Review paper

Clinical perspectives on dosimetry in molecular radiotherapy

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ABSTRACT

Molecular radiotherapy is the use of systemically administered unsealed radioactive sources to treat cancer. Theragnostics is the term used to describe paired radiopharmaceuticals localising to a specific target, one optimised for imaging, the other for therapy. For many decades, molecular radiotherapy has developed empirically. Standard administered activity schedules have been used without the prior estimation of the resulting tumour radiation absorbed dose by theragnostic imaging, or its subsequent measurement by serial scanning. This pragmatic approach has benefited many patients, however others who should have benefited have failed to do so as the radiation absorbed dose in the tumour was suboptimal. The accurate prediction and measurement of tumour and organ at risk radiation absorbed doses allows treatment to be personalised, and offers the prospect of improved clinical outcomes. To deliver this for all molecular radiotherapy patients would require not only a significant financial investment in equipment and skilled personnel, but also a change in attitude of those who believe that simple – or simplistic – schedules are easier to deliver, and that accurate dosimetry is too much trouble. Further clinical studies are required to demonstrate beyond doubt that the advantages of individualised treatment planning outweigh the inconvenience, and that the expense is justified by enhanced results.

1. Molecular radiotherapy

Molecular radiotherapy is the currently preferred term used to describe the treatment of disease, often but not always cancer, using systemically administered unsealed radioactive isotopes. This label has been used for over 30 years [1], but has gained traction in the last decade [2]. Other phrases to describe this treatment are *radionuclide therapy*, *biologically targeted radiotherapy*, *radioimmunotherapy* and *radioligand therapy*, although they are not all completely synonymous.

The term molecular radiotherapy implies biologically targeted treatment; when a radiopharmaceutical is given systemically, either by mouth or intravenously injected, and is selectively taken up by a physiological pathway. Examples include the sodium iodide symporter in thyroid cells which takes up radioiodine, and the somatostatin receptor

on neuro-endocrine cells which takes up radiolabelled somatostatin analogues – sometimes referred to as *peptide receptor radionuclide therapy* [3]. This is in contradistinction to external beam radiotherapy, where a beam of high energy photons or protons is physically targeted at tumour volume which has been pre-defined on imaging, and brachytherapy, where a sealed radioactive substance is located within or adjacent to a tumour for a period of time [4–6].

However, the term molecular radiotherapy is sometimes also, perhaps erroneously, used to describe radionuclide therapies which are more physically than biologically targeted. For example, the injection into the hepatic artery of microspheres containing 166-Ho or 90-Y which embolise and deposit radiation in the tiniest capillaries of liver tumours; the injection of colloidal 32-P or 90-Y into joint cavities to perform a radiation synovectomy, or the use of 90-Y instilled into

craniopharyngioma cysts [7–11]. These are local physical techniques of delivering radiation, akin to brachytherapy, but still often called molecular radiotherapy.

Molecular radiotherapy is not new: 131-I radioactive iodine was first used over 80 years ago for the treatment of thyroid cancer [12]. Since then, new indications and new radiopharmaceuticals have been developed for use in a wider range of diseases, including 131-I *meta*-Iodobenzylguanidine (mIBG) for neuroblastoma and some adult neuroendocrine cancers such as phaeochromocytoma and paraganglioma, 90-Y or 177-Lu labelled somatostatin analogues for the treatment of gastro-entero-pancreatic neuroendocrine cancers, and 90-Sr chloride, 223-Ra chloride and 177-Lu prostate specific membrane antigen (PMSA) for metastatic prostate cancer.

1.1. Theragnostics

Molecular radiotherapy is the second part of a concept called *theragnostics* (sometimes spelled as theranostics). In this, pairs of radiopharmaceuticals which target the same pathway are used, one for diagnostic imaging, the other for treatment. For example, 123-I mIBG scanning for neuroblastoma coupled with 131-I mIBG for therapy; 68-Ga DOTATATE positron emission tomography (PET) scanning for neuroendocrine cancers and 177-Lu DOTATATE for therapy. The imaging part of theragnostics may be both before treatment, to indicate disease extent and assess suitability, and after therapy to evaluate the response to the molecular radiotherapy.

It can be argued that the great success of fixed administered activities of radioiodine in improving outcomes for differentiated thyroid cancer has stifled intellectual curiosity and academic endeavour to use molecular radiotherapy for other conditions in the best possible way. Even now, the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) simply recommends fixed administered activities of either 1.1 GBq or 3.7 GBq following surgery for thyroid cancer in adults [13]. Recent UK paediatric guidance suggests that consideration is given to the adjustment of the radioiodine activity for thyroid ablation and therapy based on the size of the child or young person [14]. Neither guideline recommends measuring the radiation absorbed dose in tissue for remnant ablation, although it has been shown that the radiation absorbed dose in thyroid remnants varies by two orders of magnitude, and that the likelihood of successful ablation is strongly correlated with the radiation absorbed dose when a fixed activity is administered [15]. Similarly, dosimetry following radioiodine therapy for metastatic thyroid cancer is seldom performed, although it has been shown to be clinically useful, as can be seen in the dosimetry study performed with 30 patients with advanced or metastatic differentiated thyroid cancer, which aimed to assess the usefulness of dosimetry in decision making. Dosimetry was performed on images taken on days 2, 3 and 7. Ninety percent had a less than complete response and needed repeated radioiodine administrations. There was a correlation between the dosimetry and thyroglobulin levels, which, combined with anatomical scans, helped to define refractory patients earlier, thus preventing unnecessary repeated radioactive iodine administrations [16].

