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REVIEW ARTICLE

Neuroendocrine tumor theranostics

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Abstract

Theranostics is a term coined by combining the words "therapeutics" and "diagnostics," referring to single chemical entities developed to deliver therapy and diagnosis simultaneously. Neuroendocrine tumors are rare cancers that occur in various organs of the body, and they express neuroendocrine factors such as chromogranin A and somatostatin receptor. Somatostatin analogs bind to somatostatin receptor, and when combined with diagnostic radionuclides, such as gamma-emitters, are utilized for diagnosis of neuroendocrine tumor. Somatostatin receptor scintigraphy when combined with therapeutic radionuclides, such as beta-emitters, are effective in treating neuroendocrine tumor as peptide receptor radionuclide therapy. Somatostatin receptor scintigraphy and peptide receptor radionuclide therapy are some of the most frequently used and successful theranostics for neuroendocrine tumor. In Japan, radiopharmaceuticals are regulated under a complex law system, creating a significant drug lag, which is a major public concern. It took nearly 10 years to obtain the approval for somatostatin receptor scintigraphy and peptide receptor radionuclide therapy use by the Japanese government. In 2021, ^{111}Lu-DOTATATE (Lutathera), a drug for peptide receptor radionuclide therapy, was covered by insurance in Japan. In this review, we summarize the history of the development of neuroendocrine tumor theranostics and theranostics in general, as therapeutic treatment for cancer in the future. Furthermore, we briefly address the Japanese point of view regarding the development of new radiopharmaceuticals.

KEYWORDS
neuroendocrine tumor, peptide receptor radionuclide therapy, somatostatin analog, somatostatin receptor scintigraphy, theranostics

Abbreviations: CT, computed tomography; DOTA, dodecane tetraacetic acid; DTPA, diethylenetriamine pentaacetic acid; FDG-PET, fluorodeoxyglucose-positron emission tomography; GEP, gastroenteropancreatic; mCRPC, metastatic castration-resistant prostate cancer; MSA, Medical Service Act; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; NET-G1-3, NET-grade 1-3; ORR, overall response rate; OS, overall survival; PAA, Pharmaceutical Affairs Act; PC, prostate cancer; PFS, progression-free survival; P-NET, pancreatic NET; PRRT, peptide receptor radionuclide therapy; PSMA, prostate-specific membrane antigen; RHPA, Radiation Hazards Prevention Act; SPECT, single-photon emission computed tomography; SRS, somatostatin receptor scintigraphy; SSA, somatostatin analog; SSTR, somatostatin receptor.

1 | INTRODUCTION

Neuroendocrine tumor is a type of cancer with high expression of SSTR. Octreotide is a peptide of agonistic SSA, which binds to SSTR and induces its phosphorylation and internalization.[1] Octreotide labeled with diagnostic radionucleotide is a good radiotracer for diagnostic imaging of NETs, which is named SRS. Somatostatin analog labeled with therapeutic radionucleotide is a radionuclide therapy drug for NETs, known as PRRT. Somatostatin receptor scintigraphy and PRRT are regarded as the most successful examples of "theranostics."[2]

The term "theranostics" derives from the words therapeutic and diagnostic. The term was introduced by Funkhouser, the CEO of Pharmanetics Inc., at the beginning of the 1990s as a business model for the development of diagnostic tests directly linked with the application of a specific therapy.[3] Recently, the development of diagnostics and therapeutics for cancer has advanced in an integrated manner rather than separately. The next phase of cancer treatment is the combination of diagnostics and therapeutic approach provided by theranostics, in which a single chemical entity delivers therapy and diagnosis simultaneously.[4]

In nuclear medicine, theranostics was suggested by Dr. Srivastava[5] as "theragnostics." Iodine-131 (Table 1) is not just a gamma-emitter for imaging, but a beta-emitter for internal radiation therapy; it has been a conventional theranostic material for thyroid cancer for the past 80 years.[6] Iodine accumulates in the thyroid gland by itself; however, to accumulate radionuclides within cancer tissues, it is necessary to develop chemicals with specific affinity for cancer cells. In the 1980s, the establishment of techniques to produce an intended mAb has significantly changed the strategy of cancer targeting with radiopharmaceuticals.[7] These techniques have enabled the synthesis of cancer-specific Abs and also the development of a new cancer-specific theranostic drug, by combining the technology that links the Abs to radionuclides.[8]

2 | NEUROENDOCRINE TUMOR

Neuroendocrine tumors are rare cancers categorized as NENs.[9] Neuroendocrine neoplasms are classified into two fundamentally different groups: well-differentiated, low-proliferating NENs defined as NETs or carcinoids, and the poorly differentiated, highly proliferating NENs considered as NEC.[10] Neuroendocrine tumors and NEC are quite different in nature. Neuroendocrine tumor is the primary target of this review.

