Comparison between Three Promising ß-emitting Radionuclides, $^{67}$Cu, $^{47}$Sc and $^{161}$Tb, with Emphasis on Doses Delivered to Minimal Residual Disease

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Abstract

PURPOSE: Radionuclide therapy is increasingly seen as a promising option to target minimal residual disease. Copper-67, scandium-47 and terbium-161 have a medium-energy $\beta$ emission which is similar to that of lutetium-177, but offer the advantage of having diagnostic partner isotopes suitable for pretreatment imaging. The aim of this study was to compare the efficacy of $^{67}$Cu, $^{47}$Sc and $^{161}$Tb to irradiate small tumors.

METHODS: The absorbed dose deriving from a homogeneous distribution of $^{67}$Cu, $^{47}$Sc or $^{161}$Tb in water-density spheres was calculated with the Monte Carlo code CELLODOSE. The diameters of the spheres ranged from 5 mm to 10 µm, thus simulating micrometastases or single tumor cells. All electron emissions, including $\beta$ spectra, Auger and conversion electrons were taken into account. Because these radionuclides differ in electron energy per decay, the simulations were run assuming that 1 MeV was released per µm$^3$, which would result in a dose of 160 Gy if totally absorbed.

RESULTS: The absorbed dose was similar for the three radionuclides in the 5-mm sphere (146-149 Gy), but decreased differently in smaller spheres. In particular, $^{161}$Tb delivered higher doses compared to the other radionuclides. For instance, in the 100-µm sphere, the absorbed dose was 24.1 Gy with $^{67}$Cu, 14.8 Gy with $^{47}$Sc and 44.5 Gy with $^{161}$Tb. Auger and conversion electrons accounted for 71% of $^{161}$Tb dose. The largest dose differences were found in cell-sized spheres. In the 10-µm sphere, the dose delivered by $^{161}$Tb was 4.1 times higher than that from $^{67}$Cu and 8.1 times that from $^{47}$Sc.

CONCLUSION: $^{161}$Tb can effectively irradiate small tumors thanks to its decay spectrum that combines medium-energy $\beta$ emission and low-energy conversion and Auger electrons. Therefore $^{161}$Tb might be a better candidate than $^{67}$Cu and $^{47}$Sc for treating minimal residual disease in a clinical setting.

Key words: Dose, radionuclide therapy, minimal residual disease, micrometastases, terbium-161, copper-67, scandium-47, lutetium-177.

Introduction

Targeted radionuclide therapy relies on the administration of radiolabeled compounds to irradiate tumors [1]. Iodine-131 has been used since seven decades to prevent recurrence of thyroid cancer after surgery and to treat distant metastases [2-4]. In the past years, several other tumor-targeting radiopharmaceuticals, labeled with iodine-131, yttrium-90, or lutetium-177, have successfully entered
into clinical practice. Examples include $^{131}$I-MIBG for neural crest tumors, anti-CD20 antibodies (e.g. $^{90}$Y-ibritumomab tiuxetan) for lymphomas [5], the somatostatin analogs $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATATE for neuroendocrine tumors [6] and more recently $^{177}$Lu-labelled PSMA ligands for metastatic prostate cancer [7]. Notably, an ever-increasing number of preclinical studies and clinical trials aim at using radionuclide therapy to treat minimal residual disease:

One major advantage of these radionuclides over $^{177}$Lu is the theranostic potential, i.e. the availability of $\beta^+\ (^{64}$Cu, $^{43}$Sc, $^{44}$Sc, $^{152}$Tb) or $\gamma$-emitting ($^{158}$Tb) radioisotopes that enable PET or SPECT pre-therapy imaging and dosimetry [26-30]. Table 2 summarizes the physical properties of these diagnostic radionuclides. The biodistribution of the molecule labeled with the diagnostic radionuclide is expected to faithfully match that of the therapeutic molecule.

The aim of this study was to compare the effectiveness of $^{67}$Cu, $^{47}$Sc and $^{161}$Tb at irradiating small tumors. Using the Monte Carlo code CELLOSOE [31,32], we assessed the dose deposits from these radionuclides in spheres of various sizes, simulating micrometastases and single tumor cells.

