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METHODOLOGIC PERSPECTIVES

A Proposed Methodology to Select Radioisotopes for Use in Radionuclide Therapy

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SUMMARY: The *American Journal of Neuroradiology* has played a seminal role in the history of vertebral augmentation (VA). Because VA is increasingly being included in the multidisciplinary management of malignant vertebral compression fractures (VCFs), combined therapeutic approaches that include strategies to treat metastatic disease along with the fracture have become appealing options for patients. To that end, we recently investigated the dosimetric feasibility of treating malignant VCFs with radionuclide therapy. The goal would be to provide local control of the systemic disease beyond the pain relief and structural support provided by polymethylmethacrylate cement. The purpose of this article is to propose a methodology for evaluating radionuclides for use in radiation therapy that takes into account a number of factors including radiation characteristics, biochemical effects, production capacity, and safety. The goal of such a methodology is to introduce a systematic approach to selecting radionuclides in designing treatment regimens and future investigations and also to stimulate discussion and experimentation involving new radionuclides that may provide more effective treatments than the current isotopes in widespread use.

The *American Journal of Neuroradiology* (*AJNR*) has played a seminal role in the history of vertebral augmentation (VA). In fact, the foundational paper on vertebroplasty by Jensen et al[1] is the second most highly cited article in its history, with 437 current citations, and it has also helped to develop percutaneous VA in the United States. Initially used in the treatment of osteoporotic compression fractures, VA or derivatives of the technique recently have been used more widely to treat multiple myeloma and metastatic disease. The current multisociety position statement, simultaneously published in 2 scientific journals including the *AJNR*, addressed this evolving paradigm. This position statement indicates that percutaneous VA is a "safe, efficacious, and durable procedure in appropriate patients with symptomatic osteoporotic and neoplastic fractures when performed in a manner in accordance with published standards."[2]

Although quality-of-life improvement is the major benefit of VA for both osteoporotic and neoplastic symptomatic vertebral compression fractures (VCFs), the pathophysiology of the compression fractures is somewhat different between the 2 types. Unlike osteoporotic VCFs, malignant VCFs have the added burden of residual tumor cells within the vertebral body. Although polymethylmethacrylate (PMMA) cement affords mechanical stabilization, it does not contribute to control of the tumor cells in the vertebral body. Because VA is increasingly being included in the multidisciplinary management of malignant VCFs, combined therapeutic approaches that include strategies to treat metastatic disease along with the fracture have become appealing options for patients.

To that end, we recently investigated the dosimetric feasibility of treating malignant VCFs with radionuclide therapy. The goal would be to provide local control of the systemic disease beyond the pain relief and structural support provided by PMMA cement. A computer radiation transport simulation was performed in which PMMA was mixed with 1 of 6 radioactive isotopes, and dosimetric distributions of the radioactivity were measured after injecting a bolus of the infused cement into a simulated bone phantom.[3] The isotopes chosen for the investigation were selected on the basis of their limited range in bone and minimal self-absorption within the bolus. The radiologic characteristics of each of the 6 isotopes selected were well described and readily available when making the selections of the specific isotopes to use, as summarized in the Table.

There was a relative dearth of information, however, regarding other aspects of radioisotopes that could be considered essential in determining radionuclide suitability, including individual energy profiles, delivery methods, or production capacities of isotopes that are not routinely used for radiation therapy. With additional information regarding alternative options for radioisotopes, our consideration process would be broader and more comprehensive when selecting the most suitable nuclides to use for experimentation and treatment.

Given the long-standing and increasing interest in radionuclide therapy in general, there continues to be a greater number of investigations using radionuclide therapy, along with information regarding isotope selection and delivery options.[4] Treatment designs similar to ours would benefit from a comprehensive systematic consideration of all possible radionuclidic characteristics, to select isotopes for experimentation and treatment that best fit the therapeutic need of both clinician and patient.