Neuroendocrine tumors occur almost everywhere in the body. Approximately 70% of NETs form in the GEP system, 25% in the respiratory system, and 5% in other organs.[10] In Japan, the incidence of GEP-NET is increasing, however, it is still a rare cancer. The incidence of GEP-NET in Japan was 2.10 per 100,000 in 2005 and 3.51 in 2010.[11] Sometimes, NETs induce symptoms such as carcinoid syndrome associated with autocrine hormones; nonetheless, most NETs are nonfunctional. Neuroendocrine tumors are immunohistochemically positive for neuroendocrine markers, such as chromogranin A or synaptophysin (Figure 1). Proliferation rate is an important prognostic factor for NETs. According to the WHO grading system,

TABLE 1 Radionucleotides utilized in cancer diagnosis or treatment

Radionucleotide	T1/2 (h)	Main emission	Max. energy (keV)	Max. particle range in the body (mm)	Reference
Iodine-131	193	β^-	610	2.9	66
		γ	362		
Iodine-123	13	γ	159		22
Indium-111	67.2	γ	173		31
			245		
		Conversion electrons	144-245	0.2-0.55	
		Auger electrons	0.5-25	0.00002-0.01	
Yttrium-90	64	β^-	2250	11	66
Lutetium-177	162	β^-	498	2	66
		γ	208		
Gallium-68	12.7	β^+	1899	9.8	66
Copper-64	12.7	β^+	653	3.2	66, 68
		β^-	579	2.8	
		γ	1345.7		
		Auger electrons	6262-6567	0.00012	
Fluorine-18	1.83	β^+	635	2.4	55
		γ	511		
Actinium-225	240	α	5800	0.04-0.1	67

Note: T1/2: Half life

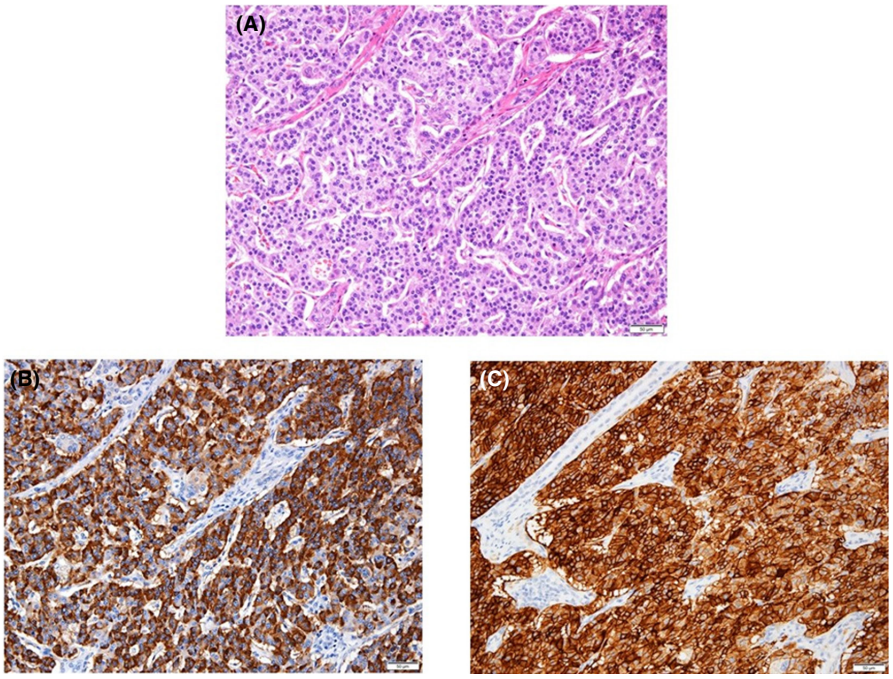

FIGURE 1 Light microscopic findings of pancreatic neuroendocrine tumor-grade 1 primary lesions. (A) Hematoxylin-eosin staining showed a trabecular or duct-like structure, forming a frequent anastomosing pattern. (B) Immunohistochemistry of chromogranin A. Granular cytoplasmic expression of chromogranin A was detected. (C) Immunohistochemistry for somatostatin receptor type 2A, which is strongly positive in the cell membrane and cytoplasm

