Low-energy Electron Emitters for Targeted Radiotherapy of Small Tumours

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The possibility of using electron emitters to cure a cancer with metastatic spread depends on the energy of the emitted electrons. Electrons with high energy will give a high, absorbed dose to large tumours, but the absorbed dose to small tumours or single tumour cells will be low, because the range of the electrons is too long. The fraction of energy absorbed within the tumour decreases with increasing electron energy and decreasing tumour size. For tumours smaller than 1 g, the tumour-to-normal-tissue mean absorbed dose-rate ratio, TND, will be low, e.g. for ^{131}I and ^{90}Y, because of the high energy of the emitted electrons. For radiotherapy of small tumours, radionuclides emitting charged particles with short ranges (a few μm) are required. A mathematical model was constructed to evaluate the relation between TND and electron energy, photon-to-electron energy ratio, p/e, and tumour size. Criteria for the selection of suitable radionuclides for the treatment of small tumours were defined based on the results of the TND model. In addition, the possibility of producing such radionuclides and their physical and chemical properties were evaluated. Based on the mathematical model, the energy of the emitted electrons should be ≤ 40 keV for small tumours (< 1000 cells), and the photon-to-electron energy ratio, p/e, should be ≤ 2 to achieve a high TND. Using the selection criteria defined, five low-energy electron emitters were found to be suitable: ^{58m}Co, ^{103m}Rh, ^{119}Sb, ^{161}Ho, and ^{189m}Os. All of these nuclides decay by internal transition or electron capture, which yields conversion and Auger electrons, and it should be possible to produce most of them in therapeutic amounts. The five low-energy electron-emitting radionuclides identified may be relevant in the radiation treatment of small tumours, especially if bound to internalizing radiopharmaceuticals.

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When radiopharmaceuticals are used in cancer therapy, one of the factors that limit treatment is the absorbed dose in the critical normal tissue. To reach a higher absorbed dose in the tumour than in the normal tissue, two criteria must be fulfilled: 1) the tumour must have a higher uptake and/or longer retention time of the radionuclide than normal tissue; 2) a high fraction of the radiation energy emitted should be absorbed in the tumour. For large tumours (> 1 g), high, absorbed fractions are obtained for the therapeutic radionuclides used today, e.g. ^{90}Y and ^{131}I. These large tumours can be detected, e.g., by CT, MRI or scintigraphy, and can be treated surgically or by external radiation. Frequently, small, disseminated tumours (< 1 g) cannot be detected and will therefore not be treated with the methods just mentioned. Radiopharmaceuticals can be used instead. A radionuclide emitting short-range radiation is then required to obtain high, absorbed energy fractions in such small tumours.

We studied electron emitters with ranges suitable for the treatment of small tumours, focusing on tumours of sizes down to single cells. Many of these radionuclides also emit extremely low-energy electrons (Auger electrons), whose effect may be enhanced if the nuclides are internalized (1). Low-energy electrons used in the treatment of small tumours has been discussed previously (2, 3) but to our knowledge no systematic evaluation of suitable low-energy electron emitters has ever been done.

If low-energy electron emitters are to be used for therapy, the photon contribution must be very low. It is often stated that the abundance of photons should be as low as possible or that a low abundance of photons is useful in following the biokinetics of the radionuclides. To our knowledge, however, no investigation has been undertaken showing how the abundance of photons influences the absorbed doses in tumour and normal tissues.

Although various alpha particle emitters have been suggested as being suitable for the treatment of micro-metastases, the range of alpha particles is in the range of a few cell diameters, which may not prove optimal for all sizes of very small tumours. Furthermore, it is still not known

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whether high linear energy transfer is of any advantage. For example, the small number of 'hits' needed to achieve a sterilizing dose has a large stochastic variation, which may be a drawback (4).

The aim of this study was to formulate selection criteria specifically for electron-emitting radionuclides suitable for the treatment of small tumours. Consideration was given to radiation and chemical properties and to production possibilities. Radionuclides suitable for the treatment of small tumours were suggested according to these selection criteria.

METHODS

Computer simulations

The effects of electron energy and photon abundance on the absorbed dose to the tumour and normal tissue were evaluated. The human body was simulated by an ellipsoid, representing normal tissue. Tumours were spherical in shape and were randomly distributed throughout the ellipsoid. The distributions of radionuclides in the spheres and the ellipsoid, respectively, were assumed to be uniform. The tumour and normal tissue were assumed to contain different activity concentrations, C_T and C_N, respectively, and the tumour-to-normal-tissue activity concentration ratio, $TNC = C_T/C_N$, was used when calculating the tumour-to-normal-tissue mean absorbed dose-rate ratio, TND.