Because the neuroradiology community includes many leaders in the field of VA, neuroradiologists are well positioned to consider advancing combination radionuclide therapy within the PMMA cement. The purpose of this article is to propose a methodology for evaluating radionuclides for use in radiation therapy that takes into account a number of factors including radiation characteristics, biochemical effects, production capacity, and safety. The goal of such a methodology

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Summary of the radiologic characteristics for the isotopes studied in Hirsch et al[3]

Radioisotope	$T_{1/2}$	Decay Mode	Decay Summary
^{32}P	14.29 days	$\beta-$	E_{avg} = 694 keV, E_{max} = 1710 keV, $(R_{csda}^{max})^{bone}$ = 4.75 mm
^{166}Ho	26.8 hours	$\beta-$	E_{avg} = 666 keV, E_{max} = 1854 keV, $(R_{csda}^{max})^{bone}$ = 5.20 mm
^{90}Yb	64.1 hours	$\beta-$	E_{avg} = 934 keV, E_{max} = 2284 keV, $(R_{csda}^{max})^{bone}$ = 6.51 mm
^{125}I	59.3 days	ε	E_{avg} = 28 keV, Y_γ = 159.6%
^{18}F	110 mo	$\beta+$	E_{avg} = 633.5 keV, E_{max} = 249.8 keV, $(R_{csda}^{max})^{bone}$ = 1.0 mm; produces 511 keV annihilation photons, Y_γ = 96.73%
^{99m}Tc	6.01 hours	IT	E_{avg} = 131 keV, Y_γ = 96.5%

Note:—^{32}P indicates phosphorus-32; ^{166}Ho, holmium-166; ^{90}Yb, yttrium-90; ^{125}I, iodine 125; ^{18}F, fluorine-18; ^{99m}Tc, technetium-Tc99m; ε, low energy photon; $T_{1/2}$, half-life; IT, mid energy photon; E_{avg}, average energy; E_{max}, max energy; $(R_{csda}^{max})^{bone}$, continuous-slowing-down-approximation of maximum range in bone; Y_γ, gamma photon yield.

is to introduce a systematic approach to selecting radionuclides in designing treatment regimens and future investigations and also to stimulate discussion and experimentation involving new radionuclides that may provide more effective treatments than the current isotopes in widespread use. This article was written for the nonradiation specialist for greater awareness of the thought process that radiation oncologists and physicists use when selecting an appropriate isotope for clinical use.

Background

Radionuclide therapy, in which the radioactive source is inserted inside or in close proximity to the tissue being treated, offers many potential advantages over external beam radiation therapy, including fewer treatment visits and lower rates of morbidity to normal tissue due to the proximity of the radioactive source to the target tissue. The first radionuclide used in this manner was radium-266 (^{226}Ra), used to treat a multitude of interstitial, intracavitary, and surface pathologic lesions. The advent of multifield external beam radiation therapy, coupled with the potential of radium for accidents and very costly decontamination projects, led radium-based therapy to fall out of favor after World War II.[5] This led to an investigation of new radionuclides and new delivery methods that would help lower toxicity to normal tissues and protect providers from radiation exposure during administration of the isotope. Substitute radionuclides that offered an improvement of these toxicities included cobalt-60 (^{60}Co), cesium-137 (^{137}Cs), and iridium-192 (^{192}Ir).[6] These radionuclides generally possessed the following:

1) A high specific activity, meaning a high rate of radiation emissions per unit mass of the radionuclide.

2) A low-photon energy, necessary for protection of surrounding normal tissue and of health care providers. Low-photon energies also allow flexibility of dose distribution.

3) An appropriate half-life for the type of implantation.

Since the initial departure from radium, there has been little variance in the selection of isotopes used for radiation therapy. Even as delivery methods have been enhanced and safety has increased, most radiation therapists have continued to rely on a limited list of radionuclides that has become unquestionably established as the extent of treatment options. There are potentially hundreds of radionuclides that could meet the criteria of the radium successors and may provide as good or better treatment profiles than those radionuclides in widespread use. To unearth these hidden sources and to better characterize the commonly used sources, one needs to consider several pieces of information before a radionuclide can be determined "suitable" for the therapeutic need. The individual requisites that determine overall suitability are depicted in Fig 1.

