Dosimetric dependencies on target geometry and size in radioiodine therapy for differentiated thyroid cancer

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\section*{A B S T R A C T}

Purpose Radioiodine therapy is used in most disease stages for differentiated thyroid cancer. Its success depends on several factors, such as lesion size, completeness of surgery, extent of metastasis and tumoural iodine avidity.

We aimed to investigate the importance of non-spherical geometries and size of metastases and thyroid remnants for the absorbed dose delivered. Methods Absorbed doses and energy depositions from homogeneously distributed iodine-131 in clinically relevant geometries and sizes were calculated using Monte Carlo simulations with MCNP6. A total of 162 volumes with different sizes and geometries corresponding to spheres, and prolate or oblate spheroids were simulated. Results Oblate and prolate spheroids had worse radiation coverage compared to spheres for equal masses, up to a difference of 38\% for the most eccentric oblate spheroids and smallest masses simulated (a micrometastasis of mass 0.005 g). The differences in coverage could be explained by different volume - to - surface - area ratios of the spheroids. The impact of size alone caused up to 71\% lower absorbed doses per decay in a spherical target mass of 0.005 g compared to 50 g. Conclusions While the iodine avidity, and therefore the total amount of decays, is the predominant contributing factor to absorbed dose in radioiodine therapy, eccentric spheroids and small target sizes can receive substantially lower absorbed doses from the same administration of radioiodine.

Introduction

Differentiated thyroid cancer is treated with surgical removal of one or both lobes of the thyroid gland. Based on the histopathological and clinical staging of the disease, radioiodine therapy is used for all but the smallest tumours, for which surgery remains the only treatment.

Depending on disease stage, the approach and dosage of radioiodine therapy varies. For radically removed tumours without, or with only microscopic spread disease, the treatment aims to ablate any remnant of the thyroid gland with a lower activity of radioiodine after surgery to enable efficient follow-up [1]. In patients with large locally invasive tumours or lymph node metastases, radioiodine can be given in larger amounts as adjuvant therapy to treat any unknown residual or metastatic disease (including micrometastases of diameters \textasciitilde 2 mm). For gross residual tumour or manifest metastatic disease, repeated high activity radioiodine treatments are used for disease control and curative intent, given that the metastatic lesions concentrate iodine [2,3]. This means that radioiodine treatment is a therapeutic option for both very small and large lesions, that can differ in geometry due to their anatomical surroundings.

The ability of thyroid cancer tissue to concentrate and retain iodine is summarised in the concept of iodine avidity. In the individual patient, the tumoural iodine avidity is usually unknown when choosing therapeutic activity after surgery. Methods to estimate avidity have been previously established for gross metastatic disease using SPECT imaging with iodine-131, and for PET imaging with iodine-124 [4-6]. However, the accuracy and feasibility of such methods diminishes as the size of the target decreases. For example, the spatial resolution of clinically available nuclear imaging systems (SPECT) of around 10 mm for iodine-131 severely limits accurate imaging of smaller targets [7,8]. The accuracy in image-based dosimetry is further hampered by the lack of complex geometries employed when using the Medical Internal Radiation Dose (MIRD) scheme [9]. The MIRD methodology continues to evolve in order to accommodate more realistic calculations, for example, in

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different surroundings and tumour sizes [10]. However, the impact of non-spherical geometries is often not considered in its use for tumour dosimetry. This in part explains the limited clinical use of image dosimetry in the treatment of thyroid cancer [11]. Instead, standardised amounts of iodine activity guided by clinical and pathological staging (TNM-staging [12]) are widely used today, taking neither avidity, size nor geometry into consideration.

This work was performed to study the radiation coverage in a range of clinically occurring geometries and sizes. Analysis of absorbed doses and energy deposition was performed, and data is presented on the impact of both target size and geometry.

Methods

Simulations

Monte Carlo simulations were performed using the Monte Carlo N-particle 6 (MCNP6) code [13]. The simulations were performed to calculate energy deposition and absorbed doses for a range of sizes and geometries. A series of spheroidal geometries of liquid water were simulated with homogeneously dispersed iodine-131 radiation sources, surrounded by liquid water without any radiation sources, allowing backscatter. The geometrical shapes were chosen to approximate relevant clinical targets, such as lymph node metastases, thyroid remnants and thin segments of unresectable tumour tissue. All shapes and sizes were discussed and selected in collaboration with a thyroid surgeon (with 30 years clinical experience). The sphere was intended to model a lymph node metastasis and thyroid remnant growing in a deformable (soft tissue) surrounding. To model tumours and metastases growing in a constricted surrounding, or onto other structures, prolate and oblate spheroids were chosen. The simulated spheres had radii ranging between 1 and 50 mm, in 18 steps (of 1 mm steps from 1 mm to 10 mm, after which 5 mm steps were used) corresponding to scaled shapes with masses between 4.2 mg and 520 g. Sizes of spherical mass equivalents of 2 mm (size threshold for cervical lymph node micrometastases [14]) and 20 mm (size threshold for pT2 stage [12]) diameter were encompassed in order to provide commonly encountered thyroid remnant, tumour and metastasis sizes. Sizes up to 100 mm diameter spheres were simulated to study the largest clinically occurring tumours. By varying the radii of one or two of the dimensions with axis proportions 1:16, 1:8, 1:4, 1:2, and 1:1, a total of 162 volumes were generated. This means that the shortest perpendicular axis of the smallest spheroid was 0.125 mm across, equivalent to the width of some 25 thyroid follicular cells. An illustration of the simulated geometrical shapes are shown in Fig. 1.

