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Current and upcoming radionuclide therapies in the direction of precision oncology: A narrative review

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HIGHLIGHTS

- As new radiopharmaceuticals are identified to target specific receptors, tissues, and tumor types, opportunities expand for the development of both diagnostic and theranostic agents.
- Theranostics is an important pillar in the management of metastatic thyroid cancer, and is becoming increasingly uimportant in other cancers such as neuroendocrine tumors and prostate cancer.

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ABSTRACT

As new molecular tracers are identified to target specific receptors, tissue, and tumor types, opportunities arise for the development of both diagnostic tracers and their therapeutic counterparts, termed "theranostics." While diagnostic tracers utilize positron emitters or gamma-emitting radionuclides, their theranostic counterparts are typically bound to beta and alpha emitters, which can deliver specific and localized radiation to targets with minimal collateral damage to uninvolved surrounding structures. This is an exciting time in molecular imaging and therapy and a step towards personalized and precise medicine in which patients who were either without treatment options or not candidates for other therapies now have expanded options, with tangible data showing improved outcomes. This manuscript explores the current state of theranostics, providing background, treatment specifics, and toxicities, and discusses future potential trends.

1. Introduction

The term "theranostics" describes the combination of treatment (*thera*py) and imaging (dia*gnostics*) and is achieved by using radiopharmaceuticals to deliver targeted radiation to specific diseased tissues. While the term came into common use in the 1990s, theranostics has existed as long as the field of nuclear medicine itself. The first use (in a non-oncologic setting) dates back to 1941 when Drs. Hertz and Roberts

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of Mass General Hospital began administering radioactive iodine to treat patients with hyperthyroidism. This procedure was soon adapted for use in thyroid cancer and remains in use today.

More recently, a wider variety of malignancies have been targeted by theranostics, thanks in part to research advances in molecular biology and imaging technology, particularly hybrid imaging such as SPECT/CT and PET/CT. Aside from the more well-known treatments for thyroid cancer, prostate cancer, and neuroendocrine tumor (NET), there have also been exciting developments in theranostics for liver-directed therapy, lymphoma, neuroblastoma and other cancers. In general, when choosing a therapeutic radionuclide, the aim is mostly to provide palliation, improve quality of life, increase survival, and decrease tumor burden. Our manuscript aims to provide an update and the current state of affairs in theranostics.

2. Ideal therapeutic radionuclide properties and modes of delivery of radionuclide therapy

An important quality of a radionuclide used in therapy, as with any cancer therapy, is the ability to cause maximum tumor destruction and minimal side effects. There are various physical and biochemical characteristics to consider when choosing a radionuclide for clinical use, including types of emission, destructive daughter products, half-life, tissue targeting, and in-vivo stability and toxicity, apart from logistics involved in the production of the radionuclide (Fig. 1) [1–6]. High linear energy transfer is a desirable property that results in excess DNA damage and ionization in the areas where it is deposited [6]. Delivery of radionuclide therapy can be achieved in multiple ways (Fig. 2), including direct delivery of radionuclide element, by using small molecules, peptides, antibodies, nanoconstructs, and microspheres [7]. Various therapeutic radionuclides available for clinical and research use are listed in Table 1.

2.1. Prostate cancer

Prostate cancer is the second most common cancer among adult men in the world [8]. Those with metastatic disease have a poor prognosis, with a 5-year survival rate of 29%. According to the National Comprehensive Cancer Network (NCCN), the general risk group is determined by a combination of Gleason scoring, Prostate Specific Antigen (PSA), and staging of the primary tumor (Table 2) [9]. The likelihood of metastatic disease increases with a higher risk group.

It is in the setting of metastatic disease that prostate cancer was first treated with nuclear medicine via the alpha emitter Radium-223 (Ra-223) dichloride, which acts on areas of active bone formation causing tumor destruction (Fig. 3) [132]. Prior to the recent discovery of Prostate Specific Membrane Antigen (PSMA), this was the only nuclear medicine treatment offered in prostate cancer patients with bone-only metastatic disease other than bone palliation agents. PSMA is a transmembrane-bound glycoprotein expressed in the prostatic epithelium secretory cells and has no or little expression in hyperplastic and benign tissue [10]. PSMA compounds using Fluorine-18 (F-18) and Gallium-68 (Ga-68) are used in diagnostic imaging, and compounds using Lutetium-177 (Lu-177) labeled PSMA has been recently approved in the United States for patients with metastatic disease.

PSMA therapy was first used bound with radionuclide Iodine-131 (I-131) as I-131-MIP-1095[11]. The advantages of this therapy were lower kidney dose and longer tumor residence time but unfortunately led to high bone marrow dose and entailed a tedious radiolabeling process [11, 12]. Subsequently, the first patient was treated with Lu-177-PSMA in 2014 and showed a complete radiologic response, resulting in heightened interest in PSMA theranostics by clinicians and researchers [12, 13]. Since then, PSMA-based treatments have been extensively investigated and administered to thousands of patients. The European Association of Nuclear Medicine (EANM) procedure guidelines for using Lu-177-PSMA were published in 2019 with PSMA therapy referred to as an 'unproven intervention in clinical practice' [14]. The United States

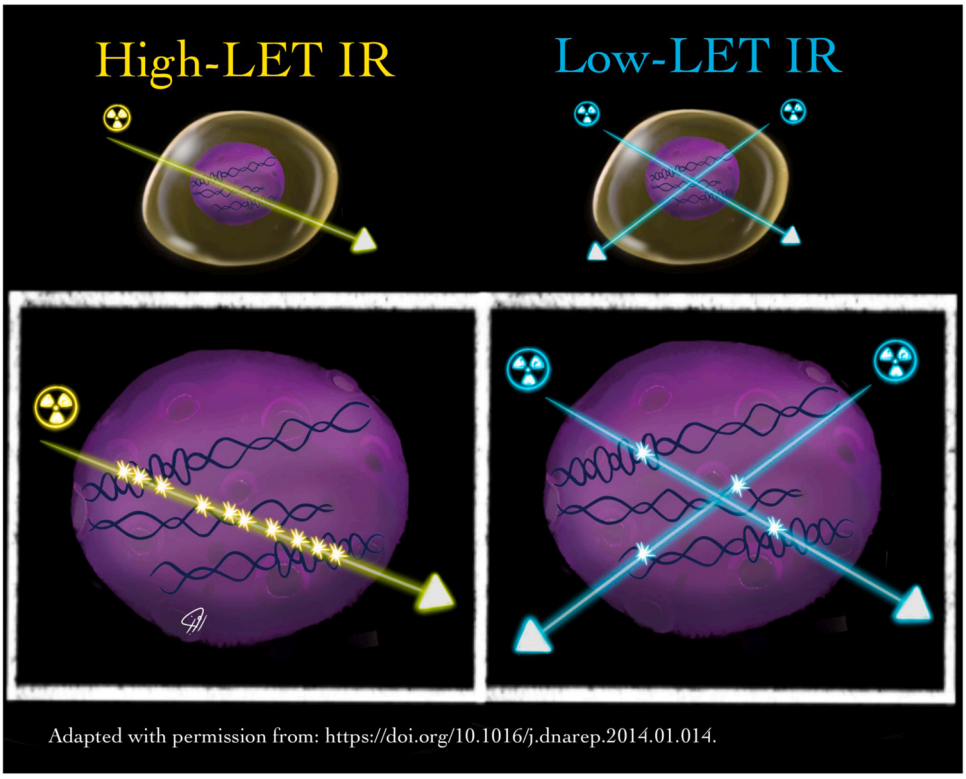

Fig. 1. showing more ionization caused in the path of radionuclide with high linear energy transfer compared to that of radionuclide with low linear energy transfer Adapted with permission from Ref. [6].

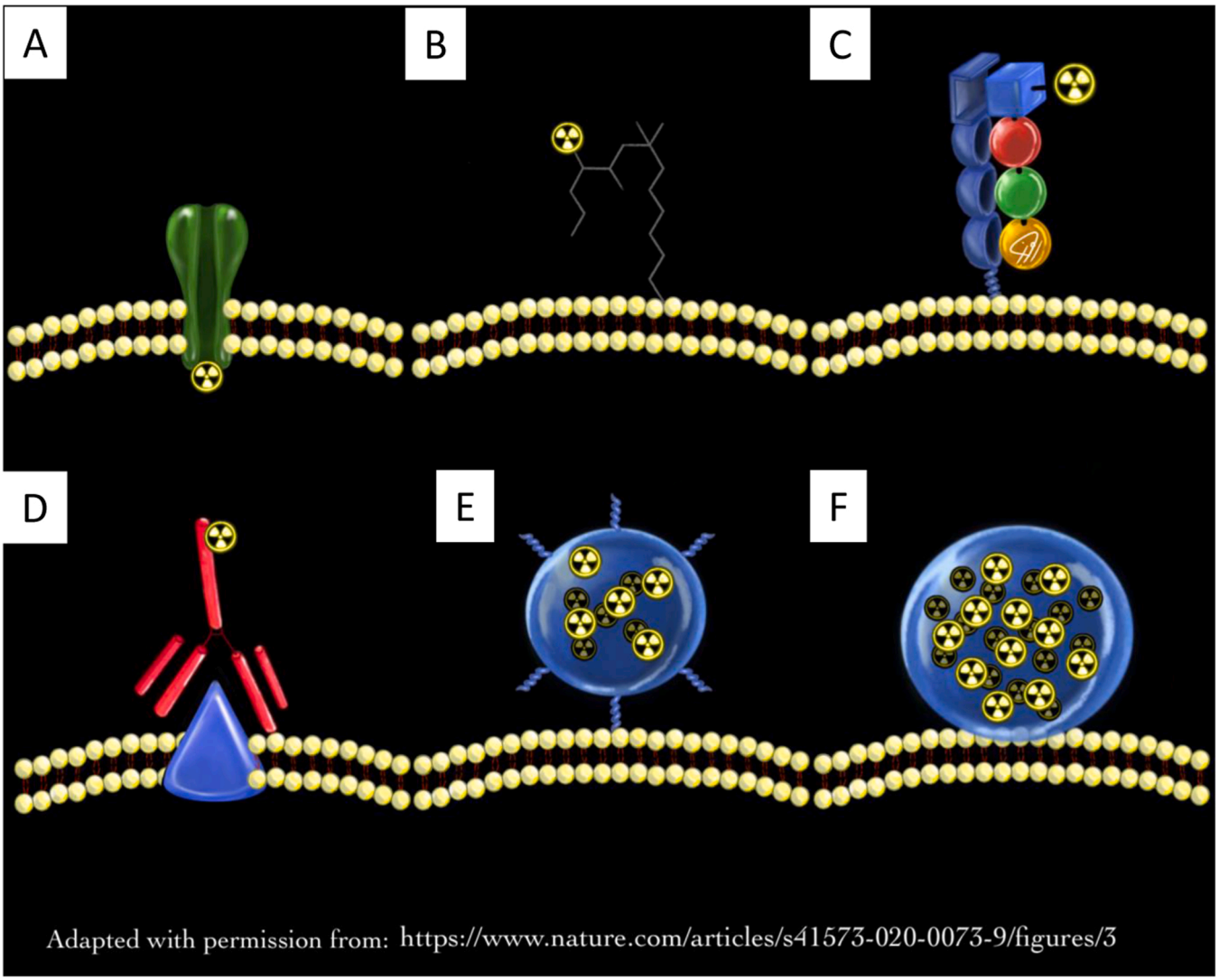

Fig. 2. showing various way in which radionuclide therapy could be delivered. Direct delivery of radionuclide element, using small molecules, peptides, antibodies, nanoconstruct and, microspheres.
Adapted with permission from Ref. [7].