2. Dosimetry

Dosimetry means the measurement of radiation absorbed dose. In chemotherapy, the term 'dose' is usually used for the amount of the drug administered at one point in time. This may be expressed simply as a weight, such as milligrams, or scaled depending on the size of the patient by weight, or body surface area, sometimes capped at a maximum 'dose'. This concept of 'dose' usually bears no relationship to the amount of drug which reaches the tumour, or the drug concentration within the blood, the tumour itself, or organs which may be exposed to toxic effects, as pharmacokinetics are seldom taken into account. In some instances, measurement of plasma concentrations and rate of clearance is performed, and an 'area under the curve' is calculated, which may relate to efficacy or toxicity.

Molecular radiotherapy is different, however. The amount of radiopharmaceutical which is injected (or given orally) is erroneously referred to as the 'dose', when it would more properly be designated administered activity. As an aside, the administered activity relates to the quantity of radioactivity (measured in Becquerels (Bq) or multiples thereof, like mega- or giga-Becquerels (MBq or GBq)), not simply the quantity of the non-radioactive drug (measured typically in milligrams or micrograms). In some readily available radiopharmaceutical preparations, each radioactive molecule is accompanied by chemically identical non-radioactive molecules, which sometimes outnumber the radioactive ones by three orders of magnitude. The pharmacokinetics and efficacy of carrier-free or no-carrier-added preparations may be different to that where the active product may be diluted a thousand-fold by inert molecules. An example is standard I-131 mIBG and carrier-free I-131 mIBG, with the carrier-free preparation having significantly increased uptake in cutaneous, cardiac and adrenal tissues compared relative to the standard preparation [17].

In molecular radiotherapy, the term 'dose' should be used to refer to the radiation absorbed dose (measured in Grays (Gy)). Clearly, the radiation absorbed dose may be varied in different parts of the body, and in different tumour deposits. In an ideal situation, using molecular radiotherapy for a metastatic cancer with several separate tumour deposits, one would know the radiation absorbed dose received by each metastatic site, or at least a sample of them, as well as by any dose-limiting organs, for example the kidneys. As haematological toxicity is sometimes the first dose-limiting toxicity, red marrow radiation absorbed dose is sometimes measured. This is not easy and, as a simple proxy, whole body radiation absorbed dose can be useful. As such, the advantage of dosimetry is that it enables ascertainment of the radiation absorbed dose given to various regions of the body and specific organs at risk.

In simpler words, radiation absorbed dose describes the absorbed radioactivity and can vary between different tumour deposits, and organs and other tissues, whereas the administered activity is the overall amount of radioactivity given to the patient without accounting for radiobiological and radiopharmaceutical interaction. It is the radiation absorbed dose, specific to each patient, that mediates the tumour-killing effect, and is therefore responsible for tumour response (Fig. 1).

2.1. The therapeutic window

Within any type of treatment there is the concept of the therapeutic window. This is used to define the optimal amount of a treatment - whether chemical or radiation - that can be applied to ensure that there is the desired treatment effect without undue toxicity. If the therapeutic window is exceeded, then there will be a good therapeutic effect but at the expense of increasing toxicity. For a molecular radiotherapy agent, the organs at risk (OAR) are normally different from the tumour target. For example, for an agent such as 177-Lu DOTATATE, the principal OAR are the kidneys, where a cumulative radiation absorbed dose of more than 23 to 30 Gy may result in permanent renal damage [18,19]. However, in an attempt to ensure that this renal radiation absorbed dose is not reached it is possible the patient will not receive sufficient delivery of radiation to kill the tumour, and thus remain below the therapeutic window. This would result in the patient receiving a significant radiation absorbed dose without any certainty of a positive treatment outcome. The concept of the therapeutic window, and its relevance to the delineation between administered activity and radiation absorbed dose, can be seen a study where 131-mIBG was used to treat neuroblastoma. A correlation was found between the whole body radiation absorbed dose and haematological toxicity, but not between haematological toxicity and administered activity. This shows the value of dosimetry over administered activity in defining the therapeutic window [20].

