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Correlation of dose with toxicity and tumour response to ^{90}Y- and ^{177}Lu-PRRT provides the basis for optimization through individualized treatment planning

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Abstract

Purpose—Peptide receptor radionuclide therapy (PRRT) with ^{90}Y-labelled and ^{177}Lu-labelled peptides is an effective strategy for the treatment of metastatic/nonresectable neuroendocrine tumours (NETs). Dosimetry provides important information useful for optimizing PRRT with individualized regimens to reduce toxicity and increase tumour responses. However, this strategy is not applied in routine clinical practice, despite the fact that several dosimetric studies have demonstrated significant dose–effect correlations for normal organ toxicity and tumour response that can better guide therapy planning. The present study reviews the key relationships and the radiobiological models available in the literature with the aim of providing evidence that optimization of PRRT is feasible through the implementation of dosimetry.

Methods—The MEDLINE database was searched combining specific keywords. Original studies published in the English language reporting dose–effect outcomes in patients treated with PRRT were chosen.

Results—Nine of 126 studies were selected from PubMed, and a further five were added manually, reporting on 590 patients. The studies were analysed and are discussed in terms of weak and strong elements of correlations.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conclusion—Several studies provided evidence of clinical benefit from the implementation of dosimetry in PRRT, indicating the potential contribution of this approach to reducing severe toxicity and/or reducing undertreatment that commonly occurs. Prospective trials, possibly multicentre, with larger numbers of patients undergoing quantitative dosimetry and with standardized methodologies should be carried out to definitively provide robust predictive paradigms to establish effective tailored PRRT.

Keywords

Peptide receptor radionuclide therapy (PRRT); Dosimetry; Absorbed dose correlations; Dose–effect; Dose–toxicity

Introduction

Peptide receptor radionuclide therapy (PRRT) with ^{90}Y-labelled and ^{177}Lu-labelled peptides has proven to be a successful approach in the treatment of metastatic/nonresectable somatostatin receptor-positive neuroendocrine tumours (NETs). Both radionuclides have demonstrated efficacy, with disease control rates in the range 70–90% for ^{90}Y-labelled peptides and 80–90% for ^{177}Lu-labelled peptides [1]. The results of the recent randomized NETTER-1 study of ^{177}Lu-DOTATATE in comparison with the nonradioactive somatostatin analogue octreotide [2] indicate that PRRT is significantly superior to octreotide, with a progression-free survival (PFS) rate at month 20 of 65%, in contrast to 11% in the control group, and median PFS not reached but longer than 28 months and 8.4 months, respectively. In addition, the analysis demonstrated a clear advantage in terms of objective response (18% vs. 3%) and overall survival (14 vs. 26 events) [2].

PRRT is generally well tolerated, with acceptable renal and haematological toxicity profiles. However, cases of serious kidney injury have been reported, especially after treatment with ^{90}Y, while treatment with ^{177}Lu is mainly associated with grade I/II kidney toxicity [3–7]. As the kidney is the major organ at risk, the available dosimetric data for the kidneys have been extensively reviewed seeking predictive models to help avoid kidney damage in patients. For ^{90}Y-DOTATOC, a linear quadratic radiobiological model has been used to interpret clinical outcomes, and an extrapolated normal tissue complication probability (NTCP) curve compared well with experience with external beam radiation therapy (EBRT). Despite these promising results, dosimetry of PRRT is performed systematically only in a minority of centres. However, it is being increasingly used and has been shown to play a remarkable role in ensuring the safety and efficacy of nuclear medicine applications, providing dose–effect relationships for various radionuclide therapies [8]. These results are very promising and have stimulated the search of further correlations.

The majority of centres use standard protocols based on fixed activities, at most modulating the activity or the number of administrations based on the patient clinical scenario and risk factors. However, some researchers have been conducting dosimetry studies, at least in subgroups of patients, for “safety” reasons, or even prospective studies based on dosimetry to personalize therapeutic activity [9–12]. The associated dosimetry results in PRRT reveal a large interpatient variability in doses to normal organs and tumour absorbed doses, as

summarized in Fig. 1 for ^{90}Y-labelled peptides [13–18] and Fig. 2 for ^{177}Lu-labelled peptides [9, 11, 12, 19–35]. Also tumour-to-kidney absorbed dose ratios were very variable, ranging typically from 1:3 to 20:1, indicating that some tumours may receive, for example, less than 10 Gy, which indicates severe undertreatment [19, 31, 36] (*see also* section Correlation with tumour response), while others may receive more than 400 Gy. This highlights the need to improve enrolment criteria and the PRRT treatment scheme.

Many interesting studies are available providing evidence of dose–effect correlations in PRRT. The aim of this study was to examine the relationships reported in the literature to assess the role of dosimetry in treatment optimization, and to suggest realistic future approaches to tailoring therapy guided by dose–effect outcomes that could improve the risk–benefit balance and avoid ineffective treatments in those who are not likely to respond.

Methods

MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed) was searched using the following five keyword search expressions to identify studies reporting dose–effect outcomes in patients treated with PRRT:

1. ((PRRT) OR (peptide receptor radionuclide therapy) OR (radiopeptide therapy)) AND (response OR toxicity OR control) AND (Gy) NOT (EBRT) NOT (external beam radiotherapy)
2. ((PRRT) OR (peptide receptor radionuclide therapy)) AND (response OR toxicity OR tumour OR control) AND (Gy) NOT ((EBRT) OR (external beam radiotherapy))
3. ((PRRT) OR (peptide receptor radionuclide therapy)) AND (response OR toxicity OR tumour OR control OR dose-effect OR correlation) AND (Gy) NOT((EBRT) OR (external beam radiotherapy))
4. (((Neuroendocrine Tumors/radiotherapy) AND (Bone Marrow/radiation effects)) OR ((Gy) AND ((PRRT) OR (peptide receptor radionuclide therapy)) AND (response OR toxicity OR tumour OR survival) NOT ((EBRT) OR (external beam radiotherapy))))
5. (((Neuroendocrine Tumors/radiotherapy*) OR (PRRT) OR (peptide receptor radionuclide therapy)) AND ((Bone Marrow/radiation effects) OR (Kidney/radiation effects*) OR (Gy)) AND (response OR toxicity OR tumour OR survival) NOT((EBRT) OR (external beam radiotherapy)))

On combining the results of these queries, papers in languages other than English and nonoriginal papers (reviews, editorials and letters) were excluded. The abstracts of the papers were read to exclude those evidently outside the scope of this review. The final choice was made on reading the full papers. The literature search was completed by manually searching the reference lists to identify relevant studies.

Findings

The MEDLINE searches revealed 126 studies of interest, of which nine [5, 10, 22, 23, 25–39] satisfied the criteria of reporting dose–effect outcomes in patients treated with PRRT. Eight reviews/editorials, four papers in a language other than English, and 105 original papers outside the scope of this review were excluded. A further five studies [11, 36, 40–42] were added manually, leading to a total of 14 studies reviewed here of 131 analysed. Eleven studies were from Europe, two from North America, and one from Asia, and collectively they reported on 590 patients (median 25, range 12–228). Six studies were prospective [5, 10, 11, 31, 34, 35]. Table 1 provides details of the studies reviewed.