A pulse height n tally (MCNP6 nomenclature) was used to score the energy deposition per starting particle. The length between resampling of the beta particles was on average 20 µm and the energy cut-off was 1 keV, corresponding to an electron range in liquid water of about 30 nm, which is a small fraction of the diameter of a thyroid follicular cell [15]. The energy deposition was separately simulated for beta, gamma, x-ray, Auger and internal conversion electrons using decay and energy distribution data adopted from ICRP Publication 107 [16].

The total energy deposition per decay was calculated by summarizing the contributions from each radiation type multiplied with the corresponding yield per decay. The absorbed doses per decay were consequently calculated using the mass of each corresponding volume. Also, the contribution from each emission type to the total energy deposition was calculated. The energy deposition data were in some cases linearly interpolated in order to be able to report values for exactly the same masses for all spheroids and spheres.

Additionally, the corresponding volume-to-surface-area (V/A) ratios for all sizes and geometries were analysed. This was done to explore any underlying dependencies that could better explain differences between geometric shapes. The surface area of the spheroids were calculated using Thomsen’s approximative formula for general ellipsoids [17].

Results

The results show that for mass 0.005 g (2.1 mm diameter sphere, just above the 2 mm threshold for micrometastases), 99.6%, 72.3% and 72.5% of the energy from Auger electron, conversion electron and beta particle emissions was deposited in the target tissue. Less than 1% of the total energy from gamma and x-ray photons was deposited in the 0.005 g sphere. For a target sphere of mass 4.2 g (20 mm diameter sphere,

Fig. 1. The simulated source geometries of oblate spheroids (upper left grid) and prolate spheroids (bottom right grid) with corresponding axis ratios. Spheres were included in both grids for illustration. Each geometry was simulated in eighteen different size scales.
threshold for pT2 stage), 97.6% of the beta particle kinetic energy was deposited within the target. Gamma and x-ray contributions increased for larger sizes, but only contributed to a small fraction of the total energy deposition even for large spheres. In the largest simulated sphere of 524 g (100 mm diameter), 20% of the deposited energy originates from gamma and x-rays combined, as illustrated in Fig. 2a. The contributions of Auger electrons and x-rays were below 0.5% of the total energy deposition for all sizes simulated.

The energy deposition in the target for oblate and prolate spheroids was lower than in a sphere for the same mass, as seen in Fig. 2b.

The absorbed dose coverage for spheres becomes more complete as the mass increases, with 71% higher absorbed dose per decay at 50 g compared to 0.005 g.

The dependence of source geometry on absorbed dose is illustrated in Table 1, where normalised absorbed doses for a given time-integrated activity coefficient were calculated for different geometries while keeping the mass constant. The co-dependence of geometry and size is highlighted in the results for prolate and oblate spheroids. For target masses above 1 g, the difference was less than 12%. For a target mass of 0.005 g, the difference can amount to 38% between a perfect sphere and oblate spheroids with a 1:16 axis ratio. Oblate geometries had worse radiation coverage than prolate geometries for a given mass.

The dependence of energy deposition on geometry was analysed with respect to the V/A ratio, and the results are shown in Fig. 3. Fig. 3a shows the inherent mathematical relationship between the V/A ratio and mass for each geometry. The overall energy deposition is shown in Fig. 3b. Since the corresponding mass for the shapes increases with the V/A ratio, the increased energy deposition is expected. However, the energy depositions were very similar for all shapes for lower V/A ratios, but diverged as the ratio increased. For beta, Auger and internal conversion electron emissions, the differences in energy deposition between spheroidal geometries was completely explained by the V/A ratio of the target, as shown in Fig. 3c (only beta shown). The divergence in Fig. 3b was only evident for substantial gamma and x-ray contributions to the total energy deposition, i.e. at higher V/A ratios; the divergence for gamma is more clearly shown in Fig. 3d. Oblate spheroids have the lowest V/A ratios for a given mass of all the simulated geometries, followed by prolate spheroids; this appears to explain their relatively lower energy deposition per decay seen in Fig. 2b.

Discussion

The results of our simulations clarify for which target shapes and sizes radioiodine treatments are impacted by geometrical factors. The factors can be important for dosimetry of micrometastases and thin layers of tumour or thyroid remnant tissue.

