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Contrast Agents, Radiodiagnostics-Radiodrugs and AI Implications- A Key Reading for a Complex World

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Abstract

Aim of this work is to provide an global focus on the characteristics and use of the contrast agents and on the radio-drugs – diagnostics: classic molecule and innovation.

The approach used is an pharmaceutical point of view. After a chemico – pharmacological classification is reported a review of relevant literature involved and an practical experiece is submitted to the reseacher. A global conclusion is then produced of interest is to analyze all this molecule together (contrast agents and radiodrugs) are also analized economic profile useful for the hospital pharmacists in monitoring of the costs of this Drugs classes. In this work are used the principle active chemical name and not the branded name and reported some use in practice. This article is focus end for the hospital pharmacist purpose.

Keywords: Contrast Agents; Radiodiagnostics; Radiodrugs; Radiology; TC; RM; Echography; Ultrasound; PET; Spect; Interventistic Radiology; Cost Management; Physical Property; Chemistry; Phamacoeconomy; Hospital Pharmacy; Radiopharmacist; AI; Physiology; Patology; Oncology

Introduction

In the wide and various imaging diagnostic procedure are currently used contrast agent to increase the quality of the images: the classic radiological contrast agent for radiology and TC, but also for RM, echographic procedure since the tracer used in nuclear medicine (radio drugs).

The contrast agent make possible to produce a difference in contrast of different anatomical structure or between a normal or pathological structure. The ideal contrast agent must to be safe and adeguate distribution. In order to manage this class of health products – drugs is fundamental for the hospital pharmacist to focus on the chemico-physico – pharmaceutical - pharmacological and toxicological profile of the single classes used in imaging settings. To the hospital pharmacist managers involved are required by the general manager of the hospital to Manage this kind of drugs: costs and right use according international and national guideline.

A classification surely help.

In this work are analized the molecule used in verious imaging settings: like classic radiology TC, SPECT single photon emission computed tomograhy, RM, echography, nuclear medicine.

Kind of radiation: Ionizating X ray classic radiologt, TC, Non Ionizating RM, ultrasound.

Source external of the patients: X RAY imaging (lower energy)

Source internal of the patient of radiation:

SPECT: Single-photon emission computed tomography, used gamma ray, nuclear medicine, gamma radiation

Scintigraphy (nuclear medicine) gamma scan

PET: positrone emission tomography, radionuclide use, beta+

Other: ultrasound

Images: X RAY classic bidimensional. TC tridimesional (second level technique), PET tridimensional.

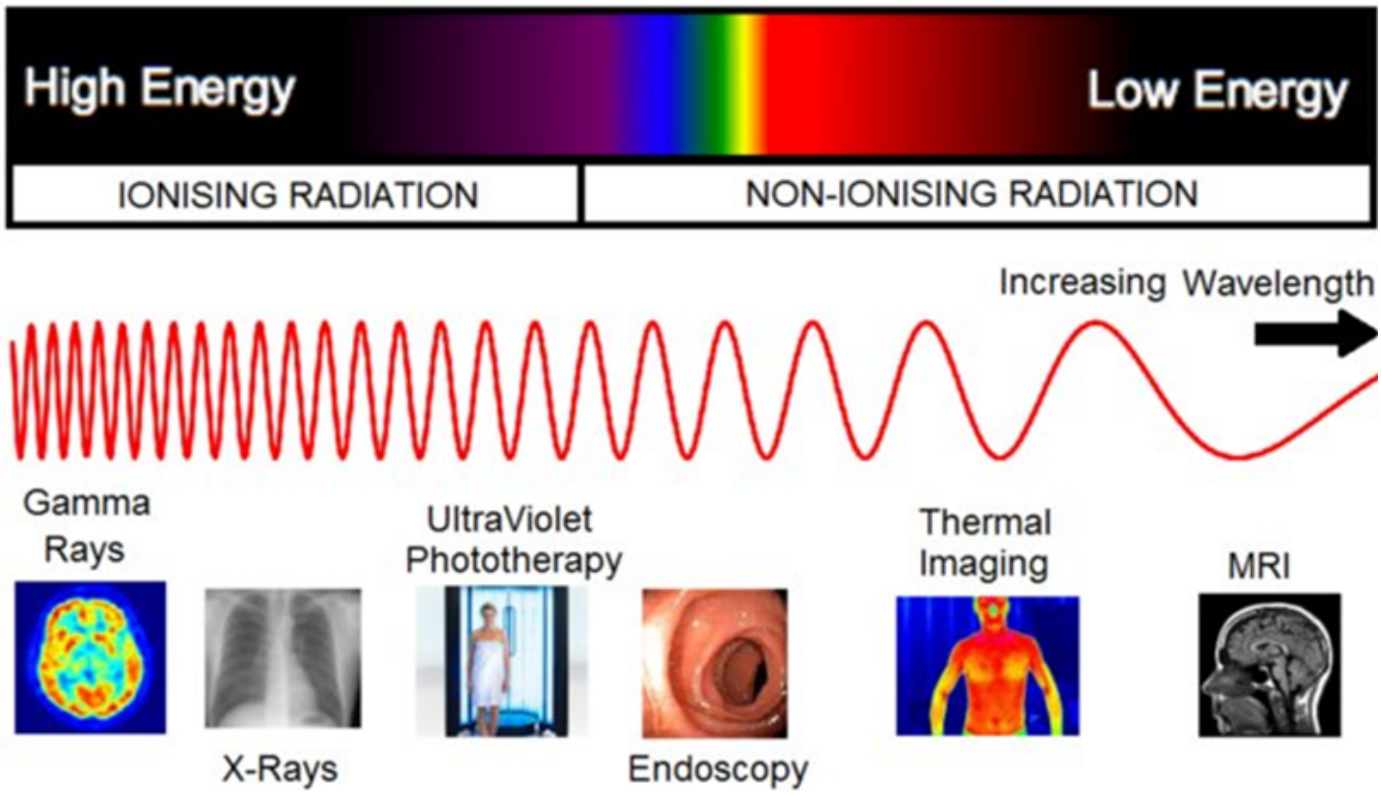

Figure 1: The electromagnetic (EM) spectrum, and applications in modern medicine. Ionizing radiationis a term used to describe radiation with enough energy to cause damage to the cells of the human body while non-ionising radiation does not have enough energy to damage cells.

Name	Symbol(s)	Representation	Description
Alpha particle	$^{4}_{2}He$ or $^{4}_{2}\alpha$		(High-energy) helium nuclei consisting of two protons and two neutrons
Beta particle	$^{0}_{-1}e$ or $^{0}_{-1}\beta$		(High-energy) electrons
Positron	$^{0}_{+1}e$ or $^{0}_{+1}\beta$		Particles with the same mass as an electron but with 1 unit of positive charge
Proton	$^{1}_{1}H$ or $^{1}_{1}p$		Nuclei of hydrogen atoms
Neutron	$^{1}_{0}n$		Particles with a mass approximately equal to that of a proton but with no charge
Gamma ray	γ	γ	Very high-energy electromagnetic radiation

Figure 2: Information about about different type of molecules and rays.

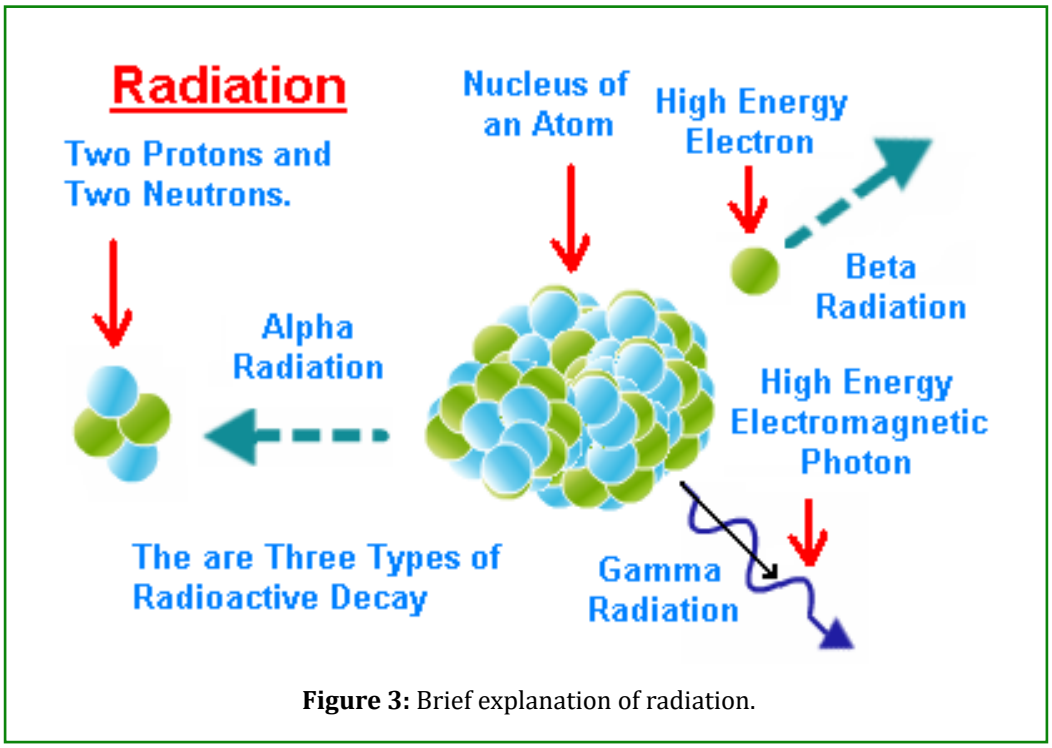

Figure 3: Brief explanation of radiation.