Correlation with kidney toxicity

Incidence of kidney toxicity—Several papers provide an analysis of irreversible kidney toxicity. Figure 3 and Table 2 summarize the toxicity rates related to PRRT with ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, and ^{177}Lu- DOTATATE [4, 6, 7, 10, 11, 22, 43–49]. Serious kidney injury (Fig. 3, red bars) was observed mainly in patients treated with ^{90}Y-PRRT. In general, high grades of toxicity (III–V) were reported due to the general irreversibility of kidney impairment, while grades I/II toxicities were reported only in some studies. Kidney toxicity was defined as an increase in creatinine levels, loss of creatinine clearance, and decrease in glomerular filtration rate (GFR), according to various standard criteria (Table 2). Among these are the Common Toxicity Criteria (CTC) version 2.0, Common Terminology Criteria for Adverse Events (CTCAE) versions 3.0 and 4.0, National Cancer Institute's Common Toxicity Criteria (NCI-CTC), National Kidney Foundation (NKF) guidelines, and World Health Organization (WHO) criteria. Of note, kidney impairment requires a minimum follow-up of 6 months to be observed, more likely 1 year. Studies with shorter follow up periods may miss such adverse events.

Concerning ^{90}Y-DOTATOC, Imhof et al. [4] and Marincek et al. [43] from the same centre observed the highest incidence of grade IV/V toxicity, leading to 9.2% of patients requiring dialysis. A higher incidence of toxicity, but of grade I only, was found by Bodei et al. [7], with the main difference being the activity administered per cycle (6.3 GBq by Imhof et al. and 2.8–3.7 GBq by Bodei et al.; *see also* section Impact of number of cycles). It must be noted that in both of these studies [4, 43] kidney protection was used only in some patients. In studies in which amino acid protection was used in all patients, the incidences of higher grade toxicity were lower. Waldherr et al. [44] and Valkema et al. [45] both reported incidences of grade II and III/IV toxicities of roughly 3%. Cwikla et al. [48] found that 12% of patients had grade II toxicity after administration of a maximum cumulative activity of 16.2 GBq of ^{90}Y-DOTATATE and an activity per cycle of 3.7 GBq. ^{90}Y-DOTATATE may give a higher absorbed dose to the kidneys per unit activity than ^{90}Y-DOTATOC [16, 51], thus accounting for the greater higher toxicity (grade II) seen by Cwikla et al. [48] than by Bodei et al. [7], although slightly lower average doses per cycle were also administered in the latter study.

With regard to ^{177}Lu-DOTATATE, regardless of the treatment schemes used (number of cycles, and per cycle and cumulative activity) the incidences of serious toxicity were low (1.5% grade III [11], 0.4–1.3% grade IV [49, 50]. 5.3–25% grade I/II [7, 11]). The

cumulative activities in all these studies were similar (approximately 30 GBq delivered in at least four cycles). Swärd et al. did not find any toxicity in 26 patients [22]. Surprisingly, Romer et al. found an incidence of severe permanent kidney toxicity of 9.2% in 141 patients treated with ^{177}Lu-DOTATOC [47]. In light of the low incidence reported for ^{177}Lu-DOTATATE, this high incidence of kidney toxicity remains without a plausible explanation, since the mean cumulative activity was about half (14 ± 7 GBq) that seen in the studies of ^{177}Lu-DOTATATE, and the absorbed dose to the kidneys per unit activity of ^{177}Lu-DOTATOC is known to be about 30% less that of ^{177}Lu-DOTATATE [51]. Unfortunately, Romer et al. [47] did not perform dosimetry, which would have allowed verification of the absorbed doses in their patients.

NTCP curves for kidney toxicity—The first study suggesting a dose–effect relationship for kidney impairment was a study by Barone et al. [40] in which 18 patients were treated with ^{90}Y-DOTATOC. Crucial to the calculation of the absorbed dose estimate was the consideration of the patient-specific kidney mass, which in itself reveals a trend between the absorbed dose and the creatinine clearance loss per year ($r = 0.54$). Converting the absorbed dose into the biologically effective dose (BED), however, consistently improved the fit of the data, leading to a correlation coefficient of 0.93, and introduced the description of dose-rate effects by the linear quadratic model, as used in EBRTand brachytherapy, to radionuclide therapy [32, 52]:

$$\mathrm{BED}(D) = D\left(1 + \frac{\lambda_e}{(\lambda_e + \mu)\alpha/\beta} D\right)$$

where D is absorbed dose, λ_e is the effective decay constant, μ is the repair rate for sublethal damage, and α/β is the radio-sensitivity coefficient.

The MIRD pamphlet 20 combined the efforts of two centres with a combined population of 43 patients [41]. An NTCP curve as a function of absorbed dose was generated considering as endpoint for nephritis a creatinine clearance loss greater than 20%. As anticipated, the curve was similar to the one derived for EBRT but, as expected, was shifted towards higher absorbed doses. When BED was introduced in lieu of the absorbed dose, the two curves for EBRT and ^{90}Y-DOTATOC nearly coincided. Table 3 summarizes the tolerated absorbed doses (TD) and BED values associated with kidney injury probabilities of 5% and 50% (TD_5, TD_{50}, BED_5, BED_{50}) derived from dose–effect and BED–effect NTCP curves provided in MIRD pamphlet 20 [41]. Values are in relation to the EBRT experience of Emami et al. [53], the more recent guidelines from the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) [54], experimental data from PRRT with ^{90}Y, and extrapolated values considering four cycles of PRRT with ^{90}Y and ^{177}Lu.

Correlation between absorbed dose and kidney toxicity—In a prospective study, Van Binnebeek et al. evaluated four cycles of PRRT with ^{90}Y-DOTATOC with a BED limit of 37 Gy in 50 patients [10]. This protocol prevented severe rapid deterioration in kidney function and evolution to severe nephrotoxicity in 98% of patients. One patient developed grade IV kidney toxicity. Otherwise, only grade I toxicity, found in 18% of patients, was

observed. There was no significant correlation between kidney BED and loss of kidney function (annual decrease in GFR). However, dosimetry was based on ^{111}Inpentetreotide, a peptide different from the one used for therapy, which may have led to non-negligible differences (e.g. 20% in dosimetry estimates [55]). In any case, the use of this protocol prevented severe rapid deterioration in kidney function and evolution to severe nephrotoxicity in 98% of patients.

In 47 patients receiving ^{177}Lu-DOTATATE therapy, Gupta et al. found no serious acute or remote adverse events, but did find a significant decrease in GFR and an increase in serum creatinine. In a multivariate analysis, the posttreatment decrease in GFR was correlated with total absorbed dose to the kidneys ($p = 0.034$) [5]. Sundlov et al. found no high-grade toxicity in 51 patients studied [12]. These authors proposed a prospective protocol based on multiple cycles of ^{177}Lu-DOTATATE with a BED limit of 27 Gy. However, kidney function moderately but gradually declined after treatment, without a particular correlation with absorbed dose or BED [12].

Bergsma et al. reported a further analysis of kidney impairment following PRRT with ^{177}Lu-DOTATATE at fixed activity per cycle (7.4 GBq for four cycles) and dosimetry [11]. Evaluation of kidney function was feasible in 323 patients, and dosimetry was performed in 228 of these patients, with mean absorbed doses to the kidneys of 20 ± 5 Gy. Only 5% of patients showed grade I/II toxicity, and 11 patients receiving absorbed doses higher than 28 Gy did not show any alteration in renal parameters. The authors considered that the absorbed dose limit of 28 Gy to the kidneys identified for EBRT and PRRT with ^{90}Y are too conservative for PRRT with ^{177}Lu.

Impact of number of cycles—The first cases of nephrotoxicity were observed after PRRT with ^{90}Y-DOTATOC in protocols involving few cycles with high activity [3]. This experience stimulated the study of kidney protectors and oriented some researchers towards the use of more prudent clinical protocols based on lower activities administered per cycle. A study by Bodei et al. with ^{90}Y-DOTATOC first highlighted the advantage of fractionation of cumulative activities, and showed that hyperfractionated schemes were associated with a lower incidence of alterations in renal parameters [37]. Figure 4 shows these findings in terms of creatinine clearance loss as a function of cumulative absorbed dose to the kidneys in relation to fractionation into 2–4 or 5–11 cycles. Patients receiving therapy over more cycles showed an increase in creatinine clearance loss at higher absorbed doses, indicating better tolerability.

