21 Moving Forward: Expected Opportunities for the Development of New Therapeutic Agents

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21.1 Introduction

Radionuclide therapy was impossible before 1896 until the discovery of radioactivity by Henri Becquerel. The first attempts at radiotherapy were limited to the few radioactive elements available, namely, radium used first in 1913 to treat various diseases, and George de Hevesy using radioactive isotopes of bismuth-214 (^{214}Bi) and lead-210 (^{210}Pb) for the first tracer studies. The invention of the cyclotron by Ernest Lawrence in the 1930s ushered in a new era of abundance of novel radionuclides. In 1936, John H. Lawrence, the brother of Ernest, became the first person to use artificial radioactivity when he used phosphorus-32 (^{32}P) to treat a patient with leukemia. This was followed by Joseph Gilbert Hamilton and Robert Spencer Stone administering sodium-24 (^{24}Na) to a leukemia patient [1].

In 1941, the therapeutic isotope iodine-130 (^{130}I) was administered to a patient by Saul Hertz. This was shortly followed in 1946 with pioneers at the Massachusetts General Hospital treating a patient with thyroid cancer with iodine-131 (^{131}I), an "atomic cocktail." Iodine-131 and phosphorus-32 were used in therapeutic nuclear medicine for the next 74 years [2], but very few therapeutic radionuclides followed. Radiosotopes, which had shown such initial promise for treatment, became increasingly more interesting as new "diagnostic radiotracers", as new diagnostic scanners, gamma cameras, and then positron emission tomography (PET) scanners allowed the visualization of hitherto invisible physiologic processes in the intact human body. Nuclear medicine, which had started as a therapeutic discipline, quickly morphed into a primarily diagnostic modality and then as a branch of diagnostic imaging/radiology. Nuclear medicine, which by the 1970s had witnessed tremendous growth due to the arrival of myriad new radionuclides and had become a recognized separate medical specialty, suddenly became challenged by new diagnostic modalities of real-time ultrasound, computed tomography

(CT), magnetic resonance imaging (MRI), and interventional radiology. This lessened the appeal of radioisotopes, and interest of new medical school graduates in nuclear medicine declined. By 2015, a proposal to disband the American Board of Nuclear Medicine and merge it into the American Board of Radiology was proposed, although not approved [3].

In recent years, however, a renaissance in nuclear medicine therapies has been underway. Theranostics, the combination of "therapies and diagnostics," has entered the nuclear medicine vocabulary. The first theranostic had been iodine-131 in the 1940s for the diagnosis and treatment of thyroid cancer and hyperthyroidism. This was based on the unique properties of the thyroid gland, including differentiated thyroid cancers of the thyroid gland, to trap and organify iodine. No real competitor to radioiodine was developed for decades, although different iodine radionuclides were introduced, such as iodine-123 for imaging, iodine-124 for PET imaging, and iodine-125 for imaging and therapy in preclinical applications, and iodine-131 first for imaging and then for radiotherapies [4].

The understanding and discovery of novel molecular targets, beginning in the 1960s and 1970s, led to the use of somatostatin receptors (SSTR), prostate-specific membrane antigen (PSMA), or cell integrins. These new molecular targets could be pinpointed by ligands carrying novel therapeutic radionuclides such as lutetium-177 (^{177}Lu) and actinium-225 (^{225}Ac). The concept of theranostic pairs using the same targeting agent, such as gallium-68 (^{68}Ga) PSMA or fluorine-18-DCFPyL (2-(3-{1-carboxy-5-[(6-^{18}F-fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid), to image the target, then followed by [^{177}Lu]Lu-PSMA or [^{225}Ac]Ac-PSMA meant that on the molecular level, physicians could both "see what they treat and treat what they see" at the microscopic level. The introduction of 2-[^{18}F]fluoro-2-deoxy-D-glucose (2-[^{18}F]FDG) as a diagnostic PET agent, first in neurology and then in oncology and cardiology, began the era of molecular imaging. Unfortunately, 2-[^{18}F]FDG could not be used as a theranostic agent, since it targeted normal brain and heart, despite high level of uptake in tumors and infection, and the glucose molecule could not be labeled readily with any therapeutic radionuclide, although several attempts to do so were made.

The use of selective theranostic molecular pairs began earnestly in the 1970s with the realization that pheochromocytomas and neuroendocrine tumors could be targeted with meta-iodo-benzylguanidine (MIBG) using iodine-123 for imaging and iodine-131 for radiotherapy. Later, it was observed that many of these tumors also contained somatostatin receptors, which could be imaged first using [^{111}In]In-octreotide and then treated using much larger doses of [^{111}In]In-octreotide. [^{111}In]In-octreotide had limited success as a therapeutic, but was followed by the more powerful beta emitter yttrium-90 octreotide. Significant renal toxicity limited the use of [^{90}Y]Y-octreotide, which was supplanted with a newer agent [^{177}Lu]Lu-DOTATATE and [^{177}Lu]Lu-DOTATOC. The NETTER-1 trial (2017) showed improved survival compared to chemotherapy. Prostate cancer had been targeted beginning with [^{111}In]In-PSMA (ProstaScint) with little commercial success, but followed in this decade by [^{68}Ga]Ga-PSMA and novel [^{18}F]F-PSMA ligands, and most recently by PSMA therapeutics such as [^{177}Lu]Lu-PSMA, [^{213}Bi]Bi-PSMA, and [^{225}Ac]Ac-PSMA [5].

A plethora of novel molecular targets are now in preclinical and clinical development (Table 21.1). Once the molecular target is identified, a ligand can be developed to bind to the target. The ligand can be an antibody, a peptide, a nanoparticle, an aptamer or a pretargeting compound, a simple protein, or other constructs. The targeting ligand can then deliver a radiotherapeutic—which can be an alpha particle, beta particle, conversion, or Auger electron. The delivery can also be passive, by using a particle, colloid, or radiotherapy coating.

Whatever the tissue, specific molecular therapies are now emerging which will change the traditional diagnostic strategy. Rather than comparing nuclear medicine diagnostic studies

Table 21.1 Summary of new radiotheranostics in clinical trials or recently approved (adapted in 2019)

Radiopharmaceutical	Radioisotope	Major emission	E_{max} (keV)	E_{avg} (keV)	E_{main} γ component (keV)	Half-life	Production	Compound ± chelator	Type of compound	Cancer biomarker/ target	Therapy form	Clinical development phase	Indications
^{225}Ac (Actimab-A CD33)	Actinium-225	α	–	5830	99.8	10.0 d	Nuclear reactor/ cyclotron	HuM195	Monoclonal antibody	CD33	Targeted alpha therapy	Phase 2	Newly diagnosed patients with acute myelogenous leukemia over the age of 60
^{225}Ac (Actimab-A-CD33 and venetoclax)	Actinium-225	α	–	5830	99.8	10.0 d	Nuclear reactor/ cyclotron		Monoclonal antibody	CD33	Targeted alpha therapy	Phase 1	Relapsed/refractory acute myelogenous leukemia
^{225}Ac (Actimab-M-CD33)	Actinium-225	α	–	5830	99.8	10.0 d	Nuclear reactor/ cyclotron		Monoclonal antibody	CD33	Targeted alpha therapy	Phase 1	Multiple myeloma (penta-refractory) patients aged 18 and above
^{225}Ac (Actimab-MDS-CD33)	Actinium-225	α	–	5830	99.8	10.0 d	Nuclear reactor/ cyclotron		Monoclonal antibody	CD33	Targeted alpha therapy	Phase 2	Myelodysplastic syndrome (MDS); myeloablation prior to bone marrow transplantation for high-risk MDS patients
^{225}Ac-FPI-1434	Actinium-225	α	–	5830	99.8	10.0 d	Nuclear reactor/ cyclotron	FPI-1434	Monoclonal antibody	Insulin-like growth factor-1 receptor (IGF-1R)	Targeted alpha therapy	Phase 1	Multiple tumor types that express IGF-1R
^{225}Ac (Iomab-ACT)	Actinium-225	α	–	5830	99.8	10.0 d	Nuclear reactor/ cyclotron	Apamis-tamab-I-131	Monoclonal antibody	CD45	Targeted alpha therapy	Phase 1	Produce myeloablation to facilitate a bone marrow transplantation
^{225}Ac (Iomab-B-CD45)	Actinium-225	α	–	5830	99.8	10.0 d	Nuclear reactor/ cyclotron	^{131}I-BC8	Monoclonal antibody	CD45	Targeted alpha therapy	Phase 3 (SIERRA)	Myeloablation prior to bone marrow transplantation for patients over the age of 55 with relapsed or refractory acute myelogenous leukemia

^{225}Ac-DOTATOC	Actinium-225	α	–	5830	99.8	10.0 d	Nuclear reactor/ cyclotron	DOTATOC	Peptide	Somatostatin receptor subtype-2 (SSTR2)	Peptide target alpha therapy	First-in-human experience	Progressive/ metastatic neuroendocrine neoplasms
^{225}Ac-DOTAGA-SP	Actinium-225	α	–	5830	99.8	10.0 d	Nuclear reactor/ cyclotron	DOTAGA-SP	Peptide	Neurokinin-1 receptor	Peptide target alpha therapy	Clinical studies	Locoregional treatment of grade 2–4 gliomas
^{213}Bi-DOTA-SP	Bismuth-213	α	1390	425	441	45.6 min	Nuclear reactor	DOTA-SP	Peptide	Neurokinin-1 receptor	Peptide target alpha therapy	Clinical studies	Locoregional treatment of grade 2–4 gliomas
^{213}Bi-DOTATOC	Bismuth-213	α	1390	425	441	45.6 min	Nuclear reactor	DOTATOC	Peptide	SSTR2	Peptide target alpha therapy	First-in-human experience	Metastatic neuroendocrine neoplasms
^{213}Bi-DTPA-PAN-622	Bismuth-213	α	1390	425	441	45.6 min	Nuclear reactor	DTPA-PAN-622	Monoclonal antibody	Human aspartyl (asparaginyl) β-hydroxylase (HAAH)	Radioimmunotherapy	Pilot study	Metastatic breast cancer
^{213}Bi-HuM195	Bismuth-213	α	1390	425	441	45.6 min	Nuclear reactor	HuM195	Monoclonal antibody	CD33	Targeted alpha therapy	Phase 1	Myeloid leukemia
$^{64}CuCl_2$	Copper-64	β+, β–	580	560	–	12.7 h	Cyclotron	N/A	Small molecule	Human copper transporter 1 (hCTR1)	Molecular therapy	Clinical study for imaging	Potentially for prostate cancer
$^{64}CuCl_2$	Copper-64	β+, β–	580	560	–	12.7 h	Cyclotron	N/A	Small molecule	hCTR1	Molecular therapy	Preclinical	Potentially for tumors that express high levels of hCtr1, like melanomas and hepatocellular carcinomas
^{64}Cu-CB-TE2A-AS1411	Copper-64	β+, β–	580	560	–	12.7 h	Cyclotron	CB-TE2A-AS1411	Aptamer	Large nucleolin complex		Preclinical	Potentially for lung cancer
^{64}Cu-BAT-2IT-1A3	Copper-64	β+, β–	580	560	–	12.7 h	Cyclotron	BAT-2IT-1A3	Monoclonal antibody	Ephrin type B receptor 4 (EphB4)	Radioimmunotherapy	Phase 1/2 clinical study for diagnosis	Potentially for colorectal cancers

(continued)

Table 21.1 (continued)

Radiopharmaceutical	Radioisotope	Major emission	E_{max} (keV)	E-$_{avg}$ (keV)	E_{main} γ component (keV)	Half-life	Production	Compound ± chelator	Type of compound	Cancer biomarker/ target	Therapy form	Clinical development phase	Indications
^{64}Cu-DOTA-trastuzumab	Copper-64	β+, β−	580	560	–	12.7 h	Cyclotron	DOTA-trastuzumab	Monoclonal antibody	HER2+ and HER2−	Radioimmunotherapy	Clinical studies	Breast cancer (HER2+ and HER2−)
^{67}Cu (SARTATE™ kids)	Copper-67	β−, γ	600	141	186	2.58 d	Nuclear reactor/ cyclotron	DOTATATE	Peptide	SSTR2	Peptide receptor radionuclide therapy	Phase 2a (meningioma); phase 1-2a (neuroblastoma)	Neuroendocrine tumors, meningioma, neuroblastoma, and other children's cancers that express SSTR2
^{67}Cu (SAR-BBN)	Copper-67	β−, γ	600	141	186	2.58 d	Nuclear reactor/ cyclotron	BBN (bombesin)	Peptidomimetic	Gastrin-releasing peptide receptor (GRPR)	Peptide receptor radionuclide therapy	–	Prostate, breast, ovarian, small-cell lung cancers, glioblastoma, gastrointestinal stromal tumors, and tumoral vessels of urinary cancers
^{67}Cu (SAR-PSMA)	Copper-67	β−, γ	600	141	186	2.58 d	Nuclear reactor/ cyclotron	PSMA	Peptidomimetic	Prostate-specific membrane antigen (PSMA)	Peptide receptor radionuclide therapy	–	Metastatic prostate cancer
^{68}Ga-GRPR antagonists RM2 and NeoBOMB1	Gallium-68	β+, β−	1900	890	–	68 min	Generator	GRPR/RM2 and NeoBOMB1	Peptide	GRPR	Peptide receptor radionuclide therapy	Clinical studies	Currently under clinical evaluation in prostate cancer and gastrointestinal stromal tumor; potentially in estrogen receptor-positive breast tumors
^{68}Ga-GRPR antagonists × ^{68}Ga-PSMA analogs	Gallium-68	β+, β−	1900	890	–	68 min	Generator	GRPR/PSMA	Peptide × peptidomimetic	GRPR/PSMA	Peptide receptor radionuclide therapy	Clinical studies	Understand the role of each radiotracer in the management of prostate cancer patients

^{68}Ga-pentixafor/^{177}Lu/^{90}Y-pentixather	Gallium-68	β+, β–	1900	890	–	68 min	Generator	Pentixafor/ pentixather	Peptide	CXCR4	Peptide receptor radionuclide therapy	Clinical studies	Hematologic malignancies, such as multiple myeloma, leukemia, and non-Hodgkin's lymphoma, and in some solid cancers (e.g., lung cancer, adrenocortical cancer, and high-grade neuroendocrine neoplasms)
^{68}Ga-NODAGA-THERANOST™	Gallium-68	β+, β–	1900	890	–	68 min	Generator	NODAGA	Peptidomimetic	$\alpha_v\beta_3$ integrin receptor	Peptide receptor radionuclide therapy	Current clinical trials only for imaging/ diagnosisa	Potentially for glioblastomas, melanomas, myelomas, ovarian, breast, and prostate cancers
^{68}Ga-satoreotide trizoxetan (^{68}Ga-OPS202 or ^{68}Ga NODAGA-JR11)	Gallium-68	β+, β–	1900	890	–	68 min	Generator	OPS202/ NODAGA-JR11	Peptide	SSTR	Peptide receptor radionuclide therapy	Phase 1/2	Gastroenteropancreatic neuroendocrine tumor
^{68}Ga-OPS202 + Lutetium-177-OPS201	Gallium-68	β+, β–	1900	890	–	68 min	Generator	OPS202/ OPS201	Peptide	SSTR	Peptide receptor radionuclide therapy	Phase 1/2	Metastatic breast and small-cell lung cancers
												–	Cholangiocarcinoma and hepatic tumors
^{131}I-di-DTPA-indium hapten and hMN-14 × m734	Iodine-131	β–, γ	606	181	364	8.04 d	Nuclear reactors	DTPA-indium/ hMN-14 × m734	Monoclonal antibody	CEA	Radioimmunotherapy	Phase 1	Potentially for progressive medullary thyroid cancer, CEA-expressing tumors
^{131}I-TX101	Iodine-131	β–, γ	606	181	364	8.04 d	Nuclear reactors	TX101	Small molecule	L-type amino acid transporter (LAT-1)	Molecular therapy	Phase 1	Glioblastoma multiforme