Federal Drug Administration (USFDA) approved Lu-177-PSMA-617 (Lu-177-vipivotide tetraxetan) in March 2022 for the treatment of men with PSMA-positive metastatic castration-resistant prostate cancer who have failed other anticancer treatments.

2.2. Agents

2.2.1. Lu-177-PSMA-617

Lu-177-PSMA-617 has been investigated in multiple studies for the treatment of metastatic castrate-resistant prostate cancer. A multicenter, unblinded phase 2 trial (TheraP) evaluated 193 men randomized to treatment with either Ga-68-PSMA-11 or Cabazitaxel. Information from diagnostic PET/CT using F-18-FDG and Ga-68-PSMA-11 was used to select the patients who received either Lu-177-PSMA-617 or Cabazitaxel. The primary endpoint was $\geq$ 50% PSA reduction and secondary endpoints were PSA-progression-free survival and overall survival. Higher numbers of patients in the group treated with Lu-177-PSMA-617 had a $\geq$ 50% reduction in PSA and there was a significant improvement in PSA-progression-free survival. More adverse events occurred in patients treated with Cabazitaxel compared to Lu-177-PSMA-617[15].

The recently concluded VISION study was a phase 3 trial involving 831 patients randomized to either Lu-177-PSMA-617 plus standard care or standard care alone. At a median follow-up of 20.9 months, the arm including Lu-177-PSMA-617 in addition to standard care significantly prolonged imaging-based progression-free and overall survival compared to standard care alone. Secondary endpoints including objective response, disease control, and time to symptomatic skeletal events were also found to be significantly in favor of the arm including Lu-177-PSMA-617. Adverse events of grade 3 or above were higher with Lu-177-PSMA-617 but without effect on the quality of life[16]. PSA decline after the first cycle of Lu-177-PSMA-617 was found to be significantly associated with prolonged median overall survival [17]. The treatment protocol consisted of two cycles of 200 mCi Lu-177-PSMA-617 given with a gap of 8–12 weeks. Blood parameters were checked before, immediately before, and after the therapy [14]. If a substantial decrease in blood counts was seen, the patient waited an additional 1–2 weeks to recover before the next therapy.

2.2.2. Ac-225-PSMA-617

Actinium 225 is an alpha radionuclide labeled with PSMA-617, which has been attractive as preclinical research has found that the smaller range of alpha particles (2–3 cell diameters) translates to more targeted radiotherapy [18].

In an initial study, 17 chemotherapy-naive patients with advanced

Table 1
Therapeutic radionuclides and their physical properties.

Radionuclides	Radiopharmaceutical	Type of destructive radiation	Imaging photon
Iodine-131	**131-I-NaI** **131-I-MIBG** 131-I-tositumomab 131-I-Rituximab	Beta - a maximal energy of 606 keV (89% abundance, range 248–807 keV) Half-life: 8.04days Range: 0.4 mm	364 keV gamma rays (81% abundance, others 723 keV).
Lutetium-177	**177-Lu-DOTATATE** 177-Lu- EDTMP **177Lu-PSMA**	Beta - a maximal energy of 497 keV (78.6%), 384 keV (9.1%) and 176 keV (12.2%) Half-life: 6.7 days; Range: 0.2 mm	208 keV (11.1%), 113 keV (6.6%) gamma photons
Samarium-153	153-Sm-EDTMP	Beta- a maximal energy of 810 keV (20%), 710 keV (50%) and 640 keV (30%) Half-life: 1.93days; Range: 0.5 mm	103 keV gamma photon (29%)
Phosphorus-32	32-P-Phosphorus Chromate	Beta-maximum energy of 1.71 MeV Half-life 14.28 days; average range: 3.2 mm	None
Strontium-89	89-Strontium Chloride	Beta- maximum energy is 1.463 MeV Half-life 50.57 days; average range: 2.4 mm	None
Yttrium-90	90-Y-DOTATATE **90-Y-microspheres** **90-Y-sirspheres** 90-Y-PSMA 90-Y- Ibritumomab Tiuxetan	Beta- maximum energy of 2.28 MeV with an average beta energy of 0.9336 MeV. Half-life:64.1days; average range: 2.5 mm	Bremsstrahlung PET imaging of 0.01%
Radium-223	**223-Radium dichloride**	radium-223 and its daughters as alpha-particles is 95.3% (energy range of 5.0–7.5 MeV). The fraction emitted as beta-particles is 3.6% (average energies are 0.445 MeV and 0.492 MeV), Half-life of 11.4 days range in tissue of < 100 μm.	and the fraction emitted as gamma-radiation is 1.1% (energy range of 0.01–1.27 MeV)
Actinium-225	225-Ac-PSMA	4 alpha particles with energies ranging from 5.8–8.4 MeV and 3 beta particles with energy ranging from 198 to 659 keV	218 keV and 440 keV gamma photon
Rhenium-188	188-Re-lipoidol	Half-life:10days, Range: 47–85 μm Beta- maximal energy is 2.12 MeV Half-life: 16.98 hr Range: 3.8 mm	155kev gamma ray and bremsstrahlung radiation
Rhenium-186	186-Re-lipoidol 186-Re-HEDP	beta particles of 1.07 MeV and Half-life of 3.8 days. Range: 4.5 mm	137 keV gamma ray

In bold are the ones, which are more commonly used.

Table 2
NCCN risk stratification for patients with prostate cancer.

Very low risk	T1c, PSA < 10 ng/mL, Gleason score of $<$ or $= 6$, < 3 core positive with $<$ or $= 50\%$ cancer in each core
Low risk	T1-T2a, PSA < 10 ng/mL, Gleason score of $<$ or $= 6$
Intermediate risk	T2b-T2c, PSA 10–20 ng/mL, Gleason score of $3 + 4$ or $4 + 3$
High risk	T3a, PSA > 20 ng/mL, Gleason score of 8, 9, or 10
Very High risk	T3b-T4, Primary Gleason pattern 5, or score of 8, 9, or 10

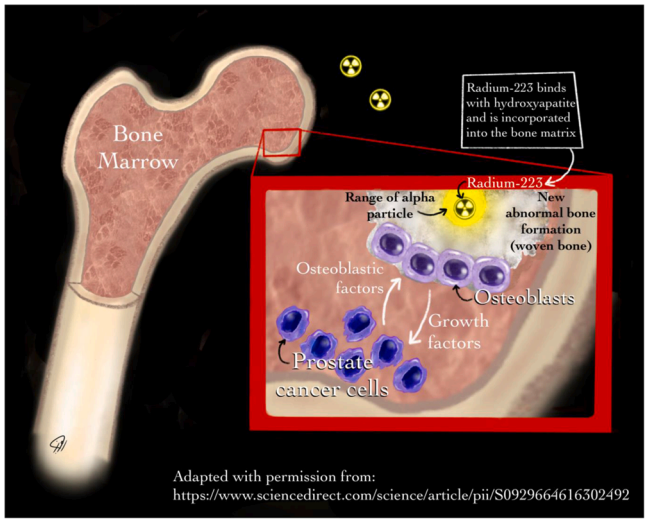

Fig. 3. showing mechanism of action of Ra-223. This radionuclide is administered as an intravenous injection. It binds with hydroxyapatite and is then incorporated into the bony matrix where it causes destruction.
Adapted with permission from Ref. [132].

prostate cancer were treated with this agent, and a decline in PSA of $\geq 90\%$ was seen in 82% of patients. A dose de-escalation model was used in this study with the majority of patients receiving up to 3 cycles at 2 -month intervals [19]. In the metanalysis of 256 patients, 62.8% of patients had a biochemical response, and 74% of patients had a response on PET imaging. Pooled median progression-free survival was 9.1 months and overall survival was 12.8 months. In 20 patients, the treatment was discontinued due to adverse events [20]. Fig. 4 shows pre- and post-treatment Ga-68-PSMA PET scan in a patient treated with Ac-225-PSMA-617.

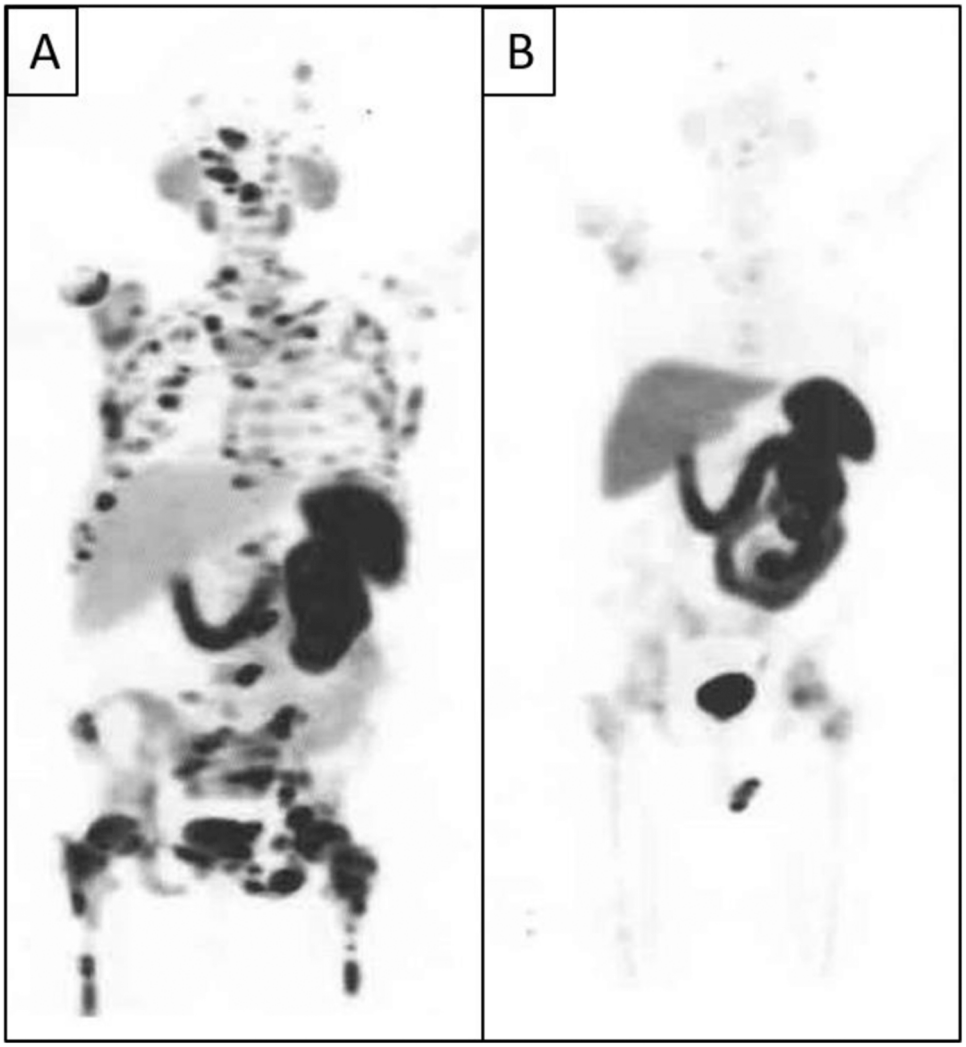

Fig. 4. 60-year-old male with metastatic Prostate cancer Gleason's score 4 + 5. Non-responder to Hormonal therapy and Docetaxel. (A) Ga-68-PSMA MIP image showing PSMA-avid disease in skeleton. PSA at this time was > 400, He was subsequently treated with 3 cycles of Ac-225-PSMA-617, (B) Ga-68-PSMA MIP image showing near complete resolution of previously seen PSMA-avid disease in skeleton. PSA at this time was 0.1.

