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STUDY THE TREATMENT PROCEDURE PROSTATE CANCER AND NEUROENDOCRINE TUMOR (NET) USING RADIOACTIVE MATERIAL LU-177

Aqeel Mitham Sabr, Maryam fakhry saeed, Aliaa Jassim Mohammed, Tuqa Azhar Nabeel
Department of Medical Physics, College of Science University of Karkh

Abstract: Lu-177 prostate-specific membrane antigen (PSMA) radioligand ther-apy (RLT) using inhibitors of PSMA is a novel therapeutic option in patients with metastatic castration-resistant prostate cancer. The cur-rent literature suggests that this therapy is well tolerated and effective. On the basis of clinical need and current evidence, the therapy is being implemented in a growing number of centers worldwide. Here, we review important aspects of Lu-177 PSMA RLT, including patient stratification, the therapy protocol, concomitant medication, and follow- up, to inform medical staff involved in the RLT and care of patients with metastatic castration- resistant prostate cancer. Introduction: Lutetium-177 It is a radioactive substance characterized by the Release of beta (β) radiation, which has a very weak diffusion Diameter (less than 1.7 mm), and (half-life 6.7 days),which helps direct therapeutic rays Only to cells affected by cancer without greatly affecting Neighboring cells . Lutetium-177 PSMA (Prostate specific membrane antigen) Treatment is a form of radionuclide therapy that alms to destroy Prostate cancer cells that have spread into parts of the body, Including diagnosis and treat men with prostate cancer.

The destruction of the prostate cancer cells may prolong life Expectancy and also potentially alleviate any symptoms such as Bone pain frequently associated with deposits of cancer in the Skeleton. PSMA therapy has many advantages Healthy tissues are not exposed to radiation , The ability to destroy metastases in any part of the body, Including liver metastases and bone metastases that are Resistant to other treatments ‹Good tolerance of treatment and No side effects‹Suitable for frail men with advanced cancer ‹High effectiveness. More than 95% of men respond well to Radionuclide therapy. This technology, called PSMA, is used to diagnose and treat Prostate cancer in men. Diagnosis involves the use of PET/SCAN Which involves imaging the body and recording beta radiation to The area of tumor formation. Also, this technique is used for a Therapeutic purpose, when cancer cell death occurs after a Course of treatment with radiopharmaceuticals[1]. The benefit of this treatment: PSMA treatment with lutetium is a very effective form of treating advanced stage prostate cancer. It has been shown to slow disease progression and improve patient outcomes . Improved quality of life: Patients who undergo Lutetium-177 PSMA therapy may experience improved quality of life compared to patients who receive traditional forms of treatment, due to the reduced side effects and the ability to continue normal activities during and after treatment. It is important to note that individual results may vary, and the benefits of Lutetium-177 PSMA therapy will depend on a number of factors, including the stage and aggressiveness of the cancer, the patient's overall health, and the presence of any underlying medical conditions.

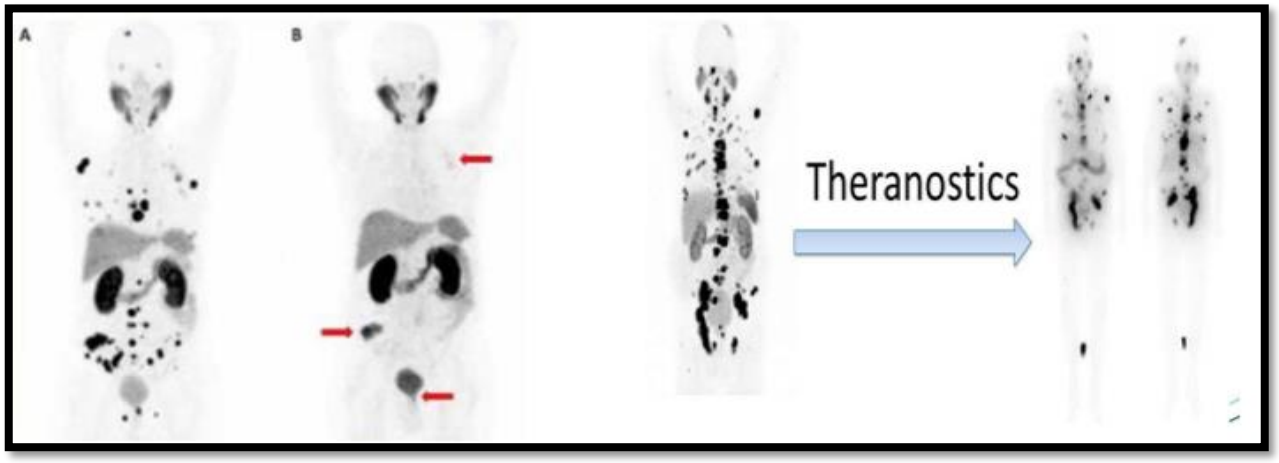


Figure (1) Lu-177 PSMA

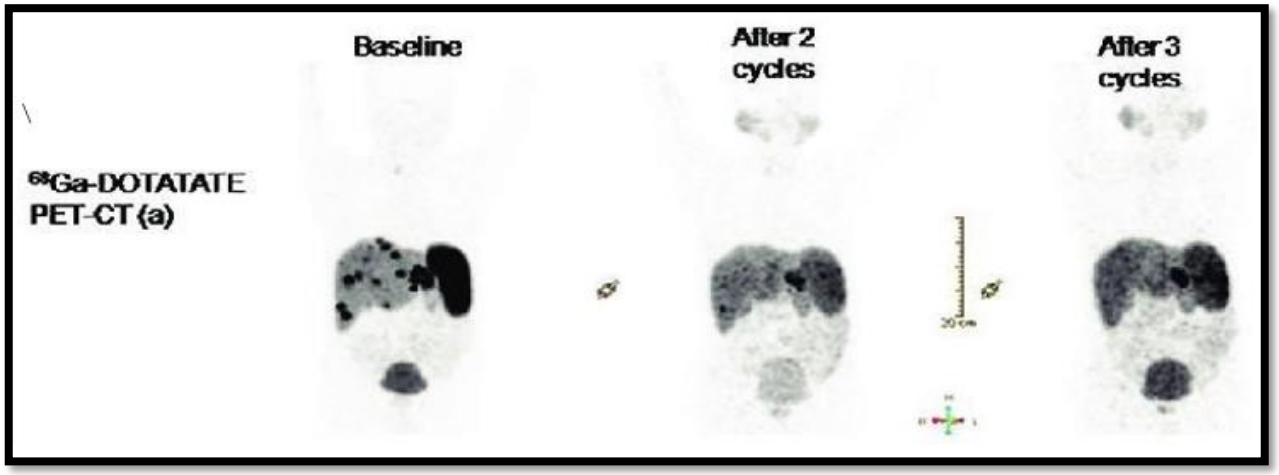


Figure (2) Lu -177 DOTATE

Oncology is a sub-specialty of medicine dedicated to the investigation, diagnosis and treatment of people with cancer or suspected cancer. It includes: Preventative medicine: Medical oncology (chemotherapy, immunotherapy, hormone therapy and other drugs to treat cancer) Radiation oncology (radiation therapy to treat cancer) Surgical oncology (surgery to treat cancer), Palliative medicine [2] .

