Radionuclide Therapy

Recep Bekiş
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Editors

Springer

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Preface

Cancer, which is the disease of our age, continues to threaten human health at an increasing rate every day. Although standard methods such as surgery, chemotherapy, radiotherapy, and hormone therapy are among the ways to deal with this threat, newly developed biological treatments, targeted treatments, personalized treatments, external beam radiotherapy, and targeted radionuclide therapies have begun to take their place in professional practice. Therefore, cancer treatment is increasingly requiring special expertise. Nuclear medicine, in addition to its role as a tracer of cancer, also assumes the role of attack and treatment with radioactive molecules directed to the cancer it traces. These traceable next-generation radionuclide therapies, whose efficacy and reliability have been proven and where diagnosis, treatment, and follow-up are carried out together, are increasingly included in oncology practice with the new radiopharmaceuticals developed with each passing day. Traceable next-generation radionuclide therapies targeting cancer ensure a high rate of damage to cancer cells while protecting the surrounding normal tissues. Molecular cancer treatment will become more effective with individualized next-generation traceable radionuclide therapies, which will be shaped by genetic studies in the future.

Radionuclide therapies include treatment of hyperthyroidism and some joint diseases. Radioactive iodine therapy is a noninvasive treatment method that is an alternative to surgical and medical treatment in the case of hyperthyroidism and achieves good results. Radiosynovectomy is a minimally invasive radionuclide therapy method with a high treatment success used in patients with joint diseases who have not benefited from surgical and medical treatment.

This book was planned to be written due to the lack of sufficient resources in radionuclide therapies in Turkey. Radionuclide therapies for many cancer types and benign diseases were prepared and written by experienced nuclear medicine experts in the light of their own experience and case studies. Systemic treatments in common cancer types and side effect management of these treatments were summarized by medical oncologists. The main purpose of writing this book is to create a reference for the indications, contraindications, patient selection, treatment practice, treatment side effect management, and follow-up of radionuclide therapies.

We wish that the book will be beneficial to all physicians.
Best regards,

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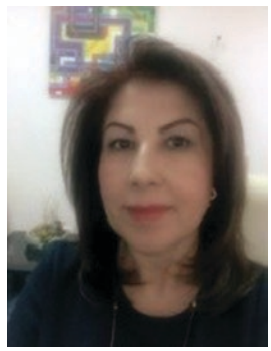

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Photographs of our physicians are sorted alphabetically.

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Part I

Basic Information

1 Basic Properties and Preparation of Radiopharmaceuticals Used in Radionuclide Therapy

Meltem Ocak

In nuclear medicine therapy, therapeutic radiopharmaceuticals are given to the patient and a therapeutic dose of ionizing radiation is sent to the disease areas in the body, thus providing treatment, control, or pain palliation of the disease. Damages caused by ionized radiation such as single or double-strand breaks in DNA play a role in the effectiveness of treatment. A therapeutic radiopharmaceutical is a drug that contains a radionuclide emitting particle radiation such as beta (β^-), alpha (α), and auger electron, which will provide the necessary ionization for bond breakdown [1]. Therapeutic radiopharmaceuticals may be present in ionic form, such as Iodine-131 (I-131) or Strontium-89 (Sr-89), or radiolabeled forms of ionic radionuclides with carrier molecules (non-radioactive part) such as peptides, proteins, and particles. The non-radioactive part is administered a small amount therefore they usually have no pharmacological effect. Therapeutic radiopharmaceuticals should have high specific activity (radioactivity/unit mass) and can be orally, intraarterially, intravenously, intratumorally, and intracavitary administered. Therapeutic radiopharmaceuticals should be specific to the disease (target), show high involvement in the target, have a high target/non-target tissue ratio, be quickly discarded from non-target tissues, and be able to stay long enough to provide effective treatment in the target.

Nuclear medicine therapy applications first started in 1936 with the use of Phosphor-32 (P-32), a cyclotron product, in the treatment of leukemia [2]. Toward the 1940s, the treatment of thyroid cancers started with ^{131}I-NaI. Today, all countries have access to radioactive iodine (^{131}INaI) treatment. With recent studies, the biochemistry of diseases started to be better understood therefore therapeutic radiopharmaceuticals targeted to different mechanisms are developed and their use is becoming common in clinical applications.