(continued)

Table 21.1 (continued)

Radiopharmaceutical	Radioisotope	Major emission	E_{max} (keV)	E_{avg} (keV)	E_{main} γ component (keV)	Half-life	Production	Compound ± chelator	Type of compound	Cancer biomarker/ target	Therapy form	Clinical development phase	Indications
^{177}Lu-PP-F11N/^{111}In-CP04/1^{77}Lu-CP04/^{90}Y-CP04	Multiple	–	–	–	–	–	–	PP-F11N/ CP04	Peptide	Cholecystokinin 2 receptor	Peptide receptor radionuclide therapy	Clinical studies	Recurrent or metastatic medullary thyroid cancer
^{177}Lu-DOTA-F(ab')$_2$-trastuzumab	Lutetium-177	β–	497	140	208	6.65 d	Nuclear reactors	DOTA-F(ab')$_2$-trastuzumab	Monoclonal antibody	HER2+	Radioimmunotherapy	–	HER2-positive breast cancer
^{177}Lu-DOTA-PEG7-Tz	Lutetium-177	β–	497	140	208	6.65 d	Nuclear reactors	DOTA-PEG7-Tz	Monoclonal antibody	SSTR	Radioimmunotherapy	Preclinical	Pancreatic cancer
^{177}Lu-DOTA0-Tyr3-octreotate (^{177}Lu-oxodotreotide)[b]	Lutetium-177	β–	497	140	208	6.65 d	Nuclear reactors	DOTATATE	Peptide	SSTR	Peptide receptor radionuclide therapy	Phase 3 (NETTER-1)	Advanced, progressive, somatostatin receptor-positive midgut neuroendocrine tumors
^{177}Lu-DOTATOC (^{177}Lu-edotreotide)	Lutetium-177	β–	497	140	208	6.65 d	Nuclear reactors	DOTATOC	Peptide	SSTR	Peptide receptor radionuclide therapy	Phase 3 (COMPETE)	Inoperable, progressive gastroenteropancreatic neuroendocrine neoplasms
^{177}Lu-OPS201	Lutetium-177	β–	497	140	208	6.65 d	Nuclear reactors	OPS201	Peptide	SSTR	Peptide receptor radionuclide therapy	Phase 1/2	Inoperable or metastatic neuroendocrine neoplasms that overexpress somatostatin receptors
^{177}Lu-PSMA-617	Lutetium-177	β–	497	140	208	6.65 d	Nuclear reactors	PSMA-617	Peptidomimetic	PSMA	Peptide receptor radionuclide therapy	Phase 2	Advanced prostate cancer and positive uptake on PSMA imaging
^{177}Lu-TX250	Lutetium-177	β–	497	140	208	6.65 d	Nuclear reactors	TX250	Monoclonal antibody	Carbonic anhydrase IX(CA-IX)	Radioimmunotherapy	Phase 2a	Clear cell renal carcinomas

^{177}Lu-TX591	Lutetium-177	β–	497	140	208	6.65 d	Nuclear reactors	TX591 (derived from the huJ591 humanized mAb)	Monoclonal antibody	PSMA	Radioimmunotherapy	Phase 2a	Metastatic prostate cancers
^{212}Pb-DOTAMTATE	Lead-212	α	570	100	238	10.64 h	Nuclear reactors	DOTAMTATE	Peptide	SSTR	Peptide target alpha therapy	Phase 1	Metastatic neuroendocrine neoplasm
^{224}Ra (alpha DaRT®)	Radium-224	α	5690	–	241	3.66 d	Generator	N/A	Particle (seeds)		Diffusing α-emitters radiation therapy	Clinical studies	Squamous cell carcinoma of the head and neck, cutaneous and mucosal malignant neoplasia
^{188}Re-SCT® (ONCOBETA®)	Rhenium-188	β–, γ	2120	795	155	17.0 h	Nuclear reactor/ generator	Sterile precipitate of carrier	Nanocolloid		Epidermal radioisotope therapy	–	Basal and squamous cell carcinomas of the skin, and keloid
^{117m}Sn-DOTA-aminobenzyl	Tin-117m	ce	–	127–152	159	14.0 d	Nuclear reactors	Aminobenzyl-DOTA	Colloid	CD206 receptor	Radiosynoviorthesis	Phase 1/2	Canine and equine osteoarthritis, human rheumatoid arthritis, and other inflammatory conditions (such as atherosclerosis)
^{117m}Sn-DOTA-annexin	Tin-117m	ce	–	127–152	159	14.0 d	Nuclear reactors	Annexin V-DOTA	molecule	Phosphatidylserine (PS)	Endarterectomy	Phase 2	Treating vulnerable plaques
^{90}Y-DOTA-biotin	Yttrium-90	β–	2280	934	–	2.67 d	Nuclear reactors	DOTA-biotin	Monoclonal antibody	CEA, tenascin, and ep-CAM	Radioimmunotherapy	Clinical studies	Glioblastomas, anaplastic gliomas, and lymphoma
												Phase 3	Relapsed/refractory follicular non-Hodgkin's lymphoma

ce conversion electrons, *d* days, *min* minutes, *h* hours, *CEA* carcinoembryonic antigen, *CD* cluster of differentiation, *HER2* human epidermal growth factor receptor 2, *mAb* monoclonal antibody, *CXCR4* C-X-C chemokine receptor type 4

[a]Copper-64 and gallium-68 are radioisotopes used only for imaging

[b]Marketing authorization throughout the European Union

against traditional imaging modalities in terms of specificity or sensitivity, the standard by which most imaging modalities are judged, with a theranostic, it will simply be necessary and sufficient to know whether a molecular target is present or not, using a radiodiagnostic tracer. If the target is present, then the only determination is whether the proposed radiotherapy will be effective or not against this target.

This chapter will review the emerging new radiotherapies now in clinical trials or just emerging as novel radiotherapies.

21.2 Target Delivery for Imaging and Therapy

The evolving strategy in radiotherapy has been to couple a molecular ligand, which can be thought of as a missile, to a molecular target on the surface of a cell of interest (cancer cell, neuro-receptor, inflammatory cell) coupled to a "warhead"—either a diagnostic radionuclide for single photon emission computed tomography (SPECT) or PET imaging, or a therapeutic radionuclide (alpha, beta, or Auger emitter) for cell death (Fig. 21.1).

The strategy can be enhanced by pretargeting or choosing a target on the cell surface, where the ligand and radionuclide are internalized inside the cell. Increasingly, the term "theranostics" has evolved into the concept of a "theranostic pair"—one radionuclide for diagnosis and a similar radionuclide for therapy, ideally using the same ligand or "missile." The reference theranostic remains iodine-123 or iodine-124 for imaging thyroid cancer and iodine-131 for therapy. However, as mentioned, recent successes have centered around somatostatin ligands as the target, with [^{111}In]In-octreotide, then [^{68}Ga]Ga-octreotide, and [^{18}F]F-octreotide agents for imaging neuroendocrine tumors, and analogs of [^{177}Lu]Lu-DOTATATE or [^{225}Ac]Ac-DOTATATE for therapy. Similarly, recent success has been achieved with [^{68}Ga]Ga-PSMA or [^{18}F]F-PSMA for imaging prostate cancer and [^{177}Lu]Lu-PSMA or [^{225}Ac]Ac-PSMA or [^{213}Bi]Bi-PSMA for therapy of prostate cancer [6].

Ideally, as with thyroid cancer, the theranostic would be the same element and would differ only in whether it was used for diagnosis or therapy. Several "theranostic pairs" have been proposed, in addition to iodine.

21.3 True Theranostic Pairs

Table 21.2 represents some examples of theranostic pairs of metallic radionuclides.

The term theranostic is defined to "combine diagnostic and therapeutic capabilities into a *single* agent" where the entire molecular targeting

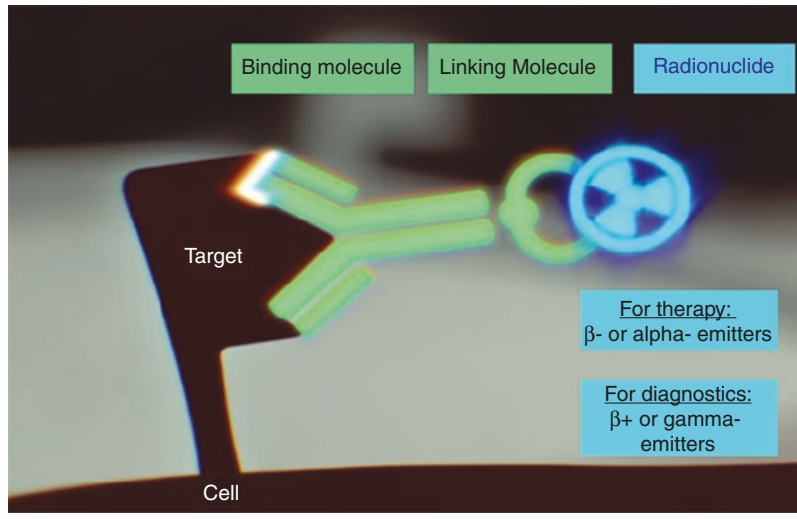

Fig. 21.1 Targeting strategy for theranostic agents

Table 21.2 Examples of theranostic pairs of metallic radionuclides

Radionuclide pair (imaging/therapeutic)	Half-life	Therapeutic particle	E_{avg} (keV)
Copper-64/copper-67	12.7 h/2.58 days	β^-	141
Iodine-124/iodine-131	4.2 days/8.04 days	β^-	181
Gallium-68/gallium-67	68 min/3.26 days	Auger/conversion electron	82–291
Scandium-44/scandium-47	3.97 h/3.35 days	β^-	162
Strontium-83/strontium-89	32.4 h/50.5 days	β^-	1460
Terbium-152/terbium-161	17.5 h/6.89 days	β^-	154
Yttrium-86/yttrium-90	14.7 h/2.67 days	β^-	934

compound, including the radioisotope, must be *chemically identical*. Apart from a few select isotope pairs noted above that interchangeably permit PET or SPECT and therapeutic applications (e.g., $^{86}Y/^{90}Y$), the use of a single element for diagnosis and targeted therapy has been impractical. Due to this difficulty, a pair of radiometals is often used. For example, DOTATATE, which is labeled with gallium-68 for diagnosis and lutetium-177 for therapy, is commonly considered to be a theranostic. Yet whereas the peptide-chelator is identical, the two isotopes differ in their chemistry. The affinity of [^{68}Ga]Ga-DOTATATE has been reported to be up to 20-fold higher than that of [^{177}Lu]Lu-DOTATATE. In human studies, these differences may account for noted discordance in lesion detection whereby lesions are revealed by one tracer but not the other, and vice versa [5, 7].

Similar discrepancies are observed with PSMA-617: in vitro, the affinity of the ^{68}Ga-chelate is twice that of the ^{177}Lu-chelate; in mice, tumor uptake values and tumor-to-non-tumor ratios differ substantially between the two chelates. Finally, for DOTA-PEG4-LLP2A, the Ki value of the ^{68}Ga-chelate is half that of the ^{177}Lu-chelate. To meet the challenge of designing a true theranostic agent, an attractive solution has been the production of "hot-cold/cold-hot" paired isotopologs (e.g., fluorine-18/natural lutetium and natural fluorine/lutetium-177) that are absolutely identical in *chemical* composition. In this scheme, a peptide designed for diagnosis is bound via chelation to a nonradioactive metal cation, also labeled with fluorine-18, whereas when designed for radiotherapy, the peptide is bound via chelation to unlabeled trifluorate and a radioactive metal cation. This concept expands the choices of radioactive therapeutic metals for treatment while simultaneously (1) allowing fluorine-18 to remain the isotope of choice for diagnostic PET, helping to alleviate the supply problems associated with gallium-68, and (2) preventing the dissimilarity in chelation chemistries arising from the use of two different radiometals for PET and therapy [7].

Going through various theranostic pairs, two elements that are of particular interest are scandium and terbium. Scandium has three radioisotopes for theranostic application. Scandium-43 (^{43}Sc) ($T1/2$ = 3.9 h) and scandium-44 ($T1/2$ = 4.0 h) are positron emitters and can be used diagnostically in PET imaging, while scandium-47 ($T1/2$ = 3.35 days) is a beta emitter, suitable for radiotherapy, but also has a 159 keV gamma emission suitable for SPECT imaging. Currently, scandium-44 is most advanced in terms of production, and with preclinical investigations, and has been employed in proof-of-concept investigations in patients. In PC-3 PIP/flu tumor-bearing mice, [^{44}Sc]Sc-PSMA-617 demonstrated high tumor uptake and fast renal excretion, similar to that of [^{177}Lu]Lu-PSMA-617. [^{44}Sc]Sc-PSMA-617 enabled distinct visualization of PC-3 PIP tumor xenografts shortly after injection. Due to the almost fourfold longer half-life of scandium-44, as compared to gallium-68, centralized production of [^{44}Sc]Sc-PSMA-617 would enable distribution to satellite PET imaging centers. Production of scandium-44 can be from titanium-44 (^{44}Ti) with its long half-life of almost 60 years, which provides a cyclotron-independent source of scandium-44 for several decades. Initial human studies with [^{44}Sc]Sc-DOTATOC PET-CT imaging of soma-

tostatin receptor-positive liver metastases in a patient at 40 min postinjection demonstrated comparable findings to [^{68}Ga]Ga-DOTATATE at 90 min postinjection in the same patient [8].

The production of scandium-43 as a therapeutic part of the theranostic pair may be more challenging, but it would be advantageous due to the absence of high-energy γ-ray emission. The development of scandium-47 is still in its infancy. However, its therapeutic potential has been demonstrated preclinically [9].

Another potentially useful new radiotherapy involves the element terbium. There are four medically useful radioisotopes, terbium-155 (^{155}Tb) ($T1/2$ = 5.32 days), that can be used for SPECT, while terbium-152 (^{152}Tb) ($T1/2$ = 17.5 h) is a potential PET radionuclide. Both have undergone preclinical studies, but terbium-152 has been used (as [^{152}Tb]Tb-DOTATOC) in a patient with a neuroendocrine tumor. Both isotopes could potentially be used to determine dosimetry prior to radio-lanthanide therapy. The decay properties of terbium-161 (^{161}Tb) ($T1/2$ = 6.89 days) are similar to lutetium-177, but the co-emission of Auger electrons makes it attractive for a combined β^-/Auger electron therapy, which was depicted to be effective in preclinical experiments. Terbium-149 ($T1/2$ = 4.1 h) is an alpha emitter which can be used for α therapy but has decays with a positron, adding the possibility of PET imaging. In terms of production, terbium-161 and terbium-155 are most promising to be made available at the large quantities suitable for future clinical translation [10].

Therapies using yttrium-90 (^{90}Y) can utilize the sister isotope yttrium-86 (^{86}Y) as an intriguing alternative to indium-111 (^{111}In) for pre-treatment imaging and dosimetry. In preclinical studies, the superiority of yttrium-86 over indium-111 has been demonstrated. However, yttrium-86 itself has some limitations such as the high-energy gamma emission and a lack of adequate commercial availability (as compared to indium-111). More than 65% of yttrium-86 decays are accompanied by additional gamma rays with energies from 200 to 3000 keV that are mostly emitted simultaneously with positron emissions and the subsequent annihilation photons resulting in increased scatter and random events, degrading image resolution [11].

