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EVOLVING FRONTIERS IN NUCLEAR MEDICINE AND NANOTECHNOLOGY: TARGETED STRATEGIES FOR NEUROENDOCRINE TUMORS

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Abstract
This review provides a detailed overview of Neuroendocrine Tumors (NETs) and the current and developing imaging and therapeutic modalities for NETs with emphasis on Nuclear Medicine modalities. Subsequently, Nanotechnology and its emerging role in cancer management, especially NETs, are discussed. The objective is to provide an insight into the developments made in nuclear medicine and nanotechnology towards management of NETs, individually as well as combine together

Introduction

Neuroendocrine tumors (NETs) are the tumors arising mainly from dispersed neuroendocrine cells and few from the neural crest. While the former are characterized by over-expression of somatostatin receptors (SSTR), the latter arising from sympathetic or parasympathetic ganglia express tyrosine hydroxylase to synthesize dopamine.NETs are usually secretory producing a number of specific and non-specific hormones.

Classification of NETs

NETs can be classified into those with and without clinical symptoms and are accordingly termed functionally active and functionally inactive or silent NETs, respectively. However, as per World Health Organization (WHO) classification scheme, given in 1980 and updated in 2000 and 2004, NETs can be stratified into three categories:

a. Well-differentiated neuroendocrine tumors with no or unknown malignancy. They are often referred to as carcinoids.
b. Well-differentiated neuroendocrine carcinomas that are low-grade neoplasms and
c. Poorly differentiated neuroendocrine carcinomas that are high-grade neoplasms. They are the aggressive forms and are generally fast growing and highly malignant.

For further grading and staging of NETs, TNM guidelines were published by European NETs society (ENETS) in 2006 and 2007. However, American Joint Committee on Cancer (AJCC) has published new TNM guidelines in 2009, slightly different from ENETS. North American NETs Society (NANETS) has published a review of nomenclature, grading and staging systems in 2010 and consensus guidelines for diagnosis and management of NETs [1-3].

Role of Somatostatin and its analogues in NETs

Somatostatin (SST) or somatotropin release-inhibiting factor (SRIF), discovered in 1970s, is reported to inhibit the secretion of growth hormone. It is a regulatory peptide hormone containing 14 (SST14) or 28 (SST28) amino acids, with one di-sulfide bridge between 2 cysteine residues. Chromosome 3 in human beings carries the gene that codes for pre-pro-somatostatin from which the precursor pro-somatostatin is formed having both SST14 and its C-terminally extended form SST28 [4-6].SST acts via specific cell membrane-bound high-affinity receptors called

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somatostatin receptors (SSTR). These receptors belong to a class of G protein-coupled receptors (GPCR) having seven 7 trans-membrane alpha helices that bind to specific ligands extra-cellularly and transduct signals intra-cellularly [1,6].

Five subtypes of SSTR have been identified so far, SSTR1-5, with different binding affinities to ligands and transmit different intracellular signals upon activation. SSTR are present on a number of organs including brain, pancreas, GI tract, pituitary gland, adrenal gland, immune cells, liver, spleen, kidney, heart and placenta. Of these, SSTR2 is the most abundantly found. SST binds to these receptors causing receptor internalization or receptor desensitization by uncoupling of the receptor from the G-proteins. It is this ligand activation of SSTR that causes inhibition of cell proliferation, inhibition of endocrine and exocrine secretion, modulation of neurotransmission, inhibition of motor and cognitive functions, decreased intestinal motility, absorption of nutrients and ions and/or vascular contractility. Depending on the SSTR subtype being activated, one or more of these biological activities can result [1,6].

Expression of SSTR by many tumors is well established. This along with the fact that SST-SSTR, particularly SSTR2 and 5, together produce inhibition of hormone secretion and proliferation, has generated considerable interest and encouraged the use of SST for treatment of SSTR-expressing tumors. However, the clinical use of SST is limited because of its short in-vivo half-life (around 3-4 min) that results from rapid degradation by peptidase and protease of naturally occurring L-isomers of amino acids in SST. Therefore, SST analogues have been synthesized which are essentially octapeptides and have longer half-life. To retain the specific receptor binding, these octapeptides have a common sequence of 4 amino acids, Phenylalanine (Phe), Tryptophan (Trp), Lysine (Lys) and Threonine (Thr), as in the original SST (7-10 position) that is responsible for biological behavior of SST. However, to prolong the half-life enzyme cleavage sites of SST14 are removed and replaced by D-isomers of Phe and trp at positions 1 and 4 of the octapeptides (figure 1) [5].

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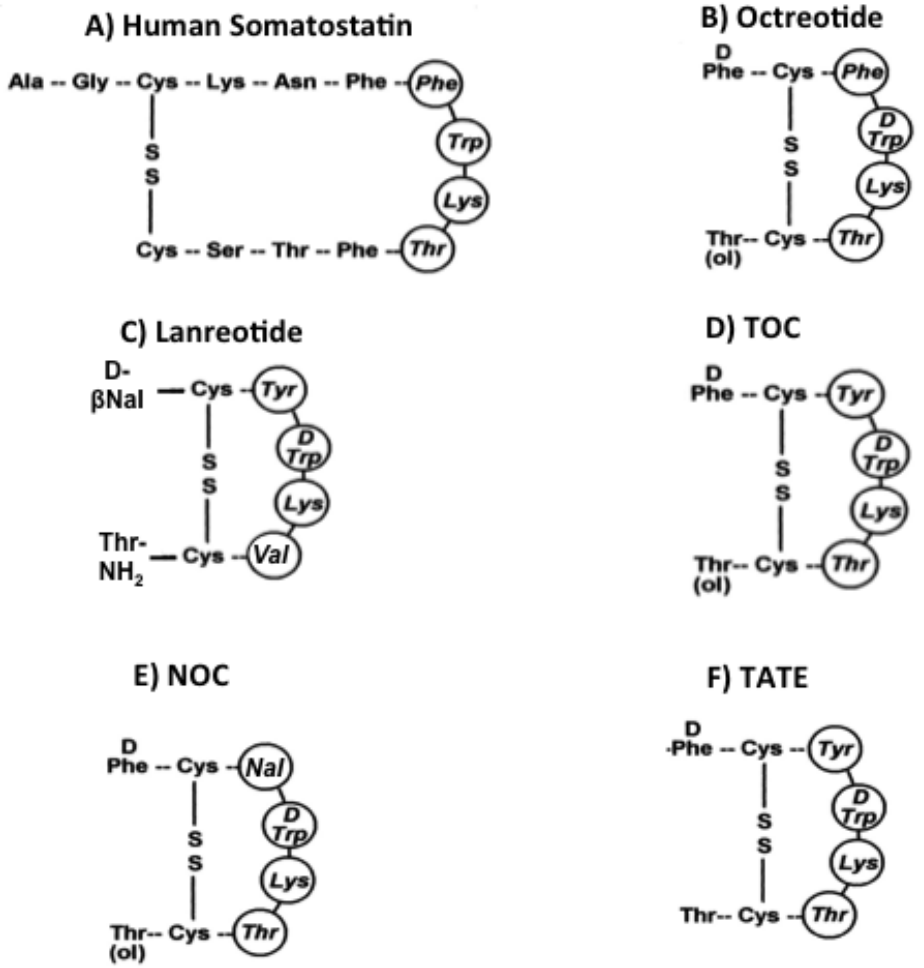

Figure 1: Structure of SST Analogues

Different SST analogues have different binding profiles towards the 5 subtypes of SSTR, with a predominant affinity for SSTR2 that is common to all. These SST analogues are used for medical therapies of NETs as well as for Somatostatin receptor scintigraphy (SRS) and Peptide receptor radionuclide therapy (PRRT) of NETs after radiolabeling with suitable diagnostic or therapeutic isotope using a bifunctional chelating agent (BFCA).

