119Sb--a potent auger emitter for targeted radionuclide therapy

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I. INTRODUCTION

In recent years the use of Auger electron emitting radionuclides for targeted radionuclide therapy has shown promising results.\textsuperscript{1-7} The low-energetic Auger electrons including the even lower energetic Coster–Kronig (CK) electrons are emitted by isotopes that decay by electron capture (EC) or have internal conversion (IC) in their decay. Depending on the isotope, many such electrons can be emitted per decay (from a few to more than 35)\textsuperscript{8} almost instantaneously, thus, creating an electron cascade. The multiplicity and the short range in tissue (from a few nm to some \(\mu\)m) of these Auger and CK electrons gives rise to a high energy density created in the immediate vicinity of the decay site and, thus, a high, very localized absorbed radiation dose to the target region.\textsuperscript{9} Additionally, the short range minimizes irradiation of the neighboring, normal cells, resulting in low observed unspecific radiotoxicities in cell experiments.\textsuperscript{3,10} The very short range of the electrons makes the localization of the radionuclides with respect to the sensitive targets in the cells (DNA) critical in determining effects from the radiation. If the decaying radionuclides are incorporated directly into the nuclear DNA or in close proximity to the DNA, extreme radiotoxicity is observed, resembling high-LET radiation with relative biological effectiveness (RBE) values much higher than 1.\textsuperscript{11,12} On the other hand, if the radionuclides are bound outside the cellular nucleus, e.g., on the cellular membrane, located in the cytoplasm or extracellular, the effects resemble those observed with low-LET radiation (e.g., X-rays) with low RBE values.

Some of the most commonly used Auger emitters for research in radionuclide therapy are \(^{125}\)I, \(^{121}\)I, \(^{111}\)In, \(^{68}\)Ga, and \(^{201}\)TI, which are all readily obtainable from commercial sources—the last four isotopes due to their wide use in diagnostics tracers (SPECT) in nuclear medicine.\textsuperscript{3,4,13-15} However, the wide use of these isotopes in research in the field of radionuclide therapy is probably more a consequence of this accessibility than because of optimal radiation physics properties for cancer therapy.

In principle, the optimal radionuclide for targeted radiotherapy must be one that, in addition to a proper half-life (hours → days), is emitting radiation with a range that is long enough to allow irradiation of the target region, but at the same time, short enough to spare healthy tissue surrounding this region. Thus, a high proportion of gamma emission as seen with the four SPECT isotopes mentioned above is an undesirable property. For dosimetry calculations, however, the emission of gamma radiation is useful to determine the time-activity curve for the administered radiopharmaceutical in, e.g., the critical organs but the gamma intensity should be low to minimize unwanted dose to healthy tissues. Alternatively, the isotope used for therapy could emit no penetrating radiation and the time-activity curve and pharmacokinetics could then be evaluated before the treatment starts or simultaneously from a tracer study with a SPECT- or a PET-isotope of the same element as the one used for the therapy. Examples of such isotope pairs are \(^{86}\)Y/\(^{90}\)Y and \(^{124}\)I/\(^{131}\)I.\textsuperscript{16-20}

There could be a need for increasing the scarce selection of available radionuclides suitable for targeted radionuclide therapy. In this study, we have performed a comparison of several Auger emitters based on theoretical dosimetry calculations at subcellular and macroscopic levels. From this we conclude that the radionuclide \(^{119}\)Sb (\(T_{1/2}=38.19\) h) is a potent Auger-electron emitter that possibly can be used in therapy of small metastasis and disseminated cancer cells. The radionuclide \(^{117}\)Sb (\(T_{1/2}=2.8\) h) can give SPECT- or SPECT/CT-based patient-specific 3D dosimetry.
II. MATERIALS AND METHODS

