NUCLEAR MEDICINE

Molecular Imaging + Endo-Radiotherapy

Istvan Szilvási
Dept. of Nuclear Medicine
HDF Medical Centre

2017/2018

DEFINITION OF NUCLEAR MEDICINE

Medical applications of unsealed radioisotopes for
Diagnosis – Therapy - Research
„Unsealed": in the functions of the living organism
by iv., sc. injections, rare: per os, inhalation
Participation in organ-tissue-molecular functions!
(Brachytherapy, In vitro laboratory techniques: NOT)
Diagnosis + Therapy of diseases (not only imaging!)

Independent medical specialty (5 yr specialization)

HEVESY GYÖRGY Georg von Hevesy

First use of radioactive isotopes
in biological systems (1924)
Tracer principle: to follow biological functions
small amount, labelled by
radioactive isotopes

„Father of nuclear medicine"
Nobel prize in chemistry, 1943

RADIOISOTOPES IN MEDICINE

Isotope: same number of protons
(bio)chemically the same element!
(e.g. C-11, O-15, I-123-124-125-127-131)
biochemically: no differences!
Proton : neutron ratio! If optimal: stable element !
Unstable nucleus changes: radiations
Two types of isotopes: the same number of protons,
the number of neutrons: either more or less
Production (only arteficial isotopes are used):
plus proton: mainly in cyclotron
plus neutron: in reactor

TYPES OF RADIATION

Plus protons:
- positron emission (positive beta particle)
meets electron : annihilation radiation
2 x 511 keV electromagnetic
- EC (K, L, M...): „avalanche"
characteristic Xray + gamma radiation
- alpha particle (Helium) + gamma radiation

Plus neutrons:
beta particle („electron" from the nucleus)
+ emission of gamma (if slowly, later: metastable „m")

Electromagnetic radiation: imaging (photons detection)
Particle radiation: therapy (energy absorbed, LET)

MOST IMPORTANT ISOTOPES IN NUCLEAR MEDICINE

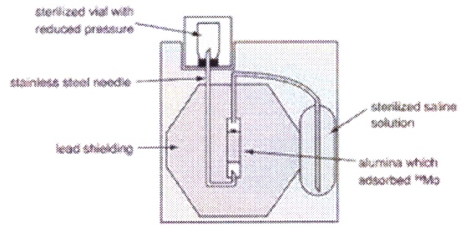
Diagnostic: electromagnetic radiation (photons)
plus neutron:
Tc-99m, I-131, Xe-133, Lu-177... gamma
plus proton:
- Ga-67, In-111, I-123, Tl-201 X-ray + gamma
- C-11, N-13, O-15, F-18, Ga-68, annihilation

Therapeutic: particle (absorption in tissue = dose)
plus neutron: beta: Y-90, I-131, Sm-153, Re-186, Lu-177, ..
plus proton: alpha - At-211, Bi-213, Ra-223, Ac-225, ..

Tc-99m GENERATOR

Mo-99, Al-oxid, elution phys.saline, T1/2: 2.75 d

used for one week, eluation by phys.saline



an example of the structure of a generator on the market

ADVANTAGES OF Tc-99m

(m=metastable: photons not immediately)
in 80 % of SPECT examinations

Physical (for detection)

140 keV: ideal for gamma camera (70-400 keV)
monoenergetic (energy window:±10%: easy for imaging)

Biologic: low radiation dose (high activity: image quality)

"pure" gamma radiation from Mo-99(metastable)
physical half-time 6 hours, optimal for most organ

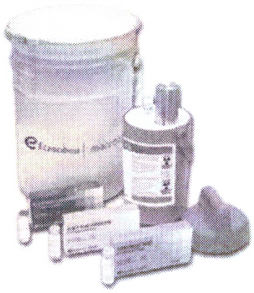
Practical

from Mo-99 generator, elution by phys. saline (!)
stable complexes with many molecules
direct or indirect labelling techniques

Tc-99m GENERATOR + KITS

Simple labelling

Many („cold") molecules



SPECT: Tc-99m When not Tc-99m ?