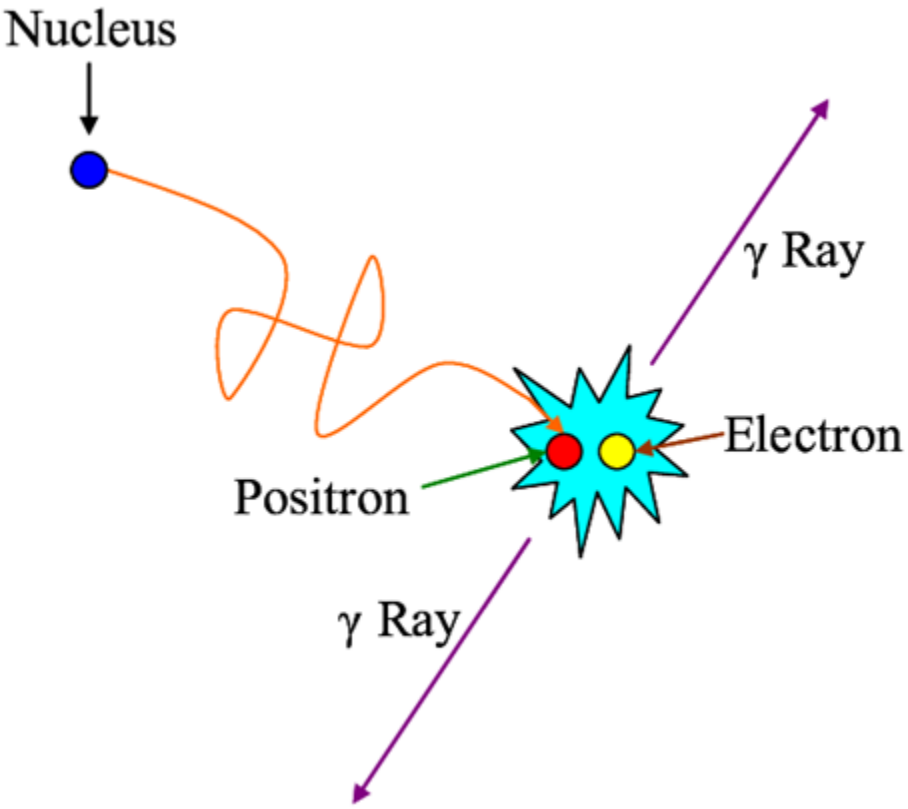

Figure 4: Radiation works as shown in above figure.

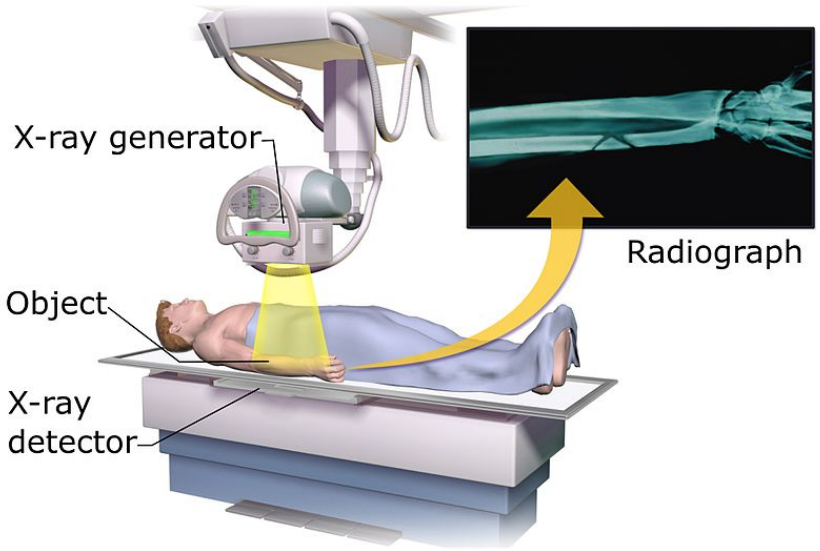

Figure 5: Projectional radiography.

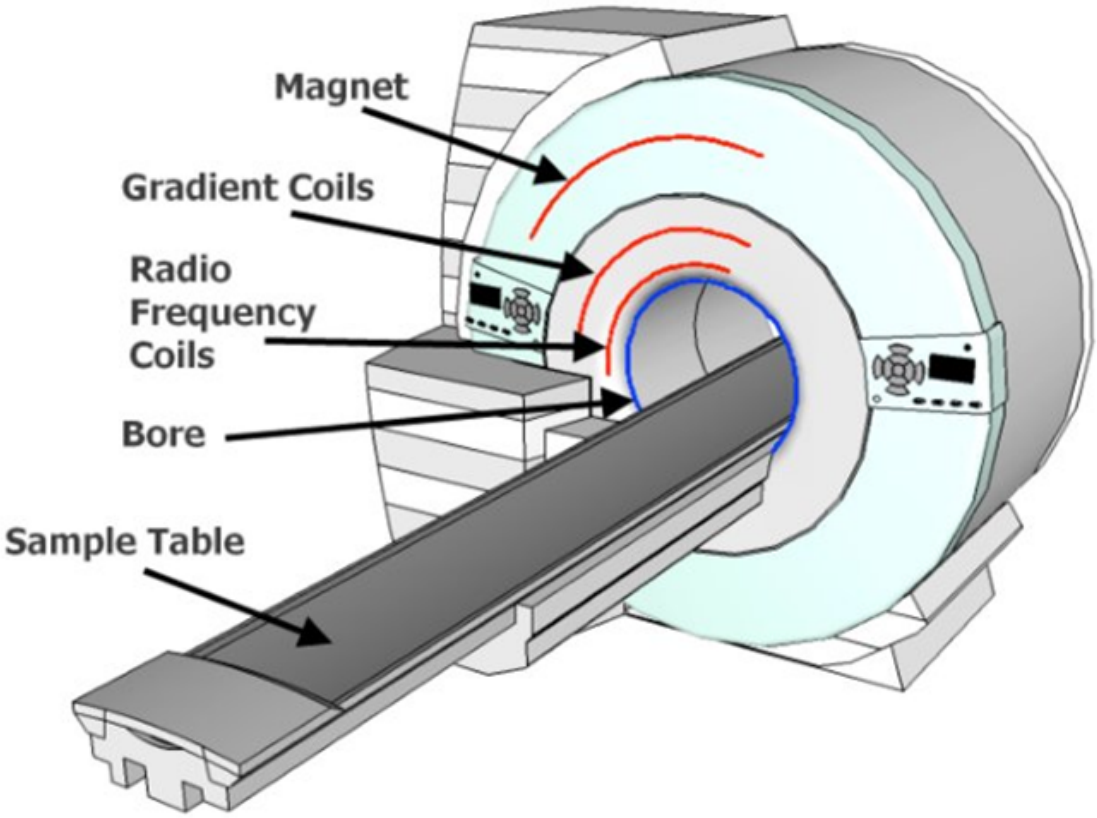

Figure 6: Schematic diagram of an MRI machine illustrating the concentric arrangement of coils (360º) and magnet.

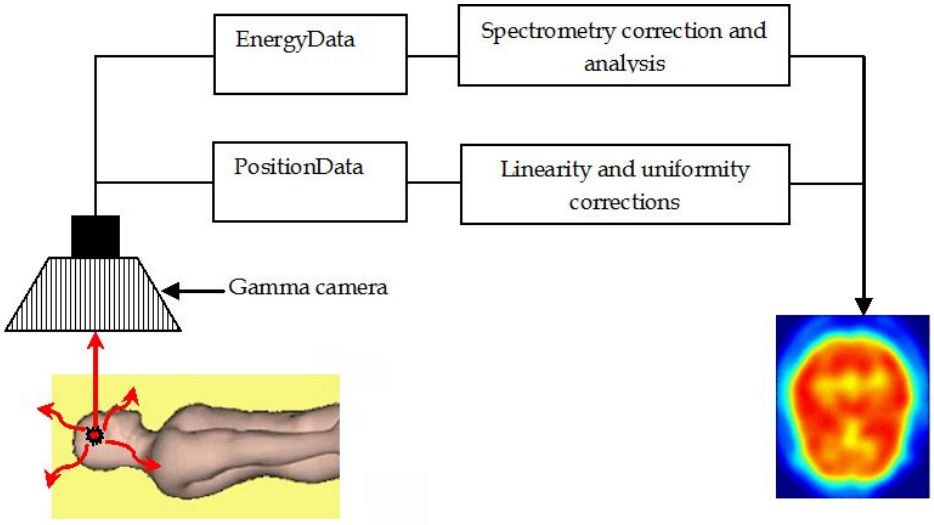

Figure 7: Illustration of data acquisition in planer gamma scintigraphy.

Modality information	PET	SPECT	MRI	CT
Measures	Physiology	Physiology	Anatomy (physiology*)	Anatomy
Resolution	3-5 mm	8-10 mm	0.5-1 mm	1-1.5 mm
Technique	Positron annihilation	Gamma emission	Nuclear magnetic resonance	Absorption of x-rays
Harmful effects	Radiation exposure	Radiation exposure	None known	Radiation exposure
Use	Research and clinical	Clinical	Clinical (research*)	Clinical
No. examinations per day	4-12	5-10	10-15	15-20

Figure 8: Comparison of imaging modalities.

Magnetic Resonance Imaging	Computed Tomography
Pros: Imaging modality of choice. High sensitivity. Low radiation risk. Detects small/subtle cortical abnormalities and temporal lobe abnormalities (e.g., mesial temporal sclerosis)	**Pros:** Used for assessment in emergency conditions. Fast scanning speed. Accessibility. Easy to use. Comparatively lower cost. Sedation not required. Better than MRI for calcified lesions (congenital infections) and neurocutaneous malformations (e.g., Sturge–Weber syndrome, tuberous sclerosis)
Cons: Sedation required. Slow scanning speed. Limitations in accessibility (less-developed countries). Comparatively higher cost. MRI cannot be done in presence of dentures, pacemakers and other metallic implants. Motion artifacts (esp. with 3 T & 7 T)	**Cons:** Risk of radiation exposure. Low-resolution images. Low sensitivity (30%). Limitations in detecting some pathologies of temporal fossa such as mesial temporal sclerosis and small/subtle changes

Figure 9: Advantages and disadvantages of MRI vs. CT.

	Advantages	Disadvantages
PET	Active lesion Whole-body imaging possible Assesses response to therapy Safely performed in patients with advanced renal dysfunction Intracardiac devices	Radiation exposure Lower spatial resolution Long acquisition time Need for specialized patient preparation Nondiagnostic scans due to physiological uptake More expensive
MRI	High spatial resolution Excellent soft-tissue contrast Non-ionizing radiation Detects morphological abnormalities including ventricular wall thinning A lower number of nondiagnostic scans No need for specialized patient preparation	Long acquisition time Limited by the incompatible cardiac devices With risk from gadolinium contrast in patients with advanced renal dysfunction

Figure 10: Advantages and disadvantages of FDG-PET and MRI.