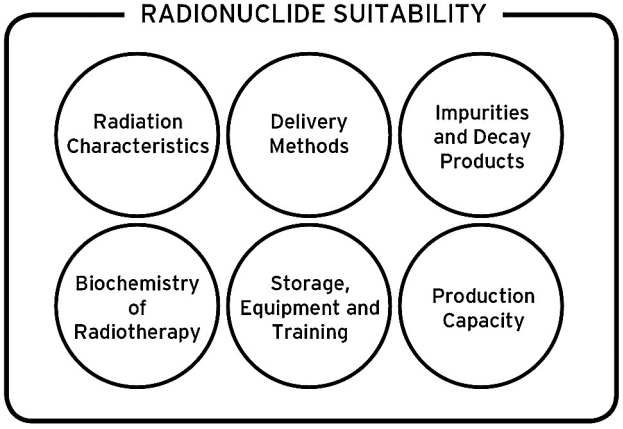

Fig 1. The factors influencing the suitability of a radionuclide for use in radiation therapy.

Radiation Characteristics

The selection of an optimal radionuclide for therapy requires one to identify an ideal isotope with characteristics that meet the therapeutic need of both the clinician and the patient. This problem is complex, taking into account the specific disease, the length of the treatment needed, the end goal of treatment, patient comfort and tolerance during treatment, and the relative efficacy of the treatment given the pathophysiology of the disease. As an example, the ideal radionuclide used in the treatment of various cancers depends on the need of interstitial-versus-intracavitary implants. Interstitial implantation involves the direct insertion of radioactive sources into tissue. It is the technique used most often when frequent implantation/removal procedures would be unsafe or impractical. Because interstitial implants are often permanent, the radionuclides selected for the implant usually have longer half-lives and lower energies (for example, Iodine-125 [^{125}I] and palladium-103 [^{103}Pd]) compared with other commonly used sources. These lower energy photon sources are less penetrating and therefore have a smaller volume of influence. They are better suited for permanent implantation in which a number of low activity sources can be implanted to better conform the radiation exposure to the treatment site.

Intracavitary implants, by contrast, are positioned in a body cavity in close proximity to the target tissue. This type of implantation is mostly reserved for treatment of tumors of the cervix, endometrium, nasopharynx, and esophagus. Because of the ability to remove the implants after treatment, the radioisotopes used for intracavitary implants have higher radiation energies (for example, ^{137}Cs and ^{192}Ir) to enable a single high-activity source to provide a more uniform radiation exposure to the treatment volume than a lower energy source.

As this example illustrates, therapeutic need requires a thorough consideration of radiologic characteristics of radioisotopes. Information regarding the energy levels, activity, and half-lives should be easily accessible and equally considered when choosing an isotope for radiation therapy. Traditionally, sources of information included radiation types and yields meant for safety purposes and often did not include information on radiation that was of little consequence from an external dosimetry standpoint. However, introduction of unshielded sources into the body gives greater importance to low-energy radiation, which must be considered in the therapeutic context.

Another point of variability among sources is the specific type of radioactivity. The radiation types that are currently in widespread use are mostly β and γ emitters, due to their long ranges and manageable energy levels. The α particle, or helium nucleus, is of a very high mass and high energy, with a very short range. In most instances, the α particle is considered unsuitable for radiation therapy because of its short range and the extensive damage it causes to tissue. In particular, it is unsuitable for vertebral augmentation treatment due to its short range in bone and PMMA cement. However, recent investigations have demonstrated that α emitters targeted to tumor cells with the use of antibodies and proteins offer the potential to limit the growth of a number of surface malignancies, solid tumors, and leukemias.[7,8] Further, because α particle radiation is of such a high energy, it is not subject to the normal resistance of hypoxic tissue as seen with external beam radiation. It is quite reasonable to assume that α particles will play a bigger role in future radioisotope therapies.

