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Neuroendocrine Tumor Therapy with Lutetium-177: A Literature Review

Muhammad Haisum Maqsood [1] , Asim Tameez Ud Din [2] , Ameer H. Khan [3]

1. Community Medicine, King Edward Medical University, Mayo Hospital, Lahore, PAK 2. Internal Medicine, Rawalpindi Medical college, Rawalpindi, PAK 3. Internal Medicine, Allama Iqbal Medical College, Lahore, PAK

Corresponding author: Muhammad Haisum Maqsood, haisumbajwa@live.com
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Abstract

The worldwide incidence of neuroendocrine tumors (NETs) has been increasing. They are a very diverse group of tumors which are commonly found in the gastrointestinal and bronchopulmonary tracts. These tumors usually express somatostatin receptors. Therefore, somatostatin analogs are used for symptom relief as well as treatment. Of the many therapeutic options available, peptide receptor radionuclide therapy (PRRT) has been shown to be very promising. In January 2018, the Food Drug and Authority (FDA) approved ^{177}Lu-Dotatate for use in gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Lutetium is a lower energy beta-emitting radionuclide. The therapeutic use of lutetium-^{177} (^{177}Lu) has shown better results in advanced gastroenteropancreatic and bronchial neuroendocrine tumors when compared with other therapies available. Adverse effects associated with this therapy include myelotoxicity and nephrotoxicity as the radiopeptides are reabsorbed and accumulate in the renal interstitium. Everolimus is a good and safe option in patients pretreated with ^{177}Lu-Dotatate. Lutetium, in combination with somatostatin analogs, has proven efficacy to treat gastroenteropancreatic neuroendocrine tumors in candidates with somatostatin receptor-positive advanced tumors and normal renal function. This therapy has great potential as it decreases tumor size, improves symptoms, and improves quality of life.

Categories: Internal Medicine, Miscellaneous, Oncology
Keywords: lutetium, neuroendocrine tumors, gastroenteropancreatic tumors

Introduction And Background

The worldwide incidence of neuroendocrine tumors (NETs) has been increasing [1]. This can be explained by an improvement in imaging techniques and diagnosis. NETs are very diverse and can be divided on the basis of their primary site, histologic grade, and genetic makeup. The growth rate of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is very slow [2]. Since there is great diversity in these tumors, treatment strategies should also be tailored to particular types because many treatment options are now available [3]. Of the available treatment options, radiolabelled somatostatin analogs (SSAs) are the only ones with a well-defined biomarker, which is the expression of the somatostatin receptors (SSTR) [4].

Neuroendocrine tumors can originate from the gastrointestinal tract and the bronchopulmonary tract. They are also broadly classified as functional and non-functional tumors based on the presence or absence of specific symptoms. Functional tumors manifest symptoms by producing bioactive chemicals. Nonfunctioning tumors do not produce active substances and usually present as widespread metastatic disease. SSAs are commonly used not

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only for symptom control but also for decreasing the tumor growth and improving the quality of life in affected individuals [5-7]. Carcinoid tumors, based on their origin, can be further divided into three groups, which are foregut, midgut, and hindgut [8]. The most common foregut-derived tumors are of bronchial and gastric origin [9]. Presence of somatostatin receptor Type 2 can be detected in such tumors with Indium-111 (^{111}In)-octreotide scintigraphy [10] and radiolabelled somatostatin analogs can be used for therapy.

NETs have the ability to synthesize, store, and secrete neuroamines and peptides [11]. The carcinoid syndrome, characterized by flushing, diarrhea, and right-sided valvular heart disease, is usually caused by a midgut metastasized NET [12]. Patients with localized NETs are treated with surgery, but 40% of patients already have metastasized disease at diagnosis and require systemic treatment [13]. Targeted therapy has been utilized to treat these tumors, which includes somatostatin analogs (SSAs) and peptide receptor radionuclide therapy (PRRT), as these tumors express SSTRs. Low and intermediate grade tumors express these receptors at a higher density as compared to high-grade tumors [14].

In January 2018, the Food Drug and Authority approved ^{177}Lu-Dotatate for use in GEP-NETs [15]. This literature review will highlight the clinical features of using lutetium-177 (^{177}Lu)-based PRRT in these tumors.

