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Original paper

Yttrium-90 selective internal radiation therapy, examining dose rates and radiation protection precautions

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ABSTRACT

Methods: Dose rates from 30 patients, treated over a 3-year period (2016–2018) were measured post therapy in contact with the patients' upper abdomen and at distances of 0.3 m and 1 m. Dose rates were compared with theoretical predictions and used as model inputs for calculating radiation doses received by family members and carers based on interaction patterns previously described in the literature.

Results: The average dose rate per activity from SIRT patients were:- In contact: 29 ± 23 μSv.h^{-1}.GBq^{-1}; 0.3 m: 4.1 ± 2.34 μSv.h^{-1}.GBq^{-1} and 1 m: 0.59 ± 0.42 μSv.h^{-1}.GBq^{-1}. Dose rates measured at 0.3 and 1 m followed a predictable distribution. Estimated doses based on proximity models demonstrated restrictions to be advisable, depending on the administered activity, considering the dose constraint and limit of 0.3 and 1 mSv, respectively, employed within the EU.

Conclusions: In accordance with local dose constraints, and depending on administered activities, radiation protection precautions may be necessary for those individuals in regular contact with patients who have receive ^{90}Y SIRT. A radiation protection precautions calculator has been devised to offer personalised instructions taking into account the administered activity and proximity models.

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the second most common cause of death from cancer worldwide [1,2]. The majority of patients present at an advanced stage and may be beyond curative options; however, selective internal radiation therapies (SIRT) offers as a potential therapy for those intermediate and advanced stage primary hepatocellular carcinoma and liver metastases [2]. The treatment involves exposing targeted tissue to a high dose of ionizing-radiation, of up to 150 Gy, delivered via the infusion of Yttrium-90 (^{90}Y) microspheres into the hepatic artery, while the healthy liver parenchyma is largely spared due to its preferential blood supply from the portal vein [2,3]. ^{90}Y is a pure beta-emitting isotope with a decay energy of 0.94 MeV and half-life of 64.2 h, with 94% of the radiation dose is delivered within the first 11 days after SIRT administration [3,4]. ^{90}Y beta radiation has an average penetration depth in human tissue of 2.4 mm, and a maximum particle range of 11 mm and, thus, the external beta exposure from the patient is negligible as most would be stopped in the tissue; however, there can be a considerable bremsstrahlung radiation exposure component [3,4]. Although ^{90}Y beta emissions would not be of direct radiation protection concern post therapy, it may be necessary that patients employ radiation protection precautions in order to minimize the dose from the resultant bremsstrahlung emissions to those in close proximity.

Previous studies examining contact restrictions due to bremsstrahlung dose rates from SIRT patients have been carried out in the United States (US) and the Republic of Korea [3,4] jurisdictions where dose limits and constraints to members of the public differ from those within the European Union (EU). Within the EU, dose constraints of 0.3 mSv are typically used, while the dose limit for a member of the public is 1 mSv, as per the Euratom basic safety standards directive [5]. For the US and the Republic of Korea, patients may be released regardless of administered activity if the total effective dose equivalent (TEDE) to another individual due to exposure from the released patient is not likely to exceed a dose limit of 5 mSv. In the case where the dose is likely to exceed a dose constraint of 1 mSv, it is necessary to provide written instructions to the patient in order that the exposures to other individuals are kept as low as reasonably achievable [3,4]. The TEDE, in this case, is determined according to guidance set out by the United States National Regulatory Commission (USNRC), which assumes that a household member is likely to receive the highest dose due to an exposure from a patient if they receive a dose of 25% (occupancy factor of

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Table 1
Comparison of the contact patterns assumed for patients interacting with infants and children.

Distance (m)	Occupancy (hours per day)							
	Bartlett et al. 2013 [9]	USNRC* [5,6]	Perry et al. 2014 [10]			O'Doherty et al. 1993 [7]		
	Child	Child	Young infant	Child 2–5 yrs	Child 5–11 yrs	Young infant	Child 2–5 yrs	Child 5–11 yrs
0.1	1	1	15 × 35 min	4	2	–	–	–
0.5	1	–	–	–	–	8.75	4	2
1	–	–	–	8	4	6	8	4
2	4	–	–	–	–	6	6	2
3	2	–	–	–	–	–	–	–
5	8	–	–	–	–	–	–	–

* United States National Regulatory Commission.