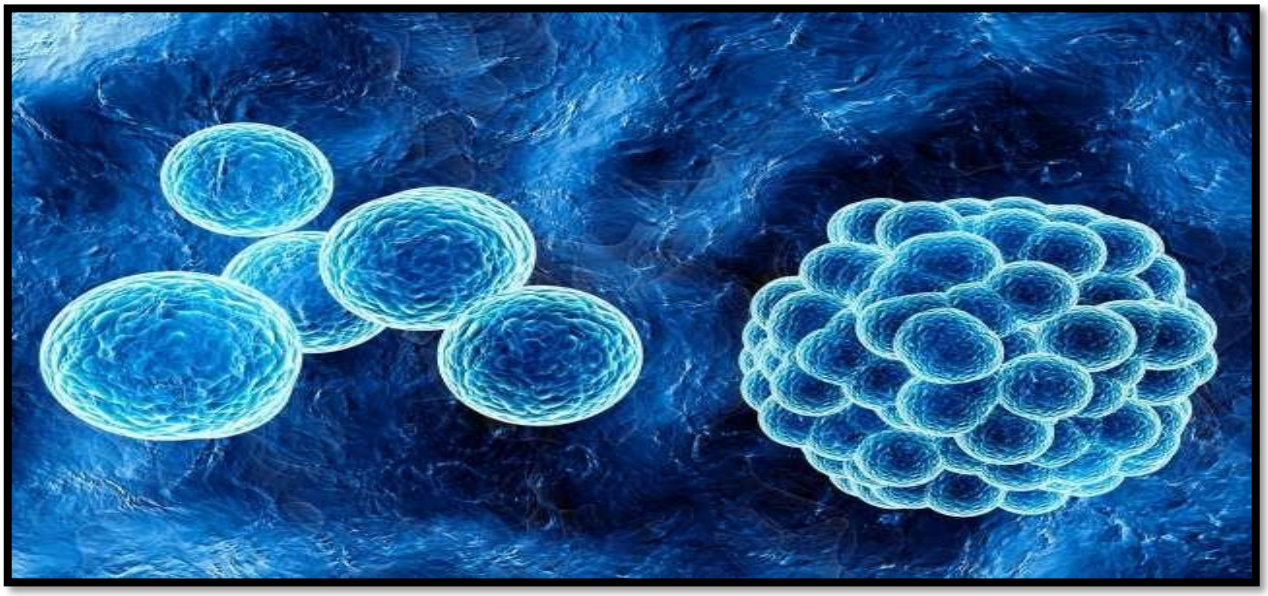


FIGURE (1.1) ONCOLOGY

Prostate: The prostate is a gland below the bladder and in front of the rectum in men and people assigned male at birth (AMAB). It consists of connective tissues and glandular tissues. It adds fluid to semen, and its muscles help push semen through your urethra. Conditions that affect your prostate include cancer, prostatitis and benign prostatic Hyperplasia. Depending on the cause and type of your prostatitis, your healthcare provider may recommend: Medications. Some medications help relax the muscles around your prostate and bladder to help improve urine Flow. Antibiotics help kill infection-causing bacteria. Stress management. Counseling for anxiety and depression Can help relieve symptoms. Exercises. Pelvic floor exercises can help reduce or Eliminate muscle spasms

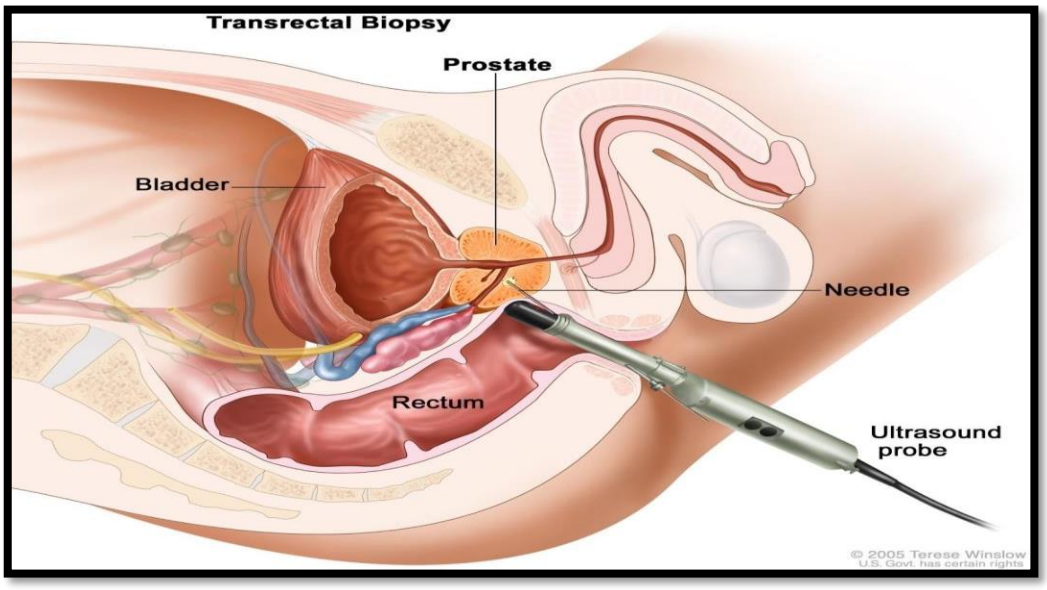


Figure (1.2) prostate Anatomy

The main prostate problems are divided into three categories

Prostate congestion

It begins to occur with puberty or shortly after it as a result of increased secretions and blood flow in the genital area with every sexual arousal and the absence of continuous discharge.

Prostate enlargement: Prostatic hyperplasia, or benign prostatic swelling, often affects men after the age of fifty and leads to urination problems such as intermittent urination, frequent urination, pain when urinating, in addition to urinary retention in some cases.

Prostate tumors:They are usually malignant tumors and are common in men after the age of sixty, and their percentage increases significantly after the age of eighty[3]. Neuroendocrine tumors (NET): Neuroendocrine tumors are tumors that arise from cells of the endocrine (hormonal) and nervous systems. The most common ones occur in the intestine, where they are often called cancerous tumors, but they are also found in the pancreas, lungs, and the rest of the body. Neuroendocrine tumors are well differentiated and are further divided into benign tumors and those with uncertain behavior. Well-differentiated (low-grade) neuroendocrine carcinomas with lowgrade malignant behavior Carcinoid neuroendocrine tumors (high grade) are undifferentiated, small cell neuroendocrine carcinomas[10].

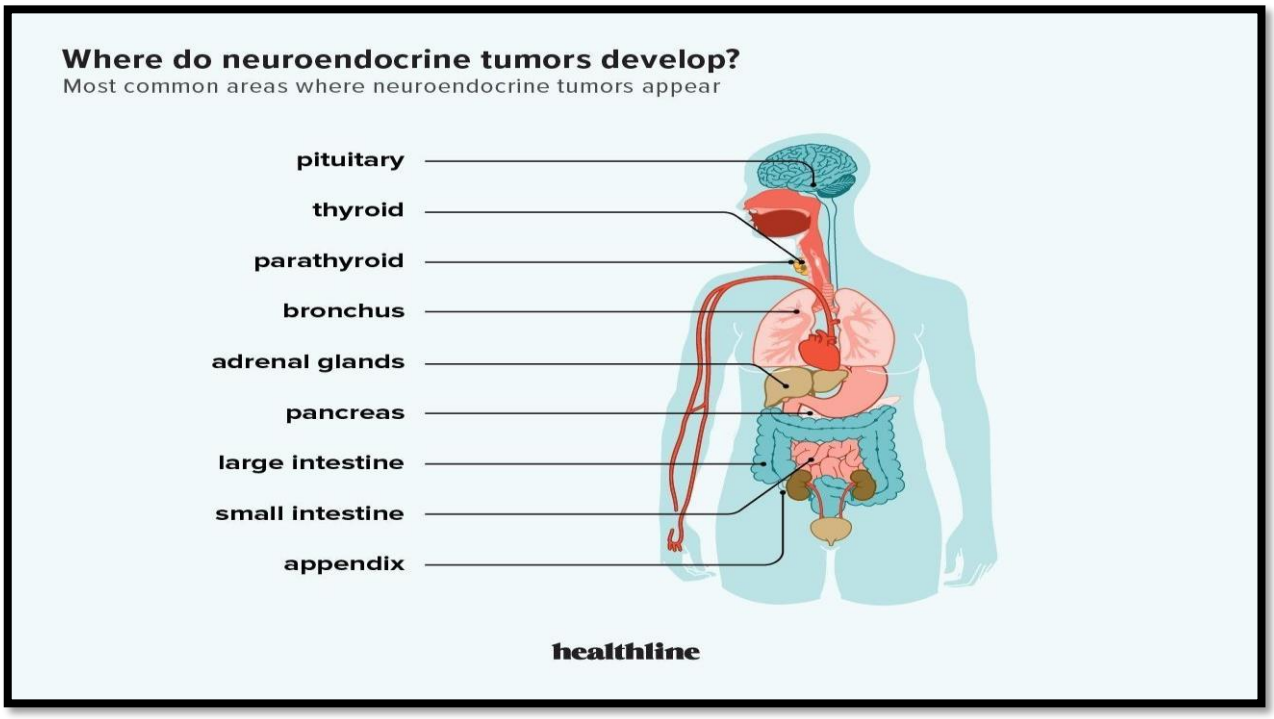


FIGURE (1.3) common areas (NET)