1. Not possible to label with Tc-99m
   most of the biomolecules (e.g. glucose)
   e.g. glucose (success of PET!)
   (bifuncional chelate eg. DOTA)

2. Too slow is the function (biokinetics)
   e.g. steroid hormon synthesis

RADIOPHARMACEUTICALS

THE FUTURE OF NUCLEAR MEDICINE!

Organ- tissue- molecular-
function-specific labeled molecules
(sometimes the radioisotope alone
(e.g. I-131, Sr-89, Rb-82, Tl-201, Ra-223)

In diagnosis:
Functions: organ, tissue, molecular (quantitativ!)
Tissue characterization – identification

In therapy:
targeted, molecular (selective) endo-radiotherapy
(low dose rate, but high dose: continous radiation)
„targeted",„tailored", „personalized" therapy
„precision medicine": the appropriate
drug, amount, patient, time

THERANOSTICS CONCEPT (essence of nuclear medicine)

Function-specific molecules !

The role of radioisotope:
for detection-imaging or for therapy (or for both)

„Theranostics" concept: the same molecule!

e.g.	Radioiod:	Dg: I- 123 -124 -125
		Th: I-131
	SMS ligands:	Dg: In-111, Tc-99m, Ga-68,
		Th: Y-90, Lu-177, Bi-213, Ac-225
	PSMA ligands:	Dg: Ga-68, Tc-99m, F-18
		Th: Lu-177, Ac-225

Prognostic for herapeutic effect! Even dosimetry!

BIOLOGICAL MECHANISM in living organism

Physical	SLN
Compartment	MUGA blood pool
Diffusion	DTPA, ventilation
Chemical reaction	MDP, PIB
Phagocytosis	colloid spleen
Cells	leucocyte
Excretion	HIDA, EC

MOLECULAR FUNCTIONS:

Active transport	*thyroid (NIS), adrenerg (NET)*
Metabolism-nzymes	*FDG, FET, FCH, FLT,..*
Antigen	*antibody, fragments, peptides, affyb.*
Receptor	*ligands, small molecules*
Beta-amyloid	*florbetapir, florbetaben, flutemetamol*
Others	*hypoxia, angiogenesis, apoptosis..*

FUTURE OF NUCLEAR MEDICINE

FUTURE OF NUCLEAR MEDICINE

More specific radiopharmaceuticals

Molecular imaging and molecular-endoradiotherapy
Molecular functions
Select important targets + molecular probes
Radiocuclide: appropriate radiation, physical half-life
Labeling: efficient, stability, high concentration
Radiochemical and -nuclide purity
Animal studies: similar biodistribution, translation
Human application: Phase-I, -II, clinical trial
Registration
Reimebursement – coverage: cost-effectiveness?

MOLECULAR IMAGING

(All radiopharmaceuticals are molecules), but:
Molecular imaging (and molecular-based therapy):
at the cellular/molecular level
Commodore: the nuclar medicine
(mainly the PET, because: biomolecules label)
Reasons: 1. amount is small: pico-nano-femtomolar
2. many viomolecules can be labeled
Thousends of potential targets and radiopharmacons
but clinical usefulness?
today 40-50 are used in the clinical practice

IMPORTANCE OF MOLECULAR IMAGING

Disease: functional changes
Function before morphology !
Early diagnosis
Targeted diagnosis
Targeted therapy
Personalized/precision medicine

DETECTION (MAINLY): IMAGING

Gamma camera (SPECT)
scintillation crystal, rectangular detectors
static or dynamic aquisitions
spot or whole-body images
planar or SPECT (emission CT: 64-128 projections)
ECG-gated myocardial perfusion
dedicated for organs (cardiac, breast, thyroid)
(new: semiconductors, multipinhole, small animal…)
Positron camera: PET („double-photon ECT")
BGO, GSO, LSO, LYSO,… crystals, semiconductors,
„ring detectors" (small block detectors), today digital
16-28 cm axial FOV (whole-body: 5-6 bed positions)
coincidence detection, 3D data aquisition, time-of-flight

DETECTION: NON-IMAGING

Ex vivo measurements
of biological samples
renal clearance (blood), Schilling test (urine)

