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REVIEW ARTICLE

Milestones in dosimetry for nuclear medicine therapy

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ABSTRACT

Nuclear Medicine therapy has reached a critical juncture with an unprecedented number of patients being treated and an extensive list of new radiopharmaceuticals under development. Since the early applications of these treatments dosimetry has played a vital role in their development, in both aiding optimisation and enhancing safety and efficacy. To inform the future direction of this field, it is useful to reflect on the scientific and technological advances that have occurred since those early uses. In this review, we explore how dosimetry has evolved over the years and discuss why such initiatives were conceived and the importance of maintaining standards within our practise. Specific milestones and landmark publications are highlighted and a thematic review and significant outcomes during each decade are presented.

1900S – INTRODUCTION

The use of radioactivity in the treatment of ailments and disease has arguably had a somewhat chequered history. Soon after the initial discovery of radioactivity by Henri Becquerel in 1896 and of Radium by Marie and Pierre Curie in 1898, the exciting opportunities offered by this strange phenomenon were exploited. Despite no understanding of the true biological effects of radiation, commercialisation for its supposed health benefits were readily encouraged. Marie and Pierre Curie both suffered from effects of radiation poisoning, including anaemia, fatigue and bone pain, from which Marie Curie would later fall victim. Yet this potentially dangerous and misunderstood element was quickly integrated into everyday products for its supposed magical healing powers and 'glow in the dark' novelty.[1] Examples included items such as toothpaste, cosmetics and chocolate. Supposed remedies from radioactive water included ailments of anything from ingrowing toenails, to sexual impotence and arthritis.[2]

This article explores the scientific and technological advances since the early discoveries and applications, and how these led to the current status of internal radiation dosimetry for nuclear medicine therapy.

1910S – THE NEED FOR STANDARDISATION

During the initial years following the discovery of radium, many of the standard concepts, now taken for granted, were still being conceived. In a report following the International Congress of Radiology and Electricity in 1910[3] Ernest Rutherford recalled the need to increase the accuracy and reduce the uncertainty of radioactive measurement. At that time, scientific results were expressed in terms of arbitrary radium standards kept in each laboratory. In the course of the congress, a "primary standard" was proposed, that Marie Curie volunteered to produce. The name Curie (in honour of her late husband) was also suggested as a new unit to express the quantity of radioactivity. The amount of emanation (emission) in equilibrium with one milligram of radium would be called 1/1000 curie or one millicurie (although this term would not be formally adopted until 1950). A second new term "half-value period" was also devised to describe the time required for a substance to be transformed to half its value.

1920S – CONCERNS REGARDING DANGERS OF RADIATION

Whilst also of scientific interest, commercial interest in radium was abundant and radium became a precious material. One of the most famous misuses of radium was that of the clock dial painters. Between 1917 and 1926, the U.S. Radium Corporation employed more than a hundred females to paint watch and clock faces with luminous paint, comprising glue, water and radium powder. Workers would maintain a fine point to the paintbrushes with their mouths and some used the material to paint their nails and teeth. In February of 1929, Harrison Martland, an examining physician published an extended report documenting the clinical effects of radium poisoning in the painters.[2] Side-effects

included anaemia, osteitis, necrosis of the jaw, deformities of the spine, spontaneous fractures, acute myeloid leukaemia, myeloma and osteogenic sarcomas.

To respond to the growing concerns of these and other reports of radiation induced injuries including hair loss and burns resulting from scientific and medical experiments with x-rays, in 1928 the International X-ray and Radium Protection Committee (IXRPC) was formed. This was a sister organisation of the International X-ray Unit Committee conceived three years previously. The organisations would later be renamed to the International Commission of Radiological Protection (ICRP) and the International Commission on Radiation Units and Measurements (ICRU).

Early publications of the IXRPC are evidence of what would become the on-going theme for the use of radioactivity for therapeutic purposes. Notably, an extract from a report of 1931 is an early request for proper recording of medical exposures.[4]

> "…request to the doctor to add to his statement of the exposure as detailed information as possible regarding all data of importance to the treatment. The information given on this point, at least in the literature, is remarkably scanty. This may possibly be the main reason for the fact that different doctors, using the same method of radiation, frequently obtain very divergent results of the treatment."

In 1928, the Roentgen was formally defined as the first unit for the measurement of exposure from X-rays and γ-rays.This was a major milestone in the standardisation of radiation measurement. However, the roentgen was only a measure of air ionisation and not a direct measure of radiation absorption in other materials. The unit of exposure was also limited to photon radiations with energy less than 2.5 MeV.

1930S – THE FIRST CLINICAL APPLICATIONS

By 1930, it was recognised that further clarification was needed on the unit of radioactivity and specific definitions were required for the radioactive constants. This responsibility was tasked to the International Radium Standards Commission.[5] The Curie was defined as the number of α particles emitted per second from 1 g of radium equal to $3.7.10^{10}$. The unit quantity of any other radioactive element would then be expressed in terms of the mass equivalent to 1 g of radium with respect to the number of atoms decaying per second.

Whilst standards for the measurement of radiation exposure were being developed, discovery and advances in the field of nuclear physics also continued. Frederic Joliot and Irene Curie first synthesised artificial radioactivity in 1934[6] and by 1937 over 200 radioactive isotopes had been identified and produced by artificial means.[7] A list that included many of those in common use today, such as ^{90}Y, ^{131}I, ^{177}Lu and ^{223}Ra.

The first reported medicinal uses of an artificial radioisotope was that of radio-phosphorous in 1936 by John H. Lawrence of Berkley for the treatment of leukaemia and polycythaemia. In a 1940 report in *Radiology*[8] Lawrence described the unique possibilities offered by these therapies.

> "The radiations really "label" the element and the presence of a fraction of a given dose of any element, deposited in tissue or biologic materials, may be determined accurately by counting the radiations emitted by that tissue."

Attempts were also made to measure and record the radiation exposure to the patients.

> "In no case has the patient received more than an equivalent of 3 roentgen daily whole body irradiation"

The most successful radiotherapeutic isotope was ^{131}I, first investigated by Saul Hertz and Arthur Robert at the Thyroid Clinic of the Massachusetts General Hospital and the Physics Department of the Massachusetts Institute of Technology. In a paper of 1939 Hertz et al reported the bio-distribution and kinetics of radio-iodine in the thyroids of rabbits and the therapeutic application of radio-iodine was first proposed.[9] Different iodine isotopes were investigated, and a method to calculate the required administered activity to deliver a desired exposure was established.

