RADIO-GUIDED SURGERY WITH B- EMITTERS

12-04-2017

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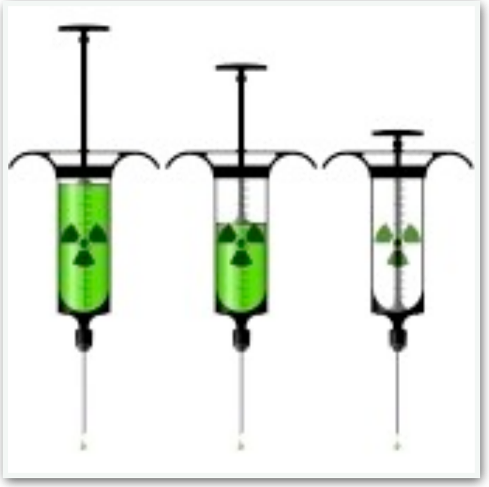
INFN - ROME

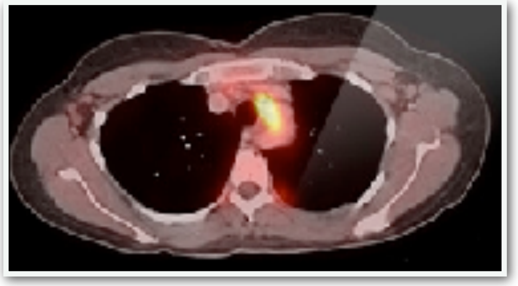
OUTLINE

- Medical applications of nuclear decays
  - Radio-Guided Surgery (RGS)
  - Probes for RGS
- β- radio-tracers
  - Clinical cases of interest
  - Detector development
  - Phantoms' techniques
  - Test on ex-vivo specimens

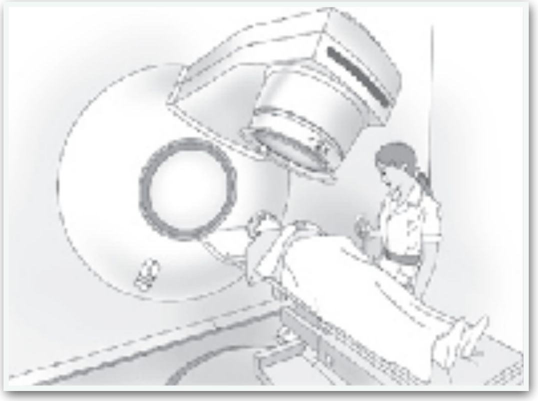
NUCLEAR DECAYS AND MEDICAL APPLICATIONS

- Basic concept: Inject a radioactive material **inside** the patient
  - If the particle escapes the patient
    ➜ Diagnostics
    - Scintigraphy (SPECT),
      Positron Emission Tomography (PET)
    - Low Activity (~MBq/kg)
    - Life time radionuclide: minutes/hours



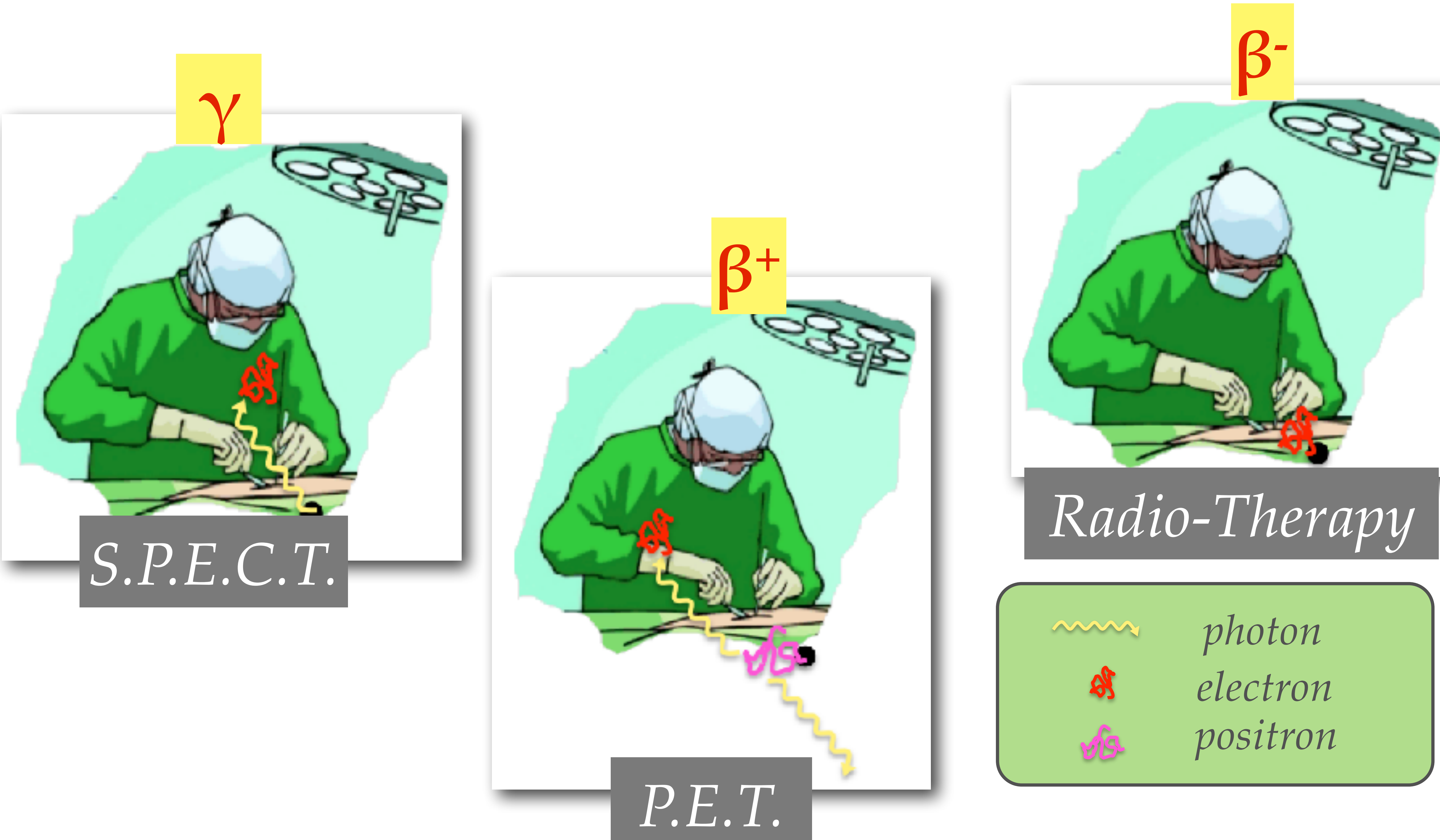


  - If the particle interacts inside the patient
    ➜ Radiotherapy
    - Radio-Metabolic Therapy, Brachytherapy
    - High Activity (10-100MBq/kg)
    - Life time radionuclide: days



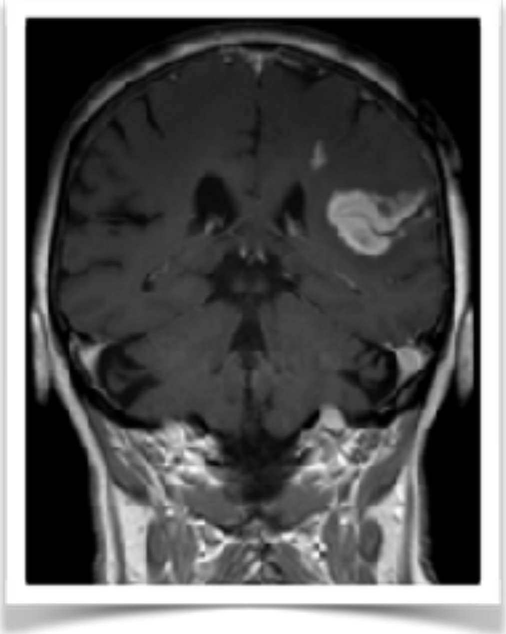
NUCLEAR DECAYS AND MEDICAL APPLICATIONS

➤ Types of decays of interest:



OVERVIEW

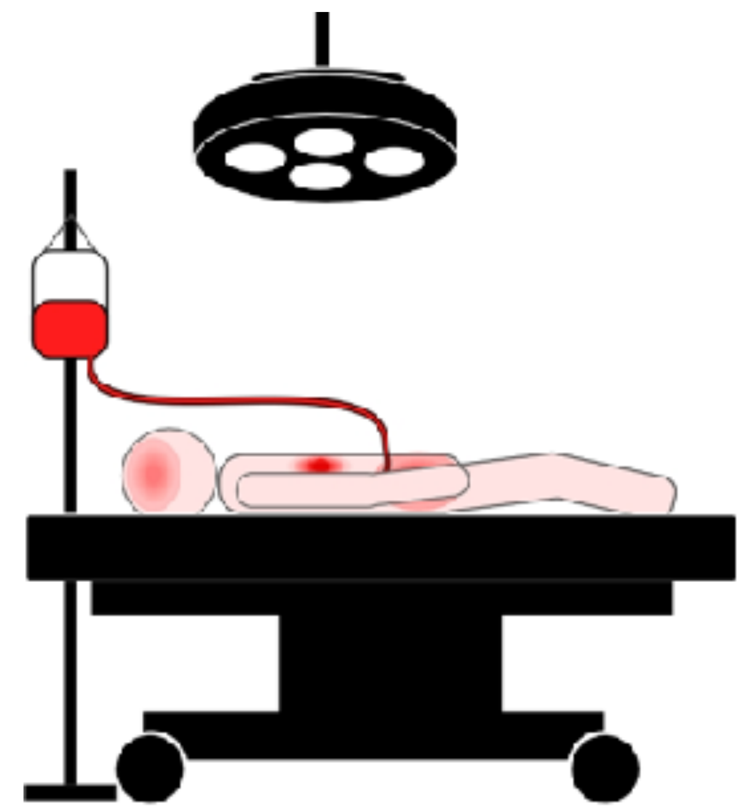
- **Surgery** remains the most frequently technique undertaken in cancer treatment
- **Imaging** techniques *(CT/PET/NMR)* provide very clear and precise images of tumours **before** surgery
  - The identification **during the operation** is far from being trivial
    - E.g. the tumor mass may slightly **change its position** during the surgery, especially after craniotomy since the brain is made of soft tissue



- Necessity to identify the tumour during the operation
  - Neuro-navigation systems, Fluorescence-Guided Surgery
  - RadioGuided surgery

RADIOGUIDED SURGERY

- Radioguided surgery is a technique that helps the surgeon to perform an as **complete** as possible **tumor resection** (mass and remnants)
  - A radio-marked tracer is administered to the patient before surgery



RADIOGUIDED SURGERY

- Radioguided surgery is a technique that helps the surgeon to perform an as **complete** as possible **tumor resection** (mass and remnants)
  - A radio-marked tracer is administered to the patient before surgery
  - The tracer is preferentially uptaken by tumor cells, transforming them in radiations sources
    - Each tumor (signal) requires **its own tracer**
    - There is an uptake of the tracer from the surrounding health tissue
    - The uptake of healthy tissue represents a limitation (noise)

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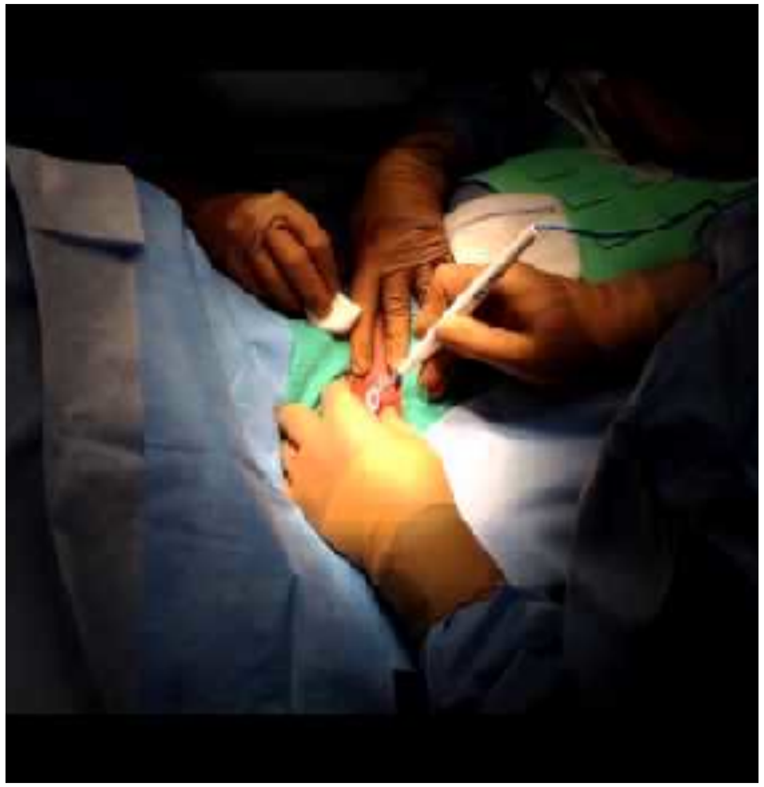
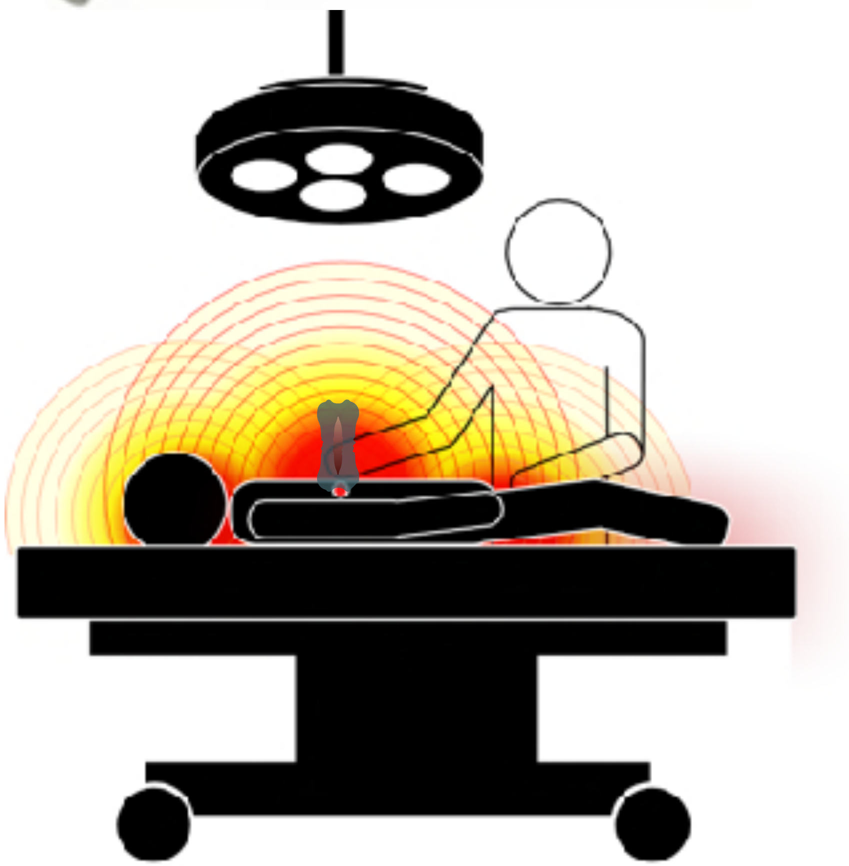


- A specific detector (probe) makes possible to identify in real time the tumor remnants **(0.1 ml)** and to remove them

GAMMA PROBE

Neoprobe model 2300

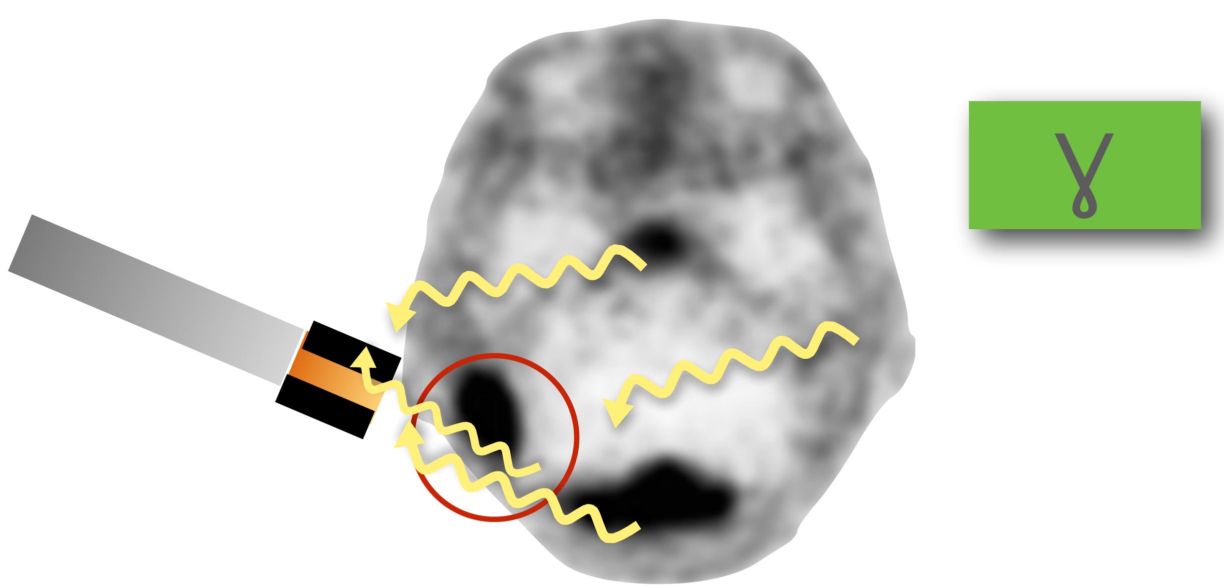


- Commercially available
- γ tracer emitter
  - ^{99m}Tc, $E_\gamma \sim 140$ keV
  - Long range of photons (~1/3 of gammas traverses 8 cm)
- Exposure of medical personnel

Established Technique

GAMMA PROBE

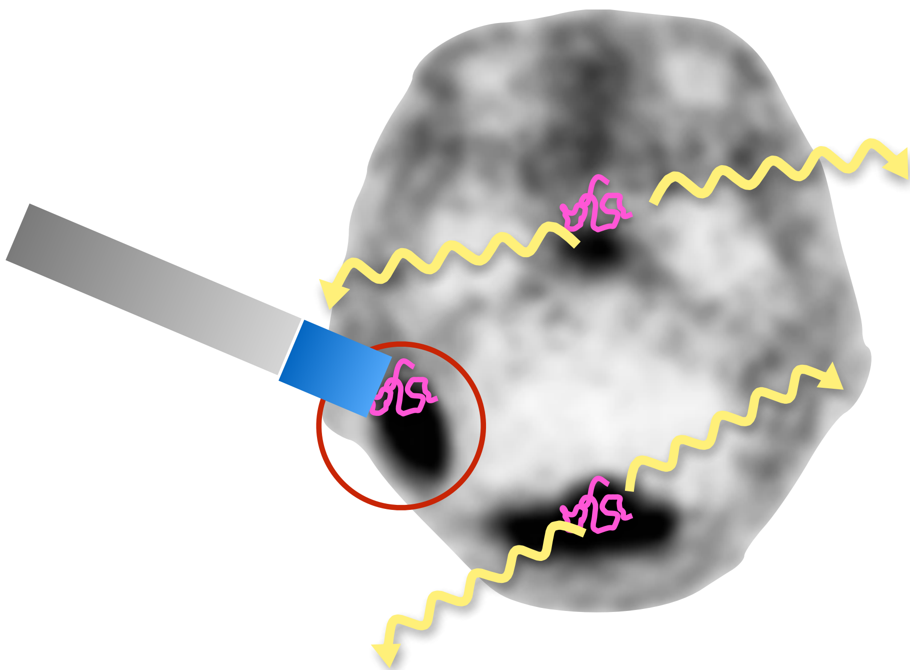
Established Technique



- γ tracer emitter
  - ^{99m}Tc, $E_\gamma \sim 140$ keV
  - Long range of photons (~1/3 of gammas traverses 8 cm)
- Tumor Not tumor Ratio (**TNR**)
  - High background from nearby healthy organs (S/N)
  - Necessity of a shielding
- Applications of interest:
  - Search for **tumor residuals** (colon, parathyroid, …)
  - Full **sentinel-node mapping** (malignant melanoma, breast cancer, …)

β+ PROBE

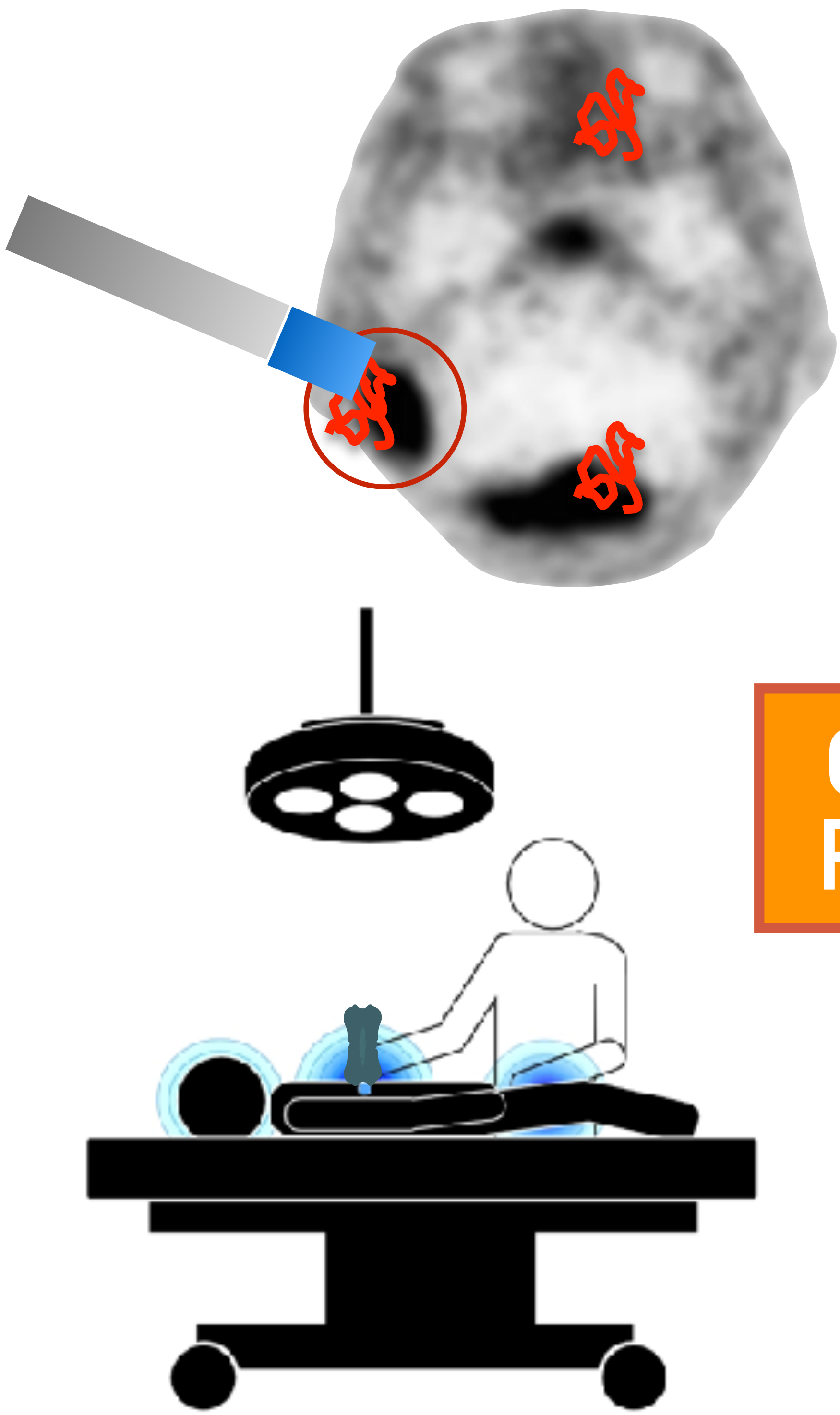
Daghighial et al 1994
Raylman et al 2001
Bonzom et al 2007
Bogalhas et al 2009



- Use of β+ tracers:
- Positive
  - Positrons travel only few mm
  - PET tracers can be used
- Negative
  - Background due **annihilation**
  - Need to subtract **background**
  - Longer time to have a response
  - More encumbering detector

ß⁻ PROBE

E. Solfaroli Camillocci,
***F. Collamati** et al,*
Sci. Repts. 4,4401 (2014)



β^-

Change in Paradigm!