### Methods

The absorbed dose in each sphere was assessed with Monte Carlo simulations by taking into account all electron emissions: $\beta$-spectra, conversion electrons (CE) and Auger electrons (including Coster-Kronig electrons). Emission data were obtained from the International Commission on Radiological Protection (ICRP) publication ICRP-107 [30]. Photons were neglected. For all simulations, the distribution of radioactivity within spheres was assumed to be homogeneous. This was achieved by random Monte Carlo sampling throughout the sphere volume using a high number of simulations (2,100,000 per sphere). Decay characteristics of $^{67}$Cu, $^{47}$Sc and $^{161}$Tb are reported in Table 1. The spectra of electron emissions are shown in Figure 1.

### Table 1: Radionuclide characteristics (see also Figure 1 for electron emission spectra.)

| Radionuclide | $^{67}$Cu | $^{47}$Sc | $^{161}$Tb |
|--------------|----------|----------|------------|
| Half-life (day) | 2.576 | 3.349 | 6.906 |
| Type of Decay (%) | $\beta$ (100 %) | $\beta$ (100 %) | $\beta$ (100 %) |
| $\beta$ particles mean energy (keV) | 135.9 | 161.9 | 154.3 |
| Daughter | 67-Zinc (stable) | 47-Titanium (stable) | 161-Dysprosium (stable) |
| CE emission (energy per decay in keV) | 13.74 | 0.48 | 39.28 |
| CE energy range (keV) * | 81.6 – 184.5 | 154.4 – 158.9 | 3.3 – 98.3 |
| Auger and Coster-Kronig electrons (energy per decay in keV) | 0.75 | 0.01 | 8.94 |
| Auger and Coster-Kronig electrons energy range (keV) * | 0.087 – 9.4 | 0.027 – 4.8 | 0.018 – 50.9 |
| Total electron energy per decay (average in keV) | 150.4 | 162.4 | 202.5 |
| $\gamma$ radiation useful for imaging (Energy in keV and % abundance) | 184.6 (49.6%); 93.3 (3%) | 159.4 (68.3%) | 74.6 (10.2%) |
| Photons X and $\gamma$ (total energy per decay in keV) | 114.9 | 108.9 | 36.35 |
| Energy per decay in keV (photons + electrons) | 265.3 | 271.3 | 238.9 |
| Percentage of energy emitted as photons | 43.3 % | 40.1 % | 15.2 % |

* Conversion and Auger electrons with probability 0.0001 were neglected (30).
Table 2: Physical characteristics of the diagnostic radionuclides $^{64}$Cu, $^{43}$Sc, $^{44}$Sc, $^{152}$Tb and $^{155}$Tb.

| Radionuclide | $^{64}$Cu | $^{43}$Sc | $^{44}$Sc | $^{152}$Tb | $^{155}$Tb |
|--------------|-----------|-----------|-----------|-----------|-----------|
| Half-life    | 12.7 h    | 3.89 h    | 3.97 h    | 17.5 h    | 5.32 days |
| Type of Decay| EC, $\beta^+$, $\beta^-$ | EC, $\beta^+$ | EC, $\beta^+$ | EC, $\beta^+$ | EC (100%) |
|              | $\beta^+ (17.6\%)$, $\beta^- (38.5\%)$ | $\beta^+ (88.1\%)$ | $\beta^+ (94.3\%)$ | $\beta^+ (20.3\%)$ | $\beta^+ (100\%)$ |
| Mean energy of $\beta$ particles (keV) | $\beta^+ : 278$ | $\beta^+ : 476$ | $\beta^- : 632$ | $\beta^- : 1140$ | - |
| Main $\gamma$ emissions (25%) | 372.9 keV (22.5\%) | 1157 keV (99.9\%) | 271.1 keV (9.5\%) | 105.3 keV (25.1\%) | 16.7 keV (5.5\%) |

X and $\gamma$ emission (total energy per decay in keV) $\S$ ~ 8 ~ 85 ~ 1177 ~ 1146 ~ 176

$\S$ Photon emissions following $\beta^+$ annihilation are not considered.