Patient selection: PSMA-targeted therapy will only be effective against tumor lesions with sufficient expression of the target-receptor. The pattern of tumor PSMA expression should be evaluated per molecular imaging (preferred: 68 Ga/18F-PSMA PET; alternatively: 99mTc-PSMA SPECT/scintigraphy) together with a conventional comparator (e.g., CT, MRI, or bone scan) to rule out a relevant fraction of PSMA negative lymph-node or visceral metastases or active/lytic bone lesions (strong recommendation) . Suitable for Lutetium PSMA therapy : Currently, Lutetium-177 PSMA Is used inpatients with metastatic prostate cancer who have failed other forms of treatment such as hormone therapy or Chemotherapy. Before

commencing treatment, patients will need to undergo a PSMA PET-CT Scan to confirm PSMA receptors on the cancer cells, which will be targeted byLutetium177 PSMA [14]. The stringent exclusion of all FDG/PSMA mismatch patients on the Thera P trial reduced patient eligibility, but provided higher PSA-response rates compared to VISION that omitted [18F]FDG-PET/CT evaluation [1, 14]. Radioactiv material LU- 177: Lutetium-177 It is a radioactive substance characterized by the Release of beta (β) radiation, which has a very weak diffusion Diameter (less than 1.7 mm), and (half life 6.7 days),which helps direct therapeutic rays Only to cells affected by cancer without greatly affecting Neighboring cells[7].



Figure (1.4) vial containing Lu-177

Radiopharmaceuticals: Both [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T belong to the group of PSMA inhibitors that are based on the glutamate-urea-lysine targeting moiety. The precursor PSMA-617 is tagged with a DOTA chelator and has a molar mass of 1042 g/mol (lutetium-labeled: 1216 g/mol). PSMA-I&T is tagged with the DOTAGA chelator, and the precursor molar mass is 1498 g/mol. The sterile therapy solution is typically diluted to ≤ 1000 MBq/ml to reduce the activity concentration in case of extravasation. It is a clear, colorless to slightly yellow solution, free from visible particulates with a radiochemical purity of ≥ 97%. Currently, only [^{177}Lu]Lu-PSMA-617 is available as an approved drug in the USA, Canada, UK, and EU (^{177}Lu vipivotide tetraxetan, Pluvicto™). The product liability and compliance to Good Manufacturing Practice, according to USP (US Pharmacopeia) or EP (European Pharmacopoeia) standards, is the responsibility of its commercial provider. This formulation should be used for all approved in label applications of [^{177}Lu]Lu-PSMA-617. Whenever ^{177}Lu-PSMA-RLT is considered outside the already-approved indications, the aim should be to recruit patients into a formal clinical trial. In this setting, the compliance of the respective radiopharmaceutical to the Investigational Medicinal Product Dossier or the Investigational New Drug application is ensured by the respective sponsor of the trial. According to article 7 2001/83/EG, in particular situations, drugs can be used without formal approval. National regulations must be considered. Retrospective analyses of “unproven interventions in clinical practice” and some prospectively performed single-arm studies (Annex, Table 1, 2 and 3) reported safety and efficacy for various formulations of [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA-I&T following site-specific, in-house labeling conditions. Advice for production and QC of such formulations is not in the scope of this guideline and should only be done in centers with an adequately qualified radio pharmacy. Otherwise, we recommend off label use of the approved formulation whenever patients cannot be recruited to clinical trials when it is possible to obtain the drug and full reimbursement.

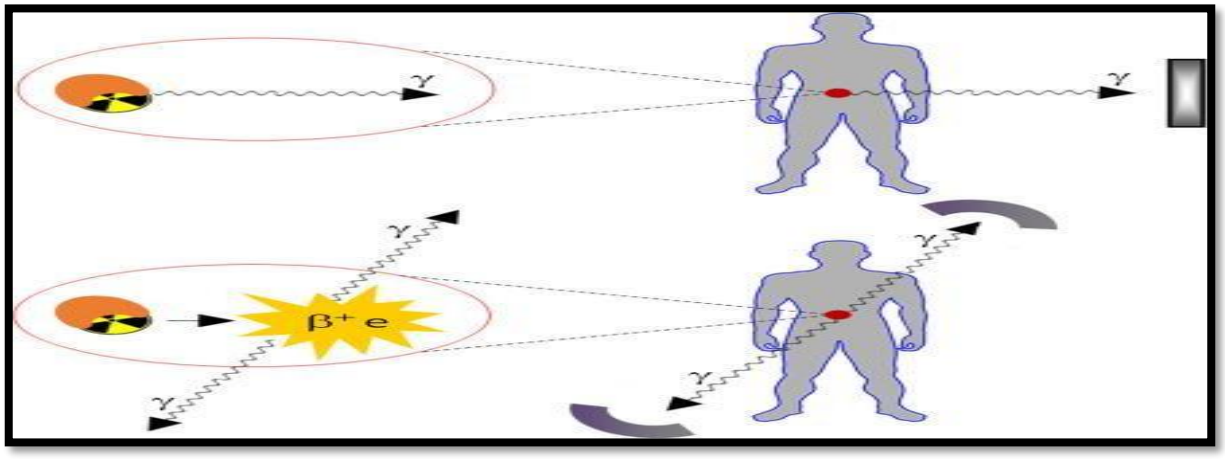


FIGURE (1.5) Radiopharmaceuticals

Lu-177 PASMA: It is a type of radiation that specifically targets a molecule found on the surface of prostate cancer cells called PSMA. This treatment is used with the companion diagnostic drug gallium 68 gosetotide (Leukamitz), which is more commonly known as the latter. The latter uses imaging to identify cancer [8].

