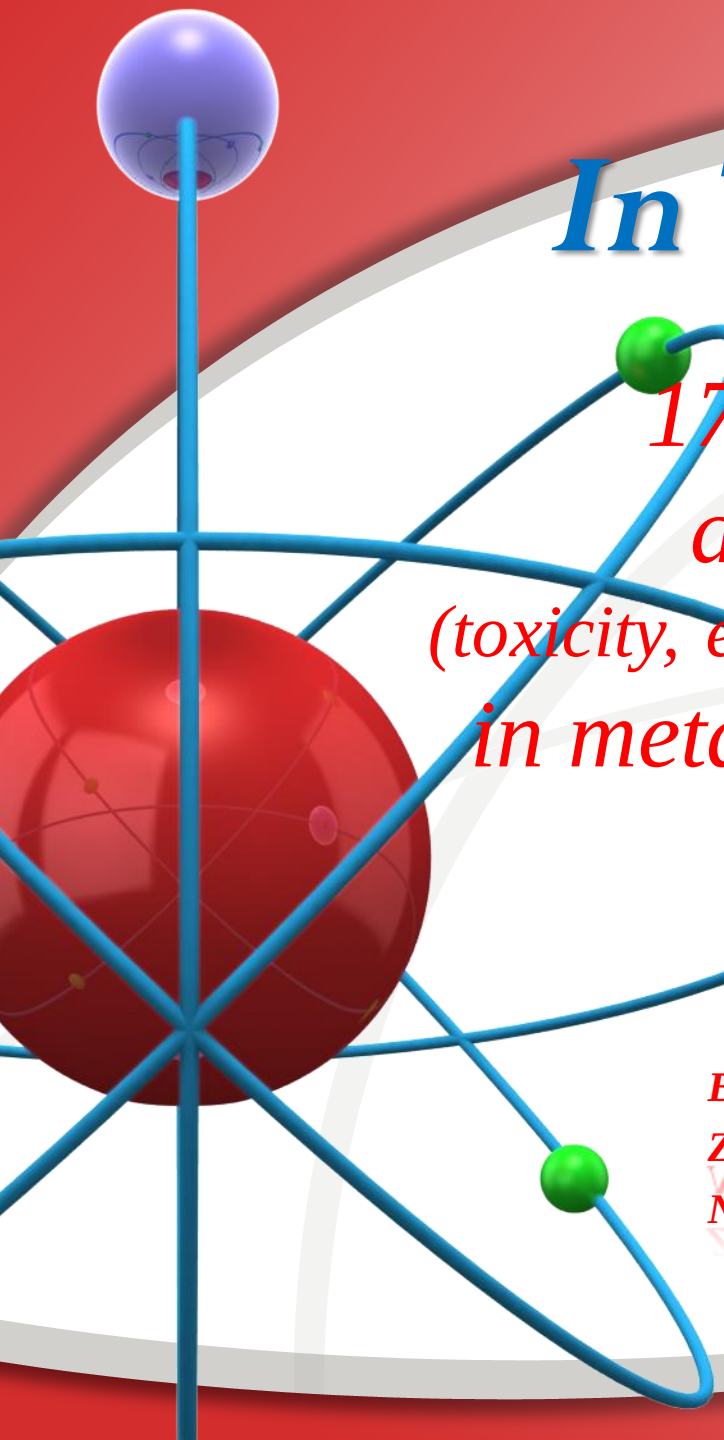

In The Name of God

177Lu-DOTATATE therapy and response assessment (toxicity, efficacy and prognostic biomarker data) in metastatic/progressive/inoperable pheochromocytoma/ paraganglioma

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ORIGINAL RESEARCH | VOLUME 6, ISSUE 4, 100171, AUGUST 01, 2021

Peptide receptor radionuclide therapy in patients with metastatic progressive pheochromocytoma and paraganglioma: long-term toxicity, efficacy and prognostic biomarker data of phase II clinical trials

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SPECIAL CONTRIBUTION

NANETS/SNMMI Consensus Statement on Patient Selection and Appropriate Use of ^{177}Lu-DOTATATE Peptide Receptor Radionuclide Therapy

Thomas A. Hope[1,2], Lisa Bodei[3], Jennifer A. Chan[4], Ghassan El-Haddad[5], Nicholas Fidelman[1], Pamela L. Kunz[6], Josh Mailman[7], Yusuf Menda[8], David C. Metz[9], Erik S. Mittra[10], Daniel A. Pryma[11], Diane L. Reidy-Lagunes[12], Simron Singh[13], and Jonathan R. Strosberg[14]

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ORIGINAL ARTICLE

Safety and efficacy of peptide receptor radionuclide therapy with ^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate in combination with amino acid solution infusion in Japanese patients with somatostatin receptor-positive, progressive neuroendocrine tumors