EC = Electron capture.

Figure 1: Electron emissions of $^{64}$Cu, $^{43}$Sc and $^{155}$Tb. $\beta$-spectra are in red (integral of the curve = 1), conversions electrons (CE) are in blue and Auger electrons (including Coster-Kronig electrons) in green. Conversion and Auger electrons whose probability was <0.0001 [30] were neglected and are not represented.
Results

S-values for \( ^{67}\text{Cu}, ^{47}\text{Sc} \) and \( ^{161}\text{Tb} \) and contribution of the different electron emissions

S-values measured with the Monte-Carlo dose CELLDOSSE are reported in Table 3. Results agreed (differences <10%) with those reported by Bardiès for \( ^{67}\text{Cu} \) and \( ^{47}\text{Sc} \) in spheres >20 µm using analytic methods based on scaled dose point kernel [34]. Bardiès and colleagues did not report on smaller spheres and did not study Terbium-161. The relative contributions of β-particles, CE and Auger electrons are also reported in Table 3. In the case of \( ^{47}\text{Sc} \), almost all the absorbed dose was due to β-emission (>99% for all spheres). β-emission was also the main contributor to the doses delivered by \( ^{67}\text{Cu} \), with only modest contribution from CE and Auger electrons (10.1 to 29.3%). By contrast, \( ^{161}\text{Tb} \) displayed a significant contribution from CE and Auger electrons. The combined contribution from \( ^{161}\text{Tb} \) CE and Auger electrons to the total absorbed dose was 25.9% in the 5-mm sphere and reached 88.3% in the cell-sized 10-µm sphere (Table 3).

Electron dose deposits after normalization

When 1 MeV per µm\(^3\) was released, the absorbed dose in the 5-mm sphere was similar for the three radionuclides (146 to 149 Gy). The absorbed dose progressively decreased when the sphere size decreased, but the dose reduction was more abrupt for \( ^{67}\text{Cu} \) and \( ^{47}\text{Sc} \) than for \( ^{161}\text{Tb} \) (Fig. 2). \( ^{161}\text{Tb} \) was clearly superior to the other radionuclides for spheres with less than 1mm diameter. For example, in a 100-µm micrometastasis the absorbed dose was 24.1 Gy with \( ^{67}\text{Cu} \), 14.8 Gy with \( ^{47}\text{Sc} \) and 44.5 Gy with \( ^{161}\text{Tb} \) (Table 4). The largest dose difference was found in cell-sized spheres: in the 10-µm sphere, the doses delivered by \( ^{67}\text{Cu} \), \( ^{47}\text{Sc} \) and \( ^{161}\text{Tb} \) were 3.42 Gy, 1.74 Gy and 14.1 Gy, respectively (Table 4).