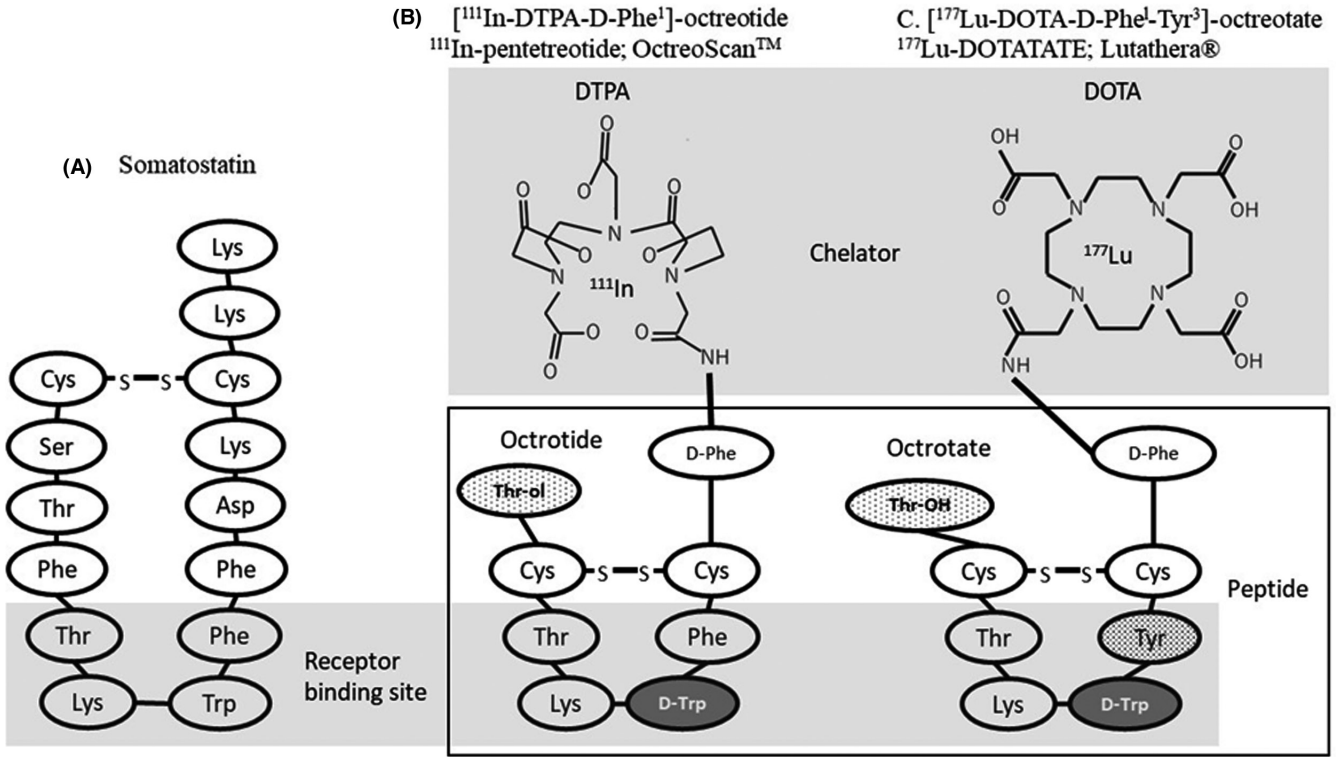

FIGURE 2 (A) Primary structure of somatostatin. (B) Structure of pentetreotide. Pentetreotide is octreotide conjugated to diethylenetriamine pentaacetic acid (DTPA). DTPA can bind tightly to ^{111}In. (C) Structure of DOTATATE, an octreotate that conjugates to dodecane tetraacetic acid (DOTA). DOTA can bind tightly to ^{177}Lu

low-grade proliferative NETs (NET-G1) show good prognosis, intermediate grade (NET-G2) show poor prognosis, and high grade NETs (NET-G3) show poor prognosis.[12]

Neuroendocrine tumors are frequently characterized by high SSTR expression levels (Figure 1). SSTRs are receptors for somatostatin. Five types of SSTRs have been identified. Somatostatin receptor type 2, especially type 2A, is highly expressed in NETs.[13] Both NET-G1 and -G2 showed high expression of SSTR irrespective of the primary organs, and in NET-G3 or NEC, SSTR was weakly detected.

Somatostatin receptors are G protein-coupled receptors activated by somatostatin (Figure 2A), which inhibits hormone secretion and cell proliferation.[14] Somatostatin has the ability to inhibit the growth of NETs or control hormonal symptoms by NETs. The half-life of somatostatin in the body is very short (approximately 1-3 minutes), and many SSAs have been developed to maintain sufficient serum concentrations.[15] Agonistic analogs, such as octreotide and lanreotide, have been approved for gastrointestinal NETs or P-NETs in many countries.[16]

3 | SOMATOSTATIN RECEPTOR SCINTIGRAPHY

The diagnosis of GEP-NETs has been difficult over an extended period. Advances in diagnostic images have improved the diagnostic ability of NETs. Somatostatin receptor scintigraphy is the most important diagnostic tool for NETs.