Noritoshi Kobayashi[1] · Shoko Takano[2] · Kenichi Ito[3] · Madoka Sugiura[2] · Matsuyoshi Ogawa[4] · Yuma Takeda[1] · Naoki Okubo[1] · Akihiro Suzuki[1] · Motohiko Tokuhisa[1] · Tomohiro Kaneta[5] · Daisuke Utsunomiya[3] · Masaharu Hata[2] · Tomio Inoue[6] · Makoto Hosono[7] · Seigo Kinuya[8] · Yasushi Ichikawa[1]

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^{177}Lu-DOTATATE therapy in metastatic/inoperable pheochromocytoma-paraganglioma

Sanjeet Kumar Jaiswal, Vijaya Sarathi, [...], and Tushar R Bandgar

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7487189/

Huizing *et al. Cancer Imaging* (2020) 20:57
https://doi.org/10.1186/s40644-020-00335-w

Cancer Imaging

RESEARCH ARTICLE Open Access

Early response assessment and prediction of overall survival after peptide receptor radionuclide therapy

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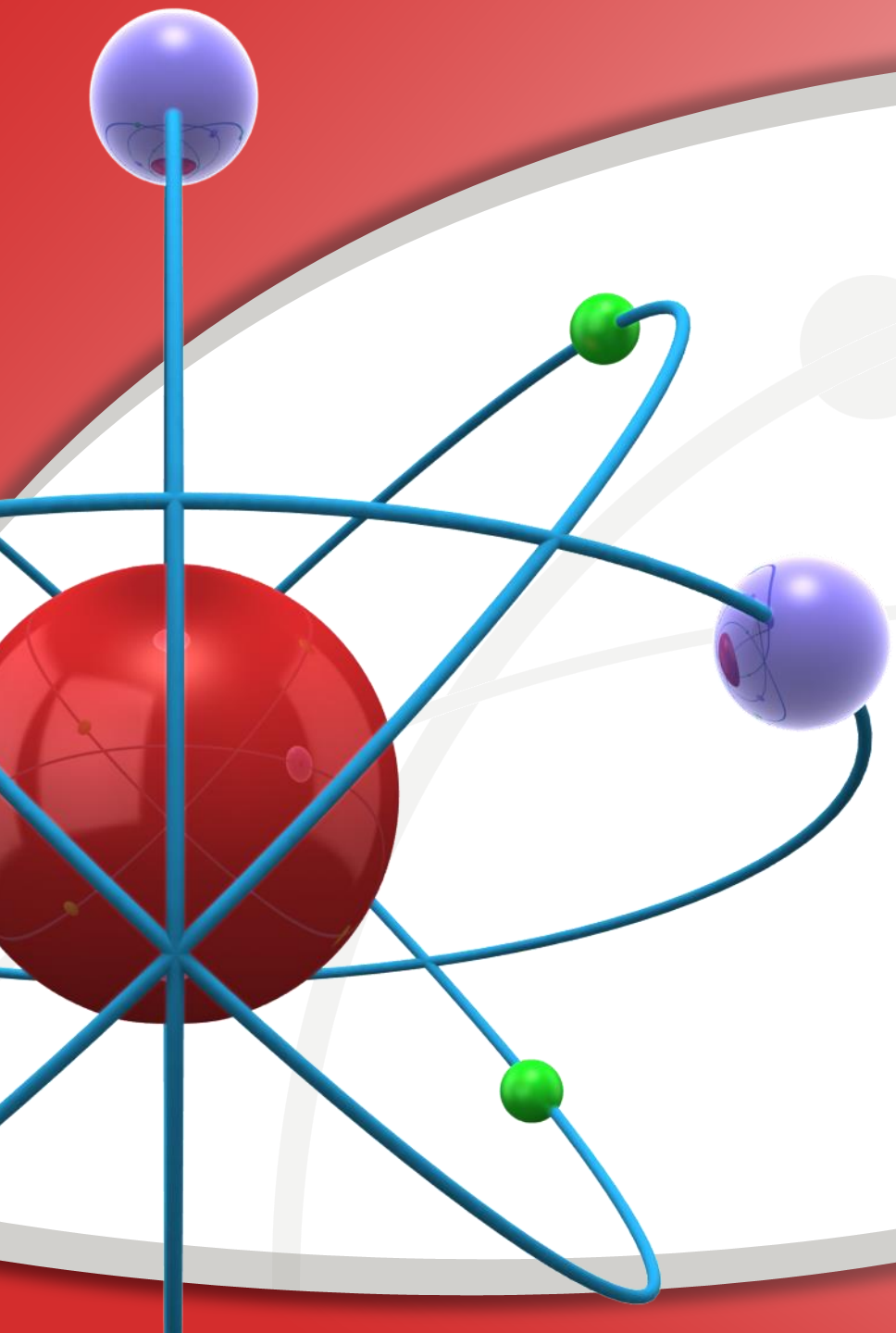


GENERAL VIEW

- Pheochromocytomas (PCC)–paragangliomas (PGL) (PPGL) are rare tumors of neural crest origin with malignant potential.
- The prevalence of metastasis ranges from 2–13% in PCC to 2.4–50% in PGL.
- These tumors can occur anywhere in the parasympathetic and sympathetic autonomic nervous system from the base of the skull to the pelvis. In particular, sympathetic PPGL cells produce and release catecholamine that may cause cardiovascular and gastrointestinal problems.

