13 Basis of Therapeutic Nuclear Medicine

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13.1 Introduction

Therapeutic applications of nuclear medicine are expanding (Table 13.1). Until 5–10 years ago, the use of radioisotopes in therapy was limited predominantly to treatment of hyperthyroidism and thyroid cancer with I-131, polycythemia rubra vera with P-32, bone metastases(palliative) with strontium-89 (Sr-89), rhenium-186 (Re-186), samarium-153 (Sm-153), tin-117m (Sn-117), liver tumor and metastases with Y-90 microspheres and neuroblastoma, pheochromocytoma, and paraganglioma with I-131 MIBG. In recent years Lu-177 and Y-90 labeled somatostatin analogs for the treatment of neuroendocrine tumors (NETs), Lu-177 labeled PSMA ligands and Ra-223 dichloride for metastatic prostate cancer have been increasingly used.

It is not the objective of this chapter to discuss different protocols and experiences in the treatment of various conditions using radioisotopes. Rather, the objective is to explore some of the pathological features of the disease processes being treated, the underlying theory behind the action of the radioisotopes that induce therapeutic effects.

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Generally, treatment options for cancer may be local (surgery or external beam radiation) or systemic. The role of nuclear medicine focuses on a targeted systemic approach (Fig. 13.1), whether dealing with a primary tumor or with its metastatic foci.

13.2 Treatment of Hyperthyroidism

For more than 60 years, iodine-131 has been used to treat most cases of Graves' disease and hyperfunctioning nodules. It has become the modality of choice in treating Graves' disease, with the result that surgeons are becoming less and less

Table 13.1 Therapeutic applications of nuclear medicine

Oncologic
1. Lymphomas and leukemias
2. Polycythemia rubra vera
3. Solid tumors (thyroid carcinoma, neuroblastoma, ovarian, prostate, breast, osteogenic sarcoma, others)
4. Treatment of metastasis-induced bone pain
Non-oncologic
1. Benign thyroid disease particularly hyperthyroidism
2. Radionuclide synovectomy
3. Bone marrow ablation
4. Intravascular radionuclide therapy for prevention of restenosis

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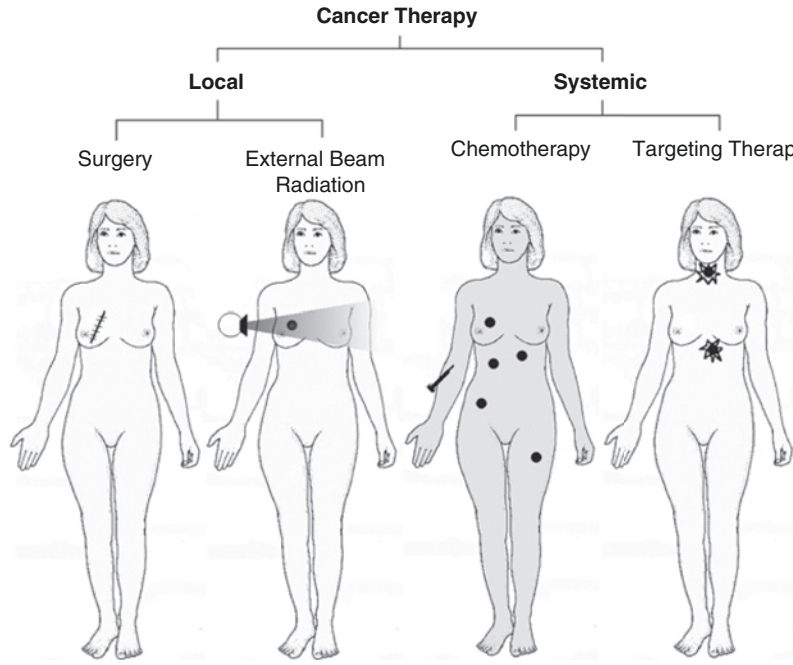

Fig. 13.1 The major types of cancer therapy. Nuclear medicine uses principally the targeting method in treating cancer and cancer metastases (modified from Prvulovich et al. [1])

experienced in thyroidectomy since the number of operations has decreased significantly. In a recent Canadian survey study, endocrinologist were found to be the most common to prescribe I-131 for malignant, while nuclear medicine physicians were the most in prescribing it for benign disease [2].

The normal thyroid gland varies in shape between individuals, and the average weight is approximately 20 g. The gland utilizes iodine for the synthesis of thyroid hormones (see Chap. 7). The cells of the gland do not differentiate between stable iodine and radioactive iodine. Accordingly, if radioactive iodine is administered, it is trapped and then organified by thyroid follicular cells exactly like nonradioactive iodine.

13.2.1 Pathophysiology

After oral administration, I-131 iodide is absorbed rapidly from the upper gastrointestinal tract, 90% within 60 min. After entering the blood stream, the iodide is distributed in the extrathyroid compartment similar to the stable iodide and leaves this compartment to be taken up by the thyroid and by renal excretion. Approximately 20% of the administered activity is taken up normally by the thyroid gland. A small amount of I-131 is also found in the salivary glands, gastric mucosa, choroid plexus, breast milk, and placenta. Up to 75% is excreted by the kidney and 10% by fecal excretion. Approximately 40% of the administered activity has an effective half-life of 0.43 days while 60% has an effective half-life of 7.6 days.

Graves' disease is the most common form of hyperthyroidism, comprising approximately 56% of all cases. It is also the major immunologically mediated form. It occurs most commonly in young women and is characterized by symptoms of hyperthyroidism with or without ophthalmopathy and dermopathy. Rarely, lymphadenopathy and splenomegaly may be present. The thyroid gland is usually diffusely enlarged but sometimes normal in size. The condition is an autoimmune process with autoantibodies directed against the TSH receptors on thyroid follicular cells which may be stimulatory and/or destructive [3]. Thyroid stimulatory antibodies include long-acting thyroid stimulator (LATS). This antibody is detected in most patients with Graves' disease and behaves like TSH, stimulating the production of thyroid hormones and consequently trapping and organifying radioiodine. The other stimulatory antibody is the LATS protector, the antibody

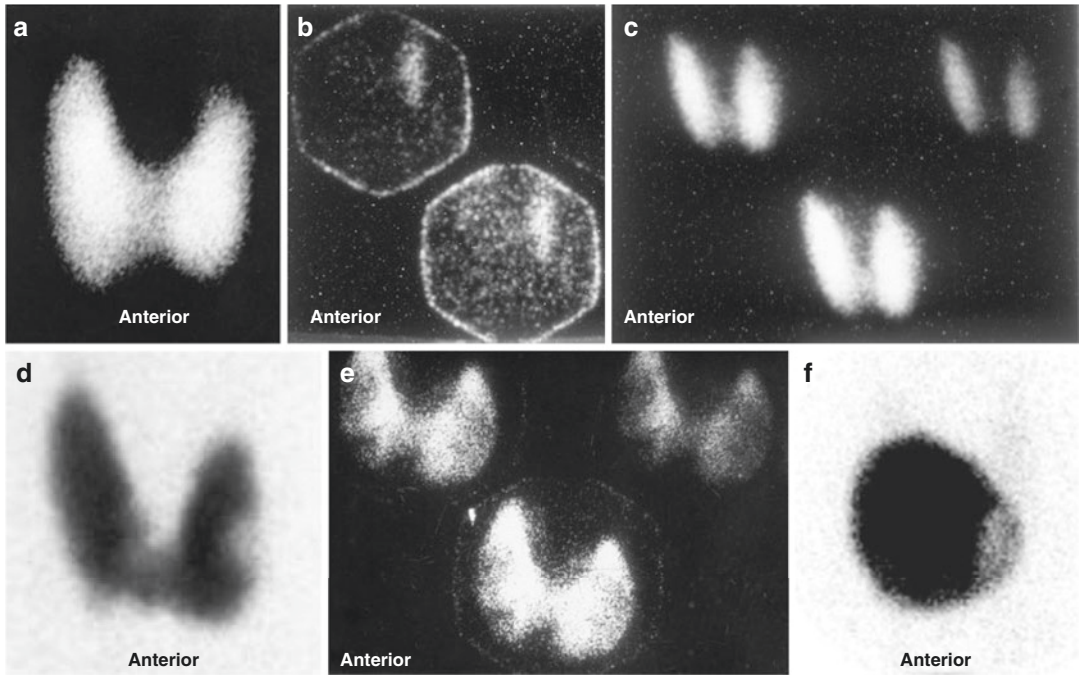

Fig. 13.2 Examples of thyroid scans of patients with hyperthyroidism illustrating patterns that affect the treatment strategy using iodine-131. (**a**) Illustrates pattern of uniform uptake in a patient with Graves' disease. Note that scans of patients during recovery phase of thyroiditis may simulate Graves' disease scintigraphically and show high uptake. Example (**b**) is of a patient with subacute thyroiditis. Scan shows decreased and nonuniform uptake with a 24-h uptake of 1%. Follow-up scan (**c**) shows uniform uptake throughout the gland with an uptake of 38%. This may be mistaken for Graves' disease if the patient is referred first during this phase. Example (**d**) shows diffusely toxic gland with significant nonuniformity and multiple cold nodules. Example (**e**) shows a scan of a patient with Graves' disease and a colloid nodule illustrating another pattern of "Marine–Lenhart" syndrome which is more resistant to iodine-131 therapy. Compare this pattern to that of multiple toxic nodules (Fig. 7.2). This pattern also needs to increase activity per gram of tissue for successful treatment. Example (**f**) is for autonomous single toxic adenoma which is treated by relatively high activity

that prevents degradation of LATS; accordingly, it helps to stimulate thyroid cells indirectly. The disease is associated with other autoimmune disorders such as pernicious anemia and myasthenia gravis.