1.1 Development of Therapeutic Radiopharmaceuticals

The process of developing therapeutic radiopharmaceuticals includes multidisciplinary studies in many fields such as molecular biology, microbiology, chemistry, physiology, pharmacology together with some radiation physics. And chemists, pharmacists, microbiologists, veterinarians, radiation physicists, and nuclear medicine doctors should work together.

1.1.1 Target

The first step in the development of a new therapeutic radiopharmaceutical involves determining

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the target in the diseased area with appropriate biochemical mechanisms. The target could be a receptor or groups of receptors or antigens, or enzymes that are densely located in the diseased area. Ideally, the target should never be found in normal tissues. However, this is not the case in reality.

Therefore, the statistically high concentration of the target in the diseased area (tissues) compared to normal tissues increases the success of therapeutic radiopharmaceuticals.

1.1.2 Carrier Molecule

Once the appropriate target is identified, the selection of carrier molecules that carry the therapeutic radionuclides to the target (target-specific) should be defined-. Carrier molecules could be target-specific peptides, antibodies, small drug molecules, or enzyme inhibitors.

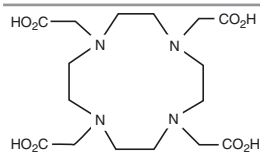
1.1.3 Radionuclide

The characteristics of therapeutic radionuclides can be evaluated according to their physical and biochemical properties [3]. While physical half-life, particulate radiation type and emitted energy, production method, radionuclide impurities, and decomposition products constitute the physical properties, biochemical properties consist of the capability of being targeted, staying on target, in vivo stability, and toxicity [4]. These features will be discussed in more detail in the following sections.

1.1.4 Radiolabeling

The chemical properties of the selected radionuclide play a major role in labeling the carrier molecule. Non-metallic radionuclides such as I-131 can be directly bound to the carrier molecule. Metallic radionuclides bind to the molecules by forming complexes with bifunctional chelates (DTPA, DOTA, NOTE, DOTAGA, etc.) conjugated to the molecule in a way that does not change the interest of the molecule in the target [5, 6]. The ionic state and size of radionuclide are very important in complex formation with bifunctional chelates. Concentration, chemical impurities, reaction pH, duration, and temperature of reactions are important parameters to obtain radiopharmaceuticals in high radiochemical purity and radiolabeling efficiency. Table 1.1 summarizes the ideal labeling conditions for radiometals used in DOTA-chelated therapeutic radiopharmaceuticals [6]. It should also be noted that the molecule (deterioration of the structure of DOTA-antibodies at high temperatures, etc.), which is in complex form with DOTA chelate, plays a major role in determining the radiolabeling conditions. Radiolabeling efficiency and radiochemical purities can be calculated using physicochemical techniques such as TLC (thin-layer chromatography) and HPLC (high-pressure liquid chromatography). Radiochemical purity tests to be performed for a certain period of time after radiopharmaceutical preparation also provide information about the stability of the radiopharmaceutical. Therapeutic radiopharmaceuticals are intended to remain stable in vitro and in vivo.

Table 1.1 Radiolabeling conditions of DOTA chelate with therapeutic radionuclides used in clinical applications (In-111: Indium-111, Lu-177: Lutetium-177, Y-90: Yitrium-90, Ac-225: Actinium-225, Bi-213: Bismuth-213)

Chelate	Radiometal	Radiolabeling conditions
	$^{111}In^{+3}$	37–100 °C, 15–60 min, pH 4.0–6.0
	$^{177}Lu^{+3}$	25–100 °C, 15–90 min, pH 4.0–6.0
DOTA, 1,4,7,10 Tetraazacyclododecane	$^{90}Y^{+3}$	25–100 °C, 15–90 min, pH 4.0–6.0
1, 4, 7, 10-tetraacetic acid	$^{225}Ac^{+3}$	37–60 °C, 30–100 min, pH 6.0
	$^{213}Bi^{+3}$	95–100 °C, 5 min, pH 4.0–6.0

1.1.5 Biological Assessment

Biological evaluation of therapeutic radiopharmaceuticals can be performed by in vitro and in vivo tests. In vitro tests often include serum stability studies and cell studies. Within the scope of cell studies, radioligand binding studies, radioligand internalization, and externalization studies are frequently performed. In addition, cytotoxic properties are also examined. Cytotoxic properties are frequently determined by cell viability studies. In vivo tests mostly include biodistribution and imaging (if the properties of radionuclide are appropriate). Appropriate therapeutic radiopharmaceuticals obtained as a result of in vitro studies are examined in healthy and diseased animal models. Therefore the pharmacokinetic properties of the therapeutic radiopharmaceutical and the radiation doses that different organs are exposed to are determined.

