Nuclear Medicine and Molecular Imaging (2019) 53:182–188
https://doi.org/10.1007/s13139-019-00589-8

REVIEW

ISSN (print) 1869-3482
ISSN (online) 1869-3474

Quantitative Imaging of Alpha-Emitting Therapeutic Radiopharmaceuticals

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Received: 3 January 2019 / Revised: 2 February 2019 / Accepted: 7 February 2019 / Published online: 18 February 2019

Abstract

Targeted alpha therapy (TAT) is an active area of drug development as a highly specific and highly potent therapeutic modality that can be applied to many types of late-stage cancers. In order to properly evaluate its safety and efficacy, understanding biokinetics of alpha-emitting radiopharmaceuticals is essential. Quantitative imaging of alpha-emitting radiopharmaceuticals is often possible via imaging of gammas and positrons produced during complex decay chains of these radionuclides. Analysis of the complex decay chains for alpha-emitting radionuclides (Tb-149, At-211, Bi-212 (decayed from Pb-212), Bi-213, Ra-223, Ac-225, and Th-227) with relevance to imageable signals is attempted in this mini-review article. Gamma camera imaging, single-photon emission computed tomography, positron emission tomography, bremsstrahlung radiation imaging, Cerenkov luminescence imaging, and Compton cameras are briefly discussed as modalities for imaging alpha-emitting radiopharmaceuticals.

Keywords Targeted alpha therapy · Quantitative imaging · SPECT · PET · Alpha-emitting radionuclide · Compton camera

Introduction

As for any other drug development, radiopharmaceuticals for targeted alpha therapy (TAT) of cancers are evaluated for their efficacy and safety. The efficacy can be evaluated in living systems (animals and human subjects) by administering an alpha-emitting radiopharmaceutical and assessing response to the therapy, and the safety can be measured by dose escalation and evaluation of adverse events based on the dose. Alpha particles (i.e., nucleus of helium) are basically four nucleons (two protons and two neutrons) bound together by strong nuclear force, and they exhibit much higher rest energy than that of other radiation such as betas or gammas. High linear energy transfer of alpha emission (i.e., the loss of energy per unit distance) is thus understood well.

The unique feature of alpha-emitting radiopharmaceutical for TAT is that not only the dose does depend on the mass of the pharmaceutical but also the radiation dose (i.e., energy deposit) from alpha emission and other radioactivity in the radionuclide's decay chain. In comparison to beta-emitting radiopharmaceuticals for targeted radionuclide therapy, the dose of alpha-emitting radiopharmaceuticals is much higher per unit activity and the range of alphas is much shorter. In addition, alpha-emitting radionuclides typically have several daughter radionuclides that emit either alpha or beta particles contributing additional dose.

Since the primary mechanism of cytotoxicity of TAT is based on highly targeted radiation dose delivery rather than the toxicity of the molecules, understanding where the alpha-emitting radiopharmaceutical propagates over time (i.e., biokinetics) is essential to optimize this very promising therapeutic modality that is under active development for many types of cancers and other diseases. The information on biokinetics can be used to further refine the design of radiopharmaceutical's properties such as rate of accumulation and internalization to the target site, and, most importantly,

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estimation of radiation dose at the target (i.e., tumor dosimetry) for efficacy, and radiation dose to the normal tissue for safety can be derived from the biokinetic data.

During the developmental phase of TAT, animal models can be used to investigate the biokinetics of radiopharmaceuticals by dissecting them and counting using scintillation counters. Since alphas do not penetrate the tissue deeply, even counting using sensitive scintillation counters may not be accurate to determine the amount of activity in dissected tissues and organs. Noninvasive detection is ideal in both animals and human subjects; however, it is very challenging although noninvasive imaging is still possible because decay chains of alpha-emitting radionuclides typically involve gamma emissions and sometimes positron emissions. In addition, decay chains of these radionuclides sometimes involve energetic beta emissions, from which meaningful bremsstrahlung radiation or Cerenkov luminescence imaging is possible. Minimally invasive, but tissue-level, implantable radiation detectors can be also used to measure the alpha particles or beta particles in decay chains, directly.

Ultimately, microimaging or microdetection of alpha-emitting radiopharmaceuticals is desirable since the range of emitted alpha particles is confined mostly within 100 μm. The depiction of how this small range compares to mm scales of beta particles in beta-emitting radionuclides is shown in Fig. 1 [1]. However, noninvasively, microimaging at this level of spatial resolution particularly in human subjects with currently available technologies is not readily available.