- Lower penetration power (~ 1 cm)
- Avoid the background of γ
  - *Extension to different types of cancer (abdomen, brain, pediatric)*
- Radio-tracer marked with β^-
  - **Need to develop specific radio tracers**
  - ^{90}Y-DOTATOC, E_{max} 2.3 MeV

OUTLINE

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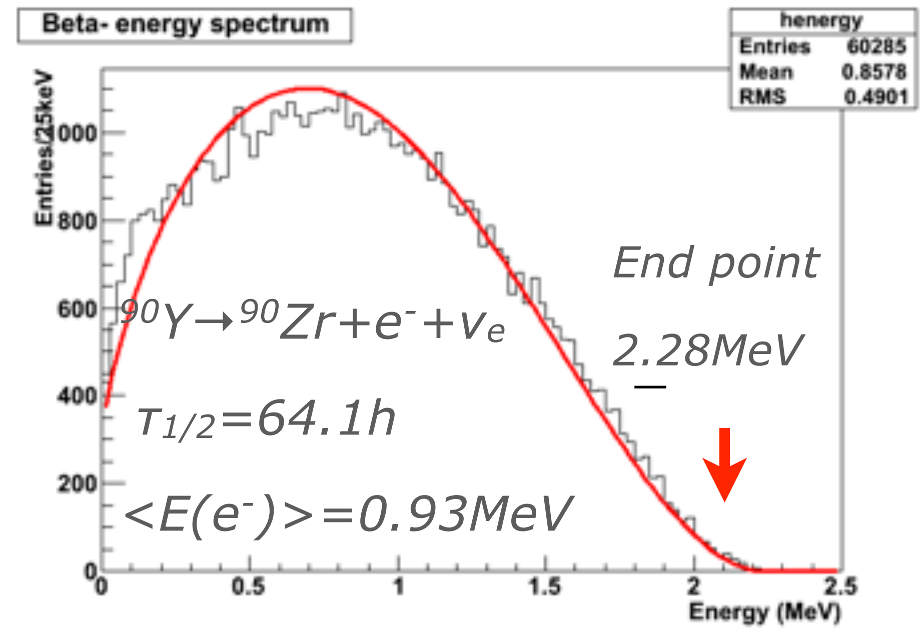
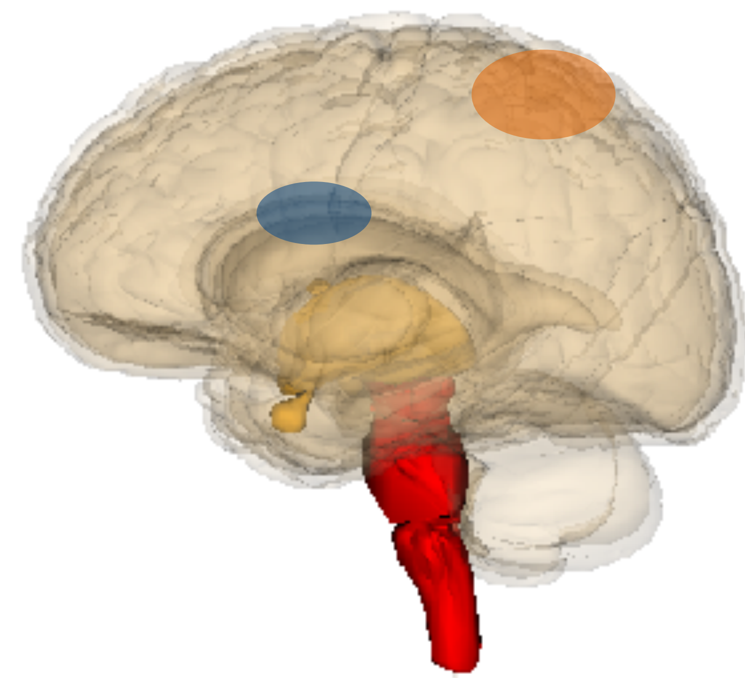
RADIOTRACER UPTAKE

- *Studies on existing radio tracers*
  - ➤ **DOTATOC**: Somatostatin analogue marked with ^{90}**Y** used for radio-metabolic treatment
  - ➤ Clinical cases: **Neuroendocrine tumors** and brain tumors (**Meningiomas** and **Gliomas**)
  - ➤ Neuroendocrine tumors (liver, intestine..)
    Annual incidence 2.5-5 /100.000 people
    5-year survival 17%
  - ➤ Meningiomas
    Annual incidence 3-4 /100.000 people
    Usually benign in nature (90%, 3y survival 86%)
  - ➤ Gliomas
    Annual incidence 6-7 /100.000 people
    Infiltrations are difficult to detect
    High-grade glioma median survival 1 year



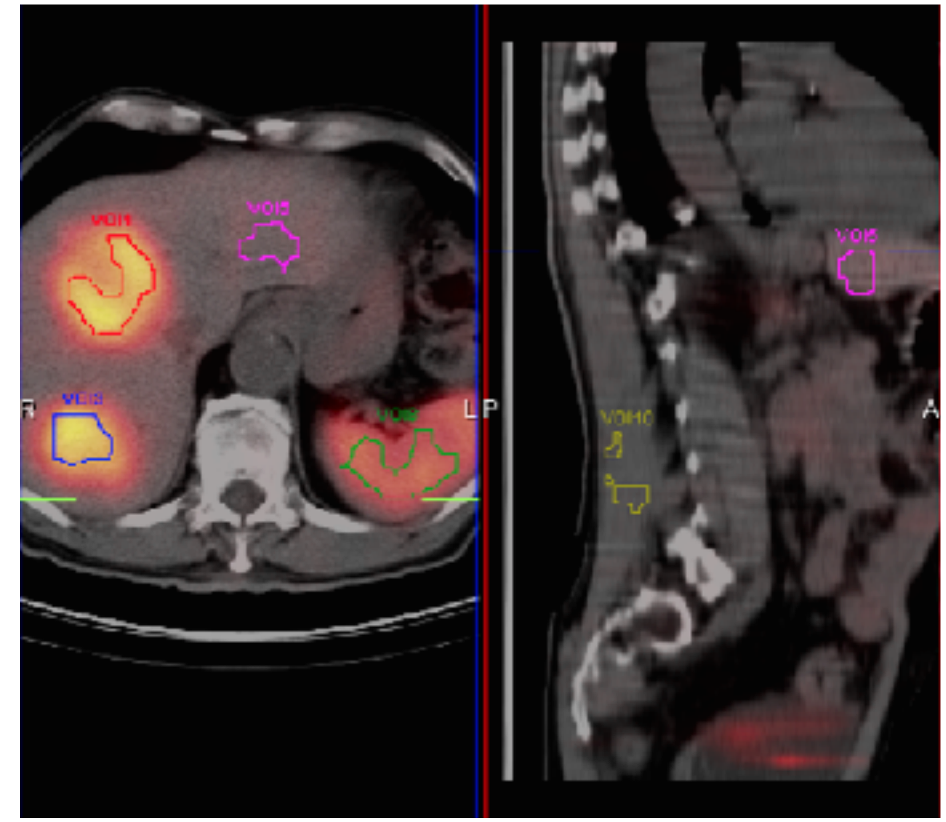


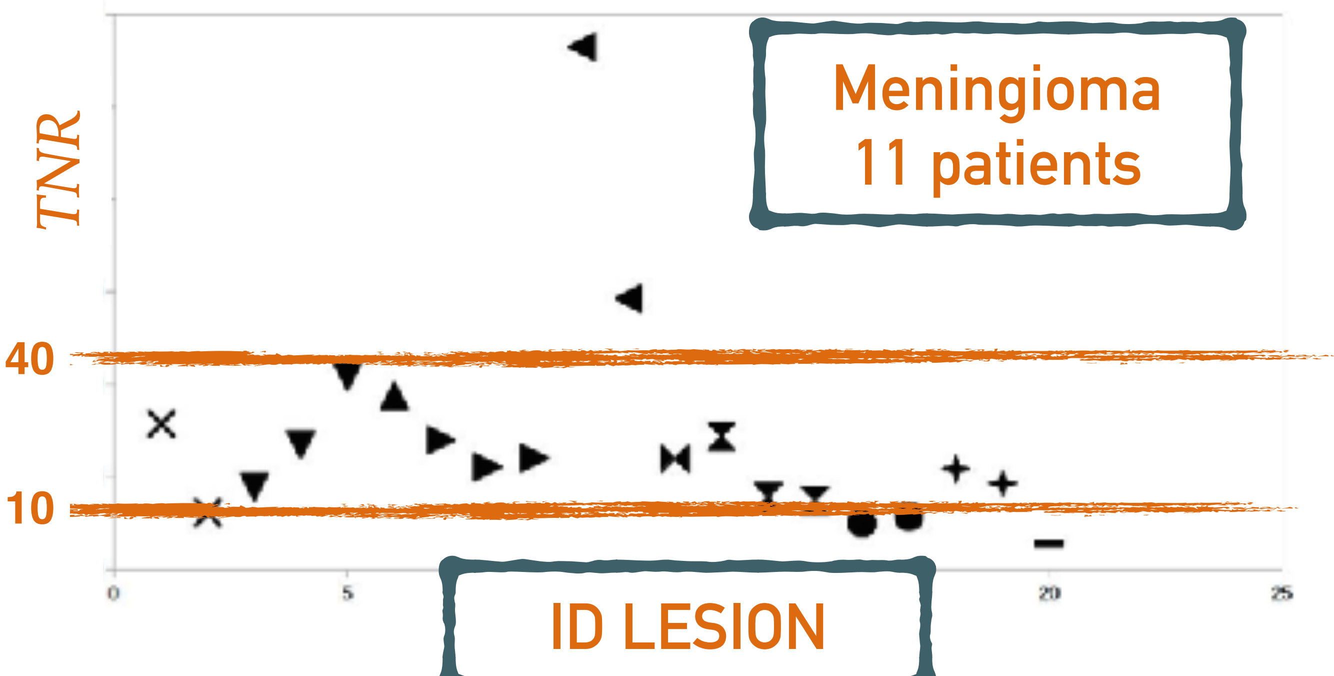
SUV: Standardised Uptake Value

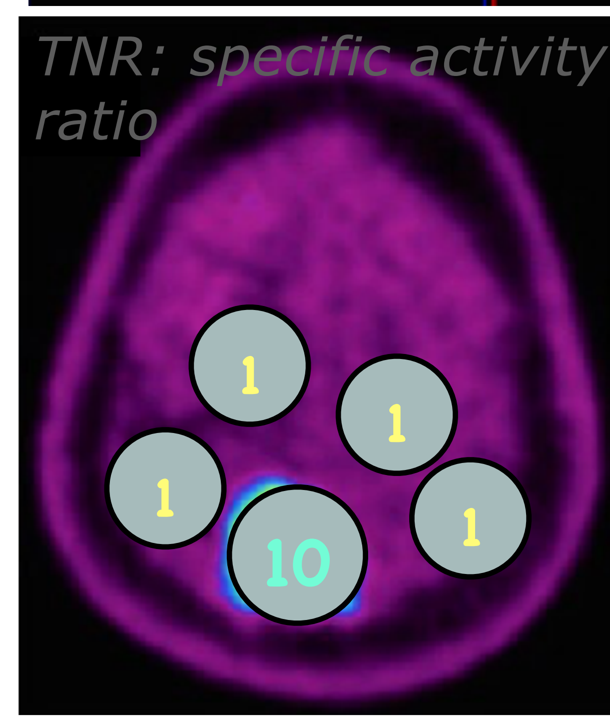
$$SUV = \frac{A_{\text{spec}}}{\frac{A_{\text{inj}}}{W[g]} e^{-\frac{\Delta t}{\tau}}}$$

EXPECTED BACKGROUND

- TNR estimated from
  - PET ^{68}Ga-DOTATOC (brain)
    SPECT ^{177}Lu-DOTATOC (liver)
  - The tracer uptake is independent from the marker
- Background is the result of the uptake from the healthy tissues **near** the lesion



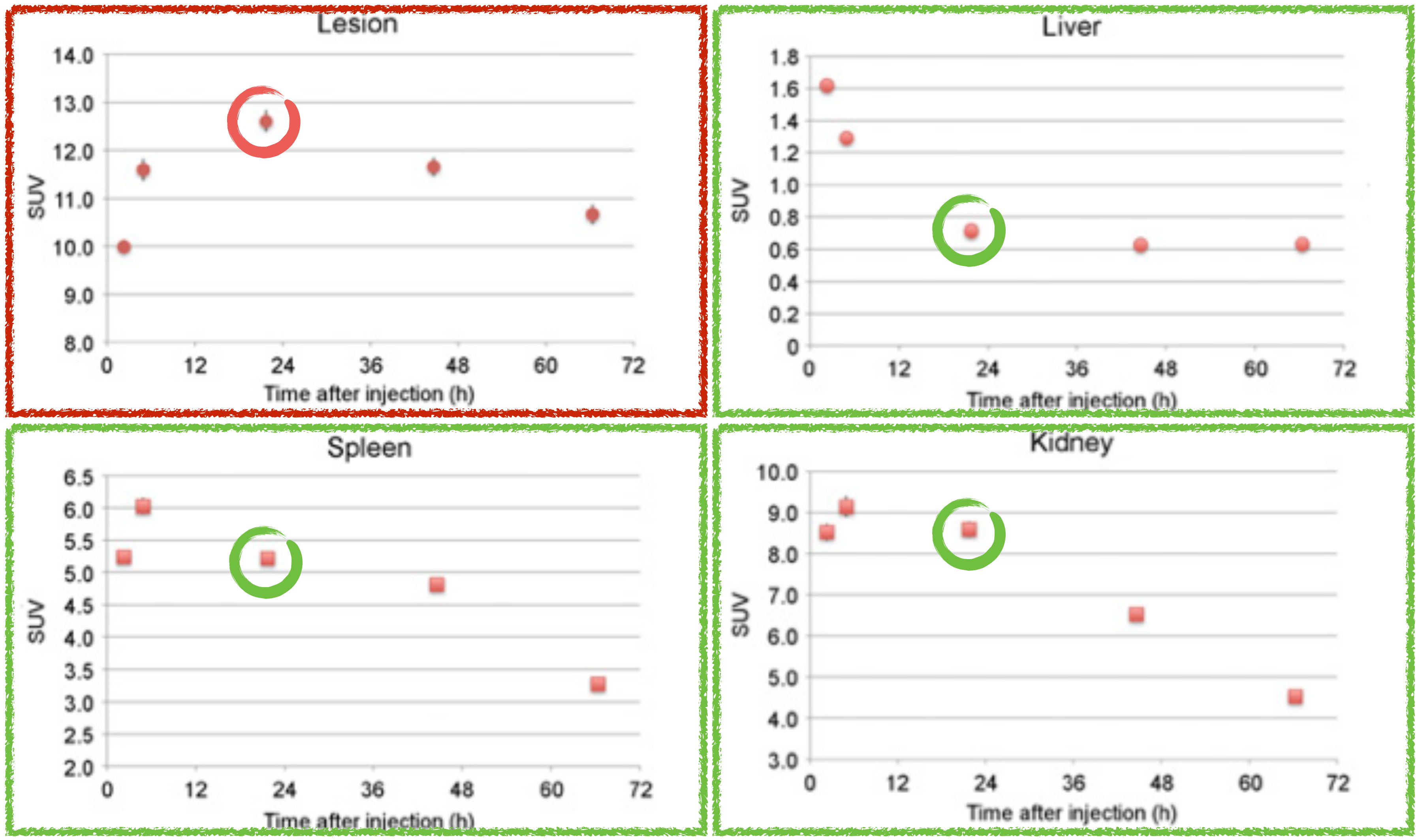




F. Collamati et al, Towards a Radio-guided Surgery with b- Decays: Uptake of a somatostatin analogue (DOTATOC) in Meningioma and High Grade Glioma. J Nucl Med 56 (2015) 3-8

TNR: EVOLUTION IN TIME

➤ Study on the radio-tracer accumulation in tumor and washout from the healthy organs for 72h after injection:



Injected Activity 60MBq/kg
Counts corrected for the ^{177}Lu $\tau_{1/2}$=6.7d

- Best time for RGS ~ 24h after injection
  - Two different mechanisms: accumulation and washout
  - Patient depending behaviour

F. Collamati et al, Time evolution of DOTATOC uptake in Neuroendocrine Tumors in view of a possible application of Radio-guided Surgery with β- Decays. J Nucl Med 2015

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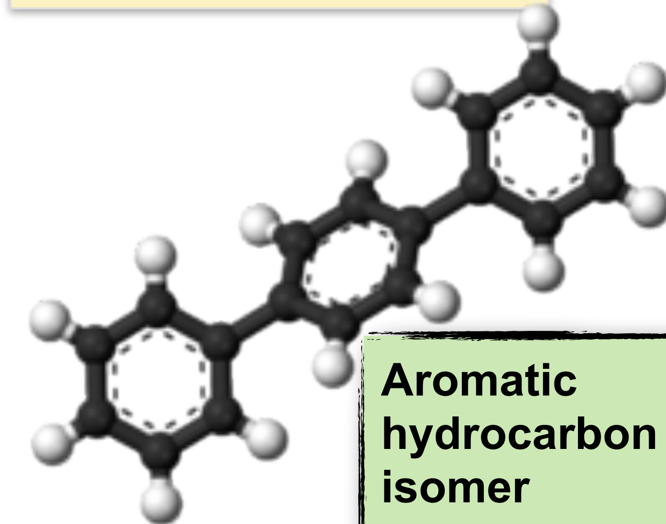
PARA-TERPHENYL

- Project started in *April 2012*
  - Detector developed from the scratch, designed as a single channel counting device (active material coupled with a photo detector)
- Active material choice:
  - Counter device based on **para-terphenyl** doped with 0.1% diphenylbutadiene
  - **Organic scintillator** with crystalline structure
  - High Light Yield
    - $\lambda = 5.03 \pm 0.23$ mm
  - Low sensitivity to photons

S.V.Budakovsky et al., Functional Materials 16, 1 (2009)