0.25) of the dose to total decay at a distance of 1 m [6,7]. Occupancy factors (O) and distances (D) are also provided for individuals such as caregivers of significant care (O = 0.5, D = 0.3 m), sleeping partners (O = 0.25, D = 1 m), infants, children and pregnant women (O = 0.042, D = 0.1 m).

Numerous studies have estimated patient contact patterns with family members, staff and members of the public for patients having received positron emission tomography (PET), nuclear medicine imaging investigations or radionuclide therapies [8–11]. By considering the contact patterns in addition to estimates of radiopharmaceutical clearance and measured dose rates, usually acquired around the time of radiopharmaceutical administration or as the patient is leaving the nuclear medicine department, individual dose estimates for a range of routine investigations and contact scenarios have been calculated. This has allowed for appropriate contact restrictions to be implemented where necessary. While the measured dose rates for many imaging investigations common to these studies have proven similar, there appear to be significant differences between contact patterns employed in the literature [8–11].

In contrast to the majority of the investigated procedures involving radionuclides [10], the effective half-life in the case of SIRT is relatively long due to the physical half-life length and the assumption that there is no biological decay component, as a result of the ^{90}Y microspheres being fixed in position post SIRT administration [3]. Adhering to proposed radiation protection restrictions for longer periods, as is the case for SIRT, may not be as straightforward as for other radionuclide procedures [10]. Many SIRT patients have later stage liver cancer and, thus, their time with loved ones is valuable. To the authors knowledge there have not been any published studies carried out on how dose constraints and limits local to the EU affect radiation protection precautions. In addition, proximity models within the literature vary considerably and as do the estimated individual doses arising from patient proximity. Accordingly, there is a need for clear radiation protection guidelines for patients and, preferably, precautions tailored to the individual needs of the patient and family members.

This work aims to firstly present measured bremsstrahlung dose rates for SIRT patients immediately post therapy. The acquired data will then serve as an input to dose estimations based on proximity models for different individuals interacting with the SIRT patient. Furthermore, for those individuals in regular contact with SIRT patients, particularly children and partners of patients in need of significant care, we aim to provide a radiation protection precaution calculator capable of optimising radiation protection advice by accounting for the administered activity and for patient-specific circumstances.

2. Methods

Dose rates for all 30 SIRT patients, treated between 2016 and 2018 at St Vincent's University Hospital, Dublin, were measured using a RadEye™ G-10 personal radiation detector (Thermo Scientific™, Massachusetts, US) in contact with the patients' upper abdomen and at distances of 0.3 m and 1 m. Dose rates were measured immediately after infusion of ^{90}Y TheraSphere® glass microspheres (BTG plc, UK) while patients were in the supine position. For the contact rate measurement the dose rate detector was slowly swept over the patient's abdomen in order to locate the point of maximum exposure. The reading accuracy of the RadEye™ G-10 is reported to be ± 20% according to the manufacturer's calibration certificate. Annual in-house calibration tests carried out against a ^{137}Cs reference source between 2016 and 2018 showed the detector to exhibit an accuracy of ± 8.5%.

Regression analysis was performed to examine the relationship between administered activity and dose rates for each respective distance by calculating Pearson's correlation coefficient; Significance was assumed with $p < 0.05$. The relationship between the dose rate and distance, returned as the exponent of the distance, was established for each patient using a least squares linear fit of the natural logarithm of the dose rate and the distance. Dose rates ($\mu Sv.h^{-1}$) and dose rates per administered activity ($\mu Sv.h^{-1}.GBq^{-1}$) were investigated for normality and log normality using the Shapiro-Wilks test. Measured dose rates per activity ($\mu Sv.h^{-1}.GBq^{-1}$) were also compared with theoretical data using a beta emitter bremsstrahlung calculator [12–14]. Dose rates per activity ($\mu Sv.h^{-1}.GBq^{-1}$) at 1 m were simulated for a 1 GBq ^{90}Y point source positioned behind polyethylene, employed as a tissue equivalent material approximation for soft tissue within the abdomen area, with a range of 1–10 cm material thickness.