Review

Mechanism of action and use

Radiolabelled SSAs bind SSTRs on tumor cells and are internalized and later stored in lysosomes, thereby delivering the radioisotope to the tumor cells [16]. This is how the tumor cells are targeted in this therapeutic technique [17]. ^{177}Lu is a β-emitter and has a higher range and energy as compared to other radionuclides. Variation in the tumor absorbed fraction for lutetium was less in the models studied as compared to the other radionuclides [18]. Its emission of γ-rays also makes it useful for monitoring tumor response [19]. Radionuclides other than ^{177}Lu, such as yttrium-90 (^{90}Y) and ^{111}In, have also been used in PRRT.

Patients with somatostatin receptor (SSTR)-positive NETs and near-normal kidney and bone marrow function are good candidates for PRRT. ^{177}Lu-Dotatate, the most commonly used radiopeptide, has been shown to have comparable efficacy and a better hematological toxicity profile than yttrium-90 Dotatoc (^{90}Y-Dotatoc) [20-21]. In many studies, ^{177}Lu-Dotatate has been shown to have a good response rate and a positive impact on the quality of life [22]. ^{177}Lu-Dotatate, in comparison with high-dose octreotide, has been shown to result in a 79% reduction in risk of progression or death [23]. Retreatment with the same or a different radiopeptide has been shown to be safe but less effective than the initial treatment. Radiopeptides have been tried sequentially or in combination with other drugs. Different radiopeptides have also been used in combination with success but definitive proof requires prospective randomized trials. PRRT has proven efficacy as a neoadjuvant treatment for NETs [24]. Its combination with other drugs needs further research.

In addition to SSRs, mutated epithelial cadherins (E-Cad) are also exclusively found in gastric cancer cells, which makes them a preferable target for therapy using immunoglobulins [25]. Antibodies against the mutated delta 9 E-cadherin (d9 E-Cad) are combined with bismuth-213 (^{213}Bi), which is an α-emitter [26]. The α-particles cause necrosis in the cancer cells [27], whereas lutetium, as discussed, is a β-emitter and these particles have a 50x greater range as compared to α-particles. Thus, where α-emitter therapy is useful for early-stage disease, β-emitter therapy has been explored for comparatively more disseminated disease.

It has been demonstrated that ^{177}Lu peptide receptor radionuclides are effective in treating patients with metastasized neuroendocrine tumors [28]. The therapy increased the global health of the treated patients, especially those that had a proven tumor regression. The treatment improved not only the functional status but also the symptoms experienced by the patients [29].

Side effects

PRRT can cause myelosuppression by irradiating the bone marrow, even though it is mild and reversible. Ten percent of patients treated with Lu-Dotatate develop World Health Organization (WHO) Grade 3/4 hematotoxicity [30]. Radiopeptides can accumulate in the renal interstitium because of their reabsorption in the proximal tubule and cause damage. This can be reduced by administering a positively charged amino acid infusion [31]. Other less common adverse effects include lymphopenia, acute leukemia, and myelodysplastic syndromes.

A dose-limiting factor for the use of ^{177}Lu-PRRT is myelotoxicity. A method to mitigate the myelotoxicity, such as extracorporeal affinity adsorption treatment (ECAT), can be used [31]. It can decrease the blood content of ^{177}Lu after treatment is given and thus reduce the myelotoxicity. Another method of increasing the clearance of the radionuclides is modifying the conjugates with carbohydrates [32].

Brabander et al. studied the side-effects of this therapy related to bone marrow and kidney function. Giving an infusion of lysine and arginine before therapy has resolved the nephrotoxicity. ^{177}Lu-octreotate is also implicated in causing cytopenias and myelodysplastic syndrome but this is relatively uncommon. An increase in aminotransferases (aspartate transaminase and/or alanine transaminase) was observed in a few cases. Acute leukemia (AL) occurred during follow-up in 0.7% of patients [33].

Combination therapies

Radiopeptides are used for targeting tumors for localized or internal radiotherapy [34]. In the case of GEP-NETs, somatostatin analogs, combined with radionuclides, are used as these tumors expresses SSTRs. As there are many types of SSTRs expressed by tumors, a radiopeptide that can bind with most of these receptors is desirable. A new radiopeptide based on somatostatin was developed called DOTA-(Nal3)-octreotide (DOTA-NOC). This ligand can target more SSTRs and possibly treat a larger spectrum of tumors. DOTA-NOC can be used with radionuclides, such as ^{90}Y, ^{177}Lu, and ^{111}In [35].