21.3.1 Copper-64/Copper-67 Theranostic Agents

The copper-64 (^{64}Cu) and PET imaging can be used to verify where the target vector goes into the body and confirm targeting. For therapies, copper-67 can be used taking advantage of the 2.58-day half-life and the 184 keV gamma ray and the 150 keV average energy of the beta particles and conversion electors. This has led to the commercial development of several targeted agents, most notably ^{64}Cu/^{67}Cu chelate (SARTATE) with PSMA for prostate cancer, somatostatin receptor for neuroendocrine tumors, and gastrin-releasing peptide (GRP) bombesin analogs for prostate cancer [12, 13].

Radiolabeled octreotate using alpha or beta emitters is now recognized as an effective treatment for somatostatin receptor 2 (SSTR2)-expressing neuroendocrine malignancies. The diagnostic and therapeutic characteristics of the copper isotopes, copper-64 and copper-67, respectively, deliver the potential for using a single SSTR2-targeted peptide conjugate as a theranostic agent. Copper-Sartate, consisting of a bifunctional chelator, MeCOSar, conjugated to (Tyr)-octreotate, was successfully trialed as an imaging agent and a potential prospective dosimetry tool in ten patients with NETs [13].

A number of copper agents are currently being assessed in clinical trials such as "imaging CXCR4 expression in subjects with cancer using [^{64}Cu]Cu-plerixafor," "evaluation of a new radiotracer ([^{64}Cu]Cu-DOTA-AE105) for diagnosing aggressive cancer with positron emission tomography," "[^{64}Cu]Cu-DOTA-trastuzumab PET-CT in studying patients with gastric cancer," "[^{64}Cu]Cu-DOTA-trastuzumab positron emission tomography in women with advanced HER2-positive breast cancer," "[^{64}Cu]Cu-DOTA-trastuzumab PET in predicting response to treatment with ado-trastuzumab emtansine," "use of [^{64}Cu]Cu-Anti-CEA mAbs M5A PET in diagnosing patients with CEA-positive cancer," and

"image-derived prediction of response to chemo-radiation in glioblastoma ([^{64}Cu]Cu-ATSM)" [14, 15].

21.4 Targeting Vectors

21.4.1 Simple Physical Carriers: Microspheres

Microsphere classification depends on particle size. Particles in the submicrometer size range (10–1000 nm) are called nanoparticles, whereas larger particles are called microparticles or microspheres. The term "colloid particle" is, in nuclear medicine, often used for both nanoparticles and small microparticles (less than a few micrometers). By definition, colloid particles in suspension are small enough not to form sediment but large enough to scatter the incoming light [16].

After intravenous or intra-arterial injection or injection into a joint cavity, particles in the size range of about 5 nm to 2 μm will be rapidly cleared from the bloodstream by macrophages of the reticuloendothelial system (RES). Particles larger than 7 μm will be mechanically entrapped in the lung capillaries.

The simplest approach has been to attach a radionuclide- to attach a radionuclide—either for therapy or diagnosis to a simple inert molecule, such as glass or resin microspheres, or a colloid, and let the physical property of the molecule take the agent to the organ of interest. Delivery can be by blood flow (albumin, glass or plastic spheres), where the targeting moiety wimply occludes the first capillary it encounters, or in the case of colloids, where the agent is simply phagocytosed by reticuloendothelial cells. Many different kinds of microparticles are used for both diagnostic and therapeutic medical applications. Microparticles or microspheres are defined as small spheres made of any material ranging in size from about 10 nm to about 2000 μm. In contrast to microparticles, the term nanospheres is applied to smaller spheres (sized 10–500 nm) to distinguish them from larger microspheres. Ideally, microspheres are completely spherical [16, 17].

Due to delayed detection of hepatic tumors and poor underlying liver function, only 10% of patients with liver metastases currently qualify for curative therapies such as ablation, segmental resection, and transplantation [18].

Agents which are already approved for the treatment of hepatic metastases, Therasphere® (BTG Interventional Medicine; London, UK), made of glass, and SIR-Spheres® (Sirtex Medical Limited; New South Wales, Australia), are made of resin. These agents are injected under angiographic fluoroscopy into the hepatic artery and preferentially occlude the capillary beds or arterioles of hepatic tumors or hepatic metastases, as these are highly vascular. QuiremSpheres® using holmium-166-embedded microspheres were developed as a competitive alternative to yttrium-90 microspheres for treating unresectable liver tumors, a procedure known as "selective internal radiation therapy" (SIRT). Holmium-166 microspheres can be imaged with SPECT and MR, with high sensitivity and resolution, respectively. Labeling of Lipiodol or microspheres with rhenium-188 (^{188}Re) offers an alternative treatment option for patients with colorectal liver metastases or hepatocellular carcinomas. As a generator product, rhenium-188 has excellent availability, which permits on-site labeling. The long shelf life of 3–5 months results in low costs, especially if it is used for other therapeutic modalities, such as bone pain palliation, intravascular radionuclide therapy, or labeling of antibodies.

Rhenium-188 microspheres are proposed to have several advantages over current yttrium-90 agents. Current microspheres labeled with yttrium-90 cannot be labeled instead with a diagnostic radioisotope, such as technetium-99m (^{99m}Tc). Instead, to rule out the deposition of microspheres in undesired organs, patients first undergo a hepatic perfusion study, where macroaggregated albumin (MAA) is labeled with technetium-99m. [^{99m}Tc]Tc-MAA and yttrium-90 microspheres ([^{90}Y]Y-MS) do not have the same size and distribution, and [^{99m}Tc]Tc-MAA is prone to disaggregation, potentially leading to misdiagnosis.

One of the major advantages of [^{90}Y]Y-MS is size and uniformity. Compared to prior

^{90}Y-agents, which may bypass the liver and deposit in the lungs due to arterial/portal shunting of tumor blood flow, [^{90}Y]Y-MS are retained in the patient's capillary bed indefinitely as they are made of nonbiodegradable materials, preventing reopening of the embolized capillaries after treatment [17].

Imaging of yttrium-90 β^- particles is not straightforward, as only bremsstrahlung photons can be used to create images using single photon emission computed tomography (SPECT). But such bremsstrahlung images are very poor for diagnostic imaging and are not useful for quantitation. It is possible, however, to use the limited positron decay in yttrium-90 for PET imaging, by exploiting its low-yield internal pair production. This allows quantitative images that could subsequently be used for dosimetry calculations. PET systems, however, are relatively unavailable. Rhenium-188, in comparison, decays with a half-life of 17.0 h to stable osmium-188 (^{188}Os) by the emission of β^- particles with maximum and mean energies of 2.12 and 0.76 MeV, respectively. These β^- particles with a maximum and a mean penetration distance in the tissue of 11.0 and 3.8 mm, respectively, are very similar to yttrium-90. Rhenium-188 also emits 155 keV γ photons with an abundance of 15.6%, so patients treated with rhenium-188 can be imaged simultaneously by SPECT, allowing for simultaneously specific dosimetry calculations and biodistribution studies [19].

21.4.1.1 Rhenium-188 Lipiodol Therapy of Hepatocellular Carcinoma

[^{188}Re]Re-Lipiodol has been studied in several early phase clinical trials in patients with hepatocellular carcinoma (HCC), advanced cirrhosis, or those with extensive portal vein thrombosis in second-line therapy as a way of managing recurrences or to stabilize patients waiting for liver transplants.

To assess the maximum tolerated dose (MTD), several dose-escalation studies have been carried out. The main at-risk organs are the lungs and healthy liver. The International Atomic Energy Agency (IAEA) phase 1 and 2 clinical trials were coordinated in several countries. The overall results demonstrated favorable responses and potential usefulness of [^{188}Re]Re-Lipiodol for the therapy of HCC, which is now almost routinely used in several centers in India. One limitation of these studies is that, except for the IAEA-sponsored trials, all other trials included a very small number of patients, making it difficult to be conclusive. Another limitation was the low labeling yields and high urinary excretion (more than 40% at 72 h). The next generation compounds, such as [^{188}Re]ReN-DEDC and [^{188}Re]Re-SSS, demonstrated higher yields and higher in vivo stabilities [20].

21.4.2 Simple Physical Carriers: Colloids

Colloids have been used since the earliest days of nuclear medicine, first to target the reticuloendothelial cells in the liver/spleen/bone marrow and then to target lymph nodes during lymphoscintigraphy—in both cases mainly for diagnosis.

Historically, radiolabeled colloids are also used for therapy, e.g., [^{90}Y]Y-citrate and [^{90}Y]Y-silicate colloids have been used in the treatment of pleural and peritoneal carcinosis, while intra-articular treatment has been used for the treatment of rheumatoid arthritis of the knees, and colloidal gold-198 (^{198}Au) has been used in the past for intrathecal treatment of leukemia. Radiocolloids which have been used in the therapy of rheumatoid arthritis, were originally with ^{198}Au-colloids, and then with colloids of yttrium-90, rhenium-186, and erbium-187 (^{187}Er), using the term "radiosynoviorthesis." The rationale of using therapuetic radionuclides with colloids for treating arthritis is that bound to colloids, they will be phagocytosed in the inflamed synovial membrane in the affected joint, and by destroying the inflamed synovial cells, reduce the inflammation and halt the destruction of the joint cartilage. Synovial inflammation is implicated in many signs and symptoms of osteoarthritis (OA), including joint swelling and effusion [21].

Radiation synovectomy was first used by Fellinger and Schmid in 1952 as a therapeutic

method to cure chronic synovitis in hemophilia, orthopedic troubles, or rheumatoid arthritis. Kamaleshwaran and co-workers described the first case report of the use of [^{90}Y]Y-albumin particulates in a 33-year-old male who presented with diffuse pigmented villonodular synovitis (PVNS) of the knee joint as a primary modality of treatment. PVNS is a joint disease characterized by both inflammation and thickening of the joint lining. Treatment of PVNS demonstrated that [^{90}Y]Y-albumin could potentially become an ideal agent for radiosynovectomy of the joints. Davarpanah et al. were the first to optimize the routine use of ^{90}Y-human albumin (HA) for radiosynovectomy. The first human study in the treatment of painful synovitis and recurrent effusion of knee joints in rheumatoid arthritis using ^{177}Lu-labeled HA was reported by Shinto and co-workers. The preparation and preliminary biological assessment of ^{177}Lu-labeled HA as a promising agent for radiation synovectomy of small joints were formerly portrayed by Chakraborty et al. The use of [^{153}Sm]Sm-HA for knee synovectomy in hemophilia was reported by Calegaro et al. Effectiveness of radiation synovectomy with yttrium-90 and samarium-153 (^{153}Sm) particulate hydroxyapatite in rheumatoid arthritis patients with knee synovitis was reported by dos Santos and co-workers [22].

A novel agent for radiosynoviorthesis is tin-117m (^{117m}Sn). Tin-117m (T1/2 = 14 days) is an interesting radionuclide for the development of theranostic radiopharmaceuticals. Tin-117m decays via isomeric transition, with the emission of three major monoenergetic conversion electrons, unlike most radiotherapeutic beta emitters. These have energies of 127, 129, and 152 keV, with an abundance of 65%, 12%, and 26%, respectively. The conversion electrons have a very high linear energy transfer (LET), and short discrete penetrations, ranging between 0.22 mm (127 keV) and 0.29 mm (152 keV) in water [23].

In osteoarthritis, the synovium exhibits both inflammation and destruction in response to macrophages. The effects are cytokine driven, through the action of interleukin (IL)-1 and tumor necrosis factor (TNF)α. The production of these cytokines induces synovial cells and chondrocyte production of IL-6, IL-8, and leukocyte inhibitory factor, as well as stimulating protease (matrix metalloproteinases (MMPs) and aggrecanases) and prostaglandin production. Therapy with tin-117m suggests that radio-destruction of macrophage function in OA decreases both inflammatory synovitis and the production of degradative enzymes of importance for the progression of the disease [24].

A veterinary product using tin-117m is currently being commercialized to treat canine osteoarthritis. Human clinical trials are expected to start, treating human osteoarthritis and rheumatoid arthritis, and are expected to have several advantages over the traditional beta emitters [25, 26].

The ^{117m}Sn-colloid gamma ray (159 keV), similar to Tc-99m (140 keV), allows confirmation of the presence of the radiocolloid in the joint space. The tin-117m colloid is large enough to stay in the joint, but small enough for macrophage engulfment and not leak out of the joint (Fig. 21.2). The colloid is retained in the patient's joint with no need for splinting.

In addition to serving as a potential therapy for osteoarthritis and rheumatoid arthritis, tin-117m is being investigated as a possible therapeutic in other diseases. It also shows promise for the noninvasive molecular imaging and treatment of active atheromatous disease, especially vulnerable plaque (VP). Thin-cap fibroatheroma in the coronary arteries and other areas of vasculature has been treated in animals through the use of coronary stents electroplated with tin-117m and in human trials using specific ^{117m}Sn-labeled molecules systemically targeted to vulnerable plaque components. Additionally, human phase 1 and 2 trials have been completed using [^{117m}Sn] Sn-diethylenetriaminepentaacetic acid (DTPA) for the treatment of metastatic bone pain, which appears likely to be involved in additional new clinical trials [27, 28].

21.4.3 Simple Physical Carriers: Calcium Analogs

The principle of alpha radiotherapy is to induce double-stranded breaks in DNA. Radium-223

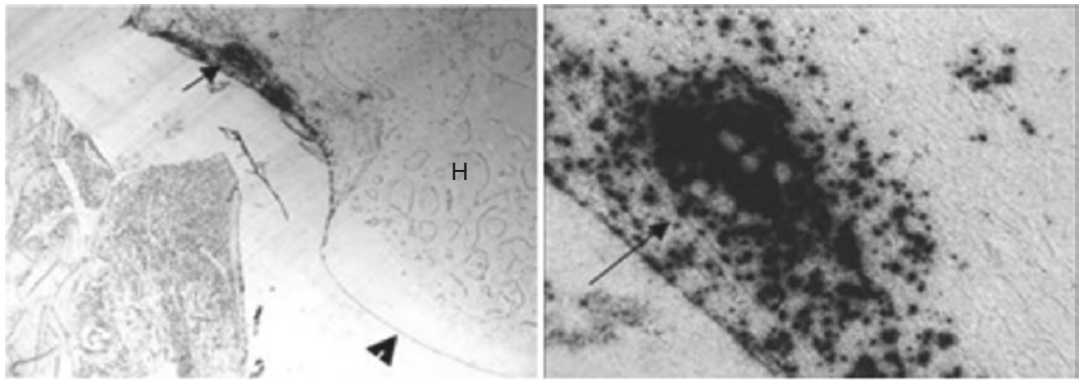

Fig. 21.2 Targeting of tin-117m colloids in the synovium. Radioactive colloidal particles are collected on the synovial lining and then transported deeper into the synovial tissue. The arrow indicates an area of inflammation in the autoradiographs

(^{223}Ra) is a bone-seeking alpha emitter which has been studied extensively in preclinical models. Its half-life is 11.4 days. Studies of radium-223 biodistribution confirmed that in mice, the uptake was preferentially retained in the bone matrix. Radium-223 is well tolerated, with doses of 50–250 kBq/kg, and therapies are now available in symptomatic patients with castration-resistant prostate cancer with two or more bone metastases. In light of the marked retention of radium-223 in the bone matrix, a phase 1 trial was set up for osteosarcoma to determine the maximum tolerated dose. In a dose-escalation study of monthly intravenous [^{223}Ra]Ra-dichloride, 18 patients (age >15 years) with osteosarcoma were treated. The phase 1 starting intravenous dose was 50 kBq/kg [^{223}Ra]Ra-dichloride, injected over several minutes on day 1 during a 4-week cycle. Patients received between 1 and 6 cycles of [^{223}Ra]Ra-Cl_2. Using this protocol, subjects' cumulative doses were 6.84–57.81 MBq. Fluorine-18 sodium fluoride ([^{18}F]NaF) PET revealed more sites of metastases than did 2-[^{18}F]FDG PET. One patient showed a metabolic response on 2-[^{18}F]FDG PET and [^{18}F]NaF PET. Four patients had mixed responses, and one patient had a response in brain metastasis. The median survival was 25 weeks. Evaluation of the safety and efficacy of alpha particles in patients with osteosarcoma led to a recommended phase 2 dose for [^{223}Ra]$RaCl_2$ of 100 kBq/kg monthly in patients with osteosarcoma (twice the dose approved for prostate cancer) with minimal hematologic toxicity, setting the stage for combination therapies [29].