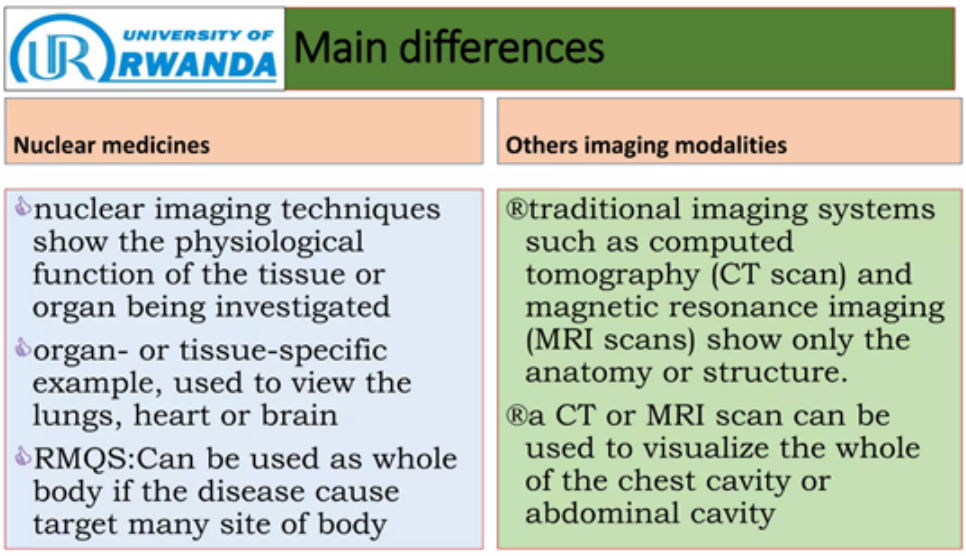

Figure 11: The following differences were mentioned in the project of university of rawanda.

Concept of contrast agent: molecule used in medical imaging in order to increase the contrast of structure analized of the human body. They can be divided in natural and artificial.

In the natural methodology: air, or other gas, the calcium of the bone (X-RAY). The artificial methos imply the use of foreging molecule in order to increase or reduce the capacity of absorbtion the X-photon.

Various are the way of subministration: EV, OS, clisma, endovasal, retrograd cavity fillinng, naso gastric tube.
Aim of htis use it to increase the quality of the medical images for diagnostic scope but at a minimum level of toxicity possible. It is needed that the agent show a good distribution into the organ under testing.

X-ray contrast agent: can be divide in negative-radiotransparent (air, metilcellulose, Peg in electrolitic solution) or positive: iodate or baritate agents. The gas used must to be: non irritant, non emboligen and rapidly reabsorbed (CO2 for endoscopy).

The iodate can be classified as: idro or liposoluble. The negative contrast agent show an lower level of radioation absorbtion vs the organ under investigations: are used commonly: air, oxigen, CO2, water (TC), metilcellulose. Today in use for radiology tube gastroenteric: double contrast procedure.

In the radioopaque molecule is is possible to find: increased absrobtion of the x ray vs tissue and the organ analized. Re used molecule with high atomic number Z (the abssorbtion deoend on the number of electron)
BARIUM and IODINE.

This last are linekd in stable compounds in order to avoid the breack free in the body. Charactheristic searched for this kind of agent: high radioopacity, good tollerability, no pharmacological effects, rapid elimination form the body, high tropism.

$BASO_4$: barium solfate (the first introduced), used only in gastroenterologic field, inorganic.
BA Z= 56

Not water soluble, high radioopacity, good tollerability, no pharmacolgical property, total elimination. No intestinal absortion. (it is used as sachets or oral suspension ready to use) Double contast method: used $BASO_4$ agent in order to paint the mucose under testing then rettal air insufflate (opaque climsa) or effervescent product for first digestyve tracts: sodium bicarbonate and citric acid, or introduction of metilcellulose with nasogastric tube in the tenue clisma.

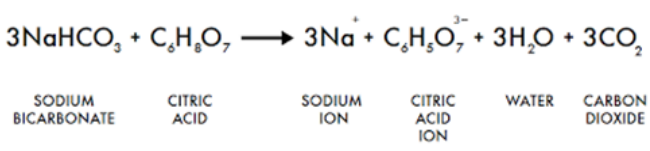

Figure 12: Effervescent product.

Classic Radiology: used at 20-250%, TC 0,1-2%
Rare adverse reaction similalleric 1 every 750.000 procedure.

Controindication of baritate: intestinal occlusion or suspected or intestinal drilling (also supected)
Iodate: Z= 53 high X -photon ray absorbtion, stabile link with benzene.
Used: Intravenous, intraarterial, oral, clisma, directly in cavic viscera, biliar way,endoscopic retrogad cateterism.
TC: rapid diffusion in interstitial space and producing in parinchematose organs increase in contrast enhancement.

Introduced in Blood diffuse into the interstitial space and then excreted trought ultrafiltration glomerular. Used at 150- 400 mgI/ ml. Idrosoluble (for biliar and urinar ways, arterious or venous vessels, myeolography, TC. The idrosolubility make psosible the direct subministration into EV or ENDOARTERIOUS WAY Uroangiographic agents: this are the eliminated by the renal way. this property make possible to detec informative images of this structure.

Mono-bioiodate first generation introduced in the 1930 years (toxicity problem, low contrastographic power) and in solution they dissolve in anion and cation.

Triodate second generation 1950 years (ionic) and third generation (non ionic)
Structure: benzenic ring with 3 iodine in position 2,4,6 and in position 1 an-COOH group that make possible to produce idrosoluble salts. In solution they dissociate in cation and anion (classifyed ionic):theyr osmolarity is about 5-7 times higher than of the plasma.

The sobstitution on position 3-5 make possible to increase tollerability and improve the elimination phase.

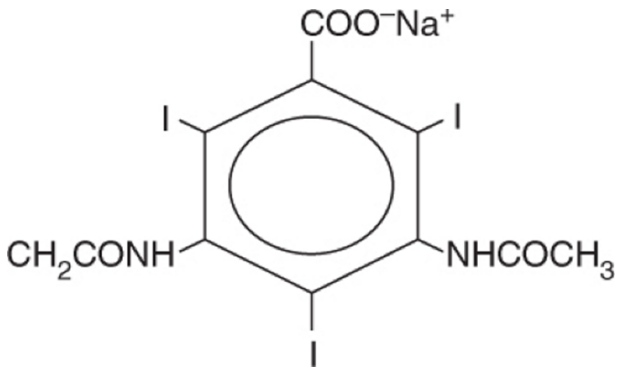

Figure 13: High-osmolar ionic agent, ratio 1.5 (3:2).

The new molecule was discovered in order to reduce the toxicity and to increase the efficacy.
The margin safety level depends on the DL50 (medium letal dose) / diagnostic dose
And the efficacy index = number of iodine atoms in the molecule / particle in solution

Ionic: great iperosmolarity (disvantage).
The iperosmolarity produce: capillary endoteliad damage, BEE permeabilization, emodimamic modification.
Iodate thrd generation: introduced in Years 70-90.

NON IONIC: in position 1 of the benzene group there is a non ionizable group, it is non needed salification.
The idrosolubility depends on the various idrofile group intraduced in position 1,3,5.

It is so possible to produce really concentrate solution but with osmolarity low (400-700 mOSM/ kg) similar to the human plasma value: 300

Their chemotoxicity is reduced vs ionic.
Non ionic dimeri: 2 molecule of non ionic contrast agent are linked trought and policarbioniose chain

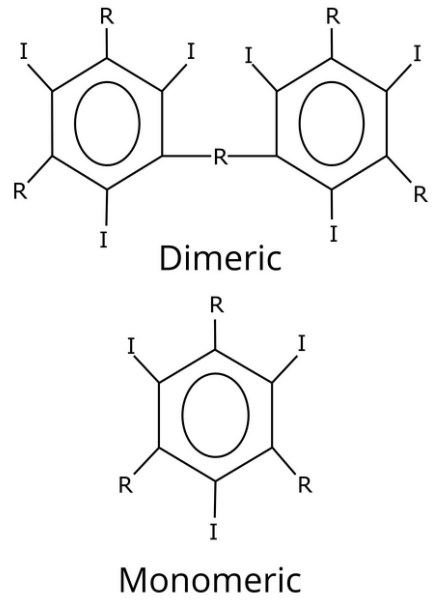

Figure 14: 6 iodine atoms are in 1 molecule.

In this way 6 iodine atoms are in 1 molecule of the contrast agent.
But this have viscosity more high vs monomer.

Viscosity measured in millipascal/ sec is related to the force needed to inject, it can be reduced lowering the concentration but this can produce unsatisfactory contrast: the viscosity is inversely related to the temperature so it can be used this strategy (to be used at 37 grades).

The effect of an High viscosity must to be take in consideration expecially not to be subminitsrate in little arterybecause prolonged time of contatct MDC-endotelium (BEE, or

vasodilatation in other microcircula). Dimera at equal osmolarity show higher viscosity vs monomers, because influenced by MW and by -OH group into the molecule.

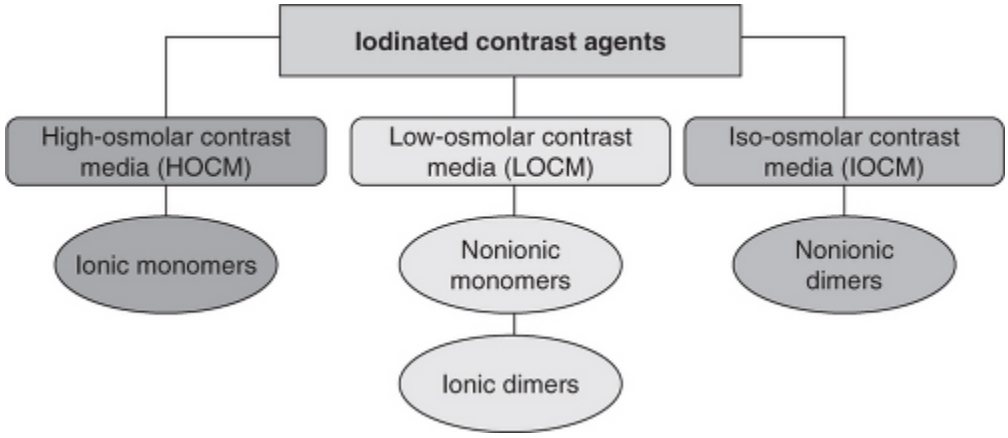

Figure 15: From Radiologykey.com.

