

Dosimetry of yttrium-labelled radiopharmaceuticals for internal therapy: ^{86}Y or ^{90}Y imaging?

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Received: 12 January 2011 / Accepted: 22 February 2011 / Published online: 11 March 2011
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Abstract This paper reviews issues concerning ^{86}Y positron emission tomography (PET), ^{90}Y PET and ^{90}Y bremsstrahlung imaging. Specific methods and corrections developed for quantitative imaging, for application in preclinical and clinical studies, and to assess ^{90}Y dosimetry are discussed. The potential imaging capabilities with the radioisotopes ^{87}Y and ^{88}Y are also considered. Additional studies required to assess specific unaddressed issues are also identified.

Keywords Yttrium · Peptides · SIRT · Imaging · Dosimetry

Introduction

^{90}Y together with ^{131}I and ^{177}Lu are the most widely used isotopes for internal radiotherapy [1]. The different characteristics of these radionuclides present various potential advantages and disadvantages. The longer half-lives of ^{131}I and ^{177}Lu (8.02 and 6.7 days, respectively), compared to that of ^{90}Y (2.7 days), can improve the irradiation ratio between the target and critical tissues if the washout in the target is slower than that in the critical tissues. The shorter β -range of ^{177}Lu provides superior irradiation of small

tumours although the longer β -range of ^{90}Y allows more uniform irradiation in large tumours commonly expressing heterogeneous perfusion and hypoxia. This was illustrated in an animal model, where a combination of ^{90}Y - and ^{177}Lu -labelled somatostatin analogues showed better tumour response than the use of each label separately [2]. ^{131}I has the drawback of having abundant high-energy γ rays that can sometimes deliver significant irradiation to remote critical tissues, such as the lungs and red marrow in ^{131}I -lipiodol liver tumour therapy. Further, the binding of ^{131}I is relatively unstable in vivo, whereas ^{90}Y and ^{177}Lu display better stability. Therefore, ^{90}Y labelling was developed for preparation of compounds belonging to four classes of therapeutic agents: peptides, antibodies, microspheres and citrate.

Internal treatment planning has not yet been implemented in clinical practice, and simplistic dosimetry assessment procedures are frequently reported that cannot accurately predict or retrospectively evaluate the absorbed doses delivered. This to some extent explains the failure to determine dose-effect relationships. However, it can be argued that there is no justification for performing dosimetry assessments in a more simplistic fashion than is routinely performed for external beam radiotherapy (EBRT) treatment planning. Accurate dosimetry requires accurate multiple quantitative regional uptake measurements, the use of complex physical formalisms and ideally the incorporation of biological data, such as particle ionization efficiency and kinetics of the repair mechanisms. Where adequate procedures were applied, toxicity and tumour response have often been shown to correlate with the absorbed doses [3–12].

The main direct effect of irradiation is to induce cell death by producing breaks in the DNA, rather than by cell lyses for which the deposited energy is several orders of magnitude too low: 100 Gy corresponds to an energy that raises the tissue temperature by only 0.02°C. Measurement

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of the tumour response using metabolic assessment is therefore preferable than monitoring the reduction in tumour size, which is a late and indirect consequence of cell death [13–15]. Due to the delay between changes in tumour size and cell death, it is even possible that tumour shrinkage will never be observed due to regrowth of the surviving fraction of cells (Fig. 1). Absorbed dose alone, or even biological effective dose alone, can only predict the fraction of tumour cells killed. The assessment of the tumour volume evolution requires sophisticated tumour growth modelling including numerous considerations such as tumour cell proliferation rate, doomed cells removal rate, inflammation processes and variation of the tumour cell density [15].

For conventional drug therapy, such as antibiotics, analgesics, anti-inflammatory agents, the efficient dosage is usually far below the toxic one. As a result it is usually sufficient to administer a standard dosage between the two limits. In external beam or internal radiotherapy besides ^{131}I thyroid therapy, these limits are often very close to each

other and highly patient dependent [8–10]. EBRT groups have developed highly sophisticated dosimetry procedures to individualize treatment planning [16]. Recent improvements in quantitative single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging have led to the potential for nuclear medicine to aim at the same level of excellence in therapy optimization as that achieved in EBRT. This will result in improvement of patient outcome by maximizing the absorbed dose delivered to the tumours whilst avoiding acute or long-term side effects to critical organs. It is noticeable that in internal radiotherapy, due the β -range, a uniform distribution of uptake within a tumour can nevertheless result in a significantly lower absorbed dose delivered to the outer edge of the volume, as this region is not isotropically irradiated.

To perform dosimetry, the regional pharmacokinetics of the therapeutic compound must be assessed for each patient. This can be achieved only using external imaging techniques including SPECT and PET. PET imaging may be preferred because, contrary to SPECT, the sinogram tails provide information helpful to correct the scatter. Alternatively, SPECT should be preferred to planar acquisition for compounds whose uptakes result in significant superimpositions of different tissues having variable pharmacokinetics. Among the isotopes of yttrium having a half-life long enough to assess the cumulated activity in ^{90}Y therapy, only four emit detectable rays (Table 1). Other radionuclides with similar labelling properties have been proposed as surrogates, including ^{111}In or ^{89}Zr , but care must be taken to ensure that this does not induce significant variations in the pharmacokinetics.