[^{111}In-DTPA-D-Phe^{1}]-octreotide (^{111}In-pentetreotide, Figure 2B) was radiolabeled with indium-111 (^{111}In, Table 1), using the chelator DTPA.[17] ^{111}In-pentetreotide is intravenously injected into patients with NET, and the octreotide binds to SSTR expressed on the NET (Figure 3). Gamma rays emitted by ^{111}In are detected by the gamma camera, and NETs can be detected anywhere in the body (Figure 4). In the 1980s, Iodine-123 (^{123}I, Table 1), which was previously used to detect thyroid cancer,[18] was used for imaging of NETs for the first time. ^{123}I-Tyr-3-octreotide could be successfully synthesized; however, it was rapidly cleaved in the liver and easily excreted in the intestine, making detection of NETs in the upper abdomen difficult.[19] Due to its renal clearance, ^{111}In-pentetreotide is more suitable for detecting NET in the abdomen, including GEP-NET. Compared with ^{125}I-Tyr-3-octreotide and ^{188}Re-octreotide, ^{111}In-pentetreotide was the most suitable agent to detect small-cell lung carcinoma.[20]

Yao et al[21] reported that the incidence rate of NET increased from 1.4/100,000 in 1974 to 5.25/100,000 in 2004 in the United States. Based on these results, from 1987 to 1994, the increasing rate of incidence was calculated to be approximately 0.09 per year, and from 1995 to 2001, it was 0.178. After 1995, the rate of incidence was twice that before 1995. In 1994, the FDA approved ^{111}In-pentetreotide. In particular, ^{111}In-pentetreotide was more sensitive to detect liver or bone metastases of NET than the conventional tools, including CT, MRI, ultrasonography, or bone scintigram.[22,23]

Fluorodeoxyglucose-PET is the most popular functional imaging method for detecting cancer. ^{111}In-pentetreotide was more sensitive than FDG-PET for well-differentiated NENs, whereas FDG-PET revealed superior sensitivity for poorly differentiated NENs.[24] Most NET-G1 lesions are undetectable by FDG-PET but detectable by ^{111}In-pentetreotide SPECT/CT (Figure 4B). Moreover, patients with FDG-PET positivity showed a worse prognosis than FDG-PET-negative patients.[25] Usually, it is inversely correlated with FDG uptake and ^{111}In-pentetreotide uptake in NET lesions.[26] The malignant potential of each NET might be predicted using these images.

4 | PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

^{111}In-pentetreotide was used as the therapeutic agent. Krenning indicated that ^{111}In produced two types of electrons, Auger and conversion electrons. A high dose of ^{111}In-pentetreotide could be used for internal radiation therapy.[27] For scintigraphy, 122 MBq of ^{111}In-pentetreotide was given to human patients. Anthony et al used at least 180-mCi (6660 MBq) of ^{111}In-pentetreotide twice each month in patients with GEP-NET.[28] They concluded that PRRT using ^{111}In-pentetreotide was well tolerated and increased the expected survival. Electrons emitted by ^{111}In showed at most 500 μm of tissue

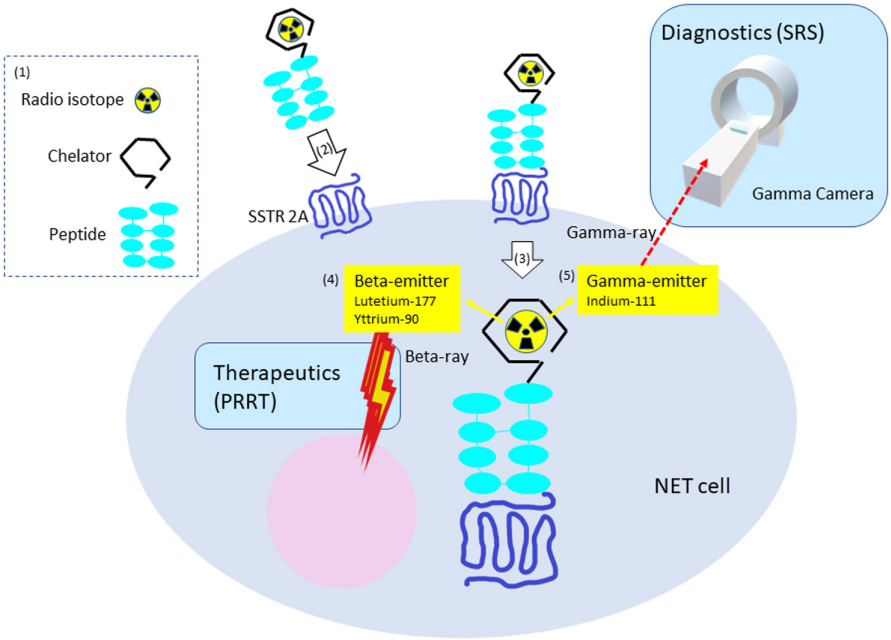

FIGURE 3 Theranostics of SRS and peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumors (NETs). (1) Drugs for PRRT or SRS are formed by peptides possessing specific affinity to somatostatin receptor (SSTR) 2A, chelators binding to radionuclides. (2) A drug binds to SSTR 2A on NET cells and (3) is internalized into the cells. (4) When radionuclides are beta-emitters, such as lutetium-177 or yttrium-90, drugs work as therapeutics for NETs. (5) When radionuclides are gamma-emitters, such as indium-111, drugs work as diagnostics for NETs