- Surgery is the curative approach for local disease.
- However, 15%-20% of patients with PPGL have metastases, a rare condition with only 100-200 new cases diagnosed annually in the USA.
- Patient prognosis is fairly heterogeneous and it is difficult to predict the clinical behavior of each case given that only 50%-60% of patients with metastatic PPGLs (mPPGLs) are still alive 5 years after their initial diagnosis.

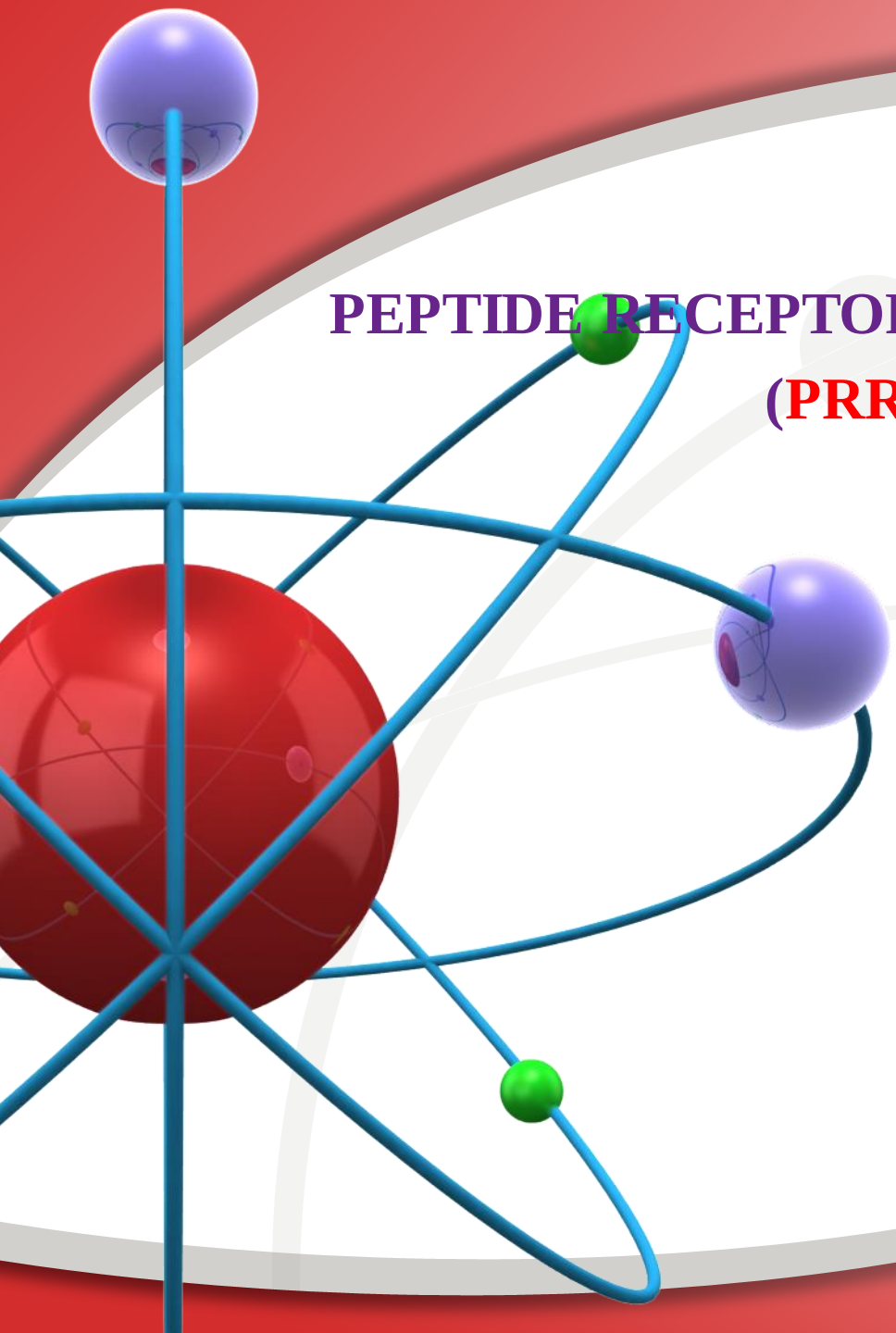
- In 30% of cases, PPGLs are associated with mutations of SDHB, SDHC, SDHD, SDHAF2, SDHA, TMEM, MAX, and VH genes.
- There are >20 different genes with both germ line or sporadic driver mutations and an increasing number of potential disease- modifying genes.
- Mutations in the succinate dehydrogenase (SDHx) gene predispose up to 70% of patients to aggressive phenotypes, resulting in distant metastasis, tumor multiplicity and disease recurrence, thus highlighting the need for effective therapies against SDHx-mutated PPGLs.
- Targeted therapy//////

- PPGL was diagnosed on basis of histopathology; and in unresectable or metastatic disease, on biochemistry and imaging.