Graves' disease is also known to be associated in Caucasians with HLA B8, DR2, and DR3 and with an inability to secrete certain glycoproteins coded for on chromosomes 6 and 19. A 50% concordance rate is seen among monozygous twins while 5% concordance is noted in dizygous twins. These facts suggest a genetic susceptibility for the disease. The observation that *Yersinia enterocolitica* and *Escherichia coli* and other gram-negative organisms contain TSH binding sites raised the possibility that the initiating event in the pathogenesis of the disease may be infectious in genetically susceptible individuals.

Histologically, there is hyperplasia of the thyroid epithelium, sometimes with papillary unfolding. Lymphocytic infiltration is present, usually less than in other forms of autoimmune diseases as postpartum thyroiditis. Little colloid storage is also seen. With time, the untreated gland will show progressive fibrosis and the end stage will lead to hypothyroidism, which may be considered part of the natural history of the disease [4, 5].

Thyroid scintigraphy shows uniform uptake throughout the gland or, less commonly, varying degrees of nonuniform uptake. This nonuniformity is related predominantly to different stages of involution of the disease with variable amounts of fibrosis based on the duration of the disease or the presence of nodules (Fig. 13.2). The presence of a TSH-dependent functioning nodule in a dif-

fusely toxic gland has been referred to as Marine–Lenhart's syndrome (Fig. 13.2). Since the function of such nodule is much less than the surrounding hyperfuctioning tissue, it appears scintigraphically cold.

Ophthalmopathy occurs in approximately 50% of patients with Graves' disease [6]. Infiltration of extraocular muscles by an inflammatory reaction consisting predominantly of lymphocytes is the main pathological feature of ophthalmopathy. These lymphocytes are believed to be sensitized to antigens common to the orbital muscles and thyroid gland. Similar inflammatory infiltrates may also be present in the dermis, causing the dermopathy or pretibial myxedema which may be present in up to 10% of patients with unclear etiology.

Single thyroid nodules can, via an autonomous function, secrete sufficient thyroid hormone to cause hyperthyroidism. These nodules are usually greater than 3 cm in diameter in order to be capable of producing this level of function [7]. Hyperfunction may also arise in a gland containing multiple nodules [8]. In this case, the secretion of thyroid hormones can be either from hyperfunctioning nodules that are assumed to be autonomous or from the internodule parenchyma, which may be an expression of Graves' disease in an otherwise nodular goiter. The nodules in the latter situation may be cold or a mixture of cold and hot, hypertrophic nodules. The term Plummer's disease, or toxic nodular goiter, has been used to designate hyperthyroidism in glands with both single and multiple toxic nodules. The term nodular toxic goiter may be reserved for a toxic gland that contains nodules that are not hyperactive. The presence of cancer in toxic nodular goiter is extremely rare and varies from 0.1 to 0.9%. The toxic nodular goiter may have a cold nodule representing a TSH-dependent adenoma. Scintigraphic imaging cannot exclude malignancy in the cold nodule that is not TSH dependent.

The therapeutic effects of I-131 sodium iodide are due to the emission of ionizing radiation from the decaying radionuclide. In benign conditions such as Graves' disease, division of some metabolically active cells is prevented by the effect of this ionizing radiation. Cell death is another mechanism activated when the cells are exposed to high levels of radiation, particularly when high doses are given to patients with toxic adenoma, where the suppressed normal thyroid tissue is essentially spared with delivery of a very high concentration to the cells of the toxic nodule. Cell death is followed by replacement with connective tissue, which may lead to hypothyroidism, depending on the number of cells destroyed and replaced by fibrous nonfunctioning tissue. Since 90% of the radiation effects of I-131 are due to beta radiation, which has a short range in tissue of 0.5 mm, the extrathyroid radiation and consequently the side effects are minimal. It has been estimated that 15% of patients treated with I-131 may show worsening of ophthalmopathy [9, 10]. Since posttreatment hypothyroidism has been associated with exacerbation of ophthalmopathy, lower-dose radioactive iodine or starting replacement hormones early (2 weeks) after therapy along with the use of prednisone 40–80 mg per day tapered over 3 months may prevent severe eye disease in up to two thirds of patients [11, 12]. It is interesting that cigarette smoking has been also implicated as a risk factor for progression of Graves' ophthalmopathy [10].

13.2.2 Factors Affecting the Dose of I-131 Used for Therapy of Hypothyroidism

Several factors affect the therapeutic dose to be administered to patients suffering from hyperthyroidism. These include some parameters related to the patient, such as age, sex, medical history, and duration of treatment with antithyroid medications, and factors related to the gland itself, particularly its size, the level of radioiodine uptake, scintigraphic findings of uniform or nonuniform uptake, and whether nodules are present. Additionally, the dose is dependent on how the therapist defines the goals of therapy. If the control of thyrotoxicosis is the most important consideration, the total dose or the dose per gram of estimated thyroid tissue weight will be higher than when the therapist is trying to avoid or delay

hypothyroidism [13]. Using empirical low-dose iodine therapy to avoid hypothyroidism has been shown to result in persisting hyperthyroidism in up to 54% of patients [14]. Additionally, it has been found that the rate of hypothyroidism is not different among those treated with low-dose and high-dose radioiodine [15].

13.3 Treatment of Differentiated Thyroid Cancer

Radioactive iodine is the mainstay of therapy for residual, recurrent, and metastatic thyroid cancer that takes up iodine and cannot be resected, for presumed disease (adjuvant therapy), and ablation of residual thyroid tissue. Radioactive iodine adjuvant therapy is routinely recommended after total thyroidectomy for high-risk differentiated thyroid cancer patients by the American Thyroid Association (ATA) [16]. Per ATA, radioactive iodine remnant ablation is not routinely recommended after lobectomy or total thyroidectomy for patients with unifocal papillary microcarcinoma, in the absence of other adverse features [16]. The tissue of normal thyroid and its tumors expresses a variety of oncogenes, growth factors, and growth factor receptors. There is increased expression of some oncogenes, namely, c-myc/c-fos and c-ras, in some epithelial and medullary thyroid carcinomas.

C-myc mRNA and c-fos mRNA are found in high levels in papillary carcinomas compared with the surrounding normal thyroid tissue. Patients with an unfavorable prognosis were twice as likely to overexpress c-myc as patients with good prognosis [17].

Ras oncogenes were found in 80% of follicular and 20% of papillary carcinomas. This high prevalence of transforming ras oncogenes in follicular carcinomas may explain its aggressive behavior in comparison to papillary carcinoma and may suggest a role of this oncogene in the metastatic phenotype of this cancer [18]. Recently a tissue-specific oncogene associated with papillary carcinoma has been identified.

Excessive growth factor and increased expression of oncogenes encoding growth factors or growth factor expression, such as the oncogene of c-ras B were identified in papillary carcinoma, adenomas, and anaplastic carcinoma.

Besides the importance of growth factors in the development of thyroid carcinoma, links have also been found to certain risk factors. The most important of these is radiation exposure. Exposure to radiation following the explosion of the atomic bombs in Japan, as well as after head and neck radiation, resulted in a 30-fold increase in the incidence of thyroid cancer [19].

About 90% or more of thyroid carcinomas are well differentiated, of the papillary, papillofollicular, follicular, and Hürthle-cell types, which take up iodine and accordingly can be successfully treated with I-131. The therapeutic effects on differentiated thyroid cancer, where larger doses of radioactive iodide are administered, are based on destruction of cells of the residual thyroid tissue and the functioning carcinoma cells by the high dose of administered radionuclide. The mortality of patients treated with subtotal thyroidectomy and limited I-131 therapy was found to be three to four times higher than that of patients treated with total thyroidectomy and I-131 therapy to ablate known foci of radioiodine uptake [20] (Fig. 13.3). Because of the larger dose of radionuclide and the lower uptake by the tissue in the case of thyroid cancer, more side effects can be seen, particularly transient sialadenitis, than in treatment of hyperthyroidism. This however does not justify using limited therapy such as 30 mCi. A recent study confirmed the high rate of efficiency of the high ablative dose of 100 mCi of I-131 particularly in patients with less than 2% neck uptake values [21]. This study confirmed also that success rate is dependent on the pre-therapy neck uptake. The success rate was 94% when pre-ablation uptake was less than 2, 80% with uptake between 2 and 5, and 60% when uptake value was more than 5% [21].