For 25 min Iodine : $100r$ = 0.1 millicurie per gram thyroid (I-128)

For 8dayIodine : $100r$ = 0.6 millicurie per gram thyroid(I-131)

where r is the exposure in Roentgens. Hertz also postulated on the biological effectiveness of different dose rates.

> "These activities are very different from each other, and we must now consider the Bunsen-Roscoe reciprocity law. It is a question still under debate as to whether a weak source supplying radiation for a long time will have the same effect as a strong source supplying the same total radiation."

1940S – INITIAL CONCEPTS OF DOSE AND DOSE EQUATIONS

During this time, the field of radiotherapy was also at the height of development with influential work from pioneers such as Louis Harold Gray and William Valentine Mayneord. Independent papers by Gray in 1937,[10–12] Mayneord in 1940[13] and Cantril in 1945[14] were some of the first works suggesting that the Roentgen was not a suitable unit to described the effects of an exposure. It was suggested that a more suitable measure would be that based on the energy absorbed in the tissue. Gray suggested the term "Energy unit" and Cantril the "Röntgen equivalent physical (rep)". Mayneord coined the term the gramme-röntgen (g.r.) demonstrating that the energy required to produce one pair of ions in air is approximately 33 electron-volts and that a dose of 1 röntgen corresponds to the absorption of 0.11 ergs[*] per 0.001293 gram of air such that

* One erg is the amount of work done by a force of one dyne exerted for a distance of one centimetre. A dyne is the force required to accelerate a mass of one gram at a rate of one centimetre per second squared. Both units originate from the CGS base unit system. In modern units, 1 ergs/g is equivalent to 0.1 mGy.

$$1\ \text{g.r.} = 85\ \text{ergs/g}$$

Similarly, for exposures resulting from radioactivity Leonidas Marinelli[15] made a similar proposal, noting that as the roentgen applied only to X- or γ radiation it could not be used for isotopes emitting β particles. However, if the energy absorbed per gram of air per roentgen were the unit of exposure, it would be possible to establish a comparable basis for β ray dosage. The unit of dose, termed equivalent roentgens (e.r.), due to complete disintegration of a biologically stable radioelement present in a uniform concentration of C microcuies per gram of tissue was expressed as

$$D_\beta = 88\bar{E}_\beta TC\ \text{e.r.},$$

where T is the half life of the isotope in days and $\bar{E}_\beta$ is the average energy per disintegration of the β emission in MeV.

In 1946 Samuel M. Seidlin, Leo D. Marinelli and Eleanor Oshry described the first case of successful therapy of a case of metastatic thyroid carcinoma treated with radioactive iodine using a cocktail of ^{131}I and ^{130}I.[16] The report describes the use of a Geiger counter to confirm localisation of the iodine in all known tumour sites including the discovery of unknown disease. Using the Geiger counter, activity measurements in urine and a dissection biopsy of a rib lesion the authors were able to calculate a total radiation dose of 18,200 e.r to the tumour and 64 e.r to the blood. Following three therapeutic administrations over the course of two years the response to treatment was evident.

> "The patient's general well-being improved, his pains diminished, his locomotion improved, and he complained of getting fat."

1950S – ABSORBED DOSE IS DEFINED

By the 1950s, the field of therapeutic nuclear medicine was developing at a rapid pace with an abundance of clinical applications under development. A review article, by Professor Joseph Mitchell[17] based on a lecture to the society of apothecaries in 1950 and subsequently published in the British Medical Journal in 1951, nicely summarises this development. Most notable are the early observations made by Mitchell, which reflect the modern controversies regarding delivery of nuclear medicine therapy.

> "The use of radioactive isotopes in treatment is essentially a form of radiotherapy, and in general requires the experience of a radiotherapist and the collaboration of a hospital physicist who is trained in radiotherapeutic dosimetry"
>
> "it is essential to try to estimate from the amount of the radioactive isotope administered the dose of radiation, specified in roentgen units or rep (roentgen equivalent physical), received by both the abnormal cells and the normal ones".
>
> "At the present stage, dosimetry is largely empirical, and correlation with the roentgen unit is an incompletely solved problem, although nevertheless -the only available logical guide."

In 1953, the ICRU formally adopted the curie as the unit of radioactivity, although it had been in use for many years previous. As the science of radiation dosimetry developed, it was formally recognised that the ionising effect, and hence tissue damage, was linked to the energy absorbed. The commission recommended the rad, equal to 100 erg/g, as the unit of a new radiation quantity termed absorbed dose. This move from roentgen to rad prompted an editorial by Louis Gray in 1956[18] in which he heralded the adoption of absorbed dose as a milestone for radiation therapy, describing the need for not just accepting a new unit, but a new way of thinking. Gray concludes by stating.

> "The transition from röntgen to rad involves only an understanding of the significance of absorbed and radiation dose… …and a limited and definable programme of physical measurements is well within the scope of most Physics Departments".

In this statement, Gray was primarily referring to external beam radiotherapy. However, it is interesting to reflect that such a transition has yet to be fully embraced for many nuclear medicine therapies and debate continues as to whether treatments should be prescribed based on an administered activity or absorbed dose.[19–21]

1960S - A GENERALISED SCHEMA FOR ABSORBED DOSE CALCULATIONS

Until the 1960's *in-vivo* uptake measurements of these new radiotherapeutics were being acquired using rudimentary hand-held Geiger-counters. Distribution of the radiotracer could only be determined by manually plotting the count rate on graph paper and drawing iso-contours between points.[22] Development of automatic scanning methods are summarised by McCready in a review article celebrating the 70th anniversary of automated radionuclide imaging.[23] The greatest contribution to this aspect of the field came in 1958 when Hal Anger invented the "scintillation camera," a device that moved technology from an era of scanning to one of imaging. David Kuhl and Roy Edwards later constructed the first tomographic emission scanner in 1964[24] and developed the first techniques of Single Photon Emission Computed Tomography (SPECT). For the first time the three-dimensional distribution of a radioisotope could be visualised.