2.3. Treatment protocols

Current EANM guidelines for Lu-177-PSMA therapies in appropriate patients suggest doses between 100 and 250 mCi accompanied by oral or IV hydration, 4–6 cycles given 6–8 weeks apart, with regular monitoring of renal and hepatic function to assess capability for clearance of unbound agent as well as hematologic profile to monitor for marrow suppression, which evaluates eligibility for subsequent cycles. Treatment response should be assessed by PSA and post theranostic emission scans at each administration, as well as cross-sectional imaging (preferably PSMA PET/CT) every 2 cycles [14].

2.4. Toxicities

Xerostomia is the most common side-effect of PSMA radionuclide therapy. In a multicenter study of 145 patients who received 248 Lu-177-PSMA-617 therapies, xerostomia was seen in 8% of the patients [21]. Strategies to prevent xerostomia include local cooling, Vitamin C, and 2-(phosphonomethyl) pentane-1,5-dioic acid] (PMPA) [22–24]. Hematological toxicity, including grade 3–4, was seen in 18 of 145 patients in the German multicenter study investigating Lu-177-PSMA-617 radioligand therapy in advanced prostate cancer patients. 10% experienced anemia, 4% had thrombocytopenia, and 3% of the patients had leukopenia [21].

Lu-177-PSMA-617 is mainly excreted through the kidneys. Nephrotoxicity due to Lu-177-PSMA-617 was evaluated in a study of 55 patients, where 0/55 had grade 3 or 4 nephrotoxicity, however, an increase in creatinine was observed in 14/55 patients [25]. In a meta-analysis study of Ac-225-PSMA-617, clinically significant toxicities were xerostomia in 1.2%, anemia in 12.3%, leukopenia in 8.3%, thrombocytopenia in 6.3%, and nephrotoxicity in 3.8% [20].

2.5. Future trends

A wide variety of PSMA tracers are in development, and a full description of the research is beyond the scope of this review, however many types of PSMA with therapeutic potential are under investigation (Table 3) [26,27].

3. Neuroendocrine tumor

Neuroendocrine tumors (NET) are a heterogeneous group of tumors arising from neuroendocrine cells present throughout the body, but frequently originating in the foregut and midgut organs. These tumors are characterized by distinctive histological patterns and immunohistochemical markers including chromogranin A, synaptophysin, and

Table 3
Various PSMA tracers and their key features.

Various PSMA tracers	Key features	Reference
PSMA-617	Most widely used for therapy Can be labeled with multiple radionuclides Slower renal clearance compared to PSMA-11	[21]
PSMA-I and T	Higher receptor affinity. Biodistribution studies showed slightly lower physiologic tracer uptake in the liver, spleen and intestine and slightly higher uptake in the proximal tubules of the kidneys and salivary glands	[128]
JF91	Anti-PSMA antibody Has slow diffusion in solid lesions Long circulation time High hematologic toxicity	[104]
PSMA/CD3-bispecific BiTE antibody BAY2010112 (AMG212, MT112)	In preclinical studies, found to have suppress tumor growth Acceptable safety profile	[129, 130]

CD56 [28]. Well-differentiated NET also usually overexpress the somatostatin receptor on the cell surface, forming the basis of peptide receptor radionuclide therapy (PRRT) [29,30].

Some NET secrete hormones leading to specific symptoms. For example, gastrinoma results in Zollinger-Ellison syndrome causing elevated levels of gastrin in the blood manifesting with symptoms such as peptic ulcers, abdominal pain, and diarrhea. Other hormonally active NET includes glucagonoma, VIPoma, and insulinoma which cause symptoms related to increased levels of respective hormone secretion and often have a negative impact on quality of life. Carcinoid crisis is a paraneoplastic presentation of NET which is due to the secretion and release of serotonin and other substances, with resultant vasodilation, flushing, diarrhea, and hypotension, which in rare cases can be life-threatening [31].

Surgery remains the mainstay of treatment, but adjuvant treatment with somatostatin analog and targeted therapy is needed in patients with metastatic/inoperable disease. PRRT is an important therapeutic option available to patients with metastatic well-differentiated NET.

Eric Krenning is credited with the initial development of diagnostic and therapeutic radiotracers for the management of NET. The Auger and conversion electron-emitter Indium-111 (In-111)-pentetreotide was used as an experimental theranostic agent in 1992, binding to surface somatostatin receptors, however, suffered from a short tissue penetration range [32]. Development continued with Tyr3-octreotide, which had a similar affinity profile for somatostatin receptors and could be linked to a macrocyclic chelator named DOTA for simple yet stable radiopharmaceutical labeling [33]. This led to the development of Yttrium-90 (Y-90)-DOTATOC in 1996, followed by Lu-177-DOTATATE in 2000, developed in light of concerns for renal toxicity [34,35].

The World Health Organization (WHO) system of grading is used for NET to assist with outcome prediction and is also useful for PRRT. Mitotic count and Ki-67 are important pathologic markers for proliferation and grading [36]. PRRT is favored in the lower grade of tumor, due to a higher affinity for somatostatin receptors. As the grade of the tumor increases or as the tumor becomes less differentiated or dedifferentiated, it loses its potential to express somatostatin receptors and, in turn, decreases affinity for DOTA binding. Interestingly, in these cases, there is an increase in GLUT expression making 18 F-FDG the preferred diagnostic agent for these tumors.

Using functional imaging with Ga-68-DOTA-analogs and F-18-FDG PET, it is possible to create a more detailed map of differentiation than by biopsy alone (Fig. 5). In a retrospective analysis, Chan et al. derived a "NETPET" score system, with lower grades associated with better overall survival (Table 4) [37]. This scale has the potential for better patient selection for PRRT versus other therapies. The authors have also

Table 4
NETPET score system based on information obtained on Somatostatin Receptor and FDG PET scans.

NETPET Scoring	
P0	Negative on 68Ga-DOTATATE and 18 F-FDG
P1	Positive on 68Ga-DOTATATE and negative on 18 F-FDG
P2	Positive on 68Ga-DOTATATE and 18 F-FDG; 18 F-FDG uptake less than 68Ga-DOTATATE uptake
P3	Positive on 68Ga-DOTATATE and 18 F-FDG; 18 F-FDG uptake similar to 68Ga-DOTATATE uptake
P4	Positive on 68Ga-DOTATATE and 18 F-FDG; 18 F-FDG uptake more than 68Ga-DOTATATE uptake
P5	Negative on 68Ga-DOTATATE and positive on 18 F-FDG

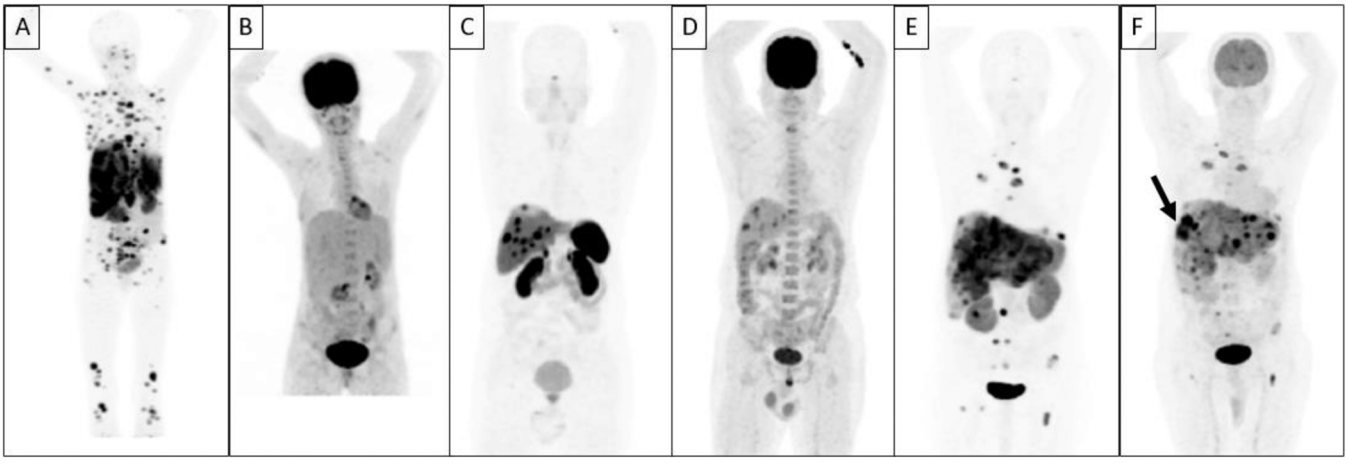

Fig. 5. (A) Ga-68-DOTATATE and (B) F-18-FDG Maximum Intensity Projection (MIP)images of a patient with Grade 1/well-differentiated NET showing multiple areas of somatostatin receptor expressing metastatic disease in image A and negligible FDG uptake in image B. PRRT is suitable in this patient. (C) Ga-68-DOTATATE and (D) F-18-FDG MIP images of a patient with Grade 2/moderately differentiated NET showing multiple areas of somatostatin receptor expressing metastatic disease in the liver in image C and only a few lesions showing concurrent FDG uptake in image D indicating Grade 1/well-differentiated NET. PRRT is suitable in this patient. (E) Ga-68-DOTATATE and (F) F-18-FDG MIP images of a patient with mixed NET showing multiple areas of somatostatin receptor expressing metastatic disease in image E and many lesions showing FDG uptake in image F. One of the area in image F marked with arrow without somatostatin receptor expression in image E indicating that this is high grade/poorly differentiated focus of NET. By using FDG and DOTATATE PET imaging, tumor grade mapping can be done in the whole body.

expanded their work to include bronchial neuroendocrine neoplasms [38].