Thyroglobulin and calcitonin are the major tumor markers for thyroid cancer of the follicular epithelium and parafollicular C cells, respectively. These markers are unique, in the sense that they are not only specific for tumor tissue but are also specific components of normal thyroid tissue. Thyroglobulin is an iodinated glycoprotein

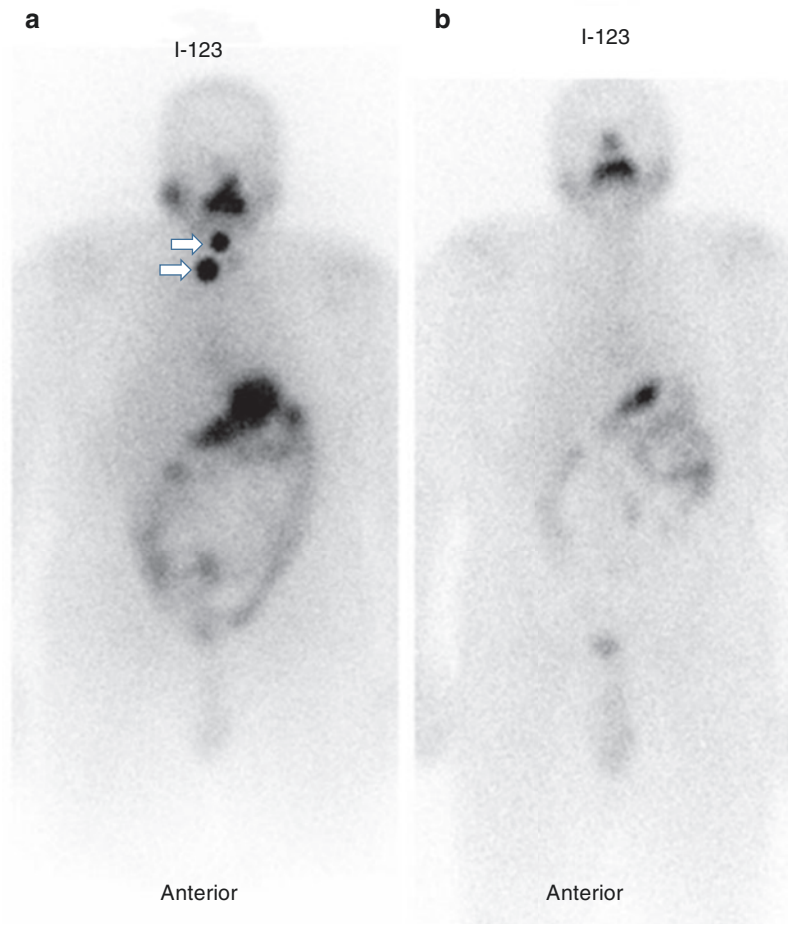

Fig 13.3 ^{123}I whole-body scan (**a**) for a patient with papillary thyroid carcinoma treated with total thyroidectomy. The scan shows neck activity (*arrows*). Follow-up scan (**b**) one year after I-131 ablation shows complete resolution

essential for synthesis and storage of thyroid hormones. Since thyroglobulin is produced exclusively by thyroid tissue, only very small amounts can be found in the blood after thyroidectomy and ablative radioiodine therapy. Accordingly, any post-therapeutic elevation of its levels indicates either remnant thyroid tissue, requiring further ablative treatment, or the presence of metastases or local recurrence. Other tumor markers used for many other tumors, such as carcinoembryonic antigen (CEA) and tissue polypeptide antigen (TPA), are not specific for thyroid cancer. TPA, which is a cytokeratin-related nonspecific proliferation marker, has a sensitivity of 40–60% for thyroid cancer. However, it has a good correlation with tumor progression or therapeutic response, with a high positive predictive value of 90%. Evaluation of ablative therapy and follow-up of patients post ablation to monitor disease recurrence has further improved and facilitated by the availability of recombinant human thyrotropin as well as the use of F-18 FDG positron emission tomography. The value of recombinant human thyrotropin (rhTSH) rests on providing the opportunity to obtain diagnostic whole-body I-131 scan under adequate TSH elevation as well as representative thyroglobulin levels while the patients receiving their thyroid hormone [22]. FDG-PET is useful in evaluating patients in instances where radioiodine imaging fails to identify known or suspected recurrent or metastatic disease [23]. Additionally, the use of Tl-201 and Tc-99m MIBI particularly when FDG-PET is not available is of value for this purpose [24].

There are many purposes to ablate postoperative normal residual thyroid tissue with I-131. Residual thyroid tissue, if large, can cause start

artifact and obscure the surrounding nodal uptake on radioiodine images. It can also take up most of the activity and leave small amount of activity for metastatic foci. It can mimic local/regional disease. It can harbor micrometastases. Residual thyroid tissue will also continue producing Tg and make Tg measurements unreliable. The usual amount of I-131 activity for ablation of the thyroid remnant is 1.11–3.7 GBq (30–100 mCi) which depends on the radioactive iodine uptake measurement and amount of residual thyroid tissue.

13.4 Treatment of Pain Secondary to Skeletal Metastases

Approximately 75% of patients with advanced cancer have pain, with a high percentage due to skeletal metastases. Bone metastases cause intractable pain, which affects the quality of life for the patient, especially if it is associated with immobility, anorexia, and anxiety, with the consequent long-term use of narcotic analgesics. The mechanism of bone pain may not be clear in many of these patients and could be due to cell-secreted pain modulators such as interleukin-1 beta, interleukin-8, and interferon [25]. Depending on the extent of bone metastases, radiation therapy or radiopharmaceuticals can be used instead of narcotics to alleviate the pain with the objective of improving the quality of life.

Radiotherapy for focal painful metastases with delivery of 2000–3000 rads induces pain relief in 60–90% of cases [26, 27]. Controlling pain of multiple metastases using external beam radiotherapy is difficult. Hemibody irradiation using 800 rads to the lower half of the body and 600 rads to the upper half has resulted in complete response in 30%, partial response in 50%, and no response in 20% of patients. Radiotherapy used for painful skeletal metastases often produces significant side effects such as nausea, vomiting, and diarrhea, as well as bone marrow toxicity in one third of patients. Vomiting and diarrhea can be severe in 10% of cases and hematological side effects can be life threatening in approximately 9% of patients [28].

Bone-seeking radiopharmaceuticals emitting beta particles have been used to deliver local radiotherapy to metastases to decrease pain at their sites. Radiopharmaceuticals which are taken up at the sites of bone metastases will cause less toxicity than external radiation therapy. These radiopharmaceuticals control pain while causing only transient bone marrow depression, which is usually mild. The uptake of these radiopharmaceuticals by metastases is several fold (up to 15–20 times) that of normal bone. These agents are absorbed to hydroxyapatite crystals at the site of active new bone, similar to Tc99m-MDP. They include phosphorus-32, strontium-89, rhenium-186 diphosphonate, and samarium-153 EDTMP. The list of radiopharmaceuticals for bone palliation has been increasing including Re-188, Lu-177, and others [29].

13.4.1 Radiopharmaceuticals

13.4.1.1 Strontium-89 Chloride (Sr-89 Chloride)

Systemic radionuclide therapy with Sr-89 chloride was first used to relieve pain from bone metastases in 1937 and regained popularity in the 1980s. It is a pure beta emitter with a relatively long half-life of 50.5 days. It is a chemical analogue of calcium, and accordingly it concentrates avidly in areas of high osteoblastic activity. After intravenous injection, strontium quickly accumulates in the mineral bone matrix where active bone formation takes place. Therefore, there is preferential uptake in and around metastatic tumor deposits which has been confirmed by external measurements using the gamma emitting radionuclide Sr-85 and by autoradiography. It was found that Sr-89 concentration is 2–20 times greater in bone metastases than normal bone [30]. The biological half-life of Sr-89 in bone lesions is about 90 days, compared to about 2 weeks in normal bone which can be explained by the immature nature of reactive bone compared to normal lamellar bone. This selective uptake and prolonged retention at sites of increased bone mineral turnover provide precise targeting of bone lesions. The radionuclide is

typically administered as a single 150 MBq (4 mCi) intravenous dose. Overall, pain relief occurs in up to 80% of patients, of whom 10–40% became effectively pain free. The mean duration of palliation is 3–4 months [31, 32]. Furthermore, 89Sr-chloride may cause slowing of metastatic progression due to inhibition of expression of cell adhesion molecules (E-selectins) that participate in the metastatic process. The significant transient decrease in serum E-selectin concentration as observed after systemic radionuclide therapy in a study on 25 men with metastatic prostate carcinoma is an indication of such an observation [33] and may provide opportunities for clinical trials.

13.4.1.2 Samarium-153 Ethylenediaminetetramethylene Phosphonate (Sm-153-EDTMP)

Samarium-153 is produced in the nuclear reactor by neutron activation of both natural Sm-203 and 98% enriched Sm-152 targets. It has a relatively short half-life of about 48 h. Coupling of the radionuclide to ethylenediaminetetramethylene phosphonate (EDTMP) leads to the high uptake of the radionuclide by bone. Gamma camera imaging is possible due to the 103 KeV gamma ray emitted during decay of Sm-153. The resulting images are similar to those obtained with Tc99m-MDP or other diphosphonates showing increased uptake at the site of metastases. The calculated lesion to normal-bone ratio was reported to be 4.0 and to soft-tissue ratio to be 6.0 [34].

Administration of 153Sm-EDTMP according to the supplier's recommendations at 37 MBq (1 mCi)/kg would deliver a bone marrow dose of 3.27–5.90 Gray (Gy) which would induce myelotoxicity as a side effect. Dosimetric calculation by urine collection and whole-body scintigraphy has been used to limit the bone marrow dose to 2 Gy by Cameron and associates [35]. This was achieved by anterior and posterior whole-body images obtained 10 min and 5 h after the intravenous injection of 740 MBq (20 mCi) of 153Sm-EDTMP with determination of bone activity by imaging and by counting urine collected for 5 h. The total administered activity of 153Sm-EDTMP predicted on a 2 Gy bone marrow dose was found to be 35–63% of the standard recommended dose of 37 MBq/kg. The authors reported pain relief in eight of the ten patients treated using this dosimetric method [35].