Delivery Methods

The form by which the source will be delivered to the treatment site can also influence radioisotope selection. There have been numerous manipulations of radioactive sources that have increased tissue specificity and minimized collateral radiation to both normal tissues in the patient and to health care staff. These enhancements have included coupling nuclides to antibodies[9,10] and bone localizing agents[11] to ensure proper tissue localization. The practice of using an afterloading device, in which an empty applicator is inserted into the treatment site before the radioactive source, has also been very effective at reducing unnecessary exposure. Finally, there is perhaps no better illustration of how delivery methods can influence radionuclide selection than a discussion of the use of sealed sources.

Sources used in therapy may be obtained in a sealed or unsealed form. Radioactive sources are considered "sealed" when the radioactive material is encapsulated. Typically, these sources have a double wall encapsulation constructed of titanium or stainless steel. Manufacturers must meet sealed source specifications as outlined in ANSI/HPS N43.6–2007.[12] Unsealed sources, by their lack of encasement, present a number of safety concerns ranging from the biodistribution of the radionuclide in the body causing an unwanted dose to a patient's nontarget organs to the potential for radioactive contamination spreading to workers, the public, and facilities and equipment.

The shape, construction method, and material of a sealed source influences its radiation dose profile to surrounding tissue; therefore, the dose profile must be thoroughly understood before treatment planning. For most sealed sources, a significant amount of attenuation occurs within the radioactive material itself and by the encapsulating material. This self-attenuating property of sealed sources is most apparent in the isodose profile for ^{125}I sources, in which manufacturers have manipulated the shape of the encapsulating material to produce the most desirable dose profile surrounding the source, thereby optimizing dose delivery. Because of this, medical physicists use the concept of air kerma strength as a way to characterize source dosimetric output. By applying different thicknesses of wall material or by nonhomogeneous packing of the radioactive material into the capsule, one can achieve a nonuniform dose profile.

Other characteristics useful in defining the therapeutic potential of a radionuclide include the suitability of the isotope for use in novel delivery systems, including our use of radionuclide infused vertebral augmentation cement. The selection of radionuclides, therefore, should include consideration of whether a sealed or unsealed source is desired and whether there is the possibility of coupling unsealed sources to antibodies, peptides, ligands, or other materials to increase localization to specific cells or regions of the body. Characterizing radionuclides by their potential to be sealed/unsealed, coupled, or afterloaded would prove a valuable tool in the process of selection of radionuclides for radiation therapy.

Impurities and Decay Products

There also should be consideration of the impurities of the source being used. Sources may be contaminated with additional radioactive nuclides that are formed during the production of a desired source. These contaminants can cause a significant therapeutic burden and can often lead to unforeseen additional radiation doses.[13] The same additional radiation dose burden may be seen with daughter products of nuclides that have substantial half-lives and stay in the body. There is, however, the potential to use these characteristics of manufactured radioisotopes to work in synergy rather than in detriment to the treatment goals. Uusijärvi et al[14] proposed dividing radionuclides into groups on the basis of their dosimetric properties, so that this characterization could be taken into account when choosing radionuclides for specific therapeutic applications. Specifically, the authors found differences in the dosage delivered to normal tissue among different types of emitters because of photon contribution in addition to the charged particles they emitted. If the impurities, daughter products, and the associated additional radiation doses are well characterized, organized, and reported in a systematic way, then these characteristics could be additional parameters that indicate the use of one radionuclide over another.