The mean absorbed dose rate to the normal tissue, D_N, for uniformly distributed activity in the ellipsoid:

$$D_N = \frac{\sum_i E_{e,i} n_{e,i} \phi_{N,e,i} + \sum_i E_{p,i} n_{p,i} \phi_{N,p,i}}{m_N} A_N \qquad [1]$$

where $E_{p,i}$ and $E_{p,i}$ are the energies of the emitted electrons and photons, respectively, $n_{e,i}$ and $n_{p,i}$ are the numbers of emitted electrons and photons per transition, respectively, m_N the normal tissue mass, $\phi_{N,p,i}$ the mean absorbed photon energy fractions and A_N the activity in normal tissue. The deposition of the electron energy was assumed to take place at the decay site, i.e. the fraction of the electron energy absorbed in the normal tissue, $\phi_{N,e}$, was 1.

For a certain TNC the excess amount of activity in the tumour is $(TNC-1)(m_T/m_N)A_N$, where m_T is the mass of the tumour. Assuming that 1) the mean absorbed dose in the normal tissue from the photons and electrons originating from the tumour, and 2) the absorbed fraction in the tumour for photons originating from the tumour can be neglected, due the small size of the tumours considered (≤ 1 g), the mean absorbed dose rate to the tumour, D_T:

$$D_T = D_N + (TNC-1)\frac{m_T}{m_N}\left(\frac{\sum_i E_{e,i} n_{e,i} \phi_{T,e,i}}{m_T}\right) A_N \qquad [2]$$

where $\phi_{T,e,i}$ is the mean absorbed electron energy fraction in the tumour.

The tumour-to-normal-tissue mean absorbed dose-rate ratio, TND, was calculated:

$$\mathrm{TND} = \frac{D_T}{D_N} = \frac{\sum_i E_{e,i} n_{e,i} + \sum_i E_{p,i} n_{p,i} \phi_{N,p,i} + (TNC-1)\sum_i E_{e,i} n_{e,i} \phi_{T,e,i}}{\sum_i E_{e,i} n_{e,i} + \sum_i E_{p,i} n_{p,i} \phi_{N,p,i}} \qquad [3]$$

The mean absorbed photon energy fractions, $\phi_{N,p,i}$, for a 70 kg ellipsoid, with principal axes in the ratio 1/1.8/9.27, were taken from the MIRD pamphlet, no. 3 (5). The decay properties of the radionuclides were taken from Table of radioactive isotopes (6). The mean absorbed electron energy fraction to tumours, $\phi_{T,e,i}$, was calculated using the method of Howell et al. (7). The calculation of the mean absorbed fraction to the tumour, $\phi_{T,e}$, was carried out for different tumour sizes and electron energies. The tumour sizes were in the range from one single cell with a mass of 1 ng ($R_c = 6.2$ μm) to a small tumour of 1 g ($R_c = 6.2$ mm). The impact of photons on TND vs. tumour mass was calculated for different photon-to-electron energy ratio, p/e:

$$p/e = \frac{\sum_i E_{p,i} n_{p,i}}{\sum_i E_{e,i} n_{e,i}} \qquad [4]$$

The activity required for systemic therapy was calculated as the activity amount that will give the normal tissue a mean absorbed dose of 2 Gy.

All calculations were made using a program written in IDL (Research Systems Inc., USA) and carried out on a Macintosh Quadra 950 computer.

RESULTS

The influence of tumour size, electron energy and photon abundance on the tumour-to-normal-tissue mean absorbed dose-rate ratio, TND, was estimated by computer simulations. For tumours smaller than 1 g, the TND depends strongly on the energy of the emitted electrons (Fig. 1). In the electron energy range studied ($\leq 1\,000$ keV) the TND will be high for tumours larger than 1 g but decreases rapidly with decreasing tumour size and electron energy. The energy of the emitted electrons should be below about 40 keV to reach high values of TND for small tumours. The TND was found to decrease with increasing photon contribution in the decay of the radionuclide, as demonstrated in Fig. 2, where the impact of emitted 100 keV photons on TND was simulated for 100 keV electrons and for photon-to-electron energy ratios, p/e, of 0, 0.1, 1 and