Seidl et al. depicted that the longer half-life of ^{177}Lu, as compared to ^{213}Bi, prolonged the circulation time of the drug in the blood which leads to adverse effects, such as myelotoxicity. This was demonstrated in a mouse model of peritoneal carcinomatosis [36]. ^{213}Bi-immunotherapy is preferable in early stage peritoneal carcinomatosis because it has good efficacy and is without toxic adverse effects. While ^{177}Lu-immunotherapy is effective for late-stage disease, the adverse effects, such as myelotoxicity, make it problematic to use.

In particular, the therapeutic use of the beta-emitting radionuclide ^{177}Lu has shown better results in bronchial neuroendocrine and gastroenteropancreatic tumors when compared with other therapies available [37]. For the past many years, somatostatin analogs have been the mainstay of treatment for well-differentiated tumors but not many options were available for the advanced disease [38]. PRRT with radiolabeled somatostatin has shown better outcomes in metastatic GEP-NETs [39]. Everolimus, a mammalian target of rapamycin (mTOR) inhibitor has shown good results in early as well as advanced tumors [40]. The use of everolimus in patients

pretreated with ^{177}Lu-octreotate radionuclide therapy is a good option in terms of safety [41].

Fluorouracil (5-FU) is routinely used to treat many malignancies [42]. The doses used caused significant toxicity. In the radiopharmaceutical technique, this molecule can be tagged with a beta-emitting radionuclide, such as ^{177}Lu, and used for therapeutic purposes. This decreases the dose of 5-FU the patient is exposed to and can lead to less severe toxic adverse effects. A standardized methodology for radiolabelling of ^{177}Lu-5-FU with high efficiency and stability has been developed. The biodistribution and pharmacokinetics of the radiopharmaceutical were studied in a mouse model. No cytotoxic effects were observed in vivo and very low nephrotoxicity was expected because of the short, effective half-life. This drug has the potential to be useful for the therapy of many malignancies [43].

Recent randomized trials have shown that ^{177}Lu-Dotatate has very good response rates as compared to high-dose octreotide in patients with mid-gut NETs [44]. Data has shown that the effects of ^{177}Lu-Dotatate are not limited to midgut NETs. Further studies are needed to compare it to everolimus, liver-directed therapies, and other systemic options. The choice of which treatment to use can depend on factors, such as the location of metastases, primary site, and level of SSTR expression. ^{177}Lu-Dotatate has been recently approved for treatment of SSTR-positive advanced GEP-NETs. The NETTER-1 study (A Study Comparing Treatment With ^{177}Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours, NCT01578239) demonstrated a 79% reduction in the risk of progression or death compared to high-dose octreotide. Adverse effects associated with ^{177}Lu-Dotatate have been discussed previously. A regimen of ^{177}Lu-Dotatate consists of four cycles of the drug over eight weeks. Retreatment in patients has also been shown to be beneficial [45].

In another study, ^{177}Lu was combined with low-dose capecitabine chemotherapy, but the efficacy in comparison to ^{177}Lu alone was not well-established [46]. Recently, a comparison was done to assess the efficacy of PRRT in using ^{90}Y alone versus alternating cycles of ^{90}Y and ^{177}Lu. The combined therapy yielded better results than using a single agent [47]. Recent use of nanocarriers in experimental models to transport these PRRT drugs like ^{177}Lu has shown decreased renal retention which can help in reducing the nephrotoxicity associated with these therapies [48].

Neuroendocrine tumor therapy with lutetium-177-octreotate and everolimus (NETTLE) study

When radiosensitizing chemotherapeutic agents are combined with PRRT, there has been a significant improvement in the efficacy of the therapeutic regimen with a modest increase in overall toxicity. To conclude, the use of everolimus in combination to PRRT has shown promising results in the efficacy of the treatment of low-grade NETs. The main side effects, when used in combination, are related to hematology, such as neutropenia and thrombocytopenia [49].