- All of theses evaluations including symptomatology, biochemistry (plasma-free metanephrines (metanephrine (PFMN); normetanephrine (PFNMN)), imaging (contrast-enhanced CT (CECT), 68Ga-DOTATATE PET/CT, and I-MIBG scintigraphy) are important.

- In patients with unresectable, locally advanced or metastatic PPGL, symptomatic or progressive disease is usually treated with chemotherapy, radionuclide therapy (I-metaiodobenzylguanidine (I-MIBG) and peptide receptor radionuclide therapy (PRRT)), external radiotherapy, radiofrequency ablation therapy or tyrosine kinase inhibitors .

- There is no head to head trials that compare the superiority of one modality of therapy over the other.



PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

(PRRNT OR PRRT)

- The overexpression of somatostatin receptor in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) forms the rationale for the theranostic application of radiolabeled somatostatin analogs in these tumors.
- FDA approval///

- A diagnostic approach with 68Ga Dota-peptide PET/CT and the therapeutic use of 90Y-DOTATOC and 177Lu-DOTATATE in GEP-NETs has paved the way for their use in other NET histologies, including paragangliomas.
- PHEO/PARA///

- The two most frequently used radiopharmaceuticals differ in terms of the physical characteristics of the radionuclides and the sensitivity for somatostatin receptor 2 (SSTr2) (widely expressed in NETs), which is nine-fold higher for octreotate than for octreotide.

- In particular,

✓90Y (T/2 2.67 days and energy 2.3 MeV) has a tissue penetration of 5-7 mm, which makes it more suitable for larger lesions.

- Conversely,

✓177Lu (T/2 6.7 days and energy 0.5 MeV) is generally preferred in small lesions and in the presence of risk factors for renal toxicity.

- In this scenario, peptide receptor radionuclide therapy (PRRT) experiences in PPGLs are prevalently retrospective, performed in small cohorts of patients and administered with highly variable activities and low numbers of cycles.

- Recently, however, several prospective studies have used more homogeneous dosages and numbers of cycles, obtaining encouraging results and good disease control (85%).

- Lu-tetra-aza-cyclo-dodecanetetraacetic acid–DPhe1-Tyr3-octreotate (DOTATATE) has shown favorable efficacy in controlling symptoms and tumor progression in most of the previous studies.

- A recently published meta-analysis has reported good efficacy (disease control rate: 80% (95% CI: 77–89%)) with an encouraging safety profile .

- But availability, cost, and potential adverse effects limit the use of PRRT.

PRRT:
administration protocol

Eligibility for 177Lu-DOTATATE therapy was a high level (Krenning score more than II) and low I-MIBG uptake.

PRRNT is indicated for the treatment of patients with positive expression of sstr2, or metastatic or inoperable PPGL.

CONTRAINDICATIONS

- **Absolute**

1. Pregnancy
2. Severe acute concomitant illnesses.
3. Severe unmanageable psychiatric disorder.

RELATIVE

- Patients with compromised renal function may still be considered for 177Lu-labelled peptide treatment.
- Severely compromised bone marrow: noncom promised hematological reserve should be present before PRRNT.

- Baseline parameters (clinical, biochemical, hematological, functional renal scintigraphy) were noted.

- PRRT was deferred for patients with one or more cytopenias (hemoglobin <9 g/dL, total leukocyte count <4000/ µL or platelet count <100,000/µL), Karnofsky performance status (KFS) less than 60% or the Eastern Cooperative Oncology Group (ECOG) performance status score more than two .

- ✓Baseline imaging included
- Functional imaging: [68Ga]Ga-DOTA-TATE PET/ CT within 6 months and
- morphological imaging: (CT or MRI) within 2 months prior to start of PRRT according to clinical protocol.

- PET/CT imaging was performed 45 min after the intravenous administration of 100 MBq of [68Ga]Ga-DOTA- TATE. Acquisition parameters included 3 min/bed from base of skull to mid-tights on Gemini TOF PET/CT systems (Philips, Best, The Netherlands) with 4x4x4mm voxel BLOB-OS-TF reconstruction.

- Low-dose CTs were additionally acquired for attenuation correction and anatomical correlation.