With external beam radiotherapy, careful treatment planning ensures that the desired amount of radiation is delivered to the planning
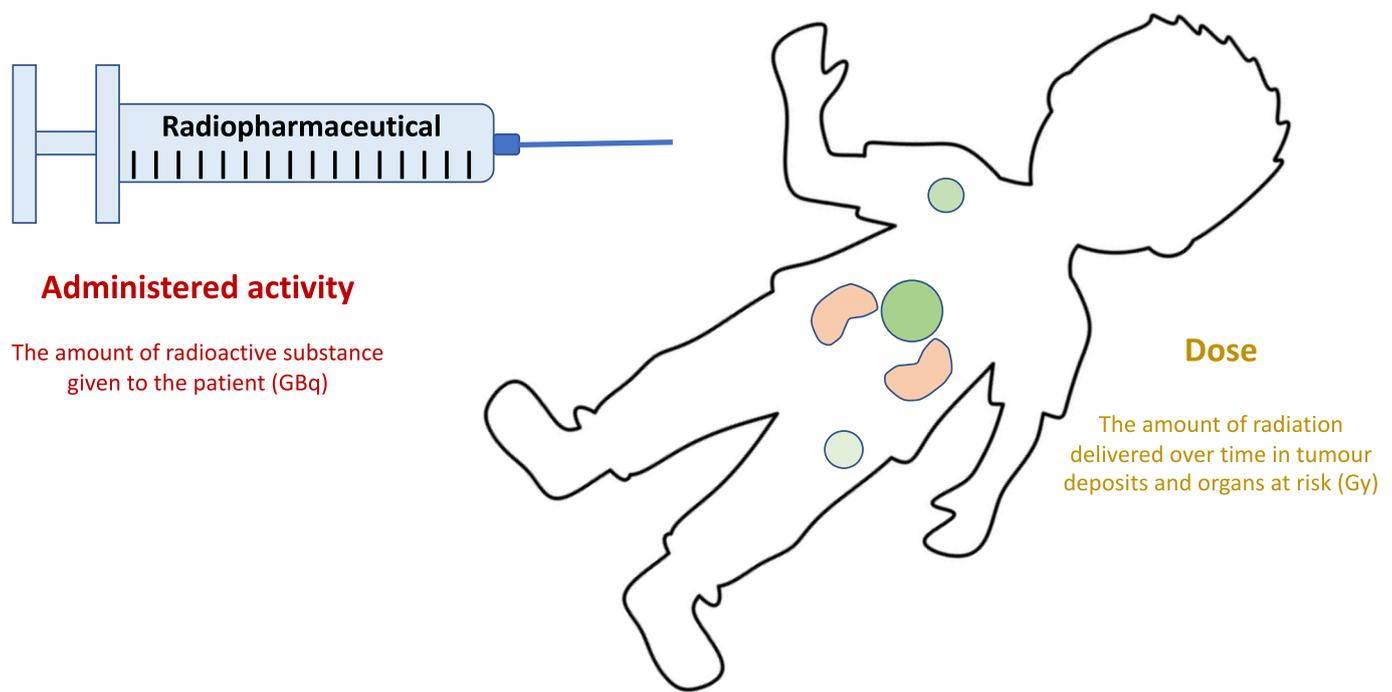
Fig. 1. The amount of the radiopharmaceutical given to the patient is called the ***administered activity***, measured in GBq. The distribution of this within the body is not homogeneous as the drug is targeted to specific tissues, and the pharmacokinetics varies over time in different tumour deposits and organs. The cumulative amount of radiation absorbed in tumours and in organs at risk varies, and this is known as the ***radiation absorbed dose***, measured in Gy.

target volume (PTV), using a beam arrangement which keeps the amount of radiation received by adjacent OAR as low as reasonably achievable. In external beam radiotherapy, the word 'dose' used alone is well recognised as being the prescribed or actual amount of radiation absorbed in tissue, and so in this context is not normally called the "radiation absorbed dose", although we have used the term in this article to avoid confusion. The tolerance of normal tissues to external beam radiotherapy is by and large clearly defined [21]. It is not always possible to keep OAR doses within these radiation absorbed dose objectives while giving the prescribed radiation absorbed dose to the PTV. In such cases, compromise is called for, relying on clinical judgement as to whether reduce the radiation absorbed dose to all or part of the PTV risking reduced tumour control in order to preserve normal tissue function, or to exceed OAR tolerance knowingly, judging the risk of treatment related morbidity to be less than the risk of inadequately treating the tumour. Every external beam radiotherapy department has many dosimetrists and physicists to undertake this planning in conjunction with the responsible clinicians. Molecular radiotherapy, having developed largely within nuclear medicine departments, and independently of external beam radiotherapy, does not have access to this plethora of manpower and technical resources.

With systemic molecular radiotherapy there can be a number of confounding factors such as the biodistribution of the radiopharmaceutical used, and the methods of urinary or faecal excretion, and how this may be affected by co-morbidities such as impaired renal or hepatic function (which may be affected by the tumour which is being treated), or other medications the patient is taking. Whilst it may be possible to use pre-treatment imaging to have some idea of the biodistribution, it is not possible to be certain a therapeutic agent will have the exact same distribution as its diagnostic partner. Therefore, without a dosimetric assessment it is not possible to ensure the radioactivity delivered is enough to have a therapeutic effect without excessive toxicity, and the treating clinician cannot make subsequent adjustments to the activity administered to ensure that treatment is within the therapeutic window for that patient (Fig. 2).