More recently, Imhof et al. reported the results in 1,109 patients receiving ^{90}Y-DOTATOC therapy at activities of 3.7 GBq/m^2, generally repeated for two cycles [4]. The authors observed severe permanent kidney toxicity in 9.2% of patients (grade IV in 67 patients; grade V in 35 patients), with no difference in survival between patients with and without posttreatment kidney toxicity. The clinical response rate was 30%, similar to that obtained by groups applying less aggressive protocols, including comparable total activities divided into more cycles. In a subsequent study, Marincek et al. showed that administration of increasing activities of ^{90}Y-DOTATOC (2.4, 3.3 and 6.7 GBq/cycle) is associated with increasing toxicity, and grade IV/V toxicity was observed in 8.4%, 6.5% and 14.0% of

patients, respectively [43] (*see also* Fig. 3). The same authors reported that fractionated ^{90}Y-DOTATOC treatment leads to reduced kidney toxicity and improved overall outcome.

Risk factors—Following a study in 23 patients receiving ^{90}Y-DOTATOC, Bodei et al. reported the first considerations about absorbed doses and BED to the kidneys and risk factors in relation to creatinine clearance loss [37]. The results showed that for the same absorbed dose or BED, kidney impairment was more evident in patients with risk factors (e.g. hypertension, diabetes, age, kidney morphological abnormalities, previous chemotherapy and chemoembolization), and the kidney toxicity occurred almost exclusively in patients with risk factors. In these patients, the lowest BED above which toxicity was observed was 28 Gy, while in patients without risk factors, the BED threshold was 40 Gy. A further matter was the recovery of renal parameters in patients without risk factors, whilst in patients with risk factors the decline in creatinine loss was progressive without recovery.

In 47 patients receiving ^{177}Lu-DOTATATE therapy, Gupta et al. found that the increase in serum creatinine in patients with grade 1 kidney toxicity at baseline was greater than in patients with normal creatinine levels at baseline [5]. Similarly, in 51 patients treated with ^{177}Lu-DOTATATE, Sundlov et al. found that patients with risk factors for nephrotoxicity had a more rapid decline in kidney function than their healthier counterparts [12].

Comparison between ^{90}Y-labelled and ^{177}Lu-labelled peptides—In a study based on autoradiography seeking to overcome the limitations of macroscopic imaging, Konijnenberg et al. found nonuniform activity distributions of radiolabelled octreotide derivatives in human kidneys [56]. In particular, the authors derived the dose–volume histograms (DVH) for ^{90}Y-labelled and ^{177}Lu-labelled peptides and found absorbed dose deposition in the renal cortex that showed a nearly uniform distribution when ^{90}Y was used and a nonuniform striped pattern when ^{177}Lu was used. As a consequence, for a given mean absorbed dose, D_m, close to the threshold for kidney failure, the uniform absorbed dose distribution for ^{90}Y is such that a large fraction of the volume receives an absorbed dose of about D_m and the whole parenchyma is likely to be damaged. In contrast, for the nonuniform absorbed dose distribution of ^{177}Lu only a fraction of the volume receiving an absorbed dose higher than D_m is likely to be damaged, while the remaining volume is undamaged. Thus there is an overall sparing effect with ^{177}Lu in comparison with ^{90}Y. Valkema et al. also suggested that 1 Gy from ^{177}Lu may lead to a lower average glomerular absorbed dose than 1 Gy from ^{90}Y, because of the much shorter range of ^{177}Lu beta particles [45].

To investigate the role played by the nonuniform absorbed dose distribution in the dose–effect correlation at the microscopic level, Sarnelli et al. [32] used the microscopic DVH approach of Konijnenberg et al. [57]. The authors found that the NTCP curve resulting from uniform absorbed doses of ^{90}Y is shifted to lower BEDs, as opposed to the curve calculated for nonuniform absorbed doses of ^{177}Lu. According to this model, using the commonly employed treatment schedules (e.g. three cycles of 2.8 GBq ^{90}Y and four cycles of 7.4 GBq ^{177}Lu), the risk of developing kidney toxicity would be significant for ^{90}Y, but not for ^{177}Lu.

Correlation with haematological toxicity

The absorbed dose to the red marrow is not the major concern in PRRT, although it could become a concern in salvage or extended treatments. Haematological toxicity is usually absent or of low grade, and therefore the red marrow is not the main organ at risk. Absorbed doses to the red marrow seem to be quite low. For this reason, correlation studies are challenging, since in this absorbed dose region differences in absorbed dose among individual radioresistance prevails over differences in irradiation effects. Concerning chronic long-term toxicity, Bodei et al. found that for subsequent cycles of ^{90}Y-DOTATOC there is a cumulative progressive impoverishment of the marrow reserve, especially after a cumulative absorbed dose of 1.2 Gy has been received, although a significant relationship was not obtained [58]. Others have found similar results with ^{177}Lu PRRT, although often the haematological values might be lower than the threshold for toxicity [59].

The first study looking specifically for a dose–effect association is that by Forrer et al. [34], who interestingly found that^{177}Lu-DOTATATE activity concentrations in the blood and red marrow aspirates show a good correlation. This supports the validity of the blood-based model for red marrow dosimetry, although no correlation between red marrow absorbed dose and short-term acute haematological toxicity has been reported so far.

In ^{86}Y-labelled and ^{111}In-labelled peptide images, Walrand et al. observed a slight late accumulation in the red marrow that was not somatostatin receptor-dependent, but was probably related to transchelation of radiometals to free serum transferrin [42]. The authors found a good correlation ($R = 0.96$) between absorbed doses to the red marrow (median 1.1 Gy, range 0.3–1.7 Gy) and platelet count reduction at the nadir [42]. In a recent dosimetric study in 24 of 320 patients, Bergsma et al. found a correlation between platelet and white blood cell variations in a subgroup of 12 patients who received 7.4 GBq per cycle of ^{177}Lu-DOTATATE, while no relationship was found in other patients receiving different activities per cycle (1.9 and 3.7 GBq) [35]. Absorbed doses were not higher than in the rest of the patients, but the authors did not provide an explanation for this observation. Haematological toxicity of grade III/IV was found in 11% of patients, in three of whom dosimetry was studied. The authors concluded that ^{177}Lu-PRRT seems to have an absorbed dose threshold for haematological toxicity to the red marrow of more than 2 Gy, albeit this assertion was not supported by the data provided.

Del Prete et al. reported a moderate inverse correlation between the variation in platelet count 4 weeks after each cycle and the per-cycle absorbed dose to the red marrow based on SPECT imaging (Spearman's $r = -0.48$, $p = 0.0001$) [33]. Svensson et al. found an interesting correlation with haematological toxicity in 46 patients [38]. These authors developed a particular method for red marrow dosimetry of the lumbar vertebrae based on planar imaging. Two compartments, one with high uptake (liver, spleen, kidneys, tumours) and the other with low uptake (muscle, fat, bone), were differentiated on planar images by an automatic segmentation algorithm and the contributions of both compartments were summed to derive the absorbed dose to the bone marrow. The relative declines in haemoglobin, white blood cells and platelets were found to be correlated with the total absorbed dose (Pearson regression coefficients −0.45, −0.36 and −0.43, respectively). These results are significant, despite the fact that the strength of these correlations is not high.

Lastly, another study by Svensson et al. drew attention to the association between the absorbed dose to the spleen and haematological toxicity [39]. Correlations were not strong, but still statistically significant (Pearson coefficient −0.39, $p = 0.02$). This can be explained by the fact that the spleen is the most irradiated organ – due to the presence of somatostatin receptors on lymphocytes – and is a major reservoir of blood cells. Thus, damage to these cells induced by the high levels of irradiation might reduce the number of peripheral blood cells. A study by Sabet et al. showed that splenectomy exerts a protective effect against haematological toxicity [50]. On the contrary, a previous analysis by Kulkarni et al. found no correlation between the incidence or grade of haematological toxicity and the absorbed dose to the spleen [60].