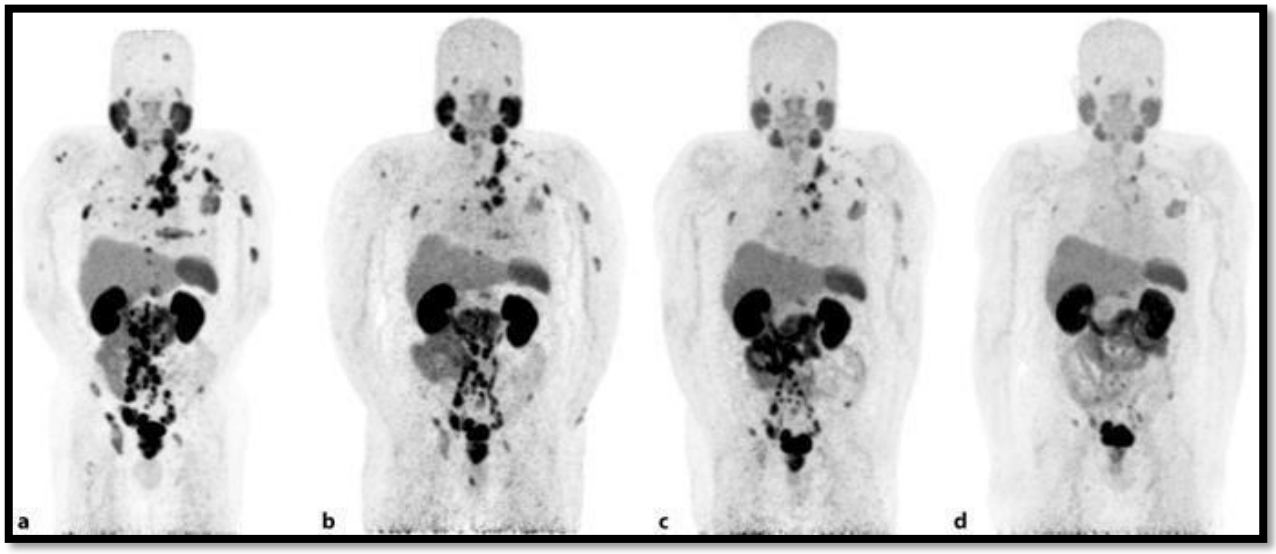


FIGURE (1.6) Lu-177 PSMA treatment cycles

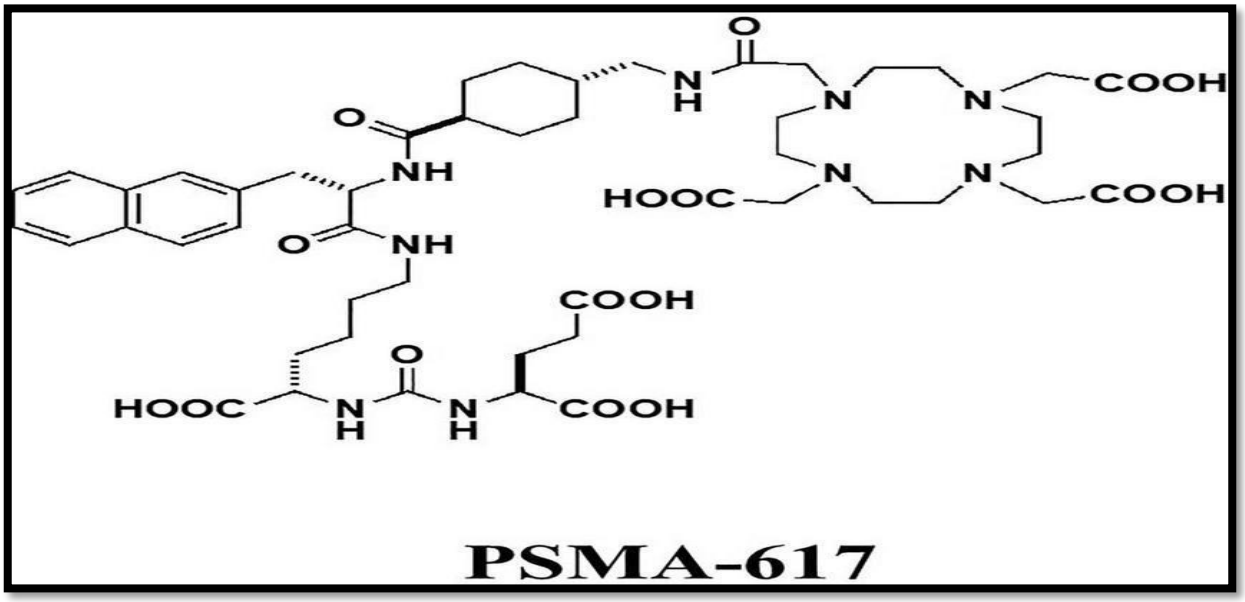


FIGURE (1.7) Lu_177 PSMA structure

Lu-177 DOTATE: Lutetium DOTATE Lu 177 is a radiopharmaceutical that attaches itself to a specific part of cancer cells, allowing radiation to enter those cells and destroy them. It is used to treat endocrine tumors [9].