Imaging

^{86}Y

^{86}Y has a significant positron emission branching of 33% that allows for PET imaging. However, ^{86}Y also emits approximately 75% prompt γ rays per decay with an energy that will be included into the PET acquisition window, and 231% prompt γ rays per decay that have an energy ranging between 650 and 3,900 keV [17]. These γ rays have the potential to scatter down into the PET energy window when travelling through the PET shielding or through the patient. When accepted by the energy discriminator, a prompt γ ray can produce a coincidence triggering together with a 511-keV γ ray or with another prompt γ ray, both coming from the same decay. The second scenario can also occur for decay by electron capture (67%). As a prompt γ ray is not emitted at 180° from the other recorded γ ray, these so-called spurious coincidences give rise to

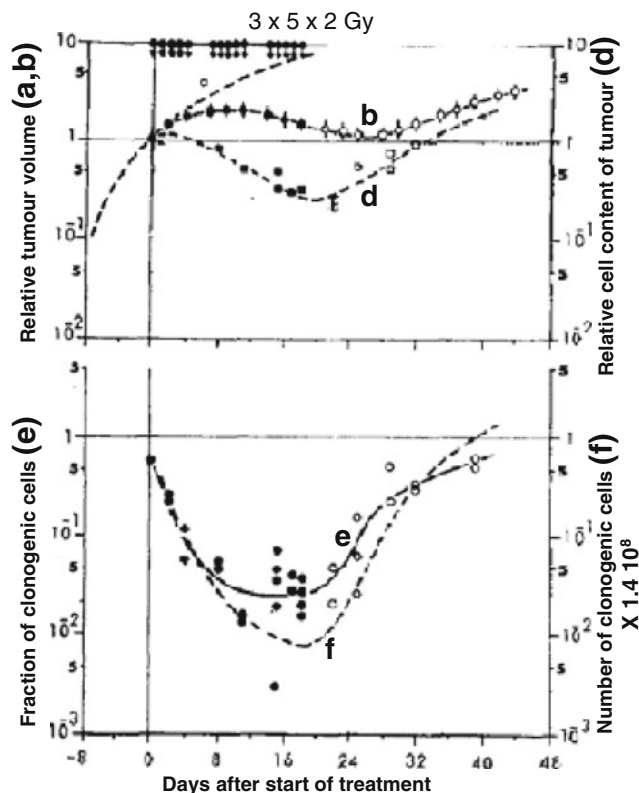


Fig. 1 Typical evolution of the volume (curve *b*) and of the number of clonogenic cells (curve *f* obtained as the product of curves *d* and *e*) of progressive tumour rat rhabdomyosarcoma after 30 Gy ($3 \times 5 \times 2$ Gy) of 300 kV X-rays (each upper arrow shows the 2-Gy irradiation). Although the irradiation killed about 98% of the tumour clonogenic cells (curve *f*), a tumour volume reduction compared to pre-irradiation is never observed at any time point due to the proliferation of the survival cells jointly with the delay needed to remove doomed cells [15]. Note the change in tumour cell density (curve *d/b* ratio). (Reprinted with permission of Elsevier from [13])

Table 1 The four yttrium isotopes allowing image-based cumulated activity estimation of the ^{90}Y therapeutic compound. ^{87}Y is shown with its daughter $^{87\text{m}}\text{Sr}$ that also emits γ rays and atomic electrons. Daughters of the other yttrium isotopes are stable

	$T_{1/2}$	γ [MeV] (%)	β^+ [MeV] (%)	β^- [MeV] (%)	SPECT	PET
^{86}Y	14.6 h	0.4→3 (300)	0.2→3.1 (31)		No	Yes
^{87}Y	80 h	0.48 (93)	0.45 (0.18)	0.002 (87), 0.4(15)	Yes	No?
$^{87\text{m}}\text{Sr}$	2.8 h	0.39 (100)		0.002 (13), 0.4(15)	Yes	No
^{88}Y	106.7 days	0.90 (93) 1.84 (99)	0.76 (0.21)		No	Rodent?
^{90}Y	64.2 h	2.2 (0.0001)	1.71 (0.003)	2.3 (100)	Yes	Yes

projection lines that do not cross the decay location. Originating from a single decay, these additional coincidences are not distinguishable from the 511-keV coincidences and cannot be removed by the delay window technique. Without correction this induces significant overestimation in the uptake assessment.