- Contrast-enhanced (CE) CT imaging of thorax and/or abdomen was performed.

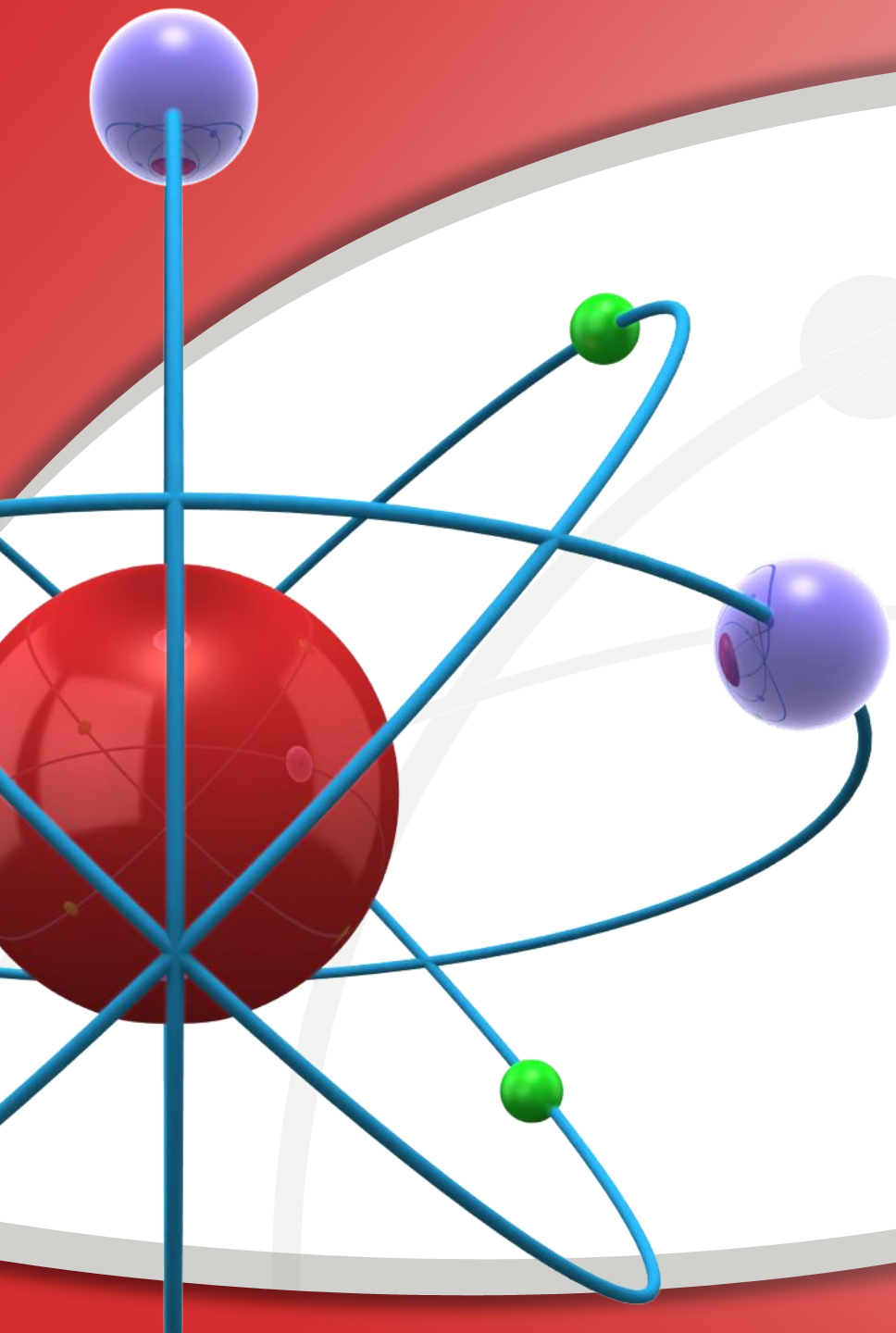
- If liver metastases were better visualized by MRI, contrast-enhanced MRI acquisitions of the liver only with mDixon, T2, and DWI sequences were performed.

- Patients were premedicated with antihistamines, ondansetron, and positively charged renoprotective amino acids (L-lysin, L-arginine, etc.) infusion.

- Preparation of 177Lu-DOTATATE (by in house generator) and labeling of octreotate with 177Lu was done at Radiation Medicine Centre (RMC).

- 177Lu-DOTATATE was administered as a slow I.V infusion over 30–45 min (150–200 mCi/cycle) and observed for a day.

- A maximum of six cycles was given with a minimum interval of three months was maintained between 2 consecutive cycles???.