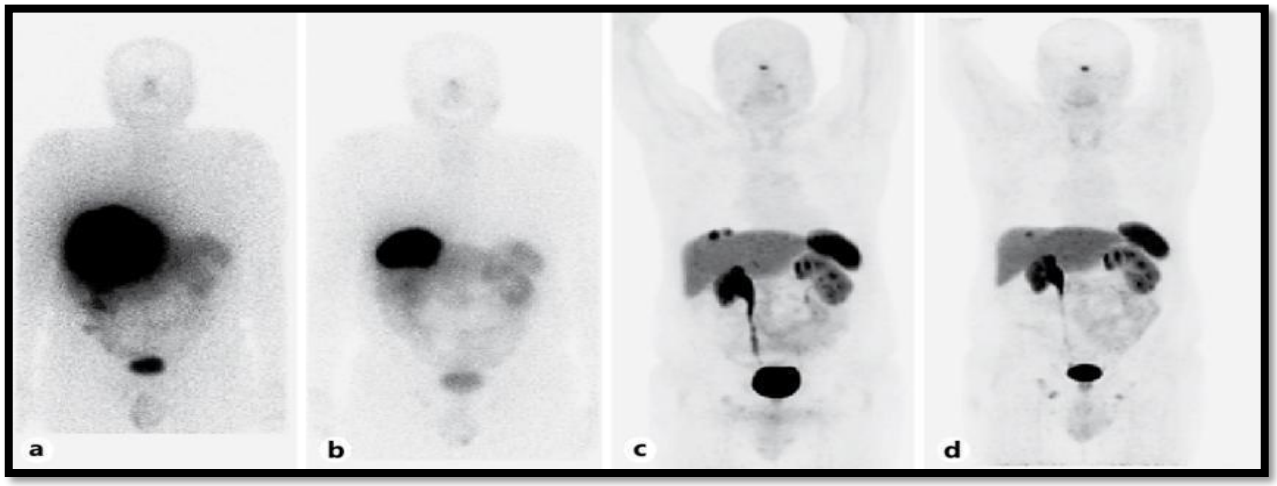


FIGURE (1.8) Lu-177 DOTATE treatment cycles

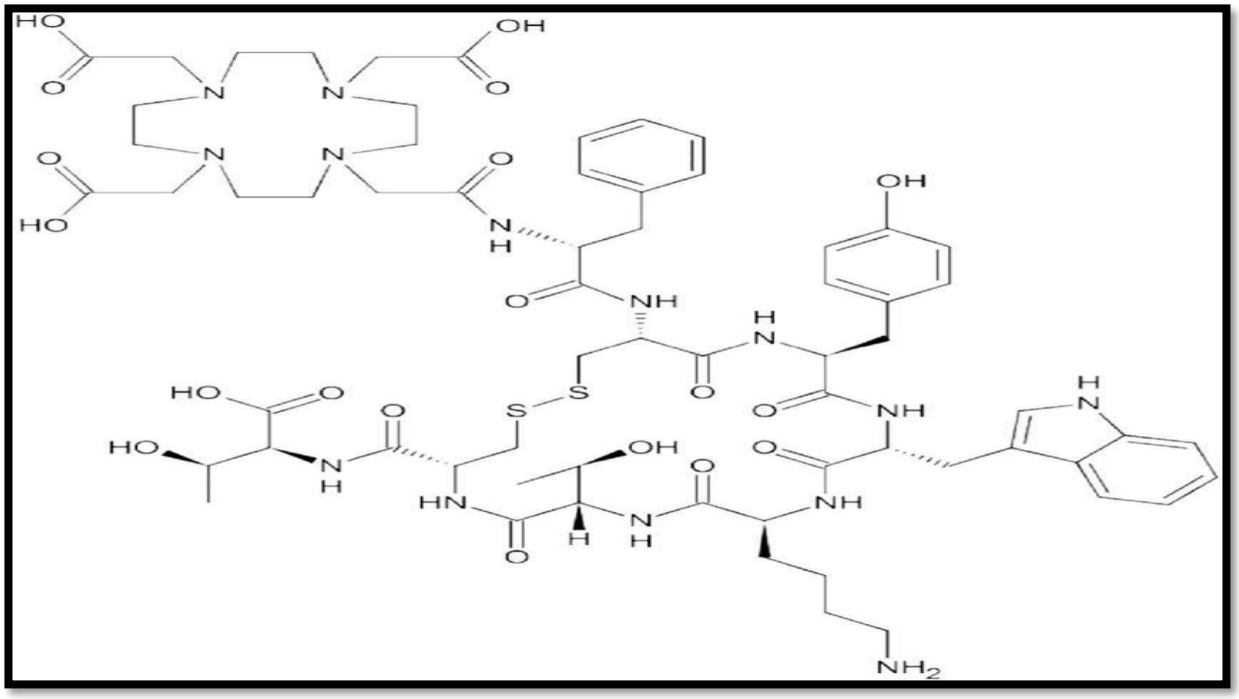


FIGURE (1.9) Lu _177 DOTATE STRUCTURE

Principle of treatment technique Lutetium 177: Lu-177-PSMA-therapy stands for Lutetium 177 prostate-specific antigen radioisotope therapy. Thus, the membrane antigen binds selectively to cancer cells. The isotope lutetium 177 (Lu- 177) attaches to this substance and is a beta emitter. After the transparent radioactive material PSMA is introduced into the human body, it only binds to malignant tumor cells in the prostate gland. Because beta radiation extends a short distance (several millimeters), healthy tissue is not exposed to radiation. After a course of PSMA treatment, the cancer cells die, and the tumor size decreases significantly. The main advantage of this method of treatment is that, due to selective binding, radiation affects not only the primary tumor located in the prostate gland, but also metastases (sub-malignant tumors) that can localize in different places of the human body[6].

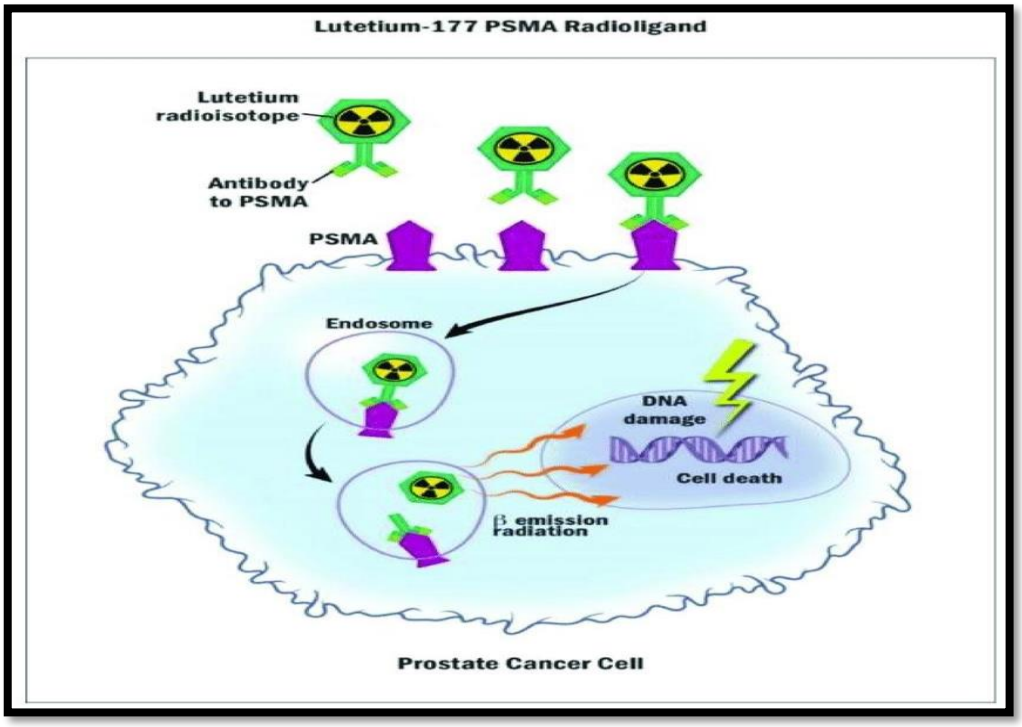


FIGURE (1.10) Targeting cancer cells

PET -CT SCAN: A positron emission tomography (PET) scan is an imaging test that allows the doctor to Check for diseases in the patient's body. The scan uses a special dye containing radioactive tracers. PET (positron tomography) is a scan that shows how organs and tissues are working inside the body. These tests help doctors diagnose and treat cancer because they can see and track the activity of cancer and other cells. Processes that can be measured include blood flow, tumor growth rate, and effectiveness of chemotherapy drugs [13]. PET scans are most commonly used to detect: Cancer, Heart problems, brain disorders.