Diagnosis of NETs

Diagnostic tools for NETs include tissue pathology, measurement of circulating biochemical markers in blood and urine and radiologic and nuclear imaging.

Histopathology and tissue markers

NETs often present as uniform cells aligned variedly with oval stippled nucleus (blue) and show immuno-reactivity with neuroendocrine tissue markers like chromogranins, synaptophysin and Protein Gene Product 9.5 (PGP9.5). The cytoplasm, stained pink, is usually scant and granular.

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Circulating biochemical markers

Most NETs are secretory and can therefore be characterized by certain biomarkers in blood and urine. In addition to being used for diagnosis, assessing tumor response to treatment and monitoring disease progression, these biomarkers are also prognostic indicators.

General biomarkers for NETs are chromogranins (CgA and B), Neuron Specific enolase (NSE) and synaptophysin. Of these, CgA is the most sensitive. However, CgA is not a universal NET marker owing to its absence in benign and poorly differentiated NETs. In some of these, CgB may be raised instead. There are other markers associated with certain specific NETs such as gastrin, vasoactive intestinal peptide (VIP), glucagon that are expressed in NETs of pancreatic origin. Serotonin (measured by its metabolite 5-hydroxyinolacetic acid (5-HIAA) in urine); tachykinins Neurokinin A (NKA) and substance P (SP) are expressed in NETs of GI origin. Ki-67 is a general biomarker used to assess the proliferative activity of tumors. Low Ki-67 values indicate better prognosis. A detailed account of circulating biomarkers of Gastro-Entero-Pancreatic NETs (GEP-NETs) and their applications by Ardill and O'Dorisio was published in 2010 [1,7].

Imaging

Imaging helps to locate primary tumor and to evaluate the presence and extent of metastases. Selection of imaging technique is governed by the desirable outcome, that is whether imaging is to be done for detecting NETs in patients with suspected disease or for staging, restaging, post-therapy response evaluation or recurrence in a known case.

Anatomy based imaging modalities for identifying NETs include: Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Sonography and Endoscopy. While CT and MRI are commonly used in diagnosis of NETs, the role of sonography and endoscopy is limited depending on tumor location. With various technological advancements and introduction of contrast media, the sensitivity and specificity of CT and MRI have improved considerably [1,8].

Functional imaging of NETs is based on neuroamine uptake mechanisms or targeting various receptors, transporters and hormones present or secreted by NETs.It is mainly the arena of nuclear medicine and is discussed in detail. Nuclear medicine techniques of imaging and therapy of NETs have been reviewed by Gotthardt et al in 2006 [9] and more recently by Teunissen et al in 2011 [10].

Nuclear Medicine Techniques of Imaging NETs

A. Radio-iodinated meta-Iodo-benzyl-guanidine (mIBG)

The first radiopharmaceutical used for imaging of NETs was Radio-iodinated [Iodine-123/131 (^{123}I/^{131}I)] mIBG. It is still widely used particularly for imaging NETs secreting catecholamine such as pheochromocytoma, paraganglioma, neuroblastoma and medullary thyroid carcinoma. mIBG labeled with ^{131}I is also used for therapy of the same class of NETs [8].

Molecular basis of imaging and therapy with radioiodinated mIBG is its structural resemblance with norepinephrine, due to which it is taken up by energy-dependent amine uptake mechanism (uptake-1) in the cell membrane of sympatho-medullary tissues and is stored into the intracellular catecholamine storing granules. Apart from NETs, physiological uptake of radioiodinated mIBG is seen in heart, lungs, salivary glands, liver, spleen, colon and bladder [8]. It has been reported to have an overall sensitivity of ~90% and specificity as high as 99% for detecting tumors arising from chromaffin cells such as phaeochromocytoma, paraganglioma and neuroblastoma. However, mIBG scintigraphy in carcinoid tumors has shown lower sensitivity than the more frequently used [^{111}In-DTPA^{0}] Octreotide scintigraphy [10].

B. Somatostatin/Peptide receptor scintigraphy (SRS or PRS)

SRS with Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) plays a pivotal role in functional imaging of NETs. It is the first modality of choice for staging, localization of

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metastases and post-therapy response evaluation [1, 8]. The hybridization of SPECT with CT and PET with CT and MRI has made SRS the most sensitive imaging modality for NETs, by far.As already mentioned, majority of NETs can be targeted by radiolabeled SST analogues. The target cells internalize SST analogue-SSTR complex, which favors retention of the radio-ligand in SSTR-positive NETs [8].

Indium-111 (^{111}In) labeled peptides

^{111}In-DTPA-Octreotide (Pentreotide)/lanreotide is commonly used for SPECT imaging of NETs. The diagnostic use of ^{111}In-labeled-DTPA-octreotide (OctreoScan) has been extensively reviewed. In 1994, ^{111}In-OctreoScan became the first peptide-based agent approved by the FDA. It localizes in a wide variety of NETs and has been established for the cost-effective diagnosis of most GEP NETs. However, it has limited diagnostic usefulness in pituitary tumors, islet cell tumors and medullar thyroid cancers [11].

Society of Nuclear Medicine in 2001 laid the procedure guidelines for SRS with ^{111}In-Pentreotide [12]. Subsequently many studies have been conducted that established the diagnostic potential of ^{111}In-DTPA-Octreotide. Its overall reported sensitivity is 80% to almost 100% for carcinoids and 60–90% for pancreatic NETs, mostly depending on tumor type and lesion size [10].

There are few studies comparing ^{111}In-DTPA-Octreotide with conventional imaging techniques such as ultrasound, CT and MRI for NETs. In 2 separate studies by D. Dimitroulopoulos et al [13] (2003) and Schillaci et al [14](2004), SRS with ^{111}In-Octreotide was reported to have a higher sensitivity for the detection of GEP-NETs and their metastases, except liver metastases, than conventional imaging. The former also emphasized that the sensitivity could be even higher with a combination of CT and SRS. Some^{111}In labeled peptides have DOTA instead of DTPA as the chelating agent such as [^{11}In-DOTA]-lanreotide; ^{111}In-DOTANOC; ^{111}In-DOTANOCATE and ^{111}In-DOTABOCATE. However, human studies of these tracers are limited [10].

One^{111}In-labeled tracer that has a high sensitivity for insulinoma is (Lys^{40}-(Ahx-DOTA)-NH_2)exendin-4 (^{111}In-DOTA-exendin-4). It targets specifically the glucagon-like peptide 1 receptor (GLP1R), expressed in very high density in almost all insulinoma. However, most of them are benign and endoscopic ultrasound is proven to have a high sensitivity for them. Therefore, further studies into its efficacy and advantage over existing modalities are needed before this tracer can be applied in routine clinical practice [10].