| Sphere diameter (µm) | S-values (Gy Bq\(^{-1}\) s\(^{-1}\)) | Contribution of the different electronic emissions |
|----------------------|--------------------------------------|--------------------------------------------------|
|                      | \( ^{67}\text{Cu} \) | \( ^{47}\text{Sc} \) | \( ^{161}\text{Tb} \) | \( ^{67}\text{Cu} \) | \( ^{47}\text{Sc} \) | \( ^{161}\text{Tb} \) | \( ^{67}\text{Cu} \) | \( ^{47}\text{Sc} \) | \( ^{161}\text{Tb} \) |
| 5,000                | 3.37 x 10\(^{-10}\) | 3.69 x 10\(^{-10}\) | 4.47 x 10\(^{-10}\) | 89.9 | 9.5 | 0.6 | 99.7 | 0.29 | 0.1 | 74.1 | 21.0 | 4.9 |
| 2,000                | 4.67 x 10\(^{-10}\) | 4.74 x 10\(^{-10}\) | 6.22 x 10\(^{-10}\) | 89.0 | 10.4 | 0.6 | 99.7 | 0.29 | 0.1 | 71.0 | 23.5 | 5.5 |
| 1,000                | 3.07 x 10\(^{-10}\) | 2.77 x 10\(^{-10}\) | 4.14 x 10\(^{-10}\) | 87.2 | 12.1 | 0.7 | 99.7 | 0.29 | 0.1 | 65.5 | 27.9 | 6.6 |
| 500                  | 1.77 x 10\(^{-10}\) | 1.40 x 10\(^{-10}\) | 2.54 x 10\(^{-10}\) | 84.1 | 14.9 | 1.0 | 99.6 | 0.35 | 0.05 | 55.9 | 35.5 | 8.6 |
| 200                  | 1.52 x 10\(^{-10}\) | 1.05 x 10\(^{-10}\) | 2.76 x 10\(^{-10}\) | 79.3 | 18.9 | 1.8 | 99.7 | 0.24 | 0.06 | 40.1 | 47.7 | 12.2 |
| 100                  | 6.89 x 10\(^{-10}\) | 4.58 x 10\(^{-10}\) | 1.71 x 10\(^{-10}\) | 79.4 | 17.3 | 3.3 | 99.7 | 0.19 | 0.11 | 29.3 | 55.1 | 15.6 |
| 50                   | 2.95 x 10\(^{-10}\) | 1.95 x 10\(^{-10}\) | 1.02 x 10\(^{-10}\) | 81.2 | 12.8 | 6.0 | 99.7 | 0.17 | 0.13 | 21.4 | 58.1 | 20.5 |
| 20                   | 2.12 x 10\(^{-10}\) | 1.30 x 10\(^{-10}\) | 9.70 x 10\(^{-10}\) | 77.3 | 10.0 | 12.7 | 99.5 | 0.16 | 0.34 | 15.3 | 52.3 | 32.4 |
| 10                   | 9.80 x 10\(^{-10}\) | 5.38 x 10\(^{-10}\) | 5.41 x 10\(^{-10}\) | 70.7 | 8.3 | 21.0 | 99.2 | 0.15 | 0.65 | 11.7 | 43.4 | 44.9 |
Table 4: Absorbed dose from $^{67}$Cu, $^{47}$Sc, and $^{161}$Tb assuming a uniform concentration of the radionuclide. Data for $^{177}$Lu are shown for comparison.

| Sphere diameter (µm) | $^{177}$Lu | $^{67}$Cu | $^{47}$Sc | $^{161}$Tb | $^{177}$Lu | $^{67}$Cu | $^{47}$Sc | $^{161}$Tb | $^{177}$Lu | $^{67}$Cu | $^{47}$Sc | $^{161}$Tb |
|---------------------|------------|----------|----------|-----------|------------|----------|----------|-----------|------------|----------|----------|-----------|
| 5,000               | 21.6       | 22.1     | 24.2     | 29.3      | 145        | 147      | 149      | 146       | 1          | 1.01     | 1.03     | 1.01      |
| 2,000               | 19.0       | 19.6     | 19.8     | 26.0      | 128        | 130      | 122      | 129       | 1          | 1.02     | 0.95     | 1.01      |
| 1,000               | 15.4       | 16.1     | 14.5     | 21.7      | 104        | 107      | 89.6     | 108       | 1          | 1.03     | 0.86     | 1.04      |
| 500                 | 11.1       | 11.6     | 9.19     | 16.6      | 74.8       | 77.1     | 56.7     | 82.7      | 1          | 1.03     | 0.76     | 1.11      |
| 200                 | 6.18       | 6.37     | 4.39     | 11.6      | 41.8       | 42.4     | 27.2     | 57.6      | 1          | 1.01     | 0.65     | 1.38      |
| 100                 | 3.63       | 3.61     | 2.39     | 8.95      | 24.5       | 24.1     | 14.8     | 44.5      | 1          | 0.98     | 0.60     | 1.82      |
| 50                  | 2.08       | 1.93     | 1.28     | 6.67      | 14.1       | 12.9     | 7.89     | 33.3      | 1          | 0.91     | 0.56     | 2.36      |
| 20                  | 0.98       | 0.89     | 0.54     | 4.06      | 6.61       | 5.91     | 3.35     | 20.2      | 1          | 0.89     | 0.51     | 3.06      |
| 10                  | 0.58       | 0.51     | 0.28     | 2.83      | 3.92       | 3.42     | 1.74     | 14.1      | 1          | 0.87     | 0.44     | 3.60      |

§ The absorbed doses from $^{67}$Cu, $^{47}$Sc and $^{161}$Tb (dose for 1 MeV released per µm$^3$) are divided by the doses from $^{177}$Lu, which is used as a reference. $^{177}$Lu data are taken from [18].