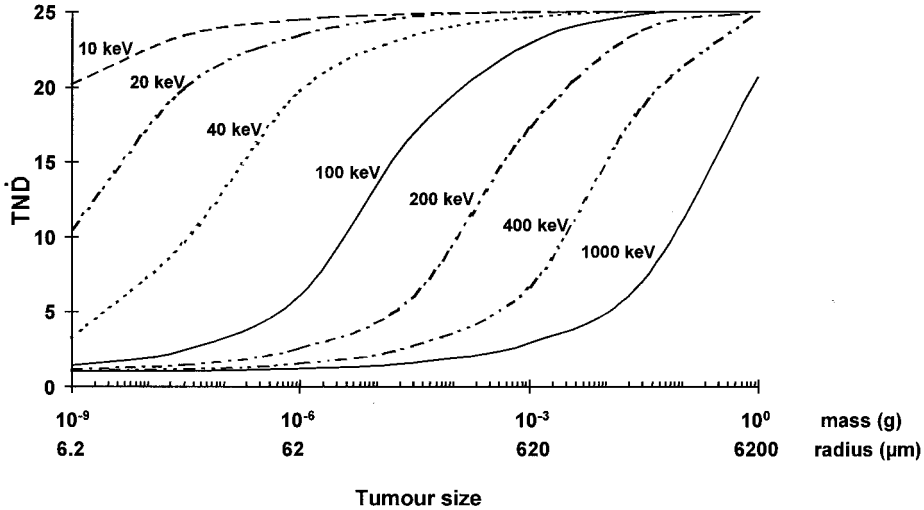

Fig. 1. Tumour-to-normal-tissue mean absorbed dose-rate ratio (TND) for mono-energetic electron-emitting sources distributed uniformly in spheres of unit density matter. TND was calculated for sphere masses between 1 ng and 1 g and for seven mono-energetic electron sources, 10, 20, 40, 100, 200, 400 and 1 000 keV. The tumour-to-normal-tissue activity concentration ratio (TNC) was assumed to be 25.

10. At p/e of 2, TND decreases by about 50% on account of the photons.

Based on the results from computer simulations, and considerations regarding decay, chemical properties and production possibilities of the six radionuclide criteria were defined for selection of radionuclides for the treatment of small tumours.

(i) The abundance of the electrons emitted by the radionuclides should be ≤ 40 keV.
(ii) The p/e should be ≤ 2.
(iii) The half-life should be between 30 min and 10 days.
(iv) The daughter nuclide should be stable or have a half-life longer than 60 days.
(v) It should be possible to produce the nuclides via neutron capture or proton-, deuteron-, ^{3}He- or α-particle-induced reactions.
(vi) Noble gases should be excluded, as their chemical properties make them unsuitable for labelling reactions.

The chart of nuclides (6) was systematically scanned for radionuclides fulfilling these selection criteria.

Using the selection criteria, five radionuclides were found: ^{58m}Co, ^{103m}Rh, ^{119}Sb, ^{161}Ho, and ^{189m}Os. Their physical properties are listed in the Table 1. All the selected radionuclides are cations in aqueous solution, and they form complexes, e.g. with various chelates. Such complexes may then be linked to many types of tumour-seeking compounds. The selected radionuclides decay by internal transition or electron capture, yielding conversion and Auger electrons. Calculation of TND vs. tumour size for these electron emitters showed high TND, even for a single cell (Fig. 3). As a comparison, Fig. 3 also shows the results for four radionuclides used for radiation therapy: ^{131}I, ^{90}Y, ^{111}In, and ^{125}I.

The initial activities in the normal tissue required to reach a mean absorbed dose of 2 Gy are about 4 000, 1 000, 900, 700, and 100 GBq for uniformly distributed ^{103m}Rh, ^{161}Ho, ^{189m}Os, ^{58m}Co and ^{119}Sb, respectively. With a TNC of 25, the mean absorbed dose to a 1 µg tumour will then be 40, 23, 44, 43 and 28 Gy for the selected radionuclides, respectively.