Whilst the probability for high-energy prompt single γ rays to be scattered down into the PET energy window increases with the patient size, the count rate of 511 keV γ rays decreases exponentially due to attenuation. The activity overestimation is therefore highly dependent on the size of the patient, as observed in the ^{86}Y -SMY-487 study comparing non-corrected total body PET activity with that derived from measurement of urine collection [18]. Validation of a correction method should therefore be performed in a phantom of transverse size similar to that of patients. Other “non-pure” positron emitters such as ^{124}I and ^{76}Br have a lower abundance of prompt single γ rays above 650 keV, 35 and 104%, respectively, compared to 231% for ^{86}Y [17]. This special feature of ^{86}Y implies that a method only validated for ^{124}I or ^{76}Br could be inaccurate for ^{86}Y . $^{94\text{m}}\text{Tc}$ is even more problematic than ^{86}Y with 307% of prompt single γ rays above 650 keV. To date the correction methods validated for ^{86}Y or $^{94\text{m}}\text{Tc}$ 2-D PET can be divided into two major classes: projection tail fitting and global tail fitting. Tail fitting is based on the rationale that all detected coincidences corresponding to projection lines not crossing the patient are scatter or spurious coincidences. Assuming a special shape for the profile of these coincidences in the sinogram representation, the profile normalization is fitted to give the coincidence signal measured from the projection lines not crossing the patients. This signal is located in the left and right tails of the sinogram.

In projection tail fitting, the spurious coincidence contamination in each slice is estimated by fitting, projection tail by projection tail, a uniform [19–21] or quadratic [22] background contamination. In large patients, where the spurious contamination is the highest, these methods have the pitfall that the projection tail lengths are short and even null for some angles. In clinical practice this can lead to large measurement uncertainties, especially for the quadratic model where three parameters have to be

fitted at each projection angle. It is noticeable that these methods have been validated only using 20-cm diameter phantoms [19–22] that are significantly smaller than real patient transverse sizes.

This problem is overcome in global tail fitting where the simple uniform or quadratic background profile is replaced by a spatial variant convolution of a kernel together with an estimation of the patient activity distribution or projection. As the kernel describes the spurious coincidences originating from each point of the body, the angular dependence is directly accounted for by the convolution process. As a result, the convolution is simply normalized by fitting the total counts of all the projection tails of the slice. This makes the method statistically robust. Three kernels have been investigated so far: a modified Bergström scatter kernel [23], an empiric spurious coincidence kernel measured by moving a ^{86}Y point source inside a 30×40 cm elliptical + arms phantom [18] and an analytical kernel modelling the spurious coincidences attenuation [24]. These three methods were validated in realistic size phantoms: 22×30 cm elliptical, 22×30 cm elliptical + arms and 24×32 cm elliptical, respectively. The analytical kernel has the benefit that the patient size and attenuation variation is explicitly taken into account during the convolution process. For the time being only the empirical kernel has been validated in patient studies in a direct way by comparison of the collected urine activity with the total body PET activity [18].

In 2-D mode a γ ray has to be emitted inside a transverse thin cylinder to be accepted by the longitudinal collimation. If the accepted γ ray has an energy of 511 keV, the second 511-keV γ ray is obviously emitted inside the same thin cylinder and has a high probability to be recorded by the system. On the other hand, an associated prompt single γ ray has a low probability to be emitted inside this cylinder. Alternatively, if the accepted γ ray is a prompt single γ ray, there is also a low probability that another γ ray, 511 keV or prompt single, is emitted in this cylinder. These features reduce the probability of spurious coincidences detection. In 3-D mode, these features are removed, and an increase of the spurious coincidence contamination is observed [20, 25]. No ^{86}Y correction method has been validated so far for 3-D PET on realistic size phantoms.

^{86}Y was abundantly used in biodistribution studies in rodent models where spurious coincidences contamination is minimal [26–33].

^{87}Y

^{87}Y has the benefit of a half-life (80 h), similar to that of ^{90}Y , facilitating acquisitions of the late time points needed to perform accurate dosimetry. Acquisition of its high-energy γ rays (0.39 MeV) is no longer a problem for modern gamma cameras. High-energy collimators already developed for 511 keV as a low cost alternative to PET should be used to avoid septal penetration of the γ rays emitted by the daughter $^{87\text{m}}\text{Sr}$ (0.48 MeV). Kutzner et al. [34] demonstrated in a study of six patients that ^{87}Y provided a good scan quality that allowed assessment of the kinetics of ^{90}Y -citrate in treatment of bone metastases.

^{88}Y

As ^{87}Y , ^{88}Y has the benefit of a long half-life (106.7 days) albeit too long and presents more significant challenges with regard to contamination issues. The energy levels of the γ rays are very high (0.90 and 1.84 MeV), but can still be easily counted, and ^{88}Y is the most widely used yttrium isotope in animal models for ex vivo biodistribution studies [35–54]. Imaging γ rays of this energy is beyond the capability of commercial gamma cameras since a dedicated collimator and a very thick crystal would be required to achieve sufficient resolution and sensitivity for quantification. However, in 1985, ^{88}Y was used in human volunteers to measure the long-term retention of particles in the respiratory tract [55], using an array of NaI(Tl) detectors placed around the subject's chest. The future of ^{88}Y could lie in its positron branching ratio, which is low at 0.21%, but nevertheless two orders of magnitude greater than that of ^{90}Y . This could allow replacement of ex vivo counting by 3-D PET imaging in rodents, where the body size is sufficiently small to prevent significant scatter of the prompt γ rays into the PET energy window. This will facilitate study procedures, will enable the study of the pharmacokinetics in the same animal and the use of the animal as its own control in therapy models. This would reduce the number of animals sacrificed.