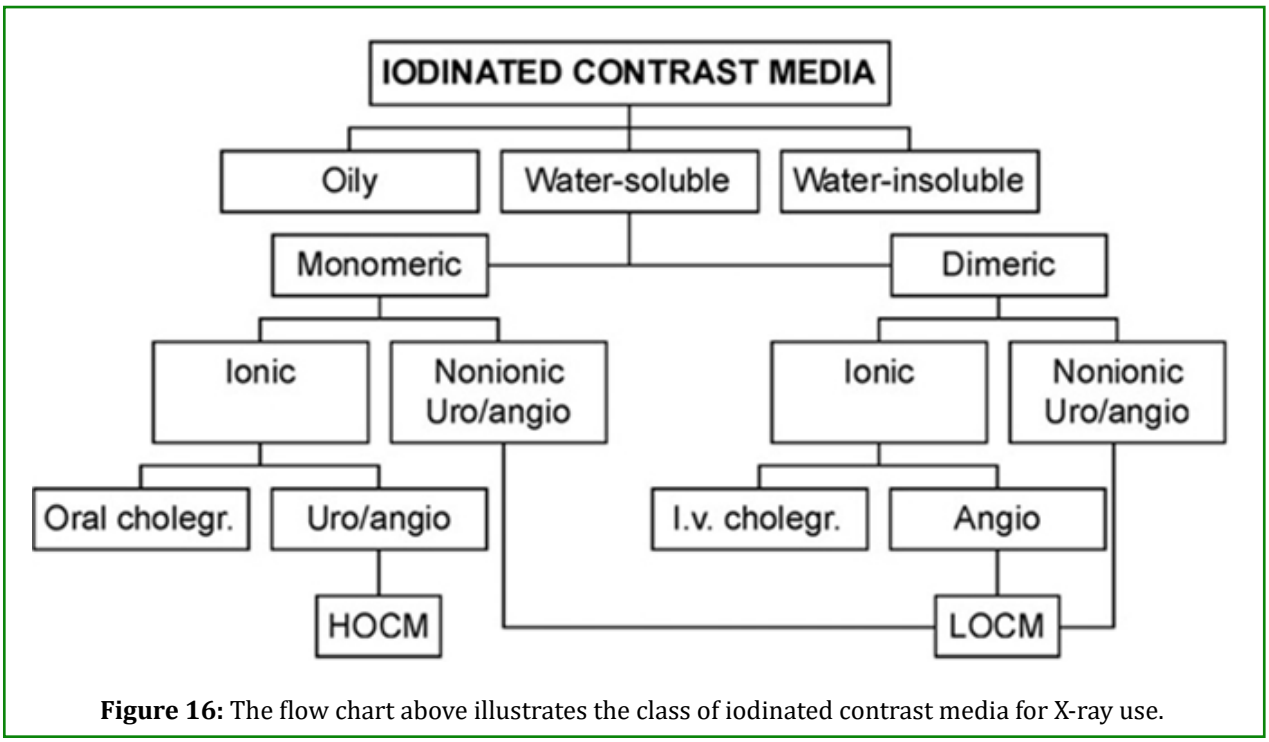

Figure 16: The flow chart above illustrates the class of iodinated contrast media for X-ray use.

Iodate: uro -angio -mielography (idrosoluble non-ionic), coleicsto cholangiography (idrosoluble oral-ev).
Artrography, vases and cardiac chambre, mielography.
Liposoluble: lymphography,bronchography, mielography, isterosalpingography, scialography

Characteristics required for a good IODINE contrast agent: high radioopacity, idrosulubility, low osmolarity, good viscosity, good tolerability (local and general) non pharmacological properties, rapid elimintion form the body trough renal way.

Lateral chain: because toxicity is related the link with protein and cell membrane the lipophilic molecule can be more dangerous than idrophilic.It seem that in iodate the lateral chain with various idorphilic group reduce the global toxicity.

The binding properties depend on also the electrical charge: non ioni MDC show less link.
At high concentration the link is more higer.
Advantages of the non-ionic vs ionic: less lowe level of nausea, vomit, heat sensation, reduced level of allergic -like events, reduced neurotoxicity

Iodate contrast agent idrosoluble for oral subministration:
ionic and non-ionic (Sodio Amidotrizoato + Meglumina Amidotrizoato, iodamide)
colangiographic agents: are used
Triiodate, oral iopanoic acid and 2 benzenic ring linked, ionic: the position 5 of the benzene is free to produce link with plasma protein and increase the biliar escrection. (iodipamide EV)

Liposoluble iodate: fatty acids linekd to iodine, mixed with inert powders to increase viscosity.
in use: olio etiodate for chemioembilization of HCC and other diagnostic use (TC).

Nonionic contrast media studied

Generic name	Content I/ molecule	Iodine-to-particle ratio	Concentrations, mg I/ml
Iodixanol	6	6	200, 270, 320
Iohexol	3	3	200, 300, 350
Iopentol	3	3	200, 300, 350
Iopamidol	3	3	200, 300, 370
Ioversol	3	3	240, 320, 350
Iopromide	3	3	240, 300, 370
Iotrolan	6	6	240, 300
Ioxaglate	6	3	200, 320

Figure 17: non-ionic contrast substances and there ratios.

Side effects – accidents
due by intollerance -dose independent not preventivalble or toxicity, linked to the pharmaclogiclal effect and so dose depenedent (nephrotoxicity).

Side effects: low moderate severe.(similallergic or due by phisiopharmacological effects).
Similallergic: not prevedible, dose independent, low incidence, rapid development and evolving rapidly(into 30 min).

Ortcary, congiuntivite, edema diffuse, bronchospasm, cardiopulmunar arrest, pulmunary edema. More risk conition: atopic diatesi, drug ipersensibility, previous reaction to MCI, ADR physio-pharmacological: more prevedible, dose dep. High incidence, rare evolution due by their chemotoxicity, osmo toxicity and viscotoxicity.

Nausea, vomit, cefalea, vasofvagal reaction, CV arrest, edema pulmonary, aritmia, convulsion, ipertension. Nefrophaty 2-7% cases 24-72 h after subministration, increase of serum creatinine (50%) or significative reduction of urinary volume for 6 hour.
Risk factors: cardiopaty, IR, beta and calcium blokers, thromboflebitis, BEE alteration, plasma cellular discrasie.

Tardive reactions: similallergic and cutaneous.
Iodate low osmolarity: show an high tollerability.

Contrast-Induced Nephropathy
Kalgi Modi, Sandeep A. Padala, Mohit Gupta 2024 Jan.
"There is a lack of consensus on the definition and treatment of contrast-induced nephropathy (CIN). Currently, the understanding of CIN is that it is the impairment of the renal function gauged as either a 25% rise in serum creatinine from baseline or an increase of 0.5 mg/dL (44 µmol/L) in absolute serum creatinine value within the 48-72 hours following intravenous contrast administration.

The renal impairment that is linked with the administration of contrast is acute, usually occurring within 2-3 days. It has been recommended that renal impairment developing up to seven days post-contrast administration should be considered CIN if it is not attributable to any other possible cause of kidney failure KF. A temporal link is thus implied. Post-contrast exposure, serum creatinine levels peak between two and five days and usually return to baseline in 14 days."

The reaction can ben low level, moderate,severe (about 0,0025%), immediate (into 1 hour) or tardive even since 7 days after subministration
Mild: nause, metallic taste, weathing, pain in the subminitration site, urticaria.
Moderate: also dispnea, ipotension, thoracic pain
Severe: bronchospams, face edema, hands, high ipotension, bradicardia, schock, pulmunar edema arytmia, coma, exitus.
Etipathology: iperosmalarity, chemio toxicity, histamin release, allergy reaction, central neurotoxicity
Renal damage, cardio vascular damage or on the veinous system.
Renal damages: tubular damages (attention to the disidratation situations), increase of the creatininemia after 4-5 days.
Risk factors involved: IRA acute renal failure, diabetes, ipovolemia, FANS, nephrotoxic drugs like cisplatinum aminoglucoside, high dosages of the contrast agent used, repeated dosages in few time.
Preventive measure to reduce risk: us iodate contast agent at low osmolality, non ionic, good hydratation during procedure and after, no co subministation of nephrotoxic drugs, consieder adeguate time between procedures, reduce dosage when possiblwe, i dialized patients set a session after the use, check the creatininemia 4 days

TC tridimensional images various generation of instruments, also Spiral TC
High doses of radiation use

Iodate contrast agent:
concentration mgI/ ml
volume ml 50-500 ml
posology: iopromide 300/370: 1,5 ml/Kg body weight.
Iomeprol: AD 10-250 ML
Ioexol: form 0,5 ml to 250 ml (maximum volume for multiple procedure)
Befgor the use: it is mandatory to inspect the bottles to veryfy absecnce of particulate matter or abnormal colour.
Subministration ev, intrararterial, other Manual methods, injectors
Automatic injectors: mdoule of erogation, monitoring, patient lines and valvle. (siringe and volumetric pump).
Erogation module: trought siringe or volumetric pump.
Velocity of flux: fixed or variable
Injectors at 2 – 3 way (2 way for contrast agent and 1 for saline)

Figure 18: MDC injector

Flux max: RC RM 1Oml/sec, angiography since 50 ml/sec
Injector at fixed/variable velocity
Temperature: increasing (at 37 grades) reduce the viscosity
The open bottle must to be used immediantly, not to be reused
Subministration: IV or intrararterial with a cateter: angiography TC, RM
Automatic injectors (module of injection, control module, centralization module, valvle and patients line).

TC: are needed appropriate prescription dute by the high cost, insostituibility in some cases forc certain clinical need or interventistic purpose
Higer doses of radiation vs conventional radiology.
ANGIOGRAPHY: arteriography, flebography (venous), interventistic radiology(emoraggy control

Vases Stenosis dilatation,endoarterious drug infusion, positioning of biliar or uretral protesis and other.)
Anatomic, flux and perfusion evaluation (partial).
Three phases: arterious, parenchimographic, venous return

RM: based on the NMR phenomena
Natutral isotope: 1H, 13C, NA23, 31P, 39 K
Isotope 1H is present in all body water
Magnetic properties: paramagnetic, superparamagnetic, CEST Chemical exchange saturation transfer
Paramagnetic: based on gadolinium or manganese (they are positive, increasing the signal)
Superparamagnetic: based on particles of ferrum oxide. (this are uptaked by reticuloendotelial system of liver, limphonode, spleen)
Biodistribution: IV, extracellular, tissue specific
Kind of Contrast enanchement: T1 Positive, they increase signal where they localize, T2 Negative if they reduce the signal.
contrast agents: gadolinium, MN, Fe derivates.
because toxicity this molecule must to bes used chelated.
the use of MDC is crucial for evaluation of focal lesions, and study of physiopatologic phenomena.
For demonstrate condition not easily to do with other tecnique.
This are divided in agent for: general or extracellular use, epatotrope, limphotrope, reticoloendotelial
Intravascular, GI
The mechanism used is different form classic other contrast agen and nuclear medicine treacers based on the cacacity to absorbe X-ray or emission of rediation.
They act in indirect way modifying the time of relaxation of nuclei H1
They are classified as paramagnetic (gadolinium) and superparamagnetic
They are trapped inside chelants molecule,whit high stability, and not metabolized in vivo.
When subministrated ev they modify the relaxion time of the Hidroge nucleo (T1 and T2)
Gadolinium reduce T1 and increase intensity of the signal, instead the superparamagnetic molecule reduce the T2.
This can be divided in molecule for general use or orgenospecific use (hepatic, reticoloendotelial, linphonode accumulation, GI, IV).
The gadolinium derivated can be divided in: linear molecule and macrocyclic, ionic and non ionic

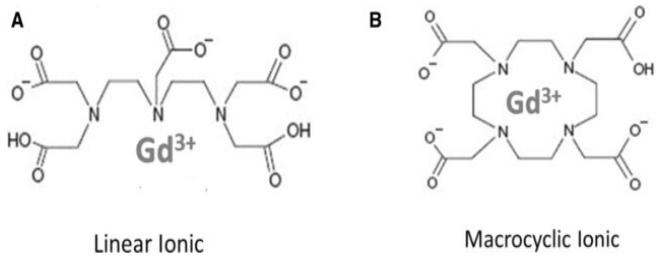

Figure 19: Gadolinium contrast agents.