At the same time, the Society of Nuclear Medicine initiated a committee to fill the growing need of standardising absorbed dose estimates in patients administered with radiopharmaceuticals. The new Medical Internal Radiation Dose (MIRD) Committee, proposed to develop, collect and critically appraise information relating to the calculation of absorbed doses, for which the committee continues to provide through a series of pamphlets. A generalised schema was proposed for absorbed dose calculation,[25] that would form the basis of modern clinical dosimetry in nuclear medicine.

$$\bar{D}\left(r_1 \leftarrow r_2\right) = \tilde{A}_2 \sum_i \Delta_i \Phi_i \left(r_1 \leftarrow r_2\right)$$

where $\bar{D}\left(r_1 \leftarrow r_2\right)$ is the mean absorbed dose to target region r_1 from a source of activity in region r_2 . $\tilde{A}_2$, termed cumulated activity is the total number of radioactive disintegrations within r_2 , over a time interval, $t_2 - t_1$, which can be expressed as the integral of a time varying activity function,

$$\tilde{A} = \int_{t_1}^{t_2} A\left(t\right)\ dt.$$

An equilibrium dose constant Δ_i was introduced equal to the energy emitted per disintegration of radiation type .

$$\Delta_i = n_i E_i$$

The absorbed fraction, $\phi_i\left(r_1 \leftarrow r_2\right)$ and specific absorbed fraction

$$\Phi_i\left(r_1 \leftarrow r_2\right) = \frac{\phi_i\left(r_1 \leftarrow r_2\right)}{m_{r_1}},$$

were originally conceived by Ellet *et al* in 1964,[26] who, using Monte-Carlo simulations, calculated the fraction of emitted γ ray energy absorbed by a phantom of specified mass and geometry for a range of different energies. Prior to this, calculations were based on numerical integration of measured or analytically derived isotropic point source dose distributions.[27,28] This approach paved the way for development of more complex computational models.

As recommendations concerning radioactive materials began to be formulated by the ICRP, a set of biological parameters to calculate permissible levels for work with radioactive nuclides[29] was required. Specifications such as mass, dimensions, and elemental composition of the organs and tissues were gathered and the first "Standard Male" data were presented and formalised in 1949.[30] These data, and later iterations, were used by Snyder et al, at Oak Ridge National Laboratory to design a phantom representing the average adult worker in the Western hemisphere, for which specific absorbed fractions were calculated and published.[31] Iterations of this and similar phantoms would later be developed to encompass different ages and genders and also transitions from mathematical models to voxel and eventually computational mesh phantoms[32–36]

1970S – NEW DEFINITIONS AND DATA COMPILATION

The 1970s saw further revaluation of physical units and quantities as scientific nomenclature moved to an International System of Units (SI). The most notable changes for nuclear medicine therapy and dosimetry was the introduction of a new definition for radionuclide activity and absorbed dose. The Becquerel (Bq), defined as the quantity of radioactive material in which one nucleus decays per second, replaced the Curie, and the Gray (Gy), named after the pioneer Louis Gray, was the new SI unit of absorbed dose.[37] The absorbed dose, $\bar{D}$, is defined as

$$\bar{D} = \frac{\partial E}{\partial m},$$

where ∂E is the mean energy imparted to matter of mass ∂m, so that the unit Gy is equivalent to J\kg. The MIRD committee also further developed the MIRD schema to encompass the physical and anatomical data into a new quantity,

$$S\left(r_1 \leftarrow r_2\right) = \sum_i \Delta_i \Phi_i\left(r_1 \leftarrow r_2\right)$$

Values for this new quantity, termed S-value, S-factor or dose factor, were subsequently published for an array of common isotopes and source/target geometries.[38]

A change in focus of the ICRP was also evident. In the past the organisation had been unable to make firm recommendations on the appropriate therapeutic exposure to patients,[39] noting that.

> "The contributions to the doses in various organs and the part played in the overall effects on the individual are practically impossible to evaluate at the present time. "

In 1969, the ICRP published the first report dedicated to the protection of patients undergoing radionuclide investigations[40] and provided the first compilation of estimates of the absorbed doses resulting from the administration of pharmaceuticals. Within the report, the author Dr R. E. Ellis, made a plea for continued research into the long-term retention and biokinetics of the radiotracers, noting that if investigators, whenever appropriate, secure the maximum information practicable from any investigation, and if this information is subsequently published, it would be of great value in assessing the tissue doses involved and of great importance in the proper use of such tests.

Similar pleas from the ICRP were repeated in further reports and addendums as this compendium of radiopharmaceuticals and dose was increased.[41–44]

> "Collection of such data should be encouraged by professional and scientific societies and by regulatory authorities, and the data should be made available by publication and by storage in accessible data bases. The editors and referees of scientific journals are encouraged to request such information in papers on new radiopharmaceuticals."

1980S – SOFTWARE AND DOSE RESPONSES

One of the most successful and widely implemented internal dosimetry tools was developed in the early 1980s and presented by Evelyn Watson and Michael Stabin during the 1984 midyear topical symposium of the Health Physics Society. Noting that implementation of the MIRD expression involved a somewhat tedious lookup and evaluation of parameters, Stabin proposed it would lend itself well to treatment within a computer program.[45] The software code, originally named MIRDose and later superseded by Olinda/EXM,[46,47] uses in-built decay schemes for a wide range of radioisotopes. The code interpolates specific absorbed fractions for the different emissions and calculates the summation terms across all sources and target regions with a number of reference person geometries. The user input for the code is residence time ($\tau = \tilde{A}/A$) and the output is the mean absorbed dose

for a selection of target organs and effective dose, taking into account ICRP weighting factors for tissue sensitivity.[2,3] These dosimetry packages were the first of their kind, and after Olinda/EXM received FDA exemption (premarket notification, 510K) for production and distribution[48] provided the predominant means of dosimetry evaluation of new radio-pharmaceuticals and therapeutics.

The 1980s also saw the earliest dose response data coming from clinical trials. One of the landmark publications was in relation to ^{131}I NaI in the treatment of metastatic thyroid carcinoma.[49] Maxon et al observed a clear increased success rate in patients where a higher absorbed dose was measured in the thyroid remnant or metastatic sites. Reported dose thresholds of 30,000 rads to thyroid remnant and 8,000 rads to metastases were associated with a statistically significant increase in response to therapy.

Of the new therapeutics developed, ^{131}I labelled meta-iodobenzylguanadine was one of the first to be successfully used in a dosimetric setting. Initially presented by William Beeirwaltes in an article of 1981,[50] and later with response data in 1983,[51] toxicity, biodistribution, pharmacokinetics and dosimetry were quickly established.[52,53] This led to a Phase I/II study that reported a clear relationship between haematoxicity and the absorbed dose averaged over the whole-body.[54] A dose threshold of 2.5 Gy was reported beyond which 80% of patients presented with Grade 3 or 4 haematoxicity. The most astounding and key factor in this study was the simplicity with which the dosimetry could be performed. This methodology lead to further studies over the coming years, demonstrating that treatments could be optimised and safely delivered when treating to a whole-body absorbed dose,[55–58] and is today the subject of a large multicentre European clinical trial called VERITAS (https://clinicaltrials.gov/ct2/show/NCT03165292).