Technitium-99m (^{99m}Tc) labeled peptides

^{111}In has the drawback of suboptimal imaging properties. Therefore, researchers have used ^{99m}Tc; the most commonly used diagnostic radionuclide in nuclear medicine, to label SST analogues.A tetra-amine-functionalized [Tyr^3] octreotate derivative (Demotate 1) was labeled with ^{99m}Tc at high specific activities [15] and could detect 11 GEP lesions in 6 patients as compared to 10 lesions detected by ^{111}In-Octreotide. Later, biodistribution and elimination characteristics of ^{99m}Tc-Demotate 1 was investigated in rats [16]. Similar agent, ^{99m}Tc-Demotate 2, showed equally promising biological qualities as ^{111}In-DOTATATE for SRS of SSTR2-positive tumors [17].Other two ^{99m}Tc-labeled peptides: HYNIC-TOC and HYNIC-TATE were compared in 12 patients with proven GEP-NETs [18]. Although, the two tracers showed similar sites of tumor, HYNIC-TATE had a slight edge in the total number of lesions seen (115) than HYNIC-TOC (110).

Various ^{111}In and ^{99m}Tc labeled SST analogues and their comparison to ^{111}In-DTPA-Octreotide as reviewed by Teunissen et al [10] are given in figure 2.

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Radioligand (references)	Setting	Comparison with [^{111}In-DTPA^{0}]octreotide	Other reported results	Comments
[^{111}In-DOTA^{0},Tyr^{3}]octreotide (Kwekkeboom *et al.* 1999)	Clinical	Yes; equal to [^{111}In-DTPA^{0}] octreotide Scan protocol adequate	Higher background radioactivity	
[^{111}In-DOTA^{0},Tyr^{3}]octreotide (Gabriel *et al.* 2007)	Clinical	Not performed	Inferior to [^{68}Ga-DOTA^{0},Tyr^{3}] octreotide	
[^{111}In-DOTA]lanreotide (Virgolini *et al.* 2002)	Clinical	Not performed	Inferior to [^{111}In-DOTA^{0}] octreotide	
[^{111}In-DOTA[1-Nal^{3}] octreotide (Wild *et al.* 2003)	Preclinical	Not performed	High affinity to hsst$_2$, 3 and 5	No clinical studies published
[^{111}In-DOTA[Nal^{8}Thr^{8}] octreotide (Ginj *et al.* 2005)	Preclinical	Not performed	High affinity to hsst$_2$, 3 and 5 Superior to [^{111}In-DOTA^{0}] octreotide	No clinical studies published
[^{111}In-DOTA^{0},BzThi^{3},Thr^{8}] octreotide (Ginj *et al.* 2005)	Preclinical	Not performed	High affinity to hsst$_2$, 3 and 5 Superior to [^{111}In-DOTA^{0}] octreotide	No clinical studies published
^{99m}Tc-depreotide (Lebtahi *et al.* 2002)	Clinical	Yes; inferior to [^{111}In-DTPA^{0}] octreotide Scan protocol adequate	High lung and bone marrow uptake	Both registered radio-pharmaceuticals
[^{99m}Tc-EDDA/HYNIC^{0},Tyr^{3}] octreotate (Hubalewska-Dydejczyk *et al.* 2006)	Clinical	Yes; superior to [^{111}In-DTPA^{0}] octreotide Scan protocol inadequate	No 24/48 h p.i. imaging possible	
[^{99m}Tc-EDDA/HYNIC^{0},Tyr^{3}] octreotide (Gabriel *et al.* 2003)	Clinical	Yes; superior to [^{111}In-DTPA^{0}] octreotide Scan protocol inadequate		No 24/48 h p.i. imaging possible
[^{99m}Tc-EDDA/HYNIC^{0},Tyr^{3}] octreotide (Bangard *et al.* 2000)	Clinical	Yes; equal to [^{111}In-DTPA^{0}] octreotide: liver lesions superior to [^{111}In-DTPA^{0}] octreotide: extrahepatic Scan protocol inadequate		No 24/48 h p.i. imaging possible

NA, not applicable; hsst$_2$, human somatostatin receptor subtype 2; p.i., post-injection.

Figure 2: ^{111}In and ^{99m}Tc-labeled SST analogues compared with ^{111}In-DTPA-Octreotide Scintigraphy [10]

PET tracers for SRS

Galium-68 (^{68}Ga) labeled peptides

The first ^{68}Ga-labeled SST analogue studied in patients was ^{68}Ga-DOTA-TOC. In 2001, Hoffman et al reported that ^{68}Ga-DOTA-TOC has a high tumor to non-tumor contrast, low kidney accumulation and higher detection rates as compared with ^{111}In-octreotide.^{68}Ga-DOTA-TOC scan shows uptake in organs expressing SSTR that is spleen, liver, kidneys, pituitary and thyroid. Because of tracer excretory route, uptake is also seen in renal collecting system and urinary bladder [19]. PET imaging with^{68}Ga-labeled SST analogues has the advantage of higher spatial resolution with excellent image quality than ^{111}In-Octreotide scintigraphy. Also, ^{68}Ga has easy accessibility and availability, favorable acquisition protocol, with relatively short scanning time, and low radiation exposure to the patient [10].^{68}Ga-DOTATOC PET has a sensitivity of 97%, a specificity of 92% and an overall accuracy of 96% [20].

Various other ^{68}Ga-labeled SST analogues have been developed with improved sensitivity and wider affinity profile such as ^{68}Ga-DOTA-NOC and ^{68}Ga-DOTA-TATE. However, despite 9 to 10-fold higher affinity for SSTR2, diagnostic accuracy of ^{68}Ga-DOTATATE for NETs is comparable to ^{68}Ga-DOTATOC (2011)[21]. ^{68}Ga-labeled peptides have been reviewed by Al-Nahhas et al in 2007 [22].

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F-18 labeled SST analogues have been experimented with in animals. However, they have not gained popularity owing to a tedious labeling procedure and low labeling yields[23,24].

PET Tracers for NETs other than SST analogues

^{18}F-FDG

PET imaging with ^{18}F-Fluorodeoxyglucose (FDG) has high sensitivity for rapidly growing, aggressive tumors. Uptake of FDG in tumors depends on regional blood flow and is an indicator of glucose metabolism, that is, proliferative activity of tumor cells. Since most of NETs are slow growing, the role of FDG-PET is limited so far as the diagnosis of NETs is concerned [8]. Recently, a combination of ^{18}F-FDG PET and ^{111}In-DTPA-Octreotide scintigraphy has been reported to yield an overall sensitivity of 96% compared with 89% sensitivity of the latter alone (2010)[25]. Though ^{18}F-FDG PET may provide complementary diagnostic information, use of two tracers is expected to reduce patient compliance. In addition, SRS with PET tracers is preferred for NETs as they have better radiation characteristics than In-111 and easy production and accessibility. However, ^{18}F-FDG PET is recommended for staging pathologically proven NETs that do not visualize on SRS, owing to more aggressive behavior and faster growth of such tumors [10].