13.4.1.3 Rhenium-186 Ethylene Hydroxy Diphosphonate (Re-186-EHDP)

Similar to Sm-153, Re-186 has been coupled to a bone-seeking phosphonate, ethylene hydroxy diphosphonate (EHDP). This radionuclide emits beta particles with a maximum energy of 1.07 MeV and gamma photons with an energy of 137 keV which allows bone scanning. Re-186-EHDP undergoes renal excretion within 6 h after intravenous injection, as is the case with the common bone-scanning agents. At 4 days, 14% of the radioactivity remains in bone [36].

Several studies have shown encouraging clinical results of palliative therapy using 186Re-HEDP with an overall response rate of approximately 70% for painful osseous metastasis from prostate and breast cancer. Myelosuppression has been limited and reversible, which makes repetitive treatment safe [37, 38]. In a study of 31 patients with various cancers (10 prostate, 10 breast, 4 rectum, 5 lung, 2 nasopharynx) and bone metastases treated with a fixed dose of 1295 MBq (35 mCi) of Re-186 HEDP. When necessary, the same dose was repeated two to three times after an interval of 10–12 weeks. The mean response rate was 87.5% in patients with breast and prostate cancer, 75% in patients with rectal cancer, and 20% in patients with lung cancer. The overall response rate was 67.5% and the palliation period varied between 6 and 10 weeks. The maximal palliation effect was observed between the third and seventh weeks [38].

13.4.1.4 Tin-117m-Diethylenetriaminepentaacetic Acid (Sn-117m-DTPA)

Tin-117m is a reactor produced radionuclide, with a half-life of 13.6 days. Contrary to the other radionuclides mentioned above, this radionuclide emits internal conversion electrons. Tin-117m is linked to diethylenetriaminepentaacetic acid (DTPA). More than 50% of the administered

activity is absorbed by bone in patients with metastatic carcinoma with a bone to red marrow ratio of up to 9:1. Its 159 keV photon energy allows correlative imaging with a similar uptake pattern as Tc99m-MDP [39].

In a preliminary study in 10 patients by Atkins et al. [40], none of the patients who received Sn-117m-DTPA for palliation developed marrow toxicity. Another recent study on 47 patients treated with Sn-117-DTPA showed that the experimental mean absorbed dose to the femoral marrow was 0.043 cGy/KBq. In comparison to P-32-orthophosphate, Sn-117m-DTPA yielded up to an eightfold therapeutic advantage over the energetic beta emitter P-32. Accordingly, it was suggested that internal conversion electron emitter Sn-117m offers a large dosimetric advantage over the energetic beta-particle emitters allowing higher administered activity for alleviating bone pain, while minimizing marrow toxicity [41].

13.4.1.5 Phosphorus-32 Orthophosphate

This radionuclide is used uncommonly for the treatment of bone metastases. Dosimetric studies have demonstrated a relatively high dose to the bone marrow from the highly energetic beta particles of this radionuclide causing myelosuppression with pancytopenia. Increased incidence of acute leukemia has been reported although this was reported following P-32-therapy in patients with polycythemia vera.

13.4.1.6 Rhenium-188 Dimercaptosuccinic Acid Complex [Re-188(V)DMSA]

Re-188(V)DMSA, a potential therapeutic analogue of the tumor imaging agent Tc99m(V) DMSA, is selectively taken up in bone metastases. In a study by Blower et al. [42] on ten patients with metastatic prostate cancer studied by Tc99m(V)DMSA and 188Re(V)DMSA to compare their biodistribution, only minor differences between both radiopharmaceuticals were found. Accordingly, Tc99m(V)DMSA scans are predictive of 188Re(V)DMSA biodistribution and could be used to estimate tumor and renal dosimetry and assess suitability of patients for Re-186(V) DMSA treatment [42]. This advantage makes this tracer a candidate for more trials as a potentially successful agent for bone metastases palliation.

13.4.1.7 Ra-223 Dichloride

Ra-223 dichloride has both palliative and therapeutic effect approved for the treatment of castration-resistant prostate cancer with symptomatic bone metastases. This will be discussed in Metastatic Prostate Carcinoma section.

13.4.2 Mechanism of Action

Metastatic bone pain is believed to be due to mechanical factors due to local bony destruction and to humoral factors resulting from secretion of certain mediators by tumor and peri-tumoral cells (Table 13.2). Although the mechanism of action of these radiopharmaceuticals in relieving bone pain is not completely known, the therapeutic effect is thought to be achieved by delivering suf-

Table 13.2 Types of cellular damage in relation to approximate radiation dose

Dose (grays (rads))	Type of damage	Comments
0.01–0.05 (1–5)	Mutation (chromosomal aberration, gene damage)	Irreversible chromosome breaks, may repair
1 (100)	Mitotic delay, impaired cell function	Reversible
3 (300)	Permanent mitotic inhibition, impaired cell function, activation and deactivation of cellular genes and oncogenes	Certain functions may repair; one or more divisions may occur
>4–10 (>400–1000)	Interphase death	No division
500 (50,000)	Instant death	No division
		Proteins coagulate

Modified from Maxon et al. [4] with permission

ficient energy from the sites of reactive bone directly to the cells of metastases and/or to peritumor cytokine-secreting cells that may be responsible for the patient's pain. Pain relief by radiation was found to be independent of the radiosensitivity of the tumor and therefore the mechanism of action does not involve actual killing of the tumor cell. It is more likely that radiation interrupts processes that are maintained by humoral pain mediators in the microenvironment of the tumor [43]. This view is also supported by absence of a dose-response relationship [44].

13.4.3 Choice of Radiopharmaceutical

It has been demonstrated that myelosuppression is less severe using radionuclides with relatively shorter half-lives favoring the use of Sm-153, Re-186, Sn-117, and Sr-89. Other physical properties including radiolabeled conjugate biological uptake and clearance, product-specific activity, range and type of emissions, and resultant effects on tumor and normal tissue cellular survival should be all considered along with the clinical outcome to choose a radiopharmaceutical. The response rate of different radiopharmaceuticals currently in use appears not to differ significantly [45].

13.4.4 Clinical Use

Radiopharmaceutical therapy is indicated for the treatment of patients with painful widespread bone metastases. However, the patient with pain secondary to either spinal cord or peripheral nerve invasion by adjacent metastases will not benefit from such treatment. The contraindication in pregnancy is absolute, and relative contraindications include preexisting severe myelosuppression, urinary incontinence, severe insufficiency, and spinal cord compression or pathological fracture. A pre-therapy bone scan within 3 mos, neurological examination, and blood counts should be available before the patient is treated. Follow-up blood counts should be performed at least biweekly to evaluate myelotoxicity. The response to these radiopharmaceuticals is more or less similar, with an average success rate of 70–80% [46–52].

The difference in half-life of the radiopharmaceuticals and the extent of bone metastases has consequences for both the onset and the duration of pain relief. Relief rates using the newer agents are not significantly different and are comparable with those of external beam radiotherapy, but side effects are minimal and compare favorably with those of the older agent P-32.

Using radionuclide along with chemotherapy for palliation is being investigated and may proof useful. Palmedo et al. reported a case of a patient with disseminated bone metastases due to breast cancer and multifocal pain. Because of persisting pain after a first cycle of chemotherapy, 1295 MBq Re-186 HEDP was administered and pain relief was significant. Subsequently, the patient received combined chemotherapy along with Re-186 HEDP therapy and remained pain free. Follow-up Tc99m-MDP bone scan showed significant regression of osseous metastases. The authors speculated that the combination of Re-186 HEDP and chemotherapy resulted in significantly increased palliation of metastatic bone disease [53].

The side effects, which are mainly hematological, vary among the agents used, being more pronounced with P-32 than with the newer agents. Some agents have the advantage of emitting gamma energy suitable for scintigraphy such as samarium-153 EDTMD (ethylenediaminetetramethylene phosphonate). Tin-117m DTPA differs from the other radiopharmaceuticals in that it emits conversion electrons rather than beta particles. These conversion electrons have low energy and a shorter path in tissue and may then result in less marrow toxicity [50, 54].

13.5 Treatment of Neuroendocrine Tumors

Neuroendocrine tumors constitute a heterogeneous group of neoplasms originating from neuroendocrine cells that secrete biogenic amines and polypeptide hormones. Recently, the incidence of these tumors has gradually increased worldwide. The clinical behavior of neuroendocrine tumors is significantly variable; they may be hormonally active or nonfunctioning, ranging from very slow-growing tumors to highly aggressive and very malignant tumors. Surgery is currently the only available curative treatment for these tumors, but for patients who have inoperable primary, recurrent or metastatic disease, few therapeutic options are available. The goals of radionuclide therapy for neuroendocrine tumors are to control symptoms and pain, improve the quality of life, reduce medical requirements, and stabilize the disease. Additionally, in limited disease it is used to reduce tumor volume, reduce hormone secretion, and help complete remission.

Several neuroendocrine tumors are candidates for radionuclide therapy. I-131 has been used to treat neuroblastoma, pheochromocytoma, and paraganglioma. More recently octreotide and other analogues labeled with In-111, Y-90, and Lu-177 are being used [55–57] (see later).

I-131 metaiodobenzylguanidine (MIBG) is being used for the treatment of pheochromocytoma, malignant paraganglioma, neuroblastoma, medullary thyroid carcinoma, and symptomatic carcinoid tumors. The radiopharmaceutical resembles guanethidine and is concentrated by normal and abnormal sympathetic adrenergic tissue.

When I-131 MIBG is administered intravenously, it is transported by blood to be taken up by normal adrenergic tissue such as the adrenal medulla and sympathetic nervous system and by tumors of neuroectoderm-derived tissue. The uptake by these tumors is secondary to active uptake-1 mechanism and passive diffusion through the cell membrane, followed by active intracellular transport to the neurosecretory granules in the cytoplasm, where it is retained.