1.1.6 Toxicity Studies

Therapeutic radiopharmaceuticals may exhibit toxic properties due to both their radiation and carrier molecule. Radiation-induced toxic property is an important requirement in therapeutic radiopharmaceuticals. Radiopharmaceutical toxicity studies include both general toxicity studies (for the carrier molecule) and radiotoxicity studies. Radiotoxicity studies should be conducted for the target and other organs and tissues, usually involving studies to determine damage or necrosis occurring at the cellular dimension of radiation emitted from radionuclides. Since the general purpose of radiotoxicity studies is to determine the amount of live/dead cells, there are many methods applied to determine cell viability. These methods can be generally colorimetric, luminescent, and enzymatic.

1.2 Physical Properties of Therapeutic Radionuclides

In the preparation of therapeutic radiopharmaceuticals, radionuclides emitting various particular radiation (alpha, beta, auger electron) with different chemical properties, specific activities, and different physical half-lives are used. The success of therapy depends on the use of the suitable radionuclide for treatment. Although there are many radionuclides that can be used in treatment applications, very few of them are suitable in terms of nuclear, physical, and biological properties [7].

1.2.1 Particulate Radiation Emission

In nuclear medicine therapy, radionuclides emitting particular radiation such as beta, alpha, or auger electron, which cause cytotoxic effects due to their high LET (linear energy transfer) value, are used. The choice of radionuclide to be used for treatment depends on its LET value and the distance of progression within the tissue. Therapeutic radionuclides commonly used in nuclear medicine applications and their properties are shown in Table 1.2 [8–10]. Effective distance and relative biological activity of each particle emitted from radionuclide within the tissue are different from each other. The distance in the tissue of the radionuclide to be used in the treatment should be consistent with the size of the tumor or area to be treated.

1.2.1.1 Radionuclides Emitting Beta Particles

The maximum kinetic energies of radionuclides that undergo radioactive decay by emitting beta particles are between 0.3 and 2.3 MeV, and the distance is approximately 0.5–12 mm in soft tissue depending on their energy [11].

Their LETs are approximately 0.2 keV/μm [8]. The distance of beta particles in tissue is effective up to approximately 10–1000 cell distances compared to cell sizes. In addition, crossfire effects can also cause cytotoxic effects in non-target areas. This provides an advantage especially in the treatment of heterogeneous tumors [12]. Radionuclides emitting beta particles are effective in the treatment of medium and large masses, but the radionuclides to be used differ according to the size and localization of the mass [11].

Table 1.2 Frequently used therapeutic radionuclides (I-131: Iodine-131, Cu-67: Copper-67, Re-186 (188): Renium-186 (188), Ho-166: Holmium-166, Ga-67: Galium-67, Ac-225: Actinium-225, Th-227: Thorium-227, Ra-223: Radium-223)

Radionuclide [β^-], (LET:0.2 keV/μm)	$T_{1/2}$	Max β^- energy (keV)	Max. distance (μm)	Emission type
Y-90	2.7 days	2280.0	11.300	β^-
I-131	8.02 days	606.31	2300	β^-, γ
Lu-177	6.65 days	498.3	1800	β^-, γ
Cu-67	61.8 h	577	2100	β^-, γ
Re-186	3.7 days	1069.5	4800	β^-, γ
Re-188	17.01 h	2120.4	10.400	β^-, γ
Ho-166	26.6 h	1854.9	8700	β^-, γ
Radionuclide [auger], (LET:4-26 keV/μm)	$T_{1/2}$	**Max auger energy (keV)**	**Max. distance (μm)**	**Emission type**
In-111	2.80 days	26	17	Auger, γ
Ga-67	3.26 days	9.6	3	Auger, β^-, γ
I-125	59.4 days	32	20	Auger, γ
Radionuclide [α], (LET: 50–230 keV/μm)	$T_{1/2}$	**Max α energy (keV)**	**Max. distance (μm)**	**Emission type**
Bi-213	45.6 min	8400	90	α, β^-, γ
Bi-212	60.5 min	7800	100	α, β^-, γ
At-211	7.2 h	7500	80	α, EC
Ac-225	9.9 days	8400	90	α, β^-, γ
Th-227	18.7 days	7400	70	α, β^-, γ
Ra-223	11.4 days	5640	80	α, β^-, γ