Miscellaneous PET tracers

Similar to mIBG, there are certain PET tracers that act via catecholamine transport and storage mechanism such as ^{11}C-epinephrine (^{11}C-E), ^{11}C-hydroxyephedrine (^{11}C-HED), ^{18}F-fluorodopamine (^{18}F-FDA), and ^{11}C or ^{18}F L-dihydroxyphenylalanine (^{11}C/^{18}F-DOPA). They can be used for imaging the same class of NETs as mIBG. Another tracer ^{11}C-5-hydroxytryptophan (^{11}C-5-HTP) can be used to image serotonin-producing NETs (most GEP NETs) because of its ability to specifically and irreversibly bind to them [8]. Most of these PET tracers have not gained popularity due to their limited availability and high cost of production except ^{18}F-DOPA that has emerged as a promising imaging tool for NETs.

^{18}F-DOPA

The amino acid PET tracer ^{18}F-DOPA, its synthesis, mechanism of uptake and its application in imaging of NETs have been separately reviewed by Vesa Oikonen, Jager et al and Minn et al [26,27]. Uptake mechanism of ^{18}F-DOPA in neuroendocrine chromaffin cells is represented in figure 3[27].

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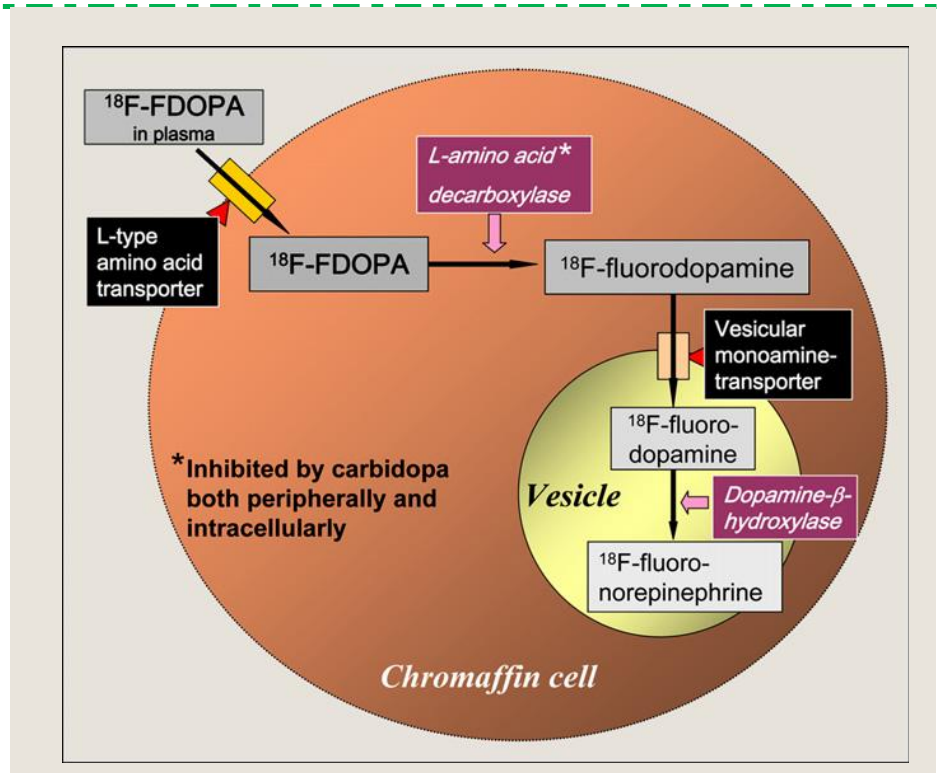

Figure 3: Uptake mechanism of ^{18}F-DOPA [27]

While most GEP and lung NETs can be better studied with ^{68}Ga-labeled peptide analogs, ^{18}F-DOPA has a primary role in the diagnosis of pheochromocytoma, focal form of congenital hyperinsulinism of infancy (CHI), and Medullary Thyroid Cancer (MTC) owing to its potential to monitor metabolic activity of entero-chromaffin cells [27].

Management of NETs

Management of NETs employs more than one discipline and is governed by tumor type, burden, and symptoms. The treatment may be curative or aimed at symptomatic relief and improving survival and quality of life depending on the stage of disease and general health condition of the patient [1].

A. Surgery

The first line of treatment of NETs with the primary aim of curing the disease is surgical resection of primary tumor and affected lymph nodes. However, most of the NETs have already metastasized on diagnosis so complete surgical resection is often not possible. In such cases, palliative surgery or tumor debulking is performed to assist in further medical management through various therapies. By reducing tumor mass and secretion of bioactive substances from tumors, it helps in symptom control and stabilizing disease progression in combination with other therapeutic modalities [1].

B. Medical Therapies

Patients with un-resectable NETs are candidates for chronic medical therapies with the primary aim of suppressing tumor growth and spread. Various medical therapies used for NETs are discussed below. They may be used alone or in combination of two or more depending upon tumor type and response to therapy.

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Somatostatin Analogues

Inhibitory effects of SST analogues on hormone secretion and proliferation, which explains their application in therapy of NETs, have been discussed. Octreotide was the first FDA (US) approved SST analogue and acts by blocking hormone release from NETs. It is now available as long-acting repeatable (LAR) formulation that is well tolerated. The side effects are mild that resolve spontaneously within a week of administration. Another FDA approved,though less extensively studied SST analogue, lanreotide has been reported to have similar efficacy as octreotide. A multi-receptor SST analogue, Pasireotide that binds to SSTR1, 2, 3 and 5, has been developed for use in patients refractory to octreotide or lanreotide. It is still facing clinical trials [1].

Therapy with SST analogues is effective for symptomatic relief and biochemical control of NETs. SST analogues have direct or indirect anti-proliferative effects on NETs, by stimulation of SSTR2, mediating cell cycle arrest and apoptosis or inhibition of the anti-apoptotic hormone IGF-1 (Insulin-like growth factor-1), growth factors, trophic hormones and angiogenesis modulation. SST analogue therapy has resulted in improved survival and stabilization of disease [1].

Interferon Therapy

Interferon (IFN) therapy, with IFN-α, is the second line of medical therapy for functioning NETs after SST analogues. IFN-α-2a and 2b bind to IFN receptors on NETs, thereby activating signal transduction for transcription of tumor suppressor genes. IFN-α also degrades peptide hormones and inhibits protein synthesis by acting on certain enzymes like 2',5'-A-synthetase and p68 kinase [2].IFN-α has symptom control efficacy comparable to that of octreotide and lanreotide therapy and a higher anti-proliferative activity but acts slower than SST analogues. Side effects include fever, fatigue, anorexia, and weight loss [1].

Mammalian Target of Rapamycin (mTOR) Inhibitors

mTOR is a conserved serine or threonine kinase that regulates cell growth, proliferation, angiogenesis and metabolism. Two mTOR inhibitors temsirolimus and everolimus have been studied in NETs, of which everolimus is more extensively studied. mTOR inhibitors block mTOR pathway and hence proliferation by binding to intracellular receptor, FKBP-12 (FK-506 or tacrolimus binding protein-12)[1, 2].