In summary, direct quantitative imaging of most alpha-emitting radiopharmaceuticals is certainly possible using available imaging technologies such as gamma cameras and single-photon emission computed tomography (SPECT), and positron emission tomography (PET). How practical and useful these imaging methods for TAT will be is an area of refinement and improvement. If direct imaging of these radionuclides and their decay chains is not practically feasible, surrogate radiopharmaceuticals with more imaging-friendly radionuclides instead of alpha-emitting radionuclides may be a compromise, and still may add valuable information for the development and implementation of TAT as long as there is a verification step to show similar biokinetics between a therapeutic alpha-emitting radiopharmaceutical and its surrogate imaging radiopharmaceutical. In addition to gamma imaging, direct or indirect detection of alphas and betas is another way of "imaging" although this method requires proximity for the measurement. Imaging of bremsstrahlung radiation, if there is a good amount of its radiation, and Cerenkov luminescence imaging for radionuclides emitting energetic beta particles are other possibilities. Finally, for imaging of high-energy photons (e.g., > 0.5 MeV) that are not very well captured by conventional gamma cameras, Compton imaging method can be employed since very sensitive Compton cameras can be designed and built with high spatial resolution [2].

In this mini-review, a survey of imageable signals like gamma and positron emissions in decay chains of currently pursued alpha-emitting radionuclides for therapy is primarily focused. Although principles of imaging modalities such as SPECT, PET, and Compton imaging are not described in any details, relevance of each imaging method to corresponding imageable signals is briefly described.

Imageable Signals from Alpha-Emitting Radionuclides

Terbium-149 (Tb-149), Astatine-211 (At-211), Bismuth-212 (Bi-212) (decayed from Lead-212 (Pb-212)), Bi-213, Radium-223 (Ra-223), Actinium-225 (Ac-225), and Thorium-227 (Th-227) (in the order of atomic weights) are alpha-emitting radionuclides with some favorable properties that are considered for developing TAT applications [1, 3, 4]. There are certainly more than these radionuclides that are alpha-emitters, and could be used for TAT; however, for this article, let us focus on the aforementioned radionuclides that have been reported more or less extensively in the literature.

Favorable properties of alpha-emitting radionuclides like these are mostly governed by their half-lives which should not be too short (e.g., minutes or seconds) or too long (e.g., more than a month) since the molecules that are used in conjunction with these radionuclides for TAT need time to

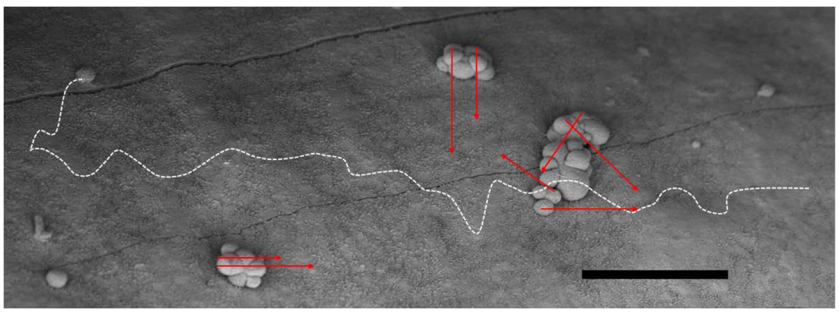

Fig. 1 A scanning electron microscopy image of micrometastatic clusters from ovarian cancer on the peritoneal lining (mouse). The red arrows indicate the range of alpha particles (here 50–70 μm) and the white arrows indicate the range of beta particles (here ~ 700 μm). This figure was originally in [1] and used under Creative Commons Attribution License (CC BY)

accumulate and wash out. The lessons from Ra-223 dichloride ($^{223}RaCl_2$) alpha therapy being safely used and administered are very encouraging since handling of these alpha-emitting radiopharmaceuticals could be complex since there are many daughter radionuclides from the mother, and, during the decay processes, there are many emissions of alphas, betas, and gammas/x-rays. Alphas and betas are relatively easier to block or shield since the range is limited from microns to a few centimeters maximum through normal matter (e.g., water, plastic, etc.); however, gammas and x-rays produced during the decays of alpha emitters are typically in high energy, and not very easy to block. Safety concerns for these radionuclides are often alleviated by the low level of activity required for TAT.