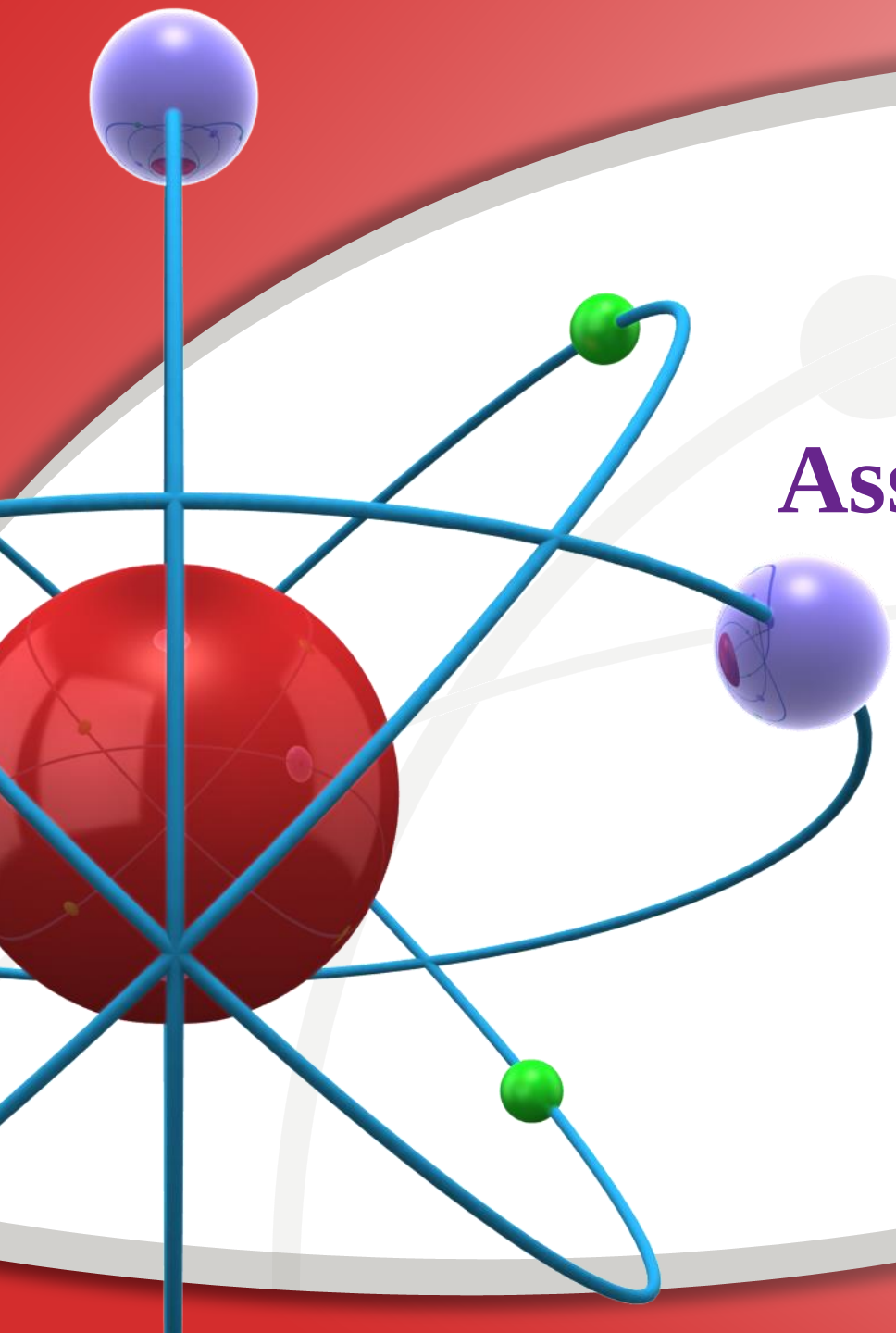
FOLLOW UP

- The follow-up should include the evaluation of serum creatinine levels and the determination of creatinine clearance.

- In patients with pre-existing risk factors for delayed renal toxicity (high-risk group), in particular long-standing and poorly controlled hypertension and diabetes mellitus, single kidney or previously documented renal insult, mainly nephrotoxic chemotherapy, more precise methods to assess renal function are recommended.
- These techniques may include GFR measurements by means of 99mTc-DTPA, 51Cr- EDTA or measurement of 99mTc-MAG3 clearance.

- **Between-cycle follow-up**
- A complete blood cell count should be performed every 2– 4 weeks.
- Renal and liver function tests should be available before confirming subsequent cycles.

- **Intermediate and long-term follow-up**
- A complete blood cell count (including mean corpuscular volume), and renal and liver function tests should be performed every 8–12 weeks for the first 12 months, and thereafter twice a year if clinically indicated.



Assessment of efficacy

- was assessed based on:

✓Clinical (compressive or catecholaminergic features, change in antihypertensive medications)

✓Biochemical (plasma-free metanephrines (PFMN and PFNMN))

- but have a moderate sensitivity and specificity in the follow-up setting for recurrence and/or progression . The relationship between CgA and tumor load, however, remains debatable.