Vascular Endothelial Growth Factor (VEGF) Inhibitors

Role of VEGF inhibitors such as monoclonal antibody bevacizumab and tyrosine kinase inhibitors (sunitinib and sorafinib), in management of NETs is being evaluated recently. Bevacizumab has been reported to decrease tumor perfusion and Sunitinib, a VEGF tyrosine kinase inhibitor, might have anti-proliferative effect. Reported side effects are diarrhea, nausea, asthenia and fatigue [1,2].It should be noted that medical therapy using mTOR and VEGF inhibitors are new evolving strategies and are still under development.

C. Chemotherapy

Routinely used chemotherapeutic drugs, such as 5-fluorouracil, doxorubicin, streptozotocin, have not yielded encouraging results in NETs. However, they may be used in combination with each other, octreotide LAR or IFN-α to act synergistically [1].

D. Radionuclide Therapy

While external beam therapy has limited efficacy in NETs, systemic delivery of radiolabeled ligands is a potent therapeutic option for NETs. However, delivering an adequate radiation dose to the tumor can damage the surrounding normal tissue and the challenge in radionuclide therapy is to develop a radiolabeled tracer that would specifically bind to tumor cells without damaging non-tumor tissues, thus limiting the adverse effects.

Radionuclide therapy is based on the same targeting principles as radionuclide imaging, discussed previously. Two targeting ligands used routinely for radionuclide therapy of NETs are mIBG and SST analogues that are labeled with

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various therapeutic radioisotopes, that is ^{131}I for mIBG and ^{111}In, ^{90}Y and ^{177}Lu for SST analogues. The radiation characteristics of these isotopes are given in table 1.

Table 1: Radiation characteristics of radionuclides used for radionuclide therapy

Radioisotope	Physical Half-life (days)	Radiation emitted	Energy (KeV)	Maximum particle range in tissue (mm)
^{131}I	8.04	γ, β-	γ = 365 (83%) βmax = 610 (90%)	2.4
^{111}In	2.8	γ, conversion e-	γ = 247 (94%) e- = 150-240 (15%)	0.5
^{90}Y	2.67	β-	2280	11.3
^{177}Lu	6.7	γ, β-	γ = 113 (6%); 208 (11%) β = 497	2
^{186}Re	3.78	γ, β-	1370 (11%) β = 1071 (73%)	4.6

mIBG therapy is used to target NETs of neuro-ectodermal origin and therapy with SST analogues (PRRT) is more effective in GEP-NETs.A preliminary requirement for radionuclide therapy is that the tumor and metastatic sites should show avidity for the specific ligand used for targeting, as seen by a significant uptake and considerably high tumor-to-background ratio on pre-therapy scan using the corresponding ligand with diagnostic radiolabel. Criteria for selecting candidates for radionuclide therapy are listed in table 2[28].

Table 2: Patient inclusion criteria for radionuclide therapy [28]

Indications	Inoperable/metastatic NET
	Increased uptake at all known tumor sites in pre-therapy scan
	Stable haematology: Hb>100g/l WBC>3.0X109/l Platelets>100X109/l
	Stable histochemistry: Urea<10mmol/l Creatinine<160µmol/l GFR>40ml/min
	Co-operative
Contraindication	Pregnancy/lactation
	Haemodynamic instability precluding isolation
	Unmanageable urinary incontinence
	Myelosuppression
	Renal failure

Hb: Haemoglobin; WBC: White blood cell count; GFR: Glomerular filtration rate

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^{131}I-mIBG Therapy of NETs

The therapeutic use of ^{131}I-mIBG was first reported in 1984. Of the first 5 phaeochromocytoma patients, partial remission was observed in 2 with symptomatic relief and the rest 3 did not show any objective response [29]. Later in 1991, pooled results of ^{131}I-mIBG therapy conducted at 14 centers worldwide in 117 patients of metastatic phaeochromocytoma were reported, showing an overall tumor response rate of ~58% (40). As per European experience of ^{131}I-mIBG therapy, reported in 1999, an overall objective response in 38% and subjective response in 52% patients was observed. Data of 537 patients that underwent ^{131}I-mIBG therapy for a range of NETs (mainly neural crest tumors) was included. Side effect included temporary myelosuppression (mainly grade I/II) [28].

Two retrospective studies of ^{131}I-mIBG therapy for metastatic NETs (2003 and 2008) have reported symptomatic response in ~80-89%, hormonal response in ~55-67% and tumor response rate in ~47% patients as per WHO criteria. 5-year survival rate was reported to be ~59% and the side effects were minimal and mainly included nausea and a transient fall in platelet count [29,30].

^{131}I-mIBG therapy in patients with disseminated NETs resulted a higher symptomatic response (37/38) as compared to hormonal response (20/38) by Navalkissoor et al (2010) [31]. More recently (2011), ^{131}I-mIBG therapy in stage III and IV neuroblastoma patients has been reported to have favorable therapeutic effects with overall improved outcome and good quality of life. The overall survival was 75% in grade III and 69% in grade IV neuroblastoma [32].Various groups have extensively reviewed ^{131}I-mIBG therapy. Two updated and detailed reviews are given by Grunwald et al (2010) and Voo et al (2011) [33, 34].

Peptide Receptor Radionuclide Therapy (PRRT)

PRRT targets over-expression of SSTR on NETs, similar to SRS, using various SST analogues, that is Octreotide, lanreotide, DOTATOC, DOTANOC and DOTATATE.

For radiolabelling, SST analogues are conjugated to bifunctional chelating agents (BFCA) to facilitate binding of metal ion as well as targeting ligand. Selection of an appropriate BFCA is important for adequate sequestration of the metallic radionuclide resulting a stable radiolabeled compound. Itis based on charge; cavity size of the chelating agent and appropriate number & chemical character of donor binding groups. Also, the rate of metal complex formation and dissociation are important factors to be considered. Based on these, a number of BFCA have been used for radiolabeling peptides, of which ethylenediamine tetraacetic acid (EDTA); Diethylenetriaminopentaacetic (DTPA) & its derivatives; 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and NOTA are among the most commonly used. There are other less commonly used BFCA like TETA; TCMC; PEPA and HEHA. DTPA and DOTA are the two most versatile and commonly used BFCA for radiolabeling of SST analogues. Of the two, DOTA forms more stable metal ion complexes owing to its cyclic structure as compared to open chain DTPA (figure 6) and is the BFCA of choice for labeling SST analogues with β-emitting radionuclides such as ^{90}Y and ^{177}Lu [35].