3.1. Agents

Lu-177-DOTATATE, as mentioned above, links the beta-emitter Lu-177 to Tyr3-octreotate via the macrocyclic chelator, DOTA. In the NETTER-1 study which led to FDA approval of Lu-177-DOTATATE for midgut NET [39], 229 patients were randomly assigned to either PRRT or long-acting repeatable Octreotide. The group receiving Lu-177-DOTATATE had a significantly higher response rate and longer progression-free survival in the interim analysis. In the final analysis, 36% of patients had crossed over to receive Lu-177-DOTATATE with statistically significant improvement in the primary endpoint of progression-free survival. There was also an improvement in median overall survival which was deemed clinically meaningful [40].

Treatment consists of an empiric dose of 200 mCi every 8 weeks for four cycles. Treatment is usually well tolerated. The side effects, mainly nausea and vomiting which occur during therapy are usually attributed to the amino acid solution given for renal protection. This is more common with the general amino acid solution rather than lysine-arginine only preparation. Amino acid infusion is administered slowly to prevent electrolyte imbalance and arrhythmia. The total duration of therapy is usually 4–6 h, of which the Lu-177-DOTATATE infusion takes 30 min. Hydration should be maintained before, during, and after therapy.

A potential rare complication of this therapy includes carcinoid crisis; a multitude of symptoms that occur due to sudden release of hormones (particularly serotonin), characterized by flushing, breathing difficulty, and hypotension, and can be accompanied by diarrhea [41]. This can be seen during PRRT and is more common during the initial therapies but can occur at any time. It is also common in patients who previously experienced carcinoid crises prior to therapy. Treatment of carcinoid crisis during therapy is immediate administration of octreotide, usually as an intravenous injection, and supportive management including fluid administration, electrolyte correction, and management of hypotension [42].

Apart from high somatostatin receptor expression and lower tumor grade and proliferation rate, certain serologic parameters are required for consideration of Lu-177-DOTATATE therapy. North American Neuroendocrine Tumor Society (NANETS) recommendations to guide appropriate patient selection for treatment with PRRT are in Table 5 [43,44].

3.2. Comparison to molecular targeted therapy

PRRT is generally well-tolerated as compared to targeted chemotherapeutic agents such as everolimus [45]. In a meta-analysis of 22 studies with 1758 patients treated with Lu-177-PRRT, the pooled disease response rates (patients who showed complete and partial responses) were 33% and 35%, and by imaging (patients who showed complete and partial responses and stable disease) were 79% and 83% utilizing RECIST and RECIST 1.1 respectively [46]. For pancreatic NET, the median disease control rate was found to be 83% with the range of 50–94%, and the median objective response rate was 58% with the range of 13– 73% [47].

In NETTER-1, statistically significant improvement in PFS was seen in patients treated with Lu-177-DOTATATE, however, no significance was seen in the median OS which was 48.0 months in the patients treated with Lu-177-DOTATATE and 36.3 months in the high-dose octreotide LAR arm; high crossover rate of 36% to the Lu-177-DOTATATE may be responsible for no statistical difference in the two groups in OS. Prolongation of PFS was regardless of baseline liver tumor burden or the presence of a large target lesion [40,48]. Fig. 6 shows pre-and-post-PRRT Ga-68-DOTATATE scans and Lu-177-DOTATATE imaging obtained 24 h after the therapy in a patient treated with PRRT.

Table 5
Recommendations for treatment of NET with PRRT.

North American Neuroendocrine Tumor Society (NANETS) Recommendations (2013)	
Hemoglobin	> 8 g/dL
White blood cell (WBC)	> 2000/mm3
Platelets	> 70, 000/mm3
Estimated Glomerular filtration rate (GFR)	> 50 mL/min
Total Bilirubin	< /= 3times the upper limit of normal
Serum albumin	> 3.0 g/dL
Joint International Atomic Energy Agency (IAEA), EANM and Society of Nuclear Medicine and Molecular Imaging (SNMMI) Recommendations (2020)	
WBC	> 3000/μl, with absolute neutrophil count < 1000/μl
Platelets	> 75,000/μl for 177Lu-DOTATATE, < 90,000/μl for 90Y-DOTATOC,
Red blood cell (RBC)	> 3000,000/μl

3.3. Toxicity

During the early stages of therapy using Y-90-based PRRT, it became evident that there was resorption and retention of peptide radiopharmaceuticals in the kidneys [49], which led to the development of lysine-arginine amino acid combination, which was found to reduce the renal uptake of the peptide [49,50]. This amino acid combination containing 25 gm of lysine and arginine each in a 1-liter volume is used for renal protection, given before start, and continued after administration of the PRRT. Single-day Gelofusine, a succinylated form of bovine gelatin which is used as a plasma expander, has also been found to reduce radiotracer uptake in the kidney but has been shown to cause allergic reactions including anaphylactoid reactions, and thus is less commonly used [44,51]. In a study of 200 patients treated with Lu-177-DOTATATE, grade 1 kidney toxicity was seen in 19% of patients, grade 2 in 4% of patients, and grade 4 toxicity in 1 patient 3 years after therapy which was confirmed due to histologically confirmed hypertensive nephrosclerosis [52]. Lu-177-DOTATATE can be tolerated in patients with mild to moderate renal dysfunction. Glomerular filtration rate (GFR) and tubular extraction rate (TER) should be at least 60% of mean age-adjusted normal values [44].

In the NETTER-1 trial, Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 toxicities in the form of myelosuppression were seen in 9% of patients, and 1.8% developed myelodysplastic syndrome (MDS). No new cases of MDS or acute leukemia in the long-term follow-up at 5-yr were noted in NETTER-1. In a published study from 2018, of the 200 patients treated with Lu-177-DOTATATE, 1.5% developed acute leukemia, and 15% developed grade 3 or 4 bone marrow toxicity [52]. Lastly, prophylactic steroid treatment immediately after PRRT is prescribed by some centers in the presence of mesenteric and peritoneal disease to decrease the occurrence of therapy-associated bowel obstruction [53,54].

3.4. Future trends

Somatostatin receptor antagonists have been developed, which have lower internalization and degradation, resulting in the more effective delivery of radionuclide to the target cell and thus more destruction (Fig. 7) [7]. Y-90-DOTATATE is another peptide receptor radionuclide therapy that was relatively widely used before the Lu-177-DOTA-analog availability. As the physical properties of 90Y make it a good candidate for treating larger tumors, a combination of Lu-177-DOTATATE and Y-90-DOTATATE as subsequent or concurrent therapies is an avenue for further investigation [32]. Alpha emitters such as Ac-225 and Bismuth-213 (Bi-213) for PRRT are promising but require further toxicity studies.

The combination of Lu-177-DOTATATE with chemotherapeutic agents like capecitabine and temozolomide has been evaluated in a

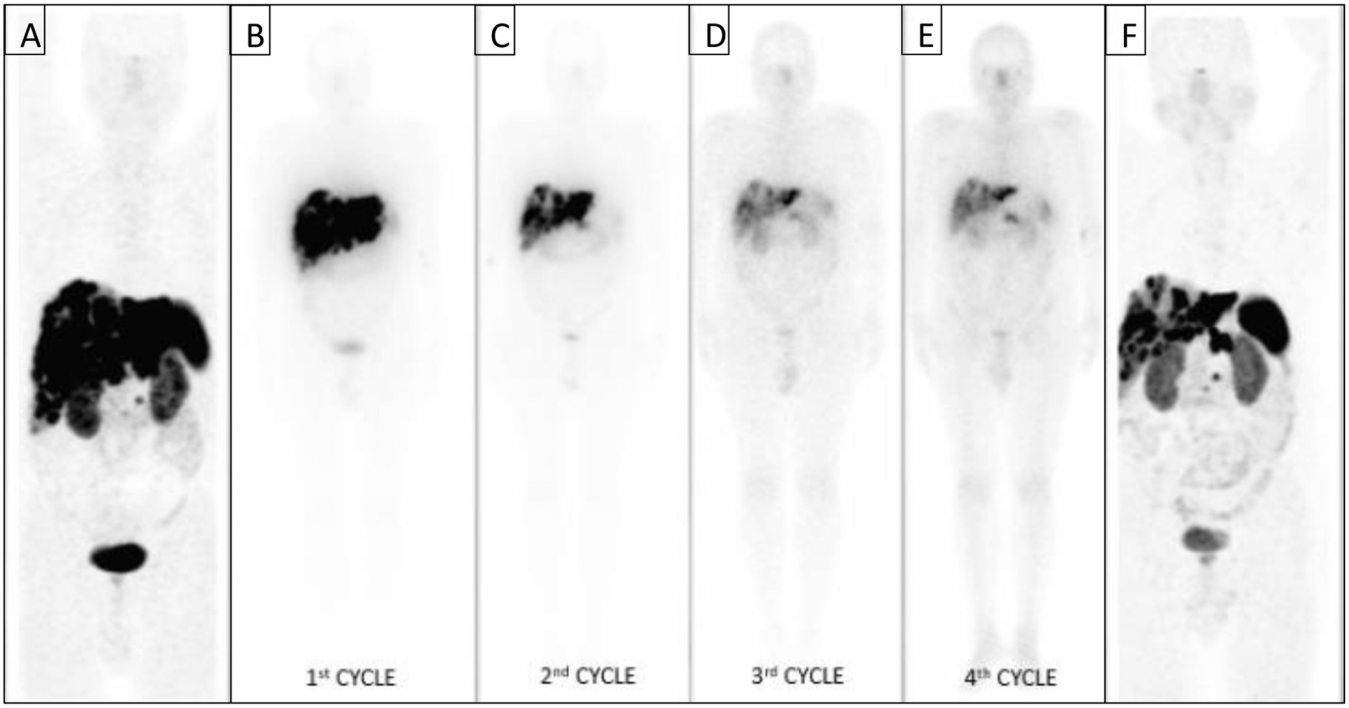

Fig. 6. (A) Ga-68-DOTATATE MIP image showing somatostatin receptor expressing disease in liver and upper abdominal lymph nodes. PRRT is a suitable treatment in this patient. (B), (C), (D), (E) Lu-177-DOTATATE planar anterior images after 1,2, 3 and 4 cycles of PRRT respectively, showing decreasing burden of the disease in the liver. Patient received 200 mCi of Lu-177-DOTATATE for each cycle of PRRT. Imaging was performed 18–24 hr after the therapy. (F) Ga-68-DOTATATE MIP post-PRRT image showing partial response to treatment.