From another perspective, these gammas and x-rays are the photons that are imageable and could be used as tracking tools of where the alpha-emitting radiopharmaceuticals are distributed. And, most of these photons are in some sense imageable using conventional gamma cameras. By the way, imageable signals could be alphas and betas themselves if we define imaging as reconstruction of signal origins in a geometric spatial coordinate, and direct detection of alphas and betas in close proximity with implantable measurement device is possible. Table 1 summarizes imageable photons and positrons that contribute to producing imageable 511 keV annihilation photons from the alpha-emitting radionuclides of current interest in TAT. For gamma/x-ray emission, the photons that are greater than 50 keV, less than 1 MeV, and greater than 5% intensity are shown. Important alpha and beta emissions (greater than 5% intensity or one or two most abundant) are also noted. This table could be used as an important dataset for investigating which imaging modality can be paired up with designed alpha-emitting radiopharmaceutical to track where the radiopharmaceutical distributes and how to develop quantitative method by improving collimators, energy windows, and detectors for gamma imaging as well as energy windows and detectors for PET imaging.

Assuming all daughter radionuclides still remain at the target site, imageable signals from daughter radionuclides can be used for imaging as well. This scenario is applicable to all of the alpha-emitting radionuclides listed in Table 1, but At-211.

Table 2 summarizes properties of important radioactive daughters of these alpha-emitting radionuclides that can be tracked or exhibit additional therapeutic effect in addition to their mothers assuming that the whole radiopharmaceutical is retained at the target (i.e., no recoiled daughters leaving the target site). For the example of Ac-225 which does not have its own imageable gamma, x-ray, or positron emission, several daughter radionuclides (Fr-221, Bi-213, and Tl-209) have gamma emissions that can be captured by gamma cameras [5]. Although the off-target toxicity by the radioactive daughters if they leave the target site is not negligible [6], it is beyond this review's scope, and there are active developments of ensuring the retention of alpha-emitting radiopharmaceuticals at the target by encapsulation of the radionuclide within a tight structure such as nanocarriers [7–9], utilizing rapid internalization [10, 11], local administration [12], etc. [13]. As in Table 1, for gamma/x-ray emission, the photons that are greater than 50 keV, less than 1 MeV, and greater than 5% intensity are shown. Important alpha and beta emissions (greater than 5% intensity or one or two most abundant) are also noted. On this list, Pb-212 that is actually a beta emitter is included because it decays ($T_{1/2}$ = 10.64 h) to Bi-212 which is a good alpha emitter and many radiopharmaceuticals developed for TAT are using Pb-212 for labeling so that the resulting decay scheme involves alpha emissions.

Since most of alpha-emitting radionuclide decay chains include high-energy charged particle emissions (i.e., alphas and betas), bremsstrahlung radiation exists. Unlike well-developed bremsstrahlung imaging techniques for a beta-emitting radionuclide, Y-90 [14–19], it is unclear how much of bremsstrahlung radiation of alpha-emitting radionuclides is imageable, and further investigation will be needed. Quantitative imaging of bremsstrahlung radiation requires a good combination of radionuclide collimator and gamma cameras [17–22]. For quantitative imaging of gammas, combined SPECT with x-ray computed tomography (SPECT/CT) will add great benefits for quantification [23]. For Tb-149, PET/CT will be a quantitative imaging tool by the same token with its position emission, a rarity for alpha-emitters [24]. Figure 2 shows microPET/CT imaging of ^{149}Tb-DOTANOC in a tumor-bearing mouse, clearly indicating a promising theranostic value of ^{149}Tb-based alpha-emitting radiopharmaceuticals.

Cerenkov luminescence imaging is an emerging imaging modality for TAT [25], and a very useful imaging method for small objects or close proximity of measurement is possible. Decay chains of Tb-149 [26], Pb-212/Bi-212 [25, 26], Bi-213 [25], Ra-223 [26, 27], Ac-225 [25, 28], and Th-227 all include high-energy beta emissions (electrons and positrons), and these radionuclides can potentially be imaged by Cerenkov imaging methods.

Finally, several alpha-emitting radionuclides such as Ra-223, Ac-225, and Th-227 have half-lives greater than a week or longer; thus, the amount of activity administrable or the desired amount (when pretherapy dosimetry data are available or trial-based empirical dose estimation is possible) is really low, implying that imaging of any photons will be practically challenging, and feasibility of practical imaging for the amount of time needed and development of high-sensitivity imaging device better be further investigated.