II.A. Dose calculations and cellular S-values

The cellular dosimetry was performed using the formalism described in MIRD Cellular S-values\(^2\) with a code programmed in MatLab 7.0.1. Using the geometric reduction factors by Berger\(^2\) (Fig. 1) and stopping powers obtained from an empirical energy-loss expression using the continuous-slowing down approximation (CSDA), the dose per cumulated decay to all parts of the tumor cell could be calculated (Figs. 3–5). The energy-loss expression, i.e., the relationship between electron energy \(E\) and range \(R\) in unit density matter was taken as experimentally determined by Cole for energies higher than 0.4 keV.\(^2\) Below 0.4 keV, a fit was made to Cole’s experimental data because these are not well described by Cole’s expression. The following expression was used:

\[
E = -53.111R^3 + 1491.4R^2 + 11.893R,
\]

with \(E\) in keV and \(R\) in \(\mu\)m. Using this approach, it is assumed that secondary electrons (delta rays) are absorbed locally. In calculating the S-values, this assumption has been shown to be valid from comparison with Monte Carlo transport codes for electron energies below several hundred keV.\(^2\)

The radioactivity in the cell was assumed uniformly distributed over one of the following spherical symmetric cell compartments: the cell surface (CS), cytoplasm (Cy), or cell nucleus (N). As target region, only the cell nucleus was considered in calculating the S-values. The contribution to the cellular absorbed mean dose from gamma radiations was not taken into account since this is negligible as reported in MIRD Cellular S-values.\(^2\)

The radiation spectra were either obtained from the Report No. 2 of AAPM Nuclear Task Group No. 6 by Howell,\(^8\) if possible, or from the Nuclear Decay Data Files for Dose Calculation (DE CDC).\(^2\) The spectra from DE CDC contain data for the K-, L-, and M-shell electrons, while the spectra reported by Howell are more complete by including the low-energy N- and O-shell electrons. The omission of these very low-energy electrons was seen to be insignificant for sphere diameters larger than 1 \(\mu\)m in agreement with the findings reported by Howell.\(^8\)

In calculating the tumor-to-normal-tissue dose ratios (TNDs) per disintegration, the dose to the normal tissue was obtained from the tabulated dose factors ([DFs], equivalent to the MIRD organ S-values), in the Radiation dose assessment resource (RADAR).\(^2\) Only the whole-body to whole-body dose contribution was considered, i.e., the S(whole-body→whole-body) assuming a uniform activity distribution in this compartment. The TND calculation was done on a simple per decay basis, i.e., differences in physical and biological half-lives and resulting differences in cumulated decays were not taken into account at this stage.

II.B. \(^{119}\)Sb and \(^{117}\)Sb productions

As the above calculations identify \(^{119}\)Sb as a potent isotope for radionuclide therapy, the proton irradiation yields of this isotope and its SPECT-analogue \(^{117}\)Sb were measured.

II.B.1. Target preparation

The production of the \(^{119}\)Sb and \(^{117}\)Sb radionuclides was performed via the nuclear reactions:\(^{119}\)Sn(p,n)\(^{119}\)Sb and \(^{117}\)Sn(p,n)\(^{117}\)Sb, respectively. Before the irradiations, each enriched tin target (enrichment: 97.4% \(^{119}\)Sn and 97.6% \(^{117}\)Sn, respectively, both from Campro Scientific) was made by either dissolving the tin metal (5–30 mg) directly in hot 2.5 M KOH containing \(\text{H}_2\text{O}_2\) or by dissolving the tin metal in 0.5 ml hot, concentrated HCl containing \(\text{H}_2\text{O}_2\) followed by adding 1.0 ml 10 M KOH to the solution. The latter route was used for larger quantities of the tin metal to speed up the etching process. The resulting solution was then diluted to 0.25 M KOH with distilled water and transferred to an electroplating cell. A coin-like silver plate with a diameter of 29 mm and thickness of 5.2 mm was used as backing (see Fig. 2). The electroplating process was carried out with a bath temperature of approximately 65–70 °C with a plating current density of 4–6 mA/cm\(^2\) for 6–8 h. The target thicknesses of the \(^{117}\)Sn and \(^{119}\)Sn targets were determined from the weight and surface area of the electroplated tin to be 7.4 and 5.5 mg/cm\(^2\), respectively.
II.B.2. Irradiations and activity measurements

The electroplated targets were mounted in a water cooled irradiation chamber with an aluminium proton energy degrader in front of the target. The irradiations were done using the external proton beam from the beamline of the GE PETtrace Cyclotron at the Hevesy Laboratory at Risoe National Laboratory. The targets were irradiated with a constant beam current of 15 μA with a collimated beam of 10 mm in diameter for 1 h. The integrated beam current was taken as reported by the cyclotron software. The proton energy was determined from prior irradiations by irradiating a precision planar scintigraphy and a single photon emission computed tomography (SPECT) scan was made of a Jaszcza SPECT phantom.