This is to some extent a simplification. There is not a single radiation

absorbed dose which controls all tumours, but a sigmoid radiation absorbed dose–response curve where increments in radiation absorbed dose dose will cure an increasing proportion of tumours. Similarly, there is not a single radiation absorbed dose which is safe for normal tissues which when exceeded causes morbidity; rather, there is a sigmoid relationship between radiation absorbed dose and morbidity. The gap between these two curves is called the therapeutic index (Fig. 2), and various manipulations in delivery of an administered activity can alter the therapeutic index to some extent.

2.2. Non-dosimetric molecular radiotherapy

Almost all forms of systemic molecular radiotherapy used worldwide are given as an empirical activity. Initially, when Dr Saul Hertz was treating his first group of patients with benign and malignant thyroid disease, the activity given was dependent primarily on the activity of the I-130 and I-131 he could obtain from the cyclotron used to make this product[3]. The fact that for most patients he treated there was a good outcome without significant toxicity was primarily due to the wide therapeutic window of radioiodine and the fact so few normal tissue cells expressed the sodium iodine symporter, meaning that only thyroid cells in most patients could internalise and fix the radioiodine via organification. In the 1950s and 1960s, the science of dosimetry was limited by poor imaging devices but it was possible to measure the administered activity with some accuracy, so most treatment regimens reflected memorable administered activities such as 30, 100, 150 and 200 mCi which were then translated to 1.1, 3.7, 5.5 and 7.4 GBq in Europe. These historical and empirical activities have continued to be used in recent clinical trials and guidelines [3,22,23]. This continued with the administration of Sr-89 chloride used to treat painful bone metastases which was administered to all patients - regardless of weight or size - in a single activity of 4 mCi (148 MBq)[24]. By the 1990s, when Sm-153 lexidronate began to be used to treat painful bone metastases, the activity given was adjusted for weight, and the same approach was taken to tailor the activity of Ra-223 chloride when it was also introduced in 2013 to treat bone metastases from prostate cancer [25,26]. This use of standardised activities has led to a deeply seated confusion

Probability
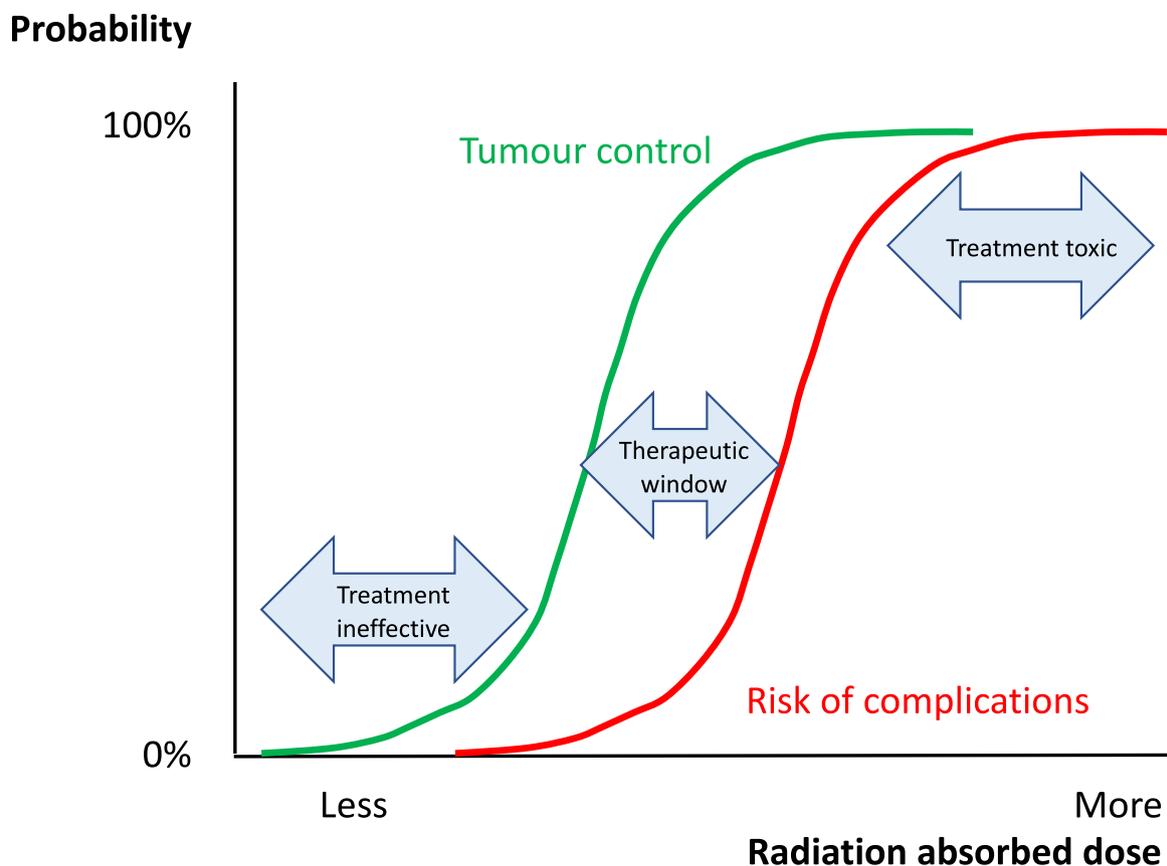
Fig. 2. This shows a stylised radiation absorbed dose response curve, and a parallel dose toxicity curve to the right. Clearly the radiation absorbed dose response curve depends on the nature of the tumour being treated, and the morbidity of the organ being considered. Depending on the steepness of the curves at different doses, a small increment or decrement in radiation absorbed dose may produce a large or small change in effect. In any treatment there is an optimal range of radiation absorbed dose called the therapeutic window. At that radiation absorbed dose there is the maximum curative effect for the patient with the minimum of side effects. Below the therapeutic window the treatment will be ineffective. Radiation absorbed doses above that window could result in increasing toxicity to the patient. Using dosimetry in molecular radiotherapy it should be possible to adjust the administered activity, so the radiation absorbed dose given to sites is within the therapeutic window. Without dosimetry this is not possible.