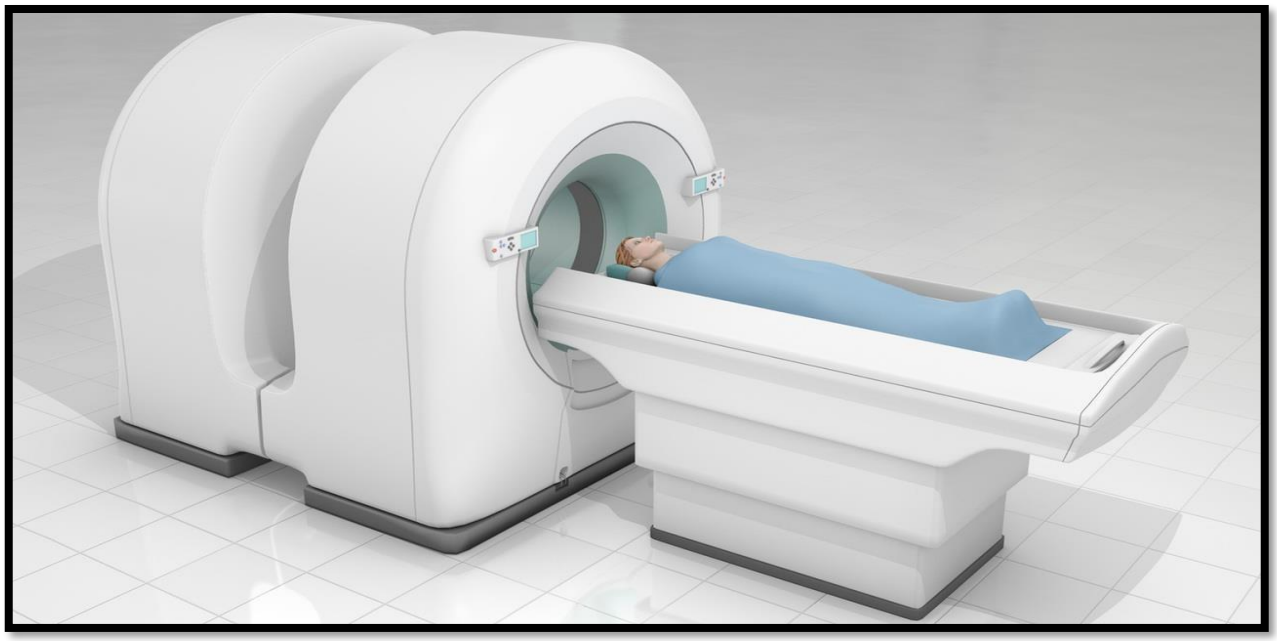


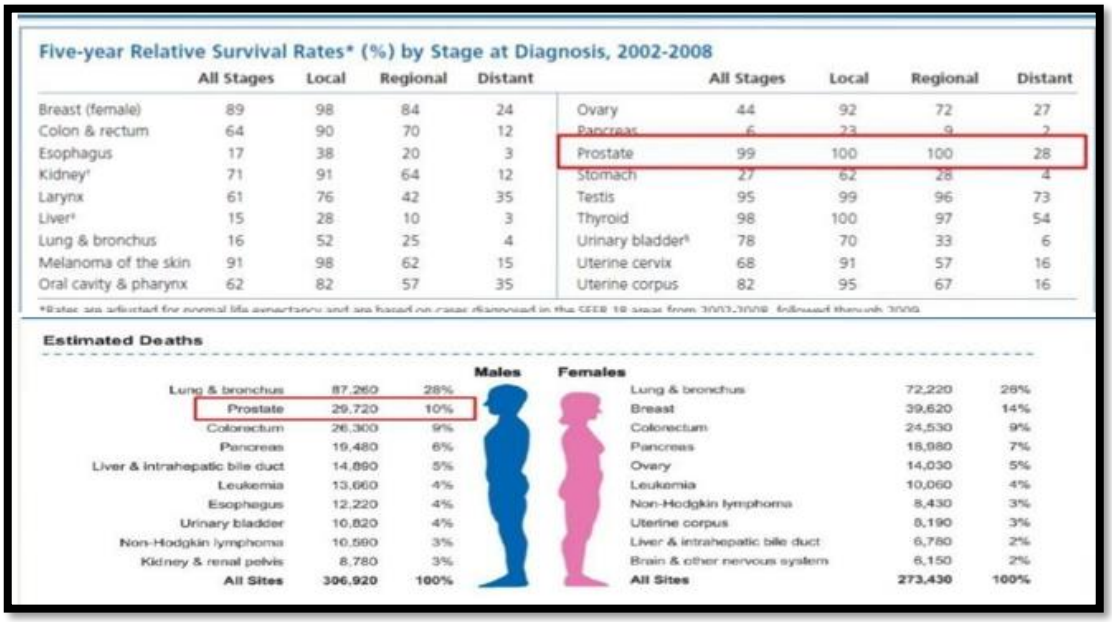
FIGURE (1.11) device PET /CT SCAN

Gamma camera: An imaging device used in the field of medicine, often in nuclear medicine, to photograph gamma rays emanating from radioactive compounds in the body. It is a device consisting of one or more detectors installed between the place where the patient is placed and connected to a control system to operate the device and store images .



FIGURE (1.12) DEVICE GAMMA CAMERA

Benefits can be expected: Approximately 60-70% of patients who have the treatment will experience appositive response (e.g, alleviation of symptoms) and in some patients. It may produce a relatively long-term remission of disease. Life expectancy could also be extended . Large-scale trials are ongoing in Australia and the USA to determine the precise extent of benefit of this treatment[15].



Five-year Relative Survival Rates* (%) by Stage at Diagnosis, 2002-2008

	All Stages	Local	Regional	Distant		All Stages	Local	Regional	Distant
Breast (female)	89	98	84	24	Ovary	44	92	72	27
Colon & rectum	64	90	70	12	Pancreas	6	23	9	2
Esophagus	17	38	20	3	Prostate	99	100	100	28
Kidney†	71	91	64	12	Stomach	27	62	28	4
Larynx	61	76	42	35	Testis	95	99	96	73
Liver†	15	28	10	3	Thyroid	98	100	97	54
Lung & bronchus	16	52	25	4	Urinary bladder†	78	70	33	6
Melanoma of the skin	91	98	62	15	Uterine cervix	68	91	57	16
Oral cavity & pharynx	62	82	57	35	Uterine corpus	82	95	67	16

*Rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2002-2008, followed through 2009.

Estimated Deaths

Males			Females		
Lung & bronchus	87,260	28%	Lung & bronchus	72,220	28%
Prostate	29,720	10%	Breast	39,620	14%
Colorectum	26,300	9%	Colorectum	24,530	9%
Pancreas	19,480	6%	Pancreas	18,980	7%
Liver & intrahepatic bile duct	14,890	5%	Ovary	14,030	5%
Leukemia	13,660	4%	Leukemia	10,060	4%
Esophagus	12,220	4%	Non-Hodgkin lymphoma	8,430	3%
Urinary bladder	10,820	4%	Uterine corpus	8,190	3%
Non-Hodgkin lymphoma	10,590	3%	Liver & intrahepatic bile duct	6,780	2%
Kidney & renal pelvis	8,780	3%	Brain & other nervous system	6,150	2%
All Sites	306,920	100%	All Sites	273,430	100%

FIGURE (1.13) The incidence rate of prostate cance

potential aside effects: The most common side effect is dry mouth and dry eyes. Occasionally, some patients may experience nausea or vomiting. Mild lethargy is also a side effect. Most of these side effects are transient and usually resolve after a few days . In patients with very extensive bone disease, marrow suppression is also a potential side effect due to "collateral damage" from the radiation on adjacent bone marrow[16]. Aim oh the work: New treatment for metastatic prostate and neuroendocrine. New treatment with out any side effect compared with different treatment (chemo, radio, biology and hormone). Preparation: PSMA, called a radioactive isotope, is a compound that can lead to the development of allergies. Therefore, hypersensitivity testing is mandatory before intravenous administration during the main course of treatment or during diagnostic pet scan. Preparatory activities also include tumor imaging methods, which include optical imaging, computed tomography, magnetic resonance imaging, and ultrasonography. These methods allow determining the size and location of malignant tumors and metastases. Radiopharmaceuticals used in the procedure of PSMA therapy are excreted by the liver and kidneys, so general clinical studies are performed before their use, including clinical analysis of urine and blood and biochemical blood test. Clinical studies help the doctor evaluate the degree of potential risks associated with the effect of radiopharmaceuticals on the liver and kidneys. During the course of treatment, these studies may be performed on the patient several times to monitor the patient's vital functions. A diet that excludes fats, fried foods, and alcohol is prescribed a few days before the start of the treatment course [17]. Treatment plan: Do a GA- 68 PSMA test before treatment To monitor the spread of the tumor. A small amount of Ga-68 PSMA radiotracer is injected into the patient's bloodstream, typically through an intravenous line . The patient waits for 30-60 minutes to allow the radioactive material to spread throughout the body Treatment with Lutetium-177 PSMA is given in 6 doses in multiple cycles, each dose ranging from (6-12) weeks. The first dose is given and waited for a period of 6-12 weeks, after which the second dose is given and waited for a period of no less than 7 days in order for a pet/ct scan to be performed to monitor the response to treatment. The number of courses and dose of Lutetium-177 PSMA is determined based on factors such as stage of disease, response to treatment, and tolerance to side effects. The radiotracer lutetium-177 PSMA is prepared in a specialized radiopharmaceutical facility. Four doses are then given to the patient intravenously Each dose is given for a period of 6-12 weeks. Lutetium-177 PSMA targets the surface of prostate cancer cells. The radiation emitted by Lutetium-177 PSMA damages the DNA of cancer cells, leading to their destruction. This process helps shrink tumors, relieve symptoms, and slow the progression of the disease. An antiemetic and a diuretic (to encourage urine clearance) are also given simultaneously.