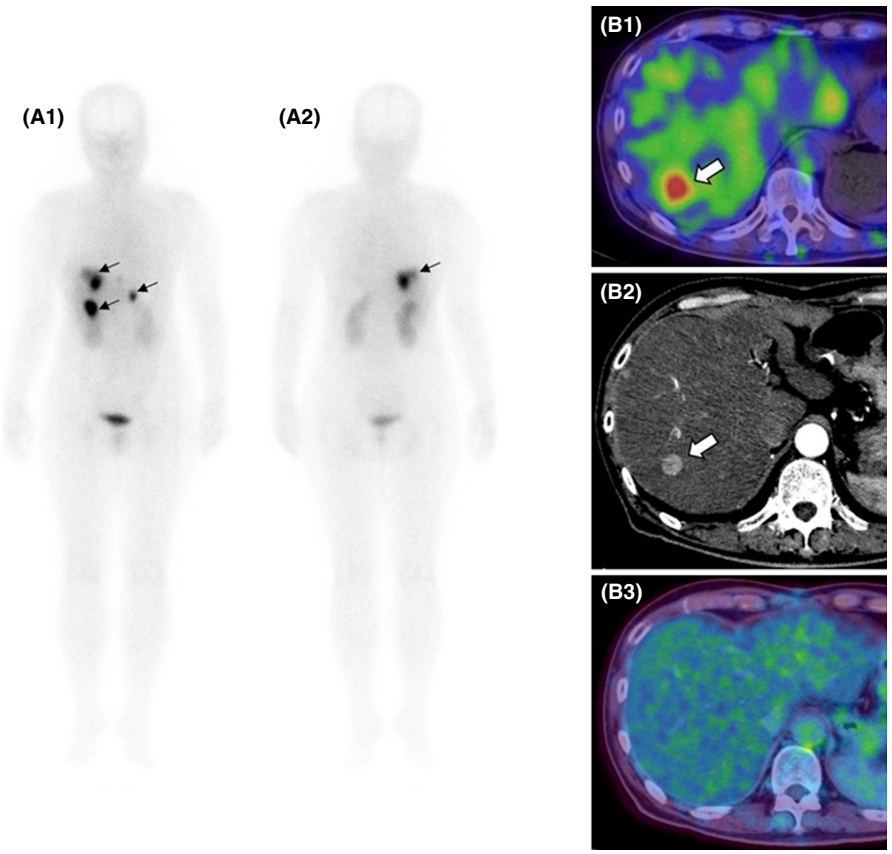

FIGURE 4 Imaging of a patient with postoperative pancreatic neuroendocrine tumor-grade 1 (NET-G1) with liver recurrences. (A) Planar imaging of ^{111}In-pentetreotide (A-1, anterior; A-2, posterior). Black arrows indicate accumulation of ^{111}In-pentetreotide in the liver. (B-1) Single-photon emission computed tomography/computed tomography (CT) imaging of liver metastasis. White arrow indicates ^{111}In-pentetreotide in the liver. (B-2) Contrast enhanced CT of liver metastasis of the same lesion as B-1 (white arrow). (B-3) Fluorodeoxyglucose (FDG)-PET imaging of the same slice of the liver as shown in B-1 and B-2. There is no accumulation of FDG in the liver. NET-G1 can be detected by ^{111}In-pentetreotide, but not usually by FDG-PET