Late effects in the red marrow are a further complication. These effects include delayed myeloid neoplasms, myelodysplastic syndrome and acute myeloid leukaemia. These have been sporadically recorded in several clinical trials of PRRT [4, 7, 33, 46, 49, 50, 61–63] and are summarized in Table 4.

Although rare, these cases are indeed a major concern because they are life threatening [64]. The reasons for the onset of these diseases remain elusive, either because cases are rare (statistical studies are not yet possible), or because they do not seem to be related to absorbed doses to the red marrow. In fact, stochastic events are sometimes unrelated to the dose, but are more probable as the dose increases. In two patients in whom absorbed doses were available, the cumulative absorbed doses were only of 1 and 1.3 Gy [7], well below the threshold of 2–3 Gy, typically associated with radiation-induced effects. Most probably the main cause is susceptibility of the stem cells to radiation in an individual patient. A higher frequency of these occurrences has been reported by some authors in association with chemotherapy, which is a collateral myelotoxic therapy also well known in combination with radiotherapy [33, 61, 62].

Correlation with sterility

Possible irradiation of the gonads deserves attention because many patients start PRRT fertile and with good life expectancy. Uptake in the gonads, that is not perceptible in women and minor – although evident – in men, is not associated with serious side effects. Kwekkeboom et al. analysed sterility parameters in patients receiving ^{177}Lu-DOTATATE [65]. They found no effects in women. In contrast, they found transient loss of fertility in men that required 18–24 months for reversal: serum testosterone and serum inhibin-B concentrations were significantly decreased, and serum follicle-stimulating hormone concentrations were increased. Permanent sterility in men has not been reported. Although there are no studies showing an association between absorbed doses and sterility, absorbed doses to the gonads are available in the literature: median doses to the testes and ovaries are 1.2 and 0.3 Gy for one cycle of ^{177}Lu peptides (7.4 GBq), and 1.8 and 0.4 Gy for one cycle of ^{90}Y-labelled peptides (2.8 GBq), respectively. These values are consistent with temporary male sterility and no predictable effects in women, considering the threshold values for sterility reported by the ICRP publication 103 (0.15/3.5–6.0 Gy to the testes for temporary/permanent sterility; 2.5–6.0 Gy to the ovaries for permanent sterility) [66].

Correlation with tumour response

Pauwels et al. presented the first correlation between absorbed dose and tumour reduction in a study of 13 patients affected by gastroenteropancreatic NET and treated with ^{90}Y-DOTATOC PRRT [36]. Quantitative ^{86}Y-DOTATOC imaging was used for dosimetry and CT for tumour response. The correlation was not high but was significant (Pearson coefficient $R^2 = 0.5$), confirming the value of tumour dosimetry and demonstrating the necessity to irradiate tumours with absorbed doses higher than 120 Gy in order to improve responses. In agreement with the results of this study, Del Prete et al. found that with ^{177}Lu-DOTATATE therapy, tumour lesions exposed to absorbed doses exceeding about 130 Gy did not progress, although no significant correlation between the radiological response and the cumulative lesion absorbed dose was found [33]. Interestingly, a strong inverse correlation was found between the biochemical response (change in chromogranin A level) and the tumour absorbed dose (Pearson $r = -0.84$; $p = 0.0006$), suggesting that PRRT has a significant effect on tumour secretory function that is independent of the radiological response, especially at absorbed doses exceeding 100 Gy.

The most relevant study is that by Ilan et al. [31]. In 24 patients treated with ^{177}Lu-DOTATATE they found a correlation between the tumour absorbed doses and tumour volume reduction, as assessed by CT, with a Pearson coefficient R^2 of 0.64 for tumours of diameter larger than 2.2 cm (higher uncertainty), and 0.91 for tumours of diameter larger than 4 cm (Fig. 5). The most significant factor influencing outcome was the accuracy of dosimetry that was based on SPECT with correction for attenuation, scatter, detector response and the partial volume effect.

Dosimetry for optimization

The possibility of optimizing treatment with dosimetry was discussed by Sandstrom et al. [9], who used a dosimetry-based protocol with a variable number of cycles of 7.4 GBq ^{177}Lu-DOTATATE, provided that absorbed dose limits of 23 Gy to the kidneys and 2 Gy to the bone marrow were respected. With this strategy, the kidney was confirmed to be the dose-limiting organ in 99% of patients. In addition, based on the above dosimetric constraints, 50% of patients could theoretically tolerate more than four (up to ten) cycles, whereas 20% of patients could not tolerate the standard four cycles and should have received fewer cycles. The study lacks an actual toxicity profile correlation as well as the demonstration of efficacy of the different dosages; however, the remarkable observation was that 50% of patients treated with the fixed four-cycle regimen were undertreated with respect to the possibility given by the dosimetric allowance.

Further endorsement is provided by the study of Sundlöv et al. who performed a prospective trial based on multiple cycles of ^{177}Lu-DOTATATE up to a BED limit of 27 or 40 Gy in patients with and without possible impairment [12]. The median numbers of cycles received by the two groups were five (range three to seven) and seven (range five to eight), respectively, and none of the patients developed high-grade toxicity. Finally, a simulation by Del Prete et al. of personalized PRRT with a prescribed kidney absorbed dose of 23 Gy over four cycles of ^{177}Lu-DOTATATE [33] indicated that the cumulative activity could have been increased by a factor of 1.5 on average (range 0.7–2.6; i.e. to 44 ± 17 GBq over four cycles)

as compared to 29.6 GBq delivered in the empirical regimen currently in use. Overall, these data corroborate the hypothesis that higher administered activities of ^{177}Lu-DOTATATE would provide a substantial increase in tumour absorbed dose, therefore with a higher likelihood of therapeutic benefit, without increased toxicity.

Discussion

Correlation with kidney toxicity

Similarities to EBRT—There are some relevant issues addressed by the extensive experience with EBRT, which are in common with the findings of PRRT and can therefore be considered as a solid guide. One is the superimposition of the EBRT and ^{90}Y-PRRT-generated NTCP curves relative to kidney injury as a function of BED [40, 41]. Additional features have been discussed in the QUANTEC publication by Dawson et al. [66], that highlights different aspects. From this publication, it is clear that the tolerability of the same cumulative absorbed dose increases with fractionation, as occurs in PRRT according to BED calculation. Moreover, previous treatments, such as chemotherapy, can enhance EBRT-associated kidney injury, and the corresponding NTCP curves are significantly different. Similarly, risk factors for renal insufficiency such as diabetes, hypertension, liver disease, heart disease and smoking, can also reduce the kidney's tolerance to EBRT, as observed with PRRT. Finally, partial/nonuniform kidney irradiation reduces side effects, so that increased absorbed doses can be tolerated. When applied to PRRT, the probably higher radiation tolerability of ^{177}Lu-labelled peptides compared with ^{90}Y-labelled peptides can be explained by the more nonuniform absorbed dose.

Impact of number of cycles—The advantage of fractionation is well explained in terms of the BED concept, since the relationship between BED and absorbed dose is not linear and the same BED corresponds to a lower cumulative absorbed dose if the activity is divided into fewer cycles [32, 67, 68]. For example, for the same BED of 40 Gy, one and four cycles are associated with absorbed doses of 25 Gy and 33 Gy for ^{90}Y, and with 28 Gy and 35 Gy for ^{177}Lu, respectively [67]. The calculation by Sarnelli et al. [32] shows that activities of ^{90}Y-labelled peptides as high as those used by Imhof et al. [4] delivered in two cycles could easily be above the threshold value for failure of kidney functional subunits, compromising kidney function. However, excessive fractionation can lead to unfavourable effects in terms of tumour response, since tumour uptake may decrease in subsequent cycles [24]. This emphasizes the importance of appropriate recruitment criteria and therapy planning based on the level of tumour uptake, so that absorbed doses able to deliver adequate tumour irradiation for response can be reached. To achieve this, levels of uptake must be considerably higher than those in the liver or even the kidney, contrary to what often occurs in clinical practice (e.g. when the so called "Rotterdam scale" is applied for recruitment to PRRT) [69].