21.4.3.1 Rhenium-188 Colloid

The rhenium-188 (^{188}Re) isotope is a beta-gamma emitter with a half-life of 16.98 h; the β particles have a maximal energy of 2.12 MeV and a mean energy of 764 keV. Rhenium-188 is a certified isotope easily obtained from the tungsten-188/rhenium-188 (^{188}W/^{188}Re) generator, making it very convenient for clinical use. The development of an in-house ^{188}W/^{188}Re generator has greatly increased the use of rhenium-188 for treating various diseases, such as non-Hodgkin's lymphoma (NHL), rheumatoid arthritis, peritoneal effusion, hepatocellular carcinoma, and other solid tumors, and for palliation of metastatic bone pain. Rhenium-188 is of widespread interest due to its attractive physical and chemical properties, making it suitable for labeling peptides, antibodies, and colloids to form radiopharmaceuticals. The main gamma-ray component energy of 155 keV accounts for 15% of the radiation intensity and is detectable by gamma cameras, for imaging, biodistribution, or absorbed radiation studies, also allowing excellent control of possible contamination. Moreover, the high-energy β particles of rhenium-188 are therapeutically effective only at short ranges and penetrate human tissue up to 1 cm. However, 92% of the doses are deposited

in the first 2–3 mm, therefore sparing healthy tissue, unlike external electron beam devices which have a large footprint and deposit a significant dose beyond the dermis due to secondary radiation. The fact that rhenium-188 is available from a generator at a reasonable cost could lead not only to greater use in research but also great use in clinical treatments with ^{188}Re-labeled radiopharmaceuticals [20].

In this chapter, a nuclear medicine therapeutic option for the treatment of basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and keloid is described. Non-melanoma skin cancer is the most common human malignancy, while keloids are benign dermal fibroproliferative scars developed during the process of healing at the site of surgery or trauma. Several treatment options are currently available. Surgical resection is curative and the gold standard for treating BCC and SCC. However, satisfactory surgical treatment can be very challenging for patients with large or multiple lesions. In those cases, the results may be suboptimal in terms of aesthetics and/or function. Moreover, the conventional surgical approach can simply not be desired, such as in elderly patients with comorbidities, which makes surgery an inconvenient option. Conversely, relapse is often common in patients with keloids as the skin has the tendency to develop keloid at surgery or trauma site.

An alternative dermatological high-dose-rate beta brachytherapy using non-sealed rhenium-188 was developed for these conditions (Fig. 21.3). The treatment basically consists of superficial high-dose radiotherapy to the epidermis without damaging the underlying layers characterized by the use of radioactive beta-emitting isotopes, incorporated in a specially formulated acrylic matrix. The application product, based on this synthetic inert resin matrix containing the radioactive beta-emitting isotope, is applied on the surface of keloids, BCC, and SCC, independently from its shape, extension, and lesion site. The available matrix containing a beta emitter brachytherapy irradiation is able to adapt to every skin surface without contamination, imparting an accurate distribution of dose strictly limited to the area and depth affected by the lesion, and sparing the healthy tissue [30].

The skin to be treated is delineated with a dermatological pen including a safety margin of 3–5 mm. The lesion is protected with a thin, flex-

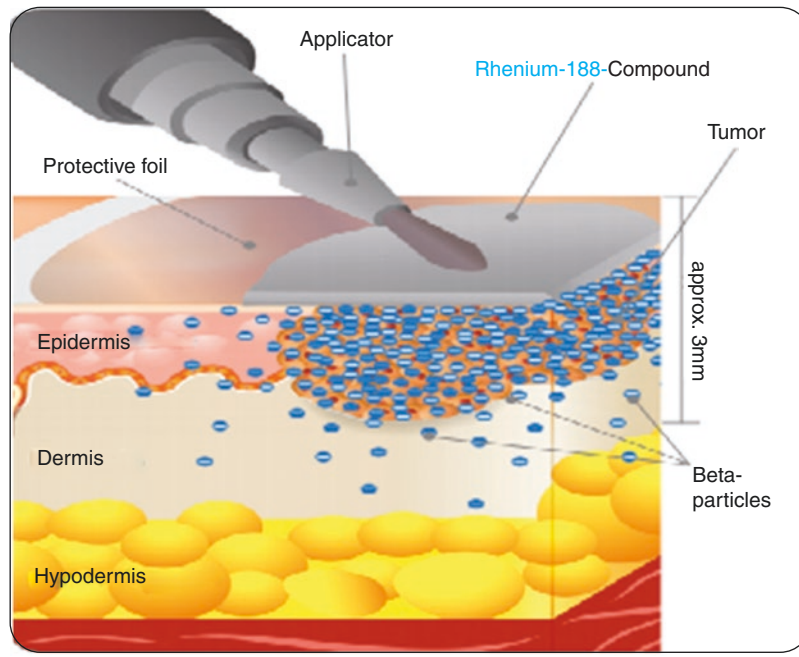

Fig. 21.3 Rhenium-188 therapy

ible, plastic foil in order to prevent direct contact of the radioactive matrix with the epidermis and minimize the risk of its incorporation through the skin or wounds. Thick tumors may need to be cleaned before the treatment by eliminating all the granulation tissue, keratinic crusts, and scabs to improve the efficacy of the treatment as the penetration path of the beta particles is short. Similarly, if surgically feasible, keloids should be reduced before the procedure to decrease both size and depth of the lesion.

The radioactive source is then applied in close proximity to the lesions above the protection layers. After some minutes, the matrix solidifies, and the radioactive mold is kept on the lesion for the time required to impart the measured dose distribution.

The thickness of matrix and protective layers is accurately measured in order to account for the beta radiation absorption effects. The total exposure (dose) to the lesion is calculated on the basis of the activity and area of the mold. For each geometry, the dose distribution depends on the initial radioactivity, isotope emission energy, the surface of the lesion, and contact time. At the end of the irradiation, the radioactive mold is easily removed, by using a specially designed dedicated remote tongs device, and is discarded.

Immediately after the treatment, faint redness is visible on the treated area and can persist for a few days. In some patients, variable erythema is present, sometimes with the emission of serum, and a crust or scab is formed. An apparent worsening of the aspect of the lesion is often observed, with the appearance of a light burn, but the bleeding, if present before the therapy, stops. It is usual to see the erythema fade after 40–120 days, although occasionally a second scab occurs, an itch may be present, but the clinical healing is much more apparent. After 60–180 days, in the majority of cases, apparent clinical healing is present, rarely with the persistence of a scab; the lesion area can become paler than the untreated skin but subsides with time.

The main advantage of the described technique lies in the usefulness in all types of BCC and SCC, without the restriction of site, dimension, clinical or histological type, and patient clinical situation. As in most of the keloid lesions, more than one treatment on the same lesions is usually needed for complete healing. The superiority of the proposed treatment with respect to the surgery is evident for all the tumors located in high-risk areas, or difficult sites on which surgery would be difficult (nose, ears, eyelids), in patients with a high number of lesions or with relapses, in patients in whom surgery would produce functional mutilations (penis, vulva, eyelids lesions), and, generally, in older, infirm, or otherwise inoperable patients. Avoidance of scarring and of suboptimal cosmetic outcome should also be considered by patients as an important decision factor in the choice of this therapeutic path. The proposed technique is a rapid, safe treatment, mostly performed in a single therapeutic session without discomfort for the patient, and offers a complete aesthetical result [31].

21.5 Alpha Emitter Brachytherapy

Diffusing Alpha-emitters Radiation Therapy ("Alpha DaRT") is a new cancer treatment modality, which enables the treatment of solid tumors by alpha particles. The treatment inserts into the tumor an array of implantable seeds, whose surface is embedded with a low activity of radium-224. Each radium seed bombards a tumor a chain of short-lived alpha-emitting daughter atoms which can diffuse into the tumor over several millimeters, creating a continuous "kill region" of high alpha particle dose. Recently, Alpha DaRT has entered clinical trials, in the framework of a new company, Alpha TAU Medical Ltd. The first clinical trial of Alpha DaRT took place at Rabin Medical Center in Israel, in the treatment of recurrent skin and oral cavity squamous cell carcinomas, with tumor sizes of less than 5 cm in the longest diameter. Fifteen of the enrolled patients have completed follow-up. Tumor locations included the ear, chin, lip, tongue, forehead, nose, scalp, and parotid skin areas. Treatment based on CT-simulation pretherapy placed DaRT seeds into squamous tumors under local anesthesia, using a special applicator. Each seed was 1 cm long and 0.7 mm in diam-

eter, carrying 2 μCi radium-224, and was placed 5–6 mm from each other. The treatment protocol was based on a prior DaRT-specific dosimetry model. Radium-224 activity administered was approximately 5 μCi/g of tumor. After 2–4 weeks, the seeds were removed. After 6 weeks, a CT scan was performed to assess tumor response. A blood test and urinalysis were also performed. A range of 7–169 seeds were inserted, and the treatment duration lasted 14–26 days. Evaluation of treatment response for a single treatment was encouraging; of 15 patients who reached the study endpoint, 73% (11/15) had a complete response to treatment, and 27% (4/15) had a partial response measured by reduction in tumor volume. The treatment was shown to be safe for both the patient and the medical staff. There were minimal side effects from the treatment, mostly erythema, swelling, and mild to moderate pain at the insertion site, which usually resolved by the time the seeds were removed. Measurements of lead-212 (^{212}Pb) in the blood, a decay product of radium-224, agreed with pre-therapy biokinetic models, which predicted negligible dose levels to distant organs. There were no clinically significant abnormalities in blood or urine laboratory tests, and no changes were observed to vital signs. Based on the successful outcomes of the first clinical trial, clinical protocols are in preparation for various indications with leading research centers worldwide, including cutaneous and mucosal neoplasia, neoadjuvant and recurrent rectal cancer, recurrent prostate cancer, inoperable breast cancer, recurrent gynecological cancer, sarcoma, and pancreatic cancer [32].

21.6 Peptide Carriers

Peptide receptor radionuclide therapy (PRRT) makes use of radiolabeled peptides to deliver destructive radiation to cancer cells. The radiolabeled peptides are able to bind specifically to peptide receptors expressed in higher density on the tumor cell membrane than in non-tumor tissues. Although antibody conjugates target the cell surface and tend to have restricted access to solid tumors, radiolabeled peptides are more desirable due to straightforward chemical synthesis, easier radiolabeling, versatility, having more rapid clearance from the circulation, more uniform distribution, deeper penetration of tumors, and less likelihood to incite an immune response.

One challenge to the use of linear peptides is degradation by peptidases. Unfortunately, peptidase degradation decreases stability and can shorten the plasma half-life to only several minutes. Stability may be increased by shortening the peptide after identification of the essential binding sequence using an alanine scan, exchange of single amino acids, the introduction of D-amino acids, peptide cyclization, and coupling to chelators such as DOTA. Although this approach may lead to increased metabolic stability, these changes frequently cause a decrease in affinity [33].

21.7 PSMA in Prostate Cancer

Prostate cancer radioligand therapy (PRLT) with ^{177}Lu-PSMA derivatives is still considered as an investigational treatment in clinics. Prostate cancer (PCa) patients usually die not from the initial local cancer, but from advanced disease, after the cancer spreads through lymphatics or blood, or locoregional spread [34]. Targeted radionuclide therapy has become an attractive and quickly developing therapy, also in prostate cancer patients [35]. Lutetium-177 has a half-life of 6.7 days and lower beta particle emission energy than iodine-131, indicating a higher probability of fewer side effects [36].

Rahbar et al. in a multicenter study of 145 patients showed that spread to visceral organs or elevated alkaline phosphatase (ALP >22 U/L) predicted negative response to therapy [34] and reported the overall survival benefit of [^{177}Lu]Lu-PSMA-RLT in comparison to a historical cohort. The estimated median survival was found to be 29.4 weeks, which was significantly longer than the 19.7 weeks of the historical controls (hazard ratio (HR), 0.44; $p = 0.031$) [37].

The 55 patients who received at least 3 cycles of radioligand therapy (RLT) with [^{177}Lu]Lu-PSMA-617 did not show any grade 3 or 4

nephrotoxicity [38]. A significant negative effect on renal function was found for age (>65 years) ($p = 0.049$), hypertension ($p = 0.001$), and pre-existing kidney disease ($p = 0.001$). Another dosimetry study with [^{177}Lu]Lu-PSMA-617 reported a mean absorbed dose/per cycle to the bone marrow, kidneys, liver, spleen, and salivary glands of 0.012, 0.6, 0.1, 0.1, and 1.4 Gy/GBq, respectively [39].

During the last decade, six new drugs have been found to increase overall survival for patients with metastatic castration-resistant prostate cancer (mCRPC); the most important of these are abiraterone (median duration of 10.0 months), docetaxel (6.5 months), enzalutamide (6.5 months), and cabazitaxel (6.0 months), respectively [40–43]. Of PCa, poorly differentiated, metastatic, and hormone-refractory adenocarcinomas express prostate-specific membrane antigen (PSMA) [42], and [^{68}Ga]Ga-PSMA HBED-CC PET-CT detects sites of cancer lesions for most patients with mCRPC [44, 45]. Patients with a positive [^{68}Ga]Ga-PSMA HBED-CC PET-CT might be treated with [^{177}Lu]Lu-PSMA radioligand therapy [46, 47]. [^{177}Lu]Lu-PSMA RLT is mainly used as compassionate treatment of patients with end-stage mCRPC [40, 47]. Over 12 studies with a total of 669 patients have reported results with [^{177}Lu]Lu-PSMA RLT. In 44% of patients treated with [^{177}Lu]Lu-PSMA, there was a decline in blood prostate-specific antigen (PSA) levels of greater than 50%, with only transient adverse effects. Sixteen studies which enrolled 1338 patients looked at prostate cancer response to third-line treatments. Following third-line treatment with enzalutamide and cabazitaxel, the symptoms caused by adverse effects with these drugs led to discontinuation of the treatment using them in 10–23% of patients. Conversely, [^{177}Lu]Lu-PSMA RLT gave a serum PSA decline of more than 50% more frequently than drug third-line treatment (mean 44% with [^{177}Lu]Lu-PSMA versus 22% with drug third-line therapy). ^{177}Lu-PSMA RLT gave greater objective remission compared to third-line treatment (overall 31 of 109 patients versus 43 of 275 patients, $p = 0.004$) [42]. Differences in median survival proved to be longer after [^{177}Lu]Lu-PSMA RLT than after drug third-line therapy, but the difference proved not to be statistically significant (mean 14 months for [^{177}Lu]Lu-PSMA versus chemotherapy). Adverse effects resulted in cessation of treatment more often for third-line treatment compared to ^{177}Lu-PSMA RLT (22 of 66 patients versus 0 of 469 patients, $p < 0.001$) [41].

According to the results of different published data, no severe adverse events immediately after injection have been reported to date. The most common side effect in the first 48 h after injection is mild nausea and vomiting (in up to 20% of patients), which can be easily treated with antiemetics. Fatigue is the most common complaint in patients after therapy, especially in the first 4 weeks (in up to 25% of patients) [3, 37, 41]. One of the most common reported adverse side effects from [^{177}Lu]Lu-PSMA is dry mouth, reported in up to 20% of cases, but this was transient in most patients.