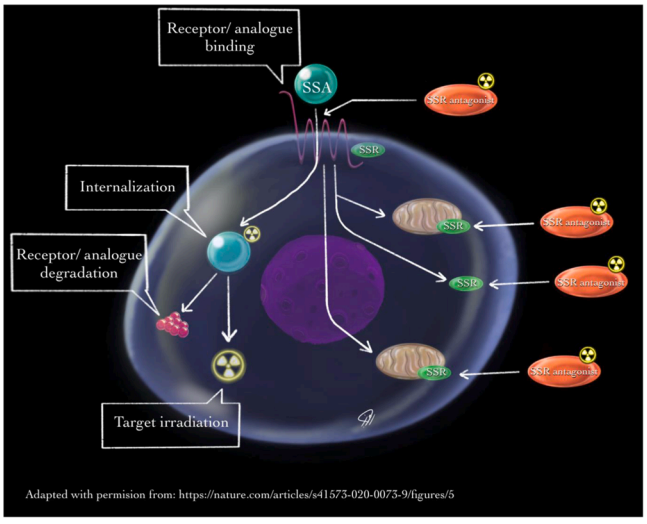

Fig. 7. depicting advantages of somatostatin antagonist over somatostatin analogues.
[adapted with permission from reference 7].

phase 2 trial and was found to meet the target of progression-free survival in midgut primary and midgut NET [55]. Another interesting concept is the use of sandwich chemotherapy with capecitabine and temozolomide between two cycles of Lu-177-DOTATATE therapy in patients with F-18-FDG- and SSTR-avid disease. Effective control of symptoms and longer PFS and OS without high-grade toxicities were observed and thus opens a new possibility of treatment in patients with high-grade NET.

Current guidelines recommend PRRT as an option only in advanced NET. In the early stages, Octreotide and other targeted therapies like sunitinib, everolimus, capecitabine, and temozolomide have shown response in this setting [56]. It is notable that, as early as 2009, PRRT has been used as neoadjuvant therapy and successfully reported in a case report [57].

4. Thyroid cancer

Most thyroid cancer histologies have good prognoses. Iodine-131 (I-131) is a cornerstone in the treatment of differentiated follicular and papillary thyroid cancer. It has no role in medullary thyroid cancer and negligible role in anaplastic thyroid cancer.

4.1. Treatment guidelines

While there have been several renditions of statements and recommendations regarding theranostic thyroid therapy, the most recent and widely accepted was created in 2019, as a joint statement released by the American Thyroid Association (ATA), EANM, SMMI, and European Thyroid Association (ETA) on the use of radioiodine and this statement proposed terminology for use of radioiodine therapy [58]:

1. Remanent ablation – ablation of benign thyroid tissue left behind after surgery
2. Adjuvant treatment – additional treatment to decrease the risk of recurrence
3. Treatment of known disease – which could be either biochemical recurrence or known structural inoperable disease.

This statement also provided 9 principles, the “Martinique principles,” about radioactive iodine therapy. Key among these is a commitment to interdisciplinary cooperation and the importance of evaluating multiple factors beyond clinicopathologic staging in decision-making about I-131 therapy [58].

In the metastatic setting, radioiodine therapy is generally recommended, unless the disease is or becomes iodine-refractory. In the setting of ablation, there are differences in opinion among various

societies and treating physicians across the world. Due to the better prognosis of differentiated thyroid cancer, the impact of additional radioiodine therapy is difficult to justify. In 2004 a meta-analysis by Sawka et al. showed the positive impact of radioiodine ablation in decreasing recurrence but questioned its role in low-risk patients who are adequately treated with surgery and thyroid hormone suppression [59].

2015 ATA guidelines recommend radioiodine therapy based on observational data only in a high-risk group. In low- to intermediate-risk groups, radioiodine therapy is generally favored, while not recommended in the low-risk group, defined as tumor less than or equal to 1 cm with no or minimal invasion, no angioinvasion, no capsular invasion, no aggressive histology, no nodal or metastatic involvement. Post-operative risk assessment using thyroglobulin is recommended and can be used to guide treatment. It is generally agreed that using radioiodine provides whole body post-therapy imaging and staging tool and facilitates easy follow-up with thyroglobulin and antithyroglobulin.

There are multiple definitions used for iodine-refractory disease, but generally, the term refers to a pattern of progression on treatment. It may be characterized in two major groups -

1. Known disease focus showing no iodine uptake in an appropriately prepared patient who received a high dose of iodine.
2. Disease increasing despite radioiodine therapy and uptake. This could either be a structural increase in disease or rise in tumor marker, or both.

The treatment for iodine refractory disease should be decided by a multidisciplinary team and often uses targeted therapy such as tyrosine kinase inhibitors [58,60].

4.2. Treatment protocols

No clear single recommendation for radioiodine therapy is available, but there is an overall trend to administer conservative doses. 2015 ATA guidelines were more conservative in dosing approaches than 2009 guidelines [61,62]. In general, dose ranges vary, and institutional protocols are used for determining the iodine-131 dose needed for the treatment Table 6 shows empiric dosing guidelines by 2015 ATA taskforce.

Figs. 8 and 9 shows post radioiodine therapy scan in two different patients treated with 131-I. Lung micrometastasis is better treated with radioiodine therapy compared to macronodular metastasis and the decision to continue radioiodine therapy in presence of macronodular metastasis should be based on the response seen on structural imaging or decrease in tumor markers. Dosimetry tools may be used to determine the appropriate iodine dose in pediatric and older patients.

4.3. Patient preparation for radioiodine therapy [61]

1. Low iodine diet for 1–2 weeks
2. Avoiding CT imaging with contrast for 4–8 weeks
3. TSH of more than 30uIU/mL prior to radioiodine therapy administration. This could be achieved either by thyroid hormone withdrawal or with recombinant-TSH administration.

Functioning thyroid tumor or a large remnant is an important consideration that may result in no increase in TSH even on stopping exogenous thyroid hormones. A good history-taking and imaging may be helpful in this case to determine iodine uptake.

Table 6
2015 ATA dosing guidelines for radioactive iodine therapy.

Dose	Site of disease
30–50 mCi	Remanent ablation
50–150 mCi	Loco-regional positive disease including nodal or metastatic disease
100–200 mCi	Lung and bone metastatic disease

4.4. Toxicity

Iodine-131 is usually well-tolerated with side effects seen as the dose or the number of doses increases. Side effects include, but are not limited to, temporary or permanent loss of taste, gastritis or stomach upset, increased, or decreased lacrimation, decreased salivation, painful swelling of the salivary glands while eating, nausea/vomiting, and/or neck swelling. Bone marrow suppression, secondary myelodysplastic syndromes or malignancy, and lung fibrosis are exceedingly rare [63].

4.5. Future direction

Lu-177-DOTAGA.(SA.FAPi)2, a radiopharmaceutical targeting Fibroblast activating protein in the tumor microenvironment, has been used in patients with iodine refractory differentiated thyroid cancer with effective pain palliation[64]. As PSMA is expressed in neovascularization of multiple tumors in addition to prostate cancer, researchers have used Lu-177-PSMA therapy in thyroid cancer refractory to iodine [65]. Tangentially, Lu-177-PSMA has been studied in salivary gland tumors [66] and has conceived its role in clear cell renal cell carcinoma [67] other than prostate and thyroid.

5. Liver-directed therapies

Transarterial radioembolization (TARE) is a recent addition to the interventional radiologist's armamentarium for localized treatment of metastatic and primary liver malignancies, which includes radiofrequency ablation (RFA), microwave ablation, transarterial bland embolization, and transarterial chemoembolization (TACE). TARE is particularly complex and expensive, requiring careful selection of patients for treatment. Along with bland embolization and chemoembolization, it shares the advantage of avoiding systemic adverse effects but can result in profound hepatic toxicity. These therapies are used both as a definitive treatment and as a bridge in controlling the tumor burden in hepatocellular cancer (HCC) patients on the transplant list. They have also been used in radiation segmentectomy or lobectomy before definitive resection, encouraging hypertrophy of the portion of the planned liver remnant [68].

5.1. TARE vs. TACE

TARE is indicated in patients with unresectable, intermediate-stage HCC and metastatic liver disease from colorectal and neuroendocrine tumors. The major alternative treatment is TACE, which has been found to have similar imaging response and median overall survival. TARE surpasses TACE in time-to-progression and toxicity profiles, despite being used in patients with generally more advanced diseases. A further advantage of TARE over TACE is that it can still be used in presence of portal vein thrombosis without causing ischemic hepatitis [69]. The comparative downside of TARE is higher upfront cost; however, this is mitigated by less need for potential multiple procedures, admissions, pain control, and treatment of toxicity associated with TACE [70].

Various methods are available for dose calculation for TARE including the empiric method. Body surface or partition method is used for resin microspheres and the Medical Internal Radiation Dosimetry (MIRD) method is used for glass microspheres therapy [71].

Many beta-emitting radionuclides are used for this purpose including Y-90, Lu-177, I-131, Holmium-166 (Ho-166), Phosphorus-32 (P-32), Rhenium-186 (Re-186), and Re-186. Of these, Y-90 is the most popular; it is delivered to the liver tumor in small spheres, either made up of glass (microspheres) or resin (SIR-Spheres). Table 7 briefly describes the differences in two types of spheres [72].

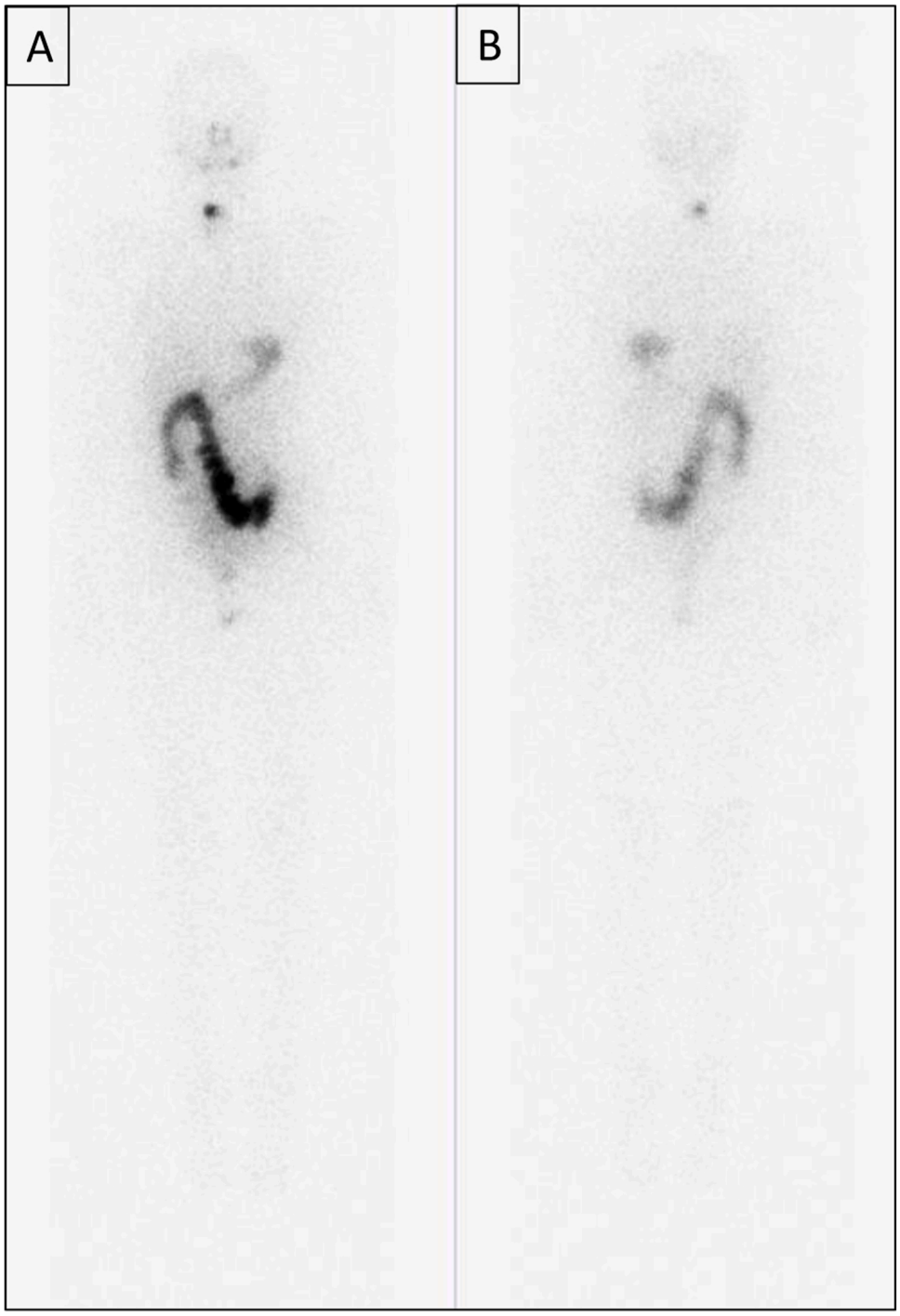

Fig. 8. (A)Anterior and (B)Posterior planar images post 30 mCi I-131 showing focal uptake in the thyroid bed. Physiological tracer in the stomach and bowel loops.