In adjuvant treatment, where metastases of very small sizes are the most common target, the incomplete coverage of beta particles can be substantial. This limits treatment efficacy, as micrometastases have to be assumed present in many clinical cases. The simulations are also based on homogeneous distribution of iodine-131 in the geometric shapes, something rarely seen clinically, where iodine-concentrating tumour structures may be present in some parts of a tumour but not others [18]. As currently available SPECT and PET systems cannot resolve lesions below a few millimetres, the direct implementation of the current results for all patients may be limited. However, the results in this work could be useful when treating patients with unresectable tumour growing onto the trachea (thin tumour segments), or miliary lung metastases (multiple small nodules). The presence of such targets are often known from perioperative inspection or sub-millimetre resolved CT-scans, and the clinician is not reliant on nuclear imaging systems with limited resolution. The target geometry and size can then be taken into account in adapting treatment, for example with an increase in administered activity. In larger lesions with heterogeneous iodine accumulation, the range of beta particles can instead be beneficial; regions with lower uptake may be irradiated from neighbouring tissue with higher uptake of iodine. The radiation bystander effect may also have an impact in the case of heterogeneous uptake, and mediate some effect onto low-uptake regions [19]. Geometric shapes in this work were chosen as regular shapes with resemblance of what can be encountered in clinical practice. The spheroidal approximation of irregular target shapes still somewhat limits the extrapolation of results to the clinical setting.

The geometric shape of the target can similarly to size have an effect on absorbed doses delivered. The difference between a perfect sphere
and the most eccentric oblate spheroids was found to only be substantial (more than 10% difference compared to a sphere) in masses below 1 g. Oblate spheroids had worse energy deposition per decay than had prolate spheroids, owing to the larger surface area for a given mass. It could be argued that metastases of small sizes are less likely to have severely restricted space, and are therefore unlikely to form the most eccentric spheroid shapes studied in this work.

The impact of geometry in radioiodine treatment has been studied before. Previous work has been performed on spheres in the context of radioiodine treatment of micrometastases, where electron tracks for iodine-131 and iodine-123 were compared [20]. Different geometrical shapes has been studied in relation to thyroid remnant ablation, in a work that briefly discusses calculative errors in assuming absorbed fractions of 1 for beta particles in targets of varied geometries, including one spheroid shape [21]. However, the current work has expanded the analysis with detailed data on spheroids, which to the authors’ knowledge has not been published before.

While the absorbed dose contribution from internal conversion electrons was approximately 5% for all sizes and geometries, Auger electrons contributed to less than 0.5%, as can be seen in Fig. 2a. It should be noted that the linear energy transfer of such emissions is higher than for high energy beta particles and gamma rays. Auger electrons can therefore have a higher therapeutic impact near the radiation source than indicated by the raw percentage contribution to the absorbed dose [22,23]. While the continuous-slowing-down-approximation may cause relatively large errors on small scales for

Table 1

| Axis ratio | Mass (g) | Oblate | Prolate |
|------------|---------|--------|---------|
|            | 1:16    | 1:8    | 1:4     | 1:2     | 1:1     |
| 0.005      | 0.62    | 0.77   | 0.84    | 0.93    | 1.00    |
| 0.01       | 0.69    | 0.81   | 0.94    | 0.97    | 1.00    |
| 0.05       | 0.75    | 0.86   | 0.94    | 0.99    | 1.00    |
| 0.1        | 0.81    | 0.91   | 0.96    | 0.99    | 1.00    |
| 0.5        | 0.85    | 0.93   | 0.97    | 0.99    | 1.00    |
| 1.0        | 0.88    | 0.94   | 0.98    | 1.00    | 1.00    |
| 5.0        | 0.92    | 0.95   | 0.98    | 1.00    | 1.00    |
| 10         | 0.93    | 0.96   | 0.98    | 1.00    | 1.00    |

Fig. 3. a) Relation between the V/A ratio and mass for the studied geometries. b) Overall energy deposition per decay for spheres and prolate and oblate spheroids for a range of V/A ratios. c) Energy deposition from beta particles per decay for a range of V/A ratios (similar agreement was observed for internal conversion and Auger electrons). d) Energy deposition for gamma emissions for a range of V/A ratios (similar behaviour was found for x-rays). The oblate and prolate spheroids absorb higher proportions of gamma energy for a given V/A ratio, as they have larger masses for a given V/A ratio.

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especially low energy Auger electrons, the low yield of Auger electrons in iodine-131 and the average resampling distance in this work of 20 μm limits this effect in the studied target size range [24].

The V/A ratio studied here has previously been discussed as a useful parameter in the context of internal dosimetry [25]. In this work it was shown that for spherical or spheroidal shapes, the energy deposition was almost equal for widely different shapes, given equal V/A ratios. It may therefore be a useful complementary parameter to mass when comparing different geometrical shapes.

The results on size and geometry should be considered together with the impact of iodine avidity. Our data suggests geometry and size can make up to a three-fold difference (for the smallest, most eccentric comparing different geometrical shapes.

Very small and compressed targets.

Schlesinger et al. [26] highlighted the dosimetric importance of iodine oblate targets in absorbed dose per decay. Previously published data by therefore be a useful complementary parameter to mass when comparing different geometrical shapes.

In conclusion, our results establish that while the most important factor in radioidine treatment success is high iodine avidity, the geometry and size of the target can have a substantial impact, mainly for very small and compressed targets.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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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