Aromatic hydrocarbon isomer

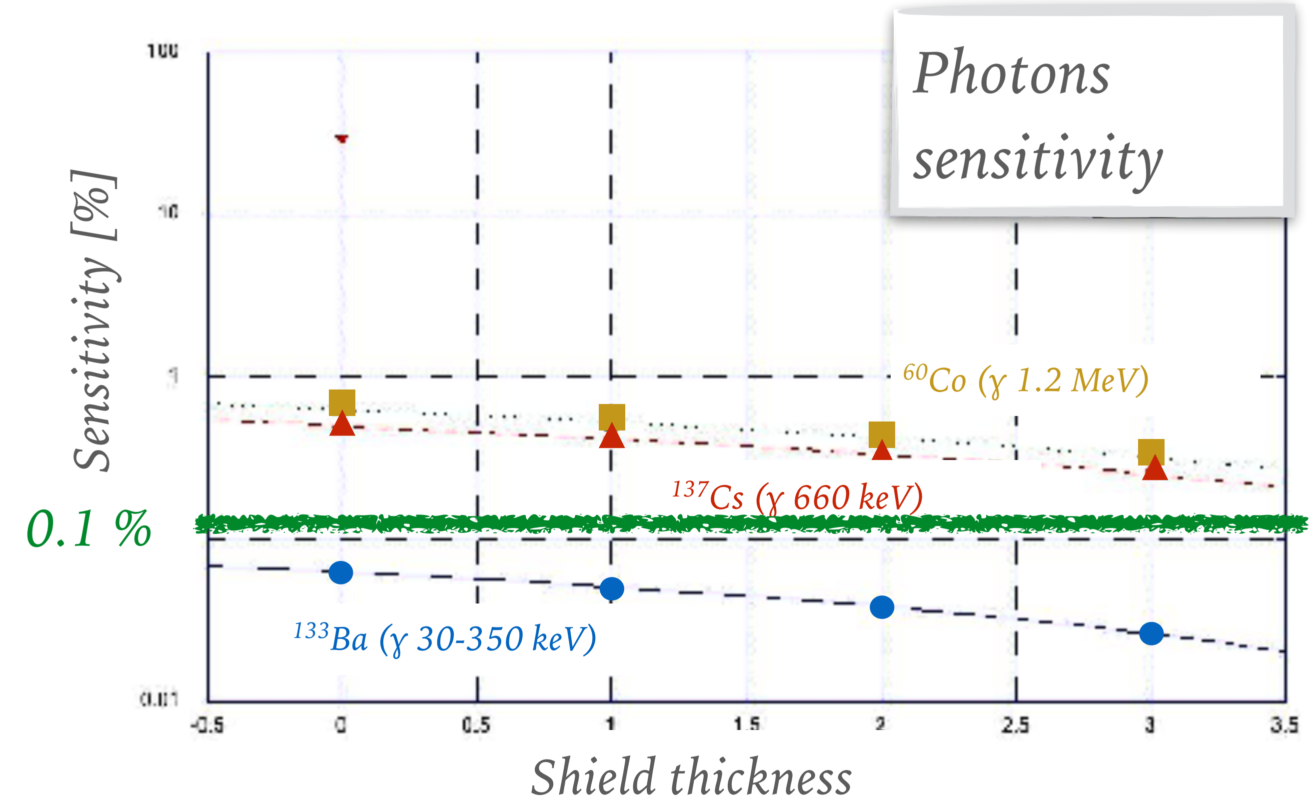
$C_{18}H_{14}$

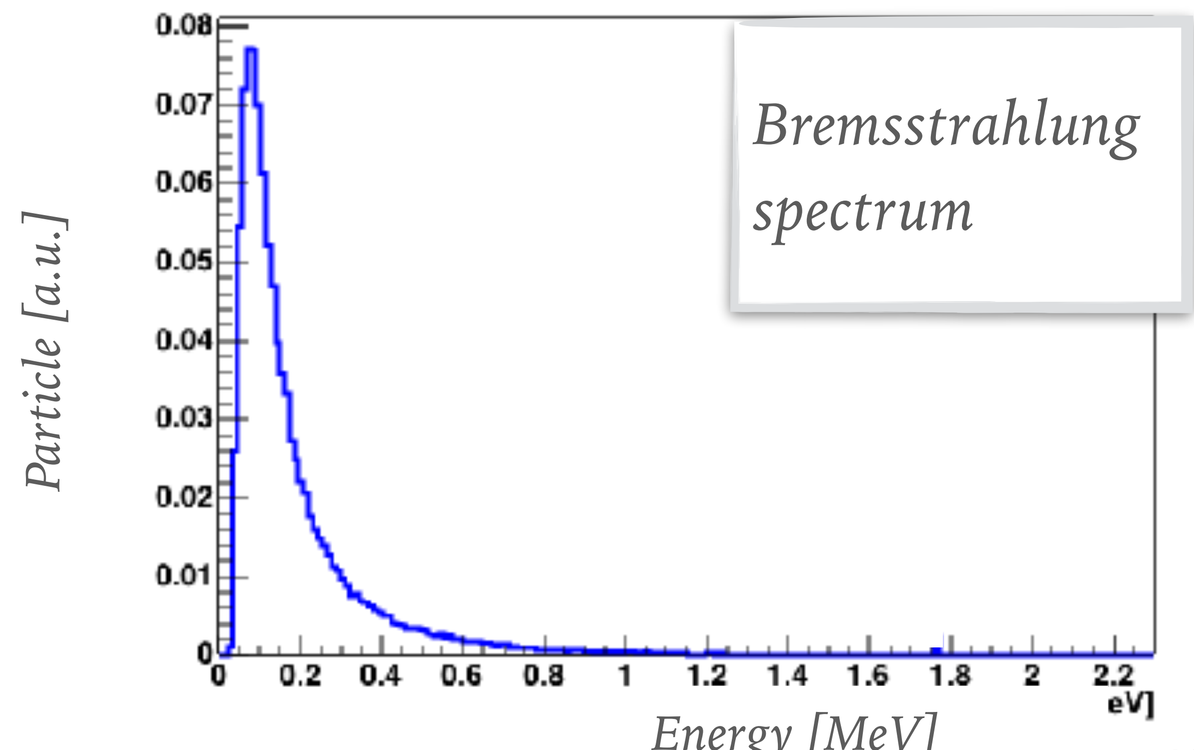
	Antracene	Doped p-terphenil	Stilbene
Density [g/cm³]	1.23	1.16	1.22
Light output [10^4 photons/MeV]	2.0	2.7	1.4
Decay time [ns]	30	3.7	3.5

M. Angelone, **F. Collamati** et al, ***Properties of p-Terphenyl as detector for α, β, and γ radiation***, *IEEE Trans. on Nucl. Sci. 2014; 61: 1483-7*

PHOTON SENSITIVITY

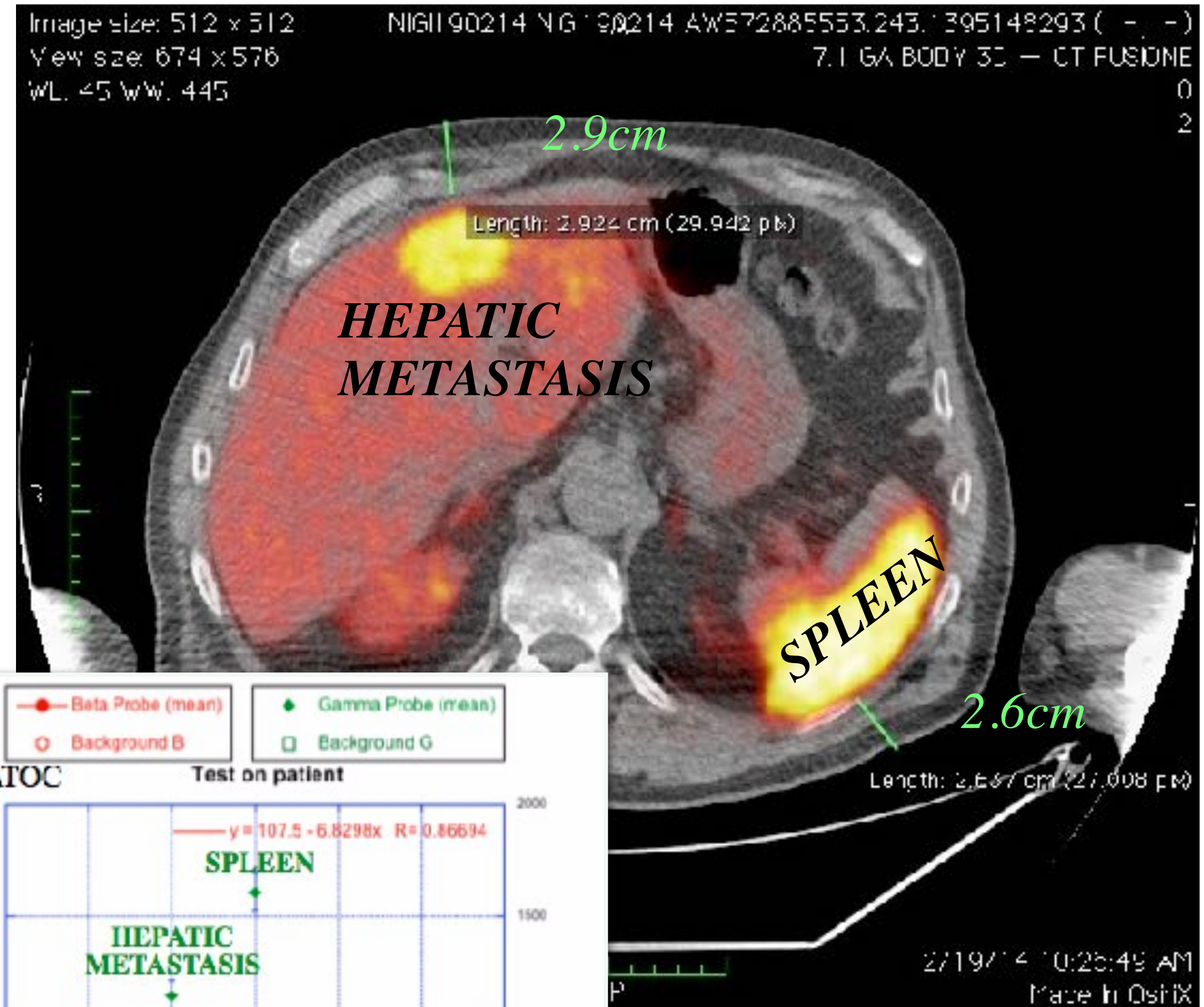
- **Bremsstrahlung** contribution could affect the detector performance
- Material exposed to different γ sources
  - Bremsstrahlung spectrum peaked at 100 keV
  - $P_{Brem}(E_e = 1 MeV) \sim 10^{-3}$
  - Expected sensitivity lower than 0.1%
- Possibility to use β^- emitters with a small percentage of γ decay

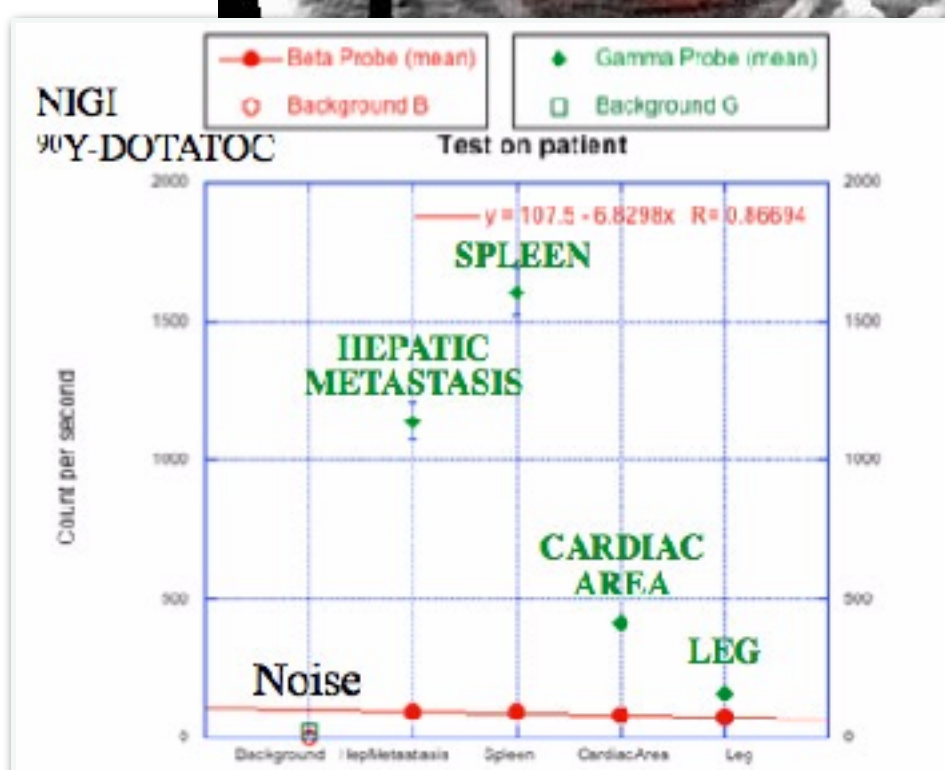




PHOTON SENSITIVITY – REAL PATIENT CASE

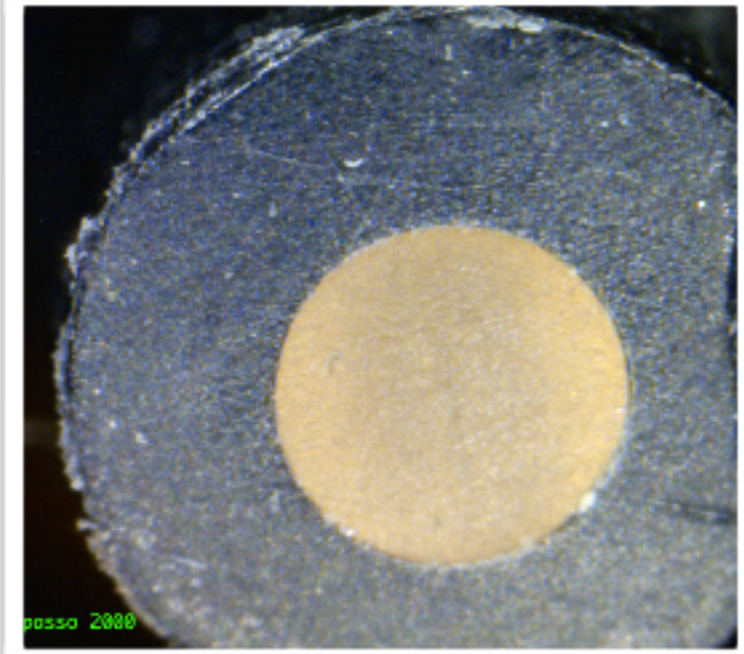
- In a real case of Bremsstrahlung background
- Injected activity (24h before):
  - ^{90}Y-DOTATOC 54mCi
  - 21MBq/kg therapeutic treatment
- Lesion of interest:
  - Hepatic metastasis from neuroendocrine tumor
- Great differences between gamma and beta probe





B⁻ PROBE FIRST PROTOTYPE

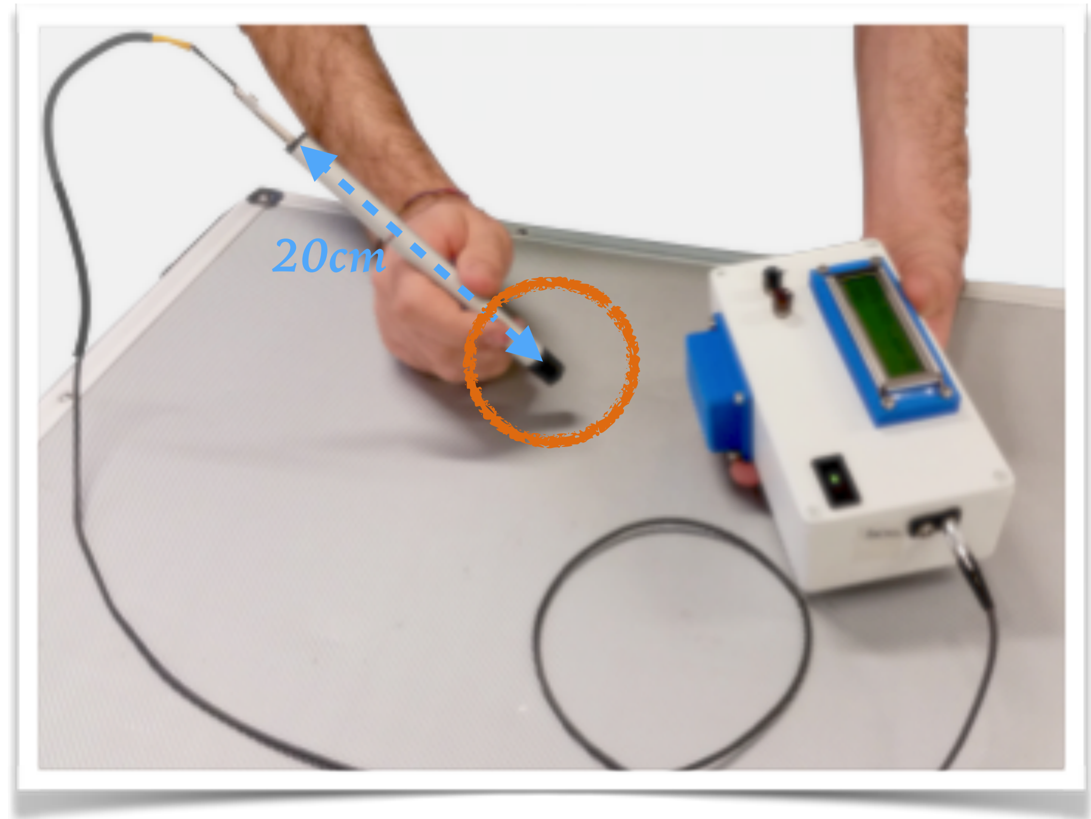
- First prototype
  - Small active volume coupled with an **optical fiber** to a **PMT**
  - Characterisation of the PMT
    - Working point
    - After pulses



- Scintillator dimensions
- Improvement using SiPM
- **Optimisation** of the electronics
  - Portable detector to match surgeons' needs

B⁻ PROBE ACTUAL PROTOTYPE

- Core: cylindrical scintillator of *p-terphenyl*
  - d=6 mm, h=3 mm
  - Direct coupling with a **SiPM** (sensL C-series, V_{th}=5.8mV)

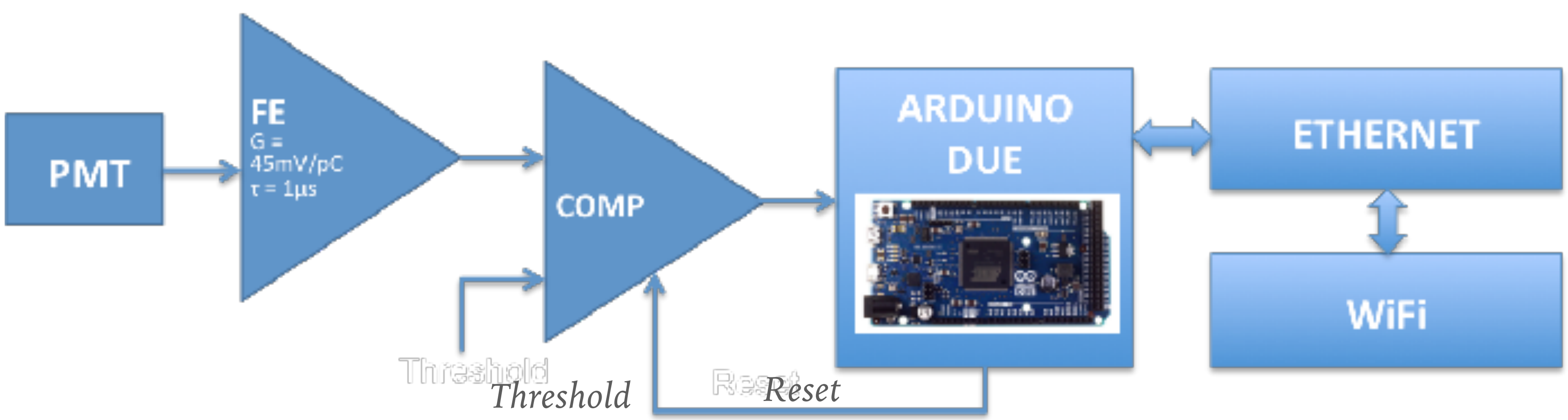


- Probe characteristics:
  - **Aluminum** body for easy handling
  - Tip: **PVC** ring to mechanical support resulting in a lateral shielding 10μm **Al** sheet to reduce the thickness of electrons entrance window
  - **Battery** (portable), thus avoiding the HV (increase patient's safety)

ELECTRONICS READ-OUT

- Electronics: **Arduino** based, made in collaboration with electronics engineers
  - Portable and customised
  - Match the surgeon needs
  - Acoustic and visual alarm
  - Wireless data transfer
  - User interface available both for PC or tablet

No risk of electric discharge on patient



FIELD OF VIEW

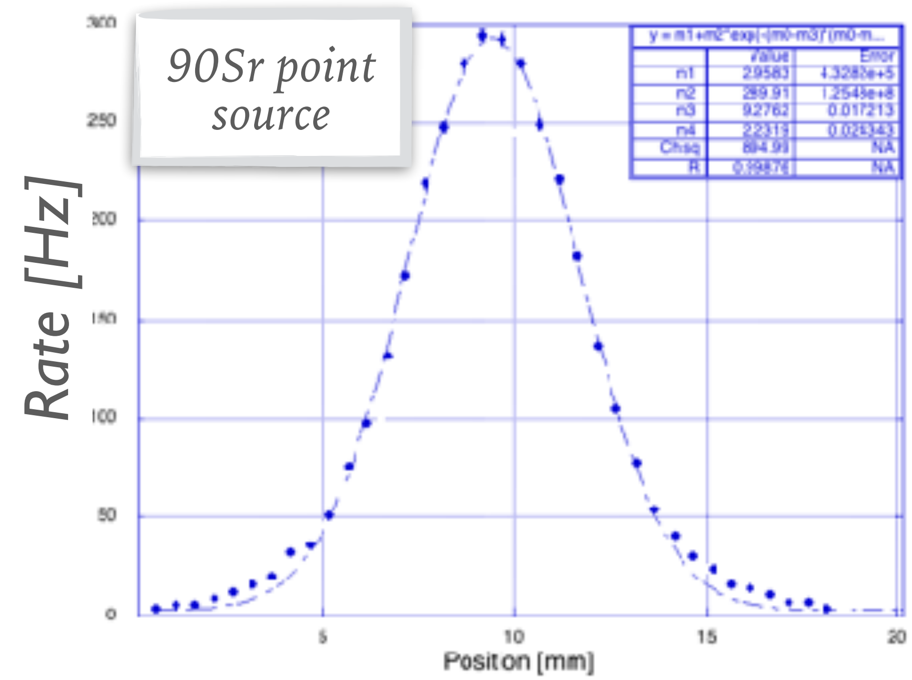
- ^{90}Sr → ^{90}Y

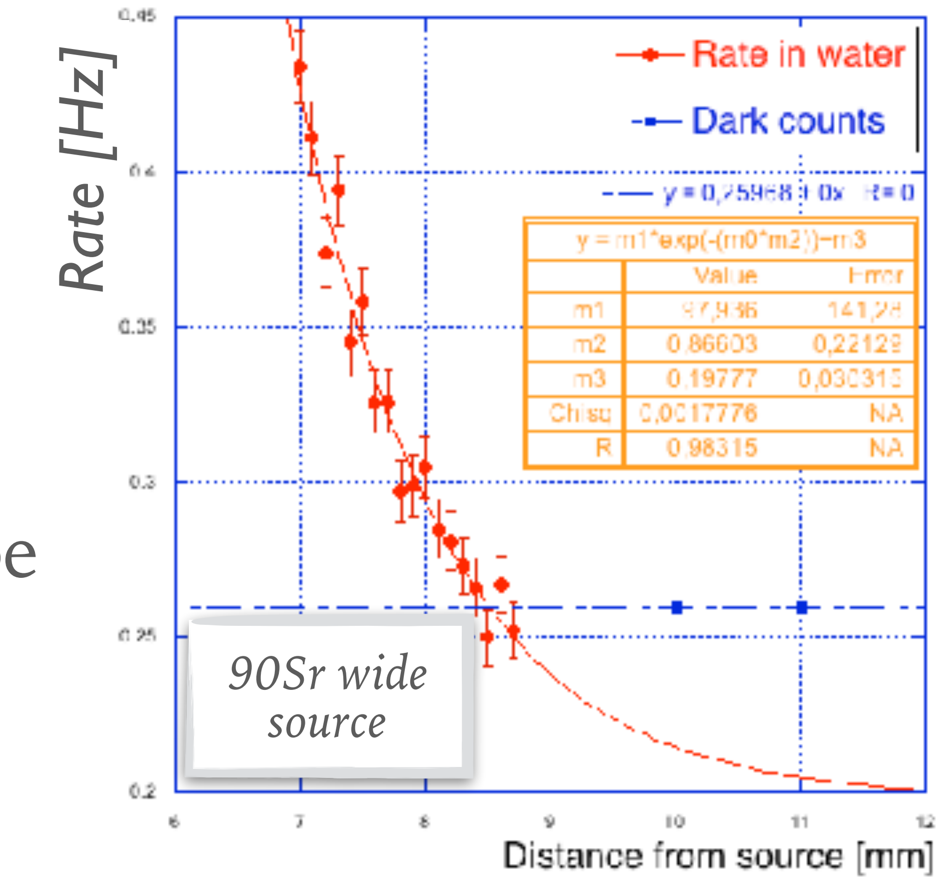
  ß$^-$, $t_{1/2}$ 28.8 y, E_{max}=0.55 MeV