among clinicians that the activity given does indeed equate with radiation absorbed dose. In the UK's recent NICE guidance for the management of adult differentiated thyroid cancer the term activity is used [13]. It must be noted, though, that this approach is not universal and in Germany and Switzerland there has always been an emphasis on the use of a dosimetric approach to the use of radioiodine in both benign and malignant thyroid disease which is reflected in national and European guidelines [27].

In addition to this empirical approach, there are two philosophically distinct forms of dosimetry-guided molecular radiotherapy. In one, the maximum tolerated amount of treatment is given, with the aim of delivering the highest possible radiation absorbed dose to the tumour while not exceeding OAR tolerance. In the other, more akin to external beam radiotherapy, the aim is to deliver as accurately as possible, a prescribed radiation absorbed dose to the tumour.

2.3. Retrospective dosimetry

The most common form of dosimetry used in molecular radiotherapy is a retrospective approach, whereby an initial standardised activity of a molecular radiotherapy agent (such as 7.4 GBq 177-Lu DOTATATE) is administered, with a series of whole-body images subsequently acquired over the next week. Ideally, this would include three or more SPECT images of the area covering the organ of interest (in this case tumour deposits), and taking the kidneys and spinal red marrow as the OAR [28]. Whilst this provides a significant amount of information, it may not be possible to complete the full imaging set due to the patient either

being too frail, too young, having significant morbidities or co-morbidities or living too far away from the hospital for this to be practical. As a consequence, some single time-point imaging protocols have been suggested [29]. The aim of this form of dosimetry has been to attempt to predict possible toxicity to the organ of interest which for 177-Lu DOTATATE is the kidneys and red bone marrow [30]. However, there appears to be a poor correlation between calculated radiation absorbed dose and side effects, such that the renal dose of 30 Gy may be exceeded without significant reduction in renal function, whereas in contrast bone marrow toxicity appears to have little relationship to the calculated radiation absorbed dose, perhaps due to inaccuracies in the methods or calculation, or resulting from pre-conditioning of the bone marrow from prior radiotherapy or chemotherapy [31]. In addition, whilst it is possible to reduce the administered activity if maximum tolerated radiation absorbed doses are likely to be exceeded, it is not possible under the present UK, European or North American product licences to increase administered activity and thus possibly enhance tumour kill, even if dosimetry shows this can be done without exceeding the maximum tolerated radiation absorbed dose [32,33]. As such an approach would undoubtedly affect patient outcomes it would need to be tested in a randomised clinical trial before it could be adopted. However, in an attempt to reduce the possibility of significant toxicity from molecular radiotherapy the UK Administration of Radioactive Substances Advisory Committee (ARSAC) requires all new individual and site holders to state what dosimetry is provided. Furthermore, the ARSAC Notes for Guidance [34] states:

IR(ME)R requires that practitioners ensure that exposures of target volumes are individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues must be as low as reasonably practicable and consistent with the intended radiotherapeutic purpose of the exposure. ARSAC recommends that:

(a) in cancer treatments with radioactive substances, the absorbed dose to the tumour, and to non-target volumes and tissues, following each administration should be measured and recorded, to permit subsequent optimisation of total doses

(b) for treatment of benign conditions or, where direct measurements are impossible, absorbed doses should be calculated or estimated and recorded.

This is in accordance with the European Union Directive 2013/59 [35] which states:

For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.