Conclusions

Lutetium, in combination with somatostatin analogs, has proven efficacy to treat gastroenteropancreatic neuroendocrine tumors in candidates with normal renal function. This therapy decreases tumor size and improves symptoms, as well as the quality of life.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Cives M, Strosberg J: An update on gastroenteropancreatic neuroendocrine tumors . Oncology (Williston Park). 2014, 28:749-56.
2. Crocetti E, Paci E: Malignant carcinoids in the USA, SEER 1992-1999. An epidemiological study with 6830 cases. Eur J Cancer Prev. 2003, 12:191-94. 10.1097/00008469-200306000-00004
3. Kunz PL: Carcinoid and neuroendocrine tumors: building on success . J Clin Oncol. 2015, 33:1855-63. 10.1200/jco.2014.60.2532
4. van Essen M, Krenning EP, De Jong M, Valkema R, Kwekkeboom DJ: Peptide receptor radionuclide therapy with radiolabeled somatostatin analogues in patients with somatostatin receptor positive tumors. Acta Oncol. 2007, 46:723-34. 10.1080/02841860701441848
5. Davis GR, Camp RC, Raskin P, Krejs GJ: Effect of somatostatin infusion on jejunal water and electrolyte transport in a patient with secretory diarrhea due to malignant carcinoid syndrome. Gastroenterology. 1980, 78:346-49.
6. Arnold R, Simon B, Wied M: Treatment of neuroendocrine GEP tumours with somatostatin analogues. Digestion. 2000, 62:84-91. 10.1159/000051861
7. Imtiaz KE, Monteith P, Khaleeli A: Complete histological regression of metastatic carcinoid tumour after treatment with octreotide. Clin Endocrinol (Oxf). 2000, 53:755-58. 10.1046/j.1365-2265.2000.01126.x
8. Williams ED, Sandler M: The classification of carcinoid tumours. Lancet. 1963, 1:P238-39. 10.1016/S0140-6736(63)90951-6
9. van Essen M, Krenning EP, Bakker WH, de Herder WW, van Aken MO, Kwekkeboom DJ: Peptide receptor radionuclide therapy with 177Lu-octreotate in patients with foregut carcinoid tumours of bronchial, gastric and thymic origin. Eur J Nucl Med Mol Imaging. 2007, 34:1219-27. 10.1007/s00259-006-0355-4
10. Krenning EP, Kwekkeboom DJ, Bakker WH, et al.: Somatostatin receptor scintigraphy with [111In-DTPA-d-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nucl Med. 1993, 20:716-31. 10.1007/BF00181765
11. Kaltsas GA, Besser GM, Grossman AB: The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev. 2004, 25:458-511. 10.1210/er.2003-0014
12. Cives M, Soares HP, Strosberg J: Clinical heterogeneity of neuroendocrine tumors impact their management in the future? Lessons from recent trials. Curr Opin Oncol. 2016, 28:359-66. 10.1097/CCO.0000000000000299
13. Modlin IM, Oberg K, Chung DC, et al.: Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008, 9:P61-72. 10.1016/S1470-2045(07)70410-2
14. Modlin IM, Pavel M, Kidd M, Gustafsson BI: Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. Aliment Pharmacol Ther. 2010, 31:169-88. 10.1111/j.1365-2036.2009.04174.x
15. FDA approves lutetium Lu 177 dotatate for treatment of GEP-NETS . (2018). Accessed: January 14, 2019: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm594105.htm.
16. Capello A, Krenning EP, Breeman WA, Bernard BF, de Jong M: Peptide receptor radionuclide therapy in vitro using [111In-DTPA0] octreotide. J Nucl Med. 2003, 44:98-104.
17. Parkin DM, Bray F, Ferlay J, Pisani P: Global cancer statistics, 2002. CA Cancer J Clin. 2005, 55:74-108. 10.3322/canjclin.55.2.74
18. Miller WH, Hartmann-Siantar C, Fisher D, et al.: Evaluation of beta-absorbed fractions in a

mouse model for 90Y, 188Re, 166Ho, 149Pm, 64Cu, and 177Lu radionuclides. Cancer Biother Radiopharm. 2005, 20:436-49. 10.1089/cbr.2005.20.436