Biochemistry

Behind the practice of radiation therapy is the concept of radiation-induced damage to malignant cells. The primary mechanism by which low-attenuation ionizing radiation sources, such as photon and β-emitting radionuclides, exert a biologic effect is through indirect damage to deoxyribonucleic acid (DNA) and other cellular constituents, including the mitochondria and cell membrane (though less so than the more radiosensitive nucleus). The mechanism through which these

damages are created is primarily through the formation of free radicals, particularly hydroxyl radicals formed from the radiolysis of water molecules. These free radicals then react with DNA and other critical molecules present within the cell resulting in their alteration. In addition, some cellular lesions are caused through ionizations created directly within the target molecules. The free-radical theory is supported by the fact that cells are more radiosensitive when irradiated in the presence of oxygen, which serves as a radiosensitizer. Oxygen binds with free radicals that have attached themselves to DNA and forms a highly stable organic peroxide, which makes permanent the DNA strand breakage resulting from free radical binding.[15] In addition, the radioresistance of dehydrated spores supports the important role for water in the cellular response to radiation.[16] It is thought that densely ionizing radiation particles, including neutrons and α particles, exert their cellular killing primarily through the creation of damage directly in target molecules, rather than via the formation of water radiolysis products.

Creation of damage to DNA results in the death of irradiated cells primarily through the formation of chromosomal aberrations that trigger mitotic catastrophe when cells attempt to traverse through the mitotic phase of the cell cycle. In addition, cells that have a pro-apoptotic tendency may die from apoptosis during interphase, either as a result of DNA damage or because of damage to the mitochondria or cell membrane. The subtleties that determine the differences in responses are not well characterized; however, it is likely that the response is dependent on the specific type of radiation, cell type, and dosage that a cell receives.

Given that the surrounding environment, the internal makeup of the cell, the type of radiation, and the dosage received are influential to the response that individual cells have to radiation, it is reasonable to assume that different radionuclides in different settings will have markedly different therapeutic effects. The selection of radiation therapy modalities requires that each of these biochemical characteristics be considered equally when defining and selecting an isotope to use for therapy. Furthermore, because only minute variations in energy or type of radiation will have significantly different effects on malignant cells, additional research is needed to investigate and characterize specific cellular responses and effects to individual radionuclides, with the ultimate goal of making this information accessible and comparable between many different possible isotope choices.

Storage, Equipment, and Training

The selection of radioactive sources must invariably take into account an institution's or individual's ability to use that source. This ability is based on several factors:

1) Transportation and storage.

2) Special equipment needed to administer or experiment with the source.

3) Training of the staff who will handle the source.

First, any special needs required to transport or store the source, such as its specific shielding requirements, and the legal or administrative certification required to accommodate those needs should be considered in advance before selecting a radioisotope. Radioactive sources, whether sealed or unsealed, must be placed into government-approved containers for shipping. The nature of the radioactive source (ie, sealed or unsealed) will dictate the design of shipping containers, handling and delivery of the radioisotope, and the emergency procedures that must be developed and practiced before the actual use of the material. Shipping containers for sealed sources are designed to contain the source in a rigid shielded assembly to meet shipping regulations with little concern for the potential release of radioactive contamination. However, unsealed sources may potentially cause radioactive contamination and require more substantial packaging and shielding. Shipping containers for unsealed sources have more rigorous requirements for structural integrity and must be able to sustain some amount of damage without releasing their contents. Emergency procedures for sealed sources include the recovery of loose sources by using special tools to minimize extremity exposures. Removal of the sources from the shipping container can only be performed by professionals specially trained in radiation safety. Emergency procedures for unsealed sources will include preventing the spread of radioactive contamination to workers and facilities/equipment, which may result in their becoming unusable for a period of time.

Furthermore, any concurrent equipment needed to effectively use the radioisotope for injections, infusions, afterloading, or surface treatments should be clearly identified and acquired. Finally, individuals who are responsible for handling and working with the source must be aware of the training requirements, hazards, and guidelines about specific isotopes. This information most importantly protects the safety of the workers but also affects the efficiency and the ability to start treating or experimenting with a source as soon as possible.