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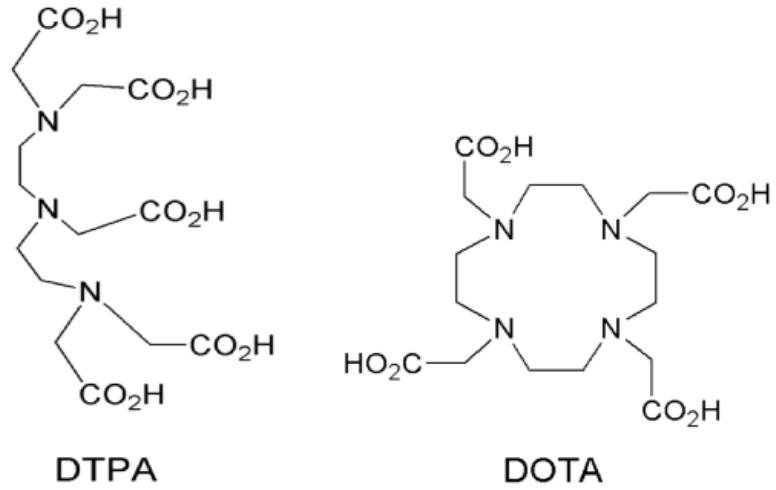

Figure 4: Structure of BFCA: DTPA and DOTA

A. ^{111}In-DTPA-Octreotide

The initial studies of PRRT were performed with ^{111}In-DTPA-Octreotide (^{111}In-Pentreotide) in 1990s.In the years to follow, studies evaluating efficacy of ^{111}In-DTPA-Octreotide have been reported and reviewed [10, 36, 37]. The results were encouraging with respect to symptomatic relief, although the observed partial responses were few and complete response has not been reported. So far as the toxicity of ^{111}In-DTPA-Octreotide is concerned, the most commonly reported side effect is bone marrow suppression. Other less common side effects include drop in lymphocytes and platelets, renal insufficiency and transient liver toxicity. In a recent study, the outcome of high-dose ^{111}In-Octreotide treatment was assessed in 14 patients with disseminated NETs of which 9 patients also underwent treatment with Sandostatin® LAR. Better response (partial and stable disease) was observed in patients who underwent both the treatments. However, no complete response was reported. The side effects reported were mild with no significant [38].

Although ^{111}In-Octreotide treatment may be efficacious in micro-metastasis for disease stabilization, itis not suitable for PRRT owing to the small particle range of ^{111}In and thus short tissue penetration.

B. ^{90}Y- labeled peptides

^{90}Y-DOTA-peptides formed the next generation of PRRT tracers. Various phase I and II trials have been performed with ^{90}Y-DOTATOC. As per the first clinical results (1999), 20 of 29 patients showed stable disease, partial remission or tumor mass reduction without any severe renal or haematological toxicity (NCI grading criteria) at a cumulative dose of ≤7400 MBq/m^{2}of ^{90}Y-DOTATOC[39].Phase II results (2001) also showed stable disease (49%) and partial (22%), minor (12%) and complete (2%) responses with 6000 MBq/m^2 ^{90}Y-DOTATOC in patients with GEP-NETs and bronchial tumors. The overall response rate was 24% with a higher response (36%) in GEP-NETs patients and symptomatic response was 83%. No major toxicity was observed [40]. Subsequently, a number of studies have been reported for response evaluation of ^{90}Y-DOTATOC therapy with different protocols. While disease stabilization has been observed to be ~70%, complete and partial responses have been less frequent (10 – 30%). However, in comparison to ^{111}In-octreotide therapy, the overall survival with ^{90}Y-DOTATOC therapy is significantly longer [10, 36, 37].

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Other ^{90}Y-labeled peptides such as DOTATATE and DOTALAN have also been explored for the same purpose. The results with ^{90}Y-DOTATATE are similar to that of ^{90}Y-DOTATOC but ^{90}Y-lanreotide yields a much higher bone marrow dose (0.94 to 1.67 mGy/MBq) as compared with ^{90}Y-DOTATOC (0.03 to 0.07 mGy/MBq) leading to more hematologic toxicity thereby limiting its use [41].

The commonly observed side effects of ^{90}Y-peptide therapy include mild bone marrow suppression and in some cases haematological toxicity and renal toxicity. The immediate side effects such as nausea, vomiting and flushing are mild and tolerable [10,37]. Despite amino acid co-infusion, kidneys are often dose limiting. Furthermore, because ^{90}Y is a pure β-particle emitter, imaging and organ specific dosimetric evaluation becomes difficult. Simultaneous or pre-therapy imaging with ^{111}In-labeled counterpart (surrogate tracer) has been used for this purpose. But using 2 radionuclides is tedious and results in unnecessary radiation dose to normal organs [5, 10].

C. ^{177}Lu-labeled peptides

^{177}Lu-labeled peptides, introduced in last decade, have gained considerable momentum because of both β and γ emission enabling simultaneous imaging and therapy and long half-life (6.7 days). In preclinical studies (2002), ^{177}Lu-DOTATATE has shown highest tumor uptake and significantly better tumor-to-kidney ratios compared with ^{111}In-Octreotide and ^{90}Y-DOTATOC [36].

In clinical setting, initial studies assessing the effects of ^{177}Lu-DOTATATE therapy in patients with GEP-NETs mainly reported stable disease and partialresponseswith few complete response. Disease progression was also observed in some patients [42]. ^{177}Lu-DOTATATE therapy significantly improves global health or quality of life as well as several function and symptom scales even in patients with progressive disease [43]. Median time to progression and overall survival from the start of treatment is ~40 and 46 months post-therapy, respectively[44]. A recently reported prospective phase I-II study showed similar efficacy results of ^{177}Lu-DOTATATE [45]. Though ^{177}Lu-DOTATOC and DOTANOC have also been evaluated, TATE is preferred over them owing to the higher tumor residence time than TOC (TATE-to-TOC=2:1) and lower whole body dose (0.07mGy/MBq for DOTANOC while 0.05mGy/MBq for DOTATATE) [46, 47].

Serious side effects such as acute renal failure and hepato-renal syndrome in single patients have been reported in intial studies [42], but no major renal or haematological toxicity is observed in the phase I-II study except one grade 3 leukopenia and thrombocytopenia. Cumulative renal absorbed doses ranged between 8–37Gy. Decrease in creatinine clearance of 27% was observed over 2 years post-therapy [45]. Acute effects occurring within 24h of therapy may include nausea, vomiting and abdominal discomfort. In addition, temporary hair loss, hormone-related crises and transient effect on endocrine function have also been reported [44].

^{177}Lu-DOTATATE is the radiopharmaceutical of choice among all the currently available agentsfor PRRT because of reported reduced renal dose with good tumor response.

D. Tandem therapy with ^{90}Y and ^{177}Lu-labeled peptides

To improve the efficacy of PRRT, combination of ^{90}Y and ^{177}Lu-labeled SST analogues has been proposed. The therapy has demonstrated more favorable tumor responses in animal experiments than either analogue tested as a single agent [48]. Although an adequate prospective randomized trial is lacking, a few patient studies have been performed[41, 49-51].

It can be concluded that while ^{90}Y is suitable for treating large solid tumors with non-homogenous receptor expression, ^{177}Lu is the radionuclide of choice for small tumors (<2cm) and micro-metastases and mixed ^{90}Y/^{177}Lu-DOTATATE may be preferred in patients with both large and small foci. Tandem therapies are usually well tolerated and yield favorable responses. However, further research is warranted to establish its efficacy. The radiation absorbed doses (Gy/GBq) by ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE as reviewed by Cremonesi et al in 2010 [52] are given in the table 3.