5.2. Administration

Pretreatment planning before TARE involves mapping of the tumor blood supply by hepatic arterial angiography and Tc-99m-MAA (macroaggregated albumin) injection followed by imaging. Radiolabeled MAA is injected into the hepatic artery intended for radioembolization helping to visualize the path of the planned radioembolization. Imaging with Tc-99m-MAA has 3 important roles:

1. Identify the shunting of the tracer to the lungs ("shunt fraction"). The presence of arteriovenous or hepatopulmonary shunt within the tumor leads to the radionuclide trapping in the lungs' capillary bed, which can result in radiation pneumonitis if a high amount of therapeutic radionuclide is delivered to the lungs. This is commonly done using planar imaging, but SPECT/CT has also been found to be useful in this calculation [73]. A lung shunt fraction of $> 20\%$ is generally considered a contraindication for treatment with resin spheres due to the risk of radiation pneumonitis [74].
2. Identify accessory vessels allowing activity to accumulate extrahepatic organs including the stomach, duodenum, pancreas, gallbladder, and falciform artery. If any of these are seen, precautions are taken to coil these vessels before radioembolization to prevent radiation-induced inflammation of these organs which could be life-threatening [75].

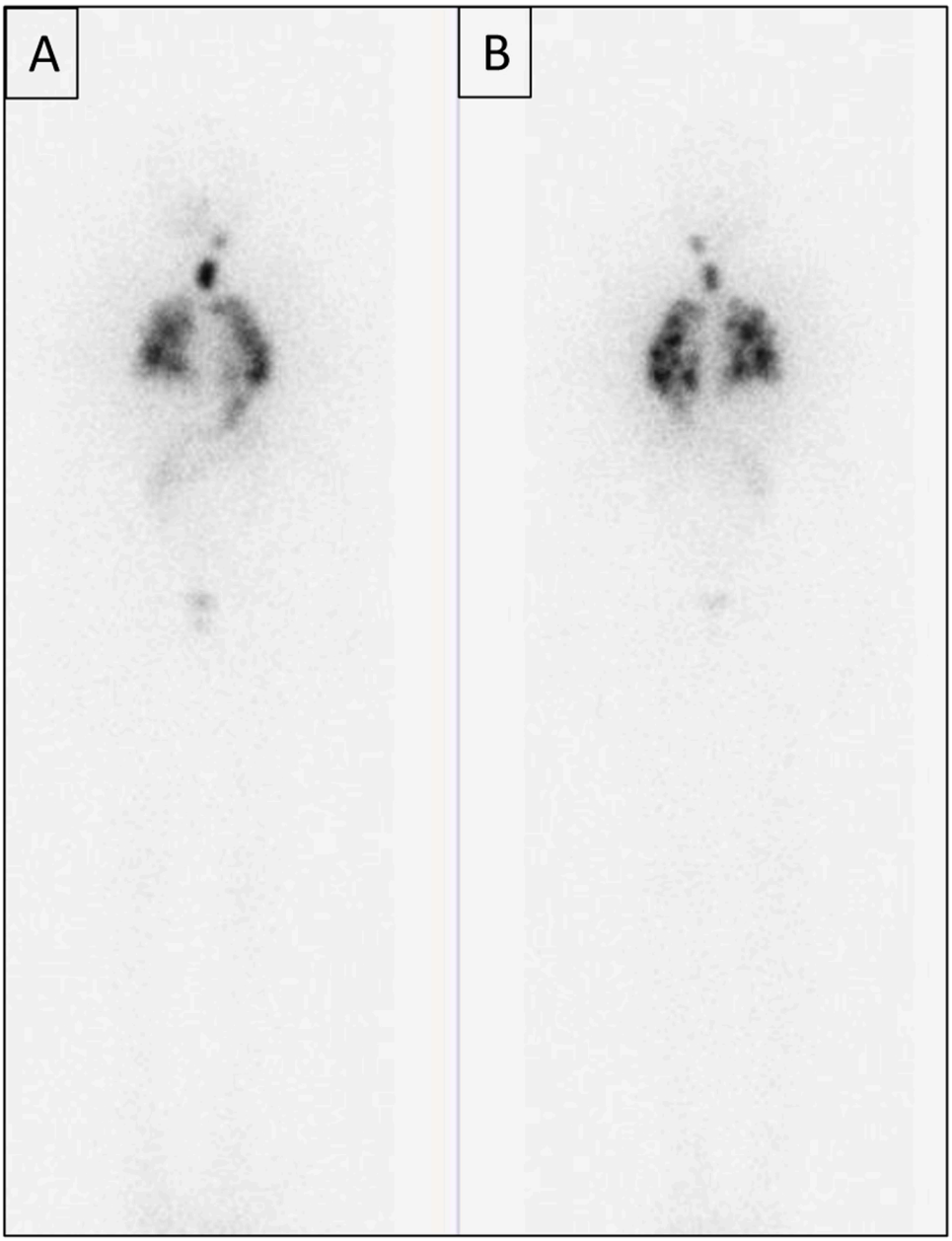

Fig. 9. (A)Anterior and (B)Posterior planar images post 125mCi of I-131 showing focal uptake in the thyroid bed and diffuse heterogeneous uptake in the lung metastatic disease. Physiological tracer in the stomach, bowel loops and urinary bladder.

Table 7
Comparison of properties in 90Y sirspheres and 90Y microspheres.

Property	90Y-sirspheres	90Y-microspheres
Diameter of the sphere	30–50 μm	20–30 μm
Maximum specific activity per sphere	75 Bq	2500 Bq
Dose size available	3GBq ± 10%	Multiple options ranging from 3 to 20Gbq
Dose calculation	Empiric, Body surface area or the Partition method	MIRD method

3. Identify the pattern of distribution of the tracer within the tumor and normal liver and calculate the dose: Tracer distribution in the liver and tumor can be categorized into 5 types (Fig. 10) [76]

   Patients in whom tracer is distributed to a greater extent in normal tissue than tumor are considered unsuitable for radioembolization. The pattern of tracer distribution is reported as a ratio that is calculated using maximal counts in the tumor and background liver. This ratio is then used in calculating the dose of therapeutic radionuclide to be used for radioembolization. Three methods for calculating the dose of 90Y for radioembolization are the empiric method, body surface area method, and partition method.

After radioembolization, a bremsstrahlung or PET scan is obtained to show the radionuclide distribution [77]. Fig. 11 shows an example of Y-90 SPECT and PET images in different patients obtained after SIRT. Radioembolization is considered an effective treatment and has shown survival benefits with tolerable side-effect profile in HCC, colorectal and neuroendocrine liver metastatic diseases [78].

5.3. Toxicity

Fatigue is the most common treatment-related side effect. Adverse

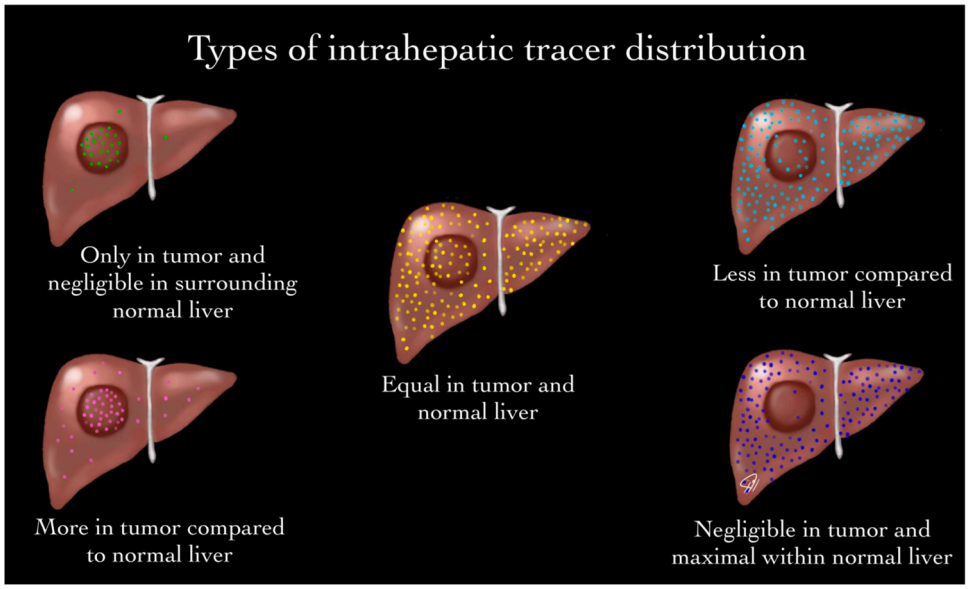

Fig. 10. showing different types of intrahepatic tracer distribution which can be seen on Tc-99m-MAA scan after injection of the tracer in the common hepatic artery.