^{90}Y PET

^{90}Y was discovered to have a low electron-positron pair emission (0.003%) in 1955 [56]. However, until recently, imaging has focused only on the β^- emission of ^{90}Y using bremsstrahlung X-rays. In 2004, Nickles et al. proposed to use this pair production to assess ^{90}Y distribution with PET, and an image of two separate syringes in air was obtained

[57]. It was found that the $e^- e^+$ pairs are produced in 32 of 1 million decays [58, 59].

In 2009, despite this very low positron abundance, a 30-min ^{90}Y 3-D time-of-flight (TOF) PET acquisition of a patient treated for liver metastasis using 1.3 GBq ^{90}Y -labelled SIR-Spheres was performed [60]. A 2.5-mm thick copper ring was inserted into the PET gantry in order to prevent detector saturation by shielding the abundant bremsstrahlung X-rays. It demonstrated a high-resolution biodistribution clearly surpassing the traditional bremsstrahlung SPECT and correlating well to the fluorodeoxyglucose (FDG) PET and CT scan modalities. This surprising image triggered studies on ^{90}Y PET which is now a work in progress.

This result was reproduced by another team using a non-TOF PET system equipped with LSO crystal but without using a copper ring [61]. A similar patient image was shown and a first study on a hot sphere phantom demonstrated that 17-mm diameter tumours should be visible in liver selective internal radiation therapy (SIRT). A comparison of ^{90}Y acquisitions between PET and SPECT found that ^{90}Y SPECT sensitivity was 6.25 times higher than that of ^{90}Y PET [62]. However, ^{90}Y SPECT must be corrected for the cross-firing due to the scattering resulting from the continuous bremsstrahlung spectrum that magnifies the noise.

Acquisitions using an anthropomorphic phantom to model liver SIRT showed that the sensitivity of 3-D LYSO TOF PET was linear up to 2.5 GBq so that a copper ring is not required, but that 3-D BGO PET sensitivity begins to saturate above 1 GBq [63]. For this system, a copper ring slightly reduces the saturation, although this induces a noticeable reduction of the sensitivity (–30%). Accurate liver SIRT dosimetry assessment by ^{90}Y BGO PET imaging will require development of specific dead-time correction methods. ^{90}Y LYSO TOF PET imaging combined with a ^{90}Y voxel S value kernel and a resolution recovery coefficient was shown to provide accurate tumour and liver dosimetry assessment with a relative deviation of 9 and 5%, respectively [63]. More recently, a study in five patients confirmed an accurate visualization of ^{90}Y glass microspheres deposition in liver SIRT using a conventional LSO PET system [64].

An anthropomorphic phantom was used to model a 4.4-GBq ^{90}Y peptide receptor radionuclide therapy (PRRT) administration that included a fillable realization of the computational MIRD pamphlet No.19 kidney phantom [65]. A four-step method was developed to compute the renal cortex absorbed dose taking into account the patient kidney geometry. Eight 45-min ^{90}Y 3-D PET acquisitions were obtained and provided a reproducible renal dosimetry estimate with a mean relative deviation of 3% using a BGO system and of 18% using a LYSO TOF system. The TOF system was affected in this low count rate study by the natural radioactivity of the LYSO crystal (i.e. ^{176}Lu , similar trouble is

also expected for LSO PET systems). This should allow the optimization of the activity to be injected in the following cycles. Estimates of absorbed doses to tumours were also accurate, but the quantification of the modelled bone marrow uptake failed to provide reliable results.

With regards to the natural radioactivity of LYSO or LSO, and to the saturation of the BGO system above 1 GBq, it is noticeable that for phantom studies, evaluation cannot be performed only on the basis of an acquired number of counts similar to that of patient studies: activity in the field of view of the system and acquisition time have both to be similar to those used for patients.

^{90}Y bremsstrahlung

Gamma cameras are designed to image low activities of low-energy γ emitters. Visualization and quantification of the uptake and distribution of a ^{90}Y -labelled radiopharmaceutical, and consequently calculation of the patient-specific dosimetry necessary to facilitate individualized treatments, are therefore challenging.

In the absence of a photopeak, imaging of ^{90}Y is dependent on bremsstrahlung radiation which is continuous up to the endpoint energy. The number of decays that emit photons with energies greater than 50 keV is less than 2%. In addition to problems caused by camera sensitivity, deterioration of image quality is further caused by high-energy photons that result in scatter and septal penetration and by the nonlinearity of camera response away from the photopeak. Determination of the ideal collimator and the optimal energy windows to employ is therefore critical to quantitatively accurate imaging.

A number of authors have explored energy windows and collimators for ^{90}Y bremsstrahlung imaging. Ito et al. [66] investigated three different energy windows using a medium-energy collimator; Shen et al. [67, 68] chose to optimize sensitivity for ^{90}Y imaging by using medium-energy collimation with a wide energy window (55–285 keV); Qian and Clarke [69] used the same energy window (57–285 keV) for ^{90}Y and ^{32}P , but with long-bore, high-energy collimation to optimize spatial resolution and to minimize its depth dependence in order to provide optimal conditions for restoration filters. Siegel [70] proposed a 75- to 125-keV window with medium-energy collimation for ^{32}P to optimize contrast and spatial resolution, but pointed out that for distributed sources the window may need to be widened to improve sensitivity.