  - ^{90}Y

    ß$^-$, $t_{1/2}$ 64 hours, E_{max}=2.28 MeV

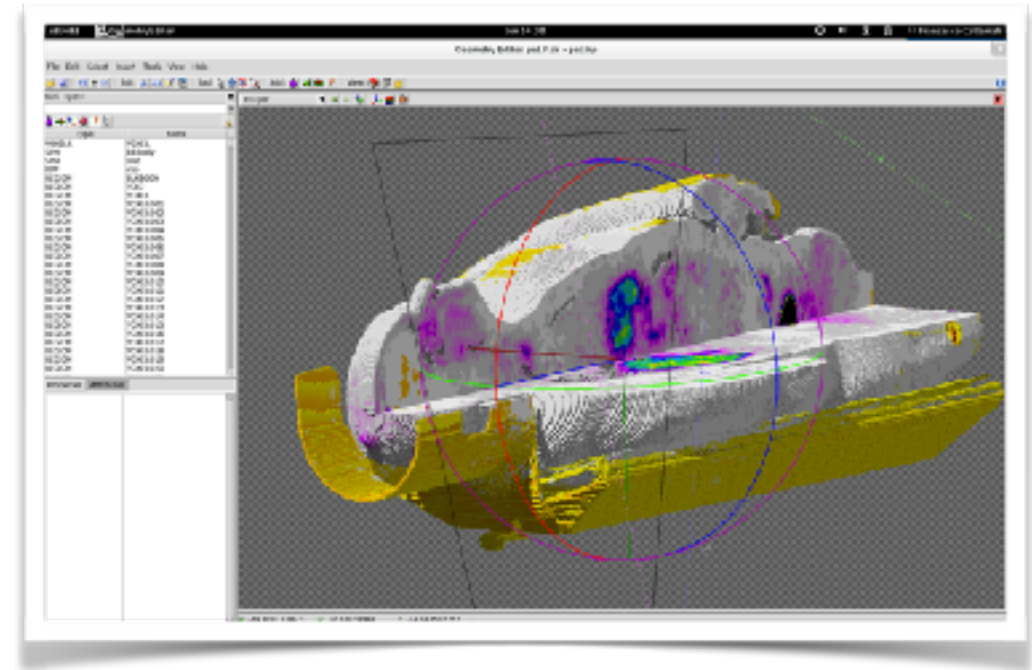
- **Profiles** reconstructed by the probe on sealed beta sources
  - Air / Water
  - Equivalence human body ⟷ water
- Lateral ~ 4 mm, Depth ~ 6 mm
  - This is the **distance from which** the probe **identifies a point size residual** during the operation



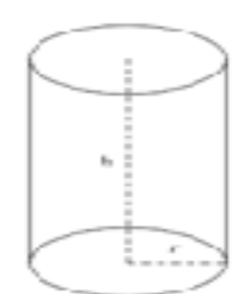


EXPECTED PERFORMANCE

- A tool was developed to import in **FLUKA** PET/SPECT Dicom files to be used as source particles' distribution to simulate the real case scenario
- Combining it with laboratory tests, the **performances** of the β^- RGS were estimated:



- t_{min} minimum time needed by the probe to **identify** a **0.1ml** tumor residual after administration of **3MBq/kg (95% C.L.)**
  - 0.1 ml is the minimal residual correctly identified by diagnostic imaging
  - 3MBq/kg is comparable with activity for diagnostic (PET exam)
  - Probability of False Positive FP<1%
    Probability of False Negative FN<5%



h=5mm

r=2.5mm

V~0.1ml

PREDICTIONS FOR B- RGS

NETs Liver: Less than 1s administering 3MBq/kg

Meningiomas: Good sensitivity to 0.1ml residuals within 1s

Gliomas: Lower uptake, the time needed is ~5s,
till acceptable

Medical Team Exposure:

Equivalent dose for surgeon	β^--RGS (^{90}Y) FLUKA simulation	γ-RGS (^{99m}Tc)
hands	0.35 μSv/h	24 μSv/h
total body	0.04 μSv/h	6 μSv/h

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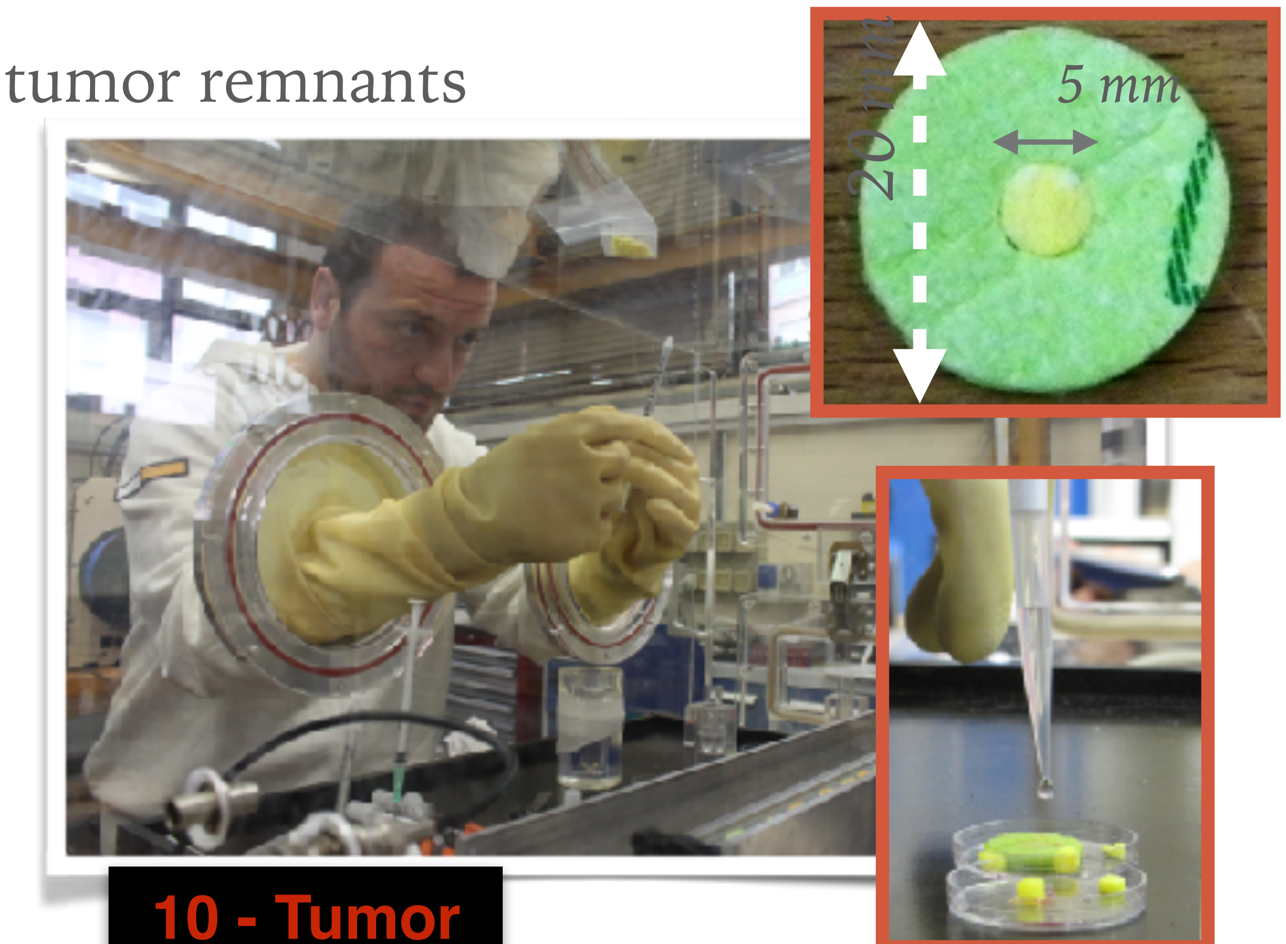
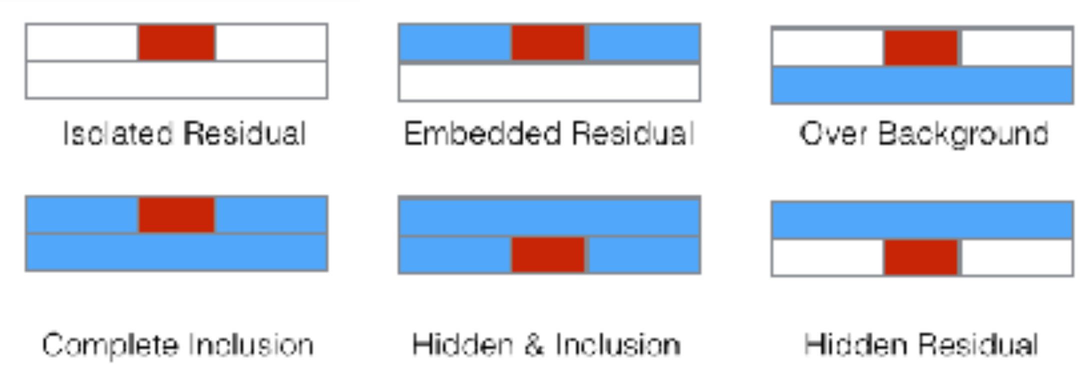
PHANTOM FACTORY

- Created "ad hoc" phantoms to simulate tumor remnants
  - Liquid radio-tracer (saline solution of ^{90}Y)
- Sponge material
  - Different activities changing ^{90}Y dilutions
- Simulation of a **tumor** embedded in **healthy tissue**
  - Typical assembly: spot (high uptake) inserted into a torus (low uptake) over a disk (low uptake)
- Exploration of different patterns

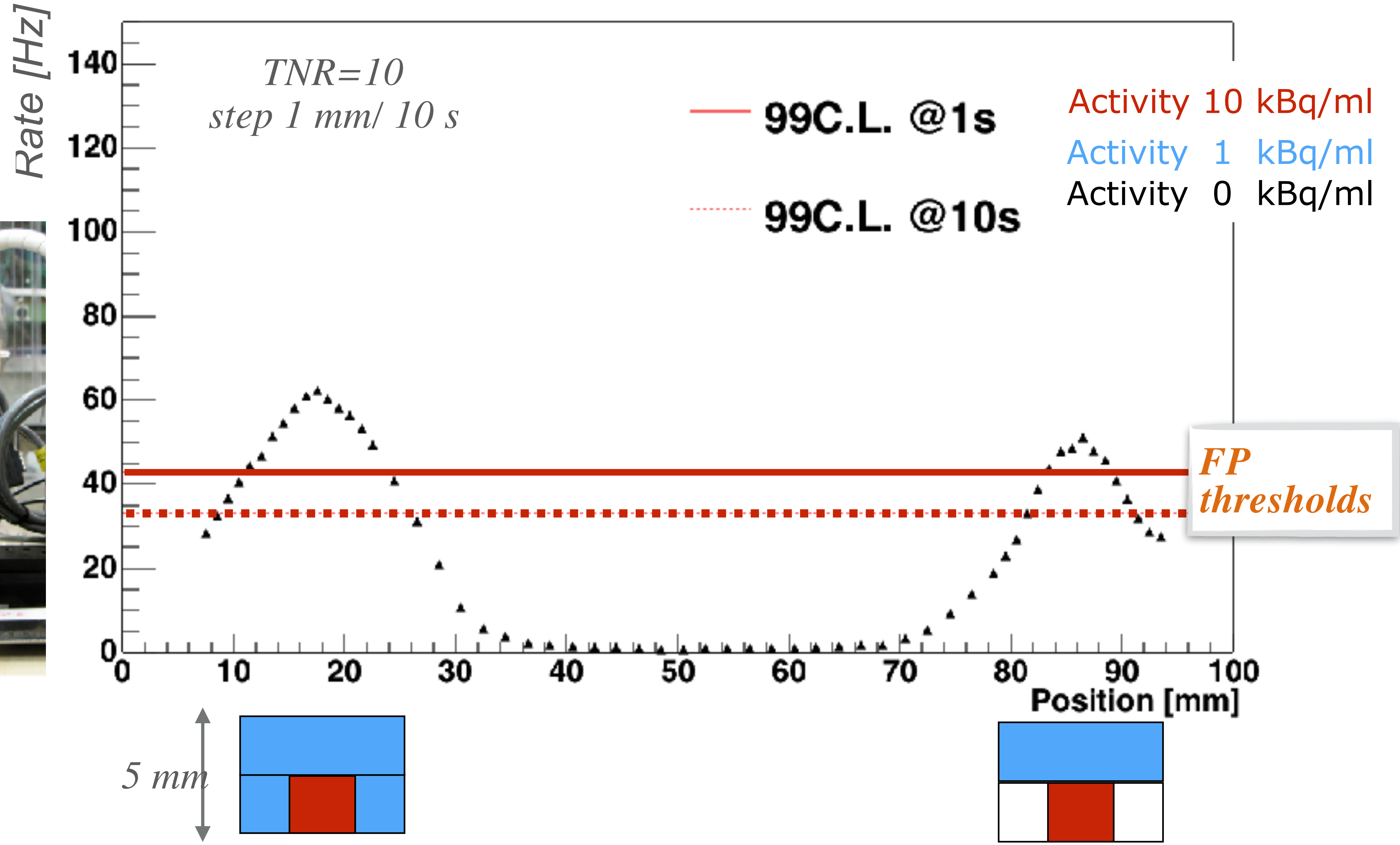


10 - Tumor
1 - Healthy
0 - Necrotic



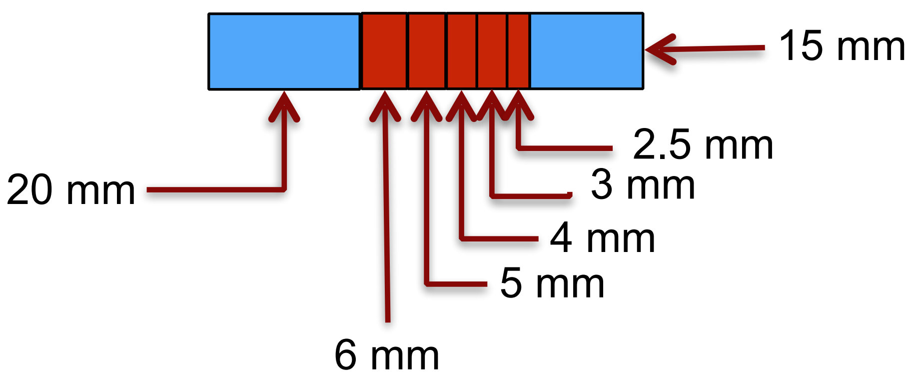
ACTIVE SPOT IDENTIFICATION

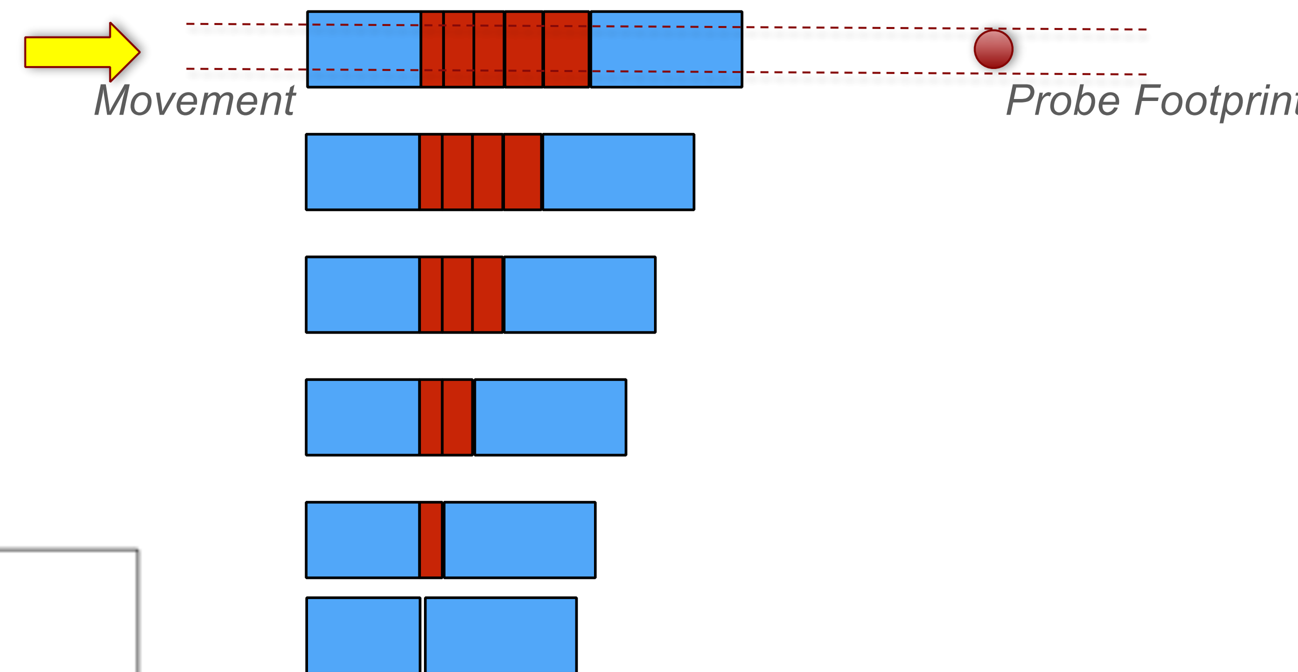
Automated set-up

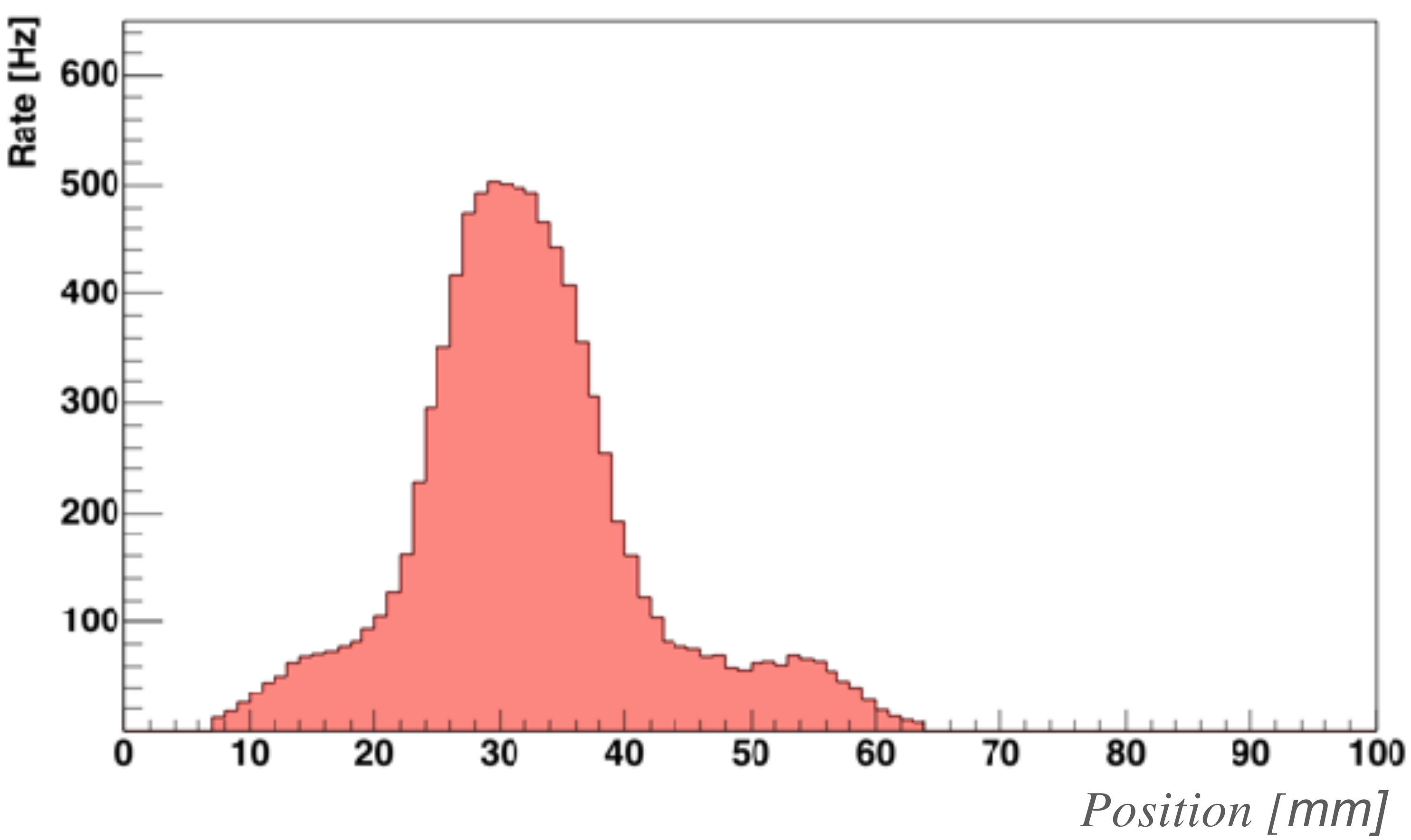


Lines represent the discovery potential of the probe with different acquisition times

