefit in randomised trials, although median survival benefit is modest, ranging between 2 and 5 months". "A combination approach is now considered a standard-of-care for metastatic hormone-sensitive prostate cancer, although it remains unclear who should receive docetaxel, abiraterone, both, or neither. As such a standard paradigm cannot be established"…"Two essential components are required to establish a treatment standard; ideally, to have molecular biomarkers to precisely select the best treatment modality and, in their absence, randomised clinical studies to assess the relative effectiveness of therapies…such knowledge is currently lacking".[32]

The specific biomarker for prostate cancer, so ardently desired by oncologists in the United States, does, in fact, exist. Furthermore, where available, it is the acknowledged gold-standard for diagnosis, staging and monitoring therapy of prostate cancer throughout Australia and Germany. A multicentre prospective Australian study of 431 prostate cancer patients undergoing gallium-68-prostate-specific membrane antigen (PSMA)- PET/CT imaging demonstrated a change in prior management intent in over half the patients.[33] These results were corroborated in a multinational study,[34] and the place of gallium-68-PSMA PET/CT imaging in the management of prostate cancer has recently been comprehensively reviewed.[35] The recent production of a commercial kit formulation for simple bench-top gallium-68-PSMA preparation,[36] and the ready availability of germanium-68/gallium-68 generators now renders theranostics accessible to all departments of nuclear medicine with PET/CT capability, worldwide.

Conventional CT and MR imaging, and bone scintigraphy, underpinning the 2018 ASCO Clinical Practice Guideline for metastatic non-castrate resistant prostate cancer led to an annual estimate in 2017 of only approximately 4% of patients with prostate cancer presented with *de novo* metastatic disease in the United States.[37] However, many patients develop metastatic disease after primary treatment, and it is likely that those metastases were occult at the time of presentation. In patients imaged with gallium-68-PSMA PET/CT at presentation for primary staging, in whom there was no clinical or conventional imaging evidence of metastasis, Roach et al,[33] demonstrated unsuspected metastases in 17% which led to a change in management from that originally intended.

The advent of gallium-68/lutetium-177/actinium-225-PSMA has revolutionised the clinical management of prostate cancer, and it is this rapid evolution of theranostics which is the new exemplar of the practice of theranostic nuclear oncology. The state-of-the-art editorial in the 18 February 2018 issue of *The Journal of Nuclear Medicine* is entitled "Why targeting PSMA is a game-changer in the management of prostate cancer".[38] However, in the definitive comprehensive review of "Metastatic prostate cancer" in the 15 February 2018 issue of *The New England Journal of Medicine* no clinical studies of gallium-68/lutetium-177/actinium-225-PSMA theranostics of metastatic castrate-resistant prostate cancer (mCRPC) are mentioned.[39] A 2018 "up-to-date comprehensive review of new horizons in the management of castrate-resistant prostate cancer" published in the *Journal of Clinical Urology* also completely ignores theranostics.[40]

The disconnect, between, on the one hand oncologists and urologists, and on the other, theranostic nuclear physicians, is stark. The excellent ORRs achieved in the seven clinical trials of lutetium-177-PSMA, and single study of actinium-225-PSMA, theranostic management of mCRPC, reviewed in *The Journal of Nuclear Medicine,*[38] do not exist as far as the oncologist evidence base is concerned, since they were all retrospective, single-centre studies in heterogeneous patient populations. For example, the *Journal of Clinical Oncology* editorial of 6 April 2018, entitled "Curing more prostate cancer; thinking through the options" whilst acknowledging that, "Targeted radiation (stereotactic body radiation therapy and targeted systemic radiation) may also play an important therapeutic role", it did not mention lutetium-177-PSMA.[41] The retrospective multicentre German study of lutetium-177-PSMA therapy of mCRPC, reporting ORR 45%,[42] was cited, but otherwise ignored.

Reasons why mainstream medical oncologists have not recognised a role for theranostics in their routine clinical practice may simply have been attributable to ignorance engendered by lack of access to nuclear physicians with therapy expertise. This inaccessibility may be due, in part, to the failure of nuclear physicians to attend tumour boards or multidisciplinary clinical meetings with oncologists, or to publish theranostic articles in specialist oncology journals.