The same groups have investigated various scatter correction techniques, including Wiener filters [68, 71], Gaussian background correction [72], maximum entropy image restoration [73] and a wavelet neural network approach [69]. For attenuation correction, all concluded that it is reasonable to use a single effective attenuation

coefficient, despite the wide range of energies which are imaged [68, 69, 71]. However, there was some discrepancy in the actual value of the attenuation coefficient, as well as a dependence on which restoration technique was applied. Optimal window settings and reconstruction parameters have been studied using Monte Carlo methods.

Heard et al. [74] performed Monte Carlo simulations of bremsstrahlung imaging with a gamma camera to determine the components of the resulting spectrum (Fig. 2).

It can be seen from this figure that primary photon events are the smallest component of the spectrum. Whilst the use of a low-energy general purpose (LEGP) collimator proved to be more sensitive than a medium-energy general purpose (MEGP) collimator by 575%, sensitivity to unscattered photons was increased by only 30%. They concluded from simulations and experimental list-mode measurements that the energy window settings for ^{90}Y bremsstrahlung imaging that would maximize image contrast whilst retaining sufficient sensitivity to be clinical useful, for a MEGP collimator, was 60–170 keV.

Monte Carlo simulations, often in conjunction with phantom studies, have also been used to optimize the accuracy of quantitative imaging by enabling corrections to be made for attenuation, scatter and collimator-detector response [75, 76], and it has been demonstrated by Rault et al. [77, 78] that image quality can be improved by using multiple energy subsets in the reconstruction process.

It is evident that with care, bremsstrahlung dosimetry studies are feasible and clinically useful. The relatively poor spatial resolution of bremsstrahlung imaging does not preclude quantitative studies, which can be used to verify or repudiate predictions made from ^{111}In biodistribution studies. It is likely that SPECT imaging will allow more accurate quantification, and 3-D dosimetry has been shown to be feasible and clinically applicable to patient studies

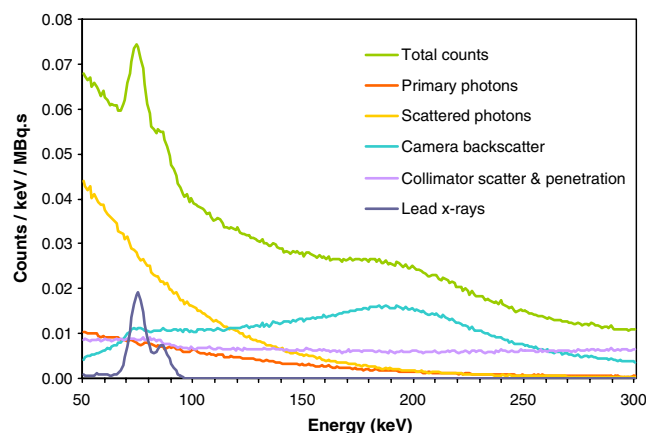


Fig. 2 ^{90}Y X-ray energy spectra according to photon origin for a point source 5 cm deep in water cube, MEGP collimation computed by Monte Carlo simulation (courtesy of Dr. Sarah Heard)

[79], although it has also been shown that whole-body planar imaging may be feasible [80].

Dosimetry in clinical applications

Individual therapy planning

Absorbed doses are proportional to the cumulated tissue activity, the assessment of which requires imaging, excluding de facto ^{88}Y that cannot be imaged.

For this purpose, ^{86}Y suffers from its short half-life (14.6 h) which is significantly shorter than that of ^{90}Y . This feature reduces the statistics of late time point measurements which can adversely impact the accuracy of the estimated absorbed dose [81], supporting the use of the surrogate ^{111}In SPECT [8]. However, compared to ^{111}In SPECT, the sensitivity of 2-D PET, which is approximately 12 times higher than that of a dual-head gamma SPECT camera, counterbalances the fast decay of the ^{86}Y up to a certain time. Indeed, ^{86}Y -1,4,7,10-tetraazacyclododecane-*N*, *N'*, *N''*, *N'''*-tetraacetic acid-D-Phe¹-Tyr³-octreotide (DOTA-TOC) PET imaging gave a probative tumour dose-response relationship [9], a kidney dose-toxicity relationship [11] congruent to that obtained in EBRT (Fig. 3) and in patients free of prior chemotherapy a red marrow dose-toxicity relationship similar to that obtained in irradiation accidents in healthy people [9, 10]. ^{86}Y PET was used to assess and compare absorbed doses in therapy of bone metastases with ^{90}Y -citrate and ^{90}Y -ethylenediamine tetramethylene phosphonate (EDTMP). A similar metastases to

red marrow ratio was obtained for both compounds [82, 83]. Absorbed dose calculations using ^{86}Y -labelled antibodies in humans were not reported to date.