In normal adrenergic tissue such as the adrenal medulla, heart, and salivary glands, as well as in pheochromocytoma, 90% of MIBG is stored in the neurosecretory granules, while in neuroblastoma it was found that up to 60% is stored within the extragranular cells. The major part of the radiopharmaceutical is excreted unchanged in urine. Other than in the adrenergic tissues, uptake is normally noted in the liver, spleen, urinary bladder, bowel, lungs, nose, near the trapezium muscle in children, and in the uterus in some women [58, 59]. The radiation effect is due to emission of beta particles from the decaying I-131 with a mechanism similar to that in treating thyroid disorders. A long list of medications is known to block the uptake and/or retention of MIBG by the target tissues, while some reports have suggested that others such as calcium channel blockers may increase its uptake. The mechanism of interference of these drugs varies. Beta-blockers, for example, interfere with the uptake by inhibiting the uptake mechanism-1 and by depleting the neurosecretory granules, while reserpine exerts this action by depleting the granules and inhibiting the intracellular transport. More recently peptide therapy has been increasingly used to treat these tumors (shown later in the chapter).

13.5.1 Neuroblastoma

Therapeutic amounts of I-131 MIBG can be delivered to neuroblastoma with acceptable bone marrow toxicity [60–62]. Among patients with stages 3 and 4 neuroblastoma who had failed treatment with chemotherapy, I-131 MIBG induced partial remission in many children and complete remission in a small number of patients. The agent has also been used for early therapy at the time of diagnosis, with a success rate comparable to that of chemotherapy with fewer side effects [61]. Since some neuroblastomas express somatostatin receptors, peptide receptor radionuclide therapy particularly with 177Lu-DOTA-TATE is also beneficial.

13.5.2 Pheochromocytoma

Malignant pheochromocytoma and its metastases are known to be resistant to chemotherapy and external beam radiation therapy. I-131 MIBG has a limited role in the treatment of malignant pheochromocytoma, functioning paraganglioma, and medullary carcinoma of the thyroid. Palliative effects have been achieved in patients with pheochromocytoma [63]. Several reports from the USA and Europe have collectively shown a response of 62.5% among patients with pheochromocytoma [45]. Soft-tissue metastases responded better than skeletal metastases.

13.5.3 Carcinoid Tumor

Carcinoid liver metastases are common and rarely can be resected. Treatment for symptomatic patients with unresectable disease includes chemotherapy, interferon alpha, and the somatostatin analogue, octreotide. The response to these medical therapies is usually poor. Hepatic artery ligation and embolization are alternatives and have a better response rate. Preliminary experience also suggests that external beam radiotherapy can be useful. I-131 MIBG and radiolabeled octreotide have recently been tried. I-131 MIBG is highly concentrated by more than 60% of carcinoid metastases. Carcinoid tumor cells stain positive for chromogranin A [64]. I-131 MIBG targets the metabolically active lesions, reduces the hormonal secretion, and improves symptoms [1, 65]. Data indicate a partial response in 20% of patients and a palliative effect in more than 50% of those with end-stage disease. I-131 MIBG causes temporary myelosuppression, which makes its use favorable compared with chemotherapy. It is also preferred to interferon alpha and octreotide, which require frequent subcutaneous injections.

Pathologically, I-131 MIBG produces gross cystic changes in liver metastases which probably are due to ischemic necrosis. Surgical deroofing and aspiration of cysts can lead to regeneration of normal liver tissue [1].

13.6 Radioimmunotherapy

Monoclonal antibodies are now contributing increasingly to cancer treatment, following early disappointments. I-131 anti-CD-20 and I-131 anti-CD-22 are good examples which are used for non-Hodgkin's lymphomas. These antibodies can be used alone to kill tumor cells or conjugated with drugs, cytotoxic agents, and radionuclides to improve their effects.

Radioimmunotherapy using monoclonal antibodies conjugated with isotopes allows the delivery of radiation to tumor tissue while sparing normal tissue. This radiation can be administered as a single large dose of radiolabeled monoclonal antibodies or, more commonly, in multiple fractions [66–68].

Although the way they work is not entirely clear, generally monoclonal antibodies can kill tumor cells through the following mechanisms [69]:

1. Activation of host immune system to lyse tumor cells, e.g., complement, antibody-dependent cellular cytotoxicity (ADCC)
2. Directing biologically active agents to tumor cells (e.g., drugs, toxins, cytokines, isotopes)
3. Triggering or interfering with the function of physiologically important cell receptors
4. Inducing indirect antitumor response by triggering the formation of autoantibodies or activation of cellular responses to tumor antigens to destroy tumor cells
5. Killing tumor cells by apoptosis, which is simply an intrinsic "programmed" cell death characterized by chromatin condensation and DNA degeneration

The use of radioimmunotherapy for treating lymphoma has been expanding in the last decade. It is currently being used for recurrent and relapsed disease of low-grade B cell and follicular and transformed lymphomas. Clinical trials are being conducted for aggressive B cell, mantle cell, and non-follicular indolent B cell types as well as chronic lymphocytic leukemia. Results of a study on the long-term impact of radioimmunotherapy using yttrium-90 (^{90}Y)–ibritumomab

tiuxetan in advanced-stage follicular lymphoma in first remission showed a median duration of progression-free survival of 4.1 years after radioimmunotherapy and 1.1 years for controls [70].

13.7 Radionuclide Synovectomy

There may be a need for a definitive solution to the joint pain of many arthropathies, particularly rheumatoid arthritis, after failure of conventional medications. Therapeutic nuclear medicine offers an alternative to surgical synovectomy. Several radiopharmaceuticals can destroy the synovial membrane when injected intraarticularly (radionuclide synovectomy or radiosynoviorthesis) and the patients become pain free.

Yttrium-90 colloid, erbium-169 citrate colloid, rhenium-186 colloid, phosphorus-32 (P-32) colloid, and others are all used to treat synovial disease [71, 72]. Since these colloids vary in their physical characteristics and thus in their range of penetrability, they are used differently to achieve the therapeutic effects and avoid injuring the surrounding tissue. Accordingly, some radiopharmaceuticals are used for the knee while others are used for small joints (Table 13.3). Yttrium-90 citrate or silicate is generally used for big joints such as the knee; rhenium-186 colloid is used for the shoulder, elbow, hip, and ankle; and erbium-169 citrate for the small joints in the hands and feet (Fig. 13.4).

13.7.1 Radiopharmaceuticals for Synovectomy

13.7.1.1 Yttrium-90 Colloid (^{90}Y)

This radionuclide is used predominantly for radionuclide synoviorthesis of the knee joint. It is also for malignant pleural and peritoneal effusions. The pharmacological characteristics of the silicate and citrate forms are the same. The average range in tissue is 3.6 mm and the maximum is 11 mm. After direct intra-articular administration the colloid penetrates into the surface cells of the synovia. Small amounts of particles are transported through the lymphatics, mainly after active or passive movement of the joint, from the knee to the regional lymph nodes. The safety of this modality of management has been reported, and hence the patients' age should not be regarded as a limiting factor [73]. It is recommended that Y-90 synoviorthesis should be performed in very young patients, when the amount of synovium is still moderate. Once the degree of synovitis has become severe, the expected results of radioactive synoviorthesis are worse [74].

Table 13.3 Physical properties and main uses of major radiopharmaceuticals for synovectomy

Isotope	Mode of decay	Physical half-life (days)	Main energy	Penetration range	Main use/adult dose
^{90}Y-silicate or citrate colloid with an average particle size of 10 nm	Emission of beta particles	2.7	2.24 MeV	3–5 mm in soft tissue, 2.8 mm in cartilage, max. 11 mm in soft tissues	Knee joint; 185 MBq
^{169}Er-citrate colloid with an average particle size of 10 nm	Emission of beta particles	9.4	0.4 MeV	Max 1 mm in soft tissue and 0.7 mm in cartilage	Small joints of hand and feet; 37 MBq
^{186}Re-sulfide colloid with an average particle size of 5–10 nm	Emission of beta particles and gamma rays (92.2%); electron capture (7.8%)	3.7	Gamma 137 keV, beta 1.07 MeV	1.2 mm in soft tissues and 0.9 mm in cartilage	Shoulder, elbow and wrist joints; 74 MBq
^{32}P-colloid with an average particle size of 5–20 nm	Emission of beta particles	14	1.7 MeV	Max 7.9 mm in soft tissue	Knee, elbows and ankles; 37 MBq