Measured dose rates were then used as model inputs for calculating radiation doses received by individuals such as family members (partner and child, respectively) and carers based on interaction patterns described in the literature [5–10] and in-house estimates (Tables 1 and 2). Contributions to an individual's dose at a particular distance from the SIRT patient can be calculated for a set time period using the formula:

Table 2
Comparison of the contact patterns assumed for patients interacting with partners and carers.

Distance (m)	Occupancy (hours per day)				
	Bartlett et al., 2013 [9]	USNRC* [5,6]		Perry et al., 2014 [10]	O'Doherty et al., 1993 [7]
	Home Partner	Partner	Carer	Home Partner	Home Partner
0.1	–	–	–	–	8
0.3	–	6	12	–	–
0.5	8	–	–	8	–
1	1	8	–	6	6
2	4	–	–	–	–
3	4	–	–	–	–
5	7	–	–	–	–

* United States National Regulatory Commission.

$$D(t) = R_0 \int_{t_0}^{t_1} e^{-\lambda.t} = \frac{R_0}{\lambda}.(-e^{-\lambda.t_1} + e^{-\lambda.t_0}) \quad (1)$$

where t_0 and t_1 were the start and end time (h) of the period, while λ is the decay constant of ^{90}Y (0.10814 h^{-1}, $T_{1/2}$ = 64.1 h). R_0 was the initial bremsstrahlung dose rate of a patient measured at a set distance. In order to calculate the total dose received at a distance, t_0 and t_1 were set to *0* and ∞, respectively.

To calculate the total dose, where it is necessary to account for distance, time period and/or occupancy factors, the following can be used:

$$D(t, d, O) = \sum_{i=1}^{n} \frac{O_i R(d_i)}{\lambda}.(-e^{-\lambda.t_{1,i}} + e^{-\lambda.t_{0,i}}) \quad (2)$$

where $R(d_i)$ is the initial dose rate at the ith distance d_i, with an occupancy fraction O_i and calculated over a period with start and end times, $t_{0,i}$ to $t_{1,i}$. This was used as a basis of the radiation protection precaution calculator.

3. Results

30 patients were treated with ^{90}Y TheraSpheres® administered over the period 2016–2018, with a mean (± 95% confidence intervals) treatment activity of 2.9 ± 3.1 GBq (Range, 0.62–7.2 GBq). The mean estimated volume of liver tissue to be treated was 1001 ± 1250 cc. The average absolute dose rates from SIRT patients were:- In contact: 73 ± 78 μSv.h^{-1}; 0.3 m: 11.3 ± 13.9 μSv.h^{-1} and 1 m: 1.6 ± 1.6 μSv.h^{-1}.

Dose rates (μSv.h^{-1}) recorded at the respective distances of 'in contact', at 0.3 m and 1 m did not appear to follow normal or lognormal distributions. The dose rate per administered activity (μSv.h^{-1}.GBq^{-1}) recorded in contact, at 0.3 and 1 m appeared lognormal ($p > 0.05$), with p-values of 0.067, 0.08 and 0.19, respectively.

Regression analysis revealed correlation between administered activities (GBq) and dose rates (μSv.h^{-1}) not to be significant for the contact dose rate measurements (R = 0.3057, p = 0.623); however, measured dose rates acquired at 0.3 m (R = 0.61, p = 0.0035) and 1 m (R = 0.704, p = 0.000014) were deemed to be significantly correlated ($p < 0.05$) with administered activity (Fig. 1 (a) & (b)).

Dose rates per activity related to distance according to d^{-n}, where n = 1.58 ± 0.45 (Fig. 2). The correlation coefficient (R^2) of the least squares linear fits of the natural logarithm of dose rate and the distance for patients were calculated to be 0.9897 ± 0.0134.