DISCUSSION

The tumour-to-normal-tissue activity concentration ratio (TNC) is commonly reported in order to show how effectively the tumour tissue has taken up the radionuclide as compared with the distribution in normal tissue. Depending on the range of the radiation emitted, the tumour-to-normal-tissue mean absorbed dose-rate ratio (TND) will be less than the TNC. In practice, the TNC will change with time according to the biokinetics of the radiopharmaceutical used. As this change in concentration is a specific radiopharmaceutical property, TNC time dependence was not taken into account in the present calculations and TNC was set to 25, which is approximately the minimum value required in internal therapy. However, the conclusions presented in this paper are valid for other TNC values as well.

The TND model is a simple model that takes into account both the electron energy and the photon contribution in the evaluation of suitable radionuclides for therapy. While some investigators have studied the optimal electron energy for internal therapy (2, 3), the photon contribution is often not included in these models. The TND model demonstrates the importance of low p/e for obtaining a

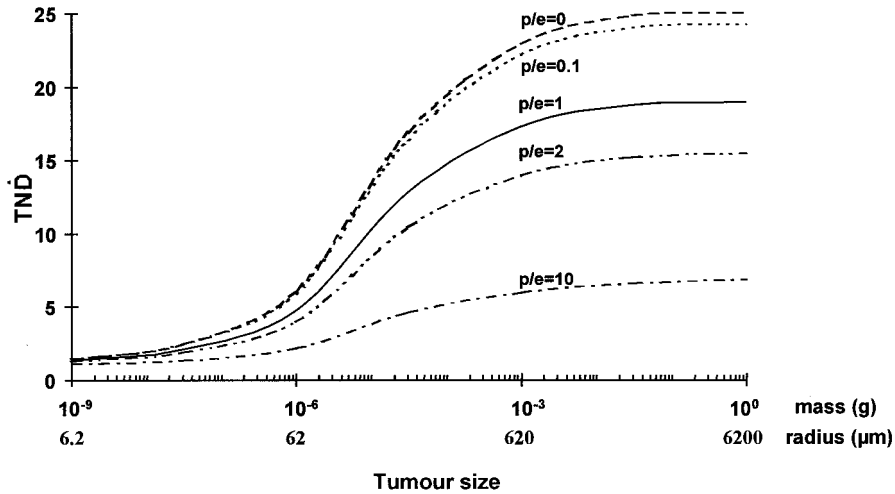

Fig. 2. Tumour-to-normal-tissue mean absorbed dose-rate ratio (TND) for mono-energetic photon and electron-emitting sources distributed uniformly in spheres of unit density matter and masses betweenl ng and 1 g. TND was calculated for photon-to-electron energy ratios, p/e, of 0, 0.1, 1, 2 and 10. The tumor-to-normal-tissue activity concentration ratio (TNC) was assumed to be 25.

high TND (Fig. 2). The simulations were performed for 100 keV photons, but they also reflect photons with energies between 100 and 1 000 keV, since the absorbed fractions in this energy range are almost constant in the present geometry model (0.32–0.35) (8). However, for lower photon energies, TND will be reduced even further, owing to the increased absorption of the photons in the body. This effect is illustrated by the ^{125}I and ^{131}I halogens, which both have a p/e of 2 but, since the photons emitted by ^{125}I have a lower energy (20–40 keV) than those emitted by ^{131}I (364 keV), there will be a greater reduction of the TND in the case of ^{125}I. The high abundance of photons associated with ^{111}In (p/e $\approx$ 10) will reduce TND more than fivefold. If the activity is not uniformly distributed in the body, the absorbed photon energy will differ depending on the location of the source. In the human body, absorbed fractions, for organs as sources, will vary between 0.2 and 0.5 (8). However, the activity is often distributed in several organs, and a mean absorbed fraction for a uniform activity distribution seems reasonable.

The TND model also demonstrated that, for homogeneously distributed radionuclides, a high TND in small tumours was obtained only for electron energies $\leq$ 40 keV (Fig. 1). This is in agreement with the results of other studies that have shown that radionuclides distributed in the cytoplasm or at the cell membrane have the highest mean absorbed energy fraction to the cell nucleus, from 10–30 keV electrons (9–11). The selection criterion for the maximum energy of the emitted electrons was therefore set to 40 keV. The TND model assumes a uniform distribution of radionuclides that might not be the case in tumours, especially larger ones. For heterogeneous activity distribution of low-energy emitters in a tumour, the dose distribution will also be heterogeneous (12). By using electrons with high energy, the cross-irradiation of cells will, of course, give a more uniform dose distribution. However, for such high-energy electron emitters, this and previous studies show that it will be difficult if not impossible to treat small tumours (2, 3). The risk of heterogeneous activity distribution is probably smaller when small carrier molecules and fractionation of the radiopharmaceuticals are used. Small molecules such as peptides (13, 14) and antibody fragments may be able to penetrate tissue better than larger ones, e.g. intact antibodies, resulting in a more homogeneous activity distribution. On of the benefits of fractionation is that different tumour cells could be targeted each time, resulting in a more uniform dose distribution (12). It is thus quite possible that low-energy electron emitters are suitable even for large tumours.