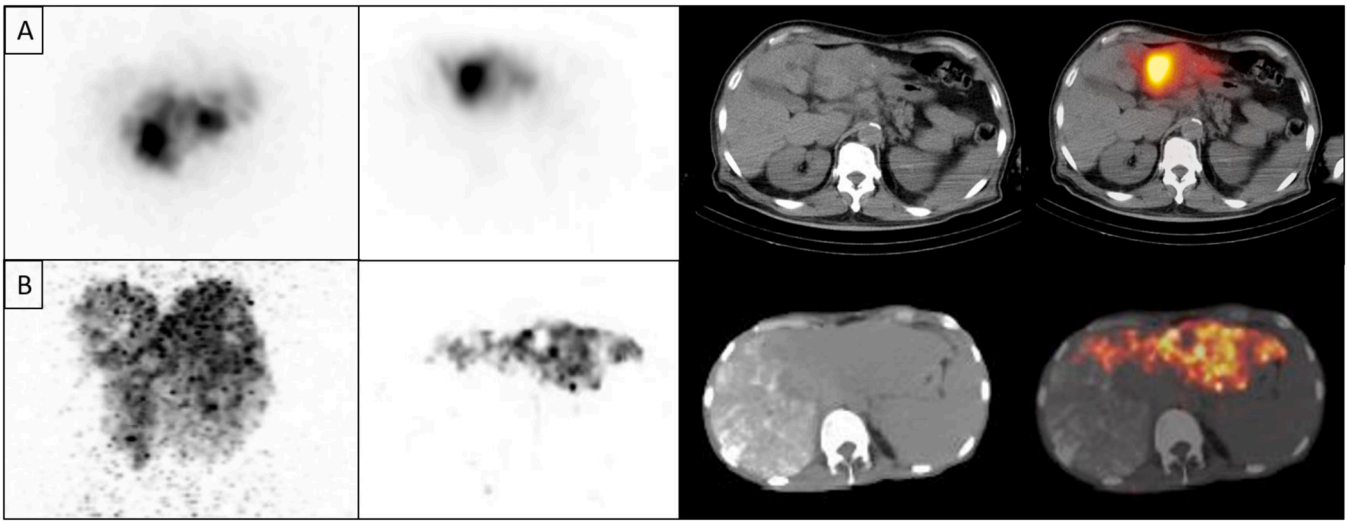

Fig. 11. (A) Y-90-resin micropheres Maximum Intensity Projection (MIP), axial SPECT, CT and fused SPECT/CT images showing heterogenous tracer uptake in the HCC involving the left lobe of the liver. (B) Y-90-glass microspheres Maximum Intensity Projection (MIP), axial PET, CT and fused PET/CT images showing tracer uptake in the left lobe of the liver. In the right lobe, bland embolization with lipiodol was performed.

events specific to radioembolization are rare, primarily off-target effects that occur when radionuclide is delivered to an extrahepatic organ [79]. Quality of life is usually not affected after the therapy [80,81].

Other radioembolization tracers include: Ho-166-microspheres [82], I-131-lipoidol [83], Re-188-HSA, and Re-188-lipoidol[84].

5.4. Future directions

Combining TARE with either targeted or immunotherapy drugs and in combination with CT-guided high-dose-rate interstitial brachytherapy for efficient tumor destruction has been conceived and applied [85,86].

6. Lymphoma

Non-Hodgkin lymphoma (NHL) is a diverse group of hematologic malignancies and the fifth most common malignancy in the United States. Most NHLs derive from B lymphocytes and express antigens such as CD19, CD20, and CD37. A wide array of monoclonal antibodies has been developed which target these antigens and the addition of radionuclides to such antibodies for the treatment of lymphoma have been developed for clinical and research use. Table 8 shows some of the CD20 targeting radiolabeled monoclonal antibodies. Despite the advantageous therapy profile of the two currently approved radioimmunotherapy drugs under the trade name Zevalin and Bexxar. These have been under-researched and underutilized. Bexxar was discontinued for manufacture and sale in 2014 after fewer than 75 patients received it in 2012[87].

There are several different diagnostic methods to determine target expression. Ideally, target expression can be determined with molecular imaging via PET or SPECT imaging of antibodies labeled with positron or gamma-emitting radionuclides. As a non-invasive test, this method can visualize all disease sites with expression as well as the extent of uptake. Scans can be repeated to assess target modulation over time. The main disadvantages are cost and availability. Alternatively, detection of a target expression can also be conducted with immunohistochemistry, and for hematological cancer, analysis such as flow cytometry can be

Table 8
Anti CD20 radioimmunotherapies for lymphoma treatment.

Antibody	Notes	Antibody type	Indications
90Y-Ibritumomab tiuxetan (Zevalin)	Paired with surrogate 111In-ibritumomab tiuxetan for gamma imaging	Murine	FDA: 1) Previously untreated follicular NHL patients who achieve a partial or complete response to first-line chemotherapy (2) Relapsed or refractory low-grade, follicular, or transformed B-cell NHL
131I Tositumomab (Bexxar)		Murine	Withdrawn: Relapsed or refractory low-grade, follicular, or transformed B-cell NHL
131I-rituximab		Chimeric	Indolent NHL
177Lu-rituximab	Paired with positron emitter 89Zr-rituximab for imaging	Chimeric	
177Lu-ofatumumab	Paired with positron emitter 89Zr-ofatumumab for imaging	Human	

employed [88–91].

6.1. Agents

6.1.1. Y-90-Ibritumomab tiuxetan (Zevalin)

Zevalin is monoclonal antibody radioimmunotherapy directed against the CD20 antigen, approved by the FDA to treat NHL in 2002. It consists of a mouse-derived antibody conjugated to the beta-emitter 90Y. The antibody binds to the CD20 antigen and delivers a cytotoxic effect via a combination of radiation and antibody-dependent cell-mediated toxicity. Due to the risk of inducing human anti-mouse antibodies, Zevalin and Bexxar are only administered once per patient. Bexxar and Zevalin are combined with rituximab to prevent excess accumulation of radioisotopes in the spleen and bone marrow.

A randomized controlled trial found that Zevalin was well-tolerated and produced a higher response rate than rituximab alone, which also targets CD20. The overall incidence of adverse effects was similar to rituximab, including asthenia, nausea, and pain [92]. Zevalin was also found to be effective in a trial of 57 rituximab-refractory NHL patients [93]. As Y-90 is a pure beta-emitter, it requires a surrogate radioisotope for imaging, generally the gamma emitter, In-111. The predictive value of pre-therapy imaging as it relates to treatment response is uncertain. A 2005 study involving 19 NHL patients with CD20 positivity found on immunohistochemistry did not show a significant correlation between the intensity of In-111-ibritumomab tiuxetan uptake and likelihood of response, instead finding that only tumor bulk predicted progression [93]. In contrast, a study of eight NHL patients found that patients with the highest quantitative concentration of In-111-ibritumomab tiuxetan uptake had a positive clinical and F-18-FDG-PET/CT response following treatment with Zevalin [94]. Lastly in a study of six patients with primary CNS lymphoma and CD20 positivity, none of the four patients with tumor uptake on SPECT responded to treatment [95].

6.1.2. I-131 Tositumomab (Bexxar)

Bexxar is also a murine antibody-drug conjugate directed against the CD20 antigen. Although no longer manufactured, it demonstrated a similar toxicity and efficacy profile as Zevalin [87]. It was first approved by the FDA in 2003 for treatment of relapsed or low-grade follicular or transformed B-cell NHL after a single-arm study demonstrated response in 68% of the 40 enrolled patients. In contrast to Zevalin, I-131 is both a beta and gamma radiation emitter, which enabled its use for therapy and imaging. A phase III randomized trial involving 554 patients with newly diagnosed follicular lymphoma compared cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab versus I-131-tositumomab and did not find a survival benefit for Bexxar[96]. There was concern that this study did not use standardized imaging procedures, and future studies were proposed to determine the potential benefits of combining R-CHOP induction chemotherapy with Bexxar consolidation, but these were not undertaken before the drug was voluntarily withdrawn.

6.1.3. I-131-Rituximab

Radioimmunotherapy using the chimeric anti-CD20 antibody was created due to the development of human antimouse antibodies after treatment with murine antibodies and the probable relapse of indolent NHL. A phase II clinical trial involving 78 patients with NHL demonstrated an overall response rate of 76%, with 53% attaining complete response or unconfirmed complete response[91]. In a separate study involving patients with relapsed or refractory B cell NHL, repeated treatment with I-131-Rituximab increased the response rate and duration of response[97]. Furthermore, a phase I/II study of fractionated I-131-Rituximab in low-grade B-cell lymphoma found that induction therapy with multiple doses of "cold" Rituximab did not compromise the clinical efficacy or increase the toxicity of subsequent I-131-Rituximab therapy [98,99].

6.2. Future directions

An additional imaging pair to target CD20 has been proposed, using the positron emitter Zirconium-89 (Zr-89) and Lu-177 conjugated to Ofatumumab. Both have been found to effectively target lymphoma xenografts in SCID mice and appear to be a promising avenue for future research [100].

The Zr-89 and Lu-177 theranostic pair has also been advanced for the treatment of other targets in the CD family but such work remains experimental at this time. This includes Zr-89-Desferrioxamine–Labeled CD30-Specific AC-10 Antibody for refractory Hodgkin and anaplastic large T cell lymphoma [101], as well as daratumumab (a CD38-targeting monoclonal antibody) radiolabeled with Zr-89 and Lu-177 for NHL and multiple myeloma [102].

7. Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor in children [103]. Treatment of neuroblastoma is multidisciplinary with the role of surgery, chemotherapy, radiation therapy, and radionuclide therapy with meta-iodo-benzyl-guanidine (mIBG). mIBG is a norepinephrine (NE) analog, the uptake of which occurs through the NE transporter. The uptake of this tracer occurs in both neuroendocrine and neural crest tumors and physiologically in tissues having sympathetic innervation such as myocardium and brown adipose tissue, among others.

7.1. Agent

mIBG labeled with radioactive iodine is an important adjunct in the management of neuroblastoma. It is useful as a diagnostic tool as well as a therapeutic agent in the metastatic setting. For diagnosis and monitoring of metastatic disease, mIBG labeled with Iodine-123 (I-123) or low dose I-131 is used. For the treatment of metastatic disease, a beta-emitting radionuclide I-131 labeled with mIBG is used. High no-carrier-added "cold" mIBG is used for therapy which acts as a competitive inhibitor to the radiolabeled mIBG to bind at the target sites [104].

Imaging with mIBG can provide diagnostic as well as prognostic information. Curie [105] and International Society of Pediatric Oncology Europe Neuroblastoma (SIOPEN) scoring [106] systems use information from diagnostic mIBG planar imaging (Table 9). A lower score is associated with a better prognosis [107]. The body is divided

Table 9
Comparison of Curie and SIOPEN scoring in assessment of MIBG avid neuroblastoma disease burden.
CURIE SCORING.

CURIE SCORING	
Maximum score	30
Soft tissue considered	Yes
Body divided in to	10 segments
Range of scores in each segment	0–3
SIOPEN SCORING	
Maximum score	72
Soft tissue considered	No
Body divided in to	12 segments
Range of scores in each segment	0–6

into segments and each segment is assigned a numerical value delineating the extent of disease involvement (Fig. 12).

7.2. Treatment protocol

mIBG labeled with 131I is used for therapeutic purposes in metastatic neuroblastoma. The foremost step in establishing eligibility is mIBG positivity on a diagnostic scan. A high percentage of neuroblastoma are mIBG positive, however, a small percentage are not (approximately 10%) [108]. The second step is appropriate patient preparation. There is a multitude of foods and drugs that can interfere with mIBG uptake for which cessation is required for a variable period before therapy [109]. The third step is thyroid blockade using oral stable iodides or potassium perchlorate. Finally, the administration of therapy itself is performed in authorized hospitals with the capability of proper and legal handling of large doses of radionuclides and radioactive accidents. The therapy is administered intravenously and the dose of I-131-mIBG varies in different clinical and research sites (Table 10), either weight-based or determined by dosimetry. Higher doses are administered in patients with a plan for bone marrow transplant post-mIBG therapy. Pretherapy GFR may also play an important role in determining the dose.