The average measured dose rate per activity at 1 m was 0.59 ± 0.42 μSv.h^{-1}.GBq^{-1} with a range of 0.24–0.97 μSv.h^{-1}.GBq^{-1} while the average simulated dose rate at 1 m for polyethylene thicknesses of 1–10 cm, calculated at 1 cm increments, was 0.59 ± 0.16 μSv.h^{-1}.GBq^{-1} with a range of 0.4–0.81 μSv.h^{-1}.GBq^{-1}.

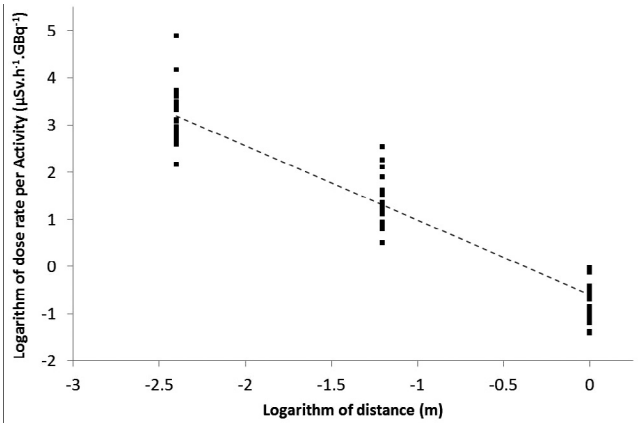

Fig. 2. Relationship between the logarithm of distance (m) and logarithm of dose rate per activity (μSv.h^{-1}), with the dash line depicting the average trend, with slope of −1.58 ± 0.45.

Using the absolute measured dose rates for each patient as input data, it was possible to simulate the radiation doses received for each individual (family member) using the interaction patterns as outlined in Tables 1 and 2. Fig. 3 shows an example of the histogram of doses received by a child when using the absolute measured dose rates for all patients together with the interaction model suggested by Bartlett [9]. The percentage distribution (%) represents the fraction of cases where a specific accumulated dose would've been received by a child interacting with a SIRT patient. The dose constraint and dose limit are also identified on the plot. Similar modelling and analysis was carried out using the measured dose rates for each of the models listed in Tables 1 and 2. The data from all patients, respectively, was used as input in each model, with the average ± 1σ determined for each model. Fig. 4 illustrates the average radiation doses, with error bars depicting ± 1σ, received for each respective proximity model. For each respective proximity model, using the absolute patient dose rates as inputs, we calculated the percentage of patients who would lead to family member accumulated doses in excess of 0.3 and 1 mSv, respectively. Fig. 5 shows the percentage of each of the modelled accumulated doses, modelled for each respective patient, which would lead to the dose to the family member exceeding 0.3 mSv and 1 mSv, the employed dose constraint and limit, respectively.

Further, a radiation protection precaution calculator was devised. Inputs included the 95th percentile measured dose rates per activity at different distances: In contact: 57 μSv.h^{-1}.GBq^{-1}; 0.3 m: 8.9 μSv.h^{-1}.GBq^{-1} and 1 m: 0.96 μSv.h^{-1}.GBq^{-1}. Absolute dose rates for each activity were calculated by simply multiplying the 95th percentile measured dose rates by the administered activity while a dose