The relation between TND and tumour mass was estimated for the low-energy electron emitters selected here and four radionuclides used for internal radiation therapy, ^{131}I, ^{90}Y, ^{111}In and ^{125}I (Fig. 3). In the interval from a single cell to a small tumour mass of 1 g, the low-energy electron emitters selected have a high TND. In the case of ^{131}I and ^{90}Y, TND decreases rapidly at about 1 mg and 1 g, respectively. These high-energy electron emitters are thus not suitable for treating small tumours.

The five radionuclides selected emit electrons with energies below 40 keV. With a specific carrier to the target cells, these radionuclides should be relevant for radiation therapy, especially if internalization occurs. For these radionuclides, the ratio of absorbed dose to the nucleus between internalized and cell-surface-bound activity will be greater than one. Consequently, TND may be even higher than TNC if the carrier is internalized into tumour cells while it is non-specifically bound in the normal tissue, i.e. is located in the extracellular space. Furthermore, DNA-bound Auger emitters have been shown to have a higher

Table 1

Some physical properties of the selected low-energy electron emitters and some conventional radionuclides for therapy

Radionuclide	Half-life	Decay mode	Electron energy (keV)	Abundance (%)	p/e	Daughter ($T_{1/2}$)
^{58m}Co	9.15 h	IT	0.02–0.8	400	0.09	^{58}Co (70.8 days)
			6–8	46		
			17–24	100		
^{103m}Rh	56.1 min	IT	0.39	150	0.04	
			2.2–3.1	76		
			16–20	12		
			36–40	90		
^{119}Sb	38.1 h	EC	0.60	280	0.09	
			2.8–4.0	150		
			19–21	76		
			23–28	20		
^{161}Ho	2.5 h	EC	17–18	51	2	
			23–26	51		
^{189m}Os	6.0 h	IT	2.2	110	0.06	
			6.6–10	26		
			18–20	70		
			28–31	30		
^{90}Y	2.67 days	β	935	100	1.8 10^{-6}	
^{111}In	2.83 days	EC	0–4	293	11	
			19–22	16		
			145–167	10		
			219–242	6		
^{125}I	60.1 days	EC	0–5	520	2	
			22–37	113		
^{131}I	8.04 days	β	191	89	2	
			46–97	14		
			250–360	2		

relative biological effect (RBE) than external radiation, e.g. ^{137}Cs (1). Thus, the radionuclides selected are relevant for binding to DNA-specific carriers, e.g. synthetic oligonucleotides (15), bleomycin (16) or oestrogen (17).

With the irradiation facilities available today, ^{103m}Rh is the only nuclide that can readily be produced in sufficient amounts. Carrier-free ^{103m}Rh is formed as a decay product of ^{103}Ru, which can be produced by the fission of uranium. The ruthenium product can be separated from the target material by distillation or solvent extraction. Since ^{103}Ru has a fairly long half-life (39 days), it is possible to use it as a generator that would allow frequent withdrawal of ^{103m}Rh (cf. 18). The most common state in an aqueous solution is Rh III). Complex formation of Rh with, for example, tetrathiacyclohexadecane diols or DOTA (1,4,7,10-cyclododecane N,N′,N″,N‴-tetraacetic acid) has been found to be fast enough to give acceptable labelling yields with the short-lived ^{103m}Rh (18–20) as well. These compounds can be linked to several kinds of tumour-seeking compounds.

To render the other four nuclides carrier-free, they must be produced by irradiation in accelerators. Reaching the high activity levels required for therapy is difficult with most of the accelerators available today. However, accelerator technology is developing rapidly to facilitate the incineration of nuclear waste, and it is likely that at least proton accelerators with beam currents more than 100 times stronger than is now the case will be common in the next 5 to 10 years.