1990S – RADIOBIOLOGY AND QUANTITATIVE IMAGING

The 1990s saw the introduction of radiobiological concepts into nuclear medicine dosimetry. Most notable were the adaptions of the linear quadratic equations, originally developed to describe the dose effects observed in external beam radiotherapy. The most commonly used linear quadratic equation characterises the fraction of surviving cells, S, following an absorbed dose, D, as

$$S = e^{-\left(\alpha D+\beta D^2\right)},$$

where the parameters α and β describe the cell's radio-sensitivity. To convert the observation of cell death into an understandable clinical context, Barendsen et al[59] proposed the term Relative Effectiveness per Unit absorbed dose (RE),

$$RE = \frac{\ln(S)}{D}\alpha = 1 + D\left(\frac{\beta}{\alpha}\right)$$

Dale[60] extended the derivation to include decaying protracted irradiation, with an initial dose rate, $\dot{D}_0$, with a decay constant λ , over an infinitely long time period, that included a term for the sublethal repair with a time constant μ.

$$RE = 1 + \frac{\dot{D}_0}{\mu+\lambda}\left(\frac{\beta}{\alpha}\right)$$

Extension to the relative effectiveness concept came in the definition of the Biological Effective Dose with units of Gy. The BED concept was originally introduced by Barendsen[59] at which time it was referred to as the extrapolated response dose (ERD) and sometimes as the Extrapolated Tolerance Dose (ETD). As is the historical theme with many dosimetry concepts, the terminology took some time to settle, and it was since re-named and given its present symbol *BED* by Fowler in 1989.[61] The BED parameter represents the dose needed to deliver the same level of effect as a treatment delivered over an infinitely long and low dose rate. I.e. when cell damage is only a result of singular radiation events[62]

$$BED = D \times RE = D\left(1 + \frac{D}{\alpha/\beta}\frac{\lambda}{\lambda+\mu}\right)$$

A number of studies have since taken place to derive values for these radiobiological parameters, either using *in vitro* cell line cultures,[63,64] pre-clinical studies[63,65] or derived from clinical radiotherapy data, inferred from two or more fractionation schedules or with brachytherapy.[66,67] Direct measurements of DNA damage and repair of lymphocytes have also been undertaken in human studies for some nuclear medicine therapies.[68–71]

By the latter half of the 1990s, a new radiobiological parameter had also been proposed[72] for external irradiation that considered the consequence of non-uniform absorbed dose distributions. The importance of such a parameter to nuclear medicine therapy was highlighted by O'Donoghue in 1999[73] as, due to variation in vascularity or receptor density absorbed dose distributions are inevitably heterogeneous. The proposed new unit termed Equivalent Uniform Dose (*EUD*) is defined as the absorbed dose that, when homogeneously delivered to a tumour or organ, yields the same response as that delivered with non-homogeneous irradiation. For N subregions, the equivalent uniform dose is written

$$EUD = \frac{1}{\alpha}\left(\frac{\sum_{i=1}^{N} e^{-\alpha BED_i}}{N}\right)$$

The subregions are conventionally taken as the voxel elements of a 3D dose map derived from SPECT imaging.

The evidential need for improved quantitative imaging saw a shift in focus from developing dosimetric models towards developing quantitative SPECT imaging. A review and recommendation by the focus committee of the Society of Nuclear Medicine, summarised the technological status at the time.[74] A notable milestone was the development of accelerated iterative reconstruction techniques.[75] Early developments in the 1980s of iterative reconstruction[76] were hampered by the speed of convergence and limitation in computing resources. With accelerated methods more advanced correction methods could be incorporated into the reconstruction algorithm. Most notable was the introduction of CT information for correction of attenuation

effects, which were otherwise limited to pre- or post- reconstruction techniques. An early application for dosimetry was that by Koral et al for intratherapy dosimetry during 131I-labelled MB-1 immunotherapy for lymphoma.[77] The group used a CT image acquired on the same day as the SPECT scan and with the aid of fiducial markers, registered datasets together. The quantified SPECT data were then used to normalise planar data acquired 2 to 5 days post administration. This method of dosimetry would later be referred to as the "hybrid method" and became a common approach across clinical centres.[78,79]

To overcome the inconvenience of, and errors introduced, in manually registering these data one of the first prototype CT/SPECT system was conceived at the University of California at San Francisco, Physics Research Laboratory and presented at the IEEE nuclear science symposium in 1994.[80] The system combined a GE 600 XR/T SPECT system with a GE 9800 Quick CT scanner for correlated anatomical and functional imaging and to aid attenuation correct of the SPECT. The project was supported by General Electric who subsequently marketed the first dual-modality SPECT and CT system, which was unveiled at the 1999 Society of Nuclear Medicine (SNM) Annual Meeting. The SPECT/CT system is today a staple component of all modern nuclear medicine departments and quantitative software is either integrated into the system or readily available from third-part vendors.[81]

2000S – NEW THERAPIES AND CLINICAL APPLICATIONS OF DOSIMETRY

By the turn of the century a wealth of new products with radiotherapeutic applications had emerged and were to receive marketing authorisation. Yttrium-90 had previously been used in a few cases as an interstitial therapy for cystic craniopharyngiomas.[82] After injecting a known activity and volume directly into the cystic fluid and subsequently extracting samples to measure concentration, treatments could be designed to accurately deliver 20,000 rads to the cyst without the need for imaging or external measurement.

Early uses of ^{90}Y also included radiolabelled microspheres for selective internal radiation therapy (SIRT). These therapies demonstrated good responses but poor correlation between activities administered and patient response. This was attributed to variation in radiation doses delivered to normal liver parenchyma. However, determination of the actual tissue radiation doses was challenging and could only be confirmed intraoperatively using probe measurements.[83,84]

The difficulty with *in-vivo* activity measurement stemmed from the lack of γ emissions from the ^{90}Y isotope. To overcome this difficulty, a theragnostic approach was adopted using a complimentary tracer. For SIRT, this was in the form of Technetium-99m-labelled macroaggregated albumin (^{99m}Tc-MAA) used in estimating pulmonary shunting and predicting the intrahepatic distribution of the ^{90}Y microspheres.[85] In 1996, Ho et al[86] proposed a partition model based on the MIRD formulism in conjunction with the MAA image to predict lesion and hepatic doses from ^{90}Y microspheres,

$$D\ (Gy) = \frac{49670\ A_0}{M}$$

where A_0 is the ^{90}Y organ or lesion uptake activity (expressed in GBq) and M is the organ or lesion mass in grams. The value 4,9670 is derived from the ^{90}Y decay data and assuming physical decay. The predicted absorbed doses were shown to agree favourably with intraoperative probe measurements. In 2002, SIR-Spheres received its CE mark as a class III active medical device for treating advanced inoperable liver tumours, and whilst the manufacturer recommended method for calculating the prescribed activity is still largely based on body surface area, calculations for lung shunt, lung dose and tumour doses are indicated in the product information sheet.