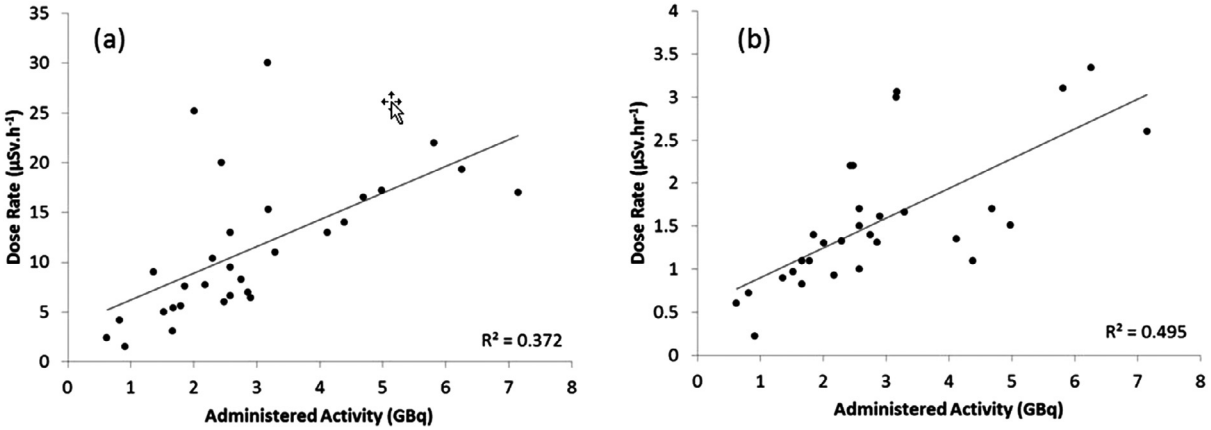

Fig. 1. Correlation between ^{90}Y glass microspheres administered activity (GBq) and dose rates (μSv.h^{-1}) measured at (a) 0.3 m and (b) measured at 1 m.

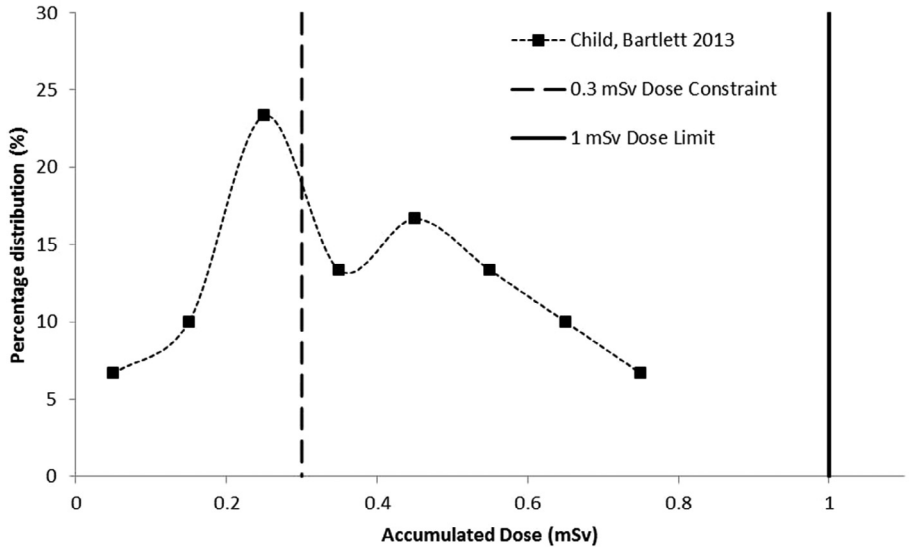

Fig. 3. Histogram of doses received by the child proximity model suggested by Bartlett [10]. The dose constraint (0.3 mSv) and dose limit (1 mSv) are also identified on the graph.

constraint was set at 0.3 mSv. A simple algorithm was devised to optimise radiation protection precautions. Time spent (occupancy) at each respective distance per day was weighted based on its dose contribution which was defined as the duration (h) at a distance multiplied by the dose rate ($\mu Sv.h^{-1}.GBq^{-1}$) at that distance. These durations were locally devised to be 1, 8, 8 and 7 h at distances of 0.1, 0.3, 1 and 2 m, respectively. The dose contribution weightings were then ranked, from highest to lowest, and the total dose received was modelled for the administered activity using the durations at distances. While the accumulated dose exceeded the dose constraint, the highest ranking term was reduced by decreasing the recommended duration at that distance in proportion until the modelled dose received fell below the dose constraint. Where further reductions were needed, the next highest contributing term was reduced in proportion until the dose fell below the set dose constraint, and so on. Table 3, for illustrative purposes, gives an example of the radiation protection precautions returned by the calculator, for a home partner, for a number of administered activity ranges. In this case, for simplicity, the precautions are based over a 2 week period with the dose contribution of the third week accounted for in week two. The restrictions in Table 3 are based on a mix of the literature [8–11], with the 1 h at 0.1 m component accounting for close contact interaction while the 8 h at 0.3 m component simulates a partner sharing a bed with the patient.