^{58m}Co can be produced, carrier-free, using the ^{55}Mn(α,n)^{58m}Co nuclear reaction. At 12–14 MeV He-ion energy, the cross-section of this reaction is about 600 mb. A manganese foil can be used as the target, and cobalt can be separated from manganese by ion exchange, solvent extraction, or precipitation. In an aqueous solution, cobalt is present as Co(II) or Co(III). Cobalt forms complexes with, e.g., DTPA (diethylenetriaminepentaacetic acid) and DOTA, which may be used to link the nuclide to a suitable carrier (21).

^{119}Sb can be produced via the ^{119}Sn(p,n)^{119}Sb and ^{118}Sn(d,n)^{119}Sb reactions. The cross-sections are estimated to be in the range of 100–500 mb. One of the most selective methods of separating ^{119}Sb from the target material is to produce SbH_3, which is gaseous and may be collected in an alkaline ethanol solution. The common oxidation states in aqueous solution are Sb(III) and Sb(V). Chemically, antimony resembles arsenic and bismuth and will thus react in a different way than the other four nuclides, which are all typical metal ions. Complex formation should be possible with several common chelating agents.

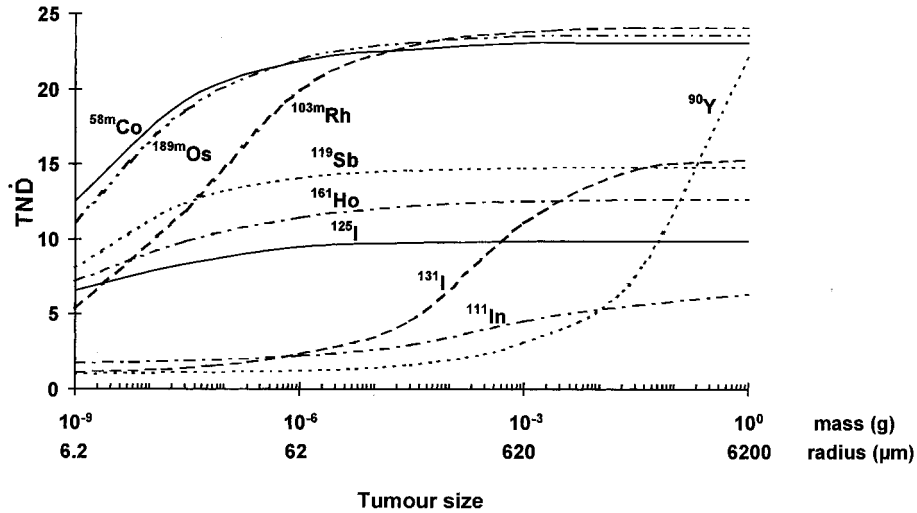

Fig. 3. Tumour-to-normal-tissue mean absorbed dose-rate ratio (TND) for the selected low-energy emitters: ^{58m}Co, ^{189m}Os, ^{103m}Rh, ^{119}Sb, and ^{161}Ho, and four radionuclides used for internal radiation therapy, ^{131}I, ^{90}Y, ^{111}In and ^{125}I, distributed uniformly in spheres of unit density matter. The tumour-to-normal-tissue activity concentration ratio (TNC) was assumed to be 25.

^{161}Ho can be obtained carrier-free via the ^{159}Tb(α,2n)^{161}Ho reaction. The cross-section is estimated to be about 800 mb at 29 MeV He-ion energy. It should be possible to separate Ho from the Tb target by ion exchange. In an aqueous solution, Ho(III) is the only possible species. It should, like the other lanthanides, form strong complexes with DTPA and even stronger ones with DOTA (21).

Carrier-free ^{189m}Os is obtained by β^--decay of ^{189}Ir ($T_{\frac{1}{2}} = 13.3$ d). The mother nuclide can be produced via reactions ^{187}Re(α,2n)^{189}Ir or ^{190}Os(p,2n)^{189}Ir. Osmium can be chemically separated from dissolved rhenium and iridium by oxidation to OsO_4 followed by solvent extraction or distillation. The (p,n) reaction has the drawback of requiring an extra chemical separation step to obtain carrier-free ^{189}Os and is therefore less suitable. Osmium has a complicated redox chemistry with 10 possible oxidation states (from Os(-I) to Os(VIII)). The most promising state for labelling reactions may be Os(VI), which has a high affinity with oxygen and nitrogen groups.