[^{177}Lu]Lu-PSMA dosimetry studies revealed that the kidneys are the critical organs, receiving a radiation dose of 0.88 Gy/GBq from [^{177}Lu]Lu-PSMA-617 and 0.93 Gy/GBq from [^{177}Lu]Lu-PSMA-I&T. No studies reported any high-grade nephrotoxicity (common toxicity criteria (CTC) grade 3, 4, or 5). Regarding tumor doses, all lesions received a mean dose per cycle of 23 ± 20 Gy (3.3 Gy/GBq). Calculations of mean absorbed dose to bone, lymph node, liver, and lung metastases were 26 ± 20 Gy (3.4 Gy/GBq), 24 ± 16 Gy (3.2 Gy/GBq), 8.5 ± 4.7 Gy (1.28 Gy/GBq), and 13 ± 7.4 Gy (1.7 Gy/GBq), respectively [48, 49].

There is a clear trend toward a lower absorbed dose with an increasing number of cycles [46, 47]. A similar trend can be seen for the subgroup of bone metastases.

Severe (grade 3 and 4) bone marrow toxicity is observed in less than 10% of patients in various publications. The European meta-analysis [37] and studies in Australia demonstrated that more than two-thirds of the patients benefit from [^{177}Lu]Lu-PSMA therapies, when PCa is already in castration-resistant phase [34].

The newest forms of PRLT introduce prostate-specific membrane antigen targeting alpha therapy, such as [Ac]Ac-PSMA-617. The patient

number in clinical studies is still small, but it seems to improve the excellent results of PRLT as compared to [^{177}Lu]Lu-PSMA-617. In the largest published study, 5 out of 40 patients discontinued treatment because of nonresponsiveness, and 4 because of xerostomia. In 38 patients treated with [^{225}Ac]Ac-PSMA-617, in patients who survived at least 8 weeks, 24 (63%) had a PSA decline of more than 50%, and 33 (87%) had at least a modest serum PSA decline. The median duration of tumor control under [^{225}Ac]Ac-PSMA-617 last-line therapy was 9.0 months. Five patients were reported to have an enduring response of more than 2 years. The response and promising duration of tumor control, especially considering the unfavorable prognostic profile of the selected advanced-stage patients, is very good but very similar to the results of [^{177}Lu]Lu-PSMA-617. On the contrary, [^{225}Ac]Ac-PSMA-617 seems to have a permanent side effect, xerostomia (and maybe xerophthalmia). The dry mouth is caused not only by inflammation but also by the direct effect of radiation. Xerostomia could be persistent on the basis of preliminary results in 11 patients and cannot be protected even with sialadenoscopic support [50–52]. Nevertheless, the PSMA agents are very selective in targeting—anecdotally, even eye metastases can be treated (Fig. 21.4).

21.8 PRRT

The history of targeting neuroendocrine neoplasms with radiolabeled peptides began in the late 1980s and treatments began in the late 1990s, first in the Netherlands. Extensive studies included ^{111}In- and ^{90}Y-labeled octreotide analogs. The current approved practice of neuroendocrine neoplasms (NENs) consists of lutetium-177-octreotate, also known as *[^{177}Lu]Lu-DOTA0-Tyr3-octreotate (DOTATATE)* or similar compounds, *and this peptide receptor radionuclide therapy (PRRT) is already a part of international recommendations (European Neuroendocrine Tumor Society (ENETS)/National Comprehensive Cancer Network (NCCN) guidelines)*. Lutetium-177-octreotate treatment is based on *somatostatin receptors*, *which are present in almost all neuroendocrine tumors* including pheochromocytoma and paraganglioma. The carrier molecule octreotate has high affinity especially to somatostatin receptor (SSTR) 2 and (SSTR) 5. For patient selection, somatostatin receptor imaging is essential, e.g., by using gallium-68-octreotate PET imaging (or [^{111}In]In-octreotide gamma imaging) in order to confirm disease that has higher SSTR expression than the liver. Nordic guidelines recommend four treatments with 7.4 GBq (200 mCi) activity typically with 8-week intervals. In real practice, the amount of treatment cycles is dependent on response and on critical organ absorbed radiation dose, i.e., kidney and bone marrow dose. Gamma imaging allows to estimate quantitatively [^{177}Lu]Lu-octreotate uptake in metastatic sites. Figure 21.5 represents a patient who has received 5 cycles of PRRT and treatment response has been followed up with [^{68}Ga]Ga-octreotate PET. [^{177}Lu]Lu-octreotate got marketing authorization in 2017 after a randomized and controlled prospective trial (NETTER-1) and has significantly improved overall survival as compared to earlier clinical practice (long-acting somatostatin analog). The treatment itself may cause fatigue and nausea due to prophylactic hyperhydration in order to decrease kidney dose. The pain in the metastatic sites is typically related to tumor-lysis. Bone marrow depression is seldom detected. Hormonal effects are also seen, because approximately half of these tumors are functional. Therefore, blood chemistry should be followed up regularly. This treatment suits NENs with World Health Organization (WHO) class of 1–2 and proliferation index Ki-67 of less than 20%. This treatment improves the quality of life and relieves symptoms significantly.

For the theranostics concept, there are currently multiple compounds under development, both for imaging in patient selection/follow-up and therapeutic compound (Table 21.1).

For SSTR imaging, some new ^{68}Ga-PET compounds are under development, such as [^{68}Ga]Ga-satoreotide trizoxetan (^{68}Ga-OPS202). The original therapeutic compound was [^{177}Lu]Lu-DOTATOC, also called [^{177}Lu]Lu-edotreotide, and this is still widely in clinical use in multiple institutions that are allowed

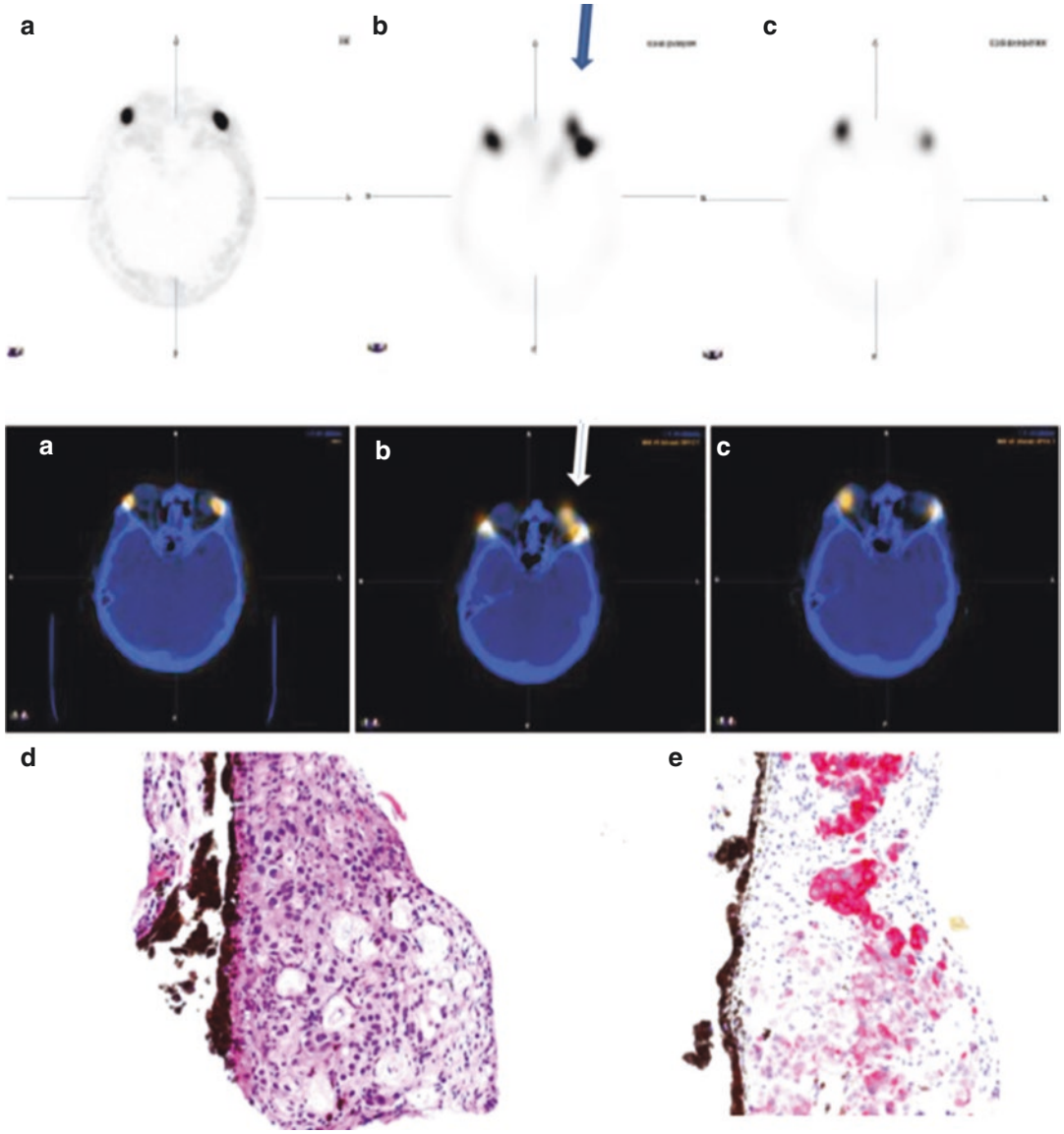

Fig. 21.4 A 60-year-old male demonstrated large PSMA-positive skeletal metastases located predominantly in the lumbosacral spine and pelvis. Metastases were seen in lung hila, mediastinal lymph nodes, and liver in the left lobe. He was decided to be treated with PRLT. In images (**A** and **a**), a cross section at eyeball level of fluorine-18-PSMA-1007-PET-CT study (PET study (**A**); PET-CT fusion image (**a**)) performed at 1 h is shown. In images (**B** and **b**), lutetium-177-PSMA-617 SPECT/CT (SPECT study (**B**); SPECT/CT fusion image (**b**)) performed 24 h after the first therapy cycle is shown; this study was performed 2 weeks later than that of (**A**). In images (**C** and **c**), the similar lutetium-177-PSMA-617 SPECT/CT study is shown after the second therapy cycle; this study was performed 4 weeks later than that of (**B**) (SPECT study (**C**); SPECT/CT fusion image (**c**)). The patient had an eye metastasis of prostate cancer, as shown in image (**D**) with hematoxylin and eosin (HE) staining and in image (**E**) with PSA immunohistochemistry, confirmed, because the eye was biopsied after the first therapy cycle due to pain. The pain disappeared as a result of treatment, and it was not anymore visible after the second cycle in image (**C**), i.e., complete response by imaging

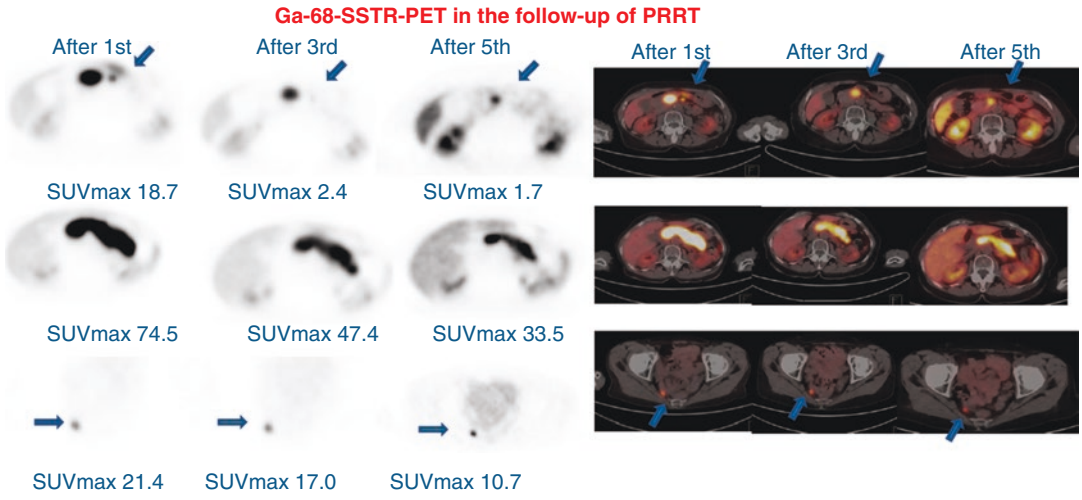

Fig. 21.5 A 70-year-old female with neuroendocrine cancer in the tail of the pancreas (Grade 2). The invasive tumor invaded the spleen, ventricle, and left adrenal gland. Lymph node metastases were seen in the upper abdomen and pelvis. She was treated with long-acting octreotide and interferon. She received five lutetium-177-peptide receptor treatments, so that the originally inoperable tumor could be removed. The images demonstrate remarkable tumor shrinkage and decrease in standardized uptake values (SUVs) by using gallium-68-octreotate PET. Chromogranin A (CgA) normalized during imaging. The cumulative absorbed radiation dose in the pancreatic tumor was 853 Gy

to use their own products. The commercial compound [^{177}Lu]Lu-DOTA0-Tyr3-octreotate (DOTATATE) is globally most widely used, but other ^{177}Lu derivatives are under development, such as [^{177}Lu]Lu-OPS201. These do not essentially differ from existing compounds, except for the fact that different chelators instead of DOTA, such as NODAGA, are used. Additionally, new indications are searched, because neuroendocrine differentiation is seen in many metastatic breast, prostate, and small-cell lung cancers besides conventional neuroendocrine tumors. New attempts include the introduction of new radionuclides, copper-67 and bismuth-213.

21.9 Gastrin in Medullary Thyroid Cancer

Different peptide receptors like somatostatin, bombesin/gastrin-releasing peptide (GRP), or vasoactive intestinal peptide (VIP) are overexpressed on cancer cells and are therefore ideal targets for the diagnosis and therapy with radiolabeled peptides in nuclear medicine. Virtually all medullary thyroid cancers (MTCs) express the cholecystokinin 2 receptor, for which the endogenous ligand is gastrin. By taking advantage of this, using peptide receptor radionuclide therapy (PRRT) with radiolabeled gastrin analogs becomes an attractive treatment paradigm for patients with recurrent or metastatic medullary thyroid cancer. Autoradiographic investigations revealed cholecystokinin (CCK)-B/gastrin receptors in over 90% of MTCs, in a high percentage of small-cell lung cancers, stromal ovarian tumors, and potentially a variety of other tumors, including gastrointestinal adenocarcinomas, neuroendocrine tumors, and malignant glioma [53]. Currently, the analogs [^{177}Lu]Lu-PP-F11N and [^{111}In]In-CP04, as a surrogate for ^{177}Lu- or ^{90}Y-labeled CP04, are in early prospective trials for medullary thyroid cancer (LUMED/NCT02088645 and GRAN-T-MTC/NCT03246659, respectively) performed for safety and to define MTD, biodistribution, and dosimetry. It was found that the stomach was the dose-limiting organ, not the kidneys, where the absorbed dose was low. Many patients given even small amounts of ^{177}Lu-radiolabeled gastrin suf-

fered marked nausea. It is hypothesized that the use of adjuvant protease inhibitors would prevent degradation of the radiolabeled gastrin and help to improve tumor uptake of enzymatically vulnerable radiolabeled gastrin analogs [33].