Where patients requested attendance at a function/family occasion which may involve interacting with the individual in the proximity model, this could be factored into the precautions by reducing the dose constraint by the estimated dose received by the individual during the function.

4. Discussion

For the patient treatments examined in this work the mean and range of administered ^{90}Y TheraSpheres® activities were similar to those in the literature, reportedly 2.75 ± 1.5 GBq (Range:

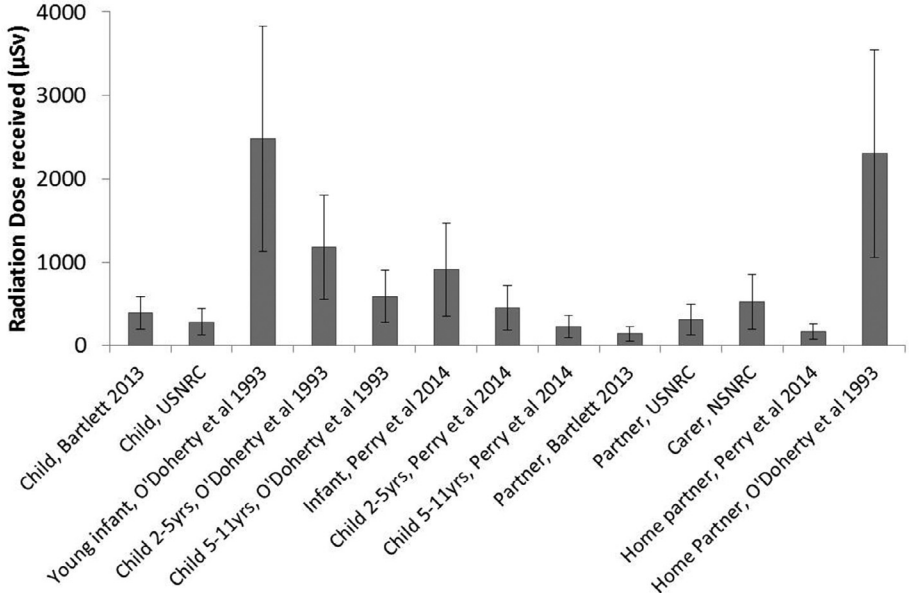

Fig. 4. The average radiation doses (± 1σ) calculated using absolute measured dose rates from SIRT patients and employing individual interaction pattern models [8–11].

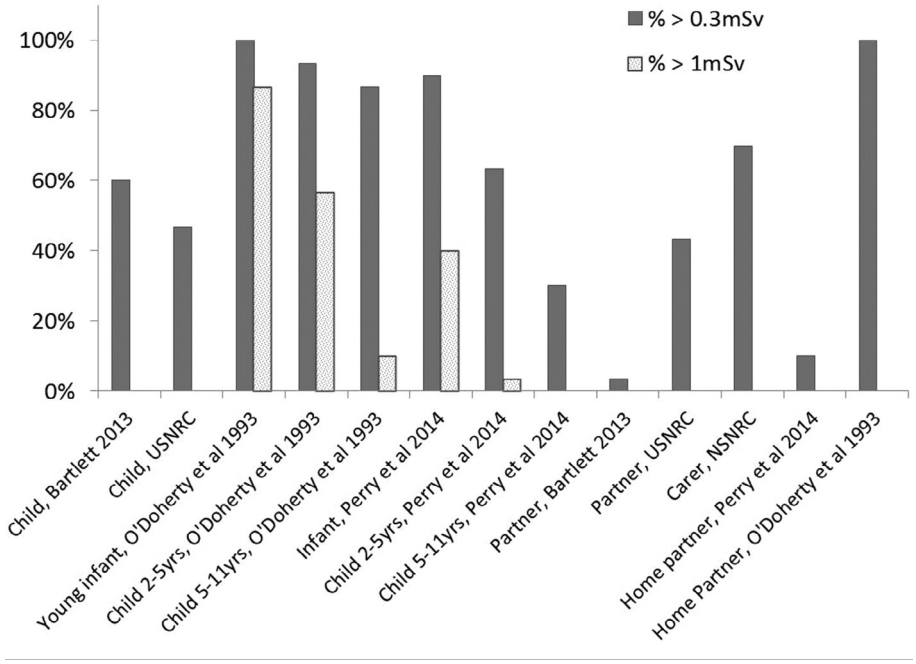

Fig. 5. The percentage (%) of individual estimated doses in excess of a dose constraint (0.3 mSv) and the EU dose limit (1 mSv), as simulated using the measured absolute measured SIRT patient dose rates and the cited models [8–11].