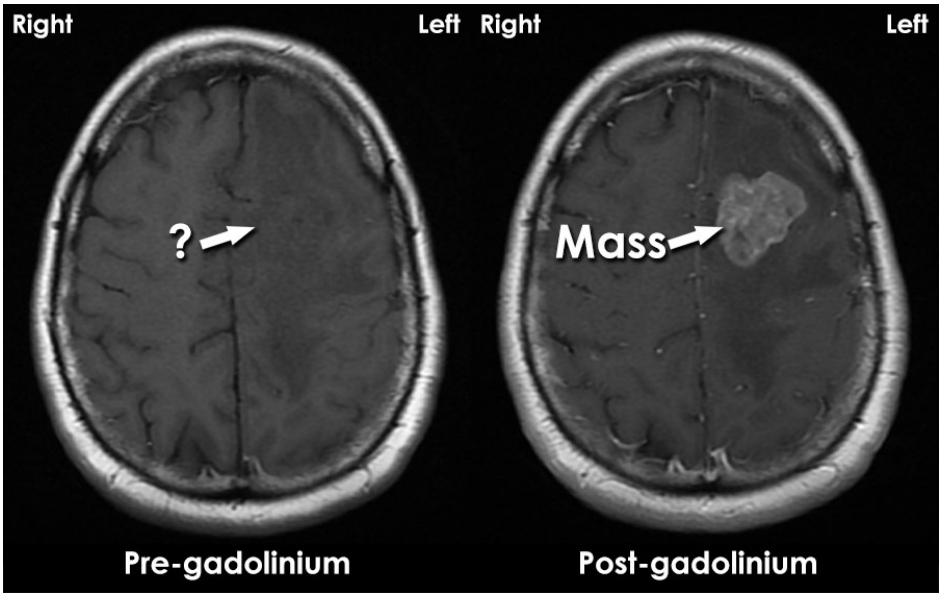

Figure 20: Projection of Gadolinium contrast in CT Scans.

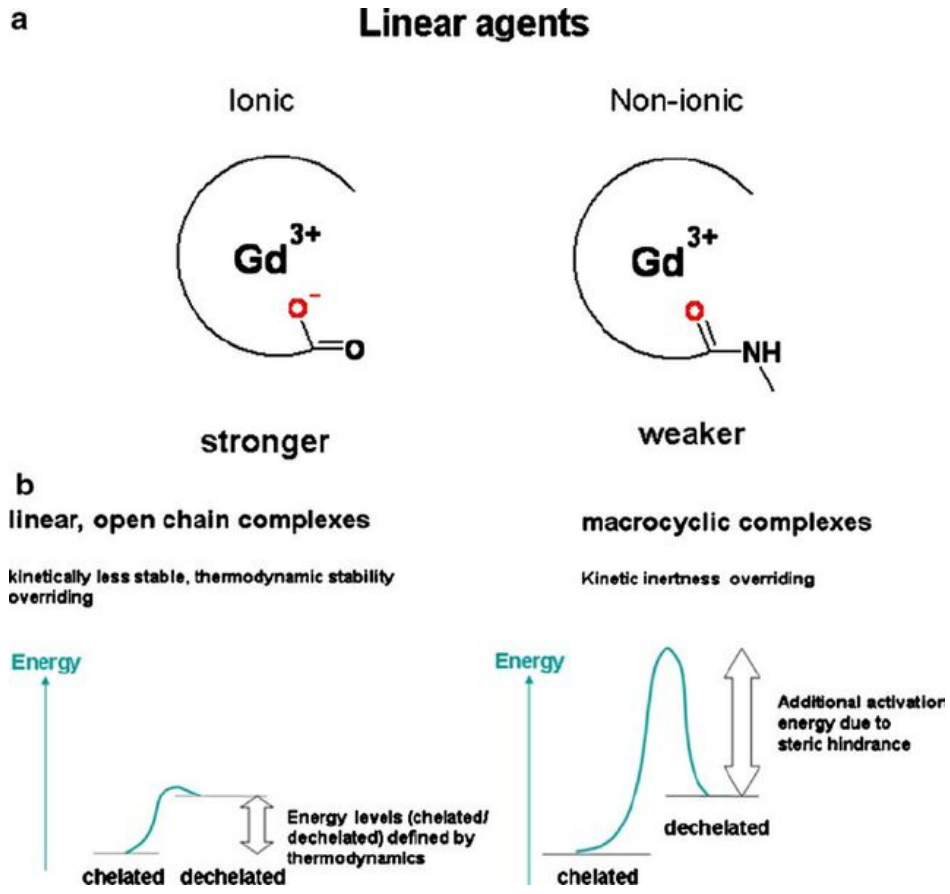

Figure 21: Differences in stability/ inertness of gadolinium- containing contrast agents. The differences between non-ionic and ionic linear agents (a) and between linear and macrocyclic agents (b) are depicted.

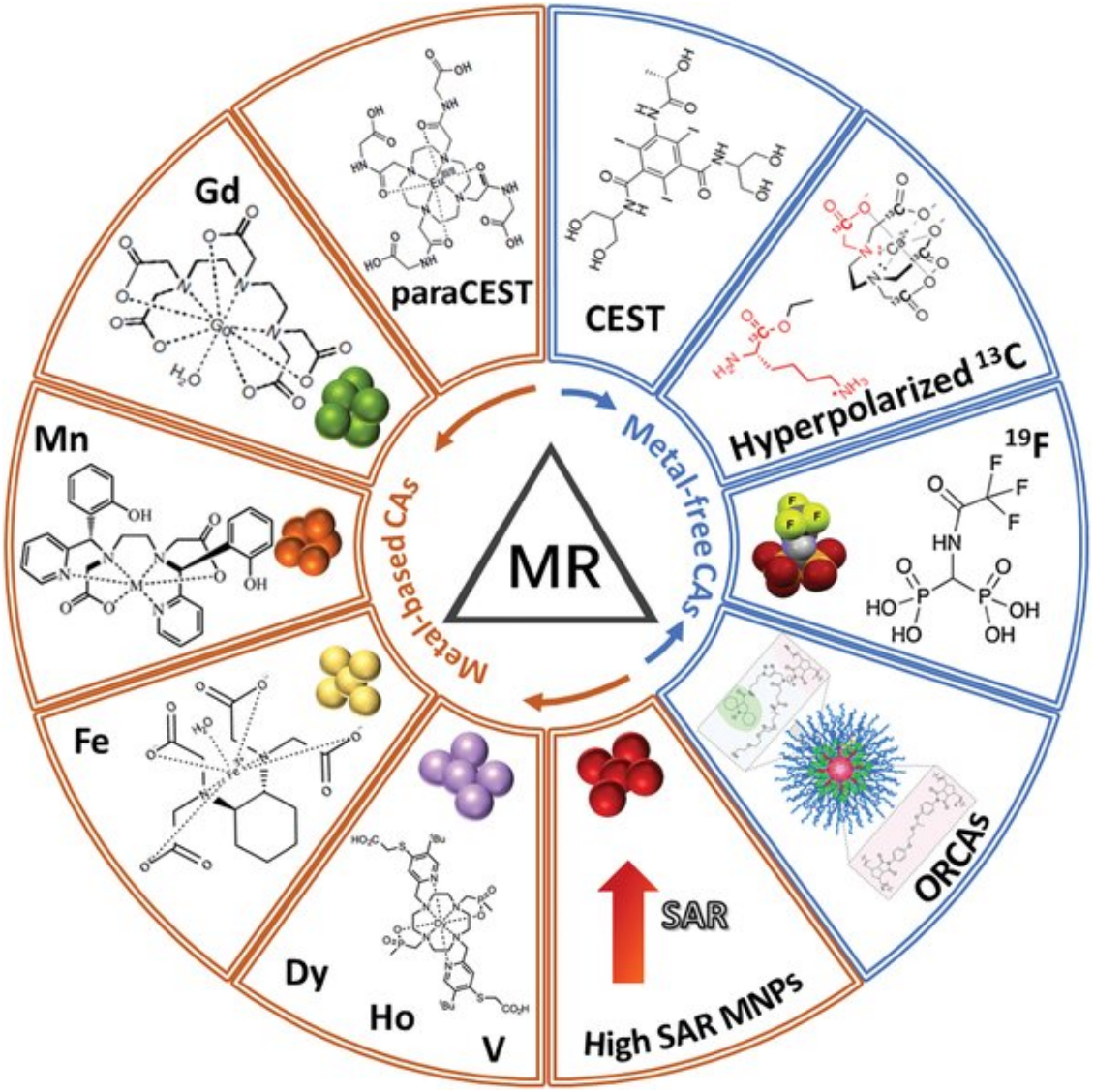

Figure 22: Schematic illustration of the most widely studied MRI contrast agents. Chemical-Exchange Saturation Transfer (CEST), American Chemical Society.

General: waider safety, vascular distribution, elimination by glomerular filtration

In example Gadoteridolo, gadopentenic acid, gadoteric acid, gadiodiamide

Use: neuroradiology, vascular systems, muskle skeletric apparatus, abdominal pelvis

Size

Organo specidifc: heaptic in example gadobenic acid, epatobiliar distribution

This make possible a double stydy: fisrt dynamic and then static (basal, arterious, venous, tardive).

GD- DTPA, GD- DOTA,GD-DTPA-BMA,GD-HP-DO3A,GD-BOPTA,GD-BT-DO3A

Ferrum oxide derivates: magnetic nucleus cristalline insoluble o magnetite (Fe3O4) or maghemite (γ-Fe2O3).

The nucleo diameter is about > 50 nm, for SPIO (small particles of iron oxide), instead molecule with smaller dimater are named USPIO (Ultrasmall-SPIO).

Le SPIO are electively capted by the sistem reticolo-endotelial bu also by ma anche da bone marrow and spleen.

New field of investigation for the USPIO: inflamation study and SNC cancer (fagocitic activity of the granulose cells and reaction vs transplanted organs (infiltration by macrophages).

Reticolo endotelial: superparamagnetic (ferrum oxide) that are captured by this cells.
Ferucarbotran
Linfonodal capture: USPIO
Gastrointestinal: positive (Increase T1 acido gadopentetico sale di dimeglumina and negative reduce T2 Ferumoxil).