SIMULATION OF SURGICAL OPERATION







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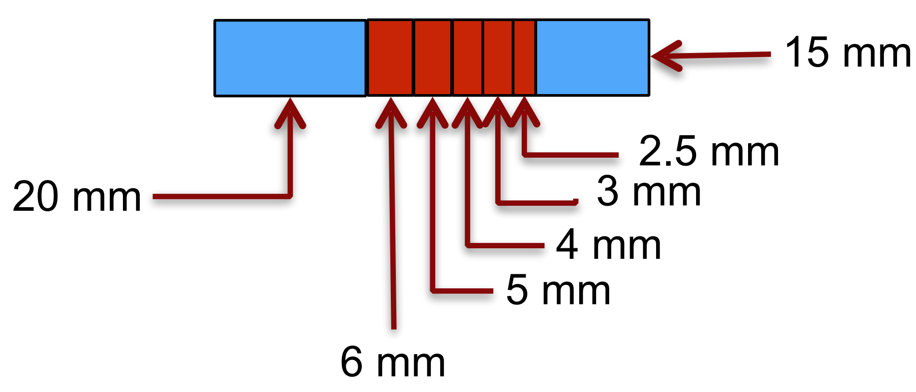

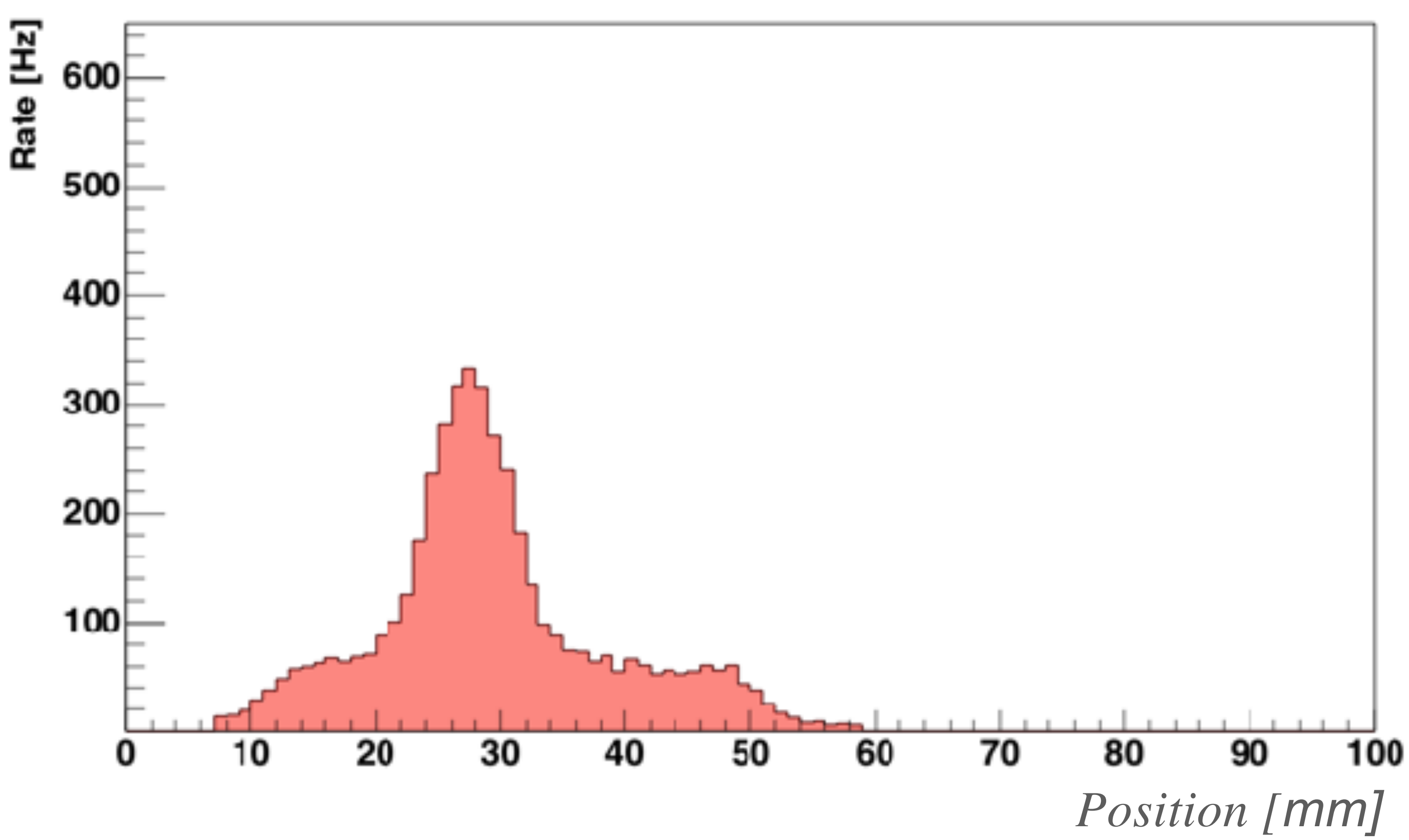

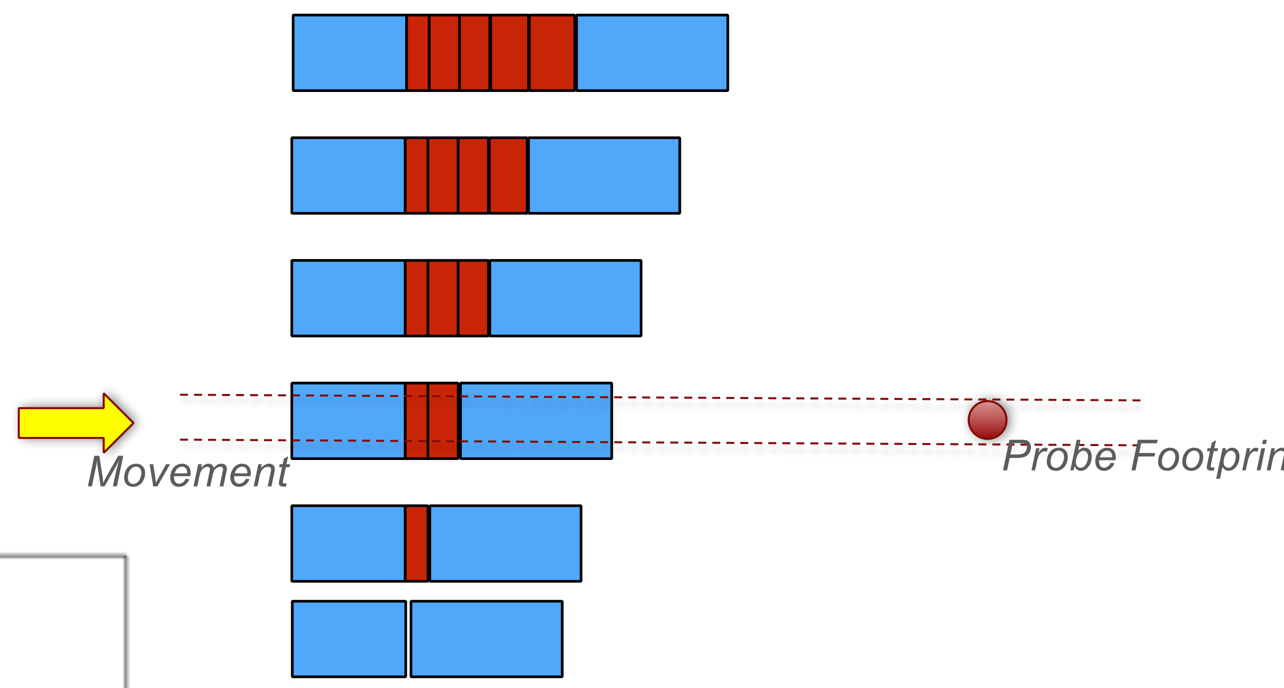

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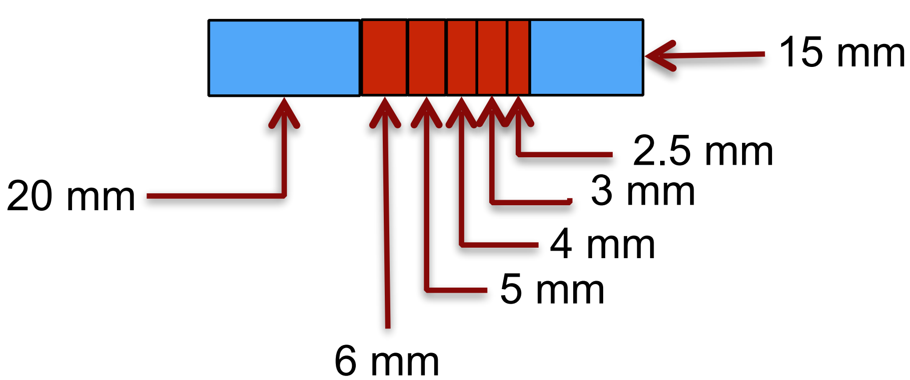
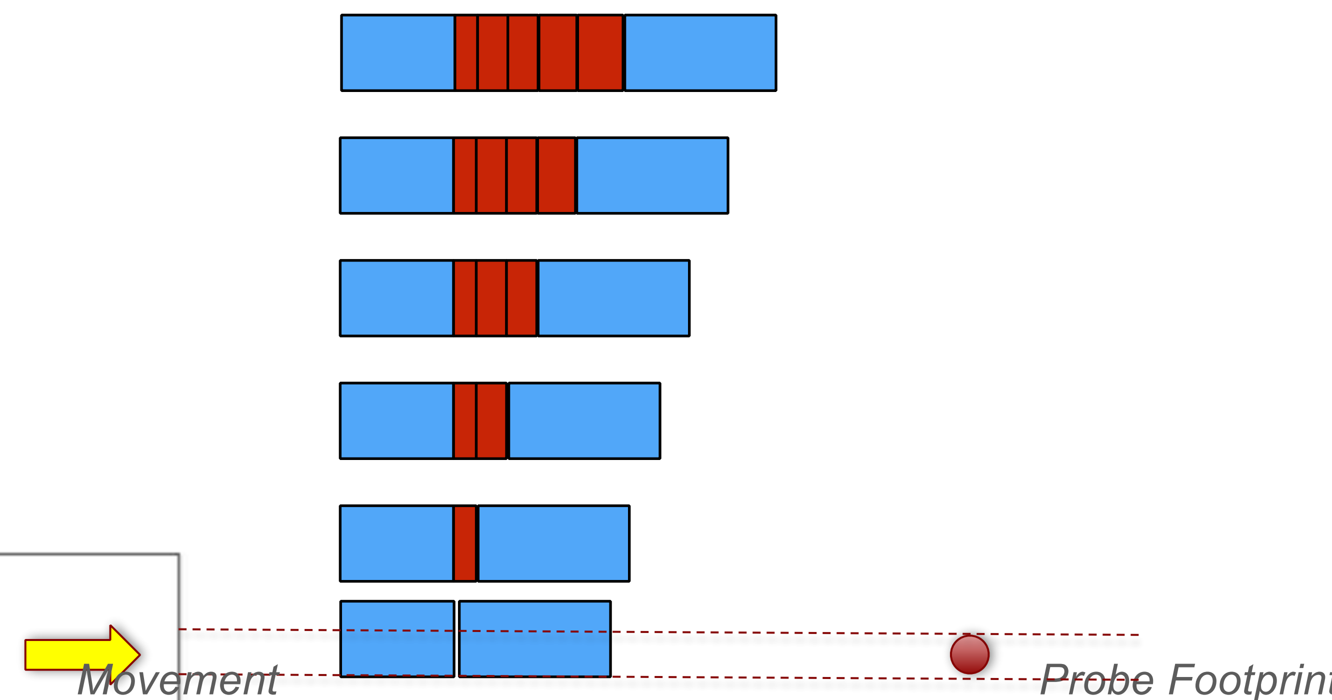
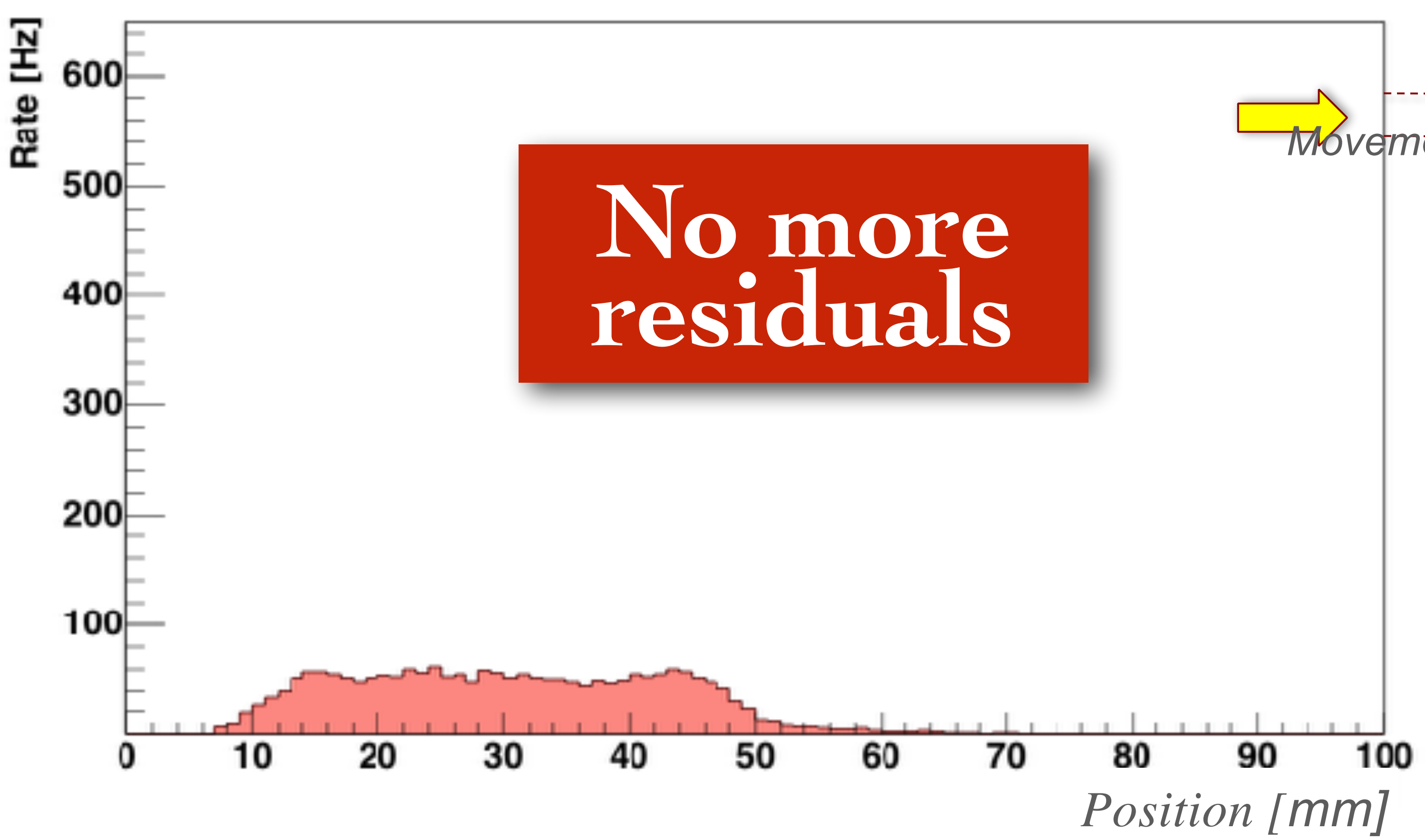


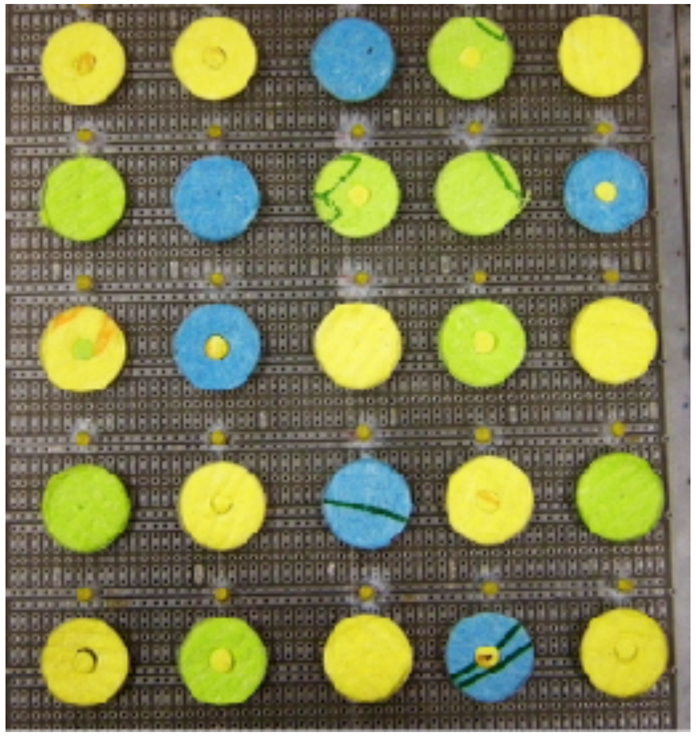


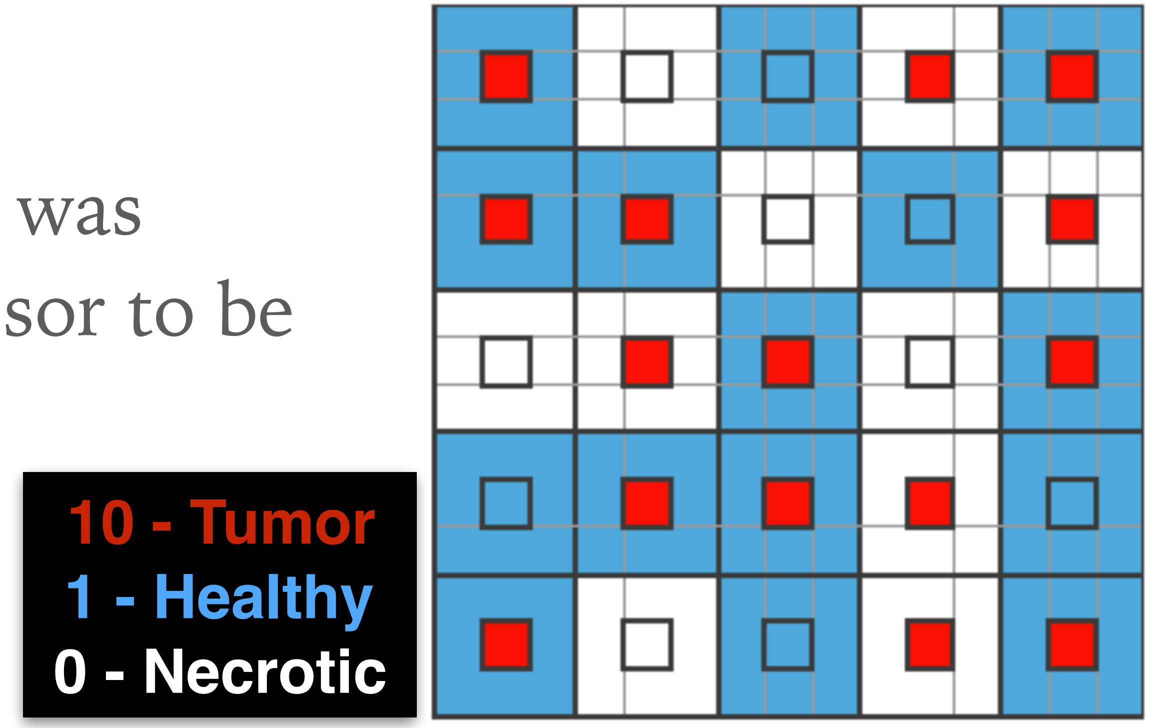


- Smallest volume detected 0.03 ml (benchmark 0.1 ml)

HUMAN PERCEPTION

- To evaluate the human factor, colleagues were asked to **simulate the surgeon**
- The testers were equipped with different feedback
  - Visual (blinking led)
  - Acoustic (buzzer)
  - Numeric (tablet)
- Sequentially each of the phantoms was randomly chosen by a microprocessor to be “active”
- **No one wanted to take a decision in less than 2-3 s**





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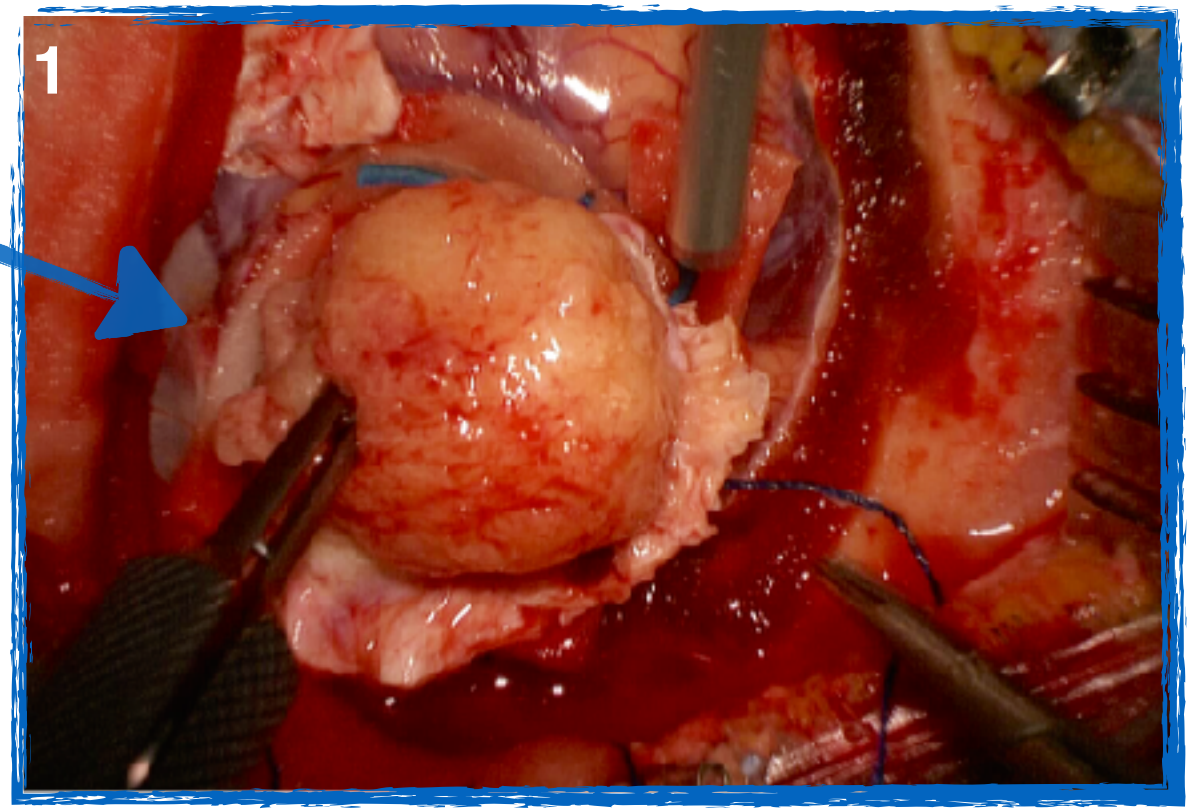
  - Brief overview
  - Probes for RGS
- β- radiotracers
  - Clinical cases of interest
  - Detector development
  - Phantoms' techniques
  - Test on ex-vivo specimens

WARNING !!!!