In 2014, a similar product, TheraSphere, received a CE mark as a class III active medical device, indicated for treating hepatic neoplasia. The administered activity of the TheraSphere product is calculated to deliver a recommended liver absorbed dose using

$$Activity\ Required\ (MBq) = \frac{M_{liver}\ D}{50}$$

where D is the desired Dose in Gy and M_{liver} is the liver mass in grams determined from CT or ultrasound scans. This calculation is not personalised as it does not account for lesion burden or heterogeneity in uptake, for which the partition model was designed. However, the lung shunt fraction can be used to estimate the average dose delivered to the liver.

$$D\ (Gy) = \frac{50\ A_{inj}}{M_{liver}}\ (1 - F)$$

where A_{inj} is the actual activity administered, in GBq and F is the fraction of injected radioactivity localising in the lungs, as measured by ^{99m}Tc MAA scintigraphy.

Verification of the actual ^{90}Y dose delivered was made possible in 2004 when it was demonstrated that in 32 out of one million decays a minor decay branch to a 0 + excited state was followed by internal pair production. The first PET images formed from the annihilation photons of this internal pair were shown during the IEEE nuclear science symposium in 2004.[87] The first clinical scan was published in 2009[88] which demonstrated a significantly more detailed distribution of ^{90}Y SIRT particles in the liver than that which could otherwise only be produced through bremsstrahlung imaging.[89–91] This potential generated excitement in the field and a number of investigations into its application where initiated. Most prominent was an industry-funded global multicentre comparison study of quantitative ^{90}Y PET/CT for dosimetry post SIRT.[92] Over 50 centres participated in the study, and today PET/CT is the recommended method for dosimetric verification of ^{90}Y SIRT.[93]

In 2000, results of a Phase I/II ^{90}Y-Zevalin (yttrium-90 ibritumomab tiuxetan, IDEC-Y2B8) radioimmunotherapy dosimetry study were reported in patients with relapsed or refractory non-Hodgkin's lymphoma[94] and preceded the FDA and EMA marketing authorisation granted in 2002 and 2004, respectively. Due to the challenge of ^{90}Y bremsstrahlung imaging,

^{111}In-Zevalin was used for the early-phase biodistribution and dosimetry studies, but was maintained as a precursor to the therapeutic administration to validate acceptable biodistribution in the patient, although administrations were not tailored or verified using absorbed dose. An alternative radioimmunotherapy product, ^{131}I-Tositumomab (Bexxar) was developed during the 1990s and was also shown to have very favourable response rates.[95] The variation in retention of Tositumomab was reported to vary by a factor of 5 across patients enrolled within the Phase I/II trials and was commercially marketed with a personalised regimen based on dosimetry.[96] A patient-specific activity calculation was recommended to deliver a 750 mGy total body dose or 540 mGy in patients with low platelets. Used for the treatment of relapsed or chemo-refractory non-Hodgkin lymphoma, Bexxar received marking authorisation in 2003, but was discontinued by the manufacturer in 2015 due to a decline in use.

^{90}Y was also labelled to somatostatin analogues for peptide receptor radionuclide therapy (PRRT). As in the case of Zevalin, ^{90}Y was often complimented with an ^{111}In labelled peptide. Early preclinical biodistribution studies of ^{90}Y and ^{111}In DOTATOC[97] demonstrated the potential of this analogue for therapeutic purposes which was quickly followed by encouraging clinical results.[98,99] Early-dose response data were reported in 2005,[100,101] applying the MIRD formalism to data derived from ^{86}Y PET images. Spherical S-values were calculated using MIRDOSE and CT derived tumour volumes. Across 30 lesions a significant correlation between absorbed dose and reduction in tumour size was reported. In the same year the group also reported dose effect relationships for late stage renal toxicity, evaluating the contribution of patient-specific adjustments to the standard dosimetric models, such as renal volume and dose rate.[102] The data provided evidence of the importance of patient-specific anatomy and dose-rate effects. The authors concluded by stating that

> "The BED model appears to be a reliable predictor of toxicity and could thus be helpful in implementation of individual treatment planning."

This study was an important achievement for PRRT dosimetry and paved the way for implementation of treatment regimens based on kidney dosimetry. The eminent emergence of dosimetry into clinical practice was answered by the official formation of a specialist dosimetry committee of the European Association of Nuclear Medicine in 2007 and was quickly followed by the publication of dedicated clinical dosimetry guidelines.[58,93,103–106] Most notable were the inclusion of recommendations for good dosimetry reporting stating that;

> "As the number and breadth of nuclear medicine procedures expand, internal dosimetry is having an increasing impact on the development and clinical implementation of new and established radiopharmaceuticals."

However,

> "Many recent publications in nuclear medicine contain data on dosimetric findings for existing and/or new diagnostic or therapeutic agents. However, in many of those articles, the description of the methodology applied for dosimetry is lacking or important details are omitted"

2010S – COLLABORATIVE STUDIES IN A GROWING FIELD

Whilst most radiotherapeutics in clinical use and with marketing authorisation used β emitting radionuclides there was continued interest in harnessing the greater potency and linear energy transfer of α emitters. This continued interest prompted a specific pamphlet dedicated to the radiobiology and dosimetry of α particles from the MIRD committee in 2010.[107] Of the pharmaceuticals under investigation, the most successful was that of ^{223}Ra dichloride (Xofigo), for which Phase I and II clinical trials took place between 2004 and 2008. The Phase III ALSYMPCA trial completed recruitment in 2011[108] and marketing authorisation within the US and Europe was granted in 2013. Results of the Phase I bio-distribution and dosimetry study were published in 2015 and 2018.[109,110] Data from these studies were also used to explore the possibility of predicting ^{223}Ra dosimetry and lesion response from ^{18}F-fluoride PET/CT imaging[111] and in further developing a compartmental model of ^{223}Ra biokinetics,[112] which was otherwise based on ingestion and inhalation in healthy humans and animal studies.[113–115] Following marketing authorisation further dosimetry studies were carried out by other groups[116–119] and multicentre dosimetry studies were initiated.[120]