This approach has been endorsed by the British Nuclear Medicine Society but has not been adopted elsewhere [2].

2.4. Prospective dosimetry

In contrast to the retrospective approach described above, prospective dosimetry is more akin to conventional treatment planning in external beam radiotherapy. Serial SPECT or PET whole body imaging is performed prior to treatment using the diagnostic radiopharmaceutical which is the theragnostic partner of the planned treatment agent, making the assumption – accepted in theragnostics – that the kinetics of the diagnostic agent are identical to the therapeutic radiopharmaceutical.

One example is the Radio-immunotherapy Trial, where initial imaging with 111-In-labelled anti-CD66 monoclonal antibody is performed; the 111-In emits gamma radiation that can be imaged to allow delineation of anatomical tumour distribution and to prove antibody-affinity to tumour cells[36]. Whole-body images are acquired with the gamma camera, and software is used to quantify uptake at specific regions of interest (ROI). This data is subsequently used to calculate the time-activity curves for each organ and to estimate radiation absorbed dose. Following this, treatment-dose radiation is administered with 90-Y anti-CD66 – the same monoclonal antibody, but this time coupled with a pure beta-emitting radionuclide, depositing high radiation absorbed dose into the tumour whilst ensuring that the radiation absorbed dose to the OAR is within acceptable limits. The aim here is to ensure that the treatment will not exceed normal tissue tolerance.

Another possible use of prospective dosimetry is in 131-I mIBG therapy for children with neuroblastoma. A standard weight-based administered activity, such as is typically used in North America results in a varying whole-body dose [37]. An administration of 444 MBq/kg results, on average, in a whole-body dose of 2 Gy – but this varies significantly [38]. In Europe, recent practice has been to give an initial weight-based activity and measure the resulting whole-body dose. A second administration is then given, with an activity designed to top up the whole-body dose to a desired, prescribed level. This is the approach taken in the ongoing MINIVAN trial, where 131-I mIBG is followed by nivolumab and dinutuximab beta for refractory neuroblastoma patients [39]. In this study, the first administration is weight-based (222 MBq/kg), then the whole body radiation absorbed dose is calculated using dosimetry based on planar images and the activity of the second administration is adjusted to give a tailored whole-body radiation absorbed dose of 2 Gy [39].

Another recent trial for poor responders in high-risk neuroblastoma is the VERITAS trial, which used the same concept of prospective dosimetry as MINIVAN. In VERITAS, an initial 131-I mIBG therapy with a fixed activity of 444 MBq/kg is administered, with dosimetry then performed and the prescribed activity of the second administration adjusted to give a whole body radiation absorbed dose of 4 Gy [40]. The overarching aim is to give a whole-body radiation absorbed dose which is standardised, and within acceptable limits of toxicity known as maximum tolerated radiation absorbed dose (MTAD); the achievement of which is not possible with a single administration. A future development in mIBG therapy, currently in trial phase, will utilise 124-I mIBG PET/CT, allowing the use of prospective dosimetry [41]. 124-I has a half-life of 4.18 days which permits serial imaging over several days, thus allowing the pharmacokinetics within an individual patient to be determined, giving a more accurate assessment of dosimetry following therapeutic I-131 administration, and allowing a more tailored administered activity of 131-I mIBG can then be administered to give a desired whole-body or tumour radiation absorbed dose as a single administration [42].

Another recently published clinical trial, SEL-I-METRY, has provided good evidence that pre-therapy dosimetric predictions using 123-I sodium iodide scans are highly correlated with the measured radiation absorbed doses in thyroid cancer metastases [43].

3. The need for clinical trials

As discussed above, the iterative development of molecular radiotherapy from the first use of radioactive iodine in thyroid cancer to its current clinical applications has been largely empirical. As newer agents have come into clinical use, the emphasis placed by the pharmaceutical companies marketing them has been on simplicity and ease of use. As a result, the clinical trials leading to marketing authorisation have often used a certain number of fixed administered activity treatments without dosimetry (for example, the use of 223-Ra dichloride in skeletal metastases in prostate cancer, where 50 kBq/kg were administered monthly for six cycles; 177-Lu DOTATATE in well-differentiated, midgut neuroendocrine tumours at a set dose of 7.4 GBq for four cycles, one every 8 weeks; and 177-Lu-PSMA-617 in metastatic castration resistant prostate cancer, with 7.4 GBq given every 6 weeks for four to six cycles), rather than develop personalised, dosimetry-based protocols which may optimise outcomes [44–46].