NEXT SLIDE COULD HURT
YOUR SENSIBILITY

BRAIN TUMOR SURGERY

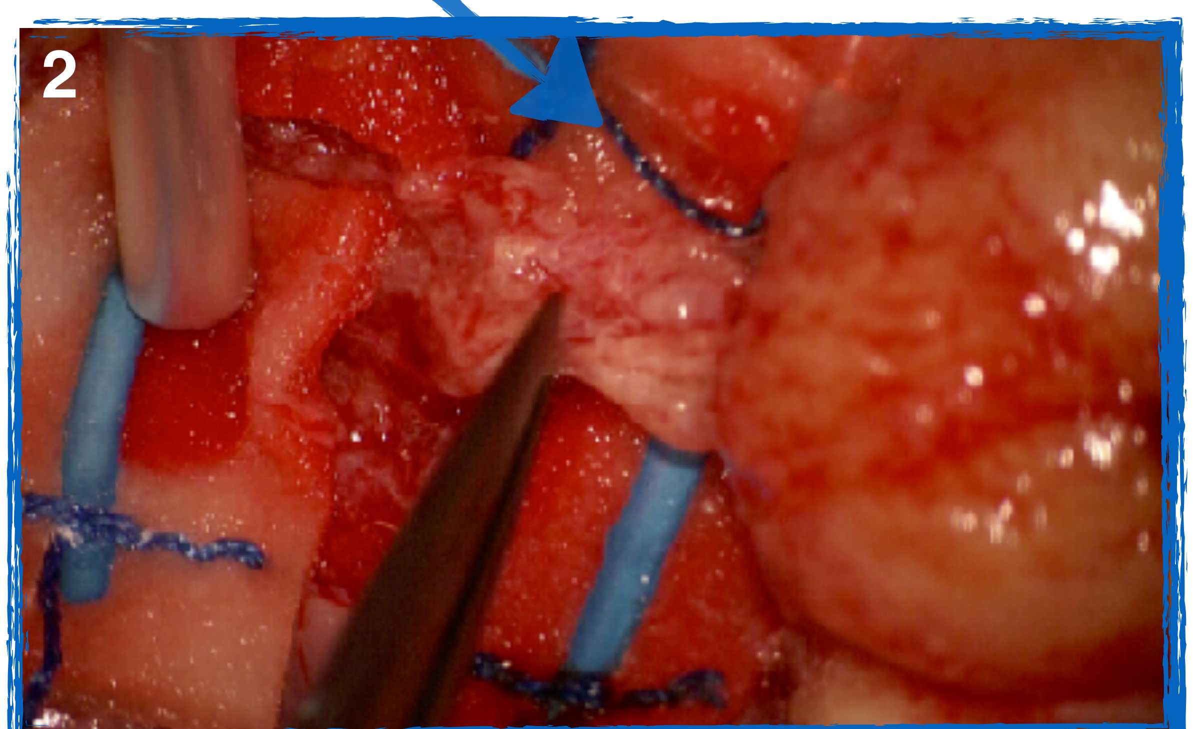
Identification of meningioma (bulk)

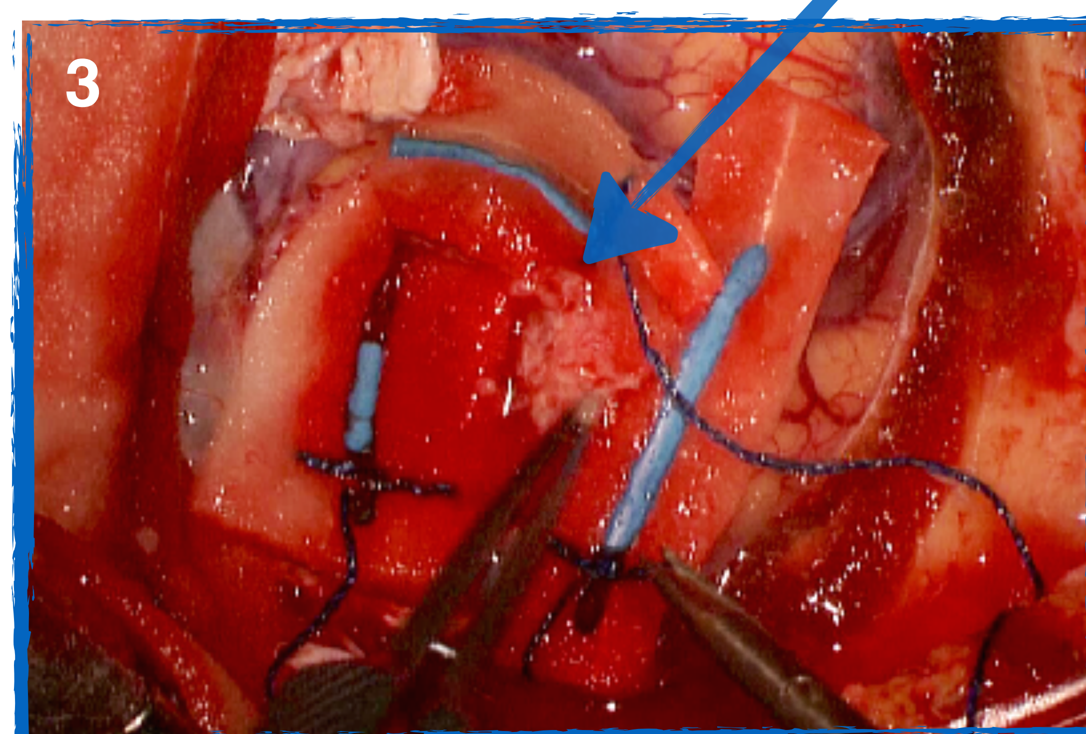


Patient injected 24 h before the operation with ^{90}Y-DOTATOC (according to uptake and renal dose)

Bulk removal

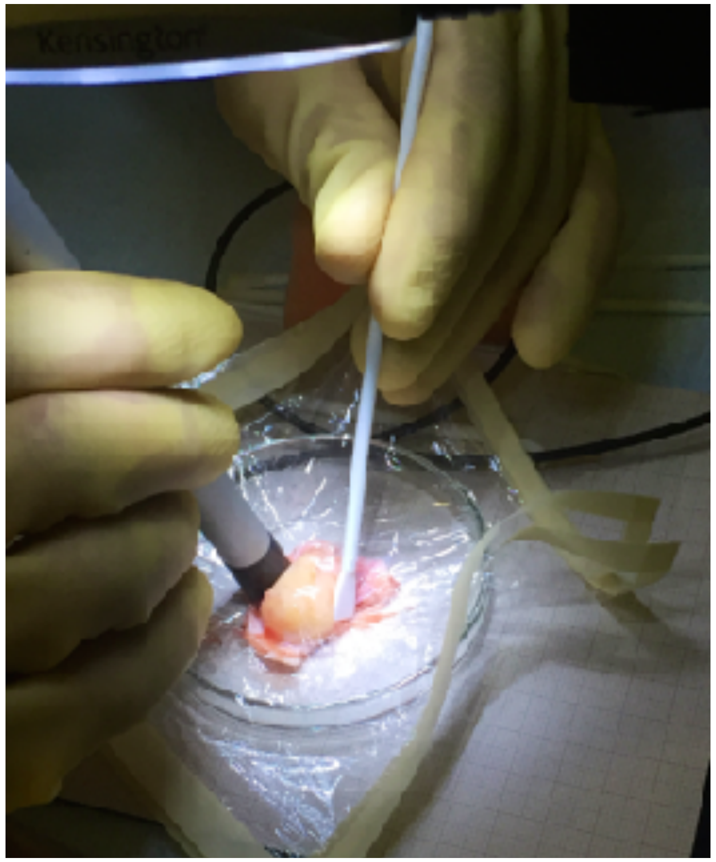
Residual?



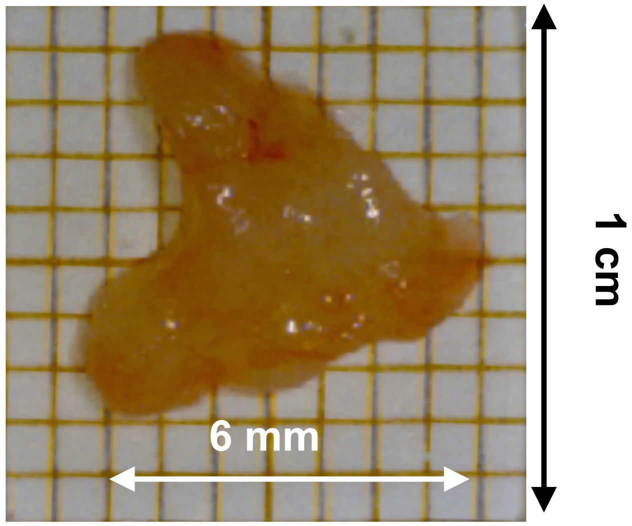


EX-VIVO SPECIMENS

- Data: Samples from 4 patients
  - Dura mater: membrane that surrounds the brain
  - Red = tumor; Green = not tumor



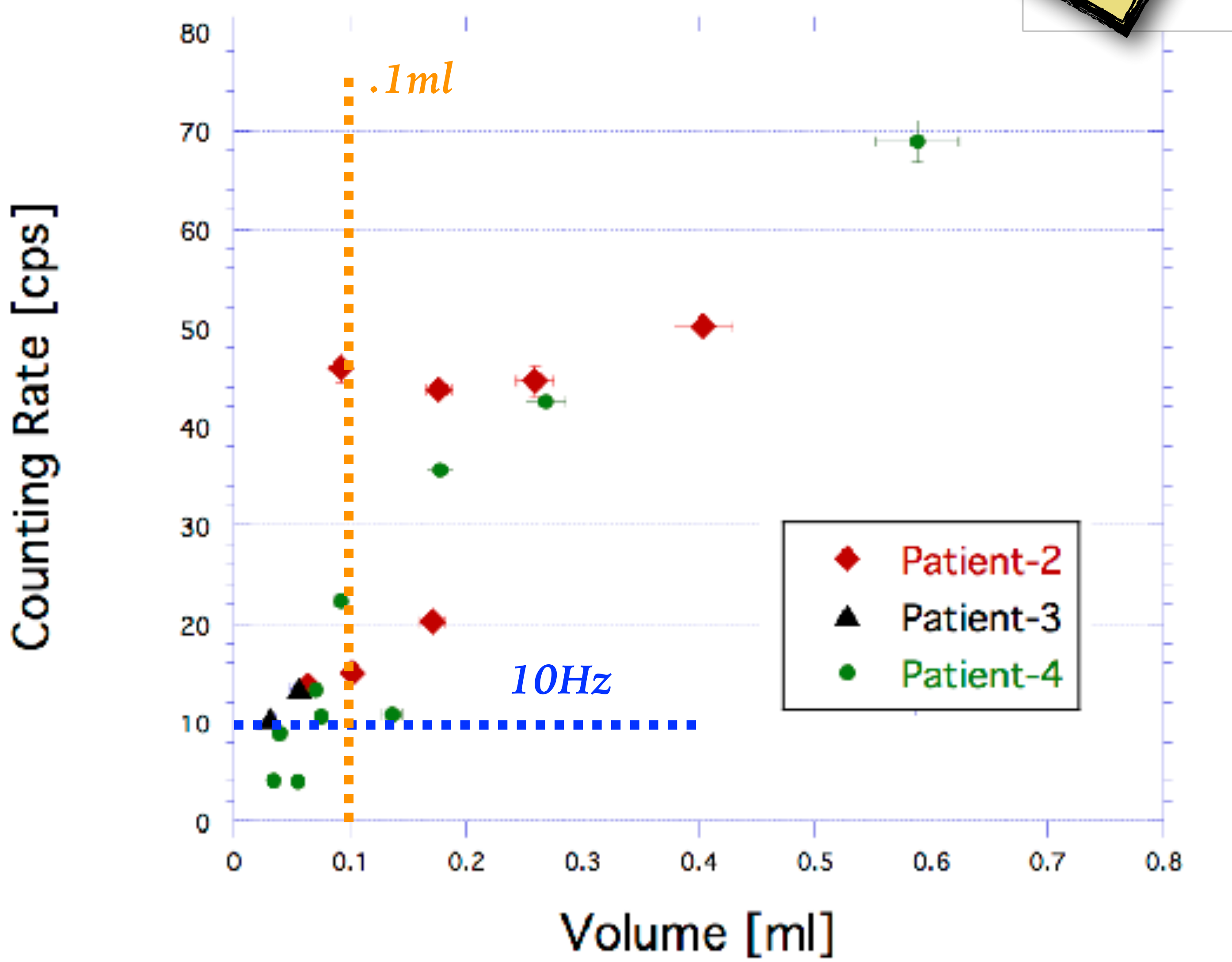
Sample	Volume [ml]	Tissue	Rate [Hz]
A	0.05	Dura	1.8
B	0.04	Dura	2.6
C	0.40	Bulk	49.7
D	0.26	Bulk	44.6
E	0.10	Margin	15.0



EX-VIVO SPECIMENS

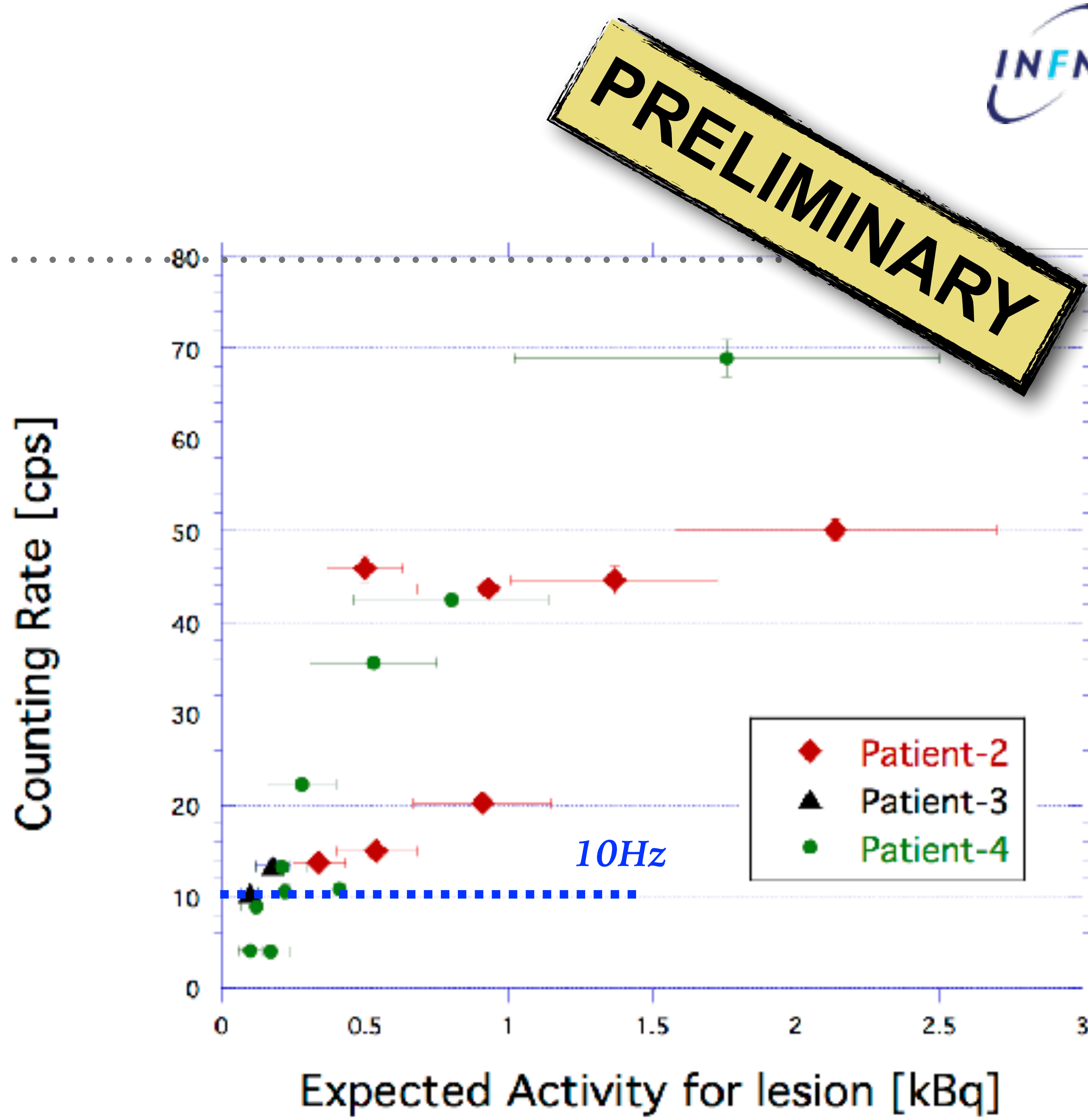
- Data: Samples from 3 patients affected by meningioma
  - In each case samples of *tumor* and of *margin* were collected
- From MC we expect a background of ~1Hz on healthy brain
  - We can use **10Hz** as a **conservative threshold**

Almost all the residuals of interest were correctly identified by the probe!



MINIMUM DOSE TO INJECT

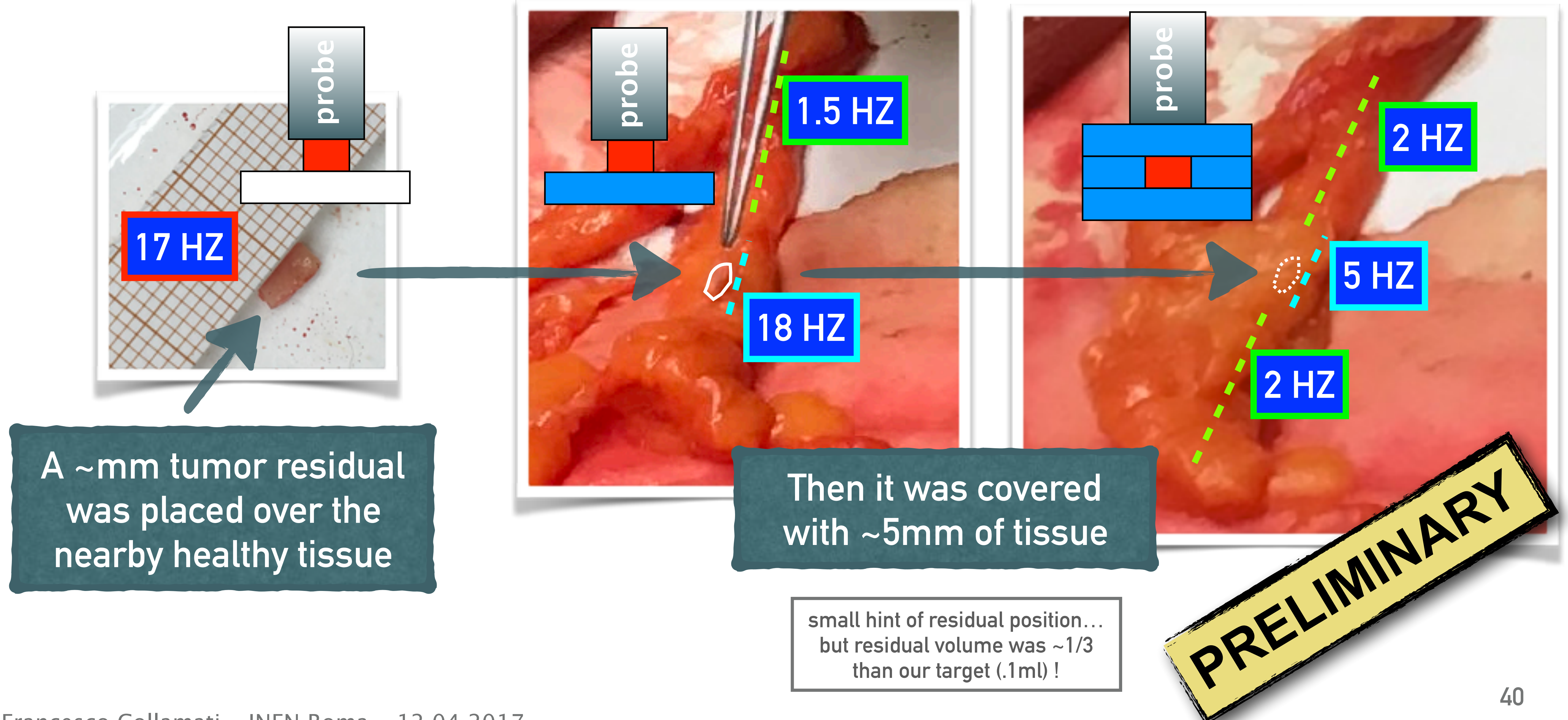
- The data collected with the first 4 patients allow to **rescale** the expected activity and to estimate the **minimum dose to be injected** to the patient to be able to discriminate the lesion
  - Affected by the **volume** and **shape** of samples of interest
  - Final decision according to renal toxicity
- Minimum dose needed to detect 0.1 ml ~ **1 MBq/kg**



Possibility to develop a Treatment Planning for the patient on the basis of preoperative imaging

EX-VIVO TEST WITH REALISTIC BACKGROUND

- The tests on meningioma sample were in the optimistic case of high TNR (the tumor was already excised)
- To evaluate the effect of a **more realistic situation** a new campaign of tests on **GEP NET** has just started @ Istituto Europeo di Oncologia (Milano)



small hint of residual position…
but residual volume was ~1/3
than our target (.1ml) !