1.2.1.2 Radionuclides Emitting Alpha Particles

Alpha particles progress at 50–100 μm levels in the tissue and their LET values are higher than those of beta particles (50–230 keV/μm) [8]. Cytotoxic properties are 100 times higher than beta particles. They are effective on small tumors and micro metastases. As long as auger electrons can pass through the cell membrane, they can only be effective on a cell-based basis. Few of the alpha particle emitting radionuclides among approximately 100 alpha particle emitting radionuclides can be used in nuclear medicine clinical applications. Many parameters such as half-life, decomposition products, chemical properties, energies, and availability play a role in the selection of alpha radiation emitting radionuclides [13]. Among the alpha radiation emitting radionuclides summarized in Table 1.3, Ac-225 is the most interesting radionuclide due to its successful applications in prostate cancer treatment in recent years [14].

Another feature to keep in mind regarding alpha radiopharmaceuticals is that other alpha-emitting radionuclides (defined as daughter radionuclides) formed by the decay of alpha radionuclides have different chemical properties and thus form unstable bonds with carrier molecules. As a result, alpha-emitting daughter radionuclides are quickly separated without binding to bifunctional chelates conjugated to carrier molecules [12]. In cases where the recoil energy exceeds 100 keV, the binding energy of radionuclide to the targeting molecule is exceeded and these released alpha radionuclides unnecessarily cause non-target organs to receive radiation and can cause serious problems in the long term. This issue is important for radionuclides that are decay by emitting multiple alpha particles, such as Ra-223 and Ac-225.

Table 1.3 Characteristics of alpha particle emitting radionuclides and decay products

Radionuclide	$T_{1/2}$	Main decomposition form	Energy (MeV)	Daughter radionuclides	$T_{1/2}$	Mode of decomposition	Energy (MeV)
Th-227	18.7 days	α	6	Ra-223	11.4 days	α, β^-, γ	
Ac-225	9.9 days	α	5.8	Fr-221	4.8 min	α, γ	7, 0.218
				At-217	32.3 ms	α	7
				Bi-213	45.6 min	α, β^-, γ	6, 0.444
				Po-213	4.2 μs	α	0.440
				Tl-209	2.2 min	β-	8
				Pb-209	3.5 hours	β-	0.659
				Bi-209	Stable		0.198
Ra-223	11.4 days	α	5.7	Rn-219	3.96 s	α	6.8
				Po-215	1.78 ms	α	7.4
				Pb-211	36.1 min	β-	
				Bi-211	2.13 min	α, β^-	
				Pb-207	Stable		
Bi-213	45.6 min	α, β^-, γ	6,0.444,	Po-213	4.2 μs	α	8
			0.440	Tl-209	2.2 min	β-	0.659
				Pb-209	3.5 hours	β-	0.198
				Bi-209	Stable		
At-211	7.2 h	α	5.9	Bi-207 Po-211 Pb-207	33.7 year 0.516 h Stable	β- α	

Radiolysis generally refers to the decay of the molecule due to radiation. Radionuclide emitting alpha particles during radiolabeling has a very high potential to produce radiolysis compared to beta-emitting radionuclides such as Y-90 or I-131. In order to prevent radiolysis, antioxidants such as ascorbic acid can be added to the reaction vial during or after radiolabeling [15].

Three different main strategies are mentioned in the preparation of alpha radiopharmaceuticals [16]. The first approach involves loading radionuclides into nano-carrier systems such as liposomes and nanoparticles. Small nanoparticles are rapidly removed from the body after involvement in the target, allowing non-target organs to be exposed to less radiation. The second approach involves rapid uptake of alpha radiopharmaceuticals into the tumor cell and rapid removal from non-target organs. This strategy ensures the administration of radiolabeled antibodies (radioimmunotherapy) and peptides (peptide receptor radionuclide therapy). The final approach is to administer alpha radiopharmaceuticals locally [16].

1.2.2 Physical Half-Life of Radionuclide

The physical half-life of radionuclide should be consistent with the biodistribution and clearance times of the radiopharmaceutical [17]. If the half-life of the radionuclide is too short, the radiopharmaceutical begins to decay before reaching the target tissue or cannot stay for the necessary time to provide effective treatment in the target tissue. On the contrary, when the half-life is too long, normal tissues are unnecessarily exposed to radiation. Radionuclides with a half-life of 1-14 days are generally considered appropriate for treatment [11].