Surrogate Imaging Radiopharmaceuticals for TAT

Somewhat too generalized concept of theranostics (therapy + diagnostics) may have led to inadequate attention to imaging of therapeutic radiopharmaceuticals themselves if we limit the

Table 1 Alpha-emitting radionuclides of clinical interest, and their imageable gammas and x-ray photons and positrons, β+ (via annihilation to two 511 keV photons) that are italicized. All imageable radioactive daughters are also italicized

	Half-life	α energy (% intensity)	β+/− energy (% intensity)	γ/x-ray energy (% intensity)	Radioactive daughters
Tb-149	4.118 h	3.967 MeV (16.7%)	*β+ = 200.1–1107.2 keV (7.1%)*	*γ = 164.98 keV (26.4%)* *352.24 keV (29.4%)* *388.57 keV (18.4%)* *464.85 keV (5.65%)* *652.12 keV (16.2%)* *817.1 keV (11.6%)* *853.43 keV (15.5%)* *861.86 keV (7.5%)*	Gd-149 Eu-149 *Eu-145* Sm-145 Pm-145
At-211	7.214 h	5.8695 MeV (41.8%)		*x-ray = 76.86 keV (12.4%)* *79.29 keV (20.7%)*	Po-211 Bi-207
Bi-212	60.55 m	6.05078 MeV (25.13%) 6.08988 MeV (9.75%)	β− = 130.1–834.2 keV (64.06%)	*γ = 727.33 keV (6.67%)*	*Pb-212* (mother) Po-212 *Tl-208*
Bi-213	45.61 m	5.558 MeV (0.181%) 5.875 MeV (1.959%)	β− = 24.6–492.2 keV, 97.8%)	*γ = 440.45 keV (25.94%)*	Po-213 *Tl-209* Pb-209
Ra-223	11.43 d	5.5498 MeV (9%) 5.60673 MeV (25.2%) 5.71623 MeV (51.6%) 5.747 MeV (9%)		*γ = 154.208 keV (5.7%)* *269.463 keV (13.9%)* *x-ray = 81.069 keV (15%)* *83.787 keV (24.7%)*	*Rn-219* Po-215 Pb-211 *Bi-211* Tl-207 Po-211
Ac-225	10.0 d	5.732 MeV (8%) 5.7906 MeV (8.6%) 5.7925 (18.1%) 5.830 MeV (50.7%)			*Fr-221* At-217 *Bi-213* Po-213 *Tl-209* Pb-209
Th-227	18.697 d	5.7088 MeV (8.3%) 5.75687 MeV (20.4%) 5.97772 MeV (23.5%) 6.03801 MeV (24.2%)		*γ = 235.96 keV (12.9%)* *256.23 keV (7%)* *x-ray = 50.13 keV (8.4%)*	*Ra-223* *Rn-219* Po-215 Pb-211 *Bi-211* Tl-207 Po-211

imaging (diagnostic) part of radiopharmaceutical to a paired radiopharmaceutical that exhibits very good imaging properties. This approach, most often Ga-68 and Lu-177 or Ac-225 pairs, works very well when the imaging (e.g., PET imaging of ^{68}Ga-labeled radiopharmaceutical) is used for therapeutic target verification, and the therapy using therapeutic radiopharmaceutical (e.g., Lu-177 for beta therapy or Ac-225 for alpha therapy) is administered with only empirically-based fixed amount of activity and multiple cycles of therapies. Not only for Ga-68, F-18 and Tc-99 m are also very popular imaging radionuclides for the surrogate radiopharmaceutical development. ^{123}I- and ^{124}I-metaiodobenzylguanidine (MIBG) imaging using SPECT and PET [29–33], respectively, which could be also good surrogates to meta-^{211}At-astatobenzylguanidine (MABG) [34] targeted alpha therapy, are another interesting approaches. One problem with this surrogate imaging approach is that dosimetry information for therapeutic radiopharmaceuticals from imaging radiopharmaceuticals is not directly possible. However, it should be also noted that surrogate imaging radiopharmaceuticals still can be very useful and may be developed as adequate dosimetric tools if biokinetic information derivable from imaging radiopharmaceuticals can be matched or correlated with radiation doses delivered by therapeutic radiopharmaceuticals. Further studies in this line of development are required to realize the full potential of imaging and therapy pairs of radiopharmaceuticals.

Conclusion

Quantitative imaging of alpha-emitting radiopharmaceuticals could be used in tracking these radiopharmaceuticals over time, and direct noninvasive imaging of most alpha-emitting radiopharmaceuticals needs significant development. By

Table 2 Important radioactive daughters of alpha-emitting radionuclides. By the way, Pb-212 is a radioactive mother of Bi-212. Their imageable gammas and x-ray photons are italicized. All imageable radioactive daughters are also italicized