IRRADIATION MEASUREMENTS

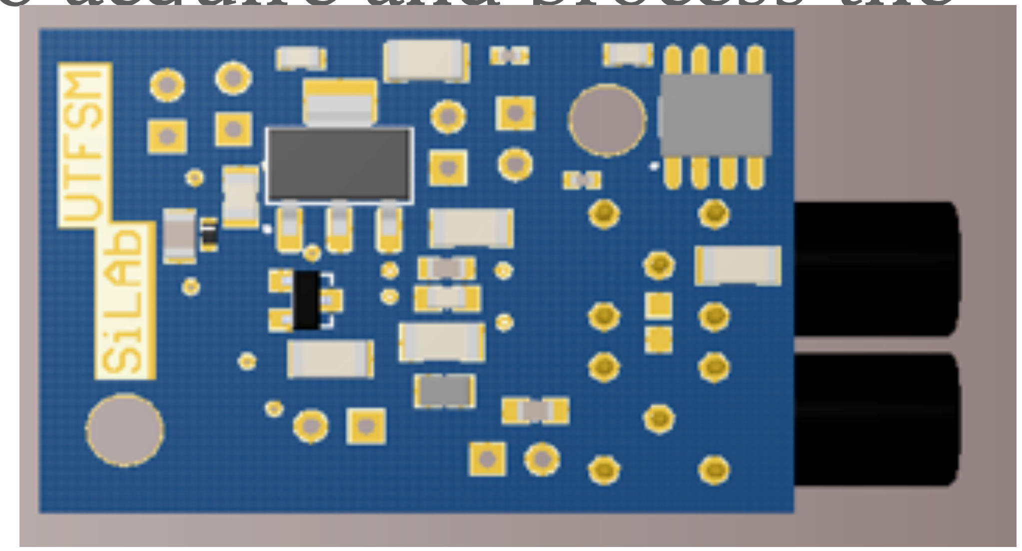
NEXT STEPS

- The test campaign on GEP NET's @IEO has just started
  - next patient next month!
- Development of new radio-tracers
  - in collaboration with Policlinico Gemelli and Chemistry Dept. Sapienza
- Probe development:
  - Study of a new possible design relying on **CMOS** sensor
    - extend sensitivity to lower energy electrons —> + radio-tracers => + application cases
  - Probe CE **certification**
    - Possibility to finally perform **in-vivo tests!!**

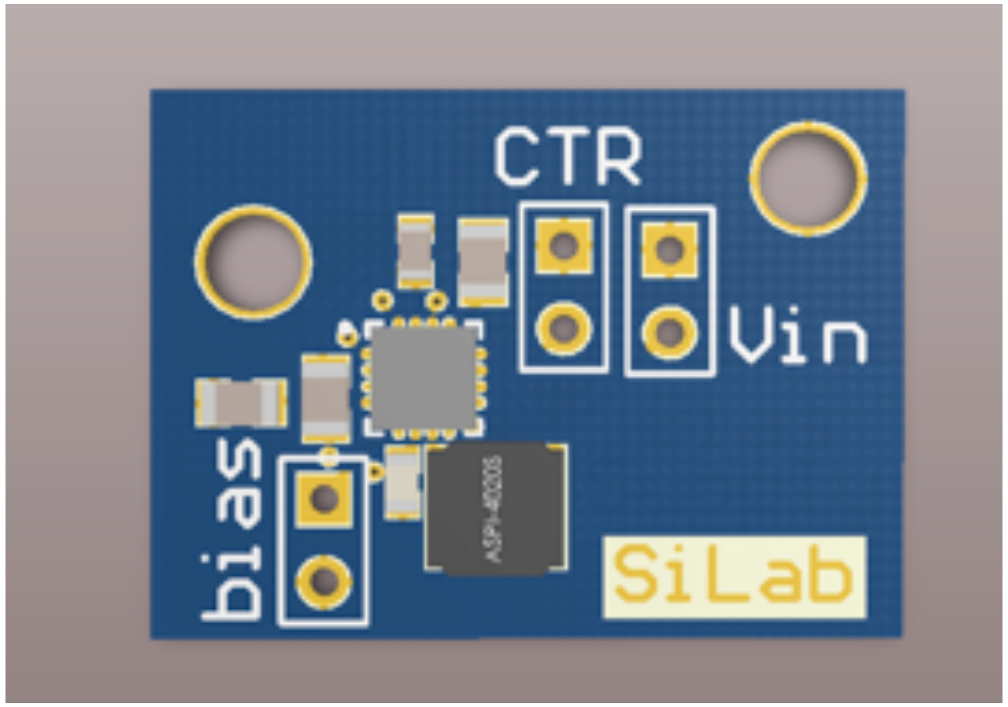
THANK YOU FOR YOUR ATTENTION!

NEXT STEPS

- Already designed the electronics to acquire and process the data
  - Thanks to Lautaro Paredes



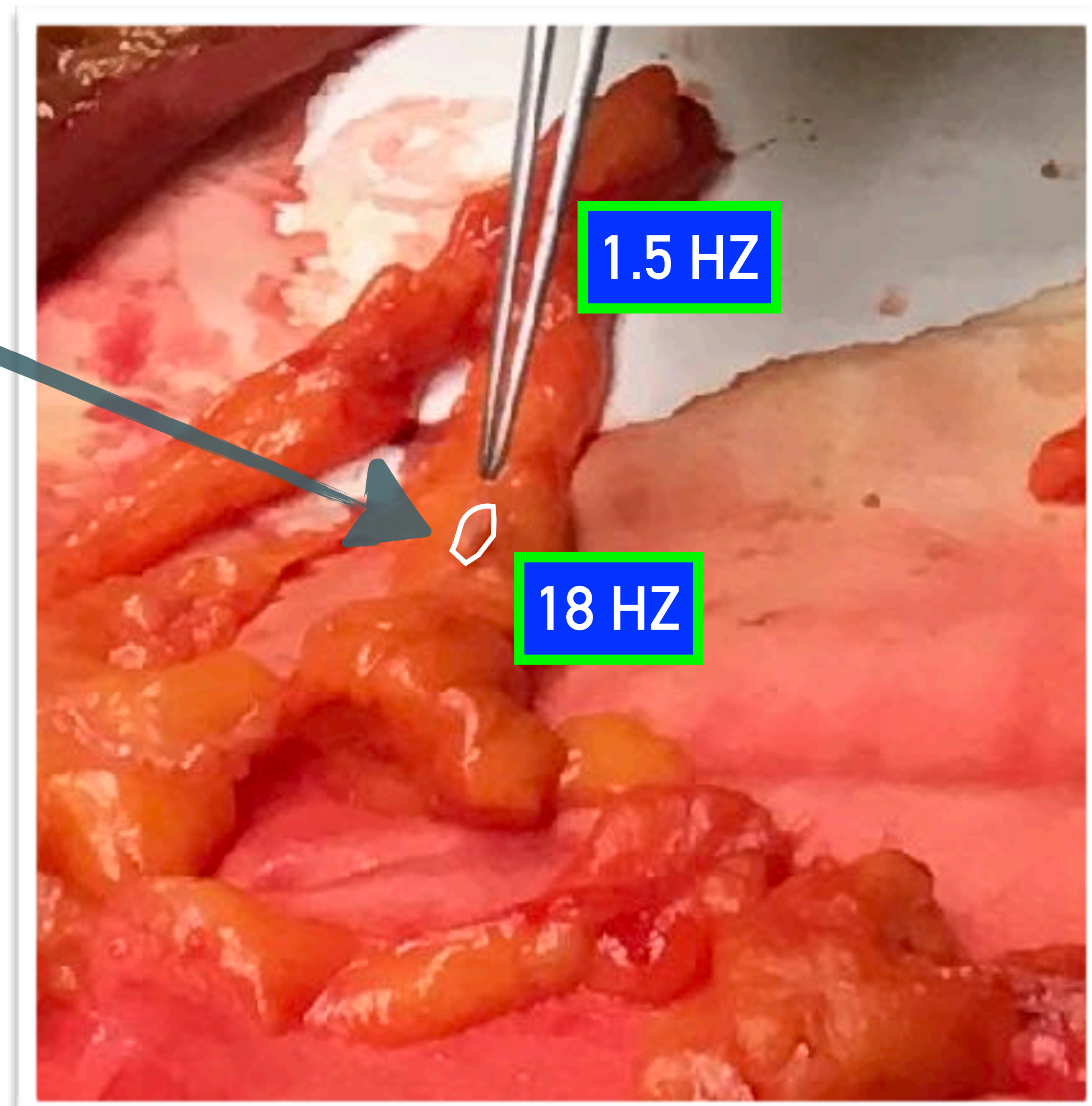
- Ready to assembly the probe
  - Hope to test it soon
  - Development of a PET-CT system for brain and small animal imaging



BACK-UP

EX-VIVO TEST WITH REALISTIC BACKGRUOND

- The tests on meningioma sample were in the optimistic case of high TNR (the tumor was already excised)
- To evaluate the effect of a more realistic situation a new campaign of tests on GEP NET has just started

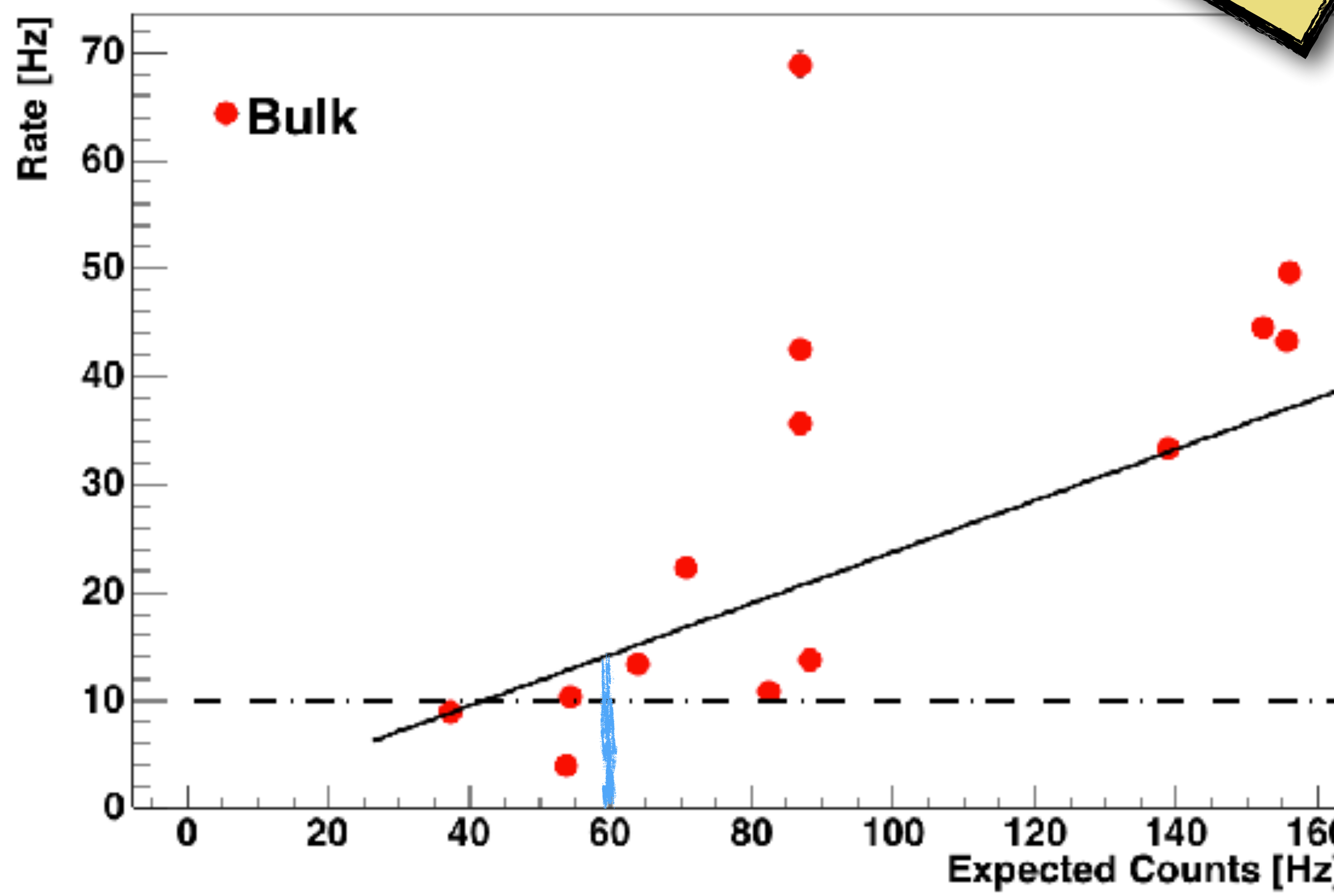


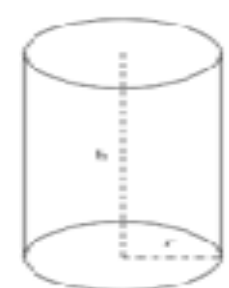
A ~mm tumor residual was placed over the nearby healthy tissue

TUMOR BULK

PRELIMINARY

- Possibility to **define** in the patient's treatment plan the **minimum dose** to be injected
  - Affected by the **volume** and **shape** of samples of interest
  - Final decision according to renal toxicity
- Minimum dose needed to detect 0.1 ml ~ 1 MBq/kg



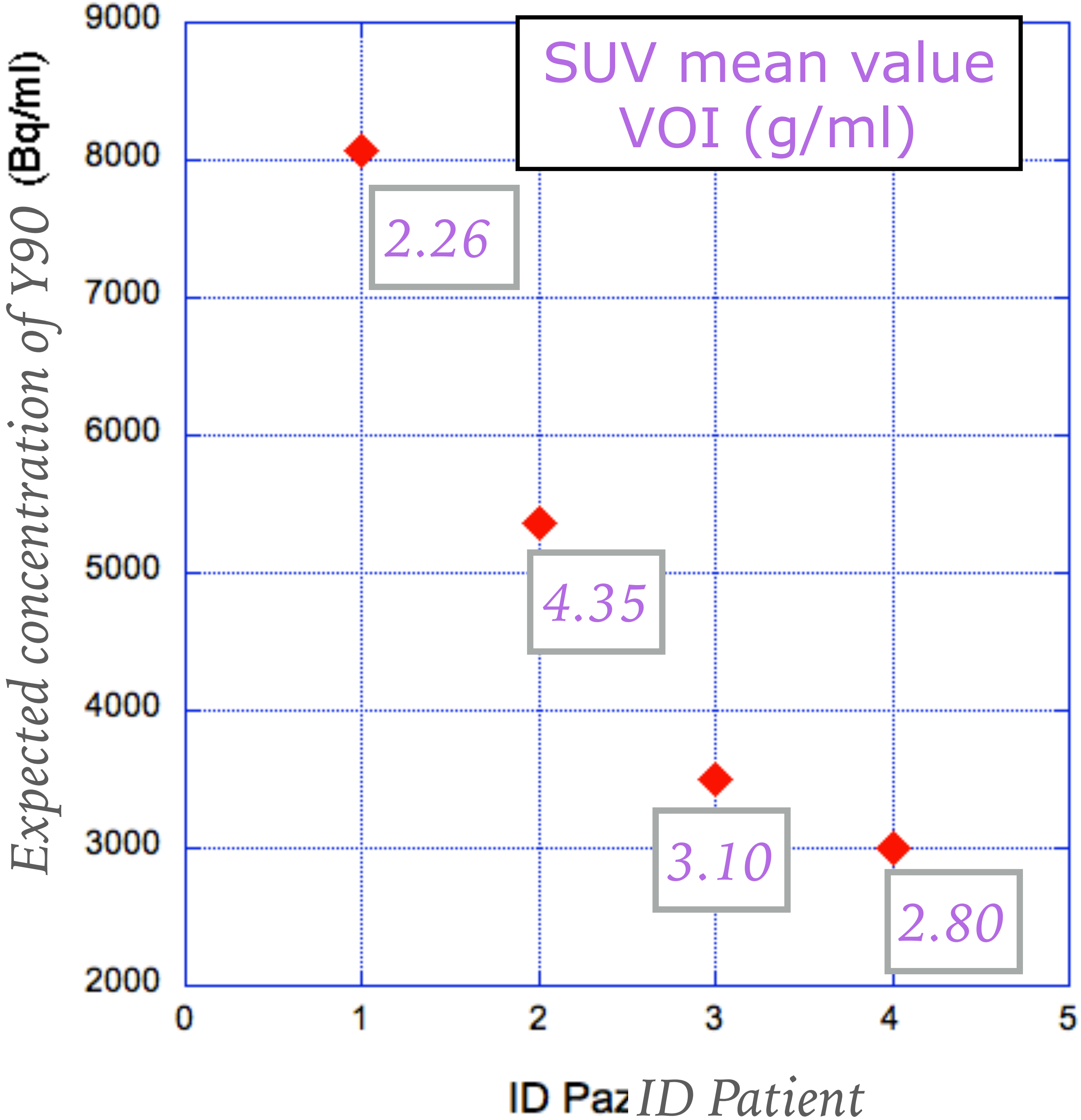


h=5mm

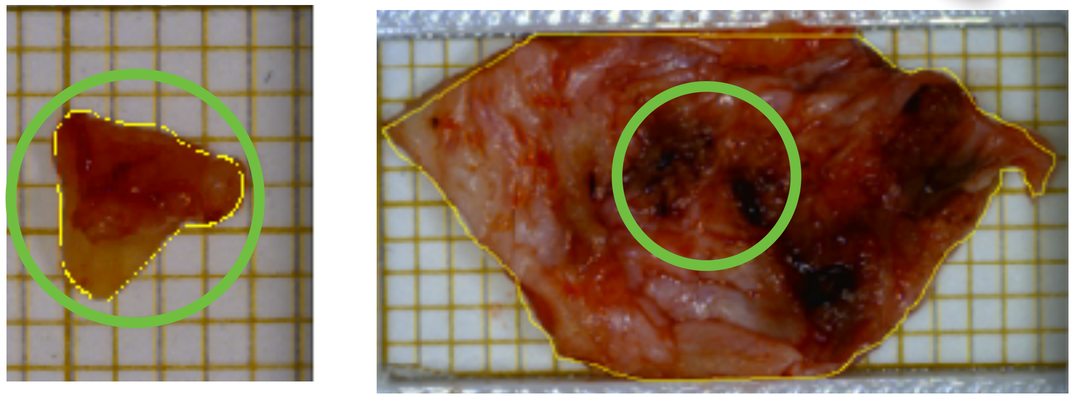
r=2.5mm

V~0.1ml

THE SAMPLES



PRELIMINARY

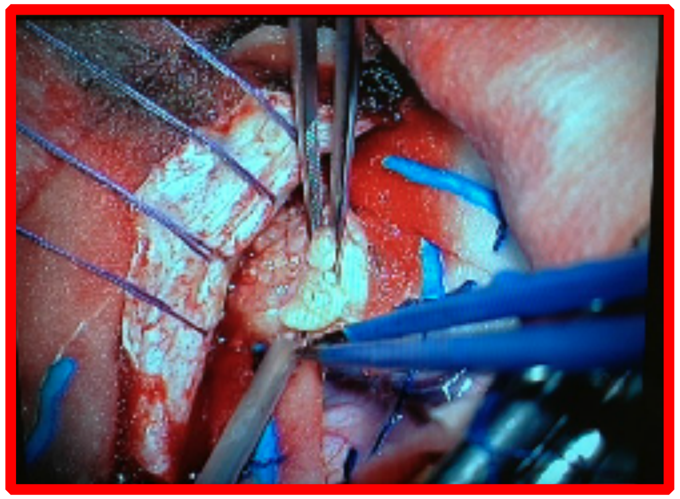


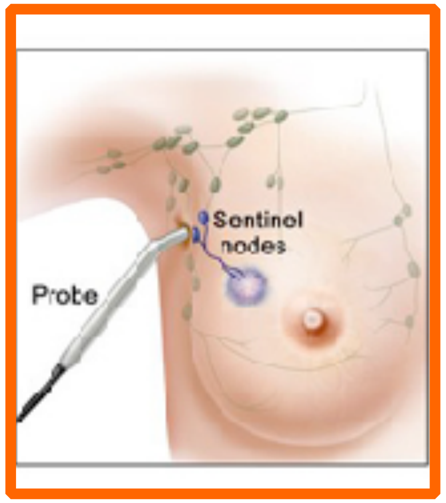
- High variability
  - Injected activity
  - Expression of receptors
  - Volumes and sample's shape
- Need of correction factors