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Table 3: Radiation absorbed doses to various body organs in ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE therapy. The doses are given as range of doses reported by different research groups[52]

Absorbed doses per unit activity (Gy/GBq)		
Organ	^{90}Y-DOTATOC	^{177}Lu-DOTATATE
Red marrow	0.03-0.17	0.02-0.07
Kidneys	1.71-6.05	0.32-1.65
Liver	0.27-0.92	0.13-0.21
Spleen	2.19-5.36	0.21-2.15
Urinary Bladder	1.03-2.61	0.22-0.36
Total Body	0.08-0.28	0.03-0.09
Tumor	1.4-41.7	0.6-56

Furthermore, newer agents for PRRT like ^{64}Cu and ^{67}Cu-labeled SST derivatives; ^{166}Ho and ^{188}Re-labeled bombesin derivatives and therapy with alpha emitters (^{211}Bi and ^{225}At) are still evolving [5].

The tumor response rate in PRRT is variable and depends on: type of SST analogue and tumor type, burden & size. Various dose regimes have been practiced and reported. The therapy protocol followed is usually experience based (self or literature) and no specific protocol or dose has been laid in any of the nuclear medicine society guidelines, so far. The therapy and criteria for dose administration should therefore be standardized.

Limitations of PRRT

A major limitation of PRRT, which hinders its therapeutic potential, is the associated toxicity in normal organs. Although haematological toxicity is mild and liver toxicity could not be reliably detected but nephrotoxicity is generally dose-limiting and is therefore the most important concern. It is attributed to high uptake and retention of radiolabeled SST analogues by kidneys. The radiolabeled peptides are re-absorbed in the renal tubules via megalin or cubulin (large endocytic receptors) resulting in high radiation exposure to kidneys. Though the efficacy reports of ^{177}Lu or ^{90}Y-labeled SST analogues are promising but renal toxicity needs to be reduced for effective tumor treatment. Methods to reduce nephrotoxicity in PRRT are discussed elsewhere in this review [9].

Also, SSTRs are expressed in a number of other normal organs resulting in their unnecessary radiation exposure during PRRT [6]. Depending on the target tissue, biodistribution profile and route of excretion, different radionuclide therapies have different critical organs that limit the dose of therapeutic radionuclide. Bone marrow is the common critical organ for most radionuclide therapies. In PRRT kidney is the dose-limiting organ, though bone marrow also gets a significant radiation dose that needs to be respected.

Another issue that needs to be addressed is individualized dosimetry for each patient. There is large variation in inter-patient doses reported for kidney and bone marrow. In view of this, if a fixed dose regimen of PRRT is followed a few patients remain undertreated if serious side effects are to be avoided [10, 37].

Various methods that have been employed to reduce renal radiation dose in PRRT include: metabolizable linker between the radio-metal–chelator complex and the peptide; competitive inhibition of proximal tubular reabsorption by co-infusion of positively charged (basic) amino acids, arginine and lysine; interference of proximal tubular reabsorption by pre-treatment with colchicine, maleate (citric acid cycle inhibitor) and Ammonium chloride (NH_4Cl)and using radio-protectors such as Amifostine [53].

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Of all the above-mentioned methods, use of lysine-arginine mixture is most commonly practiced in PRRT. Rest of the strategies are still developing and more supporting data is needed to establish their efficacy.

Role Of Nanotechnology

Among various approaches, the use of nanoparticles (NPs) in cancer medicine has gained significant popularityin recent past. As per terminology laid by the Royal Society and Royal academy of Engineering (UK) and the National Nanotechnology initiative (US), the particles sized between 1-100nm are known as NPs. However, NPs with a mesoscopic size of around 200-300nm are most commonly used in drug delivery applications [54, 55].

1. NPs as Drug Delivery Systems

Using NP-based drug delivery systems can vanquish the limitations of current cancer therapies such as poor solubility of drugs and multi-drug resistance. In principle, NPs take advantage of leaky tumor vasculature for penetration and can be easily modified for specific tumor targeting. NPs, thus, enhance the drug bioavailability and efficacy while reducing the systemic side effects associated with the drug in question [55-56]. Furthermore, multi-functional NPs have been extensively researched for simultaneous multiple applications. NPs and their application in drug delivery and mechanism of localization have been reviewed extensively; hence these aspects are discussed briefly here. However, NPs in Nuclear Medicine is a less studied topic that is emphasized in the subsequent section of this review.

2. Tumor targeting Strategies of NPs

Tumor targeting of NPs is mediated via two mechanisms:

- Passive targeting – Tumor progression is associated with angiogenesis and impaired lymphatic drainage that facilitate NP accumulation and subsequent retention in tumor. This phenomenon is known as Enhanced Permeability and Retention (EPR) effect.
- Active targeting–Passively targeted NPs are ineffective inpre-angiogenic or necrotic tumors. Therefore NPs are conjugated with ligands that bind with the peptides or hormones expressed by specific tumors enabling highly selective drug delivery.

3. Types of NPs

Depending on the design and composition, NPs can be of various types. The most extensively studied type of NPs is Liposome that is basically a phospholipid bilayer formed into a closed vesicle. It has been approved by US FDA.It has been investigated for use in radionuclide therapy after successful radiolabeling with ^{111}In and ^{186}Re [57-59].Drug molecules can be aggregated in a single crystal followed by a thin coating of surfactant to form Nanocrystals that are advantageous for oral delivery of poorly soluble drugs, eg. Quantum dots. US FDA has approved 2 nanocrystal-based drugs (Rapamune and Emend®). Carbon atoms arranged as single or multi-walled tubes are Carbon Nanotubes.Solid core containing the drug surrounded phospholipid monolayer are known as Solid-lipid NPs and are used for slow release.Central core with branched structures that bind the drug molecule are Dendrimers and have low immunogenicity.Viruses are hybridized to act as carrier for drugs and target cancer cells and have found application in gene therapy.Metals such as gold, silver, gadolinium, iron are used to form Metallic NPs[56].

The characteristics of drug and NP-matrix together govern the choice of a particular type of NP. Polymeric NPs have scored over other drug-carriersmentioned above in recent NP research as they are easily formed, cost effective, allow easy surface modification and have minimum toxicity concerns.

4. Methods for Preparation of NPs

Many formulation techniques are reported and all have their merits and demerits. Dispersion of preformed polymers, polymerization of monomers and ionic gelation or coacervation of hydrophilic polymer, are the most commonly used techniques. Both, the type of polymer and drug, play an equally important role in deciding the method of

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formulation. These methods along with many othershave been described in detail in reviews cited in this section [56, 60].

5. Fate of NPs in-vivo and related Toxicity

NPs educe an immune response in the body and are treated in the same way as foreign particles by the Reticulo-endothelial System (RES). When administered, organs rich mononuclear phagocytes like liver and spleen take up these particles. The main determinants of in-vivo fate of NPs are size, surface charge, hydrophobicity/hydrophilicity and steric effects of particle coating and immunogenicity of NP material [61, 62]. To be able to efficiently target the tumor and specifically deliver their payload, NPs must escape body's immune system.Coating the particle surface with Poly-ethylene Glycol (PEG) has been reported to effectively reduce macrophage/RES uptake. Reviews on immunological responses of NPs worth mentioning have been given by Moghimi et al (2001); Owens III et al (2006); Dobrovolskaia et al (2007) and Zolnik et al (2010) [62-65].