Although this information may be available in some way about all commercially available isotopes, what is lacking is its organization and accessibility. For efficient and thorough evaluation of all possible options for use in radiation therapy, the transport, storage, equipment, and safety/training profiles of all available isotopes should be collected, condensed, and organized into an easily accessible data base in which different radionuclide characteristics can be compared and contrasted; this will contribute to a more complete and appropriate selection process for the use of radionuclides in radiation therapy.

Production Capacity

An isotope that fits a therapeutic need may be of limited use if there is not a reasonable method of obtaining it. In the case of α emitters, the method of production of different isotopes varies widely. Bismuth-212 is relatively easily acquired through radium-224 generator systems,[17] whereas astatine-211 (^{211}At) normally requires the use of an accelerator to stage a reaction and bismuth is bombarded with helium ions.[18] Furthermore, the short half-life of ^{211}At requires that it be used near the source of production, severely limiting its usability. Tolmachev et al[19] cite ^{211}At as the "most promising therapeutic radionuclide" but note that there is a lack of production and distribution centers, contributing to its limited use. Despite these production limitations, novel approaches to isolate the ^{211}At product after irradiation have increased the yield and saved time,[20] which may contribute to increased availability and use. It is evident that a thorough consideration of all possible radionuclides to use in radiation therapy should address the most updated production capacities and cost of any radio-

active source that is or will be produced. These data could be used to support or discourage the use of certain radionuclides on the basis of their accessibility.

In the future, there is the potential for creating a demand for certain isotopes that are not currently in production. This is especially true of α emitters, which have not been sought on a large scale in the biologic sciences because of their high energy and low penetrability. As a result, there are virtually no commercial vendors that supply α-particle-emitting radionuclides. With enough investigators and clinicians willing to pursue the possibility of using α emitters, coupled with the knowledge of requirements for storage, transport, and training of staff, manufacturers might become willing and able to generate a larger pool of extremely beneficial α-emitting species.

Past Applications, Current Investigations, and Future Directions: Radionuclides in Interventional Radiology

The field of interventional radiology has set the pace in the translation of theory into the practice of radionuclide therapy. A wide variety of diseases have been experimentally treated with radionuclide therapy, most with encouraging results. Although the use of drug-eluting stents has been a popular approach, Minar et al[21] described the use of ^{192}Ir in the prophylaxis of restenosis after femoropopliteal angioplasty. Ricke et al[22] introduced a new technique of ^{192}Ir brachytherapy in the treatment of lung malignancy, and Zhang et al[23] have reported on the use of ^{125}I for the treatment of pancreatic cancer, hepatoma,[24] and pulmonary carcinoma,[25] whereas other groups have used the same radionuclide to treat metastatic lymph nodes, recurrent rectal cancer, and bone metastasis.[26-28] The most widely studied and supported application of radionuclide therapy in the field of interventional radiology, however, has been the use of yttrium-90 (^{90}Yb) microspheres in the treatment of hepatocellular carcinoma.

The liver is unique in that its tumors are relatively chemo-/radioresistant but have surrounding normal parenchyma that is unusually sensitive to the effects of radiation. External beam radiation in the treatment of unresectable carcinomas causes unnecessary amounts of damage to healthy tissue without achieving tumoricidal radiation doses. What is needed is a diffuse concentration of small radioactive sources that will localize to tumor and spare liver parenchyma. This provides a ripe environment for the practice of radioembolization with ^{90}Yb outlined by Andrews et al.[29] In their article, Andrews et al cite the profile of the tumor (increased arteriolar attenuation), the profile of ^{90}Yb (a pure β emitter with an ideally high energy with short range), and the choice of delivery material of the radionuclide as major guides in the development of the TheraSphere (MDS Nordion, Ottawa, Ontario, Canada) as a therapy for hepatocellular carcinoma. Specifically in regard to the evolution of the delivery vehicle, the previous use of resin and ceramic beads led to leaching of radioactive substance, which caused a significant increase in myelosuppression and pulmonary fibrosis among the treatment population. Glass infusion provided benefit of preventing the ^{90}Yb from leaching out into the circulation.[30-32] Feinendegen[33] expanded on the considerations that were taken into account when developing this therapy to include the following:

1) Stability of microparticles.