Multicentre and cross-site collaborations would become a major theme of the 2010's. Facilitated in part by the introduction of ^{177}Lu which, because of its favourable decay characteristics, is easier to quantify with γ camera imaging that other commonly used isotopes. ^{177}Lu had previously been used in a small number of patients for interstitial irradiation of peri-tumoral lymph nodes as early as 1955,[121] but had since gained popularity as a replacement for ^{90}Y in peptide receptor radionuclide therapy (PRRT).[122] Multicentre initiatives to investigate the quantitative accuracy of ^{177}Lu SPECT include that carried out within two European metrology projects METROMRT[123] and MRT dosimetry.[124] Both studies involved a cross-site phantom exercise and despite centres using a variety of SPECT calibration and image segmentation approaches demonstrated good agreement to the true activity. A similar study was carried out within the Netherlands evaluating the multivendor and multicentre quantitative accuracy and intersystem variability.[125] The later study demonstrated the importance of harmonised reconstruction protocols which reduced intersystem variability to within 5%..[126] Following a Phase III clinical trial[127] ^{177}Lu DOTATATE (Lutathera®), received marketing authorisation in 2017 with a fixed administration schedule of 7400 MBq delivered four times, 8 weeks apart. A landmark multicentre Swedish study that utilised BED for treatment planning of ^{177}Lu DOTATATE[126] aimed to personalise the treatment by extending the administration fractions until a biological effective dose threshold to the kidneys was delivered. This study was the first of its kind to utilise BED in this fashion and demonstrated that not only could BED be used to personalise treatments but that 73% of patients treated are potentially able to receive more than the standard four cycles.[126]

Multicentre comparisons and clinical trials were not solely limited to Lutetium, and dosimetry applied to radioiodine therapies was still of interest. The previous decade had seen the

results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal.[128] The biodistribution and dosimetry data of this study indicating longer retention in remnant thyroid tissue after rhTSH compared to withdrawal and significantly lower absorbed doses to blood. These results Indicated that higher activities of radioiodine might be safely administered after stimulation with rhTSH.[129]

Dosimetry in metastatic thyroid carcinoma was also of interest and in 2013 a US study explored the role of the MEK inhibitor Selumetinib in resensitising advanced iodine refractory differentiated thyroid cancer. Pre therapy ^{124}I dosimetry was used to determine if an absorbed dose of 200 Gy could be administered within a maximum activity limit of 11 GBq. A UK multicentre trial further developed this concept and used dosimetric calculations with ^{123}I to predict absorbed dose to target lesions and validate post therapy dosimetry with similar ^{131}I imaging..[130–132] A multicentre European clinical trial was also conducted exploring doses to healthy organs in patient treated with radioiodine[133,134] and a global exercise involving 12 countries initiated by the International Atomic Energy Agency (IAEA)[135] undertaken as a SPECT quantification comparison exercise..

Methods for quantitative imaging would soon become sufficiently harmonised across centres to support the development of international guidelines. In 2012 the MIRD committee produced their first pamphlet dedicated to quantitative imaging[136] which was followed by similar articles dedicated to ^{131}I in 2014[137] and jointly with the EANM dosimetry committee for ^{177}Lu in 2016.[138] To address concerns regarding uncertainty associated with SPECT quantification and absorbed dose calculation the EANM provided a framework to model the major sources of dosimetric uncertainty.[139] It is now widely accepted that uncertainty should be acknowledged, minimised and reported when possible to improve confidence in the calculated absorbed dose. Application of this framework was later demonstrated by Finocchiaro et al[140] who showed the impact of lesion size and system spatial resolution on the uncertainty in absorbed dose calculations.

The commercial interest in dosimetry was now also evident and by the mid 2010's a multitude of dosimetry software packages were available. The majority of these initially concentrated on ^{90}Y SIRT dosimetry. Later software would then concentrate on ^{177}Lu dosimetry following the marketing authorisation of Lutathera®. Overviews of available software with comparison of functionality are given in the reviews by Mora-Ramirez[141] and Della Gala.[142]

As the number of treatments increased and dosimetry become more accessible there was a significant rise in the number of clinical centres performing dosimetry, although practice was still varied.[143] This surge in interest is illustrated in Figure 1, which summarises the results of a PubMed query. The database was searched for the following term: ("dosimetry") AND ("iodine" AND "131") OR ("I131" OR "I-131" OR "131I") with similar searches repeated for the other commonly used therapeutic radionuclides. These data reflect the temporal increase in dosimetry related studies and the relative proportions for the different radionuclides. A clear rise in studies over the last two decades in evident for all isotopes, with an interesting peak in the iodine data during the 1960s, presumably following its first uses and the conception of absorbed dose in the preceding decade. A detailed literature review of dose response data was conducted by Strigari et al,[144] in 2014 where 79 studies were identified reporting absorbed dose alongside either response or toxicity data. More specific systematic reviews have since been performed for PRRT by Cremonesi *et al* in 2018,[145] and radioiodine for graves' disease by Taprogge *et al* in 2020.[146] The Taprogge review included a meta-analysis and demonstrated a clear relationship between the radiation absorbed to the thyroid and patient response. The 2018 review by Cremonesi et al[145] made some significant conclusions which reflect that observed throughout this historical review,

> "The available data on dose–effect correlations are scarce as compared with those that could be obtained if dosimetry were implemented as routine"

However,

> "The evidence is sufficiently strong to confirm the clinical benefit of dosimetry (in PRRT) and to stimulate the collection of dosimetric and clinical data. "
>
> "Prospective preferably multicentre trials with large numbers of patients undergoing quantitative dosimetry are mandatory to provide predictive paradigms."