The half-lives of the radionuclides selected here range from 56 min to 38 h. Although a half-life of 56 min is short, such a short-lived nuclide may nevertheless be relevant for injection into cavities and for a local injection of labelled radiopharmaceuticals. Treatment of oestrogen receptor-positive micrometastases in the peritoneal cavity with Auger-emitting radionuclides is particularly promising, since oestrogen is internalized into the cell nucleus (17). Since the residence time of oestrogen in the cell is short, the long-lived Auger-emitting ^{125}I is considered not to be suitable for therapy (17). Instead, short-lived radionuclides have been suggested for this kind of therapy. Therefore, it would be interesting to use the selected short-lived Auger-emitting radionuclides for oestrogen-radionuclide therapy. The short half-life of the radionuclides should also be advantageous for regional or local therapies, since most of the radionuclides have decayed before being distributed systemically. Furthermore, small carriers, such as octreotide and oestrogen, will rapidly bind to the receptor and internalize into the cell (17, 22, 23). This binding may even occur during the first passage, in which case, a short half-life might not be an obstacle to clinical therapy.

The low energy emitted in the decay and the short half-life of the selected radionuclides demand high activity in order to reach high, absorbed doses in tumours. We estimated the total activity required, giving an optimal whole-body dose of 2 Gy, to be about 1 000 GBq for ^{103m}Rh, ^{58m}Co, ^{161}Ho and ^{189m}Os, and about 100 GBq for ^{119}Sb. The high activity demanded will also require large amounts of pharmaceuticals to be labelled. This large amount of radiopharmaceuticals may cause a saturation in tumour uptake if injected in a single dose, thus possibly making it necessary to fractionate these low-energy radiopharmaceuticals. However, this could only be an advantage, since the tumour cells might be more uniformly labelled and the dosimetric non-uniformity would be much less with fractionation (12). Furthermore, studies in animal models suggest that fractionated administration of radiopharmaceuticals is more toxic to tumours and less toxic to bone marrow than a single injection (24–27). For ^{103m}Rh, it should be possible to produce a sufficient amount of activity for systemic internal therapy. For ^{58m}Co, ^{161}Ho and ^{189m}Os it should be possible to produce a few GBq on each occasion. Large amounts of ^{119}Sb are more difficult to produce, but up to a few hundred MBq on each occasion should be possible. For the time being, it seems that the production may be the limiting factor for

^{58m}Co, ^{161}Ho, ^{189m}Os and ^{119}Sb for systemic internal therapy.

In conclusion, the radionuclides used today for radiation therapy are not optimal for small tumours. By formulating selection criteria that take into consideration radiation and chemical properties and production possibilities, we were able to identify five low-energy electron-emitting radionuclides that are suitable for the treatment of small tumours: ^{58m}Co, ^{103m}Rh, ^{119}Sb, ^{161}Ho and ^{189m}Os. For ^{103m}Rh, it should be possible to produce the desired activity for systemic internal therapy, and an extensive study on this nuclide is already in progress (18), while production might limit the use of ^{58m}Co, ^{119}Sb, ^{161}Ho, and ^{189m}Os in local therapies.