INTRA-OPERATIVE PROBES

Needed when

- Complete tumor resection is mandatory
  - Example: brain, pediatric tumors
- Identification of lymph-node is needed
  - Example: breast tumor, melanoma
- Tumor identification can reduce invasiveness
  - Example: parathyroid adenoma, insulinoma

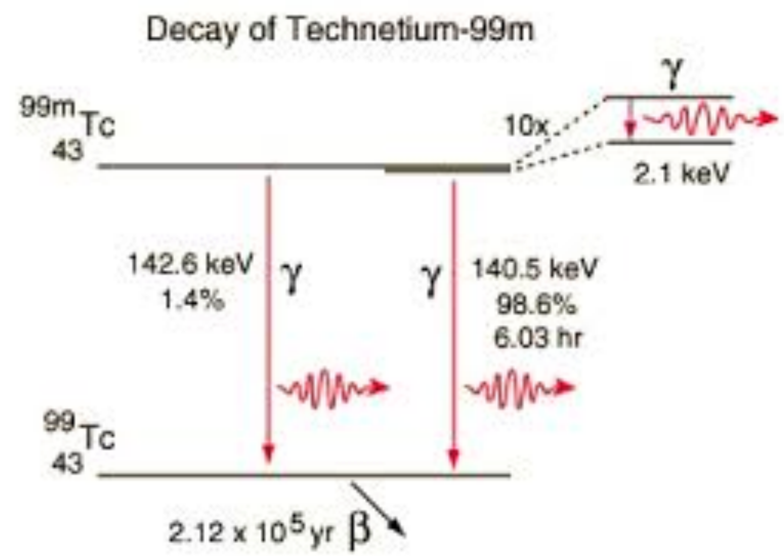




EXISTING: GAMMA PROBES

➤ Choice of radio-nuclide: **gamma emitting, in particular 99mTc**

- well known detectors (camera or probes)
- used for SPECT: large number of known radio-tracers



- Applications of interest:
  - Search for **tumor residuals** (colon cancer, parathyroid adenoma, osteoid osteoma)
  - Complete **sentinel-node mapping** (malignant melanoma and breast cancer)

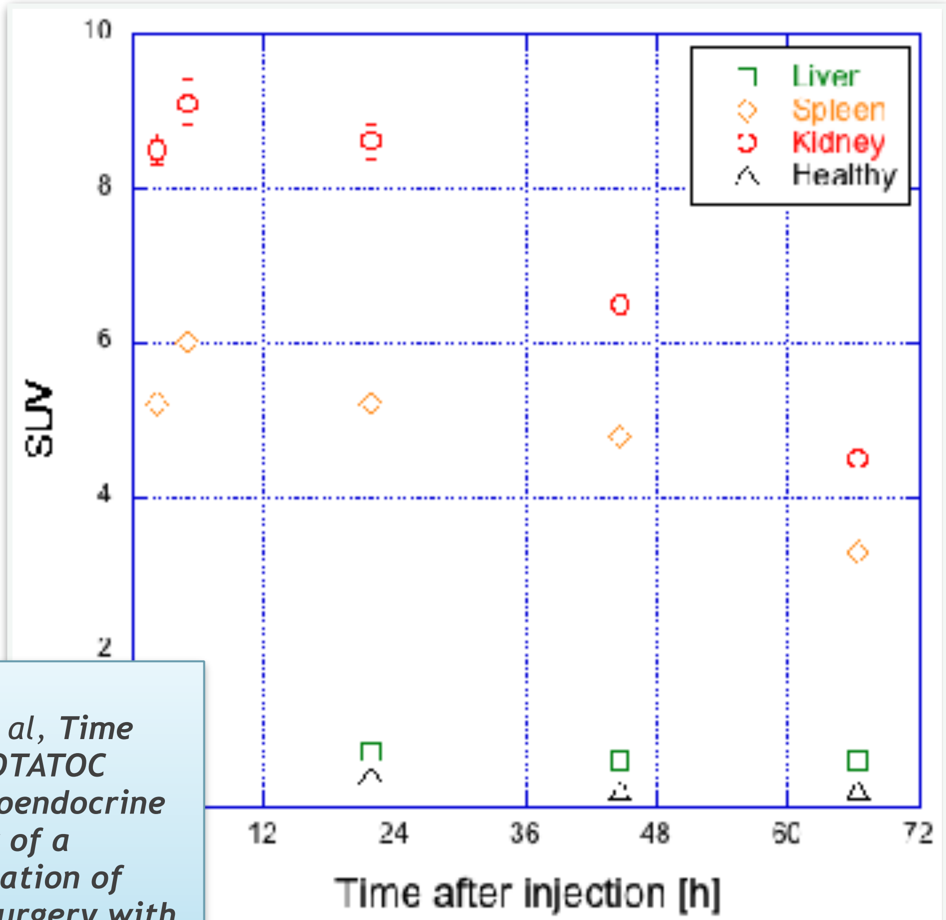
WASH OUT

F. Guerriero et al.,

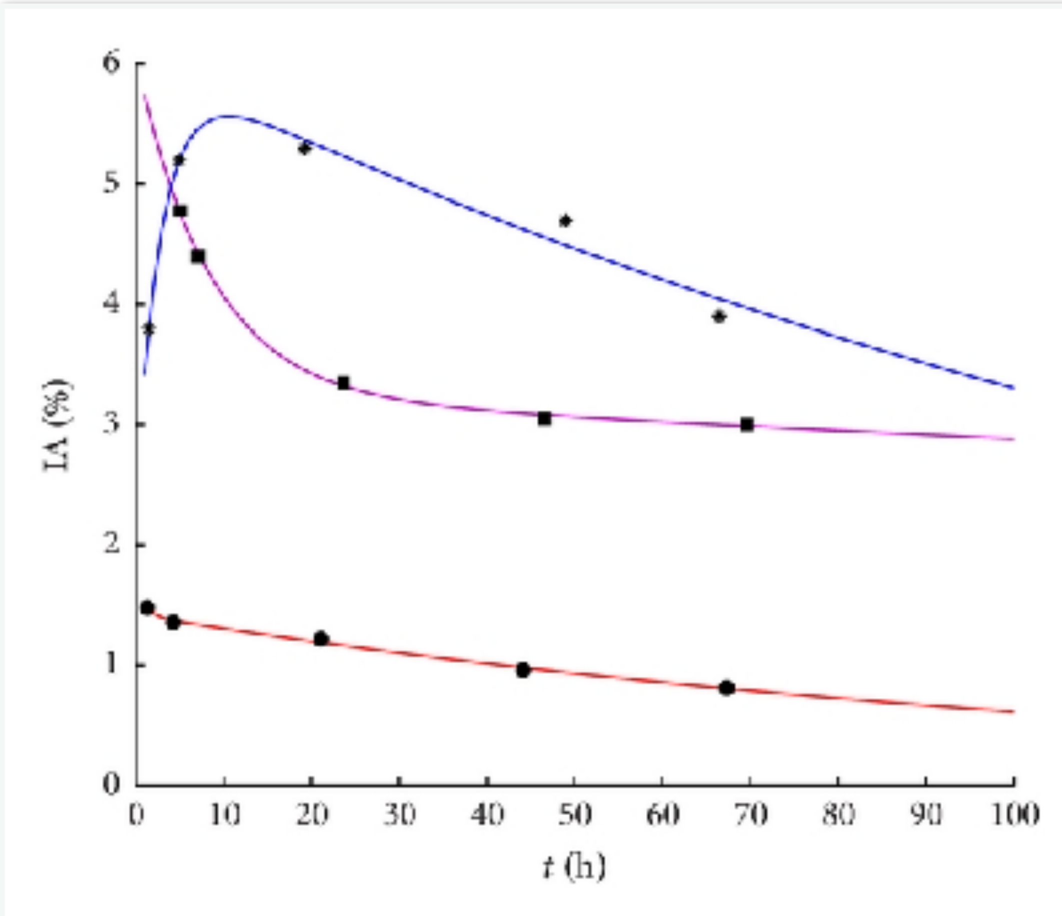
Kidney Dosimetry in 177Lu and 90Y Peptide Receptor Radionuclide Therapy: Influence of Image Timing, Time-Activity Integration Method, and Risk Factors

BioMed Research International (2013)

- Optimal time for perform ~ 24h after injection
  - Two different mechanisms: Accumulation and washout
  - Patient depending behavior

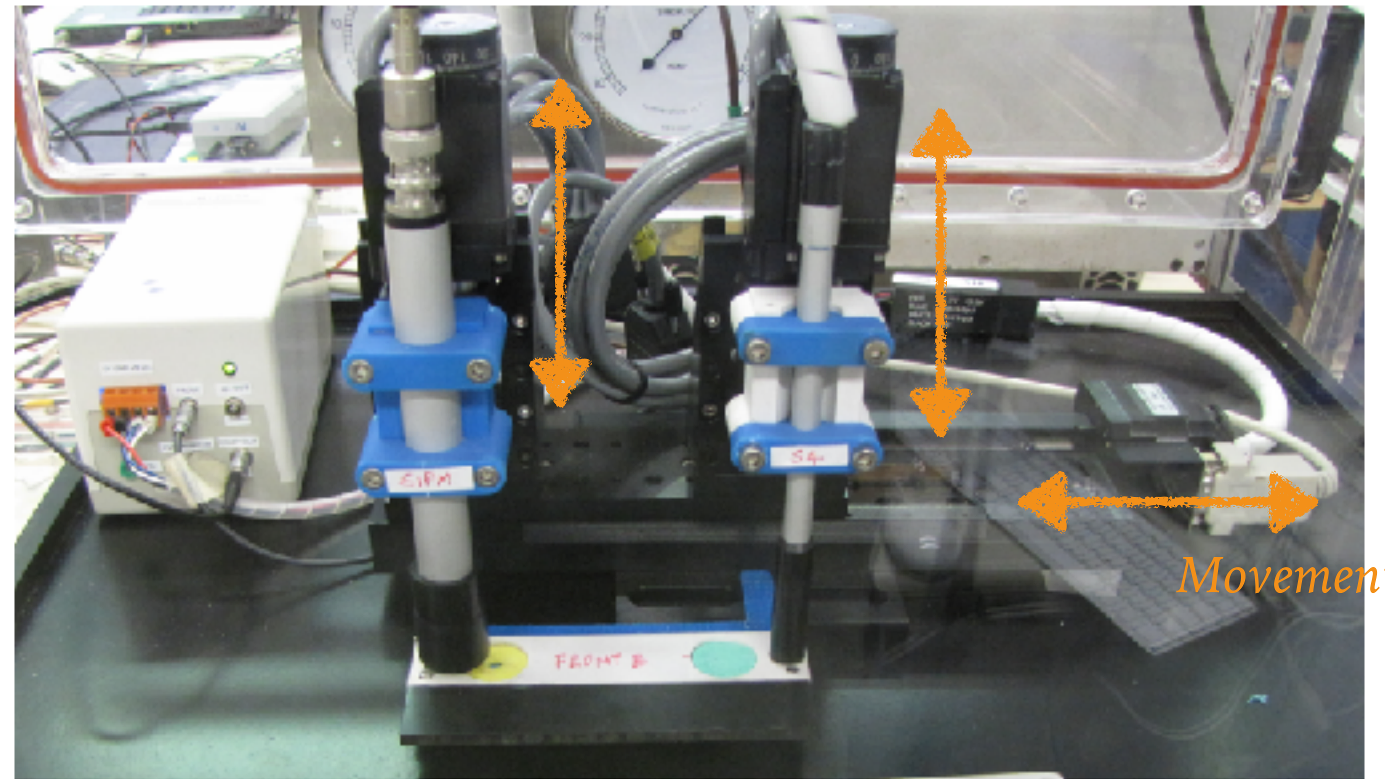


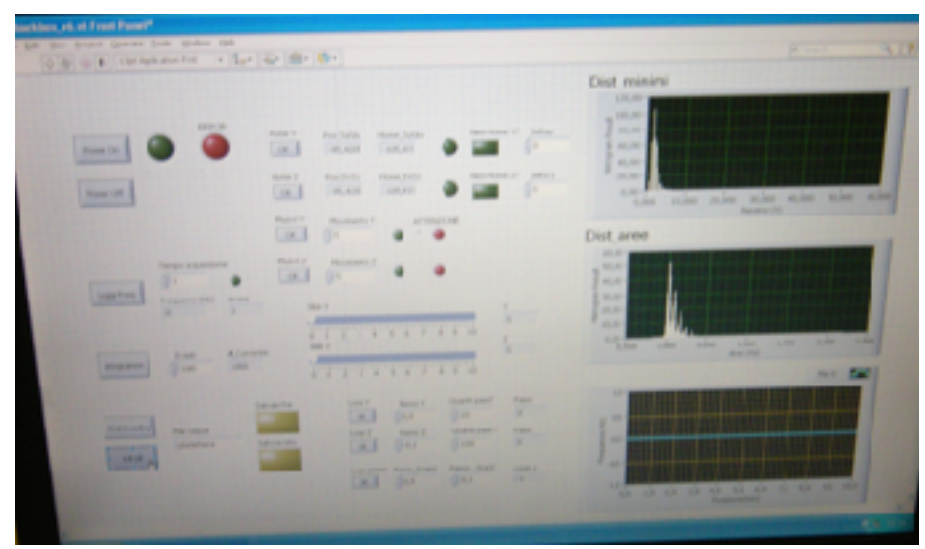
F. Collamati, A. Russomando et al, *Time evolution of DOTATOC uptake in Neuroendocrine Tumors in view of a possible application of Radio-guided Surgery with β- Decays.* J Nucl Med 2015

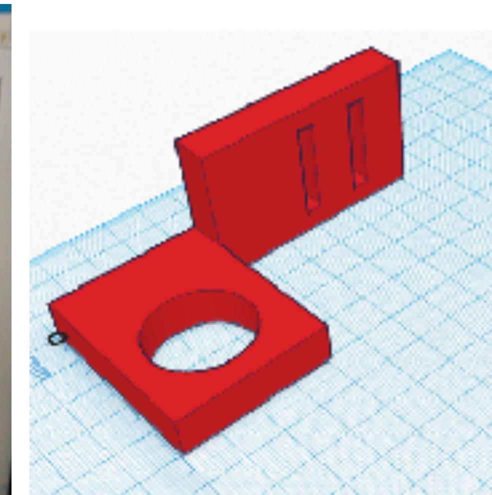


EXAMPLE OF MEASUREMENT

- Automated set-up
  - Driven by LabVIEW
  - 2-3 axis movement
  - Online data representation
  - Data stored for offline analysis
- GUI for user configuration
- Basic use of 3D cad
  - Small component printed in laboratory

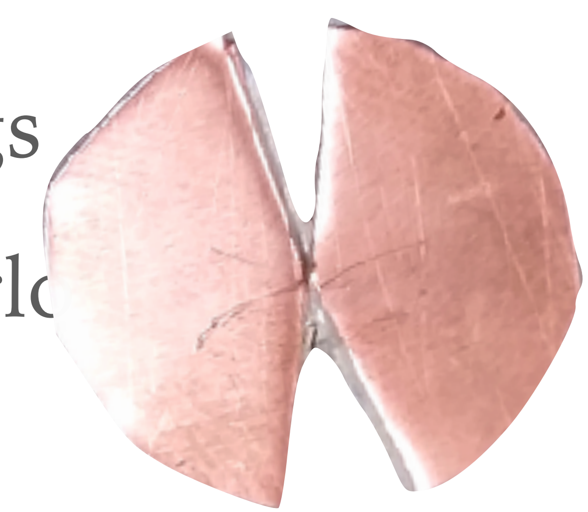


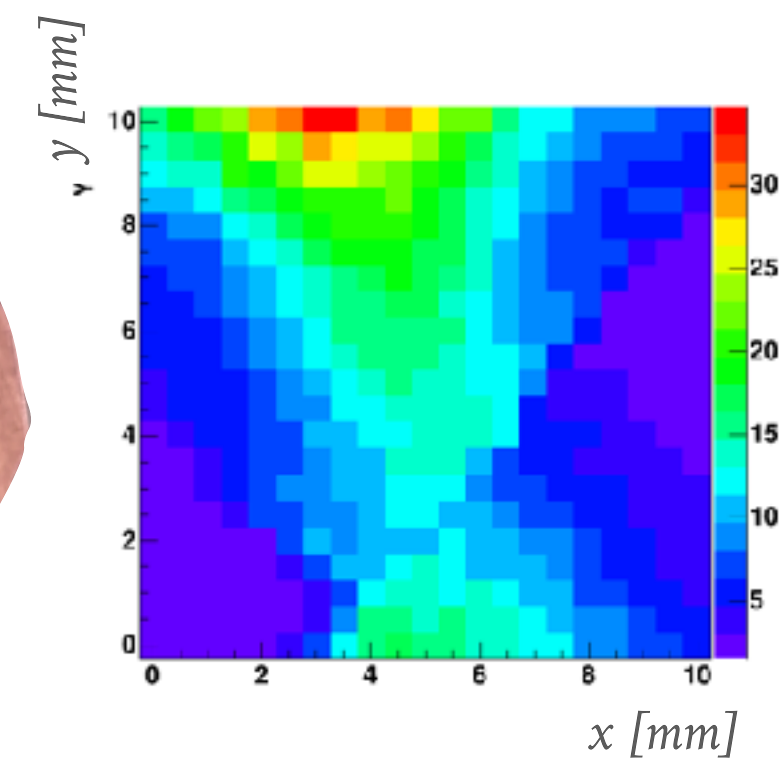




MATERIAL CHARACTERIZATION

- Stability to temperature variation
- Estimation of the light attenuation length
  - $\lambda = 5.03 \pm 0.23$ mm
  - Active volume optimization
- Diffusion
  - Effect of different wrappings
  - Fine tuning with MonteCarlo
  - Possibility of imaging (multianode PMT)





GAMMA PROBES APPLICATIONS

Local non-specific tracers

Systemic administration

TARGET Indication of	TUMOR Tumor type	UTILITY Clinical utility
Sentinel lymph node by intra- or peritumoral administration of ^{99m}Tc-colloids	Breast cancer	++
	Melanoma	+
	Skin cancer	++
	Penile/vulvar cancer	++
	Colon cancer	±
	Lung cancer	±
	Head and neck cancer	±
Tumor deposits by tumor-seeking agents (monoclonal antibodies, ^{99m}Tc-sestamibi)	Colon cancer	±
	Ovarian cancer	−
	Breast cancer	−
	Medullary thyroid cancer	+
	Melanoma	−
	Neuroblastoma	±
	Parathyroid adenoma	++
Bone abnormalities by ^{99m}Tc-diphosphonate	Osteoid osteoma	++
	Bone lesions suspected for bone metastasis	++
Occult tumors by intratumoral administration of an isotope tracer	Occult breast cancer	++

Mariani, Giuliano, Strauss 2004

Legend:
++ = proven clinical value
+ = may be of clinical value
± = clinical relevance insufficiently evaluated
− = proven not to be of clinical value

POSSIBLE RADIO-NUCLIDES

Radionuclide	Principali particelle emesse	$T_{1/2}$	Radiofarmaci
^{99m}Tc	γ	6.01 h	^{99m}Tc-MDP ^{99m}Tc-MIBI
^{18}F	β^+	110 min	^{18}F-FDG
^{111}In	γ	67.4 h	^{111}In-Octreotide
^{86}Y	β^+	14.7 h	^{86}Y-DOTATOC
^{68}Ga	β^+	68 min	^{68}Ga-DOTATOC
^{90}Y	β^-	64.1 h	^{90}Y-DOTATOC
^{177}Lu	β^-, γ	6.73 d	^{177}Lu-DOTATATE
^{131}I	β^-, γ	8.1 d	^{131}I-MIBG

SPECT

PET

Molecular RT

GAMMA RADIONUCLIDES

Table 3: Physical properties of radionuclides that have been utilized with the gamma detection probe in radioguided surgery

Radionuclides	Physical half-life	Principle gamma photon radiation emission(s)	Emission probability per decay (percent photon yield)
Cobalt-57 (^{57}Co)	271.8 days	14, 122, 136 keV	9.2, 85.5, 10.7%
Fluorine-18 (^{18}F)	110 minutes	511 keV*	19.3%
Galium-67 (^{67}Ga)	78.3 hours (3.26 days)	91, 93, 184, 209, 300, 393 keV	3.0, 37.8, 20.1, 2.4, 16.8, 4.7%
Indium-111 (^{111}In)	67.4 hours (2.81 days)	171, 247 keV	90.7, 94.1%
Iodine-123 (^{123}I)	13.2 hours	159, 529 keV	83.4, 1.3%
Iodine-124 (^{124}I)	100.3 hours (4.18 days)	511 keV*	not easily characterized
Iodine-125 (^{125}I)	1443.4 hours (60.14 days)	35 keV	6.7%
Iodine-131 (^{131}I)	193.0 hours (8.04 days)	80, 284, 364, 637, 642, 723 keV	2.6, 6.1, 81.2, 7.3, 0.2, 1.8%
Technetium-99m (^{99m}Tc)	6.04 hours	140, 142 keV	88.5, 0.023%
Thallium-201 (^{201}Tl)	73.0 hours (3.04 days)	71, 135, 167 keV	47.0, 2.7, 10.0%

* The 511 keV gamma photons are generated from positron-electron annihilation.

ONGOING STUDY

Flexible laparoscopy gamma probe with selectable field of views

- **Flexible** : Reduce limitation related to the reduced tactile sensation
- **Laparoscopic** : Lower invasiveness and better outcome for the patients, reduced dose to medical personnel
- **Gamma** : Focussing on photon with the possibility to move to other radio tracers
- **Selectable** : Easy possibility redesign of the device to match the specificity of each clinical case
- **Field of views** : Improve the informations provided to the surgeon, to a better understanding of the environment (going towards imaging surgery)

PHOTON SENSITIVITY – REAL PATIENT CASE