BLOOD POOL – intravascualr, for angio RM, Long permanence in to the blood discticts (are used molecule with high dimension and high protein bind).

SIDE EFFECTS: less frequent then vs iodate
This can be due to the less dosage used for single RM procedure (about 15 ml vs 110 ML for a TC)
Lower incidence of analphilactic reaction
It is possible to use Gadolinium in patient with allergy to iodate.

NIH NLM
Nephrogenic Systemic Fibrosis
Younus M. Shamam; Orlando De Jesus.
August 23, 2023.
"Nephrogenic systemic fibrosis NSF is a progressive multiorgan fibrosing condition mainly caused by patients' exposure to gadolinium-based contrast agents used in magnetic resonance imaging. Nephrogenic systemic fibrosis NSF is a rare disease associated with the use of GBCAs connected to impaired kidney function. The linear molecules are less stable and provide a weaker link to the gadolinium ion; thus, they are considered high-risk agents."

Indication for CONTRAST AGENT
MRI: examples
Tumor detection and charcterization location, size,vascularity vascular studies,malformations, aneurysm, arterial or venous disease
inflamations and infections,abscesses
CNS imaging, tumors, SM,spinal cord abnormalities
Liver, renal imaging
GI studies
Cardiac imaging IMA, tumors

PET: poistron emission tomography, based on the phenomena of annichilation positron -electron and related emission.

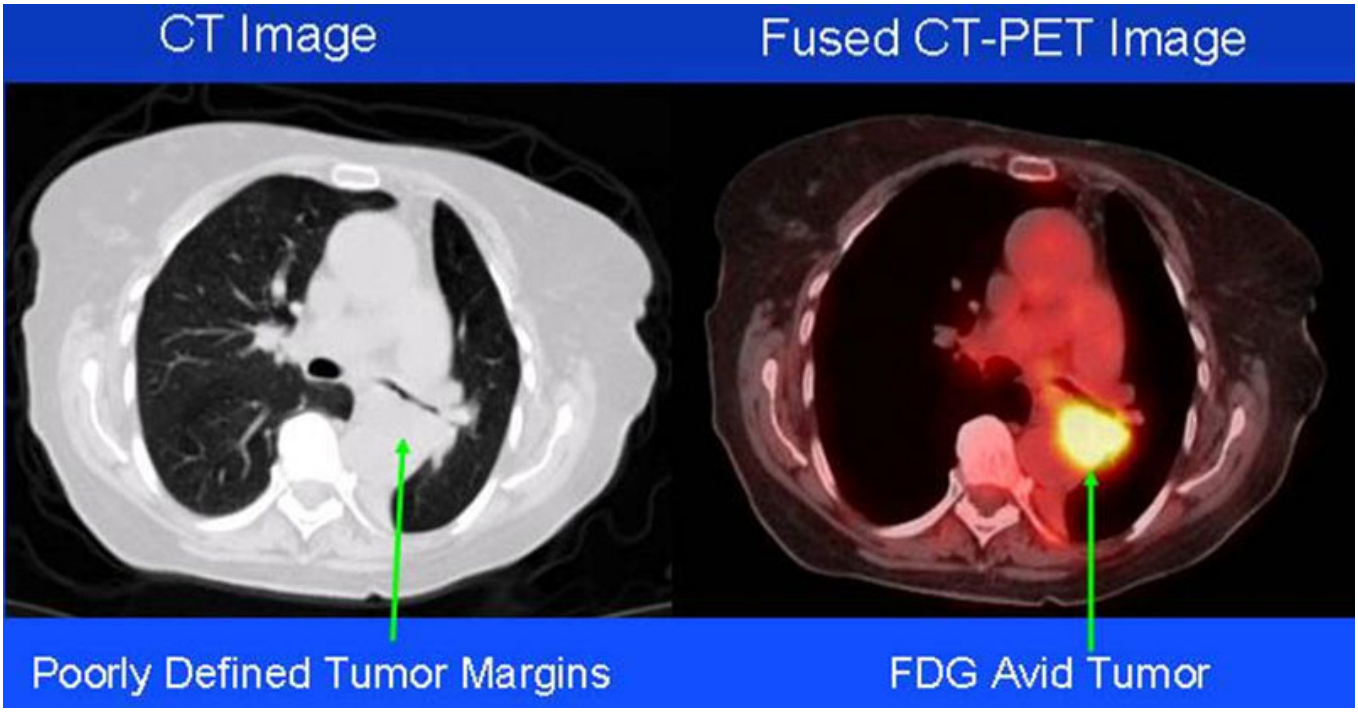

Figure 23: Fused CT-PET scans more clearly show tumors and are therefore often used to diagnose and monitor the growth of cancerous tumors.

High efficiency and resolution (about 3-4 mm)
Are used molecule treaced with radionuclides that in their decay and emitt positron beta +.

They are sintetized from precursor: the radioisotope is linked to the molecule with a covalent link.

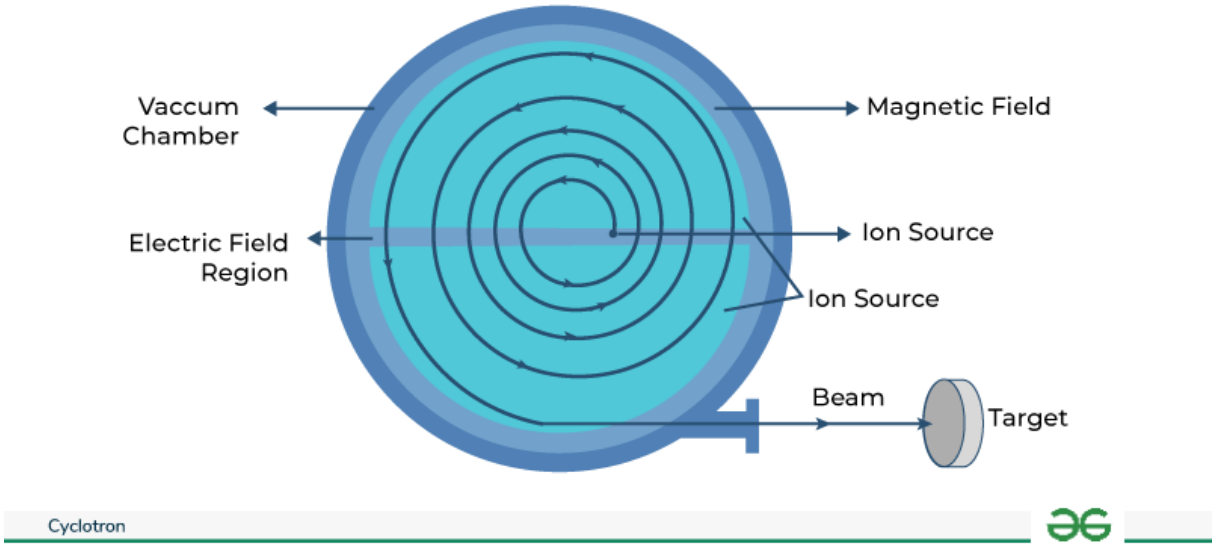

Figure 24: Above figure shows phenomenon of the ion cyclotron resonance.

Radio drugs used:
depends on the methabolic process to be investigated.
PERFUSIONAL NH3 treaced with 13 N (cerebral and miocardic)
Water treaced with 15 0 cerebral perfusion
Metabolic: 18FDG (MIOCARDIC ischemia, CEREBRAL PD, ALZHEIMER, PARTIAL EPILEPSY, TISSUE
In example neoplasia.
RECEPTORIAL: neoplasia, sovraexpression

Ecothomography: first generation, second generation
air microbubles or of inertic gas, stabilized in solution trought lipid or proteic envelope biodegradable.
Microbubbles coated whit fibrolipids, containing gas: esafluorure of sulfur, size less then red blood cells.
(less then 7 micrometers). They are mimic of the RBC behaviour into the vases.
Ev Subministrated. The enhancement can be used for all the cardiovascular system.
Used for echocardiography, doppler of great vases and microcircle, intracranial vases
Epatocarcinoma, various abdominal trauma,spleen lesion, primitive and metastatic lesion in cancer like breast, prostate, renal, muscle, in AR and other conditions.

The duration time: 2-10 minutes.This products not diffuse into the interstitium, they remain into the vascular system since the esalation trought the pulmonary system.
The diameter of the particle must to be lowe then the US wave and to make possible to pass trought the capillar filter (pulmunary and periferic).
This molecule aer atoxic.

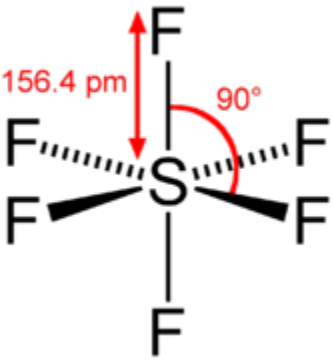

Figure 25: Sulfur Esafluorure.

This reflect ultrasonographic sound, and make the blood more ecogenic then other tissue.
They remain into the blood circle for about 8-9 minutes.
EV subministration with lower level of side effects, eliminarion thrught respiratory breathinngs.
Used for study of the heart, vessels, liver lesions and other.

Thi molecule are classified of first (nude microbubbles, very instable) second (rigid shel of galattose or albumine to increase stability) and third generation. (lipidic shell to increase stability or based on the lower solubility in liquid of perfluorocarbons or SF6).

They can amplify the echoes of ultrasound
Contraindications: IMA, HF acute or chronic and coronary disease, pregnancy and breastfeeding.