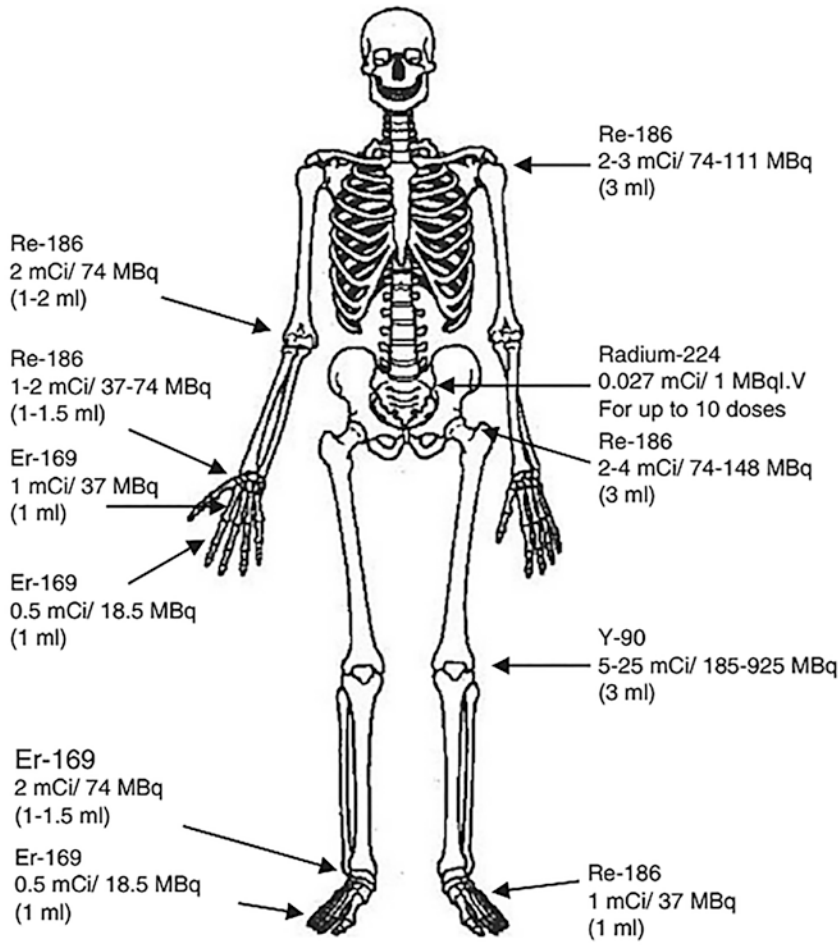

Fig. 13.4 Diagram illustrating the choice of radiopharmaceuticals for radiosynovectomy of different joints

13.7.1.2 Rhenium-186 Sulfide ([^{186}Re] Colloid)

This radiopharmaceutical is used particularly for radionuclide synoviorthesis of the hip, shoulder, elbow, wrist, or ankle joint. After intra-articular injection, it is absorbed by the superficial cells of the synovia. Beta radiation leads to coagulation necrosis and sloughing of these cells.

13.7.1.3 Erbium-169 Citrate [^{169}Er] Colloid

This is more suitable for the radionuclide synoviorthesis of metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints. Beta radiation of the absorbed radiopharmaceutical in the synovia causes coagulation necrosis and sloughing of cells, as with other colloids used for other joints. ^{169}Er colloid has an affinity to chelates; therefore, the simultaneous administration of iodine contrast medium containing EDTA should be avoided.

Absolute contraindications for the use of the three therapeutic radiopharmaceutical colloids for synovectomy are pregnancy and continued breast feeding.

13.7.1.4 Phosphorus-32 Chromic Sulfate (P-32)

^{32}P chromic phosphate has a 14 days half-life, is several times larger than ^{90}Y silicate, Re-186, Er-169, or ^{198}Au colloids, and emits only beta radiation. Its beta radiation has a soft-tissue pen-

etration midway between them at 2–3 mm. These physical advantages have led some investigators to use it for the treatment of with rheumatoid arthritis and hemophilic arthritis [75, 76].

13.7.1.5 Radioactive Gold Au-198

Radioactive gold (Au-198) has a mean soft-tissue penetration of only 1–2 mm. It has also been used also radiosynovectomy. It has a physical half-life of 197 days and a colloid particle size ranging from 20 to 70 μm.

13.7.1.6 Rhenium-188 Colloid

Rhenium-188 is a generator-produced beta-emitting radionuclide; the importance of 188Re for radionuclide therapy is increasing rapidly. Jeong [77] prepared 188Re-colloid and compared its properties with 188Re-colloid. They found that 188Re tin colloid is more advantageous over 188Re sulfur colloid since it showed higher labeling efficiency, allowed better control of the particle size, and lower residual activity in the injection syringes [9].

13.7.1.7 Dysprosium-165 (Dy-165)

This radionuclide has a short half-life of 2.3 h, energetic beta emission with a tissue penetration of 5.7 mm, and a very large particle size. Furthermore, it has a 3.6 abundance of gamma emission that can be used by the gamma camera to detect any possible leak. It showed a response rate of 65–70% with the best results in patients with early-stage joint disease [78].

13.7.1.8 Ho-166-Ferric Hydroxide

The first experience with Ho-166 was recently reported [79]. Knee joints of 22 patients were treated with a mean activity of 1.11 GBq (mCi). Ho-166 has a maximum beta energy of 1.85 MeV with a mean penetration in inflamed synovial layer of 2.2 mm and a maximum of 8.7 mm. Its particle size is 1.2–12 nm.

13.7.2 Mechanism of Action

Although the mechanism of action cannot be totally explained, the current belief is that after intra-articular administration the radioactive particles are absorbed by superficial cells of the synovium. Beta radiation leads to coagulation necrosis and sloughing of these cells.

13.7.3 Choice of Radiopharmaceutical

The choice of radiopharmaceutical depends on the physical characteristics and the size of the joint to be treated as well as the disease status. The therapeutic agents are particulate in nature and labeled with beta-emitting radionuclides. Radiation tissue penetration is proportional to the energy of the beta particles. For example, yttrium-90, with its highly energetic beta, has a mean soft-tissue penetration of 3–4 mm, while rhenium-186 has a mean penetration of 1–2 mm, the beta of phosphorus-32 has a soft-tissue penetration midway between them at 2–3 mm, and both radioactive gold and Re-186 have a mean soft-tissue penetration of only 1–2 mm. Radiopharmaceuticals with shallow depth of penetration are not optimal for large joints such as the knee or for patients with extensively thickened synovium as cases with rheumatoid arthritis and pigmented villonodular synovitis. Since the rate of exposure to the radiation is proportional to the severity of the post therapy inflammatory reaction, a radionuclide with a moderately long half-life of days may be preferred to that with a half-life of a few hours. It appears that there is an inverse relationship between the size of radioactive particle used and the tendency for the radiocolloid to leak from the joint space which, in general, makes the choice of a relatively large radiocolloid more appropriate. A radionuclide that emits only beta radiation would have more advantages than those which emit both beta and gamma radiation in order to minimize whole-body radiation.

13.7.4 Clinical Use

Hemophiliac patients with chronic synovitis and hemarthropathy, rheumatoid arthritis, pigmented villonodular synovitis, psoriatic arthritis, ankylosing spondylitis, and collagenosis are candi-

dates for this treatment modality. Furthermore, persistent effusion after joint prosthesis is a relative indication [80].

The absolute contraindications for the use of the therapeutic radiopharmaceutical colloids for synovectomy are pregnancy and continued breast feeding. Fresh fracture, serious liver disease, myelosuppression, and acute infections are other contraindications. Relative contraindications include children or young adults, in which case therapy should only be administered if the estimated benefit outweighs the potential risks [81]. The presence of a Baker cyst in the knee joint is considered by some workers in the field as a contraindication. Ultrasonography is particularly important for the knee joint to exclude the presence of a Baker cyst which is an evagination of the medial dorsal part of the joint capsule in communication with the main joint. If there is inflammation in the knee joint, the effusion can be pumped into Baker cyst by enhanced motion. If a valve mechanism exists in the connection duct, this could have a deleterious effect after radiosynovectomy. The increased pressure in the cyst might lead to its rupture and the radioactive fluid getting into the surrounding tissue of the joint. The consequence could be possible necrosis of the muscles, nerves, and blood vessels. Radiosynovectomy should be delayed for 4–6 weeks after arthroscopy [81].

Two or three phase bone scan should be obtained before planning therapy to assess the degree of inflammation of the joint and soft tissue and in order to be able to decide if radiosynovectomy is possible and if the patient would benefit from this therapy. Scintigraphy is particularly important to evaluate the extent of abnormalities in the joint being treated and quantitation methods could be used before and after therapy. History of arthroscopy must be checked. Ultrasound or MRI is also helpful to assess the amount of effusion, joint space, and the status of the synovium to ensure homogenous distribution of the radiopharmaceutical. Complete blood cell count must be obtained before therapy as well as pregnancy test for women of child-bearing age. Injection should be done using aseptic technique. Radiosynovectomy can generally be repeated in 6 months.

The largest number of treated patients are those with rheumatoid arthritis and hemophilia. Good results are generally obtained from among those patients as well as those with psoriatic arthropathy. On the other hand, in osteoarthritis with recurrent joint effusion, radiosynovectomy has not been as successful in relieving the symptoms. Good response is reported in 40–70% of patients [82]. In patients with advanced cartilage destruction or bone-on-bone interaction, the synovial membrane is likely to be practically nonexistent. Accordingly, patients with less radiological damage generally show better results than those with more severe damage. If there is initially a poor response or a relapse, more than half the patients may benefit from a reinjection [71, 83]; 2190 joints were treated with radiosynovectomy with a minimum of 1 year follow-up but without specifying the radiopharmaceutical used and the overall success rate was 73%. For rheumatoid arthritis it was 67%, whereas it was 56% for osteoarthritis, 91% for hemophilia and Willebrand's disease, and 77% for pigmented villonodular synovitis [83].