19. Pool SE, Krenning EP, Koning GA, et al.: Preclinical and clinical studies of peptide receptor radionuclide therapy. Semin Nucl Med. 2010, 40:209-18. 10.1053/j.semnuclmed.2009.12.001
20. Valkema R, Pauwels S, Kvols LK, et al.: Survival and response after peptide receptor radionuclide therapy with [90Y-DOTA0, Tyr3] octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumors. Semin Nucl Med. 2006, 36:147-56. 10.1053/j.semnuclmed.2006.01.001
21. Kwekkeboom DJ, Bakker WH, Kam BL, et al.: Treatment of patients with gastro-enteropancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [177Lu-DOTA(0),Tyr3]octreotate. Eur J Nucl Med Mol Imaging. 2003, 30:417-22. 10.1007/s00259-002-1050-8
22. Khan S, Krenning EP, van Essen M, Kam BL, Teunissen JJ, Kwekkeboom DJ: Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0,Tyr3]octreotate. J Nucl Med. 2011, 52:1361-68. 10.2967/jnumed.111.087932
23. Strosberg J, El-Haddad G, Wolin E, et al.: Phase 3 Trial of 177Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017, 376:125-35. 10.1056/NEJMoa1607427
24. da Silva TN, van Velthuysen MLF, van Eijck CHJ, Teunissen JJ, Hofland J, de Herder WW: Successful neoadjuvant peptide receptor radionuclide therapy for an inoperable pancreatic neuroendocrine tumour. Endocrinol Diabetes Metab Case Rep. 2018, 2018:pii: 18-0015. 10.1530/EDM-18-0015
25. Becker KF, Kremmer E, Eulitz M, et al.: Analysis of E-cadherin in diffuse-type gastric cancer using a mutation-specific monoclonal antibody. Am J Pathol. 1999, 155:1803-809. 10.1016/S0002-9440(10)65497-1
26. Senekowitsch-Schmidtke R, Schuhmacher C, Becker KF, et al.: Highly specific tumor binding of a 213Bi-labeled monoclonal antibody against mutant E-cadherin suggests its usefulness for locoregional alpha-radioimmunotherapy of diffuse-type gastric cancer. Cancer Res. 2001, 67:2804-808.
27. Seidl C, Port M, Gilbertz KP, et al.: 213Bi-induced death of HSC45-M2 gastric cancer cells is characterized by G2 arrest and up-regulation of genes known to prevent apoptosis but induce necrosis and mitotic catastrophe. Mol Cancer Ther. 2007, 6:2346-59. 10.1158/1535-7163.MCT-07-0132
28. Bodei L, Kwekkeboom DJ, Kidd M, Modlin IM, Krenning EP: Radiolabeled somatostatin analogue therapy of gastroenteropancreatic cancer. Semin Nucl Med. 2016, 46:225-38. 10.1053/j.semnuclmed.2015.12.003
29. Rolleman EJ, Valkema R, de Jong M, Kooij PP, Krenning EP: Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine. Eur J Nucl Med Mol Imaging. 2003, 30:9-15. 10.1007/s00259-002-0982-3
30. Teunissen JJ, Kwekkeboom DJ, Krenning EP: Quality of life in patients with gastroenteropancreatic tumors treated with [177Lu-DOTA0,Tyr3]octreotate. J Clin Oncol. 2004, 22:2724-29. 10.1200/JCO.2004.10.016
31. Mårtensson L, Nilsson R, Ohlsson T, Sjögren HO, Strand SE, Tennvall J: Reduced myelotoxicity with sustained tumor concentration of radioimmunoconjugates in rats after extracorporeal depletion. J Nucl Med. 2007, 48:269-76.
32. Aarts F, Hendriks T, Eek A, Oyen WJ, Bleichrodt RP, Boerman OC: Can antibody galactosylation be used to improve radioimmunotherapy of induced peritoneal carcinomatosis of colonic origin in the rat?. Cancer Biother Radiopharm. 2009, 24:29-34. 10.1089/cbr.2008.0521
33. Brabander T, van der Zwan WA, Teunissen JJ, et al.: Long-term efficacy survival and safety of [177Lu-DOTA0, Tyr3]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. Clin Cancer Res. 2017, 23:4617-24. 10.1158/1078-0432.CCR-16-2743
34. Behr TM, Béhé M, Becker W: Diagnostic applications of radiolabeled peptides in nuclear endocrinology. Q J Nucl Med. 1999, 43:268-80.
35. Wild D, Schmitt JS, Ginj M, et al.: DOTA-NOC, a high-affinity ligand of somatostatin receptor subtypes 2, 3 and 5 for labelling with various radiometals. Eur J Nucl Med Mol Imaging. 2003, 30:1338-47. 10.1007/s00259-003-1255-5
36. Seidl C, Zöckler C, Beck R, Quintanilla-Martinez L, Bruchertseifer F, Senekowitsch-Schmidtke R: 177Lu-immunotherapy of experimental peritoneal carcinomatosis shows comparable

effectiveness to 213 Bi-immunotherapy, but causes toxicity not observed with 213 Bi. Eur J Nucl Med Mol Imaging. 2011, 38:312-22. 10.1007/s00259-010-1639-2