Use of I-131-mIBG therapy in neuroblastoma patients includes:

1. I-131-mIBG therapy is used in relapsed/refractory disease settings, showing good results in bone/ bone marrow disease only or soft tissue disease only [110], with a response rate of 37%[111]. mIBG therapy appeared to have higher response rates when used in patients with new diagnoses [112].
2. I-131-mIBG therapy is followed by myeloablative chemotherapy with busulfan and melphalan with autologous stem cell transplant

Table 10
Various dosing regimens for 131IMIBG.

Dose of 131IMIBG	Reference
8–12 mCi/kg	[114]
13.5 + /- 12.9 mCi/kg	[131]
18 mCi/Kg followed by autologous stem cell transplant	[113]
Escalating doses of 3–18 mCi/kg	[111]
Dosimetry-based	[108]

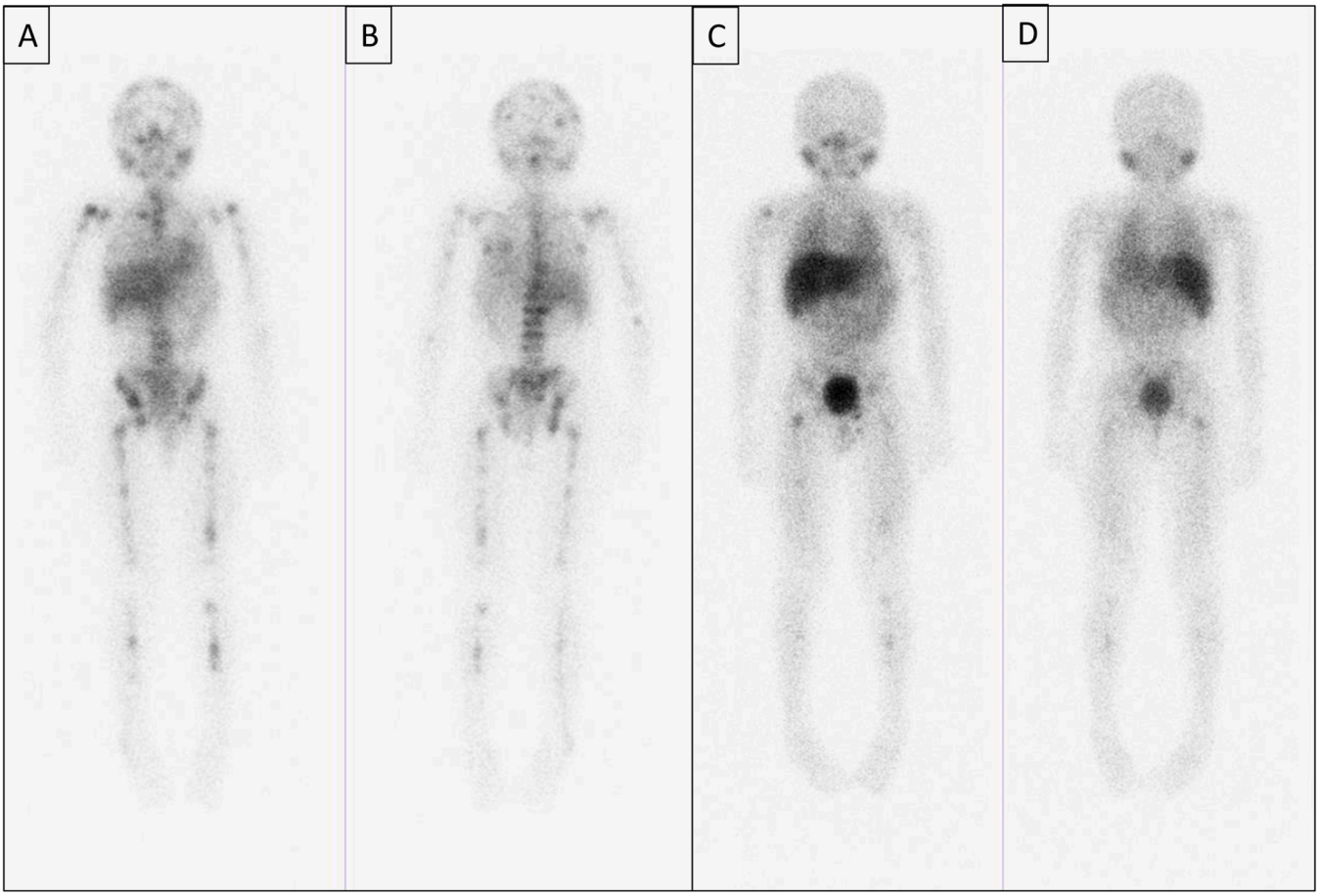

Fig. 12. (A)Anterior and (B)Posterior planar baseline pretreatment 123-I-mIBG images showing uptake in the multiple skeletal sites with Curie score of 23. (C) Anterior and (D)Posterior planar posttreatment 123-I-mIBG images showing uptake in a few skeletal sites with Curie score of 16. Physiological uptake in the myocardium, lungs, liver and urinary bladder.

[113] or carboplatin, etoposide, and melphalan with autologous stem cell transplant [114].

Absolute contraindications for I-131-mIBG therapy per the EANM are pregnancy/breastfeeding and renal insufficiency which will require dialysis in a short period and less than 3 months of life expectancy. Relative contraindications include myelosuppression, poor renal function, difficulties in isolation, and difficulty to manage urinary incontinence [109]. Thyroid dysfunction is one of the most common long-term side-effects of mIBG therapy [115]. Other rare side-effects include the development of second malignancy including leukemias [116]. In conclusion, I-131-mIBG theranostic is an important tool in neuroblastoma management.

8. Other tumors/therapies

I-131-mIBG and Lu-177-DOTATATE therapy have been used in metastatic paraganglioma/pheochromocytoma. Prerequisites for these therapies include expression of the target for these tracers, that is, mIBG positivity for I-131-mIBG and somatostatin receptor therapy for Lu-177-DOTATATE therapy. Hypertensive crises can occur during therapies with these radionuclides and blood pressure should be medically managed before the therapy. Side-effects of these therapies include bone marrow toxicity [117]. Metastatic Merkel cell carcinoma has a dismal prognosis. These tumors express somatostatin receptors and thus could be targeted using PRRT with Lu-177-DOTATATE [118,119].

Other than radioembolization of liver tumors, intratumoral radionuclide therapies have been used in the treatment of a variety of tumors including breast, prostate, lungs, and pancreas [120].

Although the literature is available in this area, these are not routinely being performed in clinical practice, likely due to the availability of other systemic and effective therapeutic options.

Intraperitoneal radionuclide therapies are largely experimental in animal models, mostly used in ovarian cancer exploring multiple alpha and beta-emitting radionuclides labeled with monoclonal antibodies [121].

Fibroblast Activation Protein (FAP)-Radionuclide therapy is one of the most discussed new avenues for theranostics in oncological diseases. The FAP molecule enters the tumor microenvironment and is expressed in a multitude of tumors including head and neck malignancy, gastrointestinal, pancreas, breast, and lung among others [122]. FAP-2268 is a FAP-binding peptide conjugate that was labeled with Lu-177, and this radiopharmaceutical was administered in patients with advanced adenocarcinoma of the pancreas, rectum, breast, and ovary [123]. FAP-46 labeled with Lu-177 was used in a variety of advanced malignancies and was found to be well-tolerated [124].

Radiation Synovectomy is used in a multitude of painful joint arthropathies including Rheumatoid arthritis, Psoriatic arthritis, Hemophilic arthritis, Pigmented villonodular synovitis, and persistent joint effusions, and other inflammatory joint diseases. The radionuclide is directly delivered in the joint space under aseptic conditions and causes ablation of the inflamed synovium as shown in Fig. 13 [133]. With time, there is a decrease in blood supply and inflammation [14,125].

Positron emitters have traditionally been used in diagnostics. A positron is a positively charged electron and when emitted from the nucleus, can deposit a high amount of penetrating radiation in a relatively small volume although with lower ionization potential. Thus, it can be considered a therapeutic radiopharmaceutical and has been studied on prostate cancer cell line and has been found to show therapeutic effect [126].

Auger electrons have high linear energy transfer due to the small range (nanometer to micrometer) and thus destroys neoplastic cells. Auger electrons emitting radionuclides like In-111 and Iodine-125 (I-125) have been studied labeled with monoclonal antibodies and with by incorporation into the DNA [127].

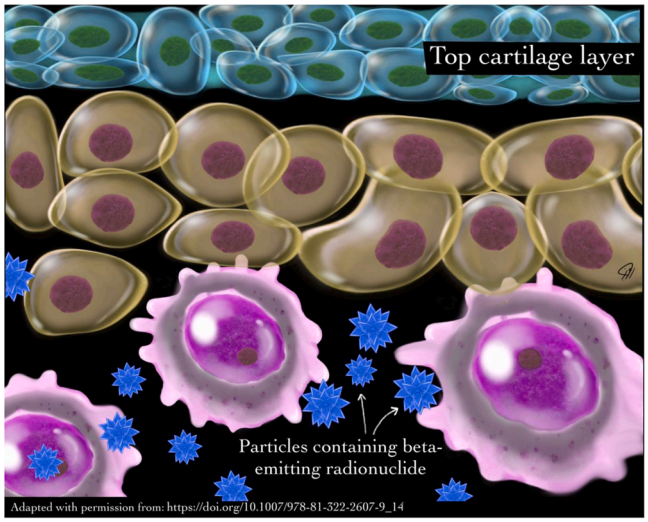

Fig. 13. showing mechanism of action of radiation synovectomy
Adapted with permission from Ref. [133].

9. Conclusion

Theranostics is used in a multitude of oncologic diseases. As new molecular compounds are identified to target specific receptors, tissues, and tumor types, opportunities will continue to expand for both diagnostic tracers and corollary theranostic agents. Theranostics is already an important pillar in disease management in some tumors like thyroid cancer, and it is becoming increasingly useful in the management of cancers such as neuroendocrine and prostate cancer. FAP targeting has the opened door of radionuclide therapy in a multitude of cancers and thus is a potential treatment option for those with advanced cancers and failed established therapeutics.

CRediT authorship contribution statement

Dr. Hina J. Shah: Conceptualization, Methodology, draft preparation, Data curation, Writing – original draft, Reviewing. **Dr. Evan Ruppell:** Writing – original draft, Writing – review & editing. **Dr. Rozan Bokhari:** Data curation, Visualization. **Dr. Parag Aland:** Data curation, Visualization, Reviewing. **Dr. Vikram R. Lele:** Data curation, Visualization, Reviewing. **Dr. Connie Ge:** Draft preparation, Reviewing. **Dr. Lacey McIntosh**: Conceptualization, Methodology Supervision, Writing – review & editing.

Conflicts of interest

None.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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