Table I. The calculated S-values for varying cell sizes with 119Sb activity uniformly distributed in one of the following cell compartments: N: Nucleus, Cy: Cytoplasm, or CS: Cell Surface.

<table>
<thead>
<tr>
<th>Cell size [μm]</th>
<th>S-values [Gy/Bq s]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S(N—N)</td>
</tr>
<tr>
<td>3</td>
<td>2.44×10⁻¹</td>
</tr>
<tr>
<td>4</td>
<td>3.72×10⁻²</td>
</tr>
<tr>
<td>5</td>
<td>3.72×10⁻²</td>
</tr>
<tr>
<td>6</td>
<td>1.28×10⁻²</td>
</tr>
<tr>
<td>7</td>
<td>3.72×10⁻²</td>
</tr>
<tr>
<td>8</td>
<td>1.28×10⁻²</td>
</tr>
<tr>
<td>9</td>
<td>6.16×10⁻³</td>
</tr>
<tr>
<td>10</td>
<td>1.28×10⁻²</td>
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<tr>
<td>11</td>
<td>6.16×10⁻³</td>
</tr>
<tr>
<td>12</td>
<td>3.60×10⁻³</td>
</tr>
<tr>
<td>13</td>
<td>1.28×10⁻²</td>
</tr>
<tr>
<td>14</td>
<td>6.16×10⁻³</td>
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<tr>
<td>15</td>
<td>3.60×10⁻³</td>
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<tr>
<td>16</td>
<td>2.34×10⁻³</td>
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<tr>
<td>17</td>
<td>6.16×10⁻³</td>
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<tr>
<td>18</td>
<td>3.60×10⁻³</td>
</tr>
<tr>
<td>19</td>
<td>1.62×10⁻³</td>
</tr>
<tr>
<td>20</td>
<td>6.16×10⁻³</td>
</tr>
<tr>
<td>21</td>
<td>3.60×10⁻³</td>
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<tr>
<td>22</td>
<td>2.34×10⁻³</td>
</tr>
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<td>23</td>
<td>1.62×10⁻³</td>
</tr>
<tr>
<td>24</td>
<td>8.74×10⁻⁴</td>
</tr>
<tr>
<td>25</td>
<td>3.55×10⁻⁴</td>
</tr>
<tr>
<td>26</td>
<td>8.74×10⁻⁴</td>
</tr>
</tbody>
</table>

was measured several times with a distance of 39 cm from the detector in the time interval from 52 h to several weeks after EOB. The long delay between EOB and the first measurement was in order to let the simultaneously produced 107Cd in the silver backing decay. The 117Sb activity was corrected for any simultaneously produced 119mSn (T1/2 = 293.1 d), which emits a single γ-ray of the same energy (23.87 keV), by measuring the target after the 119Sb had decayed. The effective attenuation of the 23.87 keV γ-ray in the “thick” 119Sn layer was calculated to be 4% and this correction was included in the activity measurement.

II.C. 117Sb SPECT

To demonstrate the imaging capabilities of the 117Sb isotope, a planar scintigraphy and a single photon emission computed tomography (SPECT) scan was made of a Jaszcza SPECT phantom.

II.C.1. 117Sb production

The enriched 117Sn target used in the yield measurements was irradiated using the setup described above with a 15 μA proton beam (14.9 μA mean current) for 90 min. After the
irradiation, the target material was dissolved with hot conc. HCl with H₂O₂ added to oxidize the strong reductant, Sn(II), to Sn(IV). This speeds up the etching of the Sn and avoids reduction of the dissolved Sb(III) to Sb⁰ on the silver backing. After the produced ¹¹⁷Sb was dissolved, the radionuclidic purity of the resulting solution was measured using the Ge detector (Princeton Gamma-Tech, LGC 5) described above. Because no radioactive tin impurities were detected in the solution, no attempt was made to separate the tin and the produced radioantimony.