	Half-life	α energy (% intensity)	β+/− energy (% intensity)	γ/x-ray energy (% intensity)	Decay chain of
Eu-145	5.93 d		*β+ = 345.0 keV (0.37%)* *740.1 keV (1.54%)*	*γ = 653.512 keV (15%)* *893.73 keV (66%)*	Tb-149
Po-211	0.516 s	7.4503 MeV (98.916%)			At-211
Pb-212	10.64 h		β− = 93.5 keV (83.1%) 171.7 keV (11.9%)	*γ = 238.632 keV (43.6%)* *x-ray = 74.815 keV (10.28%)* *77.107 keV (17.1%)*	Bi-212
Po-212	0.299 μs	8.78486 MeV (100%)			
Tl-208	3.053 m		β− = 441.53 keV (24.2%) 535.39 keV (22.2%) 649.48 keV (49.1%)	*γ = 277.371 keV (6.6%)* *510.77 keV (22.6%)* *583.187 keV (85%)* *860.557 keV (12.5%)*	
Po-213	3.72 μs	8.376 MeV (100%)			Bi-213 and Ac-225
Tl-209	2.162 m		β− = 177.8–708.9 keV (99%)	*γ = 117.21 keV (76%)* *465.14 (95.4%)* *x-ray = 72.805 (5.66%)* *74.969 keV (9.4%)*	
Pb-209	3.234 h		β− = 197.5 keV (100%)		
Rn-219	3.96 s	6.425 MeV (7.5%) 6.5526 MeV (12.9%) 6.8191 MeV (79.4%)		*γ = 271.23 keV (10.8%)* *401.81 keV (6.6%)*	Ra-223 and Th-227
Po-215	1.781 ms	7.3861 MeV (99.9997%)			
Pb-211	36.1 m		β− = 160.2 keV (6.28%) 471.3 keV (91.31%)		
Bi-211	2.14 m	6.2782 MeV (16.19%) 6.6229 (83.54%)		*γ = 351.07 keV (13.02%)*	
Tl-207	4.77 m		β− = 492.5 keV (99.729%)		
Po-211	0.516 s	7.4503 MeV (98.916%)			
Fr-221	4.9 m	6.1263 MeV (15.1%) 6.341 MeV (83.4%)		*γ = 218.12 keV (11.4%)*	Ac-225
At-217	32.3 ms	7.0669 MeV (99.89%)			

understanding the imageable part of decay chains of alpha-emitting radionuclides, a strategy of quantitative imaging method can be developed. Since most of these radionuclides emit gammas or positrons sometimes with a significant amount, quantitative imaging using sensitive gamma cameras or PET in some cases (e.g., Tb-149) is certainly possible; however, its practical method and feasibility will require carefully designed evaluation schemes, and may require less conventional medical imaging modalities such as Compton imaging and Cerenkov imaging.

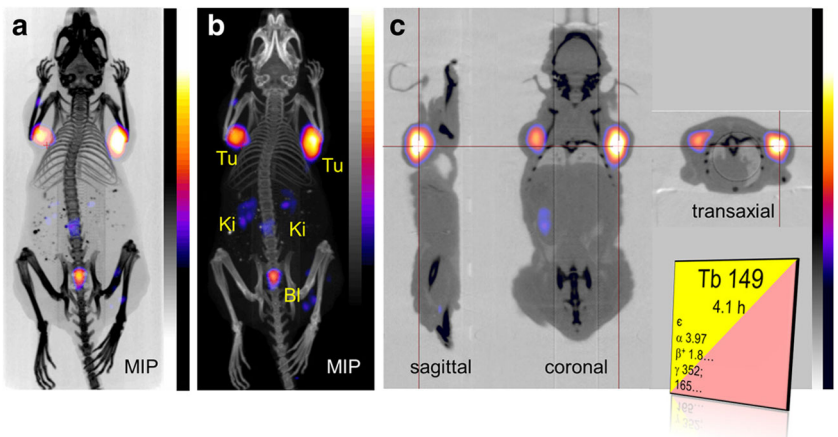

Fig. 2 MicroPET/CT images of ^{149}Tb-DOTANOC (7 MBq) injected to a tumor-bearing mouse (rat pancreatic acinar carcinoma cell line AR42J). **a**–**b** Maximum intensity projections (MIPs), **c** orthogonal cross-sectional views of tumors with high uptake of ^{149}Tb-DOTANOC. This figure was originally in [24] and used under Creative Commons Attribution 4.0 International License (CC BY 4.0)

Compliance with Ethical Standards

Conflict of Interest Youngho Seo declares that he has no conflict of interest. This work was supported in part by the National Cancer Institute under grant R01CA154561 and the National Institute of Biomedical Imaging and Bioengineering grant R01EB026331.

Ethical Approval This article does not contain any studies with human participants or animals performed by the author.

Informed Consent For this type of study, formal consent is not required.

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