This outlines an immense gap in theragnostic potential: efficacious molecular radiotherapies exist, but far higher response rates might be achieved if these therapies were used more intelligently. For example, NICE guidance for 177-Lu-DOTATATE recommends four fixed activity administrations, which we know results in a survival benefit. This recommendation was based on the NETTER-1 trial, a randomized phase 3 clinical trial, in the setting of metastatic, well-differentiated midgut neuroendocrine tumour, comparing 177-Lu-DOTATATE to high dose octreotide after failure on standard dose octreotide. There was a statistically and clinically significant improvement in progression free survival in the Lutetium arm [45]. However, this protocol was specifically designed not to exceed the therapeutic window and to avoid radiation nephrotoxicity, and there is potential to employ a dosimetrically guided schedule up to a renal tolerance in order to obtain better, and more personalised, outcomes. There is no current clinical trial ongoing where dosimetry guided increased tumour radiation absorbed dose is being evaluated, and it is imperative that good quality data, investigating the therapeutic potential here, is acquired.

In childhood neuroblastoma a series of studies and trials employing dosimetry to evaluate 177-Lu-DOTATATE therapy have been conducted; and demonstrate how the dosimetric findings of earlier studies have subsequently informed the later ones. Initially, based on the adult neuroendocrine tumour schedule, the phase IIa LuDO trial gave up to four cycles, with an administered activity of 75–100 MBq/kg, at intervals of eight to twelve weeks [47]. However, although some early

transient responses were observed, no responses were seen one month after completion of treatment. Causes for this included the relatively low administered activity, designed to avoid toxicity, and the two-month time interval between courses which allowed tumour cell repopulation [47]. Dosimetry data from this trial showed that the measured kidney radiation absorbed doses were nowhere near accepted renal tolerance levels, indicating that higher activities could safely be given. Tumour dosimetry data demonstrated declining radiation doses with successive courses, suggesting that fewer courses might be better [48]. The LUDO-N trial was developed to address these limitations, with two 177-Lu-DOTATATE administrations, separated by two weeks, with administration prescribed to a whole-body radiation dose of 2.4 Gy rather than a fixed activity [49]. This more personalised approach aims to demonstrate better tumour outcomes with no worsening toxicity, when compared to other ongoing trials - such as NEUROBLU 02 – that take a more empirical approach [50].

A more established molecular radiotherapeutic approach to metastatic neuroblastoma is 131-I mIBG therapy. A randomised trial of this radiopharmaceutical compared a fixed administered activity of 666 MBq/kg was used either as a single agent, or with vincristine and irinotecan, or with vorinostat. Response rates of 14 % were seen in the mIBG monotherapy and mIBG with vincristine and irinotecan arms, and 32 % in the mIBG and vorinostat arm [51]. Because of the sample size, this difference was not statistically significant, but the response rates were in keeping with, but relatively low compared with, a mean response rate of 32 % (range 0 % to 75 %) reported in a systematic review of 131-I mIBG therapy [52]. It is plausible that a more personalized dosimetric approach would result in better outcomes – but that is a hypothesis which requires further trials to demonstrate whether or not it is true.

As well as trials on the value of designing molecular radiotherapy protocols which aim to give a standard prescribed radiation absorbed dose to the tumour, or trials evaluating escalation of the tumour radiation absorbed dose, it is important for trials also to investigate other uncertainties in molecular radiotherapy. These include OAR constraints, where there is significant uncertainty. The limits to OAR radiation absorbed dose are largely derived from external beam radiotherapy, but the radiobiology of molecular radiotherapy, which involves a continuous but declining dose-rate, is very different. Much more work is needed to understand this fully.

4. Examples from localised "molecular radiotherapy"

Unlike systemic molecular radiotherapy, those agents which are applied locally or regionally have generally used a dosimetric approach to determine the activity to be given. This involved not only those agents designed to be given locally but those systemic agents given locally [53]. Examples of this approach was most commonly used in treatment of either metastatic disease within the liver or primary liver cancers. Initially a non-dosimetric standard activity method was used with I-131 Lipiodol [8]. This can work if the product is given via the hepatic artery via a radiologically placed catheter. It is possible to treat individual liver segments, a whole lobe or the whole liver. Some of these agents also had some embolic function. The normal hepatocytes are protected as they are supplied not just by the hepatic artery but by the blood provided by the portal vein, whereas malignant hepatic tumours derive their blood supply from new arterialised vessels and thus are far more susceptible to arterially-delivered agents. 131-I-Lipiodol was difficult to make and was expensive. The International Atomic Energy Agency (IAEA) worked with Universities in Korea and Singapore to develop a 188-Re Lipiodol which could be manufactured in a normal radiopharmacy. Early studies included a centrally determined dosimetric calculation of the radiation absorbed dose given to both the liver and the tumour showing tumour response occurred if the tumour received more than 30 Gy and liver toxicity was not significant if the normal liver radiation absorbed dose was reduced to below 30 Gy [54].