The general availability of diagnostic and therapeutic radionuclide management of cancer is evolving rapidly. Industrial

suppliers of germanium-68/gallium-68 generators, lutetium-177, actinium-225, copper-64/copper-67 are responding to the increasing global demand and Pharma industry is acquiring the expertise and intellectual property to develop an assured supply of theranostic radiopharmaceuticals. However, the training of theranostic nuclear oncologists may not be able to keep pace with burgeoning demand. Nuclear medicine over the past few decades has been viewed primarily as a diagnostic subspeciality of radiology, and its practitioners are often seen by oncologists as inappropriately trained to act as physicians responsible for all aspects of clinical care of cancer patients undergoing theranostic radionuclide treatment. Manifestly, nuclear physicians must now study oncology and molecular science, immunology and genomics, in addition to diagnostic imaging, if they wish to practice theranostic nuclear oncology. Dual training programs will not only promote communication and cross-fertilisation between the specialities, but also facilitate collaborative clinical and research practice. The recent trend toward establishment of comprehensive cancer care facilities offering one-stop medical, radiation, surgical and theranostic nuclear oncology services, such as GenesisCare in Oxford and Windsor UK, with associated controlled clinical trial capability, will foster cooperation among all specialists in oncology.

How do we gain entry into the hearts and minds of oncologists, and achieve acceptance of theranostic management of mCRPC in their routine clinical practice? What can we do that lies within our control? Perhaps we can learn from the past, by seeking advice and guidance from a historian. Theodore Zeldin, in *An intimate history of humanity*, observed that, "to have a new vision of the future, it has always first been necessary to have a new vision of the past". Theranostic nuclear oncologists must adopt the new vision of controlled, prospective, multicentre clinical trials, designed in collaboration with medical oncologists, comprising stringent pre-defined criteria of eligibility, standardised protocols and strictly-defined endpoints of OS and quality of life (QOL), preferably patient-reported outcomes (PROs), which are the key performance indicators most relevant for our patients.

The old concept of chemotherapy cure of cancer is being superseded by the new molecular oncology paradigm of control of advanced cancer. In this new model, based upon genomics, proteomics and individualised modulation of complex immune systems of tumours and their microenvironment, the importance of biomarkers to predict response and monitor durability is paramount. Medical oncologists and theranostic nuclear physicians are both on a steep learning curve to master the specialised languages of molecular and immunological oncology and apply them to clinical practice. The old certainties were enshrined in the Greek temple of oncology portrayed in the August 2017 issue of *Nature Reviews; Clinical Oncology*.[43] The four pillars of oncology, as depicted last year, comprised *Radiation oncology, Medical oncology, Interventional oncology/interventional radiology and Surgical oncology.* This classical representation of oncology may now be regarded as ancient history. Medical, radiation, surgical and theranostic nuclear oncologists, together with immunologists, geneticists and molecular biologists are constructing a new clinical academy to accommodate the rapidly evolving molecular oncology paradigm to control metastatic cancer.

Both immunological oncologists and theranostic nuclear physicians are standing on the same threshold of this molecular edifice-under construction. The foundation evidence base has yet to be established and validated according to the traditional RCT, and both molecular-targeted modalities share the same ORR evaluation difficulties. Conventional response criteria, based upon RECIST anatomical and functional CT/MR imaging, are proving inadequate accurately to define response.[44] "Pseudoprogression" in immune-check point follow-up images has prompted modification of the standard RECIST criteria and the formulation of a more complex i-RECIST system. A comparable "flare phenomenon" may also be seen in follow-up PET/CT images in theranostic patients. Monitoring response to immune-check point blockade, and the dearth of predictive biomarkers, is comprehensively addressed in *Nature Reviews;Clinical Oncology* November 2017.[45] The authors observe that: "Despite the remarkable success of clinical application of immunotherapy reported in the past decade, the efficacy and effectiveness of these therapies varies greatly across individual patients and among different tumour types. A substantial unmet need is the development of biomarkers of response to immunotherapeutic agents, in order to identify, before initiation of treatment, which patients are likely to experience a response to, and clinical benefit from such treatments".[45] This absence of definable biomarkers prior to initiating immune therapy also compromises the capacity to avoid the considerable toxicity and costs associated with such treatment in patients who are unlikely to benefit.[46,47]

Theranostic nuclear oncology has the distinct advantage that treatment is offered only to those individual cancer patients in whom tumour molecular uptake of the theranostic radionuclide pair is manifest on pre-treatment diagnostic/staging PET/CT imaging of the targeted ligand. Similarly, subsequent cycles of treatment with theranostic agents are only administered after specific PET/CT verification of continuing tumour-avidity, and monitoring of response in order reliably to predict efficacy and minimise toxicity.