Electron energy deposit around a point source

The energy deposited by $^{161}$Tb (per MeV released) was considerably higher than that deposited by the other radionuclides up to 30 µm around the point source (Fig. 3). This suggests that $^{161}$Tb would deliver a higher dose not only to the targeted cell, but also to its immediate neighbors. Beyond this distance, the differences in energy deposits leveled off: the radius within which 50% of the energy is deposited (R50) was 0.17 mm for $^{67}$Cu, 0.25 mm for $^{47}$Sc and 0.15 mm for $^{161}$Tb. The radius within which 90% of the emitted energy is deposited (R90) was 0.57 mm for $^{67}$Cu, 0.72 mm for $^{47}$Sc and 0.63 mm for $^{161}$Tb.

Discussion

In many cancers, the prognosis is linked to metastatic relapse, which may occur years after primary surgery [35-37]. Targeted radionuclide therapy may play a major role to treat occult micrometastases in high-risk patients or to eradicate minimal residual disease [2, 8-13]. Several preclinical and clinical studies suggest that radionuclide therapy is more effective when administered at an early stage of the disease [4,6,38,39], probably because the distribution of the radiopharmaceutical in tumors is still relatively homogeneous. However, radionuclides differ in their ability to irradiate micrometastases [16]. In this study we assessed the relative effectiveness of three promising medium-energy $\beta$-emitters, i.e. $^{67}$Cu, $^{47}$Sc and $^{161}$Tb.

Since the electron energy per decay of these three radionuclides differs, we assumed that 1 MeV was released per µm$^3$. If totally absorbed, this energy would always yield a dose of 160 Gy. Absorbed doses of this magnitude were measured in macrometastases of neuroendocrine tumors in patients who responded to $^{177}$Lu-DOTATATE therapy [40]. Smaller and more homogeneous tumors are expected to respond to lower doses.
Our simulations showed that, for the three radionuclides, the doses delivered to a 5-mm metastasis (146 to 149 Gy) were close to the dose that would result from total absorption. The doses decreased with sphere size, thus underscoring the fact that micrometastases are more difficult to irradiate effectively. The dose delivered by $^{161}$Tb was however consistently higher than that delivered by the other radionuclides (Fig. 2). For example, in a 100-µm micrometastasis, the absorbed dose was 44.5 Gy for $^{161}$Tb, 24.1 Gy for $^{67}$Cu and 14.8 Gy for $^{47}$Sc (Table 4). The largest differences were found in the smallest spheres: in a cell-sized sphere of 10 µm diameter, the dose delivered by $^{161}$Tb was 14.1 Gy, compared to 3.42 Gy and 1.74 Gy for $^{67}$Cu and $^{47}$Sc. Thus, relatively to the almost pure $\beta$ emission of $^{47}$Sc, the doses delivered by $^{161}$Tb were ~3 times higher in a 100-µm micrometastasis and ~8 times higher in a 10-µm single cell (Table 4). In a previous work, we showed that the dose delivered by $^{161}$Tb to small metastases was also higher than that delivered by $^{177}$Lu [18]. In Table 4, the absorbed doses from $^{67}$Cu, $^{47}$Sc and $^{161}$Tb (for 1 MeV released per µm$^3$) are compared to those from $^{177}$Lu, used as a reference.

Our Monte Carlo study provides a mechanistic framework that explains some recent preclinical findings on tumor-control efficacy [24,25]. Anti-L1CAM antibody labeled with $^{161}$Tb inhibited the growth of subcutaneous xenografts of ovarian cancer more effectively than the same antibody labeled with $^{177}$Lu and injected at a comparable activity (corresponding to 50% of the maximum tolerated dose) [25]. In a cell culture study, the radioactivity concentration of folate conjugates required to achieve the half-maximal inhibition of KB cells (human cervical carcinoma) was 4.5 fold lower with the $^{161}$Tb-labeled conjugate than with the $^{177}$Lu-labeled conjugate [24]. This difference was smaller (×1.7) for IGROV-1 cells (human ovarian carcinoma), which might be explained by the lower internalization rate of folate conjugates into these cells [24].