penetration, and the effect of ^{111}In-pentetreotide on NETs was limited.[29] Beta-emitters, such as Yttrium-90 (^{90}Y) or Lutetium-117 (^{117}Lu), were more effective because of the higher radiation dose and longer tissue penetration (Table 1). Otte et al[30] developed a new chelator of DOTA, which could hold ^{90}Y, [DOTA-D-Phe^{I}]-octreotide (DOTATOC; Figure 2). Imhof et al[31] reported a phase II single-center open-label trial of ^{90}Y-DOTATOC for NETs; 1109 patients received 2472 cycles of ^{90}Y-DOTATOC, the ORR was 34.1%, PFS was 12.7 months, and OS was 44 months. The most common adverse event was renal toxicity. One hundred and two patients (9.2%) experienced severe nephrotoxicity. This is because radiolabeled SSA was reabsorbed by the proximal tubules of the kidneys and the proximal tubules highly expressed STR, thus leading to high amounts of radiation exposure on the kidneys.[32] Rolleman et al reported that coadministration of L-lysine and L-arginine with radiolabeled SSA reduced its reabsorption and inhibited renal toxicity.[33] Peptide receptor radionuclide therapy was undertaken with coadministration of L-lysine and L-arginine. The therapeutic effect and renal toxicity of ^{90}Y-DOTATOC could be predicted by imaging of ^{111}In-pentetreotide. Higher accumulation of ^{111}In-pentetreotide in a tumor showed better prognosis than with ^{90}Y-DOTATOC treatment. Furthermore, the higher accumulation in the kidneys showed a higher occurrence of renal toxicity.[30] Diagnostic tools directly predict the effects of therapeutics. This is "theranostics".

O'Donoghue et al[34] estimated the optimal tumor cure size for several radionucleotides and the optimal tumor sphere diameter was 34 mm for ^{90}Y and 2.0 mm for ^{177}Lu. Thus, it is considered that ^{90}Y-DOTATOC is suitable for large lesions, whereas ^{177}Lu-DOTATOC is suitable for smaller nodules. Villard et al reported that a cohort study of metastasized NETs with ^{90}Y-DOTATOC monotherapy (three cycles of 3.7 GBq/m^2 of ^{90}Y) compared with ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC combination therapy (one cycle of ^{90}Y and two cycles of 7.4 GBq of ^{177}Lu).[35] The OS of combination therapy (5.51 years) was significantly longer than that of monotherapy (3.96 years). Recently, ^{177}Lu was used more preferably than ^{90}Y, because ^{177}Lu emitted lower energy at a shorter range than ^{90}Y, and ^{177}Lu caused less damage to the neighboring healthy cells.[36]

Somatostatin analogues (SSAs) have also been developed. Octreotate is an identical peptide of octreotide, except that the C-terminal threonine amino alcohol is replaced by threonine. The chelate analogue DOTA-D-Phe^{I}-Tyr^{3}-octreotate (DOTATATE, Figure 2) showed a nine-fold higher affinity for SSTR2 than DOTATOC.[37] The effect of DOTA-lanreotide was inferior to that of octreotide.[38] ^{111}Lu-DOTATATE has a high affinity for SSR, and it is a safer drug for PRRT.

In 2018, the FDA approved ^{177}Lu-DOTATATE for the treatment of SSTR+ NETs in the gastrointestinal tract or pancreas in adults. This was because the international phase III trial of NETTER-1 for metastatic midgut NETs that were to receive ^{111}Lu-DOTATATE or best supportive care including octreotide LAR, showed that PFS at 20 months and the response rate of ^{177}Lu-DOTATATE was significantly better than that of the control (PFS, 65.2% vs 10.8%; ORR, 18% vs 3%).[39] Moreover, ^{177}Lu-DOTATATE significantly prolonged time to quality-of-life deterioration of midgut NETs compared with control (28.8 vs 6.1 months).[40] The effect of PRRT on midgut NETs

was confirmed. The effects on other primaries are still unclear. Imhof et al reported that ^{90}Y-DOTATOC for nonfunctioning P-NET (n = 295) showed a good response (ORR, 49.2%) and good survival (OS, 60 months).[31] Satapathy et al[41] reported a meta-analysis of ^{177}Lu-DOTATATE for advanced P-NETs (697 patients in 15 articles) that the ORR was 47%, PFS was 25.7 months, and the therapeutic efficacy of ^{177}Lu-DOTATATE was superior to that of everolimus. Peptide receptor radionuclide therapy is becoming an important therapeutic agent for NETs. The positioning of PRRT for GEP-NET in the guidelines of several cancer societies might need to be re-evaluated depending on the final result of the NETTER-2 study on ^{177}Lu-DOTATATE with long-acting octreotide (30 mg) vs long-acting octreotide (60 mg) for G2/G3 advanced GEP-NET as a first-line treatment.[42]