II.C.2. Planar scintigraphy and SPECT

The planar scintigraphy (PS) and the SPECT scan were both made using the Jaszczak SPECT phantom. The PS was made of the phantom with the cold rod insert only. The phantom was filled with water containing 202 MBq ¹¹⁷Sb to a height of 8.8 cm, i.e., to just above the cold rod insert. The phantom was placed on the collimator face of one of the detectors of a Philips SKYLight dual-head gamma camera with medium energy general purpose (MEGP) collimators mounted. A total of 10 million counts were acquired.

The SPECT scan was made with the phantom completely filled with water containing 153 MBq of ¹¹⁷Sb. This time, both the cold rod insert and the six solid spheres (cold spots) were mounted in the phantom. To simulate a hot spot, we additionally mounted a small cylindrical vial (Ø10 mm, height 25 mm) filled with water containing 15 MBq of ¹¹⁷Sb offcenter in the volume above the cold rod insert. The phantom was then placed on its side on the bed and scanned. The acquisition consisted of 32 frames of 30 sec with the MEGP collimators mounted on the cameras.

The image reconstruction was performed using filtered backprojection with a Hanning filter followed by standard attenuation correction. All images were then transferred to MatLab 7.0.1 for noise reduction and background subtraction.

III. RESULTS AND DISCUSSION

III.A. Cellular S-values and TND

The calculated cellular S-values for ¹¹⁹Sb activity located on the cell surface, in the cytoplasm, or in the cell nucleus, respectively, for different sizes of cells and cell nuclei can be seen in Table I. Plots showing the dose per disintegration [Gy/(Bq s)] as a function of radius for activity in the three compartments for several different radionuclides are shown in Figs. 3–5. These plots are for illustrations calculated for cells with a radius of 8 μm and a nucleus radius of 6 μm—radii taken for being characteristic values for tumor cells. Of course, these values can vary between cell populations and tumor cell types.

For radioactivity bound to the cell membrane or distributed uniformly in the cytoplasm, it can be seen that ¹¹⁹Sb clearly delivers the highest dose to the cell nucleus of the radionuclides tested. The results for the cell membrane bound activity are in agreement with those reported by Sastrey et al. who calculated that the 20 keV conversion and K-Auger electrons from ¹¹⁹Sb are optimal for irradiating the nuclei of cells from radiolabeled monoclonal antibodies bound to the cell surface. For radioactivity distributed in the cell nucleus, ¹¹⁹Sb delivers a high dose compared to most of the radionuclides tested—it is only exceeded by ²⁰¹Tl and ¹⁹³Pt.

However, in radionuclide therapy, the effect of a given treatment is usually limited by the absorbed dose to the critical organs, i.e., the dose-limiting organs and, thus, it is necessary to include the normal tissue dose. For very small tumors and micrometastases with Auger-emitters located in the cell nuclei, the self-dose is dominating and the cross-dose contribution may then be neglected. Consequently, it was possible to calculate a tumor-to-normal-tissue dose ratio (TND) per disintegration for decays in the tumor cell nuclei and decays in the total body as described in Sec. II A. The
results for different nuclides normalized to the TND value for $^{119}$Sb for cells with a radius of 8 μm and a nucleus radius of 6 μm can be seen in Fig. 6.

From Fig. 6 it can be seen that despite the high absorbed doses delivered to the tumor cell nucleus per disintegration from $^{201}$Tl and $^{193}$Pt (Fig. 3), their TND values are low compared to some of the other isotopes tested. This is due to the abundance of relatively high energy conversion electrons (above 50–100 keV) emitted in the decays of these isotopes with ranges up to more than 0.2 mm in tissue in addition to the abundant photon emission ($\gamma$- and especially X-rays) from the $^{201}$Tl decay. Based on a theoretical study of different isotopes located in varying sizes of spherical tumors in a patient (modeled as an ellipsoid), Bernhardt et al. concluded that to achieve a high TND in the treatment of small tumors (<1000 cells), the energy of the emitted electrons should be $\leq$40 keV. In addition, the photon-to-electron energy emission ratio, $p/e$, should be $\leq$2 (the $p/e$ of $^{201}$Tl is 2.1). These statements are in agreement with our findings. For heterogeneous radioactivity distributions, which are often seen in larger tumors, the cross-irradiation component resulting from these high energy conversion electrons would result in a more uniform dose distribution, though, and, thus, could be an advantage. However, it has been shown that in therapy of neuroendocrine tumors with the Auger- and conversion electron emitter $^{111}$In as $^{111}$In-DTPA-Octreotide, it is the Auger electrons and not the conversion electrons (145–245 keV) that are responsible for the observed therapeutic effects.