^{87}Y arguably has the perfect half-life (80 h). This is greater than that of ^{90}Y yet sufficiently short to avoid critical problems with contamination. However, in the last decade increasing attention has focused on radiation protection issues in nuclear medicine. The daughter $^{87\text{m}}\text{Sr}$ with its half-life of 2.8 h could have time to accumulate in other tissues than those targeted by the ^{90}Y -labelled therapeutic compound. Possible biological effects from the short-range electron emissions of $^{87\text{m}}\text{Sr}$ could definitively constrain the use of ^{87}Y in humans [84]. An ^{87}Y - $^{87\text{m}}\text{Sr}$ equilibrium ratio is obtained after 20 h, and repurification of commercial ^{87}Y will thus be required in order to at least avoid direct injection of $^{87\text{m}}\text{Sr}$ to the patient. Even with pure ^{87}Y at the time of injection, decay in the patient will rapidly result in $^{87\text{m}}\text{Sr}$ production that may behave differently than ^{87}Y .

In ^{90}Y PRRT, usually performed in several cycles, kidney pre-therapy dosimetry assessments could be replaced by absorbed dose measurements using ^{90}Y PET imaging after each cycle in order to optimize the activity to inject in the following cycle [65], but ^{90}Y PET imaging has failed to provide the red marrow absorbed dose. However, the dose to the red marrow can be evaluated by its biological surrogate effect, i.e. by measuring the platelet count reduction at the nadir time (day 28 post-injection) [9, 10]. This will simplify the therapy, reduce radiation burden to the staff by avoiding additional imaging of other isotopes and, if repeated after each cycle, will also account for tumour shrinkage and change in renal function between two cycles.

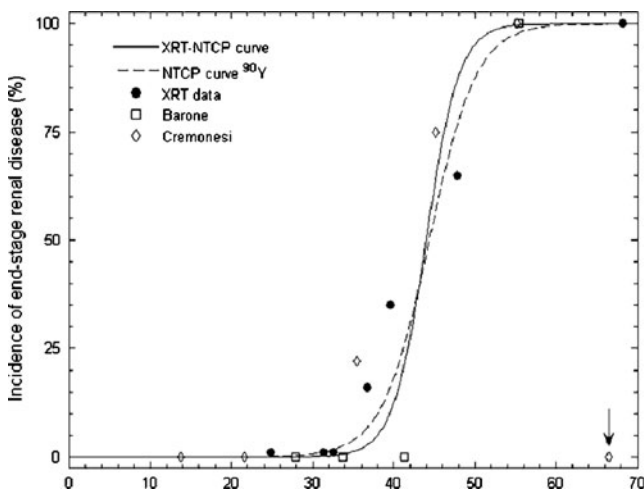


Fig. 3 Correlation between the kidney biological effective dose (BED) toxicity observed in ^{90}Y -DOTATOC therapy ($\square$, $\diamond$) and that observed in EBRT ($\bullet$). $\square$ were derived from the Y-SMT-487 trial [11] with BED obtained from ^{86}Y -DOTATOC PET ($n=18$) and $\diamond$ from [12] with BED obtained from ^{111}In -DOTATOC SPECT ($n=25$). (Reprinted by permission of the Society of Nuclear Medicine from [7])

Individual therapy quality control

Over the last decade, in addition to continuously improving the dosimetry assessment procedures for therapy planning, significant efforts have been made in EBRT to assess the actual absorbed dose delivered during the therapy itself. The residual beam exiting the patient body has been measured using detectors set on the side of the patient opposed to the beam entry [85]. This is of prime importance to evaluate the pre-therapy dosimetry assessments, to check that the therapy procedures have been performed as expected and to anticipate and prevent possible adverse radiotoxicity events. Conventional bremsstrahlung imaging is already widely used in order to qualitatively assess biodistribution after ^{90}Y synovectomy [86, 87], after ^{90}Y -Zevalin therapy [88] and after liver SIRT [89–98]. Recent developments in correction methods for quantitative ^{90}Y SPECT [99] and more recently the development of ^{90}Y PET imaging [63, 65] offer the unique opportunity to easily assess the actual absorbed dose

delivered in ^{90}Y internal radiotherapy by directly viewing activity within the patient.

In a study on two patients, quantitative ^{90}Y -Zevalin SPECT provided a similar estimate of the absorbed dose to the liver than that obtained from the ^{111}In -Zevalin SPECT [99].

Liver SIRT could also be significantly improved. Due to the high complexity of the interventional procedure, identical deposition of microspheres in consecutive treatments cannot be reproduced with certainty. Early human data on ^{90}Y PET-based assessment of absorbed dose following patient therapies has already provided a promising tumour dose-cell survival fraction relationship (Fig. 4). ^{90}Y SPECT-based biological effective dose was also shown to correlate with response evaluated using RECIST or EASL evaluation criteria [100]. This should open the possibility to immediately retreat the patient if needed, thereby preventing tumour regrowth.

Use of a surrogate: scientific investigation or individual therapy planning?