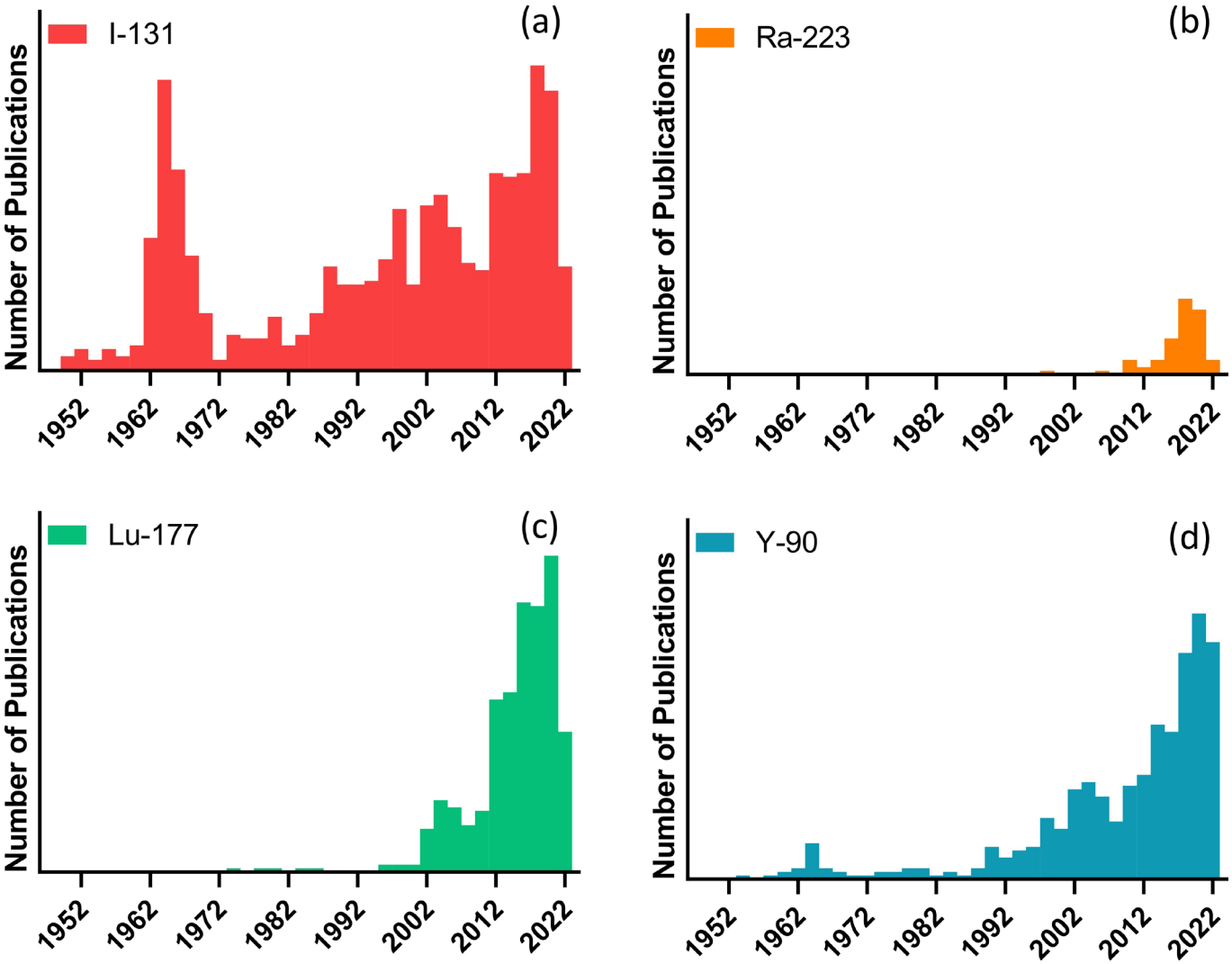
This request for prospective multicentre studies has subsequently been answered for SIRT following the randomised, multicentre, open-label Phase two trial, DOSISPHERE-01, results of which were published in 2021.[147] The trial demonstrated that an administered activity selected to deliver a lesion absorbed dose (>205 Gy) significantly increased the proportion of patients demonstrating complete or partial response in the objective lesion. Response increased from 36% in the standard treatment regimen (activity based on live/lobar dose) to 76% in the personalised group where activity was based on MAA imaging and a prescribed absorbed dose to the tumour.

2020S – THE FUTURE IS BRIGHT

It is interesting to predict how dosimetry for Nuclear Medicine therapy will progress over the next decade. No doubt our understanding of radiation, its biological effect and how best to harness its properties will continue to develop. Methodologies will be refined and technological advances will further improve the accuracy and efficiency of our calculations. With the predicted growth of Nuclear Medicine therapy,[148–151] evidence from recent publications suggests that dosimetry is emerging as an important clinical and legislative aspect to these therapies.[152] The EANM produced a position statement[153] aimed to address the legislative requirements set out in European basic safety standard directive,[154] which requires that all exposures for radiotherapeutic purposes are individually planned and there delivery appropriately verified ensuring doses to non-target volumes are low as reasonably practical. Similar statements from Italian and British societies followed[155–157] highlighting the need for implementation.

In 2018, the ICRP produced their first publication dedicated to radiation protection in therapies with radiopharmaceuticals.[158]

Figure 1. Frequency distributions of dosimetry publications from 1950 to 2022 for I-131 (a), Ra-223 (b), Lu-177 (c) and Y-90 (d).



The publication detailed a framework to perform individualised dosimetry to plan therapeutic procedures and to verify the absorbed dose delivered. An important statement in the publication mirrored that of the EU directive stipulating that

> "Treatment with radiopharmaceuticals requires administration protocols that justify and optimise the treatment. Individual absorbed dose estimates should be performed for treatment planning and for post administration verification of doses to tumours and normal tissues."

The ICRU also published a report dedicated to dosimetry guided nuclear medicine therapy and defined a conceptual framework for treatment planning.[159] Since its initiation the ICRU had set the standard for treatment planning in radiation oncology and maintained comprehensive reports pertinent to nuclear medicine therapy. These include methods of assessment of absorbed dose in clinical use of radiopharmaceuticals[160] and guidance on dosimetry for nuclear medicine therapy, providing detail of biological and Radiobiological factors in the selection of radionuclides and tumour and normal-tissue dose-responses.[161] The concept proposed by the ICRU to establish dosimetry-guided therapy is based on its successful application in external beam radiotherapy and brachytherapy. Notably the report suggests nuclear medicine should aspire to that of external beam radiotherapy.

> "it is essential to adopt strategies analogous to external beam radiation therapy where dosimetry-based treatment planning plays a critical role. In external beam therapy, this entails planning and verifying the absorbed doses received by both tumour and normal tissues to assure optimal treatment for each patient."

To do so, several initiatives are proposed, mirroring that of external beam radiotherapy. These include definitions of new nomenclature covering source regions, treatment regions and regions at risk, and ICRU levels for the prescribing and reporting of radiation exposures. In the ICRU report, level one is the minimum standard, level two is the state of the art and level three is intended for research and novel development approaches for which report criteria are not yet standardised. A major milestone in the ICRU report is specific recommendations for each level of dosimetry assessment for the current federally approved therapies.