1.2.3 Radionuclide Decay Products

Ideally, the decay product of therapeutic radionuclides is expected to be non-radioactive or a low-energy short half-life product [11].

1.2.4 Radionuclide Purity/Specific Activity

Radionuclides to be used for treatment purposes should be of high purity in terms of radionuclide, radiochemical, elemental, or chemical impurities. Production reactions and post-production purification methods are important factors in the purity of radionuclides. Low-specific radionuclides may be sufficient in the preparation of radiopharmaceuticals to be used in pain palliation in radiosynovectomy and bone metastases, while high-specific activity radionuclides should be used in the development of radiolabeled peptides or antibodies targeting limited amounts of receptors or antigens in the target region [18]. Thus, adequate treatment doses can be delivered to the target region without saturating the receptor or antigens in the target area. Non-carrier added (NCA) radionuclides are generally preferred in the preparation of radiolabeled peptides targeted at the receptor. Most NCA radionuclides are directly obtained from non-direct nuclear reactions in rectors or by the creation of a generator system of radionuclides with long half-lives [17].

1.2.5 Gamma Radiation

The fact that therapeutic radionuclides emit gamma radiation at optimal energy and abundance is advantageous in that it enables targeted radioactivity uptake and biokinetic calculations and contributes to the monitoring of treatment response and the determination of patient doses. In this case, although the use of radionuclides containing low density and appropriate energy gamma radiation is advantageous in terms of obtaining images, therapeutic radionuclides containing high energy and high-density gamma radiation cause unnecessary radiation to the patient [11].

1.2.6 Radionuclide Chemistry

Chemical properties of radionuclide such as its specific activity, radiochemical purity, and metal contamination content should be suitable for complex formation with a large number of molecules [11].

1.2.7 Economic Factors

Economically sustainable production of radionuclides suitable for radionuclide therapy is an important factor in the development and widespread applicability of therapeutic radiopharmaceuticals.

1.3 Production of Radionuclides

Radionuclides used in nuclear medicine therapy can be artificially produced by various nuclear reactions based on neutron bombardment in nuclear reactors or bombardment of particles loaded in accelerators (usually cyclotron). Alternatively, some therapeutic radionuclides can also be obtained from radionuclide generator systems. Today, research on the production and purification technologies of therapeutic radionuclides is ongoing intensively. According to the production method, carrier-added (CA) or NCA radionuclides are obtained.

1.3.1 Radionuclides Produced in Reactors

Since most radionuclides used in nuclear medicine therapy are rich in neutrons, they undergo beta decay and are generally produced in research reactors. Radionuclide production in nuclear reactors takes place by fission, fusion, neutron capture or activation and transmutation methods. Mo-99, I-131, and Xe-133 radionuclides are obtained by fission method and I-131 radionuclides are used for treatment purposes. Most other radionuclides used in nuclear medicine therapy are obtained by neutron activation or cap-

Table 1.4 Therapeutic radionuclides produced by different methods in reactors and potentially used in nuclear medicine applications

Radionuclide	T1/2	Target material	Mode of decomposition	Production method
Er-169	9.4 days	Er-168	β-	(n, γ)
Lu-177	6.65 days	Lu-176	β-, γ	(n, γ)
Lu-177	6.65 days	Yb-176	β-, γ	(n, γ) → β−
Ho-166	1.1 days	Ho-165	β-, γ	(n, γ)
Ho-166	1.1 days	Dy-164	β-, γ	(n, γ) (n, γ) → β−
P-32	14.3 days	P-31	β-	(n, γ)
P-32	14.3 days	S-32		(n, p)
Re-186	3.72 days	Re-185	β-	(n, γ)
Re-188	17 h	Re-187	β-	(n, γ)
Sm-153	2 days	Sm-152	β-	(n, γ)
Y-90	2.7 days	Y-89	β-	(n, γ)
Y-90	2.7 days	U-235	β-	(n, *f*)
Sr-89	53 days	Sr-88	β-	(n,γ)
I-131	8 days	Te-130	β-, γ	(n, γ) → β−
I-131	8 days	U-235	β-	(n, *f*)
Cu-67	2.4 days	Zn-67	β-, γ	(n, p)
Ac-225	10 days	U-233	α	U-233 decomposition product