In the late 1990 s two new agents emerged which were labelled with Y-90 which is much easier to handle for intra-arterial administration as it was a pure beta emitter. One agent from Canada used glass spheres containing Y-89 which is neutron-bombarded to make Y-90. This product was known as Theraspheres. In Australia an alternate product – Sirspheres - used a resin product with Y-90 adsorbed onto its surface. From its first use Y-90 Theraspheres were used with prospective dosimetry. A week to ten days before the administration of the Y-90 product, Tc-99 m MAA is administered via a catheter placed in the branch of the hepatic artery or the common hepatic artery that supplies the neoplastic lesion. Subsequent imaging allows calculation of the degree of blood shunting to the lungs, and the distribution of the particles within the liver [55]. In additional, the volume of the target lesion is delineated on conventional imaging (CT or MRI), with dosimetric assessment performed to determine the activity of Y-90 Theraspheres required to give a radiation absorbed dose of 80–120 Gy to the target volume, whilst also keeping the radiation absorbed dose to the non-target liver and lung to less than 30 Gy [53]. The prediction of organ radiation absorbed dose received was simpler but firstly a more predictable and limited distribution of the molecular radiotherapy agent and the very small leach rate as little as 1 % per 24 h [9].

The approach with Sirspheres was somewhat different, with three dosimetric approaches suggested:

1) An empirical activity of no more than 3 GBq, a method based on the proportion of the liver affected by the tumour and the patient's body surface area.
2) A dosimetric method.
3) If more than 15 % of the activity on pre-assessment Tc-99 m MAA study was found in the lung on imaging the activity given was reduced or treatment with Y-90 Sirspheres would not proceed[7].

There were two large-scale, phase III randomised controlled trials, one on colon cancer metastases in the liver and the other in hepatocellular cancer [57,58]. The results of both studies were to some degree disappointing. It was determined that without dosimetry it was not known how much radiation dose the tumours received and as such it may be that the tumours were undertreated in those patients with treatment failures. Subsequently, a prospective randomised controlled study of 60 patients with hepatocellular cancer was undertaken. In this, thirty were assigned to receive administered activity assessed using the body surface area method and another thirty patients were treated with a calculated tumour dose of 100 Gy and normal liver dose to less than 40 Gy and lung doses to less than 30 Gy [53]. In the group of patients treated using the body surface area method, 33 % had a greater than 50 % reduction in tumour size and 33 % had significant (normally hepatotoxic) side effects. In the group of patients given activities of Y-90 Sirspheres determined by a dosimetric approach showed 95 % of patients had a greater than 50 % reduction in tumour size and only 20 % had significant side effects [56]. It is clear that a dosimetric approach should be used for the treatment of tumours in the liver with these Y-90 agents in order to optimise tumour kill effect and minimise toxicity. This approach is reflected in the newly developed molecular radiotherapeutic agents, including 32-P-silicon in pancreatic cancer and 188-Re topical skin cancer therapy (SCT), which use only a dosimetric approach [59,60]. In 188-Re-SCT, a measured amount of radioactivity is measured using a dose calibrator, and the treatment time was calculated using a multi-point source, real-time integration software program to a defined tumour surface area to give a surface dwell time that allows precise dosimetry. Calculations assume that 50 Gy at a depth of 300–600 μm will be lethal to skin neoplasm of, or less than, that thickness, and in the study of Cipriani et. al., treating 55 lesions with 188-Re-SCT, a dose of 50 Gy at the deepest lesion point (predetermined on histology) was achieved in all patients, with complete remission seen after a single session in all patients [61].

5. Resource implications

Whether the molecular radiotherapy agent is administered via a clinical oncology, nuclear medicine or mixed setting there is a legal requirement within Europe for medical physics input[59]. The medical physics team is responsible for a range of aspects of the administration of the molecular radiotherapy agent and radiation protection but are also the primary group involved in estimation of dosimetry. There has been reported a significant shortage of medical physics staff in many European nations [63]. A recent review in the United Kingdom looking at the need for expanding services in molecular radiotherapy identified many issues [62]. In addition to a shortage of staff there were also problems with the lack of standardised software and training to use these programmes. As many centres have not previously provided a patient-based dosimetry service there may also be a shortage of required gamma camera time as well as a shortage of staff to scan patients [62]. This means that significant investment in personnel, training and equipment is required for volume of dosimetric calculations needed to supply a true patient based radiation dose service. This is also an important topic for future research. A careful health economic analysis is required to demonstrate that the additional investment required is justified, and to answer the criticism of sceptics who believe that the additional effort is not warranted.

6. Conclusions

This paper has outlined the principles underlying dosimetry in molecular radiotherapy, reviewed the literature pertaining to the current and ongoing studies in this field, and made consideration of the potential barriers to a more standardised and widely-adopted dosimetry service in the UK, as well as considering the future direction that dosimetry in molecular radiotherapy will take in the future. In summary, the discipline of molecular radiotherapy has the potential to deliver excellent clinical outcomes. Its development historically has been mostly empirically driven, in part due to its use in highly pre-treated cancers in the pre/peri-palliative setting. However, as molecular radiotherapy is increasingly considered in earlier phases of treatment, consideration of the need to give more personalised dosing of radiotherapy, both to ensure a higher tumour kill effect, and to minimise the impact on healthy background tissue.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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