In an earlier dose-escalation study, eight patients with advanced metastatic medullary thyroid cancer were injected with potentially therapeutic activities of a ^{90}Y-labeled mini-gastrin derivative at 4–6-weekly intervals (1110–1850 MBq/m^2 (30–50 mCi/m^2) per injection for a maximum of four injections). Hematologic and renal toxicities were acknowledged as the dose-limiting toxicities at the 1480 and 1850 MBq/m^2 (40 and 50 mCi/m^2) levels. Following treatment, two of the eight patients experienced partial remissions of their medullary thyroid cancer, while four had stabilization of their disease. It is hoped that CCK-B receptor ligands may become a new and useful weapon using receptor-binding proteins in patients with tumors that overexpress CCK-B receptors [53, 54].

21.10 Fibroblast Activation Protein Inhibitors

Targeting efforts against fibroblast activation protein (FAP) are becoming a promising strategy for targeting tumors. In more than 90% of epithelial cancers, fibroblasts are found to constitute a large subpopulation of tumor stroma. Because serine protease fibroblast activation protein is overexpressed in most cancers, a strategy of using inhibitors of fibroblasts labeled with radionuclides (FAPIs) was devised. FAP will be expressed in the stromal cells of most solid tumors. Overexpression is usually associated with a poor prognosis. Using radiolabeled FAP inhibitors (FAPIs), FAPI-02 and FAPI-04, the Haberkorn group at the University of Heidelberg showed that ^{68}Ga-labeled FAPI targeted various cancers on PET-CT with significantly lower background uptake in the liver and brain compared to 2-[^{18}F]FDG. To further prove this concept, a patient with metastatic breast cancer was treated with 2.9 GBq of [^{90}Y]Y-FAPI-04 and was shown to need significantly less pain medication post-treatment. It appears that higher doses of radioactivity can be delivered while minimizing damage to healthy tissue, which may improve therapeutic outcome. FAP is a molecular target that holds great potential for tumor imaging and therapy [55, 56].

21.11 Pretargeted ^{177}Lu-Peptide in CEA-Positive Cancers

A strategy that may increase the target to background ratio is pretargeting with the first injection of an unlabeled bispecific monoclonal antibody (bsMAB), followed by a second injection of a radiolabeled bivalent hapten-peptide. The concept is that the bsMAB will attach first to the cancer cell target on the cell surface and that the radiolabeled hapten-peptide will be bound to any pretargeted bsMAB, but any radiolabeled hapten-peptide which does not find the pretargeted bsMAB will clear rapidly through the circulation. Medullary thyroid cancer cells express high amounts of CEA, and encouraging therapeutic results have been obtained using anti-CEA pretargeted [^{131}I]I-di-DTPA peptide in 2 phase 1/2 and 1 phase 2 clinical trials.

A multicenter phase 2 study of 45 medullary thyroid cancer patients assessed the chimeric hMN-14x734 bsMAB targeted to MTC cells, followed by 1.8 GBq/m^2 of [^{131}I]I-di-DTPA 4–6 days after the pretargeting. A 76.2% response rate (durable stabilization plus objective response) was noted according to the response evaluation criteria in solid tumors (RECIST) on CT. One durable complete response of at least 40 months (2.4%) and 31 durable stable diseases ≥6 months (73.8%) were observed in these patients with disease progression before radioimmunotherapy (RIT) [57].

These results have encouraged the development of newer bsMABs and bivalent peptides, based on humanized, recombinant, and even trivalent bsMABs, as well as utilizing newer hapten-peptides using histamine-succinyl-glutamine (HSG) haptens and bivalent HSG hapten-peptides. A series of bivalent HSG haptens have been synthesized, offering the possibility of label-

ing with different radionuclides such as lutetium-177 and yttrium-90 for therapy purposes. The first clinical results of an optimization study assessing the anti-CEA × anti-HSG bsMAB TF2 and the radiolabeled hapten-peptide, [^{177}Lu]Lu-IMP288, in patients with metastatic colorectal cancer have been reported recently. Using this pretargeting scheme, there was rapid tumor uptake within 1 h after the peptide was injected, and high tumor-to-tissue ratios were observed by 24 h. The most successful tumor targeting occurred following a 1-day pretargeting interval and 24 μg of the peptide. High activities of [^{177}Lu]Lu-IMP288 (2.5–7.4 GBq) could be injected, with some modest reactions during the injection, and only transient grade 3–4 thrombocytopenia seen in 10% of the patients. Dosimetry studies showed relatively low radiation to renal and red bone marrow following [^{177}Lu]Lu-IMP288 peptide [58].

Another target is CEA (carcinoembryonic antigen) which is expressed in 50% of lung tumors and would be susceptible to anti-CEA radioimmunotherapy. It has been shown that pretargeting with a bsMAB delivers higher radiation than simply using a labeled antibody alone. This has led to a clinical trial using pretargeted radioimmunotherapy involving a recombinant anti-CEA bsMAB and ^{177}Lu-labeled peptide to treat small-cell lung cancers (SCLC) or CEA-expressing non-small-cell lung cancer (NSCLC). In France, two multicentric prospective phase 1 clinical studies are ongoing, assessing pretargeted [^{177}Lu]Lu-IMP288 (one injection) in patients with metastatic CEA-positive lung carcinoma and fractionated injection of [^{90}Y]Y-IMP288 in metastatic colorectal patients. Other authors have suggested that the therapeutic efficacy of pretargeted radioimmunotherapy (PRIT) might be improved using α-emitting radionuclides such as bismuth-213 [59, 60].

21.12 Bombesin in Prostate and Breast Cancers

A novel target is the gastrin-releasing peptide receptor (GRPR), a glycosylated, seven-transmembrane G-protein-coupled receptor. This receptor then activates the phospholipase C signaling pathway. Gastrin-releasing peptide (GRP) itself regulates a number of physiologic processes, from the release of gastrointestinal hormones, smooth muscle contraction, and epithelial cell proliferation. This latter property likely acts as a mitogen in neoplastic tissues. The receptor is aberrantly expressed in numerous cancers such as those of the colon, prostate, lung, and breast [61].

The ^{68}Ga-labeled GRPR antagonists RM2 and NeoBOMB1 are currently under clinical evaluation in prostate cancer and gastrointestinal stromal tumor. Treatment in humans has not been reported thus far but has been examined in animal models. Interestingly, various ongoing studies compare [^{68}Ga]Ga-GRPR antagonists with [^{68}Ga]Ga-PSMA analogs (NCT03604757, NCT03606837, NCT03698370), which is essential to understand the role of each radiotracer in the management of prostate cancer patients. It appears that GRPR and PSMA are expressed in different stages of prostate cancer, and the two radiotracers show fundamentally different biodistribution. This may lead to two complementary rather than competitive theranostic approaches.

Radiolabeled GRPR antagonists may also have potential in estrogen receptor-positive breast tumors, which represent most breast cancer patients [33].

21.13 Substance P in Glioblastoma

One of the most common brain tumors is glioblastoma multiforme (GBM). GBM has been demonstrated to overexpress the neurokinin-1 (NK-1) receptor, and as a result, substance P (SP) can be used as a ligand for targeted therapy using beta or alpha emitters. ^{213}Bi-PRRT of gliomas has been investigated with the substance P analog DOTA-/DOTAGA-SP, targeting the neurokinin-1 receptor that is overexpressed in grade 2–4 gliomas. As a way of circumventing the blood-brain barrier, the ^{213}Bi-PRRT can be injected via a catheter implanted and connected to a subcutaneous access port.

Initially, the glioblastoma was targeted with yttrium-90 and lutetium-177, with some positive

clinical results. Recent studies, however, focused on the alpha emitters bismuth-213 (^{213}Bi) and actinium-225 (^{225}Ac), allowing more selective tumor cell irradiation and limiting toxicity to adjacent healthy brain tissue. [^{213}Bi]Bi-DOTA-SP has been evaluated in 61 patients with grade 2–4 gliomas (up to a cumulative activity of 14.1 GBq). A subgroup analysis in seven patients with secondary glioblastoma showed a median overall survival of 18.6 months after conversion to grade 4 [33].

Fifty glioma patients of different subtypes were treated with targeted alpha therapy at the Medical University of Warsaw. Nine patients with secondary GBM were treated. Recurrent GBMs were treated by surgery, chemotherapy, and radiotherapy, and following this, by direct intracavitary injection of 1–6 doses of 0.9–2.3 GBq [^{213}Bi]Bi-DOTA-[Thi^{8},Met(O_2)^{11}]-substance P ([^{213}Bi]Bi-DOTA-SP) to the GBM site at 2-month intervals. [^{68}Ga]Ga-DOTA-[Thi^{8},Met(O_2)^{11}]-substance P ([^{68}Ga]Ga-DOTA-SP) was also injected along with the therapeutic radio-bismuth to image the biodistribution of the bismuth-213 with PET-CT. The therapeutic response was examined with MRI. Treatment with [^{213}Bi]Bi-DOTA-SP was well tolerated with only mild transient adverse reactions, mainly headaches due to transient edema reaction. Response to the alpha therapy with [^{213}Bi]Bi-DOTA-SP showed a median progression-free survival of 5.8 months and an overall survival time of 16.4 months. Two out of nine patients are still alive at 39 and 51 months, respectively, after the initiation of the therapy [62].

In another subgroup of 20 patients with recurrent glioblastoma, a median overall survival of 23.6 months was observed, compared with 14.6 months after standard therapy alone. Treatment with the longer-lived actinium-225 has been initiated and 20 glioma patients have been enrolled in a dose-escalation study (from 10 to 42 MBq) investigating the intratumoral or intercavitary injection of [^{225}Ac]Ac-DOTAGA-SP. The analysis of therapeutic efficacy and patient recruitment is ongoing [33].

21.14 IL-13RA2 Targeted Alpha Particle Therapy Against Glioblastomas

Chemotherapy and radiotherapy have not been completely effective as standard treatment options for patients with glioblastoma due to recurrent disease. One molecular strategy therefore has been to develop specifically targeted interleukin-13 receptor alpha 2 (IL-13RA2), a glioblastoma receptor expressed abundantly on over 75% of GBM patients.

Using Pep-1L, a peptide that binds to IL-13RA2 with high specificity, radioconjugates have been developed. Using a phage display library and bio-planning schemes in glioma cells that overexpressed or did not express IL-13RA2, three peptide ligands were identified. One of them, Pep-1L, showed the highest binding affinity to IL-13RA2. ^{64}Cu-radiolabeled Pep-1L selectively bound to IL-13RA2-expressing cells in vitro. Pep-1L was found to target GBM both in vitro and in an orthotopic model of GBM and could be monitored via PET. This study also examined conjugation of Pep-1L with an alpha particle emitter, actinium-225. Using convection-enhanced delivery, [^{225}Ac]Ac-Pep-1L improved the survival of mice compared to saline control [63, 64].

21.15 [^{131}I]Iodophenylalanine for Glioblastoma

Carrier-added 4-L-[^{131}1]iodophenylalanine ([^{131}1]IPA) is a small molecule therapeutic product that specifically targets L-type amino acid transport 1 (LAT-1), which is highly expressed in many aggressive cancers including glioblastoma and multiple myeloma.

A multicenter phase 1/2 study is underway to study its use to treat recurrent glioblastoma. The study is an international multicenter, open-label phase 1/2 dose-ranging investigation to evaluate the safety, tolerability, dosing schedule, and preliminary efficacy of carrier-added 4-L-[^{131}1]

iodophenylalanine ([^{131}1]IPA), applied as single or repeated injections in patients with recurrent glioblastoma multiforme in conjunction with external radiotherapy [65].

21.16 CXCR4 in Cancer

C-X-C chemokine receptor type 4 (CXCR4) is an attractive target for theranostic interventions since it is overexpressed in hematologic malignancies, such as multiple myeloma, leukemia, and non-Hodgkin's lymphoma, and in some solid cancers (e.g., lung cancer, adrenocortical cancer, and high-grade neuroendocrine tumors). Many high-affinity ligands targeting CXCR4 have been developed, among which the theranostic pair [^{68}Ga]Ga-pentixafor/[^{177}Lu]Lu/[^{90}Y]Y-pentixather is the most advanced one.

The imaging agent, [^{68}Ga]Ga-pentixafor, was based on a cyclic pentapeptide, with a high affinity for CXCR4 and excellent stability for in vivo applications. Several radionuclides have been used in this system, attached with the metal chelator DOTA, including gallium-68, lutetium-177, and yttrium-90. Besides [^{68}Ga]Ga-pentixafor, the investigators developed [^{177}Lu]Lu- and [^{90}Y]Y-pentixather as therapeutic agents for a pilot study with three patients with multiple myeloma. All patients had been heavily treated with other standard therapies and then underwent CXCR4-targeted radionuclide therapy. Before such treatment, baseline [^{68}Ga]Ga-pentixafor PET scans were obtained to confirm the high expression of the target in these patients; 2-[^{18}F]FDG PET scans were also obtained. Excellent therapeutic efficacy was observed in two patients, evidenced with 2-[^{18}F]FDG PET, which showed much lower metabolic activity in the lesions when compared with pre-treatment scan.

It is thought that radiotherapy with alpha emitters, such as [^{213}Bi]Bi-/[^{225}Ac]Ac-pentixather, might be more successful than using beta emitters such as [^{177}Lu]Lu-pentixather, since most hematologic cancers are widely disseminated, and targeted alpha therapy (TAT) is under serious consideration [33, 66, 67].

21.17 [^{177}Lu]Lu-3BP-227 in Metastatic Pancreatic Adenocarcinoma

Ductal adenocarcinoma remains one of the deadliest cancers, with poor prognosis. It is known that neurotensin receptor 1 (NTR1) is overexpressed in ductal pancreatic cancers, and clinical trials have been conducted using this receptor. In a phase 1 trial in Germany, eligible patients were given NTR1 antagonist [^{177}Lu]Lu-3BP-227. The phase 1 study by Baum et al. offered the first clinical evidence of the feasibility of treating ductal pancreatic adenocarcinoma with a DOTA-conjugated NTR1 antagonist, 3BP-227, labeled with the radioisotope lutetium-177. Six patients with ductal pancreatic adenocarcinoma who had failed all other treatment options received [^{177}Lu]Lu-3BP-227 for assessment of NTR1 expression in vivo. Three patients received treatment activities of 5.1–7.5 GBq. [^{177}Lu]Lu-3BP-227 was well tolerated by all patients. The largest radiation dose was identified as being to the kidneys, with the most severe adverse reaction found to be a reversible grade 2 anemia. The most successful patient survived 13 months from diagnosis and 11 months after starting [^{177}Lu]Lu-3BP-227 therapy and experienced marked improvement in symptoms. The 5-year survival rate for patients with this type of cancer is less than 5% [68].

21.18 LAT1 Synthetic Iodine-131 Amino Acid Therapy in Glioblastoma

A synthetic amino acid has been developed targeting the L-type amino acid transporter 1 (LAT1), which is strongly overexpressed in many aggressive malignancies, including glioblastoma, melanoma, multiple myeloma, primary hepatocellular carcinoma (HCC), and gastric, prostate, and breast cancers. This synthetic amino acid (LAT1) has been labeled with PET agents for diagnosis and therapeutic radionuclides for therapy. It demonstrates favorable therapeutic biodistribution and kinetics and is actively transported

across the intact blood-brain barrier into tumor cells. This radiolabeled synthetic amino acid potentially offers therapeutic benefit as a monotherapy, and in conjunction with other therapeutic agents, including radiotherapies (external beam therapy, microspheres, brachytherapy, etc.), due to its radiosensitization effect [69].

2-[^{18}F]FDG is one of the most commonly used probes for the diagnosis of cancer with PET. Although 2-[^{18}F]FDG has been of assistance in the clinical diagnosis of many cancers, it sometimes showed false-positive results, especially in the brain, because even normal brain cells take up a relatively large amount of glucose. The amino acids have attracted attention as alternative probes to glucose in order to overcome this problem. If the compounds are delivered into cells specifically through LAT1, those cells are likely to be cancerous [70].