The normalized TND values for activity distributed in the cytoplasm or on the cell membrane can also be seen in Fig.
The dose delivered to the cell nucleus per 165Er disintegration is a ratio of 4.7 caused by the abundant X-ray emission, and the high TND. For comparison, the quite low compared to the other radionuclides tested, it has a distribution 119Sb is closely followed by 125I and 165Er. How-
and membrane bound activity distributions. For the nuclear value of 0.09 reported by Bernhardt
Medical Physics, Vol. 35, No. 9, September 2008
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tained from nuclear localization of the Auger emitter,2,9,12,32 possible high-LET-like biological effects, so far only ob-
have to be taken into account. Since the rationale of using
these calculations have not been done in this study.

These results are only valid for single cells or very small cell clusters consisting of a low number of cells due to the omission of the cross-dose contribution, which starts to account for a considerable part of the total tumor cell dose when the cluster size increases.31 In order to calculate the TND values for larger cell clusters, both the cluster size, the cluster and cell geometries, and the activity distributions have to be taken into account. Since the rationale of using Auger electrons for cancer therapy is to be able to exploit the possible high-LET-like biological effects, so far only obtained from nuclear localization of the Auger emitter,2,9,12,32 these calculations have not been done in this study.

From Fig. 6 it can be seen that 119Sb has the highest TND values of the isotopes tested for both nuclear, cytoplasmic, and membrane bound activity distributions. For the nuclear distribution 119Sb is closely followed by 125I and 165Er. However, the long half-life (T1/2 = 59.4 d) of 125I is a drawback in rapid proliferating cells as reported by ODonoghue and Wheldon33 in combination with the resulting thyroidal uptake of this isotope if in vivo deiodination occurs.

The use of 165Er for targeted radiotherapy has been suggested recently by Beyer et al.34 Even though it has a p/e ratio of 4.7 caused by the abundant X-ray emission, and the dose delivered to the cell nucleus per 165Er disintegration is quite low compared to the other radionuclides tested, it has a high TND. For comparison, the p/e ratio for 119Sb is 0.9 (the value of 0.09 reported by Bernhardt et al.29 must be a misprint). Thus, 165Er may be another promising radionuclide for therapy.

Still, of all the radionuclides considered in this study, 119Sb seems to be the most promising radionuclide for tar-

gated radiotherapy of small tumors, micrometastases, or single cancer cells. This is in good agreement with the theoretical study of Bernhardt et al.29 Using predefined criteria and, as described above, assuming the tumor to be a sphere and the body an ellipsoid, both with uniform activity distributions, five isotopes were found suitable for targeted radiotherapy of small tumors, among them 119Sb.

III.B. 117Sb SPECT

Internal dosimetry constitutes a very important part of radionuclide therapy but because of the absence of penetrating photon emission from the 119Sb decay, the time-activity curves and normal-tissue uptake will be difficult to determine from this radionuclide—the same effect as observed with 90Y.16 However, by a tracer study with SPECT using the isotope 117Sb, it should be possible to partly overcome this. 117Sb decays mainly by EC (only 1.7% β+) with the emission of the nearly single γ-ray of 158.56 keV suitable for imaging. In fact, the energies and intensities of the emitted photons in the 117Sb decay are very similar to the photons emitted by the widely used SPECT isotope 123I (see Table II).

117Sb can be produced and used for labeling a precursor using the same technique as for 119Sb. Both isotopes being of the same element also ensures identical properties in vivo. In this respect, the isotope pair 117Sb/119Sb resembles the 86Y/90Y pair.