Table 3
Radiation Precautions for patients interacting with home partners.

	Distance (m)	Occupancy limits (hours per day) for activity ranges (GBq)						
		Activity (GBq)						
		0–0.5	0.5–1	1–2	2–3	3–4	4–5	5–7.5
Week 1	0.1	1	1	0	0	0	0	0
	0.3	8	0	0	0	0	0	0
	1	8	8	8	8	8	8	4
	2	7	15	16	16	16	16	20
Week 2	0.1	1	1	1	0.5	0	0	0
	0.3	8	8	8	8	6	2	0
	1	8	8	8	8	8	8	8
	2	7	7	7	7.5	10	12	16

0.37–5.14 GBq) [3]. In the case of resin microsphere therapies the activities are of a lower range than the glass microspheres in two studies, 0.71 ± 0.35 GBq (Range, 0.07–1.59 GBq) [3] and 1.22 ± 0.77 GBq (Range: 0.28–2.79 GBq) [4]. A further study which has not detailed the type of microspheres used report a range of 0.81–7.96 GBq [16]. Our dose rate results compare well with the literature where, for a distance of 0.3 m, the TheraSpheres® patient dose rates are reported to be 20 ± 30 μSv/h [3].

Regression analysis showed the dose rate to have a linear relationship with administered activity, which might have been expected. Accordingly, this would suggest that where the ^{90}Y microsphere prescribed activity is known, the bremsstrahlung dose rate from the patient could be estimated. Indeed, one study has reported the dose rate to correlate with administered activity [16]; however, this is contrary to previously studies where no correlation between administered activity and measured dose rate was reported [3,4]. This was attributed to factors such as the low sample size, variation in tumour location and measurement geometry. Kim et al. [4] studied data from 18 patients administered with ^{90}Y resin microspheres, while McCann et al. [3] examining 127 patients administered with ^{90}Y resin microspheres and 19 patients administered with ^{90}Y glass microspheres. Our sample size did not appear to affect the correlation albeit significance did increase with increased measurement distance from the administered activity which suggests that a variation in the tumour location and geometry may have affected the contact dose rate correlation and possibly the lognormality. Erwin et al. [16] showed similarly, with dose rate and activity correlating well at 1 (r = 0.88) and 0.3 m (r = 0.76) but with significance reducing with decreasing distance to the patient; Contact dose rates were not measured in their work. The effect of body mass index (BMI) on the dose rate has also been accounted for [3]; however, the administered activity proved to be a significant predictor of dose rate in the current study so it was not necessary to account for BMI.

Given the linear relationship of the dose rate and the administered activity, an examination of the dose rate per activity measurements proved the data to follow a predictable log normal distribution. Similarly, though the exponent of the distance was reported to be −1.58 ± 0.45, deviating from the conventional −2, the relationship with distance was predictable and consistent across patients. Thus, dose rates at distances for the different proximity models in the literature but different from those measured in this work could be accurately estimated.

Studies have reported the theoretical bremsstrahlung dose rate per activity for ^{90}Y in soft tissue measured at 1 m to be 0.55 μSv.h^{-1}.GBq^{-1} [3], 1.41 μSv.h^{-1}.GBq^{-1} [17] and 1.52 μSv.h^{-1}.GBq^{-1} [4]. While there

is a large range reported, our measured dose rate per activity corroborates with the lowest of these figures. The dose rate per activity measured from ^{90}Y SIRT patients in another study [16] report an average value of 0.5 μSv.h^{-1}.GBq^{-1}, with the authors suggesting a conservative estimate of 0.78 μSv.h^{-1}.GBq^{-1}, representing the average +2σ, be used when estimating whether radiation protection precautions were necessary [16]. Theoretical bremsstrahlung dose rate per activity estimates were modelled using polyethylene as the tissue equivalent material which has a lower effective atomic number (Z_{Eff}) of 5.6 [18], as compared with the Z_{Eff} of approximately 7.2–7.5 considered for soft tissue [18]. The range of polyethylene material thickness employed was to account for the range of patient size variation and tumour geometry that might be encountered in the clinical scenario. Nevertheless, the dose rates were very similar to those measured in our work.