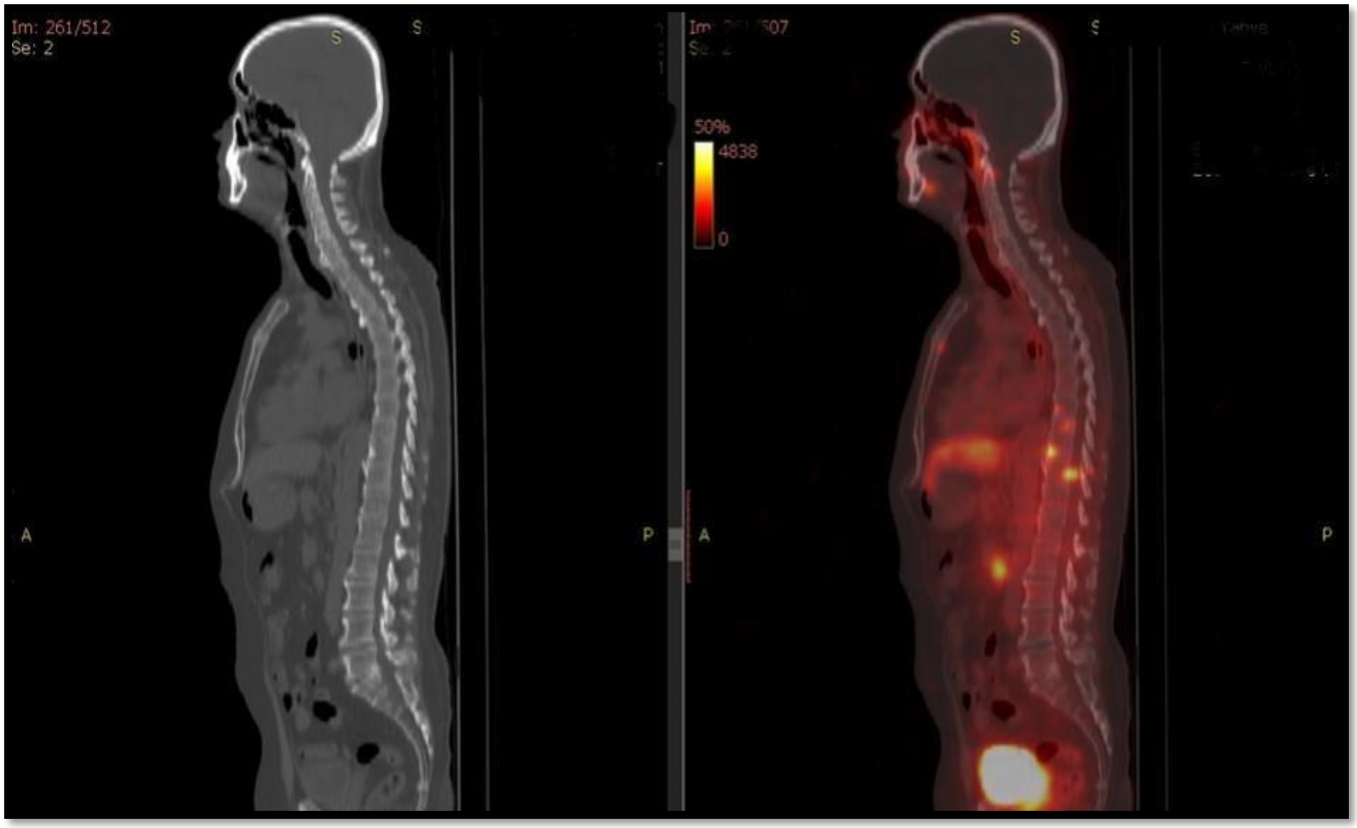
Patient preparation

- Ensure that the patient fasts for a period of no less than 4-6 hours before performing the examination.
- Avoid drinking caffeine or alcohol because they can cause dehydration
- Inform the patient of the need to drink water well before the procedure.
- Drinking water supports kidney function and helps flush out the radioactive material used in the examination
- Provide any specific instructions based on the individual's medical history and any medications they are taking.

Before injection lu_177 PSMA

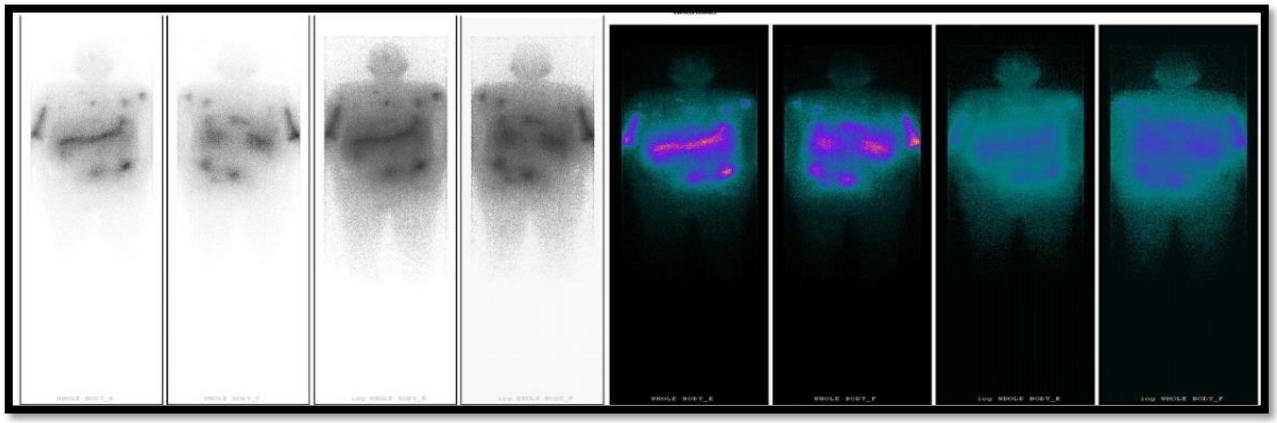
We put ice around the neck as due the lymph and salivary glands become warm.

A patient is given normal saline solution to clean the veins and move the blood injection first dose lu_177 PSMA Injecting the patient intravenously, 2 ml is given every 3 minutes until the dose is completed . After completing the dose, normal saline is given to ensure that the radioactive material reaches all the metastatic tumors. Case one: Referral reasons: Carcinoma prostate gland. Conclusion, Mildly enlarged prostate gland without pathological PSMA expressing disease to suggest residual primary disease. No evidence of PSMA expressing pathological pelvic lymph nodes. PSMA expressing metastatic sub centimeter right cervical level IV lymph node. Variable PSMA expressing metastatic sclerotic lesions and intensely

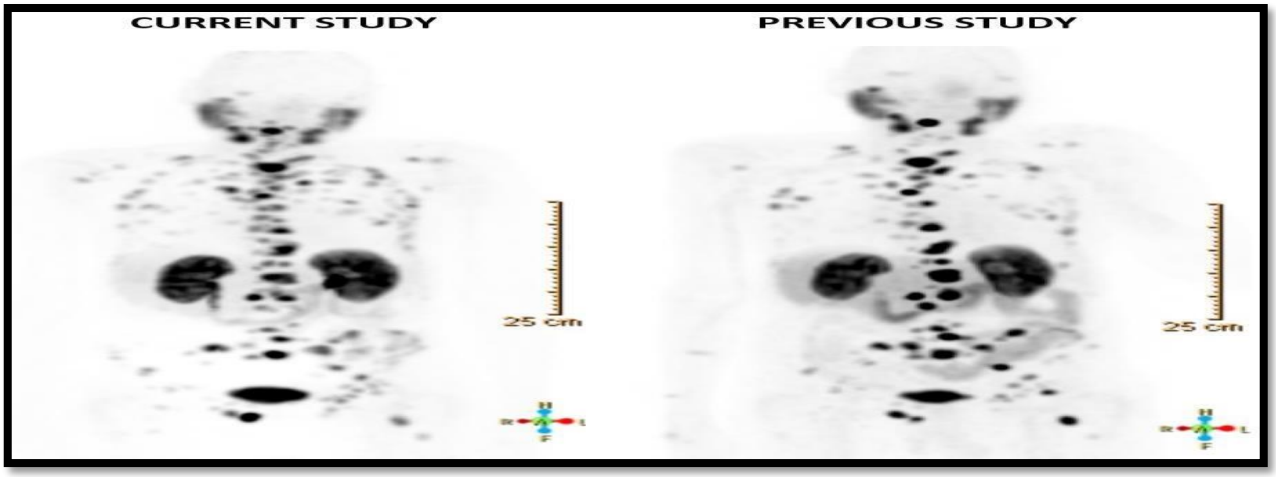


PSMA expressing metastatic marrow lesions in the almost entire axial skeleton, head of left humerus and bilateral femora.

- Overall, pattern indicating disease progression. Lu-177 – PSMA is recommended.