Of note, fractionation is particularly advantageous in PRRT with ^{90}Y. The impact is less relevant for PRRT with ^{177}Lu [32], because of the higher ^{90}Y dose-rate and absorbed dose for each administration. Theoretically, due to the lower absorbed dose to the kidneys per unit activity, the cumulative 29.6 GBq typically scheduled in four cycles of PRRT with ^{177}Lu can

even be reduced to two or three cycles to improve tumour efficacy without reaching the threshold for relevant effects on the kidneys [33]. Such a choice is not generally applied, since it is common opinion that doing so could increase the risk of bone marrow toxicity. There are, however, no experimental data to support this assumption and the absorbed dose per cycle to the red marrow is typically <0.5 Gy/7.4 GBq.

Comparison between ^{90}Y-labelled and ^{177}Lu-labelled peptides—Randomized studies comparing the ability of ^{90}Y and ^{177}Lu to deliver the same absorbed dose to the kidneys or, even more simply, at standard activities per cycle, have not been performed. Thus, conclusions about the best radionuclide for PRRT cannot be inferred. What can be considered instead is related to the fact that beta particles from ^{177}Lu are of much shorter range than those from ^{90}Y, which gives a marked nonuniformity of absorbed dose deposition at the microscopic level for the latter. On one hand, big tumour lesions can be more efficiently irradiated with ^{90}Y, while tumours of small dimensions can receive higher doses per unit activity with ^{177}Lu. On the other hand, ^{177}Lu-labelled peptides can spare the renal glomeruli (*see also* the section above Comparison between ^{90}Y-labelled and ^{177}Lu-labelled peptides). This indicates that the kidney tolerance of ^{177}Lu could be substantially greater than that of ^{90}Y in terms of BED. Therefore, the limits extrapolated for ^{177}Lu in Table 3 are purposely conservative. The NTCP curve for ^{90}Y is not expected to necessarily apply to ^{177}Lu: the mean absorbed dose renal threshold of 28 Gy, valid for ^{90}Y-DOTATOC, might not necessarily apply to 177Lu-DOTATATE.

Correlation with haematological toxicity

Evaluation of the correlation between the absorbed dose to the red marrow and haematological toxicity is most difficult for methodological and clinical reasons. A proper dosimetric method (based on blood or imaging) should be applied, depending on the specificity of the radiopharmaceutical for the bone marrow itself. In PRRT there is in general no evidence of a special tropism on post-therapy images, so imaging has rarely been used for red marrow dosimetry. On the other hand, blood-based methods have not been proven to be useful in PRRT. Most probably, individual red marrow mass and functionality, that are often unknown, are the most important factors. In addition, pretreatment with different chemotherapies and drugs must be considered. Moreover, nonuniformity of red marrow irradiation might have an impact, but is usually not taken into account in the computation of absorbed dose. As shown by experience with other radionuclide therapies [70–72], the use of more refined methods has led to consistent improvement in determining the correlation between the absorbed dose to the red marrow and haematological toxicity in PRRT [33, 38, 39, 42], although none of these results has been confirmed by other researchers and the quite elaborate method may cause problems with reproducibility among centres.

Dosimetry for optimization

There are a few studies in which dosimetry has been used to determine the activity to be administered [9, 12, 33]. ^{177}Lu-DOTATATE was investigated in all these studies probably because of the more recent use of this radiopharmaceutical as compared with ^{90}Y derivatives, which have been used more empirically. Two different approaches were used in these studies. First, Sandstrom et al. [9] and Sundlöv et al. [12] fixed the amount of activity

per cycle at 7.4 GBq and varied the number of cycles to reach the dose limit set for the kidneys (absorbed dose of 23 Gy or BED of 27 or 40 Gy depending on risk factors) and/or bone marrow (2 Gy). Second, Del Prete et al. [33] performed a simulation with a fixed four cycles and varying the activity per cycle to reach the dose limits. Unfortunately, the clinical outcomes, in terms of toxicity and response, of the above protocols were still unavailable at the time of this report (but will hopefully be available soon), so whether dosimetry is able to optimize treatments was still unproven. However, the method using fixed absorbed doses to the critical organs allowed much higher activities to be administered (up to ten cycles) compared with the standard ^{177}Lu-DOTATATE protocol of four cycles, without early toxicity. This strongly corroborates the potential of dosimetric protocols to guide therapy in the future.

The same holds true for fractionation of ^{177}Lu-PRRT, since the “standard” treatment of four cycles of 7.4 GBq has been demonstrated to be safe although not optimized, due to the risk of undertreatment. For ^{90}Y-PRRT, four cycles of 3.3 GBq or three cycles of 4.4 GBq could be a good compromise, although dosimetry should guide the total amount of activity administered. Fewer cycles and higher activities per cycle of ^{90}Y-PRRT can be dangerous in terms of kidney toxicity (the study by Imhof et al. [4] showed the same rate of kidney toxicity with two cycles of 6.3 GBq per cycle but with more than 9% incidence of endstage kidney toxicity requiring dialysis).

Overall, dosimetry should at least be used to verify that the dose limits have not been reached. In our opinion, in a wider approach, dosimetry should be used to establish the maximum activity to be injected that corresponds to a dose limit to normal organs, possibly limiting the number of cycles to four or five, to avoid reduced tumour uptake in the last cycles [24], to maximize tumour irradiation and to optimize response. Individualization through dosimetry is becoming crucial particularly in view of the increased use of intensive and salvage PRRT schemes, with cumulative activities of >29.6 GBq of ^{177}Lu [73].

Conclusion

This review discusses the dose–effect relationships described in the literature for PRRT with both ^{90}Y and ^{177}Lu. The limitations of the studies analysed include small sample sizes and differences in dosimetric methods. These limitations weaken the extrapolated dosimetric/radiobiological models. Critical examination of methodological consistency and potential weaknesses of the published studies is very important to avoid hasty conclusions, and correlations need robust calculations and accuracy of both clinical and dosimetric parameters. The available data on dose–effect correlations are scarce as compared with those that could be obtained if dosimetry were implemented as routine. Dosimetry trials are needed to show its ability to optimize treatments based on toxicity and clinical results, although the potential of dosimetry to allow consistent increases in administered activities without causing acute effects in comparison with fixed activity schedules has been shown. However, the results reported here provided appreciable evidence of correlations. 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 is crucial in view of the current emphasis on personalized approaches to medicine which, if applied to PRRT, could replace the current suboptimal protocols with fixed activities, with the aim of increasing therapeutic efficacy, while minimizing toxicity.