21.19 A High-Affinity Peptidomimetic for A_VB_3 Integrin Receptor Targeting in Breast Cancer

The cell adhesion motif $\alpha_v\beta_3$ arginine-glycine-aspartate (RGD) integrin receptor was discovered in fibronectin by Pytela, Pierschbacher, and Ruoslahti more than 20 years ago. The $\alpha_v\beta_3$ integrin receptor is overexpressed on endothelial cells and some tumor cells. The $\alpha_v\beta_3$ integrin is significantly overexpressed in certain types of tumor cells and almost all tumor vasculature. Integrins are intriguing targets as $\alpha_v\beta_3$ is known to be involved in neo-angiogenesis in solid tumors and is overexpressed in many different types of cancers (glioblastomas, melanomas, myelomas, ovarian tumors, breast and prostate cancers) [71].

It was hypothesized that any tumor overexpressing $\alpha_v\beta_3$ as part of angiogenesis would be able to be targeted for both imaging and therapy by a peptidomimetic. This is a small protein-like chain with properties similar to a normal peptide. Peptidomimetics cna either originate from modification of an existing peptide, or ariese from designing similar systems mimicking peptides. B-peptide natural amino acids in peptides can be substituted by non-proteinogenic counterparts (*proteinogenic* means "protein-building"). Such proteinogenic amino acids are able to be condensed into a polypeptide through a process known as translation. Proteinogenic amino acids are amino acids that are known to be precursors to proteins and are co-translationally (during translation to obtain drug-like targeting molecules) incorporated into proteins. The $\alpha_v\beta_3$ integrin antagonist (IAC) peptidomimetic 4-[2-(3,4,5,6-tetrahydropyrimidine-2-ylamino) ethyloxy]benzoyl-2-[*N*-(3-amino-neopenta-1-carbamyl)]-aminoethylsulfonyl-amino-β-alanine, THERANOST™, was developed to provide an alternate vector selectively targeting integrin $\alpha_v\beta_3$ receptor and clears rapidly from the whole body [71, 72].

Using this synthetic peptidomimetic for $\alpha_v\beta_3$ integrin labeled with [^{68}Ga]Ga-NODAGA, Baum et al. were able to demonstrate the superior uptake in two patients with disseminated breast cancer compared to 2-[^{18}F]FDG. A therapeutic entity using lutetium-177 in place of gallium-68 is currently in phase 1 clinical trials [72].

21.20 Antibodies

From the first report in 1975 by César Milstein and Georges J. F. Köhler describing immortalizing hybrid B cells and mouse myeloma tumor cells, it has been possible to generate large amounts of monoclonal antibodies (mAbs) of predefined specificity. Monoclonal antibodies have revolutionized biomedical research and diagnostics and led to the generation of an arsenal of therapies for many diseases. Nuclear medicine was no exception. In fact, the emergence of monoclonal antibodies for decades generated interest initially in radiolabeling whole antibodies, then Fab fragments, single-chain antibodies, mini-bodies, and finally with humanized antibodies—the latter with only the variable portion of the antibody containing mouse proteins. Several therapeutic radiolabeled monoclonal antibodies have been developed, targeted particularly at lymphoma. Two monoclonal antibody products targeting the cluster of differentiation (CD)20

antigen have been approved, the intact murine immunoglobulins [^{131}I]I-tositumomab (Bexxar®; GlaxoSmithKline, Mississauga, ON, USA) and [^{90}Y]Y-ibritumomab tiuxetan (Zevalin®; Spectrum Pharmaceuticals, Henderson, NV, USA). Sales of [^{131}I]I-tositumomab are now discontinued. [^{90}Y]Y-ibritumomab can be incorporated in clinical practice using non-ablative activities for the treatment of patients with relapsed/refractory follicular lymphoma or has been administered following induction chemotherapy in front-line treatment in lymphoma patients [73].

It is important to know whether a monoclonal antibody or other antibodies become internalized in a cancer cell after injection, as this can lead to important dose considerations after radiolabeling. For instance, when radiometal-labeled drugs are metabolized, the metal-based radionuclide is trapped intracellularly in lysosomes through residualization. This process culminates in higher absolute uptake of the tracer and leads eventually to higher tumor-to-blood ratios [74].

21.21 [^{177}Lu]Lu-J591 Anti-PSMA in Metastatic Prostate Cancer

Prostate-specific membrane antigen (PSMA) has emerged as the most favorable target in prostate cancer, although several targets had been previously identified, such as mucin, ganglioside, and adenocarcinoma-associated antigens. Prostate cancer is known to be radiosensitive, and most sites of prostate cancer spread such as bone marrow and lymph nodes are amenable to exposure to circulating monoclonal antibodies [75].

De-immunized J591 mAb, which targets the external domain of PSMA, seems to be the best clinical candidate for imaging and therapy of prostate cancer. In one study, 49 men were treated with fractionated doses of [^{177}Lu]Lu-J591 ranging from 740 to 1665 MBq/m^2 (20–45 mCi/m^2) in two cycles weeks apart. The dose-limiting toxicity in the phase 1 trial was neutropenia. The recommended phase 2 doses (RP2Ds) were 1480 MBq/m^2 (40 mCi/m^2) and 1665 MBq/m^2 (45 mCi/m^2) × 2. At the highest RP2D of 1665 MBq/m^2 (45 mCi/m^2), 35.3% of patients were discovered to have a reversible grade 4 neutropenia and 58.8% of patients had thrombocytopenia. In addition, patients treated at this dose showed a greater drop in prostate-specific antigen (PSA)—85.5% showed some PSA decrease, 58.8% showed a greater than 30% decrease in PSA, and 29.4% showed a larger than 50% decrease. In terms of survival, the median survival was 42.3 months. Those patients who were positive with PSMA PET imaging had better responses than those patients who showed less intense upake. Those with less intense PSMA uptake tended to have poorer responses. It appears that treatment with radiolabeled and de-immunized J591 is well tolerated. There was less salivary gland toxicity with the [^{177}Lu]Lu-J591 antibody than similar therapies with [^{177}Lu]Lu-PSMA peptide therapies [76].

21.22 Hematologic Malignancies

An antigen known to be overexpressed on hematopoietic cancers is CD33. It is commonly associated with myeloid malignancies including acute myelogenous leukemia (AML), but recent research has shown that CD33 can also be found on malignant cells of approximately 25–35% of all multiple myeloma patients. [^{225}Ac]Ac-lintuzumab (Actimab-A) is a radioimmunoconjugate composed of actinium-225 linked to a humanized anti-CD33 monoclonal antibody. The CD33 receptor is overexpressed in AML cells. Actinium-225 emits four α particles and has a 10-day half-life. A 53-patient multicenter phase 2 trial for patients newly diagnosed with AML aged 60 and above was conducted with [^{225}Ac]Ac-lintuzumab developed as first-line monotherapy. The [^{225}Ac]Ac-lintuzumab was given as two 15-min injects 7 days apart. Adverse effects included myelosuppression seen in all evaluable patients, including grade 4 thrombocytopenia with marrow aplasia for more than 6 weeks following therapy in three patients. The only reported in more than one patient, were penumonia and cellulitis were pneumonia and cellulitis. A 56% response rate was seen in older patients unfit for intensive chemotherapy. As the myelo-

suppression was considered to be longer than acceptable in this population, a smaller fractionation dose was felt advisable [77].

[^{225}Ac]Ac-lintuzumab is also being studied in a phase 1 clinical trial in patients who have progressing multiple myeloma disease after three prior multiple myeloma treatment regimens and are refractory to QUAD (carfilzomib, lenalidomide, pomalidomide, dexamethasone). This trial will estimate the maximum tolerated dose (MTD), assess adverse events, and measure response rates [78].

21.22.1 [^{131}I]I-Apamistamab CD45 Receptor Expressed in Leukemia and Lymphoma

Radioimmunotherapy has been used for many years in refractory/relapsed non-Hodgkin's lymphoma and shown to be effective in numerous clinical trials. The first agents were Bexxar®, a ^{131}I-radiolabeled murine monoclonal ([^{131}1]I-tositumomab) antibody, and Zevalin®, a ^{90}Y-radiolabeled murine antibody ([^{90}Y]Y-ibritumomab), both targeting CD20 receptors on the surface of lymphocytes [79].

The sale of Bexxar was terminated in February 2014 as there was a large decline in usage (fewer than 75 patients in 2012), despite the drug showing a 70% response rate; the lack of demand was because oncologists could not sell it directly to patients but had to refer patients to third parties, and because of the emergence of nonradioactive drugs that were as good, and which could be administered directly by medical oncologists.

Interest, however, has resurfaced in using anti-CD45-targeted conditioning with iodine-131 apamistamab [Iomab-B] plus allogeneic hematopoietic cell transplantation (HCT) as a safe alternative to conventional care for older patients with active relapsed/refractory AML. The treatment was shown to provide effective and tolerable therapy for ablating the patients' cancer and marrow cells. The pivotal phase trial in relapsed or refractory AML in 150 patients has been carried out as a randomized controlled clinical trial involving patients who have relapsed or refractory AML, aged 55 years and above. A durable complete remission (dCR) was chosen as the primary endpoint in this trial, and primary endpoint in this trial, .and the secondary endpoint chosen was overall survival at 1 year. [^{131}I]I-apamistamab [Iomab-B] is intended to prepare and condition patients for a hematopoietic stem cell transplant (HSCT) as a safer and more efficacious alternative to intensive chemotherapy [80].

Another murine monoclonal antibody, lilotomab (formerly tetulomab), was developed targeting CD37, a surface glycoprotein expressed on mature human B cells. It was linked to lutetium-177 using satetraxetan, a derivative of DOTA for beta radiotherapies. The compound was developed under the trade name Betalutin ([^{177}Lu]Lu-HH1 or [^{177}Lu]Lu-lilotomab satetraxetan). The compound is being utilized in relapsed/refractory follicular lymphoma patients who have received at least two previous systemic therapies. In the LYMRIT 37-01 phase 1/2 clinical study of Betalutin® ([^{177}Lu]Lu-satetraxetan-lilotomab) in 74 evaluable patients with relapsed/refractory indolent non-Hodgkin's lymphoma (iNHL), patients with iNHL received Betalutin® in a single administration with 6 months or more of follow-up. There was an overall response rate (ORR) of 61%, with 28% of the 74 patients having a complete response (CR). Durable responses, especially for patients with a CR (20.7 months) and promising response rates (ORR and CR) for dosing regimens, have been assessed in pivotal phase 2b PARADIGME study. The compound was well tolerated with a predictable and manageable safety profile [81].

21.23 Anti-HER2 in Breast Cancer

The human epidermal growth factor 2 (HER2) has been extensively evaluated since its discovery in 1987 by Dr. Slamon and colleagues, mainly as its overexpression in tumors has been associated with more aggressive tumor types. The first humanized monoclonal antibody developed targeting HER2 in HER2-positive breast cancer patients approved by the US Food and Drug Administration (FDA) was trastuzumab (Herceptin; Genentech,

South San Francisco, CA). Pertuzumab, trastuzumab emtansine (T-DM1), and lapatinib are approved for inhibiting HER2 activity in the treatment of HER2-positive metastatic breast cancers. Pertuzumab (Perjeta; Genentech, South San Francisco, CA) is a humanized mAb version developed to bind extracellularly to domain II of the HER2 epitope. This humanized mAb works by inhibiting HER2 dimerization with other growth factor receptors, such as HER2-HER3 dimerization. Preclinical experiments showed that the combination of trastuzumab and pertuzumab enhanced the antitumor effect compared to trastuzumab or pertuzumab alone due to complementary mechanisms of action that promote tumor regression more effectively [82].

Once developed, antibodies designed for radiotherapy can be labeled with a host of tumoricidal radiotherapeutics, such as alpha, beta, and Auger electron-emitting radionuclides. Trastuzumab similarly has been labeled with a series of HER2-targeted radionuclides. This antibody has been labeled with lutetium-177 (^{177}Lu), copper-64 (^{64}Cu), indium-111 (^{111}In), thorium-227 (^{227}Th), rhenium-188 (^{188}Re), yttrium-90 (^{90}Y), and iodine-131 (^{131}I) [82, 83].

Abbas et al. performed a preliminary clinical study with [^{177}Lu]Lu-trastuzumab involving 10 patients in order to assess the localization of the [^{177}Lu]Lu-trastuzumab in primary and/or metastatic lesions and in the nontarget organs. [^{177}Lu]Lu-trastuzumab accumulated in the HER2-positive lesions, but no uptake was noted in the HER2-negative sites (as delineated by IHC). Biodistribution studies showed normal uptake in the heart, liver, spleen, and nasopharynx, but did not evaluate dose or toxicity to erythrocytes or leukocytes.

Pertuzumab has also been labeled with lutetium-177 using the chelate isothiocyanate-benzyl-CHX-A″-DTPA. One preclinical study by Persson et al. used SKOV-3 OVCa xenografted Balb/c (nu/nu) mice, showed that [^{177}Lu]Lu-DTPA-pertuzumab delivered a high tumor dose of 50.86 ± 5.57 Gy with an injected activity of 7.3 MBq. The study group treated with [^{177}Lu]Lu-pertuzumab showed a clear delay in tumor growth [83].

21.24 Targeting Hypoxic Tumor Cells with Carbonic Anhydrase IX-Specific Antibody B Radioconjugates

Because many solid tumors become hypoxic, and many cancer cells can survive under conditions of hypoxia, carbonic anhydrase IX (CA-IX) has been considered an attractive target for diagnosis and therapy of solid tumors. Under low oxygen tension, CA-IX confers cancer cell survival and is accompanied by an elevated propensity for metastasis. CA-IX is a transmembrane zinc metalloenzyme which is involved in the hydration of carbon dioxide to bicarbonate ions and hydrogen. There is an increased expression of CA-IX in many malignancies, as the tumors attempt to maintain an optimal cellular pH. For this reason, CA-IX is an ideal protein for targeting hypoxic cells, and radiolabeled antibody-targeting CA-IX has been evaluated in clinical trials [84].

A number of different targeting vectors to CA-IX have been developed, including monoclonal antibodies, peptides, small molecule inhibitors, and antibody mimetics. All have been radiolabeled for either imaging or therapeutic application, including one of the more promising, cG250, a chimeric monoclonal antibody. In early clinical trials, the effect of the mouse anti-CA-IX antibody G250 labeled with the β-emitting radionuclide iodine-131 was examined in patients with metastatic clear cell renal cell carcinoma (ccRCC). Seventeen out of 33 patients responded to this treatment resulting in stable disease, but unfortunately, patients developed human anti-mouse antibodies (HAMA), which limited further treatment. In order to prevent the HAMA response, a chimeric version of G250 (cG250 girentuximab) was developed. The chimeric antibody was labeled with iodine-131 and then administered to 12 patients with metastatic ccRCC in a low dose to document tumor uptake. Uptake in metastases was observed in nine of the patients, of whom eight received a second dose of [^{131}I]I-cG250 at 1665, 2220, or 2775 MBq/m^2, leading to a partial response occurring in one patient, with stable disease lasting for 3–6 months in a second patient. Fractionated dosing of [^{131}I]

I-cG250 given at a whole-body absorbed dose of 0.5, 0.75, or 1 Gy (3–7 fractions/patient) did not enhance clinical response, with 7 of the 14 patients who completed treatment showing stable disease, while the remaining 7 patients showed disease progression. In addition, administration of [^{131}I]I-cG250 given at 2220 MBq/m^2 followed 3 months later at 1110 or 1665 MBq/m^2, in 3 and 16 patients, respectively, did not improve the clinical response, with 5 patients having a stable disease and the remaining patients having progressive disease [85].