Small dedicated instruments
Thyroid uptake test
before radioiodide therapy (dose?)
Intraoperative gamma-probes for localization
sentinel lymph node detection

SPECT

Rotation: steps, continous
circular, elliptic (close to zhe patient!)
64-128 projections (resolution)

Reconstructions:
filtered backprojection or mainly iterative

Corrections:
attenuation, Compton, detector-response (depth)

Slices:
transverse (axial), coronal, sagittal
3 D, MIP, rotating

ADVANTAGES OF PET(vs.SPECT)

double-photon vs. single-photon

1. More sensitive (no collimator!)
2. Spatial resolution is better (anatomic details)
   SPECT: 8 - 10 mm, PET: 4 - 5 mm
   (small animal: 1 mm!!m multipinhole: 2-3 mm)
3. Quantitation is easier. Relative is enough (%, SUV)
   but absolute (mL/min/g, mol/min/g) is possible!
4. **Biomolecules** !!!
   C-11, N-13, O-15, F-18, Ga-68, Sc-44,...
   glucose, tyrosine, thymidine, PSMA, H2O, etc.
   „SLICE OF LIFE"

HYBRID SYSTEMS

Function + Morphology

on the same gantry: „simultaneous" (image fusion?)
Improvement of diagnostic capabilities
1 +1 = 3 !

PET/CT (only hybrid, no PET alone today)

SPECT/CT (the „good" SPECT today is SPECT/CT)
role of CT: localization + attenuation correction
„low dose" ! (not diagnostic CT)

PET/MR
no ionizing radiation (pediatry, serial studies)
soft-tissue contrast (brain, oncology, ?)

PET/MR

Technology (PMTs in magnetic field)!

- Soft-tissue contrast excellent
- No ionizing radiation, dose!
- Duration of the study (all sequences)?
- Clinical indications (both are indicated)?
- Cost-effectiveness?
- Research !

POTENTIAL INDICATIONS

- Pediatric patients
- Follow-up studies (e.g. lymphomas)
- Brain, heart
- Head/neck, pelvic regions
- Functional MR techniques (?)
  - different sequences, STIR, DWI, ADC,..
  - arterial spin labeling ?
  - proton spectroscopy ?
  - diffusion-tensor imaging ? etc.?

NM ADVANTAGES IN DIAGNOSIS

TISSUE CHARACTERIZATION: IDENTIFICATION
What is seen on the CT/MR?

FUNCTIONS!
Organ- Tissue- Cell- Molecular Functions
Quantitative e.g. renal: split, MTT, clearance
thyroid uptake, I-131
heart perfusion score
PET: SUV, MTV, or mol/min/g

NON-INVASIVE
i.v. injection and (small) radiation dose
No toxic effects! Allergic reactions very rare.
Nano-, picomolar amount!

DISADVANTAGES OF NM I.

1. Geometric resolution is limited
   - contrast (target/backgoround) is important
     - like the stars (size?? light!!)
   - „only" the function!
   - technical resolution of the instrument
     - SPECT 8-10 (2-3?) mm, PET 4-5 mm
   - biologic resolution is different
     - hot thyroid nodule vs. large liver mets
2. Anatomy, morphology, details, localization ??
   - SPECT/CT, PET/CT, PET/MR, SPECT/MR?

DISADVANTAGES OF NM II.

3. Radiation dose (batural background 3 mSv/year)
   - Gamma (SPECT) 1- 7 mSv
   - Annihilation (PET) 5-10 mSv
   - EC, conversion electrons (SPECT 15 mSv

Principles of radioprotection of the patient
- Indication!
- Non-ionizing (e.g. US) first!
- ALARA !
  - (only reference levels)

Developments of hardware, software
Gravidity, lactation, small children: RISK-BENEFIT!