✓morphological : CECT??

✓PET/SPECT functional status

111In-pentetreotide (OctreoScan) and, if available, PET/CT with 68Ga-DOTA peptides or metabolic monitoring with, for example, 18F-DOPA.

- Response monitoring using changes in [68Ga]Ga-DOTA- TATE uptake is also challenging since reduced tracer uptake could indicate a smaller number of somatostatin receptor (SSTRs) either due to disease progression (e.g., more SSTR-negative NET-cells or therapy response by decline in the number of cells), or other parameters such as changes in perfusion.)

✓and wellbeing of the patient.

- ✓ For anatomical imaging CECT was used and the CECT response (gold standard) was based on RECIST version 1.1 (target lesion).
- ❖ Complete response (CR) was defined as the disappearance of all target lesions plus reduction of the short axis of pathologic lymph nodes to <1 cm
- ❖ partial response (PR) as at least 30% decrease in the sum of the longest diameters of target lesions (relative to baseline sum)
- ❖ minor response (MR) as smaller decrements in size not meeting the criteria of PR (10–30% decrease in maximum diameters of target lesions)
- ❖ stable disease (SD) as neither MR nor progressive disease (PD)
- ❖ PD as at least 20% increase (≥5 mm absolute increase) in the sum of longest diameters of target lesions (relative to smallest sum) or appearance of new lesions.

Controlled disease (CD) was defined as a combination of all the responses except PD (SD + PR + MR).

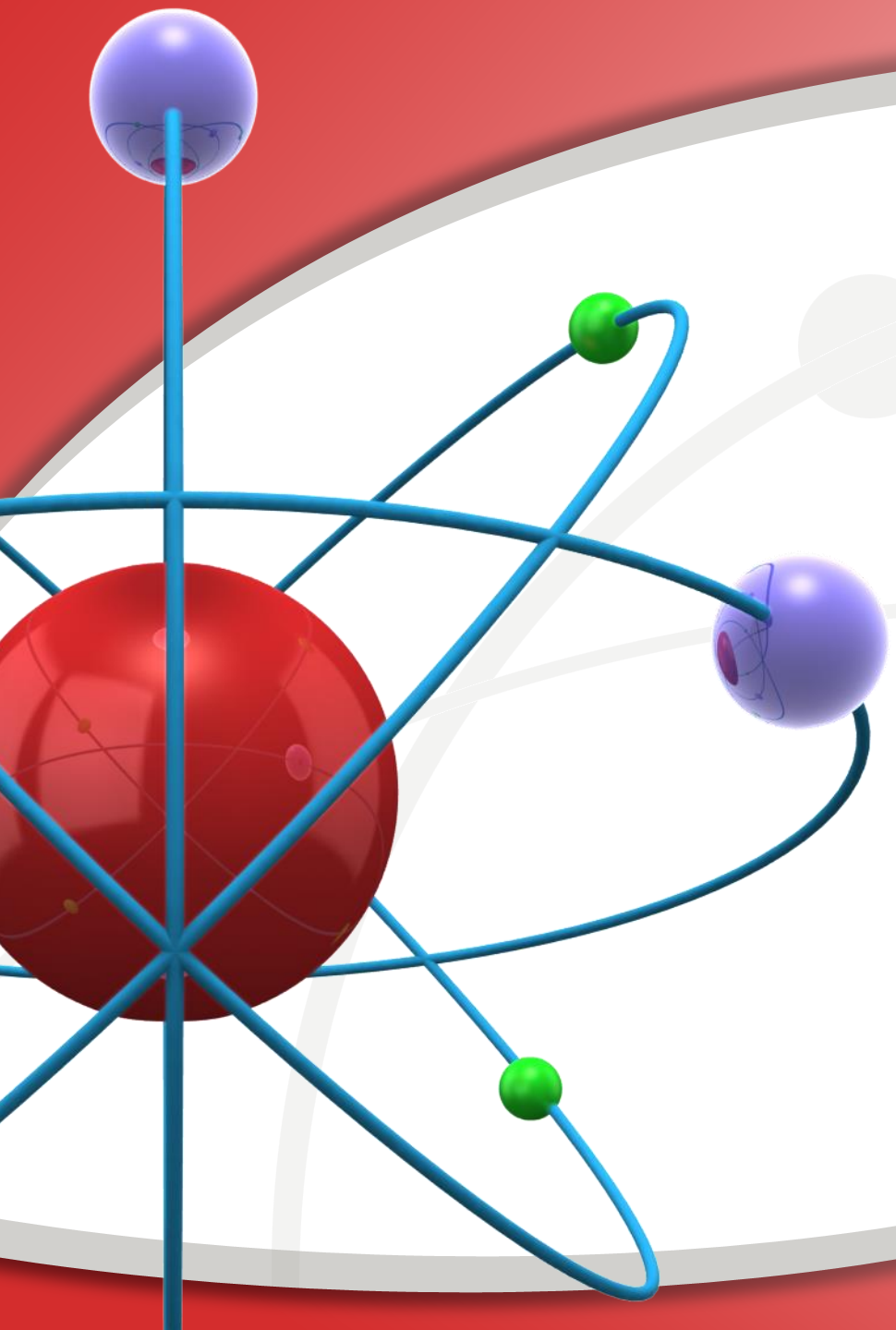
- In functional imaging:
  - traditionally [111In]Indium-octreotide scans were visually assessed using the Krenning score, which compared tumor uptake with uptake in the liver and spleen/kidney .