In this study, where the proximity models have been employed using the measured dose rates as inputs, in the majority of cases, as per Fig. 5, an estimated received dose in excess of a dose constraint set at 0.3 mSv would result. Indeed in some cases, the 1 mSv dose limit to a member of the public is exceeded. It is interesting to note the differences in the distances and durations outlined in the proximity models in the literature [8–11]. While we have not conducted an exhaustive literature review of all interaction and proximity models, even with the relatively small sample examined there is considerable variation. The reported models all originate from first world countries, albeit published in different years and from different countries and cultures [8–11]. It could be argued that interaction models may be changing dramatically in the modern era due to newly available technology which is altering how we work and entertain ourselves and others. Nevertheless, if the proximity models reported in the literature are a reasonable reflection of real interaction patterns, it demonstrates that radiation protection precautions are necessary especially within the jurisdiction of the EU.

In order to simplify the radiation protection precautions for our SIRT patients we have devised a basic radiation protection precaution calculator. Given that the measured dose rates proved to follow a predictable pattern, the choice of the upper 95th percentile dose rate per activity for use in the proximity models was reasonable, as has been previously employed for informing of restriction times post radionuclide therapy [15]. Our choice of durations at distance were devised locally but based on a mix of the literature [8–11]; however these could easily be adjusted depending on the needs of a particular patient. The 1 h at 0.1 m component was employed to account for a close contact interaction while the 8 h at 0.3 m component was used to model a partner sharing a bed with the patient. We have presented the durations such that they sum to 24 h in order that there is no confusion for patients and their family members. The metric used to evaluate the weighting of each dose rate and distance combination was the dose contribution; however, this could easily be tailored depending on the circumstance encountered. Our reported treatment activities range over an order of magnitude and, as such, what is presented is a means to offering personalised precaution instructions. While the precautions can be tailored based on the individuals dose rates measured on the day of therapy, information and advice is given in advance of the SIRT therapy to allow patients to organize and prepare for the therapy and aftermath themselves. In Table 3 we have illustrated how precautions would vary according to varying activity ranges; however, it should be noted that the precautions are based on the maximum activities in those ranges and, as such, activities at the lower end of the presented ranges would lead to family doses significantly lower, in some cases, than the dose constraint. While it would be possible to prescribe the precautions as a daily format we have chosen to present the example of precautions (Table 3) in a weekly format to keep a simplified approach. Furthermore, in some SIRT cases patients may receive a number of ^{90}Y administrations over the course of a number of days. While we have not accounted for this in the model presented here, it could be included by combining models for each administration, returning a summed dose rate and subsequently estimating restriction periods. In order to apply the radiation precaution calculator to other radionuclides it would be necessary to account for the clearance of the radionuclide and its distribution within the patient.

5. Conclusions

In this study we have measured dose rates from SIRT patients immediately post therapy. Measured dose rates compared well with those reported in the literature and theoretical estimates. Dose rates per administered activity followed a lognormal distribution and proved to follow a predictable pattern with distance from the patient. As such the measured dose rates were used as inputs to models, based on interaction patterns previously described in the literature, for calculating radiation doses received by family members and carers. These calculations showed that radiation protection precautions were necessary, in accordance with those dose constraints employed within the EU, for those individuals in regular contact with SIRT patients, particularly children and partners. As such, it is essential to provide written instructions to the patient to ensure that doses to member of the public are kept as low as reasonably achievable. Given the broad range of administered ^{90}Y activities, we have devised a simple radiation protection precaution calculator which optimises radiation protection advice taking the administered activity and patient-specific circumstances into account.

Declaration of Competing Interest

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

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