Radio-Guided Surgery for tumor resection exploiting β^- decays

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Outline

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  - ✓ Identification of clinical case candidates and feasibility study.
  - ✓ Detector development and tests.
  - ✓ First clinical tests with patients.
  - ✓ Predictions for the **β^- RGS**.
  - ➡ "Ex-vivo" test during surgery (in progress).
  - ➡ Development of new specific radio-tracer (in progress).

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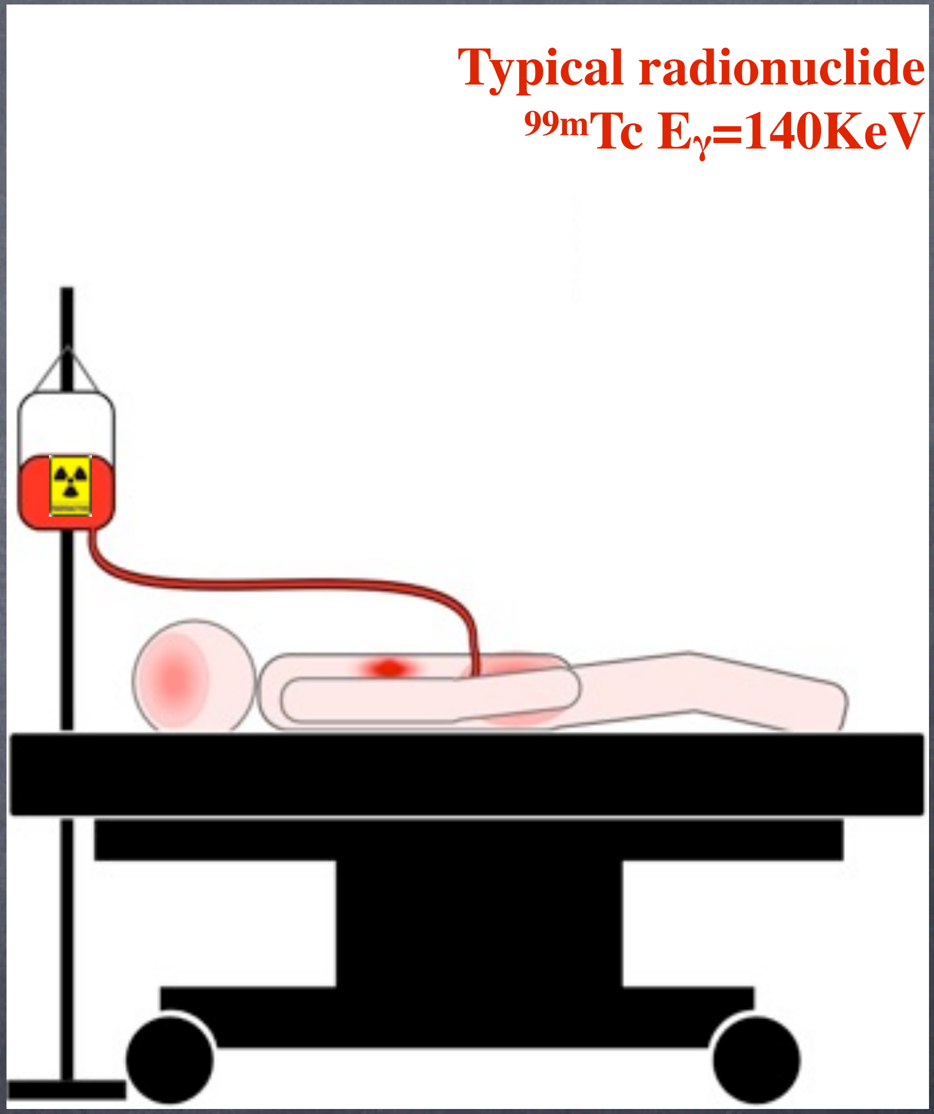
- Conclusions.

Radio-Guided Surgery: how does it work?