There is abundant literature investigating in rodent models [45–54, 101–103], and more sparsely in human studies [104–106], the possibility of using surrogates to assess the dosimetry of a therapeutic compound. Although these studies are well designed and carefully performed, almost all publications provide only the uptake or absorbed doses averaged over the data set studied (animals or patients). This is insufficient to determine whether a surrogate is

useable in individual therapy planning as clearly shown in the single paper providing individual patient data [106]. This paper compared ^{86}Y -DOTATOC PET and ^{111}In -diethylenetriaminepentaacetic acid (DTPA)-octreotide SPECT in three patients, both without amino acid infusion, and reports a similar kidney dosimetry of 3.01 ± 0.81 and 2.73 ± 1.41 mGy/MBq (mean $\pm$ standard deviation), respectively. However, on an individual basis, one patient had a kidney dose assessed by ^{111}In SPECT more than twofold that obtained from ^{86}Y PET. For the two other patients the renal dose assessed with ^{111}In SPECT was lower than that obtained from ^{86}Y PET. Results in the Y-SMT-487 study on eight patients, this time with amino acid infusion, also showed a similar kidney dosimetry of 1.97 ± 0.66 and 1.88 ± 0.39 mGy/MBq (mean $\pm$ standard deviation) using ^{86}Y -DOTATOC PET and ^{111}In -DTPA-octreotide SPECT, respectively, but again with a large inter-patient variation (unpublished data). The ^{111}In SPECT-based absorbed doses ranged from 0.5 to 1.6 times those calculated using ^{86}Y PET. With regard to the red marrow, the mean uptake measured at 24 h using ^{86}Y -DOTATOC PET and ^{111}In -DTPA-octreotide SPECT were similar in the Y-SMT-487 study [10]. However, even if there was a good correlation between the uptake of the two compounds (Fig. 5), large intra-patient deviations were observed [10]. It is likely that this surrogate can provide valuable scientific information concerning tumour and normal organ absorbed doses and responses. However, for individual therapy planning, this surrogate is clearly not suitable to optimize the activity to

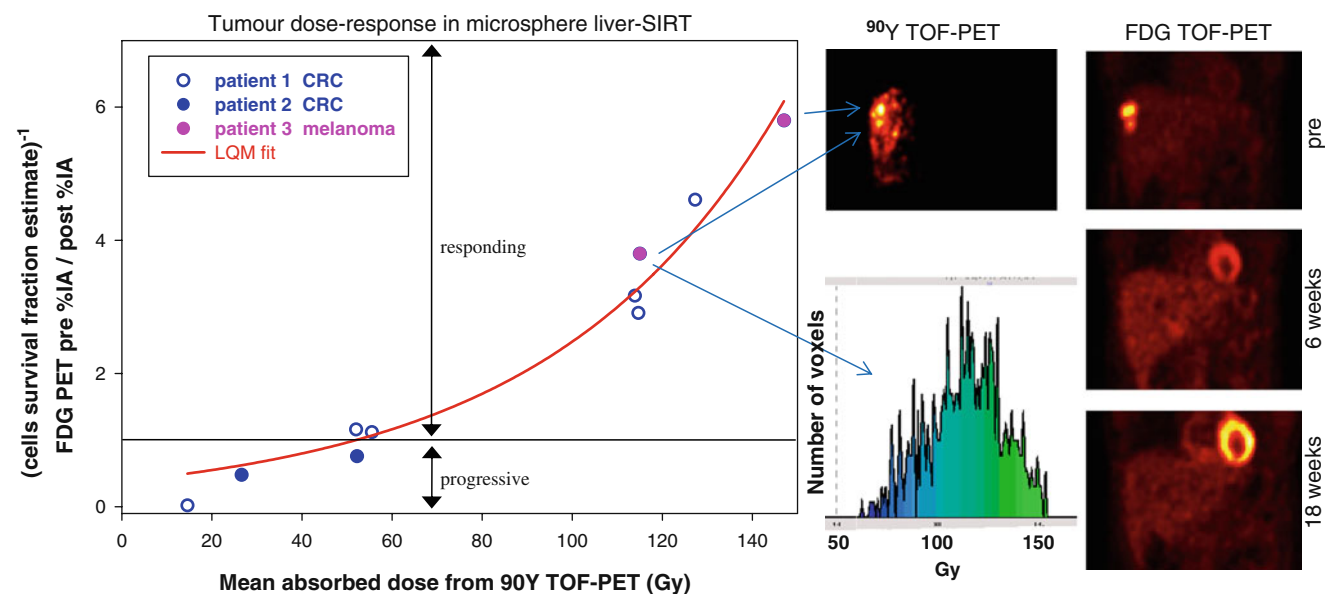


Fig. 4 Linear quadratic model (LQM) fit of the tumour dose-response in liver SIRT observed in three patients [3]. Mean absorbed doses were computed with the method described in [63]. %IA is the percentage of injected activity (standardized uptake value $\times$ volume). The coronal PET slices show the two tumours of patient 3 that

received a mean absorbed dose of 118 and 149 Gy leading to a complete metabolic remission as seen on the FDG scans. The voxel absorbed dose histogram shows that all the regions of the smallest tumour received at least 55 Gy ($\approx 118/2$ Gy)

be injected. Reports should provide individual comparison data such as that in Fig. 5, or at least show the range of ratios in uptake between the two compounds observed in the same animal or patient.