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REFERENCES

1. Sastry KS. Biological effects of the Auger emitter iodine-125: a review. Report No. 1 of AAPM Nuclear Medicine Task Group No. 6. Med Phys 1992; 19: 1361–70.
2. O'Donoghue JA, Bardies M, Wheldon TE. Relationships between tumor size and curability for uniformly targeted therapy with beta-emitting radionuclides. J Nucl Med 1995; 36: 1902–9.
3. Nahum EA. Microdosimetry and radiocurability: modelling targeted therapy with β-emitters. Phys Med Biol 1996; 41: 1957–72.
4. Palm S, Andersson H, Bäck T, et al. In vitro effects of free At, At-albumin and At-monoclonal antibody compared to external irradiation on two human cancer cell lines. Anticancer Res 2000; 20: 1005–12.
5. Brownell GL, Ellett WH, Reddy AR. Absorbed fractions for photon dosimetry. J Nucl Med 1968; Suppl 1: 27–39.
6. Browne E, Firestone RB. Table of radioactive isotopes. New York: Wiley-Interscience Publications, 1986.
7. Howell RW, Rao DV, Haydock C. Dosimetry techniques for therapeutic applications of incorporated radionuclides. In: The joint symposium on dosimetry of administered radionuclides, Proc held in Washington DC, September 1989: 215–56.
8. Snyder WS, Ford MR, Warner GG. Estimates of specific absorbed fractions for photon sources uniformly distributed in various organs of a heterogeneous phantom. nm/mird pamphlet No. 5, revised. New York: Society of Nuclear Medicine, 1978.
9. Gardin I, Faraggi M, Huc E, Bok BD. Absorbed fraction to the nucleus for low energy electrons. Acta Oncol 1996; 35: 953–8.
10. Sastry KSR, Rao DV. Dosimetry of low energy electrons. In: Rao DV, Chandra R, Graham M, eds. Physics of nuclear medicine: recent advances. New York: American Institute of Physics, 1984: 169–208.
11. Goddu SM, Howell RW, Rao DV. Cellular dosimetry: absorbed fractions for monoenergetic electron and alpha particle sources and S-values for radionuclides uniformly distributed in different cell compartments. J Nucl Med 1994; 35: 303–19.
12. O'Donoghue JA. Implications of nonuniform tumor doses for radioimmunotherapy. J Nucl Med 1999; 40: 1337–41.
13. Block D, Feitsma RIJ, Vermeij Pauwels EJK. Peptide radiopharmaceuticals in nuclear medicine. Eur J Nucl Med 1999; 26: 1511–9.
14. Reubi JC. Regulatory peptide receptors as molecular targets for cancer diagnosis and therapy. Q J Nucl Med 1997; 41: 63–70.
15. O'Donoghue JA, Wheldon TE. Targeted radiotherapy using Auger electron emitters. Phys Med Biol 1996; 41: 1973–92.
16. Kairemo KJA, Ramsay HA, Tagesson M, et al. Indium-111 bleomycin complex for radiochemotherapy of head and neck cancer—dosimetric and biokinetic aspects. Eur J Nucl Med 1996; 23: 631–8.
17. DeSombre ER, Huges A, Hanson RN, Kearney. Therapy of estrogen receptor-positive micrometastasis in the peritoneal cavity with Auger electron-emitting estrogens. Acta Oncol 2000; 39: 659–66.
18. Glänneskog H. Diploma thesis. ^{103}Rh-production and complex chemistry. Göteborg: Department of Nuclear Chemistry, Chalmers University of Technology, 2000.
19. Venkatesh M, Goswami N, Volkert WA, et al. An Rh-105 complex of tetrathiacyclohexadecane diol with potential for formulating bifunctional chelates. Nucl Med Biol 1996; 23: 33–40.
20. Jurisson S, Ketring AR, Volkert WA. Rhodium-105 complexes as potential radiotherapeutic agents. Transition Met Chem 1997; 22: 315–7.
21. Byegård J, Skarnemark G, Skålberg M. The stability of some metal EDTA, DTPA and DOTA complexes: application as tracers in groundwater studies. J Radioanalytical Nucl Chemistry 1999; 241: 281–90.
22. Andersson P, Forssell-Aronsson E, Johanson V, et al. Internalisation of indium-111 into human neuroendocrine tumor cells after incubation with indium-111-DTPA-D-Phe^1-Octreotide. J Nucl Med 1996; 37: 2002–6.
23. Andersson P, Forssell-Aronsson E, Grétarsdóttir J, et al. Biokinetics and dosimetry after repeated injections of ^{111}In-DTPA-D-Phe^1-octreotide. In: Schlafke-Stelson A, Stabin MG, Sparks RB, eds. Sixth International Radiopharmaceutical Dosimetry Symposium, Proceedings held in Gatlinburg, Tennessee 1996, Oak Ridge Associated Universities, 1999: 127–36.
24. Schlom J, Molinolo A, Simpson JF, et al. Advantage of dose fractionation in monoclonal antibody-targeted radioimmunotherapy. J Natl Cancer Inst 1990; 82: 763–71.
25. Buchsbaum D, Khazaeli MB, Liu T, et al. Fractionated radioimmunotherapy of human colon carcinoma xenografts with I-labeled monoclonal antibody CC49. Cancer Res 1995; Suppl 55: 5881s–7s.
26. Sun LQ, Vogel CA, Mirimanoff RO, et al. Timing effects of combined radioimmunotherapy of human colon carcinoma grafted in nude mice. Cancer Res 1997; 57: 1312–9.
27. Andersson CJ, Jones LA, Bass LA, et al. Radiotherapy, toxicity, and dosimetry of copper-64-TETA-octreotide in tumor-bearing rats. J Nucl Med 1998; 39: 1944–51.