ture method in nuclear reactors. Most commonly, the direct (n,γ) method is used. This reaction is based on the principle that the neutron sent to the nucleus is captured by the nucleus and a photon is emitted. The atomic number of the resulting radionuclide does not change, only the mass number increases, the main radionuclide has an isotope (CA radionuclide). In another used (n, p) reaction, the neutron emits a target nucleus proton and while the mass number of the newly formed radionuclide remains unchanged, a different product is obtained from the main nuclide (NCA radionuclide). The most known radionuclide obtained by this method is Cu-67 [19]. Table 1.4 summarizes the therapeutic radionuclides potentially used in nuclear medicine treatment applications.

1.3.2 Radionuclides Produced in Accelerators, Cyclotrons

In cyclotrons, radionuclides are neutron-deficient and thus degraded by electron capture (EC) or positron (β^+). In cyclotron, a positive charge is usually added to charged particles, and adding a positive charge to the nucleus changes the atomic number. Therefore, cyclotron products are usually NCA. Apart from electron capture or positron (β^+) emitting radionuclides in cyclotron centers, therapeutic radionuclides that emit alpha or beta can also be produced in some cases. Table 1.5 summarizes radionuclides that can be produced in cyclotron or accelerators and potentially used in nuclear medicine applications [20]. High-specific activity radionuclides are usually obtained using accelerators. Production of therapeutic radionuclides from cyclotrons is generally more costly than reactors due to reasons such as power requirement, operational costs, and obtaining products in low activities per production.

1.4 The Most Frequently Used Radionuclides for Therapy

Examples of radionuclides emitting beta or alpha particles that have recently been preferred for therapeutic use include Re-186, Re-188, Y-90, Ho-166, Lu-177, and Ac-225.

Table 1.5 Therapeutic radionuclides produced in accelerators or cyclotrons and potentially used in nuclear medicine applications

Radionuclide	T1/2	Mode of decomposition	Production method
Cu-67		EC	$^{70}Zn(p,\alpha)^{67}Cu$ $^{68}Zn(p,2p)^{67}Cu$ $^{78}Se(p,2n)^{67}Cu$
Rb-81	4.6 h	EC	$^{82}Kr\ (p,2n)^{81}Br$
In-111	2.8 days	EC	$^{112}\ Cd\ (p,2n)^{111}In$
Ga-67	78.3 h	EC	$^{66}Zn(p,n)^{67}Ga$
At-211	7.2 h	α	$^{211}Bi\ (\alpha,2n)^{211}At$
Ac-225	10 days	α	$^{226}Ra\ (p,2n)^{225}Ac$

1.4.1 Re-186

Re-186 can be produced in nuclear reactors or particle accelerators. They are obtained by Re-185 (n,γ) Re-186 reaction in nuclear reactors. Re-186 obtained by this method is CA. There are difficulties in obtaining Re-186 in high specific activity for use in antibody or peptide labeling in low neutron flux reactors. However, Re-186 obtained like that may be sufficient for the preparation of phosphonate derivatives and bone metastases for pain treatment, radiopharmaceutical preparation for use in radiosynovectomy or radioembolization. Since very few reactors in the world operate with high neutron flow, it is also desirable to obtain Re-186 with high specific activity in other ways. Although radionuclide production with nuclear reactors is appropriate in terms of quantity and unit price, cyclotrons remain the most suitable source for radionuclide production today. It is also possible to obtain NCA-added radionuclide in cyclotrons. In Re-186 cyclotrons, the proton or deuteron bombardment of the target material tungsten (W-186) is usually obtained by [W-186 (p, n) Re-186 or W-186 (d,2n) Re-186] [21].

1.4.2 Re-188

Re-188, unlike Re-186, can be produced in relatively higher specific activities by Re-187 (n,γ) Re-188 reaction in nuclear reactors, while W-188/Re-188 can be obtained in the center where it will be used more practically and economically than radionuclide generator systems. The biggest advantage of the generator system with a shelf life of more than 6 months is that it can give Re-188 without carrier in the form of Re-188-perrhenate and contribute to the development of various therapeutic radiopharmaceuticals [22]. These are summarized in Table 1.6 [23].