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1. **Administer** to patient, before operation, (either systemically or locally) a drug which:
   - the tumor takes up significantly more than the healthy tissue;
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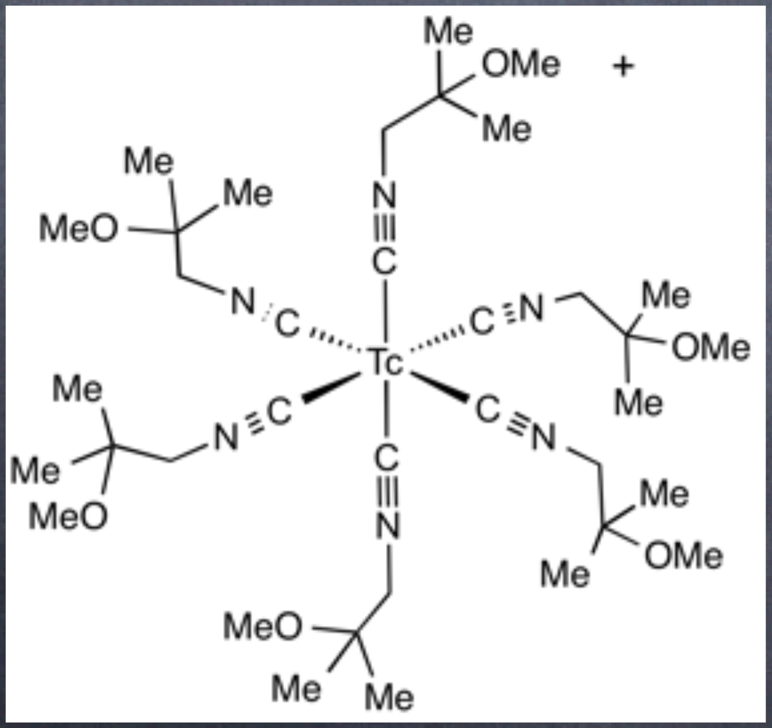