To solve the problem of assessing ^{90}Y -DOTATOC dosimetry, some authors have suggested the use of ^{111}In -DOTATOC that better mimics the therapeutic agent than does ^{111}In -DTPA-octreotide [8]. However, labelling with ^{111}In instead of ^{90}Y has been shown to induce structural changes that affect the receptor binding affinity [107]. Comparison of ^{111}In - and ^{90}Y -DOTATOC was performed in rats showing a mean ^{111}In to ^{90}Y ratio of uptake ranging from 0.5 (adrenals) to 1.6 (kidney) [108]. Due to differences in somatostatin receptor expression between species, these data cannot be directly extrapolated to clinical studies. In humans, most of the kidney uptake is not receptor dependent and ^{111}In -DOTATOC has been used to successfully predict kidney toxicity after ^{90}Y -DOTATOC therapy (Fig. 2) [7, 12].

Biodistribution studies in rodents using antibodies labelled with ^{111}In and yttrium (in vivo ^{86}Y , ex vivo ^{88}Y and ^{90}Y) displayed generally similar results but with significant differences in the uptake of some tissues depending on the antibody studied [45–54, 101–103]. As with somatostatin analogues, a direct comparison of the biodistribution of the same antibody labelled with ^{111}In and any yttrium in clinical studies is lacking. However, it is striking to note that in a ^{90}Y -ibritumomab tiuxetan therapy trial including five complete responders, with biopsy measurement of lymph node ^{90}Y uptake, Jacobs et al.

observed that four of them were ^{111}In -ibritumomab tiuxetan negative [109].

Perspectives

The studies presented in this paper have shown that the application of dosimetry to ^{90}Y therapy is currently an exciting field that is developing rapidly. Design of new studies in order to assess specific issues is still needed. With a trend to no longer commercialized 2-D PET systems, validation of ^{86}Y correction methods in 3D-PET is suitable with realistic size phantoms. Comparison in humans between ^{111}In - and ^{90}Y -labelled PRRT ($n=86$ or $n=90$) or antibodies should be performed. This will allow direct validation regarding the use of the same compound labelled with ^{111}In as a surrogate for the tumour and organ dosimetry. In PRRT, comparison has to be performed with the same amino acid infusion for the two radionuclides. ^{87}Y PRRT or ^{87}Y -antibody studies in a larger mammalian model than rodents could be required to study the regional pharmacokinetics of the daughter $^{87\text{m}}\text{Sr}$. This could be assessed in SPECT using a dual-window acquisition (0.48 MeV ^{87}Y and 0.39 MeV $^{87\text{m}}\text{Sr}$), and by ex vivo counting and autoradiography. This should determine whether ^{87}Y could be safely used in human studies. ^{88}Y PET should be evaluated in rodent phantoms, and PET validation should be performed on rodents by ex vivo counting. Studies are ongoing with ^{90}Y PET and will

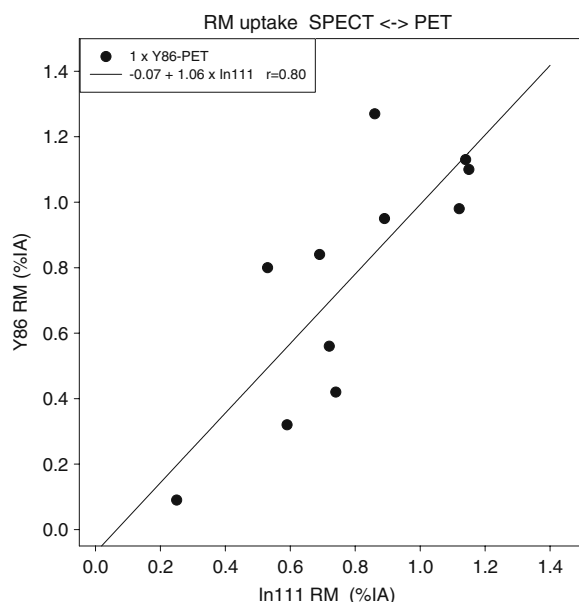
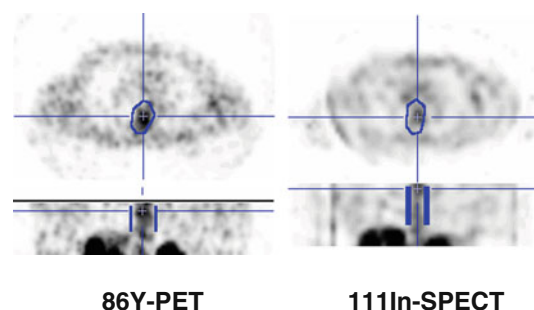


Fig. 5 Correlation between the red marrow (RM) uptake 24 h post-injection derived from ^{86}Y -DOTATOC PET and from ^{111}In -DTPA-octreotide SPECT, using the method described in [10], applied to patients of the Y-SMT-487 B102 trial who underwent a high statistics



^{111}In SPECT scan (100 MBq, 30 min acquisition on a triple-head camera). The PET and SPECT slices show the volume of interest (blue line) used to compute the uptake within the patient with the highest ^{86}Y -DOTATOC uptake

confirm the potential and limitations of the method on SIRT, PRRT and antibodies. Beyond yttrium isotopes, ^{89}Zr can also be used to predict dosimetry with ^{90}Y [51–54]. Direct comparison studies using the same ligand labelled with ^{89}Zr and any yttrium isotope are needed in humans.

Conflicts of interest None.

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