In chemotherapeutic drug development a Phase 1 study subjects small cohorts of patients to incrementally increasing doses in an effort to determine the maximum tolerated dose (MTD), which is then used in Phase 2 and 3 studies of efficacy, and usually constitutes the approved therapeutic dose. This chemotherapeutic paradigm operates on the more-is-better, dose-response rule. However, the advent of molecular oncology, where new designer drugs target and bind to a specific cancer-related molecule, often demonstrates saturation of these binding sites at doses far below MTD.[48] Such saturation of the tumour receptor target may be determined in the individual patient by quantitative theranostic imaging. Thus a minimum effective dose may then be prescribed on the basis of personalised dosimetry which will minimise toxicity, both physiological and financial. The potential of this theranostic approach is exemplified by the exploration of lutetium-177–3 BP-227 neurotensin receptor 1-targeted therapy of metastatic pancreatic adenocarcinoma,[49] the current

5-year survival rate of which is less than 5%. In a small feasibility study in end-stage salvage patients Professor Richard Baum et al achieved markedly improved quality of life and survival over 1 year.[49] It is such very early stages of clinical development of theranostic treatment of common cancers, where standard chemotherapy is ineffective, that nuclear physicians and oncologists should closely collaborate to design and coordinate large-scale clinical trials which utilise credible evaluation methodology beyond that of the traditional MTD Phase 1 and 2 studies of conventional chemotherapy research protocols.

Dialogue and cooperation with oncologists is now informing design of controlled prospective clinical trials of novel theranostic agents, exemplified by the recently published Phase 2 study of gallium-68/lutetium-177-PSMA-617 in progressive advanced mCRPC reported in *The Lancet Oncology* 8 May 2018.[50] The high response rates, low toxicity and enhancement of QOL, particularly pain relief, achieved in this single-centre prospective study will be formally validated in a Pharma-sponsored multicentre international RCT.

However, besides cost and long gestation of RCTs, a common limitation is a lack of representativeness of enrolled patients, and trial results may not be generalisable to certain patient subgroups.[51] Some important clinical questions may never be answerable by randomised trials. Prostate cancer RCTs have been especially difficult to conduct because of large patient and physician biases, which often preclude treatment determined by randomisation. On the other hand, retrospective comparisons of different treatments of prostate cancer are particularly difficult to interpret because of known inherent differences in patient characteristics between the treatment groups.[51]

In an attempt to find a viable alternative practical method of evaluation, a prospective, controlled, non-randomised, multicentre, multinational, clinical audit of a standardised gallium-68/;lutetium-177-PSMA protocol for theranostic management of metastatic prostate cancer has been proposed. The World Association for Radiopharmaceutical and Molecular Therapy (WARMTH)-sponsored National Investigators Global Harmonisation Theranostics of Cancer of Prostate (NIGHTCAP) study will audit several thousand patients worldwide, undergoing routine clinical lutetium-177-PSMA treatment of metastatic prostate cancer on a standardised protocol, based upon that of a published controlled clinical trial.[50] This real-world study will document outcomes which are achievable in the clinic, as well as providing global access to theranostic management of prostate cancer. These patient outcomes will be defined by practical measurable endpoints such as time-to-treatment-failure, OS and QOL according to PROs. Central collation and statistical analysis of the data will be performed by WARMTH, supported by the World Federation of Nuclear Medicine and Biology.

The unique design of the large population WARMTH coordinated study draws upon the strength of theranostics to personalise treatment, whilst circumventing the so-called "paradox of precision medicine" which may amplify uncertainty in clinical decision making.[52] In precision medicine, large heterogeneous patient populations are divided into smaller, more homogeneous strata, with the aim of reducing variance in the response to treatment. This fine stratification renders large, sufficiently powered RCTs that provide precise estimates of the effects of such treatments, virtually impossible to conduct. Small sample sizes also create pressure to use surrogate primary endpoints, such as tumour response, which enable greater statistical power because they are based upon events that accumulate early after starting the clinical trial, instead of using primary endpoints, such as those of the National Investigators Global Harmonisation Theranostics of Cancer of Prostate (NIGHTCAP) study, which require time for events to occur, and which reflect core long-term benefits such as OS and its quality.

A more conventional Phase 2 multicentre, open-label, randomised, stratified 2-arm clinical trial has recently commenced in Australia. The TheraP study will directly compare lutetium-177-PSMA-617 *vs* cabitaxel chemotherapy in progressive mCRPC (NCT 03392428).

Nuclear physicians are also reaching out to radiation oncologists to explore the radiobiological potentialities of combining the modalities of external beam and internal radionuclide delivery of radiation to the tumour. It is now generally recognised that, although each modality delivers a radiation absorbed dose measured in Gray, the radiation biology is not equivalent. The classic calculations of radiation oncologists cannot be meaningfully applied to the low-flux, *longue durée,* theranostic treatments for which, at the present state of knowledge, the radiobiological effects on tumour and its microenvironment are largely conjectural, particularly in relation to the stimulation of local immune reactions of the host. We do not yet know if the abscopal effects, observed with combination of chemotherapy with external beam radiation,[53] can be extrapolated to concomitant radionuclide tumour-targeted therapy. Nevertheless, in close consultation with radiation oncologists, an attempt to address these questions empirically, is being undertaken in the TARGET Phase 2 RCT 2-arm Australian study. Patients with biochemical recurrence of prostate cancer with oligometastatic nodal disease, following radical prostatectomy with curative intent, will be randomised to standard radiotherapy or combination lutetium-177-PSMA and external beam radiotherapy. (GenesisCare Theranostics CTN).