13.8 Treatment of Primary and Secondary Liver Malignancies

Blood supply to the normal liver depends on portal vein and to a much lesser extent on hepatic artery. Tumors on the other hand depend on their blood supply on arterial supply and are additionally hypervascular. This forms the basis of selective internal radiotherapy (SIRT) for hepatocellular carcinomas and metastases. This approach is considered a combination of embolization and radiation. Microscopic radioactive spheres of approximately 35 μm in size are administered through a catheter in the hepatic artery. These occlude the small branches of the hepatic artery, which reduces the blood supply to the metastatic tissue. Ho-166 microspheres, Re-188 microspheres, Re-188 lipiodol, and Y-90 microspheres are all being used [84–87]. This therapy is used as an adjunct therapy before and after surgery and it may be curative. It is recom-

mended as an option of palliative therapy for large or multifocal hepatocellular carcinomas without major portal vein invasion or extrahepatic spread. It can also be used for recurrent unresectable HCC, as a bridging therapy before liver transplantation, as a tumor downstaging treatment, and as a curative treatment for patients with associated comorbidities who are not candidates for surgery. Combined I-131 lipiodol and chemotherapy is also being studied [85].

Currently, microspheres are labeled either with pure beta emitters (e.g., yttrium-90: Y-90) or with combined beta/gamma emitters such as rhenium-188. The decay of the radionuclide results in prolonged radiation of the tumor tissue, with a dosage of approximately 150–200 Gy. Because the radionuclides used are beta emitters, the energy is deposited only in a few millimeters around the microsphere; e.g., 90% of the energy is deposited within 5.3 mm in the case of Y-90 with preservation of the normal liver tissue [86, 87].

13.9 Peptide Receptor Radionuclide Therapy

Since cells express on their plasma membranes receptor proteins with high affinity for regulatory peptides such as somatostatin, peptide analogues are used to image and treat receptor positive tumors. The amount of these receptors changes with diseases. Overexpression of such receptors is the pathophysiologic basis of visualization and treatment of receptor positive tumors [88]. Peptide receptor radionuclide therapy (PRRNT) is a molecularly targeted radiation therapy using systemic administration of a radiolabeled peptide designed to target with high affinity and specificity receptors overexpressed on tumors.

High level of expression of somatostatin receptors on several tumor cells is the molecular basis of the utilization of radiolabeled somatostatin analogues in diagnostic and therapeutic nuclear oncology. Several radiolabeled somatostatin analogues therapeutic radiopharmaceuticals (Table 13.4) have been used to treat patients with NETs in the recent years. Since peptides can be produced easily and have rapid clearance, rapid tissue penetration, and low antigenicity, several labeled peptides have been developed over the last few years. These include somatostatin, cholecystokinin (CCK), gastrin, vasoactive intestinal peptide (VIP), bombesin, substance P, and neuropeptide Y (NPY) analogues [57, 89].

Table 13.4 Radiolabeled somatostatin analogues for treatment of neuroendocrine tumors

111In-DTPAOC (111indium-DTPAO] octreotide)
111In-DOTA-TATE (111indium-DOTA-TYR3-octreotate)
90Y-DOTATOC (90yttrium-DOTA-TYR3-octreotide)
90Y-DOTA-TATE (90yttrium-DOTA-TYR3-octreotate)
177Lu-DOTATOC (177lutetium-DOTA-TYR3-octreotide)
177Lu-DOTA-TATE (177lutetium-DOTA-TYR3-octreotate)

Candidate patients for PRRNT using radiolabeled somatostatin analogues are mainly those with sstr2-expressing NET of the gastroenteropancreatic and bronchial tracts but may also include patients with phaeochromocytoma, paraganglioma, neuroblastoma [57], or medullary thyroid carcinoma. Iodine-negative metastases of differentiated thyroid cancer may express somatostatin receptors and could benefit from Y-90 DOTA octreotide or lanreotide [82]. Detection of somatostatin-positive metastases before considering this treatment should be done using diagnostic sstr imaging with Ga-68 labeled somatostatin analogs or In-111 labeled octreotide or lanreotide. Some metastases respond to octreotide while others respond to lanreotide, and there is no apparent explanation. Combination of I-131 and Y-90 DOTA octreotide or lanreotide is being considered.

NETs have proven to be ideal neoplasms for PRRNT, as the majority of these malignancies overexpress somatostatin receptors. Appropriate candidates for PRRNT are patients presenting with well-differentiated or moderately differentiated neuroendocrine carcinomas, defined as NETs of grade 1 or 2 according to the WHO classification of 2010 [90–93]. A study (82) has shown that In-111 DTPA octreotide effect is dependent on tumor size in animal model bearing

somatostatin pancreatic tumor expressing somatostatin receptor type2 (sst_2). Complete response was seen in 50% of tumors of 1 cm or less in diameter while the response was less pronounced with increasing tumor size. This study indicates that this therapy may be preferred to start as early as possible when tumors are small.

Combined [^{90}Y]DOTA-TATE and [^{177}Lu]DOTA-TATE therapy has been found feasible and effective therapeutic option in NET refractory to conventional therapy. In a study of 26 patients with metastatic neuroendocrine tumors treated with four therapeutic cycles of alternating [^{177}Lu]DOTA-TATE (5.55 GBq) and [^{90}Y]DOTA-TATE (2.6 GBq), a median progression-free survival longer than 24 months was achieved. Among patients with pretreatment carcinoid syndrome, 90% showed a symptomatic response or a reduction in tumor-associated pain [94]. Peptide receptor radionuclide therapy for somatostatin-positive neuroendocrine tumors has resulted in improved symptoms, prolonged survival, and an enhanced quality of life.

13.10 Treatment of Malignant Effusions

Radiopharmaceuticals can also be used in the treatment of malignant effusions. After intrapleural or intraperitoneal administration, Y-90 colloid is distributed in the effusion and penetrates the surface cells of tumors. The radionuclide destroys free tumor cells in malignant effusions and may have an additional radiation effect on metastases and mesothelioma by tumor penetrational intratumoral distribution.

13.11 Other Therapeutic Procedures

13.11.1 Treatment of Bone Tumors

13.11.1.1 Osteogenic Sarcoma

Targeted radionuclide therapy using 153Sm-EDTMP was reported to give substantial palliative effect in a case of relapsed primary osteogenic sarcoma in the first lumbar vertebra with progressive back pain after conventional treatment modalities had failed. The patient was bedridden and developed paraparesis and impaired bladder function. On a diagnostic bone scan, intense radioactivity was localized in the tumor. The patient was treated with 153Sm-EDTMP treatment twice, 8 weeks apart using 35 and 32 MBq/kg body weight, respectively. After a few days the pain was significantly relieved and by the second radionuclide treatment the paresis subsided. For 6 months he was able to be up and about without any neurological signs or detectable metastases. Eventually, however, the patient redeveloped local pain and paraparesis, was reoperated, and died 4 months later. The investigators recommended further exploration using 153Sm-EDTMP as a boost technique, supplementary to conventional external radiotherapy given dramatic transient improvement observed in this case [95].

Another case was also reported which illustrated high-activity Sm-153-EDTMP therapy within a multimodal therapy concept to improve local control of an unresectable osteosarcoma with poor response to initial polychemotherapy. A 21-year-old woman with an extended, unresectable pelvic osteosarcoma and multiple pulmonary metastases was treated with high activity of Sm-153-EDTMP. Subsequently, external radiotherapy of the primary tumor site was performed and polychemotherapy continued, followed by autologous peripheral blood stem cell reinfusion. Within 48 h after Sm-153-EDTMP treatment, the patient had complete pain relief. Three weeks later the response was documented by 3-phase Tc99m-MDP bone scan which showed a decrease in tracer uptake in the primary tumor and metastases. Whole-body F-18 FDG-PET also demonstrated an interval decrease of uptake. Further evaluation of feasibility and efficacy of this multimodal therapy combination of high-activity Sm-153-EDTMP therapy, external radiation, polychemotherapy, and stem cell support for unresectable osteosarcomas is warranted [96].

An animal study was conducted on fifteen dogs with spontaneous osteogenic sarcoma and local pain. They were treated with Sm-153-

EDTMP. The tumors were located in the extremities, scapula, maxilla, and the frontal bone. The dogs were injected intravenously one to four times with 153Sm-EDTMP; 36–57 MBq/kg body weight. Three dogs had surgery in addition to the radionuclide treatment. Platelet and WBC counts showed a moderate and transient decrease with no other toxicity observed. The average tumor doses after a single injection were approximately 20 Gy. Seven dogs had metastases on autopsies. Even though none of the dogs was cured, nine of the dogs had obvious pain relief, and five of them seemed pain free: one for 13 months and one for 48 months [97].

13.11.1.2 Multiple Myeloma

Recent use of high-dose Ho-166-DOTMP (Ho-166-1, 4, 7, 10-tetraazcyclododecane-1, 4, 7, 10-tetramethylene-phosphonic acid) in patients with multiple myeloma has been reported [86]. Thirty-two patients were treated with 581–3987 mCi with an average of 2007 mCi (74.3GBq). Ho-166 has a half-life of 26.8 h and a beta emission of 1.85 MeV (51%) and 177 MeV (48%) as well as an 80.6 KeV (6.6%) gamma emission suitable for a gamma camera imaging. The beta particles have a mean range of 4 mm in soft tissue and can deliver high levels of radiation to the marrow and trabecular bone [98]. This radiopharmaceutical has selective bone uptake and rapid urinary excretion of the remaining activity. However, due to the high doses used, catheterization and continuous irrigation of the urinary bladder after therapy has to be used to reduce radiation dose to bladder mucosa. This agent has a potential to treat patients with resistant multiple myeloma. However clinical studies with emphasis on the outcome in comparison with the currently used high dose of chemoradiotherapy with or without stem cell rescue are warranted to evaluate the impact on the poor survival of patients affected by the tumor. Also more studies are needed to compare the adverse effects of this agent to the high incidence of systemic toxicities of the currently available radiopharmaceuticals [99–102]. Holmium-166 tetraphosphate (Ho-166 DOTMP), a high-energy beta emitter, is now used in treating bone and bone marrow-based tumors such as multiple myeloma [103]. The mechanism of action is through cell death by beta particles.