Once inside the body, small size of these particles enables them to interact at cellular/genetic level that apart from being advantageous may even adversely affect the molecular biology. Despite routine clinical use of some particles, like Lupron depot® and Sandostatin LAR, the toxicity concerns of NPs require in-depth analysis to establish their bio-safety. The field of nanotechnology is still lacking in the short and long-term toxicology data that is hindering the realization of full potential of NPs. Non-biodegradable NPs pose an even higher threat of toxicity [56, 66]. Choi et al have nicely discussed the toxicity and safety concerns of nanoparticles in the book "Biomedical Engineering – From Theory to Applications" (2011) [66].

NPs in Nuclear Medicine Imaging and Therapy–Application for NETs

Though the use of NPs as delivery vehicles has become significantly popular for a number of chemotherapeutic drugs, their application in nuclear medicine is largely limited to research. The site-specific delivery of diagnostic or therapeutic radionuclides by NPs can enhance tumor to background ratio and reduce radiation dose to normal tissues [54,56]. After the routine clinical use of radiolabeled colloidal particles such as sulfur colloid, human serum albumin, tin colloid etc., the focus has now shifted towards using smaller (nano-scale) particles and combining them with the advancements made in molecular imaging and therapy.

A lot of in vitro and in vivo studies have been done on radiolabeled NPs for various applications in SPECT, PET and therapy. Majority of them have employed liposomes labeled with ^{111}In, ^{186}Re, ^{67}Cu, ^{188}Re, ^{90}Y, and ^{131}I [58,59, 67,68]. Rests include^{64}Cu-Labeled Folate-Conjugated Shell Cross-Linked NPs [69], ^{188}Re-DMSA(V)-PLGA NPs [70], ^{111}In-ChL6 bioprobes [71],^{111}In-carbon nanotubes [72], Lipid-based NP with ^{111}In, ^{99m}Tc, ^{68}Ga and ^{177}Lu [73], ^{99m}Tc-ferrite magnetic NPs [74], ^{99m}Tc-HYNIC-peptide/mannose-gold NPs [75] and ^{188}Re-folate-human serum albumin-cisplatin NPs [76]. A few of the above mentioned NPs are multi-functional combining two or more modalities. NPs, especially liposomes, have also been labeled with α-particle emitting radioisotopes such as ^{213}Bi, ^{211}At, ^{223}Ra, ^{224}Ra and ^{225}Ac [77,78]. For the management of NETs, a new formulation of Octreotide based on PLGA NPs, Sandostatin LAR® has been approved by US FDA.Few studies reporting the application of radiolabeled NPs for NETs are discussed in detail here.

In 2008, Surujpaul et al developed gold NPs conjugated with TOC (Tyr^3 Octreotide) to target NETs. The particles had size ranged between 15 to 35 nm. The gold NP-TOC were shown to have better targeting in vitro as well as in vivo with AR42J murine pancreatic cancer cell line that gold particles or TOC alone. The study presented interesting results of NET targeting. However, the efficacy was not reported and the toxicity issues with metallic NPs have still not been answered adequately [79].

More recently, Dubey et al (2012) have formulated NPs of Polycaprolactone (PCL) loaded with Octreotide labeled with ^{99m}Tc for evaluation in NETs. The NPs had a size of 130-195 nm and a peptide loading efficiency of 66-84%. In vitro proliferation of BON1 NET cells was inhibited by these NPs and had a significant in vivo tumor accumulation than octreotide alone. In another study, the same group loaded the PCL NPs with paclitaxel for

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chemotherapy of NETs. The size of PCL-paclitaxel NPs was 100 – 250 nm and 73% of the drug was released from the NPs within 24 h. A significant reduction in tumor volume was observed with NPs than that with the drug alone and the authors concluded that paclitaxel loaded NPs were a better chemotherapeutic option for NETs that paclitaxel alone [80,81].

So far the development of NPs to target NETs have mostly used cold SST analogues or some chemotherapeutic drugs. Most recently, our group (Arora et al, 2012) has formulated biodegradable NPs for PRRT of NETs using ^{177}Lu-DOTATATE as the model drug. As already mentioned, PRRT with radiolabeled SST analogues has yielded encouraging results in treatment of NETs over the past decade with symptomatic and biochemical control as well as tumor regression but is limited by the nephrotoxicity. PLGA 50: 50 and 75:25 NPs loaded with ^{177}Lu-DOTATATE were formulated and coated with PEG. The mean size of particles was 303.8±67.2 and 494.3±71.8 nm for PLGA 50:50 and 75:25 NPs respectively. On comparison, PLGA 50:50 NPs were found to be a more suitable carrier for ^{177}Lu-DOTATATE owing to higher encapsulation efficiency and slower release rate. In vivo biodistribution evaluation of NPs in normal wistar rats showed significantly reduced renal uptake of ^{177}Lu-DOTATATE-NPs than ^{177}Lu-DOTATATE alone and the liver uptake of NPs could be reduced by PEG coating. The results were encouraging in terms of reduction of nephrotoxicity associated with PRRT drugs and advocated their delivery through NPs. To our knowledge of literature, this is the first study evaluating the role of NPs in PRRT [82].

After these initial interesting results, we further investigated the cytotoxic effects of these nanoparticles in vivo on human glioblastoma cells (U87MG) and also tested their in vivo tumor targeting capability in C6 tumor inoculated wistar rats (ref anm). In this study the role of antibodies as a tumor-targeting moiety was also tested. The ^{177}Lu-DOTATATE loaded nanoparticles alone could not produce a significant cytotoxic effect (35.8%) on radio-resistant U87MG cells. To further enhance cytotoxicity and test the feasibility of active tumor targeting, apoptosis-inducing anti-β-hCG monoclonal antibodies were employed in vitro, after confirming expression of β-hCG on these cells. Interestingly, the use on these antibodies almost doubled the cytotoxicity (80%) acting together with the nanoparticles. Also, the tumor uptake of these particles was significantly higher than that of the plain drug (4.3 ± 0.46% and 3.5 ± 0.31%ID/g; ($p<0.001$) [83].

Conclusion

Nuclear medicine, among various other disciplines, has always played a significant role in diagnosis and treatment of NETs. With the introduction of newer and better (more specific), radiolabeled SST analogues such as ^{68}Ga-DOTATOC and ^{177}Lu-DOTATATE, nuclear medicine has become an indispensable part of NETs management. The importance of nuclear medicine therapeutics is even higher in patients with unresectable tumors. On the other hand, nanotechnology has also been vastly explored at different pre-clinical and clinical levels for its applications in NETs. This review presented the evolution of nuclear medicine modalities and nanotechnology towards NETs, individually as well as combined with each other. The studies suggest that both the disciplines together can overcome the demerits associated with each other and act synergistically thus providing improvised and more efficacious treatment options for NETs. However, there is still a lot of research that needs to be done for translating these studies to clinical practice..

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