The theranostic combination of beta and alpha-emitting radionuclides may also be contemplated. Actinium-225-PSMA has achieved dramatic ORR in advanced mCRPC which is unresponsive to, or has relapsed after lutetium-177-PSMA beta therapy.[54] Kratochwil et al established the efficacy and durable response of their heavily pre-treated salvage patients by the novel use of the swimmer plot as the preferred way to visualise the sequence and duration of different treatment options.[55] Using a patient as that patient's own intra-individual comparator attenuated the random effects which may have been introduced by selection bias. Dose-limiting toxicity of actinium-225-PSMA is xerostomia which regularly occurs at administered activities exceeding 100kBq/kg per cycle.[56] Salivary gland toxicity may be severe and degrade quality of life to such an extent that treatment is stopped. Recent anecdotal reports by Professor Richard

Baum using combination lutetium-177-PSMA and actinium-225-PSMA in a "Tandem" approach, after failure of lutetium-177-PSMA monotherapy in a salvage treatment setting, showed dramatic complete remission in two patients, as featured in the Highlights of the World Congress of World Federation of Nuclear Medicine and Biology, 24 April 2018. This combination allowed de-escalation of the actinium-225 dose and minimised salivary gland toxicity. The adverse event (AE) of xerostomia is also being addressed by the novel use of scopolamine patches for patients treated with actinium-225-PSMA. (Professor Mike Sathekge, personal communication 24 April 2018). Previous attempts to mitigate the adverse effects on salivary gland function, such as local cooling, lemon juice and vitamin C injections, have not been successful[56] but results of ongoing trial of botulinum toxin injection or vitamin E are awaited.

Toxicity of theranostic management of mCRPC is otherwise minimal. By contrast, conventional combination chemotherapy is often quite toxic and the evolving immune-therapies are associated with novel adverse event profiles involving skin, gut, liver and endocrine system in up to 70–90% of patients, with 12–24% graded as serious.[57] Whilst most adverse events are manageable with supportive treatment, hypophysitis in up to 10%, neurological complications and hyperprogressive disease are of concern, and the unpredictability and ill-defined nature of serious side effects are troubling.[58] Harmonisation of multidisciplinary expert consensus is the key to managing specific immune-related adverse events (irAEs) associated with immune-checkpoint blockade.[46] Recent trials of CD19-targeted CAR T-cell therapy in haematological malignancies report a more favourable toxicity profile.[59] Overall, the incidence of irAEs of grade 3 or greater has ranged from 7–31% across retrospectively analysed studies.[60] Whilst combinations of immune-check point inhibitors may increase toxicity, the addition of concomitant radiotherapy appears to enhance response without significant toxic side effects,[60] for example, the incidence of AEs for ipilumumab and radiotherapy in melanoma is around 25%.

Whilst the physical toxicity profile of these novel immune-chemotherapeutic agents may be ameliorated, their financial toxicity is out of control. An editorial in July 2018 issue of *Nature Reviews Clinical Oncology* emphasises "We have a problem; the rising cost of anti cancer therapies and the current regulatory environment have helped to create an unsustainable (and unacceptable) situation".[61] "The cost of cancer drugs has increased dramatically, despite the fact that most drugs are brought into the market without compelling evidence thet they prolong survival or improve quality of life.[62] The commercial development and large-scale pharmaceutical marketing of theranostic agents has yet to be realised and it is to be hoped that the favourable adverse event profile may also be reflected in general affordability and availability for cancer patients worldwide.

Given the minimal toxicity of theranostics, synergistic combination of lutetium-177-PSMA with agents such as abiraterone, which upregulates the PSMA receptor, is currently under evaluation. Potential abscopal effects of tumour-targeted radionuclide theranostics may also be envisaged in combination treatments with immune-check point inhibitors, so that efficacy might be enhanced without the increase in toxicity associated with immune therapeutic drug combinations. These speculations, together with personal communications of work-in-progress, are presented as a preface to the authoritative reviews of theranostics and precision medicine which appear in this special issue of the *Journal*. The paradigm shift represented by theranostics relates not only to clinical practice, but, more importantly, to its practitioners, as they metamorphose into nuclear oncologists.

The opportunity for fruitful symbiotic collaboration of theranostic nuclear physicians, in a multidisciplinary and multimodality *rapprochement* with oncologists, should now be embraced. Having (over)due cognizance of the lessons of history, theranostic nuclear oncology is poised to play a significant role in comprehensive co-operative care of patients with advanced cancer, as an integral component of routine clinical oncology practice worldwide.

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