Table 1.6 Commercially available Re-188 generators and general specifications

Generator provider	Column material	W-188 Specific activity
ORNL,TN,USA	Alumina	148–185 GBq (4-5 Ci)/g
Dimitrovgrad, Russia	Alumina	185 GBq (5 Ci)/g
IRE, Belgium	Alumina	185 GBq (5 Ci)/g
ITG, Germany	Alumina	185 GBq (5 Ci)/g
Polatom, Poland	$^{99}Mo/^{99m}Tc$ generator column system	185 GBq (5 Ci)/g
IDB, Netherlands	Alumina	Unknown

1.4.3 Y-90

Y-90 is a radiometal that is widely used in treatment and is a pure beta emitter in +3 oxidation state [24]. To date, we find that it has most commonly been used in the treatment of hepatocellular carcinoma, radiosynovectomy, peptide receptor radionuclide therapy, and non-Hodgkin's lymphoma in nuclear medicine clinical applica-

Table 1.7 Radionuclide generator systems used and studied in clinical applications

Generator system	Production site of the main radionuclide		Parent radionuclide		Daughter radionuclide	
			$T_{1/2}$	Main decomposition	$T_{1/2}$	Main decomposition
$^{188}W/^{188}Re$	Reactor		69.4 days	β^-	17 h	β^-
$^{90}Sr/^{90}Y$	Reactor		28.5 year	β^-	2.7 days	β^-
$^{166}Dy/^{166}Ho$	Reactor		3.4 days	β^-	1.1 days$^-$	β^-
$^{225}Ac/^{213}Bi$	Decay chain		10 days	α	45.6 days	β^-, α
$^{227}Ac/^{223}Ra$	Reactor chain	Decay	21.7 year	β^-, then Th-227 via α	11.4 days	α

tions. Y-90 is obtained via direct neutron activation of Y-89 in the reactor. Usually, this method yields Y-90 with high radionuclide purity. However, it is not always possible to obtain Y-90 in high specific activities according to the characteristics of the reactor used. Alternatively, production based on the Zr-90 (n, p) Y-90 reaction is also carried out in the reactor to obtain a non-carrier added Y-90. One of the most important limitations in this type of production is the problems encountered in obtaining Zr-90 in the long term. Apart from the reactor, Y-90 is also obtained from Sr-90/Y-90 radionuclide generators [25]. The critical situation in the use of this system is that there are no reliable methods for purifying the mother radionuclide (Sr-90) loaded on the column material from the final product obtained. Sr-90 is a radionuclide that shows involvement in bones and is allowed to be administered to patients up to a maximum of 2μci to keep the radiation received by the bones at low levels [26]. Therefore, it is necessary to know the amount of Sr-90 in Y-90 content obtained from the generator. However, since both Y-90 and Sr-90 radionuclides emit pure beta and overlap in the beta spectrum, the methods that can be used today are insufficient in terms of sensitivity.

1.4.4 Ho-166

Ho-166 is a therapeutic radionuclide emitting two gamma radiations, one is 1379 keV (1.13%) and the other one is 80.6 keV (6.2%), with a maximum of 1854 keV (50%) beta particles. Gamma radiation at 80 keV is suitable for imaging with gamma cameras. Ho-166 is produced by two different methods. One method includes direct neutron activation of Ho-165 (n, γ), while the other includes non-direct neutron activation of Dy-164, i.e. Dy-164 (n,γ) Dy-165 (n, γ) Dy-166 (beta decay). The first method yields Ho-166 in low specific activity. Even if radiolabeled peptides or antibodies can be obtained with Ho-166 obtained by this method, there is a need for molecules labeled with Ho-166 with higher specific activity in high-dose therapies [9].

The shortness of Ho-166's half-life ($t_{1/2}$: 1.1 days) is a limiting factor in the distribution from the production site. As a solution to this situation, the prototypes of the Dy-166/Ho-166 generator system have been developed and further studies on more practical versions for use in clinical applications have not yet been carried out [27]. Table 1.7 summarizes the radionuclide generator systems used in clinical applications [27].

1.4.5 Lu-177

Although the use of Lu-177 in nuclear medicine therapy has become widespread with the treatment of neuroendocrine tumors for the last 15 years, we see that many antibodies labeled with Lu-177, enzyme inhibitors (Lu-177-PSMA, prostate cancer) are involved in clinical applications. The physical half-life of Lu-177 is similar to I-131, which is commonly used in radionuclide therapies. The biggest advantage of Lu-177 is that it can be produced in high amounts and transported to remote sites without losing too much activity due to their long half-life. Lu-177