2) Choice of radionuclide bound to them.

3) Mode of delivery and subsequent exposure to normal tissue.

4) Optimization of embolization into the vasculature of the tumor.

More than any other analysis that has come before it, these considerations emphasize how important the delivery method of the agent is to the outcome of the therapy—often the "how" of the radiation therapy is as important as "which" radionuclide to use.

The use of ^{90}Yb beads in the treatment of hepatocellular carcinoma now is a widely established practice. Studies have documented a clear survival benefit and have shown that ^{90}Yb microsphere therapy contributes to the bridging of previously untreatable patients to surgical resection, ablation, or transplantation.[34] Future research should focus on multicenter randomized control trials to compare this treatment with what is considered the current standard of care for hepatocellular carcinoma.

This example illustrates the multifaceted nature of selection of radionuclides for therapy; the development of ^{90}Yb microsphere therapy required consideration of many of the proposed essential characteristics of radionuclides, including radiation characteristics, delivery, and biochemistry of the radiation on the specific tumor. To continue to investigate potential applications for radiation therapy at such an agile pace, interventional radiologists, neurointerventional radiologists, neuroradiologists, and other investigators would benefit from a more complete definition and organization of these characteristics, making for a more efficient and widespread translation of theoretic therapies into patient care.

Summary and Conclusions

The use of small mobile sources of radiation in the treatment of many conditions offers a unique and effective approach to the goal of combating disease while sparing the patient and clinician from unwanted detrimental effects. The efficacy of using radiation therapy with the source close to the target tissue in the treatment of a multitude of conditions is well established; however, the agents commonly used as radioactive sources have enjoyed undue exclusivity without being thoroughly characterized and compared with other isotopes. Recent advances in the field of interventional radiology have demonstrated a multifaceted consideration process in the development of radionuclide therapies, including characteristics of the radioactive source, the delivery methods, and the effect that a specific type of radiation has on a specific type of tumor. This multitiered approach has been extremely successful in developing a novel treatment for hepatocellular carcinoma and should be emulated in the future. The authors expect similar advances in the field of interventional neuroradiology.

Our study is a dosimetric example of the use of radionuclides in a novel approach of the treatment of metastatic VCFs and represents a trend of increasing interest and an increasing number of investigations using radionuclide therapy. To contribute to more effective investigations and treatment regimens, we propose that a data base of isotope characteristics be created, consolidated, and made easily accessible. As more experimental and practical data are gathered about each isotope, it will become possible to compare many isotopes across a

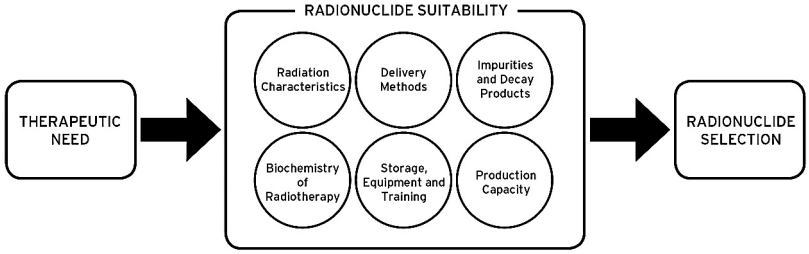

Fig 2. After defining the therapeutic need, the provider should use a well-organized collection of information that determines radionuclide suitability by evaluating numerous isotopic characteristics. This allows more informed radionuclide selection.

variety of parameters and to evaluate the results en route to making a radionuclide selection. The comprehensive process is illustrated in Fig 2.

This systematic consideration will help investigators and clinicians conduct a more thorough selection process for radionuclides with the goals of minimizing cost, eliminating waste, dampening patient side effects, and discovering new isotopes to use for future therapies.

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