The recent Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) of the European commission[162] also highlighted the need to include specific safety and efficacy data in clinical trials and drug authorisation, as well as to develop patient dosimetry and planning procedures and introduce them in clinical practise. In light of the EANM position statement, which suggested that the absorbed doses to organs at risk for the individual patient should be recorded for non-standard therapies the Care Quality Commission, in a recent report regarding the UK ionising radiation medical exposure regulations (IRMER17),[163] stipulated that:

> "We expect to see justification for why patient-specific dosimetry has not been deemed necessary and specific criteria where it would be used for individual patients."

Specific mention of new and emerging therapies was also made,

> "Patient-specific dosimetry should form part of the patient pathway for any non-standardised therapy radiopharmaceuticals, such as 177Lu-PSMA"

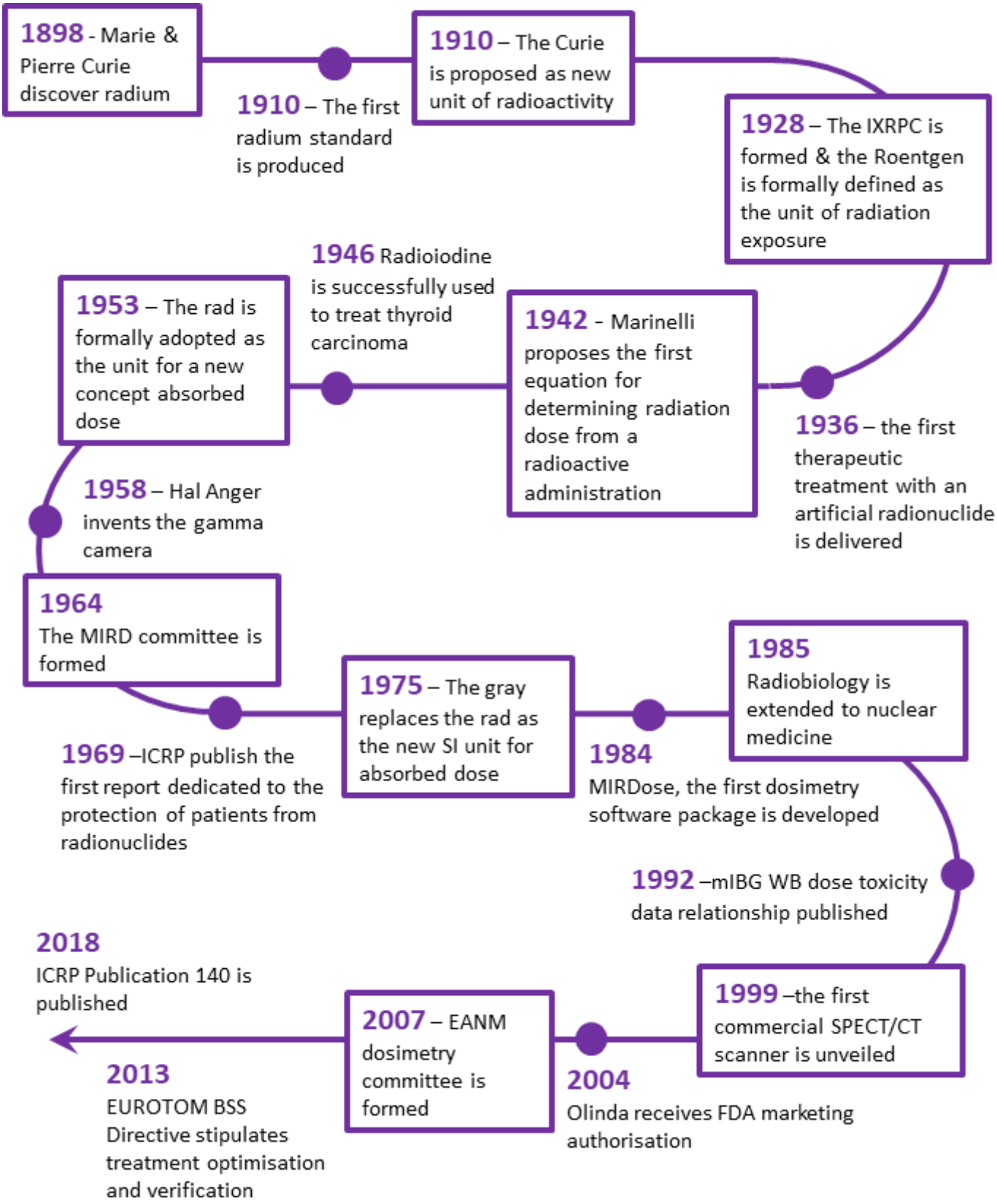
Recent surveys have demonstrated a desire and willingness of clinical centres to further optimise nuclear medicine therapies. A recent joint report of the Royal College of Radiographers (RCR), the Royal College of Physicians (RCP), the British Nuclear Medicine Society (BNMS) and the Institute of Physics and Engineering in Medicine (IPEM)[164] indicated that over 50% of centres in the UK preparing for ^{177}Lu PSMA therapy were intending to include dosimetry in the patient pathway. This is a significant improvement on the IPEM survey carried out a few years earlier for whom only 28% of respondents indicated they were currently performing some form of dosimetry.[165]

Results of Italian surveys demonstrated a similar rise in the desire to introduce dosimetry into standard clinical practice.[155] From 2007 to 2020 the use of pre-treatment dosimetric optimisation was reported to increase from 86 to 96% in centres performing SIRT and from 38 to 65% for those performing I-131 hyperthyroidism therapy. Post therapy verification dosimetry was also observed to increase for PRRT from 25 to 53% of centres and for from 40 to 65% in SIRT.

CONCLUSION

Since its initial conception there have been many advances in the field of therapeutic nuclear medicine dosimetry (Figure 2). The importance of collaboration and standardisation has been evident, and fundamental concepts and quantities have evolved to generate practical approaches to the calculation of absorbed dose. The importance of gathering knowledge to enhance safety and efficacy has been highlighted. Great technological advances have enabled dosimetry to move from a specialist area of expertise into a clinically achievable tool. Radiobiological models have been developed and demonstrated evidence of dose response relationships, which have been translated into multicentre clinical trials. And finally the importance of these achievements has been recognised and concepts incorporated into legislation, guidance and clinical practice. The challenge for the future is to maintain this momentum and continue to promote the use of dosimetry in the optimisation and development of therapeutic nuclear medicine.

Figure 2. A time line showing the main milestones in dosimetry for nuclear medicine therapy



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