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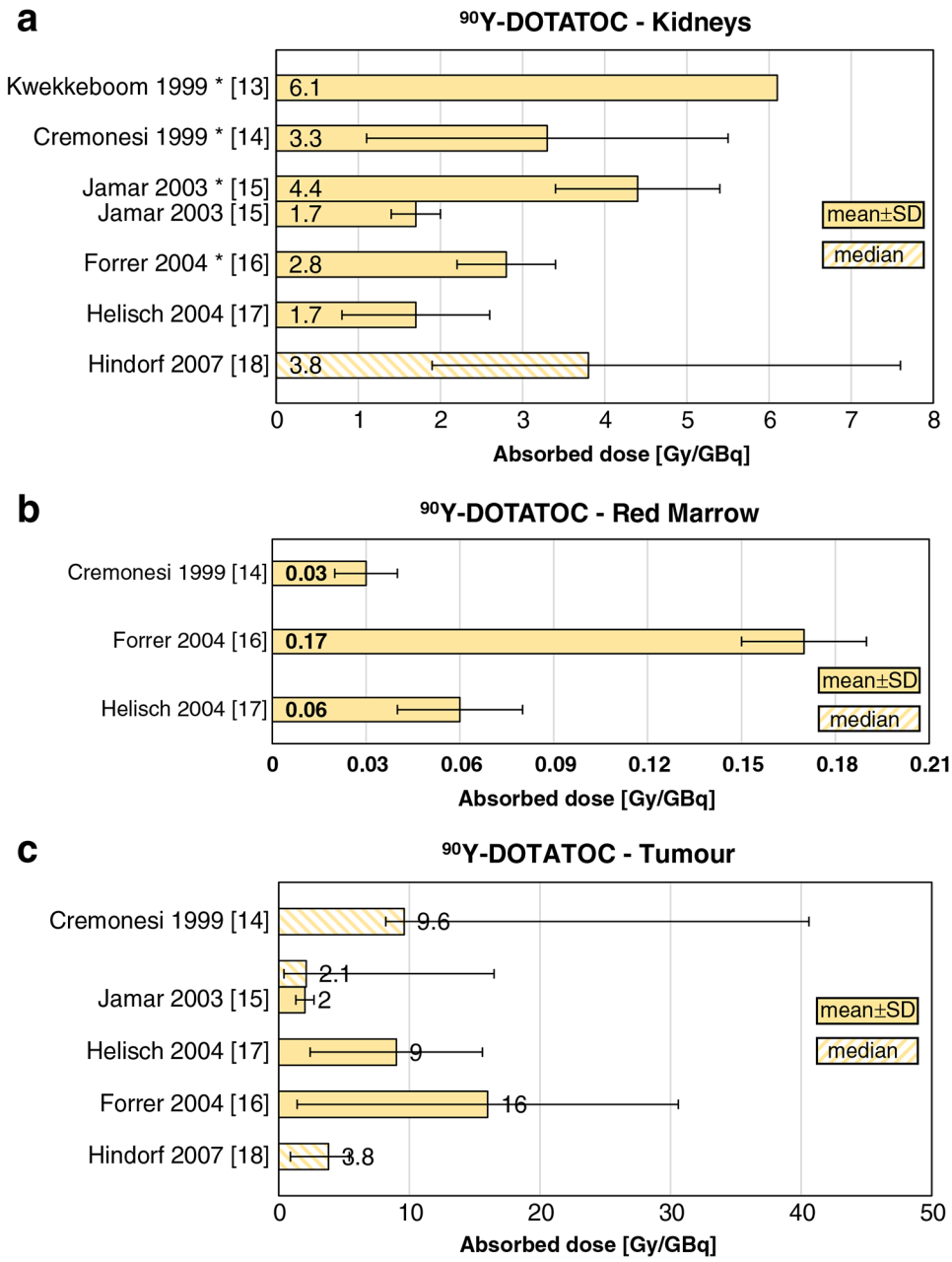

Fig. 1.

Absorbed dose of ^{90}Y-DOTATOC per unit activity in the kidneys (**a**), red marrow (**b**), and tumour (**c**). The *asterisks* indicate older studies when no kidney protection was given, so a 30% to 60% absorbed dose reduction would be expected with administration of kidney protectors. *Bars with full shading* show mean values and standard deviations of absorbed doses per unit activity; *bars with hatching* show median values and ranges of variability

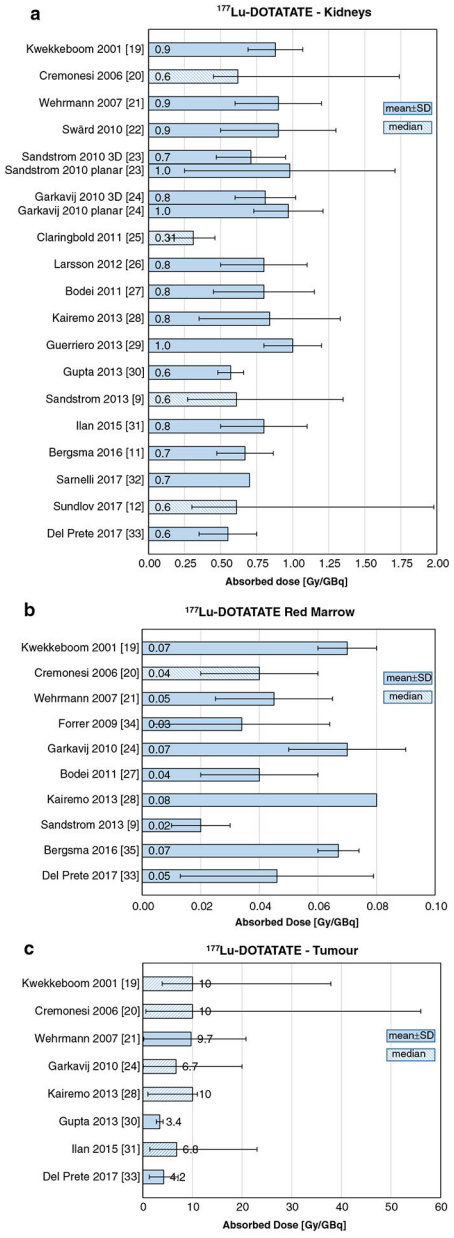

Fig. 2.

Absorbed dose of ^{177}Lu-DOTATATE per unit activity in the kidneys (**a**), red marrow (**b**), and tumour (**c**). This therapy was always administered with kidney protection. *Bars with full shading* show mean values and standard deviations of absorbed doses per unit activity; *bars with hatching* show median values and ranges of variability

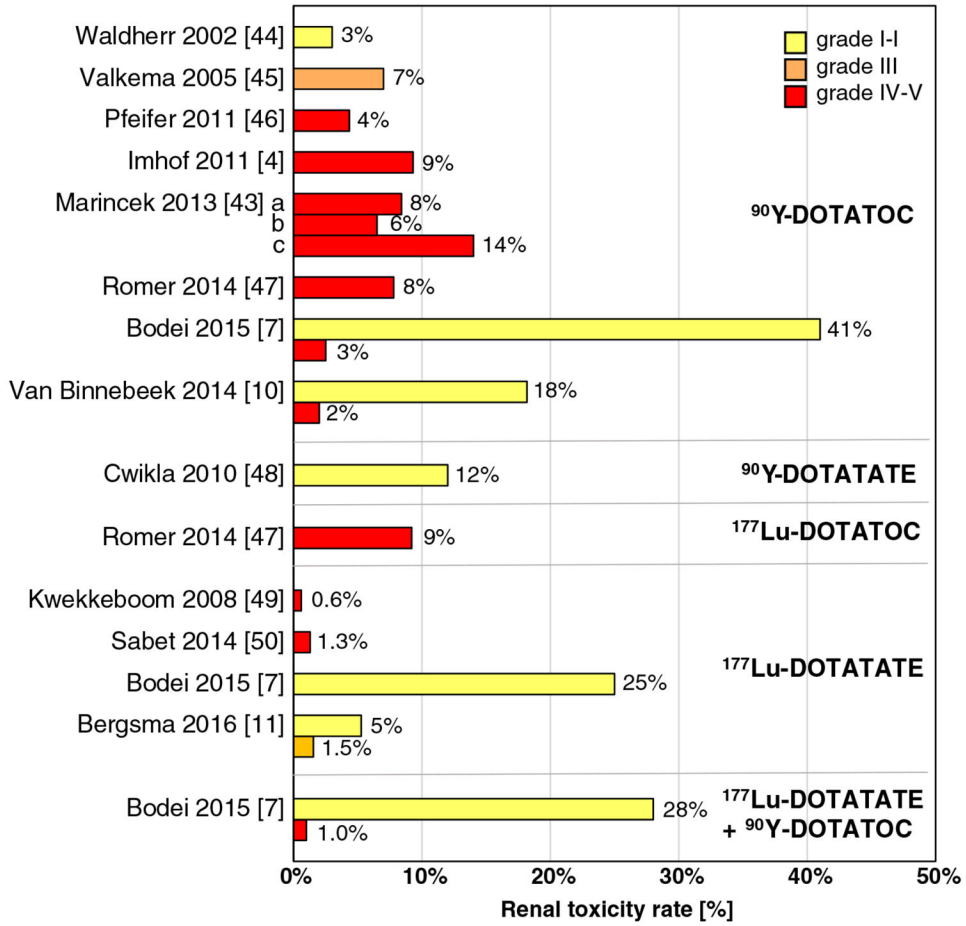

Fig. 3.