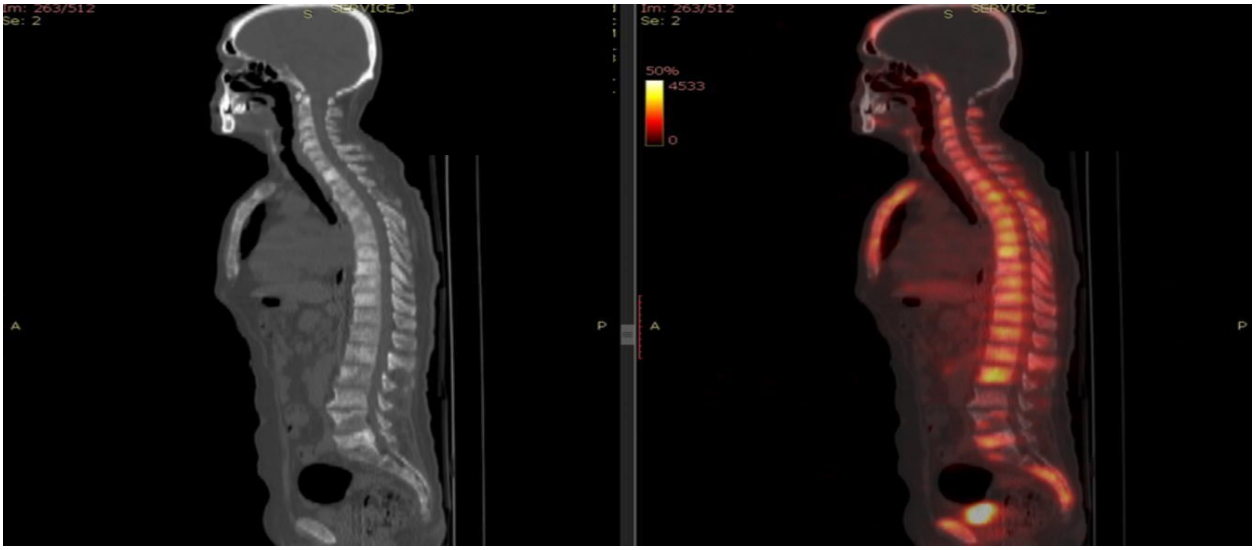


- After two dose lu-177 -PSMA patient Referral reasons: Carcinoma prostate gland, post hormonal therapy and 177Lu PSMA therapy.



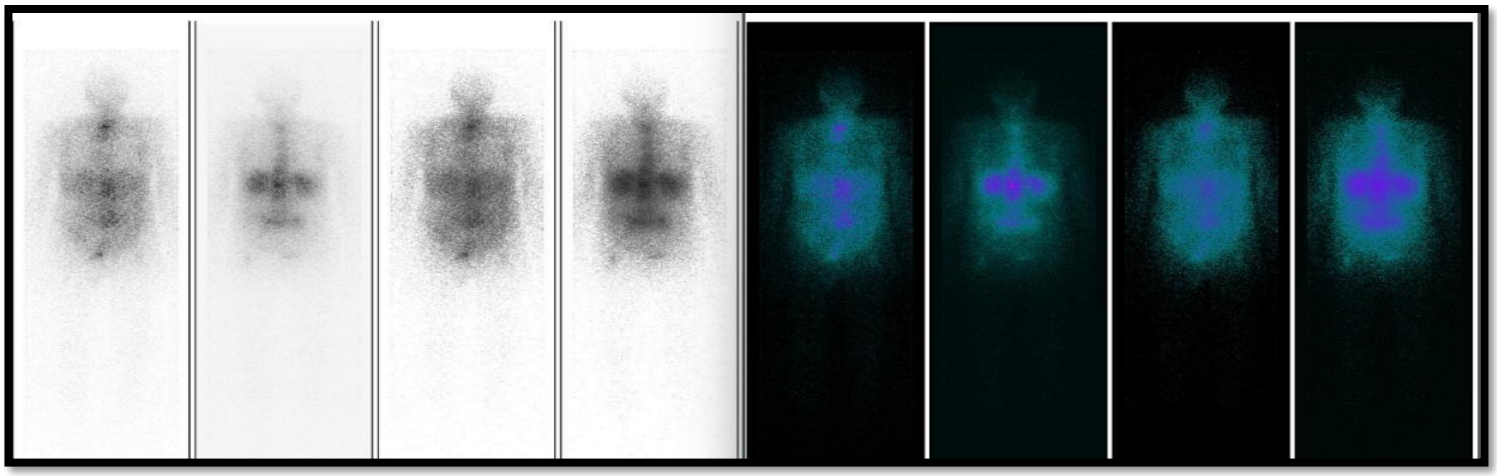
Conclusion

Mildly enlarged prostate gland without pathological PSMA expressing disease to suggest recurrent primary disease. No evidence of PSMA expressing pathological pelvic lymph nodes. Interval decrease in PSMA expression of metastatic sub centimeter right cervical level IV lymph node. Interval decrease in many of the PSMA expressing metastatic sclerotic and marrow lesions in the almost entire axial skeleton, head of left humerus, bilateral femora. Stable PSMA expression of lesions in sacrum, left ischium and right inferior ischiopubic ramus. No interval appearance of new lesion. As compared to prior PETCT, there is partial favourable therapy response. Continuation of therapy is recommended. Case two Referral reasons: Carcinoma prostate gland, post TURP in 2017 and on hormonal therapy. Conclusion Status post TURP. Focal PSMA accumulation at the central zone of prostate gland likely urinary activity along the prostatic urethra. No evidence of PSMA expressing metastatic pathological pelvic lymph nodes. Bilateral mild pleural effusions. PSMA expressing metastatic widespread sclerotic and marrow lesions in the entire axial and proximal appendicular

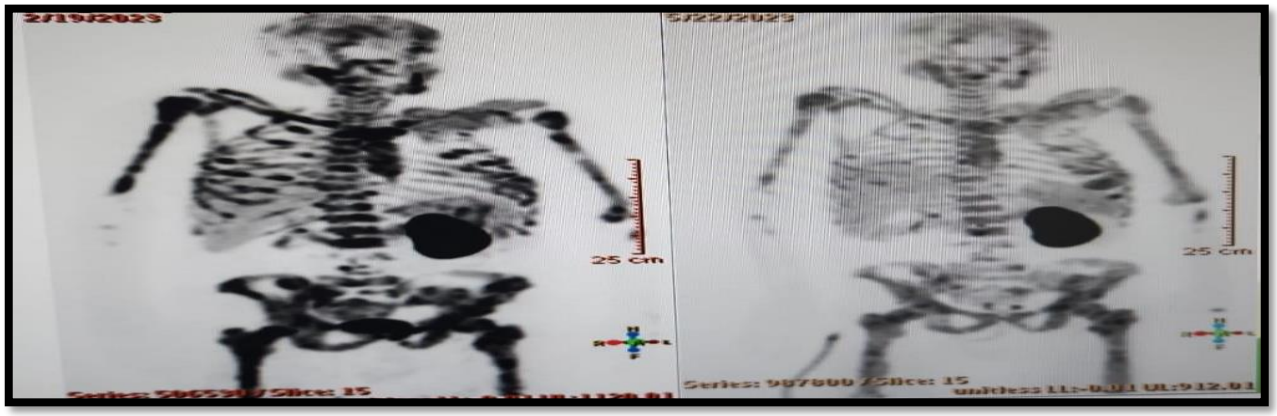


Skeleton with soft tissue component in some of the lesions more marked at left 6th rib.

- Overall, pattern indicating disease progression. Lu-177 – PSMA is recommended.



- Referral reasons: Carcinoma prostate, post Lu-177 PSMA therapy; response assessment PET CT scan. Scan findings as compared to previous PSMA PET CT scan



Conclusion

Carcinoma prostate, post Lu-177 PSMA therapy; response assessment PET CT scan as compared to previous PSMA PET CT scan, reveals:

Status post TURP. Interval resolution focal PSMA tracer uptake in left side of prostate adjacent to urethra.

No PSMA avid abdomino-pelvic lymphnodes.

Interval decrease in uptake of disseminated sclerotic bone lesions in axial and appendicular skeleton.

No other abnormal PSMA avid lesions elsewhere in the rest of the whole-body survey. No interval new lesions noted. Overall, features are showing partial favourable therapy response (good interim response).

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