TC and RM provide anatomical and morphological-strctural information
TC morpho structural images very detailed
RM: anatomical morpho functional study, blodd flux study, high resolution
The emission tecqnique (SPECT, PET) provide also functional and metabolic data
PET: isotopes used 18FDG, 11C,15 O,13N
Gamma camera SPECT: 99m TC, In111, I123, Tl 201, Ga67

DECAY: GA68 68 minutes, C 11 20 minutes N13 10 minutes
I131 = 8, 02 days, I 123 = 13,2 h
F18 110 minutes
M Tc99 = 6,02 h
111in = 67 h
Tl 201 = 3,04 days

Radio drugs and radiodiagnostics: diagnostis and therapy (direct tissue damage) 223RA,166LU,90Y, 131I, 188 RE

radiodrug: a drug that when resdy to use include on eor more radionuclide for healthcare purpose.
Radioisotope: gamma emittent: I 123, Tc 99
Beta + emmittent positron: 11C,18F,68 GA, 13N

Radiodrugs: ready to use or by generator (eluition) or KIT inactive (the utilizer must to treace- marking the substantia)

Direct use, or to mark other molecule or to mark cells
RADIONUCLIDE: simbol and mass number es 111In, chemical form (NAI), radioactivity.
Radioactivity: total in BQ or multiple or in Ci some times.,
Specific activity = radioactivity/ mass
In example Mbq/ nmol
Radioactive Concentration: Mbq/ ml
Volume total
T1/2 = physic, biologic, effective

GENERATOR
68GE ------ produce 68 GALLIUM
99MO ----produce 99Mtc

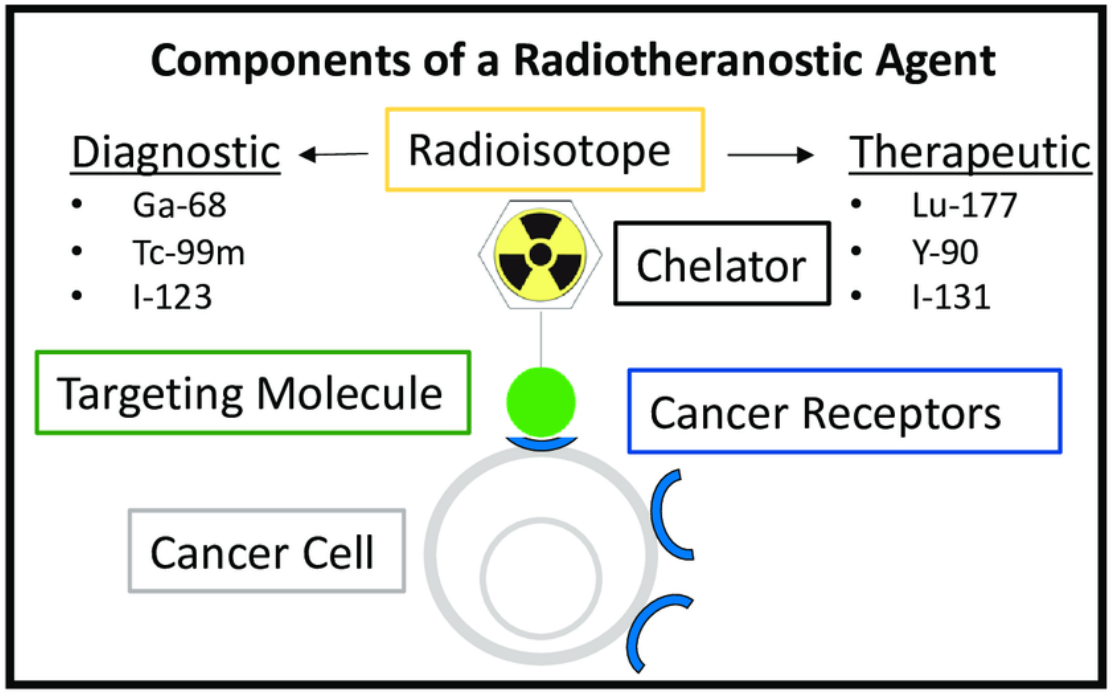

Figure 26: Components of a radiotheranostic, showing the same targeting molecule being used for either diagnostic or therapeutic applications depending on the radioisotope.

Radio drugs: molecule treaced with radioactive nuclide that have biological activity inside the body.
The emitt gamma radiation but in some casese also beta - Some times the radionuclide is used as salt (99mTc pertecnetate or 67 Gallium citrate), other times the radionuclide is linked with chemical molecule with different biological properties

that make possible after subministration the distributionto the various organs and determinate pattern of elimination trought the extretory routes.

Way of subministration: EV, oral, intradermic, subcutaneous, inalation, endocavity, local in situ (only for therapy).
The pharmaceutical form can be: solution (131I), suspension, aereosol, gas (XE 133), gas in solution,
capsules(131I).

First used I131 iodure T1/2 = 8 days about, but because high energy fotone emission was replaced
With other products with shorted t1/2 and better profile of emission.
Tc with t1/2= 6 hours and it is avaiable form the generator 99 Molibden /99m tc(trought an eluition procedure).
Molibdeno 99 show an t1/2 more long useful to make possible to be produced at distance from the place of use.
Related SPECT this treacer is the mos used.
I131 is used today for the folow up of the tiroid carcinoma.

Other radionuclide used in nuclear medicine:
67 Gallium T1/2 = 3,261 days
111indio t1/2 = 2,83 days
123 I t!/2= 13 hour ioflupane cerebral scintigraphy
(before is given to the patient potassium perclorate to protect thyroid)

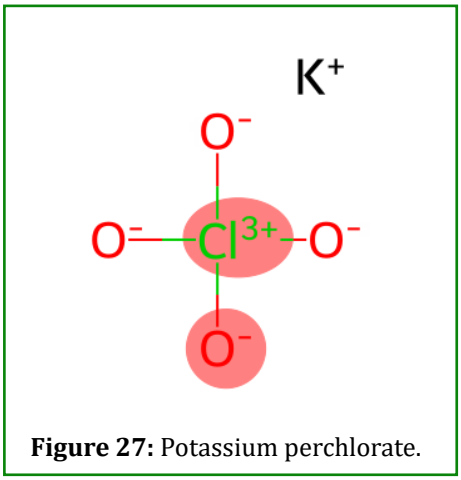

Figure 27: Potassium perchlorate.

This procedure make possible to differenciate in some movement disorder the lesion of the basal nuclei or due to other reason.

Radiodrugs treaced with Tecnetium m 99 are prepared in hot chamber in radiopharmacy labs using
Liofilized moltidose bottle.
Other radiodrugs treaced with other radionuclide are provided ready for use.

FIRST GENERATION:
perfusion agent ; small coordination complex (MW< 2000) they arrive into the hospital ready to use. (also from Generator)
In example 131I, 99Mtco4-,201 Tl +,I123 derivates
SECOND GENERATION: introduced first without know the chemica structure
99m TC macro albumin microsfphere, 99Mtc -DTPA, DMSA(renal treacer), 111In monoclonals

THIRD GENERATION
Projected based on their chemical property ; it is clear the biodistribution and biological pattern 99mTc HMPAO(cerebral perfusion agent), 99Tmc MAG3 (renal and urologic perfusion agent), 99mTc ECD (cerebral SPECT)

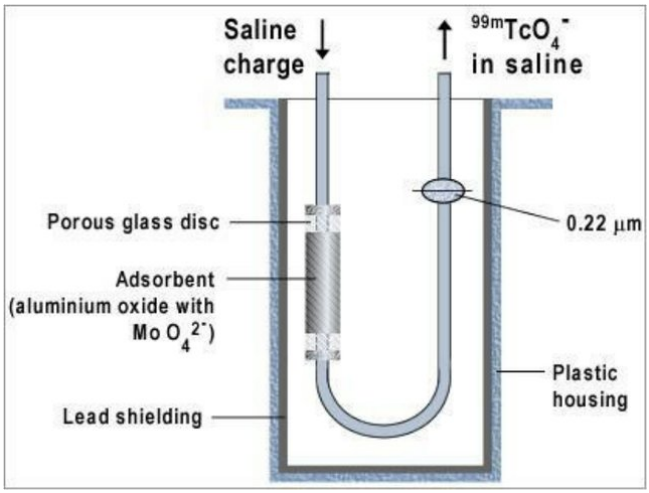

Figure 28: Typical components of a technetium generator. The molybdenum oxide is loaded on the alumina column by the manufacturer. The molybdenum decays to technetium and the resulting technetium oxide can be washed off the column using a salt solution. The process can be repeated for up to two weeks, by which time the molybdenum activity will be about 3 % of its original value.

Other example
123I
123 I MIBIG
131I tiroid diagnostic and therapy of tiroid cancer, renography and total body
131I MIBIG
F18 TRACER
68 GALLIUM TODA PEPTIDE
11 COLINA
18F COLINA
67 GALLIO CITRATE flogosys limphoma, positive indicators of neoplasia

99Mtc Scintigraphy bone, liver, renal,cerebral
99 m TC DMSA
99Mtc DTPA dynamic renal scintigrafy, esofageal transit, gastric emptyng
99m TC ECD neurology passive diffusion, enzimatic reaction
99mTC HMPAO (neurology, LEUKOCITE-infections) passive diffusion
99m TC MAG3 nephrology
99m TC pertecnetarte titoid, salivar gland
99m TC sestamibi paratiroids, miocardial perfusion
99m TC technegas
99mTc MIBI miocardial persusione agent interaction with membrane electrostatic gradient
99mTc tetrofosmin cardiology interaction with membrane electrostatic gradient
99Tc -Sestamibi -miocardial perfusion agent
99mTc MAG3 renal perfusion agent
99 m Tc dimercaptosuccinate static renal scintigraphy
99m Tc albumin aggregate pulmunary perfusion, liver cancer perfusion fleboscintigraphy
99m Tc difosfonate skeleton
99m Tc fitate liver scintigraphy
123I-BETA-FP-CIT neurology link with D2 rec.
123I ippurane dynamic renal scintigraphy, plasmatic renal flux
123I ioflupane receptorial cerebral scintigraphy
131I metilnorcholesterol surrenal cortex
111in -octreotide oncology somatostatin receptors interaction
111I ossina+ authologus leukocite infections
111I mabs immunoscintigraphy
111I pentreotide body scintigraphy – somatostatin rec.
201 Tallium miocardial scintigraphy, positive indicator of neoplasia

PET diagnostic AGENTS:
18FDG, glucose analogue, involved in glucide metabolism ortopedy oncology,neurology, cardiology, ND fever
It is accumulated by encefalus because glucose is the main energetic substrate, in neoplastic cells and sinve in Vital miocardic tissue.(this last cells use fatty acid for energetic need).
11C COLINA oncology metabolism turnover cell membrane
18F COLINA oncology metabolism turnover cell membrane
11C METIONINA oncology proteic metabolism and AA transport
11c-FLUMAZENIL neurology, interaction whit BDZ rec
18F DOPA onco, neurology, pediatry DOPAminergic metabolism
13NH3 cardiology cardiac perfusion
15 H20 neurology, oncology blood flux
68 GA DOTA peptidi DOTATOC, DOTANOC, DOTATATE oncology somatostatin rec
11 C ACETATE oncology,cardiology energetic metabolism and lipidic syntesis
18F FLT oncology TK-1 ACTIVITY and DNA SINTESIS
18 F NAF oncology ortopedy BONE metabolism
18F FMISO,FAZA, EF3 and 5 oncology tumor ipoxia
64 cu ATSM oncology tumor ipoxia
11C-PIB neurology amyloid plaque
18F FLUTEMETANOL, FLORBETABEN, FLORBETAPIR neurology amyloid plaque
82 RU – CLORURO cardiology K -mimetic
2+Rb cardiology K ION analogue

Gammacamera: acquisition static, total body, dynamic Planar or 2D, 3D Tomographic