- However, with the introduction of SSA-labelled PET-tracers response evaluation of receptor imaging could be performed quantitatively. In current SSA-PET/CT research, tumor SUV max is often used as a reference, but also the tumor-to-spleen and tumor-to-liver ratios are described.

- The SUV peak, as recommended by PERCIST, is used rarely in current literature and was therefore taken into consideration here.

- SSTR response was based on Ga-DOTATATE PET/CT (defined as:

- partial response (PR): reduction in intensity by one Krenning score in at least one tumor site
- Complete response (CR): total disappearance of abnormal uptake of previous avid lesions) or
- Progressive disease (PD): increase in intensity or extent of previous abnormal uptake, or development of new avid lesions).



Conclusion

- LU177-DOTATATE therapy is an effective and safe modality of treatment for patients with metastatic/inoperable PPGL.

- In patients with PPGL, therapy should be limited primarily to patients with negative MIBG scan.

- The decision to initiate PRRNT should be made within the setting of multidisciplinary discussion.

- Baseline SUV more than 21 on 68Ga-DOTATATE positively predicts early response to Lu-DOTATATE therapy. Although it is not prudent to withhold Lu-DOTATATE therapy in metastatic PPGL with baseline SUV < 21, baseline SUV >21 can be used to predict early response to Lu-DOTATATE therapy.

- Changing in SUV on follow-up imaging may be a useful parameter, in addition to clinical, biochemical, and radiological parameters, to monitor the response to Lu-DOTATATE therapy. However, the study findings need confirmation in larger, prospective cohorts.

- In a long-term follow-up of patients with mPPGL, PRRT demonstrated a tolerability and efficacy comparable to those obtained in GEP-NETs.

- Our results highlight the need for an appropriate cumulative administered dosage to achieve a very prolonged result and

- Given the substantial number of patients evaluated over time, the superior mOS of 177Lu-DOTATATE with respect to 90Y-DOTATOC indicates the former radiopharmaceutical as the better candidate for new prospective studies of single or associated therapies.

FUTURE DIRECTIONS

With clinical approval of 177Lu-DOTATATE, there are many possibilities for future research and optimizing clinical care with:

- ✓ optimizing the number of therapy cycles and administered activity,
- ✓consideration of repeat therapy,
- ✓delivering the therapy intraarterially,
- ✓the use of different radionuclides,
- ✓and using novel peptides to bind SSTRs.

- Although the NETTER-1 trial used 4 treatments at a fixed activity,
- optimizing the number of treatments or the administered activity of each administration may allow for decreased toxicity and improved efficacy.
- By measuring treatment effect during therapy or measuring lesion/organ dose, it may be possible to adjust the treatment schedule to increase efficacy.
- Currently, it is unclear how and even whether one should use patient specific dosimetry to adjust the administered activity, and many feel that giving a fixed activity works well for the majority of patients.

- This idea of repeat PRRT has been evaluated in retrospective studies.
- If a patient responds well to one complete course of 177Lu-DOTATATE, then it is reasonable to conclude that they may respond well to another course of 177Lu-DOTATATE when they subsequently progress.
- These studies showed that repeat PRRT is safe and effective, although the PFS is not as long compared with the initial PRRT course.

- Many patients have liver-dominant disease, and in these patients intraarterial 177Lu-DOTATATE administered via the hepatic artery has been proposed . In theory, this provides higher delivery to the tumor, while reducing the systemic circulation and associated side effects.

- Both 90Y and 177Lu have been used for PRRT, and each may provide different benefits given their different physical properties . The electron emitted from 90Y has a higher energy and would be beneficial for bulkier tumors. Conversely, the longer pathlength of 90Y will also have a greater bystander effect on normal tissues such as the bone marrow and kidneys resulting in higher toxicity.

- DOTATATE is an SSTR analogue, which becomes internalized after activating the receptor.

- SSTR antagonists have been developed that have a higher binding specificity to the SSTR such that even though they do not activate the receptor nor get internalized into the cell, they potentially deliver a high dose of radiation.


غیرممکن است
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