Treatment of ccRCC patients with a residualizing radionuclide (lutetium-177)-labeled cG250, compared to non-residualizing iodine-131, led to better responses in patients who underwent up to 3 cycles of treatment, with 1 partial responder and 17 out of 24 patients having stable disease 3 months after the first cycle of treatment. In a second, nonrandomized single-arm trial, 14 ccRCC patients received 2405 MBq/m^2 [^{177}Lu] Lu-cG250, culminating in 1 patient having a partial regression and 8 patients having stable disease. Of these responding patients, six patients received a second cycle of treatment, resulting in durable responses in five patients but with prolonged thrombocytopenia restricting further cycles of treatment [86].

21.25 Tumor Necrosis Therapy for Lung and Pancreatic Cancers

[^{131}I]I-ch tumor necrosis therapy (TNT) has received approval from the Chinese State Food and Drug Administration for the treatment of advanced lung cancer patients who had previous treatment failure with radiotherapy or chemotherapy. TNT utilizes the presence of degenerating and necrotic cells within tumors by exploiting mAbs directed against universal, intracellular nucleosomal determinants comprising histone H1 and DNA. The monoclonal antibody `, which increase the pharmacokinetic performance of the monoclonal antibody. The ^{131}I-TNT construct delivers iodine-131 to tumor cells and leads to the targeted imaging and/or destruction of cells with exposed necrotic antigens. In clinical trials, patients were treated with two doses of ^{131}I-TNT and showed a favorable response rate of 34.6%. These results confirmed that the combination of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and iodine-131 triggered apoptosis of NSCLC through caspase-9 activation [87].

Preclinically, TNT has also been studied as an antibody for targeted alpha therapy (TAT) and has been labeled with bismuth-213 for the treatment of a pancreatic cancer xenograft in this study. Antibody radioconjugate therapy was demonstrated to be more effective at controlling tumor growth with fewer side effects in comparison with gemcitabine or cisplatin. The bismuth-213 decay chain results in the emission of both α and β particles before the long-lived bismuth-209 is reached. The resulting delivery of both α and β doses would be ideal when targeting necrotic tumors for two main reasons. First, the high-energy α particles emanating from the necrotic tumor core would irradiate hypoxic cells within 2–3 cell diameters from the source located in the necrotic region, while in addition, the longer penetration of β particles can be advantageous in delivering a higher dose to well-oxygenated cancer cells, distant from the necrotic cells, and would not require as high a β dose due to the higher oxygenation [87].

21.26 Actinium-225 Insulin Growth Factor for Multiple Solid Tumors

There has been an interest in targeting type I insulin-like growth factor receptor (IGF-1R) labeled with actinium-225 to solid tumors, non-small cell lung cancers, prostate cancers, sarcomas, and breast cancers, where this growth factor is overexpressed. [^{225}Ac]Ac-FPI-1434 is a radioimmunoconjugate comprising a humanized mAb (AVE1642) that binds to the external domain of IGF-1R, a proprietary bifunctional chelate, and the alpha-emitting radionuclide actinium-225. Once internalized, the monoclonal antibody radiolabeled with actinium-225 can cause tumor cell death via double-stranded DNA breaks. An

indium-111 analog [^{111}In]In-FPI-1547 has identical antibody and bifunctional chelate activity and is used for patient selection. Patients overexpressing the insulin-like growth factor can be selected based on imaging and quantitating the bound ^{111}In-antibody [88].

A phase 1 study is currently being conducted in several centers to evaluate the safety and tolerability of [^{111}In]In-FPI-1547 injection and [^{225}Ac]Ac-FPI-1434 injection in patients with advanced refractory solid tumors. It is also hoped to determine the maximum tolerated dose of a single [^{225}Ac]Ac-FPI-1434 injection. Preliminary data on tumor uptake of the [^{111}In]In-FPI-1547 compound in cancer patients is also being assessed [89].

21.27 Camelid Single Domain Antibodies (SDAB)

These single monomeric variable domain antibodies, or nanobodies, with a molecular weight of 12–15 kDa, are smaller than common antibodies by a factor of approximately 10. A group referred to as third-generation antibodies comprise two heavy chains attached to the variable domain and have been derived from dromedaries including camels, llama, alpaca, and shark. Key characteristics of the variable heavy homodimers (VHH) include high chemical and thermal stability, good solubility, a high penetration rate into tissues, low immunogenicity, and the ability to target antigenic epitopes via the long CDR3 loop on the nanobody difficult to access with conventional monoclonal antibodies. Desirable characteristics for tumor imaging include the high binding affinity for tumor antigens, rapid blood clearance of unbound nanobodies, renal elimination, high tumor-to-non-tumor ratio achieved shortly after tracer injection, and a lack of observed toxicity [90].

Radiolabeling of nanobodies with the gamma-emitting radionuclide technetium-99m via the hexahistidine tag has been performed without causing a chemical modification of the protein, and this has enabled the use of SPECT to image molecular targets such as HER2, which is a transmembrane glycoprotein overexpressed by certain tumor cells including breast cancer [91].

Xavier et al. [92] have depicted high specific contrast imaging of HER2-positive tumors in xenografts with PET-CT using gallium-68 to label the 2Rs15d nanobody utilizing the bifunctional chelating agent NOTA. Keyaerts et al. [93] reported a high accumulation in metastases of HER2-overexpressing tumor by the [^{68}Ga]Ga-anti-HER2 VHH nanobody in a phase 1 trial in patients with breast cancer. This radiolabeled nanobody has a favorable biodistribution and safety profile with no observable adverse effects at a radiation dose similar to other PET tracers with acceptable dosimetry. A phase 2 trial is currently underway using this radiotracer to characterize HER2 presence in brain metastases of breast cancer patients.

Nanobodies labeled with radionuclides other than gallium-68 have been studied. D'Huyvetter et al. [94] have shown that ^{177}Lu-labeled anti-HER2 inhibits the growth of HER2-expressing tumors in xenografted mice and suggested further investigation of [^{131}I]I-SGMIB-2Rs15d to perform dosimetry calculations prior to therapy in HER2-positive breast cancer patients [95].

Extensive research into radiolabeled nanobodies is an ongoing process with many preclinical trials investigating molecular targets such as epidermal growth factor receptor (EGFR) for skin cancer, HER3 for non-small-cell lung cancer and head and neck cancers, and CEA for colon cancer. There is preclinical evidence that anti-macrophage mannose receptor (MMR) nanobodies selectively targeting tumor-associated macrophages in vivo, anti-CD20 in CD20-positive NHL, and anti-idiotypic molecular target in multiple myeloma show promising results for future theranostic opportunities [96, 97].

The use of radiolabeled nanobodies to image atherosclerotic disease has also been investigated in preclinical trials [98] by targeting vascular cell adhesion molecule 1 (VCAM-1) and MMR to assess plaque burden in the aorta using PET-MRI to detect vessel wall inflammation, microcalcification, and inflammatory activity [99]. The extensive preclinical work coupled with recent

phase 1 and 2 trials demonstrates that an exciting future for the use of nanobodies as theranostic agents is within our grasp.

21.28 Intraperitoneal Radioimmunotherapy of Ovarian Cancer

The antibody MX35 displays uniform reactivity with 90% of human ovarian epithelial cancers, but only a limited number of normal tissues. It has been tested in a clinical phase 1 trial. The antibody MX35 is a $F(ab')_2$ which recognizes the membrane sodium transporter (NaPi2b). It was labeled with the α emitter astatine-211 ($T1/2$ = 7.21 h) and then infused via peritoneal catheters in nine women (median age of 52 years) as part of a phase 1 study. The concept was to attempt to treat micrometastases in the peritoneum. The women subjects were initially successfully treated for ovarian carcinoma but later relapsed and were treated long term with salvage chemotherapy, including Paraplatin and paclitaxel, resulting in clinically and biochemically complete remission. [^{211}At]At-MX35 $F(ab')_2$ (22.4–101 MBq/L) was infused via the peritoneal catheter over 30 min, together with 0.2 MBq of [^{125}I]I-human serum albumin (HSA), a reference for in vivo stability. The patients were given a thyroid blocking agent, which appears to have blocked any significant stomach accumulation of astatine-211. The results of the phase 1 study showed low toxicity and low dose to critical organs. There were no signs of diminished tolerability to future therapy and no signs of thyroid dysfunction. The aim of the study was not to evaluate the clinical outcome, but to evaluate the distribution and potential side effects [100].

21.29 Targeted Radiolabeled Nanoparticles

Nanoparticles (NPs) can be used for drug or radionuclide delivery either as passive or active targeting nanocarriers. Agents have been developed to improve the biodistribution, pharmacological, therapeutic, and toxicity properties in cancer diagnostics and therapeutics.

A major advantage of nanosized radioactive particles is their potential to contain numerous radioactive atoms within a single nanoparticle. Each radioactive nanoparticle can contain hundreds of radionuclides, and, consequently, by delivering one radiolabeled nanoparticle to a tumor site, hundreds of radionuclides can be transported. Conventional radiolabels using chelates allow only one tumor-avid biomolecule to carry one radioactive atom. The nanoparticles that are surface conjugated to tumor-avid biomolecules will initiate a higher ratio of radioactive particles to tumor-avid properties and daughter retention [101].

Radionuclides with therapeutic potential alpha or beta emissions have been incorporated within nano-materials for specific radiotherapies. Alternatively, gamma or PET emitters have been paired with nanoscale materials for diagnostic imaging. Particularly, 8 MeV particles (such as those produced in the decay chain of actinium-225) deliver their absorbed dose within a distance of ~100 μm or approximately 10 cell diameters, thus limiting damage to nontarget cells. Recent clinical trials of bismuth-213 have used this radionuclide coupled to anti-CD33 mAb for the treatment of AML. Actinium-225 has also recently been proposed as an alternative to bismuth-213 treatment since this radionuclide has a much longer half-life ($T1/2$ = 10 days). A single atom can produce four alpha particle emissions with a total energy release of more than 27 MeV per decay, making it a potent radioisotope if all the energy is deposited at the tumor site. In comparison with single α-emitting therapies, the use of in vivo α generators within gold-contained nanoparticles holds the potential to convey a much larger biologically effective dose to target tissues. All the daughter radionuclides are released after the occurrence of initial R-decay following the attachment of actinium-225 to antibodies with conventional molecular chelators such as DOTA. When actinium-225 is encapsulated in fullerenes, the daughter radioisotopes can also

be released, probably as a result of breaking the fullerene cage from the energy of nuclear decay recoil. Nevertheless, by employing $LaPO_4$ NPs to contain the radioisotopes rather than chelators, it has been shown that nearly all of the actinium-225 and almost 50% of the francium-221 and bismuth-213 daughters are retained within the NPs in vitro, indicating a dramatic improvement over conventional approaches [102].

While several radiolabeled nanoparticles have been used in preclinical work, few have currently been used thus far in human clinical trials.

21.30 Radiolabeled Aptamers

Aptamers, also known as "chemical antibodies," are short (20–100 bases) single-stranded RNA or DNA oligonucleotides, binding to targets with high selectivity and with high affinity. Aptamers are capable of folding into three-dimensional structures and bind to their target in a similar manner to their antibody protein counterpart through shape recognition. Aptamers are produced by "systematic evolution of ligands by exponential enrichment" (SELEX). This process involves iterative rounds of incubation, isolation, elution, and amplification of a randomized oligonucleotide library to a target to produce aptamers with high selectivity and specificity to the target [103, 104].

Aptamers generated by SELEX depict high affinity and specificity to a target, as the nucleic acids undergo iterative rounds of incubation, washing, isolation, and amplification. The process consists of using an initial library containing random RNA and DNA molecules, which are incubated with the target of interest, that might be biomarkers, proteins, or even entire cells. After incubation, the unbound RNA or DNA sequences are washed away, leaving only the bound sequences. To further enrich these bound sequences, they are then eluted from the sample, and using polymerase chain reaction (PCR) or reverse transcription PCR for RNA aptamers, the bound sequences are amplified. Then, this enriched pool of sequences undergoes iterative rounds of selection-amplification cycles, to increase the affinity of the aptamers, as each consecutive round will diminish the heterogeneity of the pool. Following analysis of binding affinities, the pool with the best affinity and specificity is then cloned and sequenced [103].

Practical applications of aptamers in vivo demonstrated some challenges including susceptibility degradation by nucleases present in human serum and the fast excretion by renal filtration ribose. Fortunately, the short half-life of aptamers in human serum can be extended by modifying their exo- and endonuclease resistance. This modification can occur either pre- or post-selection via SELEX. Aptamers hold many advantages over antibodies such as the fact that they are more stable and resistant to changes in pH and temperature, also enabling them to be easily chemically modified, unlike antibodies, which cannot regain function after being denatured. While antibodies can vary significantly between production batches, aptamers are synthesized chemically and thus are more uniform. As aptamers are raised from nucleic acids rather than antibody proteins, they are generally not capable of generating immunological or toxic reactions. They are also considerably smaller than antibodies (5–15 kDa) in comparison with large monoclonal antibodies (15 kDa). As aptamers are much smaller than antibodies, they show superior tissue penetration (greater capabilities to be internalized by tumors). In addition, the smaller size gives aptamers the ability to bind to hidden epitopes which are not accessible to larger antibodies. These numerous advantages of aptamers have spurred their development as potentially more promising than antibodies [103].

Limited work has been completed in this area, but all molecular targets which have been selected for radionuclide therapy by antibodies or peptides can theoretically be considered as potential targets by radiolabeled aptamers and will provide new opportunities to treat cancer at a cellular level or at a metastatic stage, as well as providing opportunities for early diagnosis. Aptamers are emerging frontiers in medical molecular technology for cancer diagnostic and therapeutic applications [105].

21.31 Conclusion

The perspective of delivering treatments that have a more pronounced activity with specific molecular features will lead to improved benefits to patients, in ideal cases leading to palliation, control, or potentially even cure. A plethora of new cellular, intracellular, and membrane targets are adding new sensitivity to the diagnosis of diseases, particularly cancer, but also infectious diseases, atherosclerosis, and dementia. Once the diagnostic target is identified and successfully imaged, then a therapeutic radionuclide can selectively treat the diseased cells. The "molecular" ideal is to use true theranostic compounds, such as iodine-124 or iodine-123 for imaging and iodine-131 for therapy, but advances in chelation and nanoparticle therapy now make it possible to add any metal to a binding chelate for delivery to the target, and nanoparticles can potentially bind multiple diagnostic or therapeutic radionuclides. Preliminary treatments are now feasible using this approach for a large number of cancers, with extraordinary results achieved already in neuroendocrine tumors and prostate cancers, and almost certain to be followed in most other tumors. This chapter has focused on compounds already recently approved or in human clinical trials, but a plethora of other compounds are currently in preclinical animal studies and will shortly be entering human trials. For every agent in human clinical trials or awaiting approval, many more are undergoing evaluation in pre-clinical animal studies.

Targeted radionuclide therapy is not alone. In addition to the age-old therapies of surgery, external radiation, and chemotherapy, immunotherapies, microwaves, and thermal therapies are adding to the diagnostic and therapeutic toolbox becoming increasingly available to clinicians. This is the golden age of theranostic research with other cutting-edge treatments giving new hope to patients and also a new perspective to nuclear medicine physicians.

One of the main challenges facing radionuclide therapy, however, is the current shortage of trained nuclear medicine radionuclide therapists. In the past 35 years, nuclear medicine has evolved from a joint specialty of endocrinology, internal medicine, pathology, and radiology to a branch of radiology—or, in some countries, cardiology—but increasingly an "imaging" specialty. The problem is that most radiologists are not trained to do radionuclide therapy. Most of the oncology therapies, for example, are currently in the hands of radiation oncology and medical oncology. Radionuclide therapy is likely to change the specialty of nuclear imaging back to the specialty of nuclear medicine, as originally envisioned by Saul Hertz with the first radioiodine therapy.

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