Radionuclide for THERAPY
131I (Ibritumumab for NHL)
90Y (ibritumomab- tiuxetan for NHL)
188Re some cancer (preclinical study)
177Lu prostate cancer and neuroendocrine tumors
89 Sr- strontium body metastase
64 Cu- copper prostate, glioblastoma, melanoma, breast cancers
153 Sm osteoblastic metastase

Decay: es mo99- 99Mtc -Ru-99
99Mo ---------- t1/2 = 66 h----------99mTc--- ------t1/2 -- 6 h ----99Tc --- t1/2 -------2,1 x 10 ex 5 year Ru99

Measure unit

Units for radiological measurements in the SI and radiological systems

Measurement	Unit and symbol (SI)	Unit and symbol (Radiological system)	Correspondence
Activity	becquerel - Bq	curio - Ci	1 Ci = 3.7 x 10^{10} Bq
Absorbed dose	gray - Gy	rad - rad *or* rd	1 rad = 10^{2} Gy
Corresponding dose	sievert - Sv	rem - rem	1 rem = 10^{-2} Sv

Figure 29: Units for radiological measurements in the SI and radiological system.

x-ray roentgen (R) The unit of exposure. One roentgen equals the amount of x or gamma radiation required to produce ions carrying a charge of 1 electrostatic unit (esu) per cubic centimeter (2.58 × 10− 4 coulomb per kg) of dry air under standard conditions. The SI unit for radioactivity, becquerel (Bq), 1896. The curie (Ci) unit was created in 1910 by the International Congress of Radiology to measure radioactivity. In 1975, the becquerel replaced the curie as the official radiation unit in the International System of Units (SI) where 1 Bq = 1 nuclear decay/second. The relationship: 1 Ci = 37 GBq (giga becquerels) MRI -The field strength of the magnet is measured in teslas – and while the majority of

systems operate at 1.5 T, commercial systems are available between 0.2 and 7 T. Whole-body MRI systems for research applications operate in e.g. 9.4T, 10.5T, 11.7T. Even higher field whole-body MRI systems e.g. 14 T and beyond are in conceptual proposal or in engineering design.
PET scanner measures concentration of radioactivity (Bq/mL) as a function of time, producing quantitative 4D images that are stored in PET image files.

PET radiodrugs
18F-FDG oncology, cardiology, neurology
11C- Colina oncology
13N – ammoniac cardiology
18F-dopa oncology, neurology pediatry

Materials and Methods

Whit an observational method some relevant literature is reported involved the topic under analisys.
A classification of the contrast agents used in field: Classic radiology, TC, SPECT, MR, radiodrugs and radiodiagnostics used in nuclear medicine is reported. All is focused for the hospita pharmacist involved in this field. A experimental project is reported to test the possibility to use the lean weight method for dosing
Iodate MDC for TC instead based on body weight. A global concluson is then submitted

Results

From literature
Urol J. 2020 Jun 23;doi: 10.22037/uj.v0i0.5451.
Diagnostic Utility of Lutetium-177 (Lu 177) Prostate-Specific Membrane Antigen (PSMA) Scintigraphy In Prostate Cancer Patients With PSA Rise And Negative Conventional Imaging M. Ali Ghodsirad, et al.

“177Lu-PSMA SPECT scan can help detecting metastatic lesions in more than 1 third of patients with biochemical recurrence and negative conventional investigations, when 68Ga- PSMA PET is not available” [1].

The radiopharmaceutical radium-223 has immunomodulatory IM effects in patients and facilitates anti-programmed death receptor-1 therapy in the murine models of bone metastatic prostate cancer Philip J Saylor, et al.
“In one of the models, combining Ra223 and anti-PD-1 antibody significantly prolonged survival, which correlated with an increased CD8+ T cell infiltration in tumor tissue”[2].

Abdom Radiol (NY). 2024 Apr Prostate-specific membrane antigen-positron emission tomography (PSMA-PET) of prostate cancer: current and emerging applica tions
Shamus Moran et al
“Prostate-specific membrane antigen-positron emission tomography (PSMA-PET) is transforming the management of patients with the prostate cancer. In appropriately selected patients, PSMA-PET offers superior sensitivity and specificity compared to the conventional imaging (computed tomography and bone scintigraphy) as well as choline and fluciclovine PET, with the added benefit of consolidating bone and soft tissue evaluation into an single study”[3].

Review

MRI Gadolinium-Based Contrast Media: Meeting Radiological, Clinical, and Environmental Needs
Martin Bendszus et al: 16 January 2024

“In a recent survey of GBCA use in Europe, clinicians reported that image quality with GBCAs was “good” or “excellent” for 96% of patients, increasing the diagnostic confidence in 96% and resulting in a change in the radiological diagnosis in 74% of cases” [4].

“Considering the chemical structure CS of the chelating molecule, GBCAs can be classified as linear or macrocyclic MC, depending on whether or not they have an open or an enclosing structure, respectively. Depending on their charge, they can be ionic, like the acidic GBCA, or non-ionic, like the chelating agents with amide or alcohol groups. Linear complexes are flexible open chains that do not bind robustly to Gd (III), while macrocyclic GBCAs, with pre-arranged rigid rings, present almost the ideal size to trap the ion, offering a stronger linkage to Gd (III). The development of macrocyclic MC chelates was prompted by the low stability of linear GBCAs. Indeed, Gd (III) dissociates more quickly and easily from linear chelates, leading to higher circulating levels and increased tissue uptake of free Gd (III), which may entail long-term disturbances in multiple organs. Research Studies with fibroblasts and macrophages showed that, following endosomal internalization into living cells, acyclic GBCAs are degraded much more rapidly than macrocyclic MC chelates. The ability of Gd (III) to be retained in body tissues following its detachment from linear GBCAs led the European Medicines Agency to recommend a restriction in their use. Some linear structure contrast agents, namely gadodiamide and gadoversetamide, were suspended. According to the EMA, the use of gadoxetic and gadobenic acid should be restricted to liver MRIs, as they undergo biliary excretion BE, meeting an important diagnostic need; gadopentetic acid should be restricted to intra-articular administration for MRI of the joints, since the dose necessary for this exam is very low. The EMA recommended the use of agents with a macrocyclic molecular structure (like as gadoteric acid,

gadobutrol, gadoteridol), at the lowest dose necessary for diagnosis, and only if this is not possible without resorting to contrast agents"[5].

"The fxPET/MRI system showed image quality within the diagnostic range, registration accuracy below 3 mm and regional 18F-FDG uptake highly correlated with that of the cPET/CT" [6].

"We developed a reliable hybrid system that helps radiologists to determine the optimal contrast dose for CT angiography based on patient-specific parameters" [7].

Original Article

Reduction of Gadolinium-Based Contrast Agents in MRI Using Convolutional Neural Networks and Different Input Protocols
Limited Interchangeability of Synthesized Sequences With Original Full-Dose Images Despite Excellent Quantitative Performance Haase, Robert et al.

"The tested deep learning algorithm for synthesis of artificial T1w full-dose sequences based on images after administration of only 10% of the standard dose of a gadolinium-based contrast agent showed very good quantitative performance. Despite good image quality in all settings, both false-negative (-) and false-positive (+) signals resulted in significantly limited interchangeability of the synthesized sequences with the original full-dose sequences" [8,9].

"The injected CA dose was highly variable, with obese patients receiving a lower dose LD than underweight patients, as a radiologist-driven 'compensation effect'. Diagnostic abdomen CT examinations may be obtained using 0.63 gI/kg of LBW" [10].

"body-weight-adapted contrast injection protocols have proven successful in achieving a more homogeneous enhancement of vascular structures and liver parenchyma in patients.Total body weight (TBW) is not the only relevant body-size-related factor; lean body weight (LBW) and body mass index (BMI) might also be important. Solid organs SO have greater perfusion than adipose tissue ; consequently, using LBW (or the fat-free mass) as the basis for determining the amount of iodine is hypothesised to result in more uniform liver enhancement than using TBW or BMI We found that contrast-enhanced CT values of 40 HU and higher were of diagnostic value when assessed visually. Our data suggest the use of an artificial intelligence AI body composition-based algorithm to determine LBW can reduce interpatient variability in liver enhancement whilst saving contrast media. The automated nature of the algorithm makes real-time personalisation of contrast dosing technically feasible" [11].

"Viscosity of contrast media has only been studied in relation to the issue of contrast-induced nephrotoxicity and has been found to be a significant parameter through its effects on flow within small intrarenal vessels. Nephrotoxicity refers to the disease of the kidneys, caused from a poisonous effect of toxic chemicals and medications. Generally, the contrast media are more viscous and have greater osmolality than blood, plasma, or cerebrospinal fluid. Viscosity and osmolality play a part in the development of contrast reactions CR, such as anaphylactoid reactions and nephrotoxicity as well as contributing to local tissue toxicity when extravasation occurs" [12].

Experimental project hypotesys
In order to verify the possibility to use AI to calculate the contrast agent iodate to be used for TC based not on body weight but on the lean mass and relative cost reduction is needed to test a significative number (about 1000) of Imaging: group A (500) dosing based on body weight and group B (500) based on lean mass.
The same kind of Tc with MDC [13].

In order to verify the goodness of the imaging produced all the images are verified by human radiologist in an blinded way.

To be verified at long time it is necessary to evaluate the efficacy of the diagnostic methods related the clinical need.

If no difference between group A and B i twill be possible to consider this new method to reduce use and the cost of the contrast agent since about 10%.

Discussion

As reported in the field of contrast agent and also in treacers for nuclear medicine a chemical and pharmaceutical approach is fundamental. Aim of this work is to put inside in one publication both contrast agents and nucleare medicine treacers and radiodiagnostics.

Generally this two aspect are reported in separate way. The ADR due by contrast agent must to be take in adequate consideration rerlated the various kind of procedure used (9).

In the literature reproted the new aproach of AI is of interest as innovative approach in the management of some contrast agent (MRI).

Lean mass vs body weight method for dosing of some contrast agent can be also an interesting opportunity in the

management of costs. (13) But it is needed to test a wider group of patient to produce more robust and significative data.

The contribute of AI can be relevant also for this aspetcs.

Conclusion

As conclusioni It is possible to say that the chemical and pharmaceutical implication of this two drug classes require deeply chemical pharmaceutical but also biological and phisiopatological knowledge. This work is produced for the clinical hospital pharmacist or radiopharmacist that work in this field. But it can be of interest also for other healthcare professionals. Not only logistics, but also quality control, radiolaboratory procedure, appropriate use, monitoring of costs and pharmacovigilance are the main duty for this healthcare professional. To consider as a unique discipline contrast agent and radiodrugs it is usefull especially when applied AI principle. It is sure that it is a Nicke discipline for hospital pharmacist, but very interesting.

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