From the planar scintigraphy and the transversal slice (corresponding to 1.9 cm) through the SPECT tomography of the Jaszczak phantom (Fig. 7), it can be seen that 117Sb is a suitable imaging isotope. It was possible to locate both the hot-spot and the three largest spherical cold-spots (238 mm, Ø31.8 mm, and Ø25.4 mm) in the SPECT scan and all the cold-rods were visible in the planar scintigraphy. The cold-rods were not visible in the SPECT scan, though, but this was primarily due to a too low number of counts in the separate frames.

III.C. 119Sb and 117Sb production yields

The 119Sb and 117Sb irradiation yields at the end of bombardment (EOB) were measured to be 1.85 ± 0.12 MBq/μAh and 34.6 ± 0.8 MBq/μAh, respectively, using the irradiation conditions and target thicknesses described in Sec. II B. Based on these measurements and assuming the use of proper water cooling of the enriched tin target, one should be able to produce approximately 4.4 GBq of 119Sb at EOB in 8 h with a low energy cyclotron. This is with an electroplated target of thickness 50 mg/cm² in a

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
<th>Decay mode</th>
<th>Major γ-lines in keV (abundance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>119Sb</td>
<td>2.80 h</td>
<td>EC, 1.7% β⁺</td>
<td>158.56 (86%) 511(3.4%) 861.35(0.31%)</td>
</tr>
<tr>
<td>123I</td>
<td>13.27 h</td>
<td>EC</td>
<td>158.97 (83%) 528.96(1.39%) 440.02(0.43%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>538.54(0.38%) 505.33(0.32%)</td>
</tr>
</tbody>
</table>

Table II. Nuclear data for 117Sb and 123I. Only γ-rays with intensities above 0.3% are shown (Ref. 27).
standard 90° target/beam geometry using a collimated (Ø10 mm) 11.0 MeV proton beam and a beam current of 35 μA. In this extrapolation, we have assumed that the nuclear cross sections for the 119Sn(p,n)119Sb reaction are constant in the energy interval (11.0–9.9 MeV) represented by the 50 mg/cm² target thickness. On the other hand, by considering the reaction threshold energy of 11.0 MeV for the 119Sn(p,2n)118Sb reaction, one would expect an increase in the cross sections above the 10.1 MeV proton energy that was used in our yield measurement for the 118Sn(p,n)119Sb reaction. This means that the extrapolated production yield may be an underestimate of the real obtainable yield using the larger amount of enriched target material than what was used in this study.

If even higher activities are needed, this can be achieved by either increasing the irradiation time or by a further increase in the target thickness. Another approach is to use an inclined target/beam geometry to allow a high increase in the beam current resulting in a considerable increase in the obtainable yield. Such high current irradiations (~200 μA) on a 118Sn target using a dedicated PET cyclotron have recently been performed in our department (unpublished data) demonstrating the capability of producing several tens of GBq of therapeutic isotopes locally. Hence, it will be possible to produce the amounts of 119Sb radioactivity that is required for initial patient studies and clinical trials in radionuclide therapy using a small medical cyclotron.

The shorter half-life of 117Sb and the need for a much smaller amount of radioactivity for each patient in a diagnostic study than for therapy, makes the 117Sb production less demanding than the 119Sb production. Using the same extrapolation conditions as above, it will be possible to produce approximately 23 GBq of 117Sb at EOB in a 4 h irradiation, which should be sufficient for several patient scans.

IV. CONCLUSION

Based on theoretical dosimetry calculations for different subcellular distributions of several Auger-electron emitting isotopes, we have identified 119Sb as being a potent radioisotope for targeted radiotherapy of small tumors, micrometastases, and single cancer cells. Using the MIRD-model, we have calculated the cellular S-values for this isotope. In addition, we have measured the proton irradiation yields for the production of 119Sb and the corresponding imaging isotope 117Sb using a low-energy cyclotron. From a planar scintigraphy and a SPECT scan of a Jaszczak phantom, we have shown that the latter isotope is well suited for SPECT-based patient-specific dosimetry of an 119Sb-labeled radiopharmaceutical. The production yields show that it will be possible to produce both isotopes with a standard PET-cyclotron in sufficient quantities for patient imaging and therapy.


21S. Goddu et al., MIRD Cellular S Values (Society of Nuclear Medicine, Reston, Virginia, 1997).