37. Kwekkeboom DJ, de Herder WW, Kam BL, et al.: Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol. 2008, 26:2124-30. 10.1200/JCO.2007.15.2553
38. Rinke A, Müller HH, Schade-Brittinger C, et al.: Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009, 27:4656-63. 10.1200/JCO.2009.22.8510
39. Bergsma H, van Vliet EI, Teunissen JJ, et al.: Peptide receptor radionuclide therapy (PRRT) for GEP-NETs. Best Pract Res Clin Gastroenterol. 2012, 26:867-81. 10.1016/j.bpg.2013.01.004
40. Yao JC, Phan AT, Chang DZ, et al.: Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. J Clin Oncol. 2008, 26:4311-18. 10.1200/JCO.2008.16.7858
41. Kamp K, Gumz B, Feelders RA, Kwekkeboom DJ, Kaltsas G, Costa FP, de Herder WW: Safety and efficacy of everolimus in gastrointestinal and pancreatic neuroendocrine tumors after 177Lu-octreotate. Endocr Relat Cancer. 2013, 20:825-31. 10.1530/ERC-13-0254
42. Brix G, Bellemann ME, Haberkorn U, Gerlach L, Lorenz WJ: Assessment of the biodistribution and metabolism of 5-fluorouracil as monitored by 18F PET and 19F MRI: a comparative animal study. Nucl Med Biol. 1996, 23:897-906. 10.1016/S0969-8051(96)00122-9
43. Rasheed R, Tariq S, Naqvi SA, Gillani SJ, Rizvi FA, Sajid M, Rasheed S: 177Lu-5-Fluorouracil a potential theranostic radiopharmaceutical: radiosynthesis, quality control, biodistribution, and scintigraphy. J Labelled Comp Radiopharm. 2016, 59:398-403. 10.1002/jlcr.3423
44. Strosberg JR, Wolin EM, Chasen B, et al.: NETTER-1 phase III: progression-free survival, radiographic response, and preliminary overall survival results in patients with midgut neuroendocrine tumors treated with 177-Lu-Dotatate. J Clin Oncol. 2016, 34:194. 10.1200/jco.2016.34.4_suppl.194
45. van Essen M, Krenning EP, Kam BL, de Herder WW, Feelders RA, Kwekkeboom DJ: Salvage therapy with Lu-octreotatein patients with bronchial and gastroenteropancreatic neuroendocrine tumors. J Nucl Med. 2010, 51:383-90. 10.2967/jnumed.109.068957
46. van Essen M, Krenning EP, Kam BL, de Herder WW, van Aken MO, Kwekkeboom DJ: Report on short-term side effects of treatments with 177Lu-octreotate in combination with capecitabine in seven patients with gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2008, 35:743-48. 10.1007/s00259-007-0688-7
47. Villard L, Romer A, Marincek N, et al.: Cohort study of somatostatin-based radiopeptide therapy with [90Y-DOTA]-TOC versus [90Y-DOTA]-TOC plus [177Lu-DOTA]-TOC in neuroendocrine cancers.. J Clin Oncol. 2012, 30:1100-106. 10.1200/JCO.2011.37.2151
48. Arora G, Shukla J, Ghosh S, Maulik SK, Malhotra A, Bandopadhyaya G: PLGA nanoparticles for peptide receptor radionuclide therapy of neuroendocrine tumors: a novel approach towards reduction of renal radiation dose. PLoS One. 2012, 7:e34019. 10.1371/journal.pone.0034019
49. Claringbold PG, Turner JH: NeuroEndocrine tumor therapy with lutetium-177-octreotate and everolimus (NETTLE): a phase I study. Cancer Biother Radiopharm. 2015, 30:261-69. 10.1089/cbr.2015.1876