DIAGNOSTIC ROLE OF NM IMAGING

Functional imaging
- organ-, cell-, biochemical functions
- tissue characterization
- molecular imaging (at molecular level)

Radiology: morphology
Co-operation
- instrumentation: PET/CT, SPECT/CT
- in education (multimodality)
- in diagnostic algorhythms (changing)

FUNCTIONS

Organs: heart (perfusion, contraction)
lung (perfusion, ventilation)
flow (blood, lymphatic)
kidney (glomerular, tubular, urinary flow)
liver (parenchymal, excretion, biliary flow)
gastrointestinal (motility, excr., absorption)

Cellular: tissue characterization
e.g. antigens, receptors, enzyme expressions

Molecular: biochemical, metabolic processes
e.g. angiogenesis, apoptosis, hypoxia, etc.

Genetic: DNS („nuclear"), mRNS (oligonucleotids)

F-18-FLUORO-DEOXY-GLUCOSE

FDG is the most important molecular imaging radiopharmaceutical

F-18 is the most frequently used PET-nuclide

FDG is the most frequently used PET radiopharmaceutical

Clinical use:	Oncology	85 %
	Neuropsychiatry	5 %
	Cardiology	5 %
	Others	5 %

WHY FDG?

- „Sugar scan"
- Tumors need sugar – energy (Warburg)
  - Only uptake of glucose (hexokinase)
  - F-18-FDG-phosphate intracellular
  - Success of PET is because of FDG !
    - cost-effectiveness in oncology!
      - reimbursement!
    - (however not tumor-specific!)

PROBLEMS OF FDG IN ONCOLOGY

- Not all types of tumors
  e.g. prostate, kidney, mucinous
- Physiological uptake
  brain, urinary tract, intestinal, brown fat
- Not specific! (glucose uptake only)
  Inflammation, sarcoidosis

FDG: GENERAL INDICATIONS IN ONCOLOGY

Tumor – non-tumor	e.g.SPN
Staging	Mets
Restaging	
Therapeutic effectiveness?	interim
Therapy follow-up	Effect?
Recidiv or recurrent tumor ?	CEA, Tg..
Planning radiotherapy	tumor!

FDG INDICATIONS IN ONCOLOGY more and more

- Solitary pulmonary nodule
- Lung cancer (NSCLC)
- Colorectal cancer
- Breast cancer
- Malignant lymphoma
- Melanoma malignum
- Oesophageal cancer
- Thyroid cancer
- Head and neck cancer
- Cervical (uterus) cancer

F-18 RADIOPHARMACEUTICALS OTHERS IN ONCOLOGY

F-18-NaF	bone
F-18-cholin	prostate
F-18-DOPA	neurology, NET
F-18-FET	brain
F-18-FLT	therapy control
F-18-MISO	hypoxia
F-18-RGD	angiogenesis
etc.	

RADIONUCLIDE THERAPY GENERAL CHARACTERISTICS

- Specific (targeted, molecular)
- Effective
- Low dose rate but high dose
- Low side-effects (hematological, renal
- Excellent palliation (but ecen curative)
- Repeatable

THERAPEUTIC APPLICATIONS I.

- Hyperthyreosis: I-131
  (molecular, targeted, individual, personal)
  Grave's disease, toxic adenoma,…
- Thyroid cancer: I-131
  (ablation, then follow-up: serum-Tg)
  Papillar and follicular ca. recidives, mets,
- Bone metastasis: Sm-153- Re-186-phosph.
  Prostate, breast, lung: palliative
  Alpha emitters: Ra-223, high LET, curative

THERAPEUTIC APPLICATIONS II.

- Radioimmunotherapy Lu-177-PSMA, Y-90-anti-CD20 (B-cell lymphoma),,...
- Adrenerg receptor: I-131-MIBG, pheo, neuroblastoma,...
- Neuroendocrine tumors: Y-90-, Lu-177- SMS PeptidReceptorRadioTherapy (PRRT)
- Radiosynovectomy Y-90, Re-186, Er-169 colloids (local, not systemic!)
- Microspheres Y-90, intraarterial, liver, mets
- And....

PERSPECTIVES OF NM molecular!

■ Apotosis	Annexin V,
■ Angiogenesis	VEGF, integrin antibodies
■ Hypoxia	Misonidazol, FMISO
■	
■ Oncogens	F-18 oligonukleotides
■ Genexpressions	Gen therapy:reporter gen HSV-Tk co-expression with F-18-deoxytimidine

etc. !!!!!

THANK YOU