Kidney toxicity rates reported in studies of PRRT with ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, ^{177}Lu-DOTATATE, and the combination of ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE (*yellow bars* grades I/II, *orange bars* grade II, *red bars* grades III–V). ^{90}Y alone and ^{90}Y + ^{177}Lu were associated with significantly higher nephrotoxicity, while severe nephrotoxicity was virtually absent after treatment with ^{177}Lu-labelled peptides. The data of Marincek [43] *a*, *b* and *c* correspond to three groups of patients receiving low, medium and high activities, with median values of 9.6, 12.6, and 13.3 GBq, respectively. Table 3 provides more detailed information on the studies considered in this figure

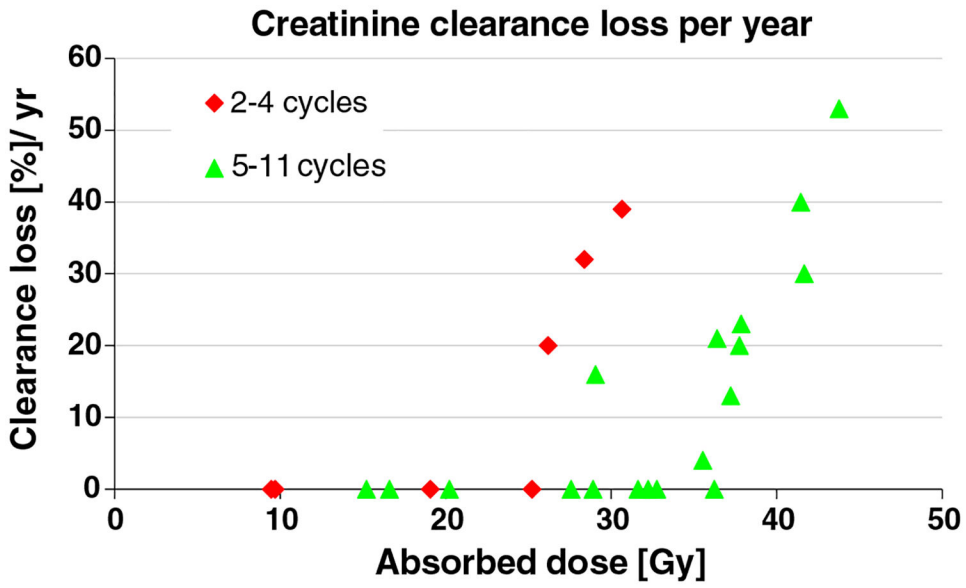

Fig. 4.

Creatinine clearance loss as a function of cumulative absorbed dose to the kidneys for 2 to 4 cycles (*diamonds*) and 5 to 11 cycles (*triangles*). Patients receiving therapy in a higher number of cycles experienced creatinine clearance loss at higher absorbed doses. Data derived from the study by Bodei et al. [37]

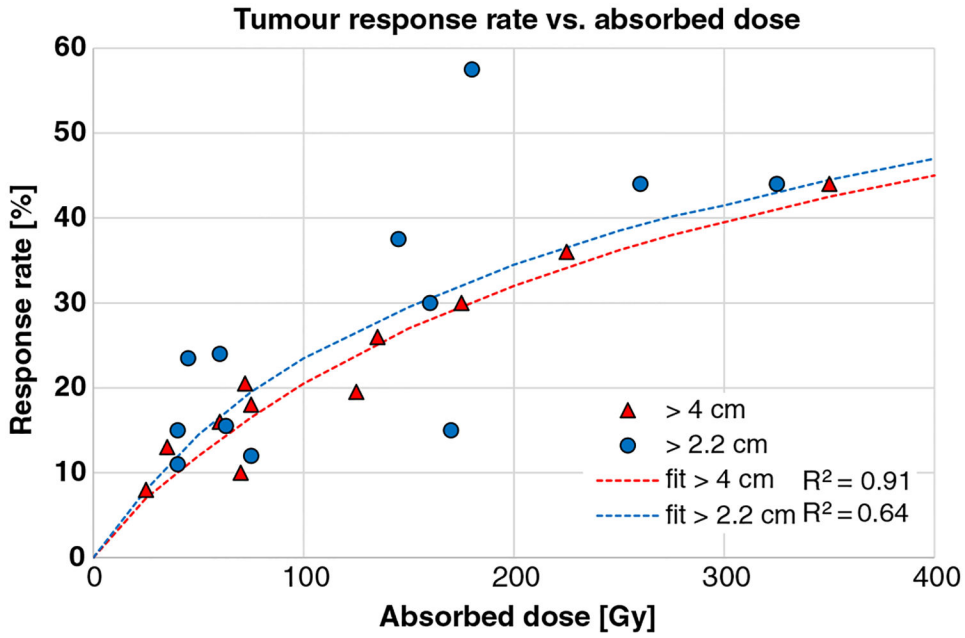

Fig. 5.

Tumour response in relation to tumour absorbed dose for all lesions evaluated with a diameter >2.2 cm (*blue circles*) and for lesions with a diameter >4.0 cm (red triangles). Adapted from Ilan et al. [31]