5 | NEUROENDOCRINE TUMOR THERANOSTICS IN JAPAN

It took a long time for the clinical use of SRS and PRRT to take off in Japan. The application for approval of ^{111}In-pentetreotide (OctreoScan, Mallinckrodt Pharmaceuticals) was submitted in the United States and European nations in 1993. At the beginning, Czechoslovakia approved it in 1994, which was followed by the United States, and then UK, France, and Germany that approved it in 1995. In Japan, a domestic phase III clinical trial was undertaken in 1994,[43] and an additional phase III trial was completed in 2005.[44] The working group for OctreoScan in Japan made an evaluation that the results of clinical trials in Japan were good enough for approval.[45] However, although nearly 10 years has passed since the completion of the phase III study, it is yet it to be approved. Moreover, 20 years has passed since the completion of the clinical trials of the United States and European nations. The cause of this drug lag remains unclear. The main reason might be that NET is a rare cancer. Moreover, there were some possible deductions that the Japanese branch of Mallinckrodt Pharmaceuticals, which was the manufacturer of OctreoScan, was newly merged with Tyco Healthcare Japan. Tyco had a recall case to deal with during that time, and it is possible that the price of OctreoScan did not match other Tyco Healthcare Japan and Japanese agents. However, OctreoScan could not be utilized for Japanese patients in routine health insurance treatment. In 2010, the Health, Labour and Welfare Ministry in Japan established "an evaluation committee for unapproved or off-labeled drugs with high medical needs" to gather the need for unapproved drugs that were already approved in the United States and/or European nations. Three medical societies, the Japanese Society of Nuclear Medicine, the Japan Endocrine Society, and the Japan Radiological Society, submitted OctreoScan to the committee, and it was approved in 2015.

The case for PRRT was more complicated. In fact, it was only recently that ^{111}Lu-DOTATATE (Lutathera, Advanced Accelerator Application) was approved in the EU (in 2017) and the United States (in 2018); however, PRRT has been in used in parts of Europe and Australia for at least a decade. In the clinical practice guidelines for GEP-NET of the European Society of Medical Oncology in 2010, PRRT was clearly stated as a treatment option,[46] before the European Neuroendocrine Tumor Society indicated the possibility of PRRT for P-NETs in their guidelines.[47] In the United States, the University of California, Los Angeles Ahmanson Theranostics Center has been treating NETs with PRRT since 2016.[48] Furthermore, in the United States and the EU, physicians were utilizing PRRT before its approval based on a system of compassionate use of experimental drugs. In the United States and the EU, medical drugs, whether radioactive or not, are regulated by pharmaceutical laws. However, in Japan, radiopharmaceuticals, especially before approval, are regulated by complex system of laws, and physicians cannot readily use them.

In Japan, commonly used pharmaceuticals are regulated under the PAA and the MSA; however, radiopharmaceuticals are regulated under the Laws Concerning the Prevention of Radiation Hazards due to Radioisotopes and Others (RHPA) in addition to PAA and MSA. Radiopharmaceuticals are regulated under RHPA from the transfer of the primary materials, to the making of the radiopharmaceuticals, and its transfer to a hospital. In hospitals, they are regulated under the PAA and the MSA laws, where radiopharmaceuticals can be utilized like other common pharmaceuticals. However, unapproved radiopharmaceuticals are regulated under RHPA, even in hospitals. RHPA does not assume that a radionuclide is a medical drug for human use. Because of these complex regulations for radiopharmaceuticals in Japan, we had to refer Japanese NET patients, who had indications for PRRT, to Europe for treatment. From 2011 to 2019, 38 patients traveled over 14 hours one-way to Professor Damian Wild, head of the Division of Nuclear Medicine at Basel University Hospital, Switzerland, from our hospital in Japan. The PFS among the referred patients was 12.8 months and 42.9% of them showed partial response.[49] Peptide receptor radionuclide therapy has become widely known in NET patients in Japan as a promising option. PanCan Japan, a nonprofit organization supporting pancreatic cancer patients, collected 33,778 signatures for immediate approval of PRRT in Japan and submitted it to the Health and Labor Ministry in May 2015. In June 2015, in the 189th session of the Diet, the condition of radionucleotide therapy including PRRT in Japan was discussed.[50,51] During the same year, the Japanese Society of Nuclear Medicine created a manual for proper use of ^{177}Lu-DOTATATE[52] and Advanced Accelerator Applications signed a distribution agreement for Lutathera in Japan with FUJIFILM RI Pharma Co. Ltd. (currently FUJIFILM Toyama Chemical Co. Ltd). In the 2017 Phase 1 study[53] and in 2018, Phase 1/2 study of ^{111}Lu-DOTATATE commenced. The 8th Annual Meeting of the Japan Neuroendocrine Tumor Society was held in Yokohama in January 2021, and the main theme was "NET theranostics." Finally, on June 23, 2021, Lutathera was approved in Japan. Ten years had passed since we referred the first patient to the Basel University Hospital. Complicated regulations for radiopharmaceuticals in Japan are still unresolved.

6 | FUTURE OF THERANOSTICS

Theranostics for NETs and for other cancers is progressing.