13.11.1.3 Metastatic Prostate Carcinoma

A study was conducted to explore the effects of Re-186-HEDP treatment on the progression of lumbar skeletal metastasis in an animal model using the Copenhagen rat model and to correlate the eventual treatment efficacy with the radionuclide tissue distribution. The 186Re-HEDP administration, given either 1 day or 8 days after surgical induction of lumbar metastasis was found to significantly increase the symptom-free survival of the animals. These results were confirmed by a significant decrease in the presence of histologically detectable tumor tissue. Biodistribution studies demonstrated the uptake of the major part of the radionuclide within bone tissue. The uptake of radioactivity within the lumbar vertebrae on a microscopic scale, as shown by phosphor screen autoradiography, was concentrated in areas of bone formation and turnover. These results show that radionuclide treatment with Re-186-HEDP is a potentially efficacious treatment option in prostate cancer disseminated to the skeleton [104]. A clinical trial on selected patients with advanced, androgen-independent, prostate carcinoma who received consolidation bone-targeted therapy comprised of Sr-89 with weekly doxorubicin after induction chemotherapy had a longer survival compared with patients who did not receive the bone-targeted therapy [105]. More recently Ra = 223 dichloride and Lu-177 PSMA are used.

The FDG-PET therapy response assessments in men with osseous metastatic prostate cancer are not always in agreement with composite clinical designations of response, stable disease, or progression [106]. Uptake and sensitivity vary in the same tumor type, for example, prostatic cancer. Generally, the FDG avidity is low in treatment naïve prostate cancer, increased in CRPC, and almost always present in docetaxel-refractory prostate cancer [107, 108]. All this indicate that

the FDG is not ideal for response assessment of prostate cancer osseous metastases especially in earlier disease states.

Ra-223 Dichloride Treatment

Ra-223 dichloride is a bone-seeking calcium analogue, an alpha-emitter, approved for the treatment of castration-resistant prostate cancer with symptomatic bone metastases. It has both therapeutic and palliative effects. Ra-223 has alpha, beta and gamma emissions with total decay energy of 28 MeV (mean 5.78 MeV). Ra-223 is produced from an actinium-227 (Ac-227) generator. Half-life of Ra-223 is 11.43 days. Its range in tissue is 0.04–0.05 mm with a highly localized effect and minimal detrimental effects on healthy tissues near tumor. Maximum α-energies of 223Ra are 5.78, 6.88, 7.53 MeV. Maximum β-energies are 450 keV and 490 keV. Gamma energy peaks of Ra-223 are 82, 154, 269, 351, and 402 keV. Ra-223 dicholoride selectively accumulates in the bone, specifically in areas of high bone turnover through forming complexes with the mineral hydroxyapatite [109]. The high linear energy transfer of the alpha radiation results in a high probability of DNA double-strand breaks in the adjacent cells [109]. Radionuclide therapy with Ra-223 is given as single or repeated intravenous administration. The treatment is usually given on an outpatient basis with respect to national legislation and regulations. Hospitalization is recommended in cases of fecal incontinence or seriously ill patients. Contraindications are listed in EANM guidelines [109]. Patients should have bone metastases seen on recent bone scan (not older than 3 mos) and no known visceral metastatic disease. Supplementation of calcium, phosphates, or vitamin D should be paused about 4 days before and after each injection of radium-223. The dose is 55 kBq/kg, given at 4-week intervals for six injections [109]. Ra-223 localization in the bone/bone metastases is around 44–77% at 4 h. Fecal excretion is the major elimination route which is approximately 60–75% of the administered activity and 5% is excreted in the urinary tract. Instructions are given for 7–10 days. The most common side effects are diarrhea, nausea, vomiting, and thrombocytopenia. Risk of hematological adverse reactions increases if patients received chemotherapy or external beam radiotherapy or if patients have advanced diffuse metastases in the bones. Pain relief is rapid but not expected in every patient. The ALSYMPCA study (ALpharadin in SYMPtomatic Prostate CAncer) is an international clinical study to evaluate the efficacy and safety of Ra-223 [110–112]. The ALSYMPCA study showed an overall survival benefit with ^{223}Ra treatment (in over 900 patients). Also, the frequency of skeletal-related events was reduced with Ra-223 treatment. Improved survival with ^{223}Ra was accompanied by significant quality-of-life benefits, including a higher percentage of patients with meaningful quality-of-life improvements and a slower decline in quality-of-life over time.

Lu-177 PSMA Ligand Treatment

Luteium-177 (Lu-177) PSMA ligand therapies have demonstrated promising results in a significant proportion of men with metastatic prostate cancer who have failed other therapies. Treatment with Lu-177 PSMA ligands is currently undergoing clinical validation. Lu-177 is a radiometal produced in reactor. Lu-177 is a medium-energy beta emitter (490 keV) with a maximal tissue penetration of <2 mm which provides better irradiation of small tumors. It also emits low-energy gamma rays, 208 and 113 keV which allows for ex vivo imaging after treatment. Lu-177 has a physical half-life of 6.73 days. Current clinical knowledge is predominantly based on two low molecular weight PSMA ligands: PSMA-617 and PSMA-I&T [113]. Patients should have adequate uptake of PSMA ligands on pre-therapy imaging. Dose calculations are based on disease burden, patient weight and renal function. Injected doses range from 3.7 to 9.3 GBq (100–250 mCi) per single injections with up to six injections, generally at a minimum 6-week intervals [113]. Contraindications to this treatment are described in detail at EANM guidelines [113]. For kidney protection (to decrease reabsorption of radiotracer via the proximal renal tubules and thereby decrease the radiation dose to the kidneys some institutes give IV amino acid infusion (lysine and arginine) over 4 h, starting 30 min

prior to the treatment. Lu-177 PSMA is given as outpatient treatment in some countries and inpatient in other countries with respect to national legislation and regulations. Lu-177 PSMA is excreted via kidneys in the first 48 h following injection. Prospective clinical trial confirmed a high response rates, low toxicity and reduction of pain in metastatic castration-resistant prostate cancer. In 30–70% of men treated with Lu-177 PSMA, there was a >50% reduction in serum PSA levels [114]. In another study, 80% of all men had a PSA response to PSMA therapy [115].

13.12 Combined Therapeutic Approach

The use of radionuclide therapy has been used alone. Recently, several trials have used a combined approach combining radionuclide with other treatment modalities [116, 117]. Sr89 in combination with doxorubicin has been used for bone metastases. This combination was found to be associated with longer time interval to disease progression and longer overall survival when compared to those who only received doxorubicin [117, 118]. Combining low-dose cisplatin to the standard dose of Sr-89 chloride was found to improve pain palliation significantly [119].

CHOP was also used in combination with I-131 tositumomab and Y-90–ibritumomab and Rituxan–CHOP combinations for untreated non-Hodgkin's lymphoma [120, 121].

Combining I-131 MIBG and chemotherapy or myeloablative chemotherapy has been also used in a limited number of patients [122, 123]. In a pilot study, Y-90 biotin was used as an adjunct to surgery and radiation therapy for malignant glioma [124]. The disease-free interval and overall survival was significantly longer among patients with this adjunct therapy than in control group. External beam radiotherapy has been used in combination with and I-131 MIBG for neuroblastoma, and paraganglioma and with I-131 for a large thyroid metastasis. This combined method takes into consideration the nonuniform dose distribution on the basis of tumor function and the radionuclide therapy dose delivered [125]. Combined chemotherapy and I-131 lipiodol for the treatment of hepatocellular carcinoma is being studied as mentioned earlier.

13.13 Summary

Radionuclide therapy is effective, safe, and cost effective and deserves consideration earlier in the management of cancer patients rather than being left as a terminal choice. Several radiopharmaceuticals are being used with varying degrees of success in treating several benign and malignant disease processes. The mechanisms of action are not entirely clear for all of them. Table 13.5 summarizes the probable mechanisms of action of the major radiopharmaceutical tracers currently used. More choices in radionuclide therapy are now available to the

Table 13.5 Effects and mechanisms of action of therapeutic radiopharmaceuticals

Therapeutic procedure/target	Probable mechanism
Hyperthyroid	Cell injury/death to reduce or ablate the thyroid gland
Thyroid cancer	Cell death to ablate residual thyroid tissue, tumor, and metastases
Synovectomy	Phagocytosis of radiolabeled colloid by synoviocytes which are distributed uniformly on the surface of the synovium, with subsequent destruction of the synovium by the beta particles
Radioimmunotherapy	Destruction of tumor cells through multiple mechanisms including cell lysis, formation of autoantibodies, and/or apoptosis
Painful bone metastases	Uptake of the radiopharmaceutical by metastases and/or surrounding bone, with radiation injury or death to the tumor cells or the surrounding cytokine-secreting cells
Peptide therapy	High expression of peptide receptor such as somatostatin and cholecystokinin by cells of specific tumors

physicians for local and systemic uses to palliation and definitive therapy. Clinical acceptance is expected to increase as oncologists accept more the limitations of the curative and palliative role of chemotherapy and external radiation. The areas of research in the field of therapeutic nuclear medicine are wide open for developing new therapeutic radiopharmaceuticals and clinical applications.

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