Table 1

Studies identified in the literature search for dose–effect correlations

Reference	Prospective/ retrospective	Number of patients	Radiopharmaceutical	Organs/tissues considered	Dose-effect correlations analysed
[40]	Retrospective	18	^{90}Y-DOTATOC	Kidneys	CCL/year vs. kidney aD: yes (r = 0.54, p = 0.02) CCL/year vs. kidney BED: yes (r = 0.93, p <0.001)
[36]	Retrospective	13	^{90}Y-DOTATOC	Tumour	Tumour reduction vs. tumour aD: yes (R^2 = 0.496)
[37]	Retrospective	25	^{90}Y-DOTATOC, ^{177}Lu-DOTATATE	Kidneys	CCL/year vs. kidney aD for different cycles: yes (see Fig. 4)
[41]	Retrospective	43	^{90}Y-DOTATOC	Kidneys	Kidney disease endpoint (CCL 20%/year) considered for NTCP NTCP vs. aD: yes (r = 0.90) NTCP vs. BED: yes (r = 0.99)
[34]	Prospective	15	^{90}Y-DOTATOC	Red marrow	Specific activity in blood vs. red marrow aspirates: yes (r = 0.914, p <0.001) Drop in PLT vs. red marrow aD: no
[42]	Retrospective	12	^{90}Y-DOTATOC	Red marrow	Drop in PLT vs. BED in red marrow: yes (R = 0.96)
[5]	Prospective	43	^{177}Lu-DOTATATE	Kidneys	Posttreatment GFR vs. kidney aD: yes (p = 0.034)
[10]	Prospective	22	^{90}Y-DOTATOC	Kidneys	GFR loss/year vs. BED: no, but BED <37 Gy and no grade 3/4 toxicity; dosimetry based on ^{111}In-octreotide
[31]	Prospective	24	^{177}Lu-DOTATATE	Tumour	Tumour response vs. aD for tumours >2.2 cm: yes (R^2 = 0.64) Tumour response vs. aD for tumours >4.0 cm: yes (R^2 = 0.91)
[38]	Retrospective	46	^{177}Lu-DOTATATE	Red marrow	Drop in Hb, WBC, PLT vs. red marrow aD per fraction: yes (r = −0.36, p = 0.01; r = −0.43, p <0.01; r = −0.45, p <0.01, respectively) Drop in Hb, WBC, PLT vs. cumulative red marrow aD: yes (r = −0.45, p <0.01; r = −0.36, p = 0.01; r = −0.43, p <0.01, respectively)
[39]	Retrospective	41	^{177}Lu-DOTATATE	Red marrow, spleen	Drop in PLT vs. spleen aD: yes (r = −0.39, p = 0.02) Drop in Hb or WBC vs. spleen aD: no
[35]	Prospective	24	^{177}Lu-DOTATATE	Red marrow	Drop in Hb, WBC, and PLT vs. red marrow aD in all 24 patients: no Drop in WBC and PLT vs. red marrow aD in subgroup of 12 patients (7.4 GBq/cycle) after the last cycle: yes (r = −0.59, p = 0.02; r = −0.51, p > 0.05, respectively)
[11]	Prospective	228	^{177}Lu-DOTATATE	Kidneys	CCL/year vs. kidney aD: no, but mean aD 20 ± 5 Gy, CCL/year 3%, and no patient showed CCL/year >20%
[33]	Retrospective	36	^{177}Lu-DOTATATE	Red marrow, tumour, kidneys	Drop in PLT per cycle vs. red marrow aD: yes (r = −0.48, p = 0.0001) Chromogranin A variation vs. tumour aD: yes (r = −0.84, p = 0.0006) GFR variation vs. kidney aD: no

aD absorbed dose, *BED* biologically effective dose, *CCL* creatinine clearance loss, *GFR* glomerular filtration rate, *Hb* haemoglobin, *PLT* platelets, *WBC* white blood cells.

Table 2

Kidney toxicity incidence published in the literature (see also Fig. 3)

Reference	Number of patients	Radiopharmaceutical	Activity[a]	Number of cycles[b]	Kidney protection	Toxicity			
						Criteria	Parameter	Percentage of patients	Grade
[44]	39	^{90}Y-DOTATOC	7.4 GBq/m^2	4	Yes	NCI-CTC	Creatinine	3.0	II
[45]	28	^{90}Y-DOTATOC	0.925 GBq/m^2/cycle	4	Yes	NCI-CTC	Creatinine	7.0	III
[46]	53	^{90}Y-DOTATOC	(9.6–18.3 GBq)	2 (1–3)	Yes	CTC v2.0	Creatinine, GFR	4.3	III/IV
[4]	1109	^{90}Y-DOTATOC	3.7 GBq/m^2/cycle	2 (1–10)	Not always	NKFg		9.3	IV/V
[43]	60 (a)	^{90}Y-DOTATOC	9.6 GBq (1.7–34.6 GBq)	2	Yes	NKFg		8.4	IV/V
	77 (b)		12.6 GBq (2.4–58.5 GBq)	4	Yes			6.5	IV/V
	222 ©)		13.3 GBq (5.7–62.2 GBq)	4	Not always			14.0	IV/V
[47]	910	^{90}Y-DOTATOC	13.1 ± 4.7 GBq	2 (1–6)	Yes	CTCAE v. 3.0		7.8	IV/V
[7]	358	^{90}Y-DOTATOC	10.1 GBq (1.1–26.4 GBq)	4(1–11)	Not always	CTCAE v. 4.0	Creatinine	41	I/II
								2.5	III/IV
[10]	50	^{90}Y-DOTATOC	12.8 GBq (8.4–16.3 GBq)	4	Yes	CTCAE v. 4.0	Creatinine, GFR	18	I/II
								2.0	IV
[48]	60	^{90}Y-DOTATATE	11.2 GBq (4.1–16.2 GBq)	3 (2–4)	Yes	WHO	Creatinine	12	II
[47]	141	^{177}Lu-DOTATOC	13.5 ± 6.5 GBq	2 (1–5)	Yes	CTCAE v. 3.0		9.2	IV/V
[49]	504	^{177}Lu-DOTATATE	(27.8–29.6 GBq)	4	Yes	Not specified		0.6	IV
[6]	74	^{177}Lu-DOTATATE	(4.8–37.8 GBq)	Mean 3.6	Yes	CTCAE v. 3.0	Creatinine, GFR	1.3	III/IV
[7]	278	^{177}Lu-DOTATATE	23.3 GBq (1.7–49.2 GBq)	5 (1–10)	Yes	CTCAE v. 4.0	Creatinine	25	I/II
[11]	323	^{177}Lu-DOTATATE	29.6 GBq (7.4–29.6 GBq)	4 (1–8)	Yes	CTCAE v. 4.0	Creatinine	5.3	I/II
								1.5	III
[7]	157	^{177}Lu-DOTATATE + ^{90}Y-DOTATOC	^{90}Y: 6.4 GBq (0.4–31.7 GBq)	5 (1–19)	Not always with ^{90}Y	CTCAE v. 4.0	Creatinine	28	I/II
			^{177}Lu: 12.7 GBq (1.9–36.2 GBq)					1.0	III/IV

CTC Common Toxicity Criteria version 2.0, *CTCAE* Common Terminology Criteria for Adverse Events versions 2.0 and 3.0. *GFR* glomerular filtration rate, *NCI-CTC* National Cancer Institute's Common Toxicity Criteria, *NKFg* National Kidney Foundation guidelines; *WHO* World Health Organization

[a] Values are median (range) or mean value ± SD

[b] Values are median (range), except as specified

Table 3

Kidney absorbed doses (TD_5, TD_{50}) and BED (BED_5, BED_{50}) values associated with 5% and 50% probability of NTCP, respectively

	Kidney injury probability		Reference
	5%	50%	
Tolerated absorbed dose, TD (Gy)			
EBRT	23	28	[53]
^{90}Y PRRT[a,b]	25	33	[41]
^{177}Lu PRRT[a,b]	26	36	[41]
EBRT from QUANTEC	18		[54]
Biologically effective dose, BED (Gy)			
^{90}Y PRRT[a]	28	40	[41]

[a] Derived from MIRD20 considering the following radiobiological parameters: α/β 2.6 Gy, T_{eff}^{90} Y = 42 h, T_{eff}^{177} Lu = 69 h, and T_{rep} = 2.8 h [41]

[b] Cumulative doses extrapolated for four cycles of PRRT

Table 4

Myelodysplastic syndrome (MDS) and acute leukaemia (AL) associated with PRRT published in the literature

Reference	Radiopharmaceutical	Number pf patients	Patients with MDS	Patients with AL
[4]	^{90}Y-DOTATOC	1,109	1 (0.1%)	1 (0.1%)
[46]	^{90}Y-DOTATOC	69	2 (2.9%)	–
[49]	^{177}Lu-DOTATATE	504	3 (0.6%)	–
[50]	^{177}Lu-DOTATATE	203	3 (1.5%)	–
[61]	^{177}Lu-DOTATATE + capecitabine and temozolomide	65	2 (3.1%)	–
[7]	^{177}Lu-DOTATATE, ^{90}Y-DOTATOC	807	19 (2.4%)	9 (1.1%)
[62]	^{177}Lu-DOTATATE + previous alkylating chemotherapy	20	3 (15%)	1 (5%)
[60]	^{177}Lu-DOTATATE	610	9 (1.5%)	4 (0.7%)
[33]	^{177}Lu-DOTATATE + several previous chemotherapy regimens	36	–	1 (2.8%)