Gallium-68 (^{68}Ga, Table 1) is a positron-emitting nucleotide, which is then utilized as a tracer for PET, and ^{68}Ga-DOTATOC/PET was utilized for NET imaging. Van Binnebeek et al[54] compared ^{111}In-pentetreotide SPECT/CT to ^{68}Ga-DOTATOC PET/CT in a lesion by lesion and organ by organ analysis using 53 patients with metastatic NETs. The PET/CT detected 1098 lesions, and SPECT/CT detected 660 lesions in 53 patients. Four hundred and thirty-nine out of 1098 lesions were detected only by PET/CT, and only one out of 660 lesions were detected by SPECT/CT. ^{68}Ga-DOTATOC PET/CT showed clear images and high sensitivity to NET lesions, and it has been widely used in the United States and European nations; however, it is yet to be approved in Japan. Fluorine-18 (^{18}F, Table 1) is a proton emitter, and it is utilized as a tracer of FDG-PET. Various types of ^{18}F-labeled SSA have been created.[55] ^{68}Ga is synthesized by ^{68}Ge/^{68}Ga-generator, and ^{18}F is a generator-independent radioisotope. They have both merits and demerits; both tracers are being developed now. Prostate cancer expresses PSMA; as will be mentioned later, PSMA is a good target of theranostics for PC. Both ^{68}Ga-PSMA PET and ^{18}F-DCFPyL PET are good tracers[56] approved by the FDA as PSMA PET imaging agents. Copper-64 (^{64}Cu, Table 1) is also a positron emitter and is chelated by DOTA. ^{64}Cu-DOTATATE has been trialed for detecting NET[57] and many other cancers[58] as a PET tracer. ^{64}Cu also emits beta rays and Auger electrons, and it is expected to be a therapeutic radiopharmaceutical. Many radiotracers are being developed and Japan has to catch up with these evolutions.

Clinical trials of PRRT combined with anticancer drugs have been carried out. Clinical studies of ^{177}Lu-DOTATATE with capecitabine and temozolomide,[59] everolimus,[60] nivolumab, and pembrolizumab[61] are ongoing.

Alpha-emitters have received widespread attention as therapeutic drugs for cancer treatment. Alpha particles, consisting of two protons and two neutrons, show a short penetration depth (40-80 μm, corresponding to 2-10 cells) and a high-energy linear transfer compared with beta particles, which then produces minimal damage to the healthy tissue and a high rate of double-stranded and cluster DNA breaks in cancer cells.[62] The effect of alpha particles is independent of cell oxygenation, and hypoxic cancer tissue could be resistant to beta particles. Actinium-225 (^{225}Ac, Table 1) is a pure alpha-emitter and is believed to be a promising treatment nucleotide. Ballal et al reported on ^{225}Ac-DOTATATE therapy for 32 GEP-NET patients with stable or progressive disease treated with ^{177}Lu-DOTATATE.[63] The response rate was 46.9%.

Theranostics utilizing radionuclides have been successfully applied to other cancers. Ibritumomab, an anti-CD20 Ab with a tiuxetan chelator, is a drug for B-cell non-Hodgkin lymphoma. ^{111}In-ibritumomab tiuxetan is used for diagnostic imaging and ^{90}Y-ibritumomab tiuxetan (Zevalin, Mundipharma) was used for treatment. Recently, PSMA, which is highly expressed in PC, has attracted attention as a new target of theranostics for PC. Prostate-specific membrane antigen ligands labeled with ^{177}Lu were utilized for the treatment of mCRPC. ^{68}Ga-DOTA-PSMA was used for PET diagnostic imaging and ^{177}Lu-DOTA-PSMA was used for treatment. von Eyben et al[64] reported a systematic review and meta-analysis of 2346 mCRPC patients who received ^{177}Lu or ^{225}Ac-DOTA-PSMA with an OS of 16 months. Currently, at least three phase III clinical trials of ^{177}Lu-DOTA-PSMA for PC are ongoing.[65] Newly developed peptide binding to cancer-specific antigens will achieve further progression of theranostics.

7 | CONCLUSION

Peptide receptor radionuclide therapy for NETs is safe and effective. Currently, agonistic analogs are mainly utilized as peptides of PRRT; however, various kinds of peptides or other materials that bind to SSTR will be developed. Using alpha-emitters, combinations of different ranges of beta-emitters, combinations of PRRT and chemotherapy, or PRRT as adjuvant, constitute some of the many ways of using PRRT for NET and they might result in better prognosis. Moreover, from these successful experiences, theranostics using radionuclides will be developed for many other cancers and improve patient prognosis.

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CONFLICTS OF INTEREST

The authors have no conflict of interest.

ETHICAL APPROVAL

This study did not include any patients/patient-related medical information. Hence, ethics approval was not needed. We used diagnostic images of patients. Our institutional review board indicated that, in this case, as only photographs of diagnostic images were utilized without any patient's details, we only required the patient's consent. Written informed consent was obtained from the patients.

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