The higher efficacy of $^{161}$Tb compared to $^{47}$Sc and $^{67}$Cu is mainly due to the larger amount of Auger and low-energy conversion electrons (Fig. 1), whose doses are deposited over relatively short distances (Fig. 4). Indeed, CE and Auger electrons accounted for 71% of the radiation dose deposited by $^{161}$Tb in a 100-µm metastasis and 88% of the dose deposited in a 10-µm single cell (Table 3). This contrasts with $^{47}$Sc data, where >99% of the absorbed energy was due to $\beta$ particles for all spheres. The interpretation of experimental results may be further refined by considering the linear energy transfer (LET) of emitted electrons. Not only emission spectra from $^{161}$Tb are rich in Auger electrons, but also the majority of conversion electrons of $^{161}$Tb have low energy (< 50 keV) and thus high LET (Table 5).

**Figure 4:** Two-dimensional plots of the tracks of two representative conversion electrons and two representative Auger electrons from $^{161}$Tb as simulated with CELDOSE. Panel A reproduces the full path of the two CE (39.9 keV and 17.87 keV). Panel B is a magnification of the paths of Auger electrons (5.25 keV, 1.02 keV). The solid and open circles represent the ionizing interactions induced by the primary and the secondary electrons, respectively.
Knowledge of the biodistribution of the radiopharmaceutical at the cellular and subcellular level is of paramount importance to rationally choose the most appropriate radionuclide. Radionuclides can be imaged and quantified with techniques such as autoradiography or secondary ion mass microscopy [41]. This distribution may be used as input to derive the dose to tumor cells [32]. The energy deposited by $^{161}$Tb (per MeV released) is higher than that deposited by the other radionuclides up to 30 μm around a point source (Fig. 3). Thus, $^{161}$Tb would likely deliver a higher dose, not only to the targeted cell, but also to its immediate neighbors. Moreover, the short tracks of energy deposit of Auger electrons and some low energy conversion electrons (Fig. 4) suggest that a putative $^{161}$Tb-labeled radiopharmaceutical would be even more effective if transported into the cell and internalized into the nucleus [42]. The impact of Auger electrons on other targets such as the cell membrane also deserves investigation [43]. Our future work will compare the dose distribution of $^{161}$Tb to that of other $\beta^-$, Auger- or $\alpha$-emitting radionuclides [44] for various cellular distributions. Also, since only limited preclinical work on $^{161}$Tb has been done so far [24,25], additional studies should be carried out to establish whether $^{161}$Tb is a good candidate for clinical use. Hopefully, preclinical data [24,25], and the theoretical framework provided by our own calculations, will encourage the development of new radiopharmaceuticals labelled with $^{161}$Tb.

Finally, the choice of radionuclides for radiopharmaceutical therapy may be driven by logistic issues. Producing $^{67}$Cu as no-carrier-added in amounts suitable for large clinical use has been difficult [19,20]. The optimal technique to produce $^{67}$Sc is still debated [21,22]. Preliminary data suggest that $^{161}$Tb can be produced in large amounts as no-carrier-added, using for example a gadolinium-160 target ($^{160}$Gd($n,\gamma$)$^{161}$Tb), and with good radionuclide purity ($^{160}$Tb to $^{161}$Tb activity ratio <0.0001) [45]. The cost for large-scale production is estimated to be comparable to that of no-carrier-added $^{177}$Lu [45].

### Conclusion
Radiopharmaceutical therapy can effectively target isolated tumor cells and occult micrometastases, provided that the optimal radionuclide is used. Our investigations on three theranostic radionuclides suggest that $^{161}$Tb might be a better choice than $^{67}$Cu or $^{47}$Sc. The promising characteristics of this radionuclide justify further preclinical investigations and, hopefully, clinical trials.

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### Competing Interests
The authors have declared that no competing interest exists.

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