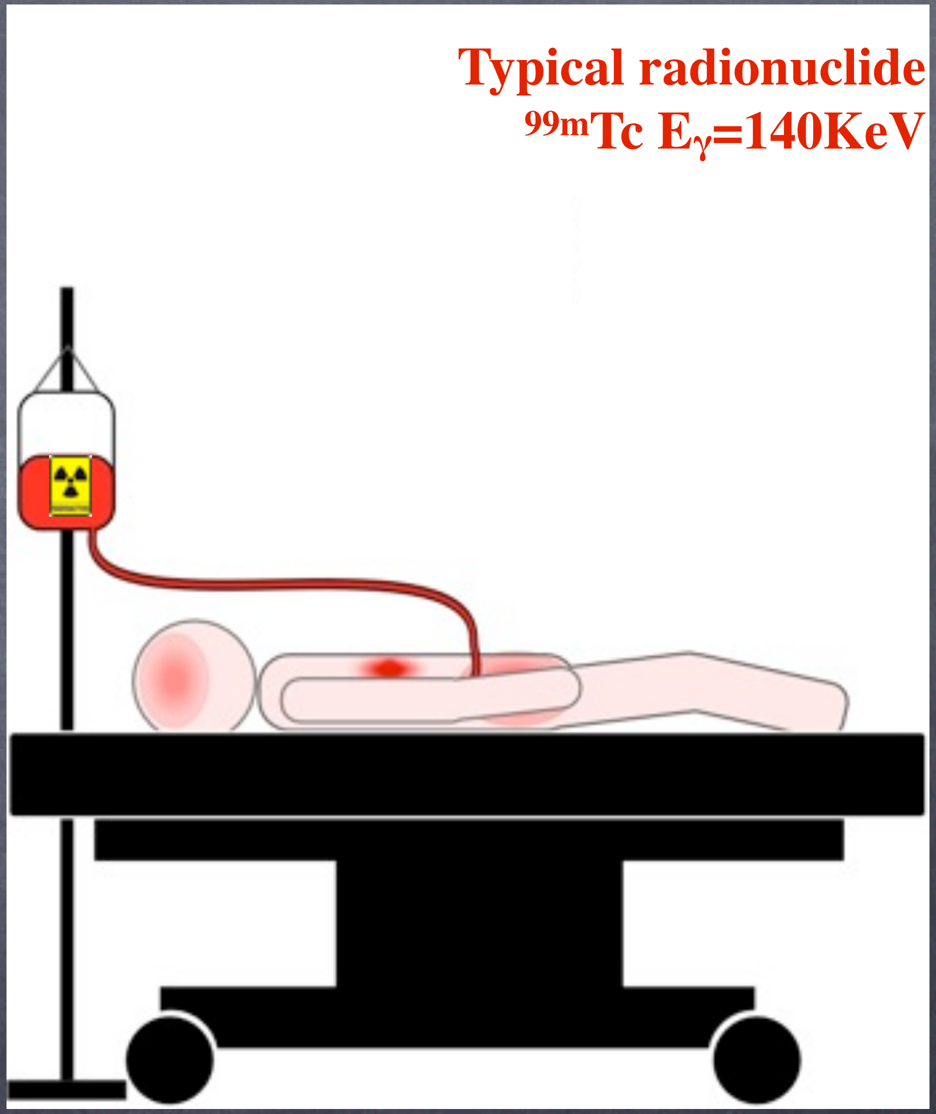

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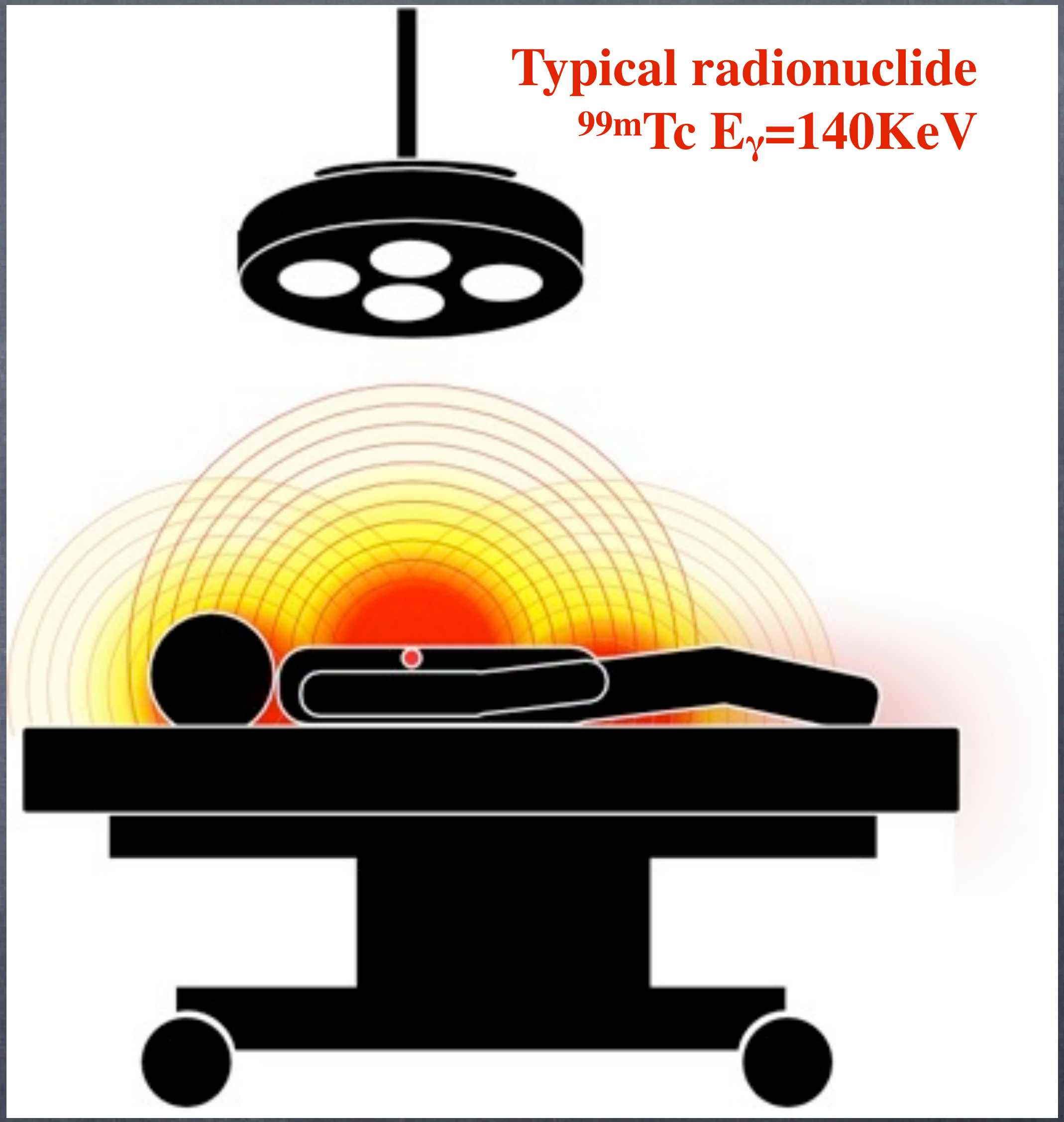

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   - the tumor takes up significantly more than the healthy tissue;
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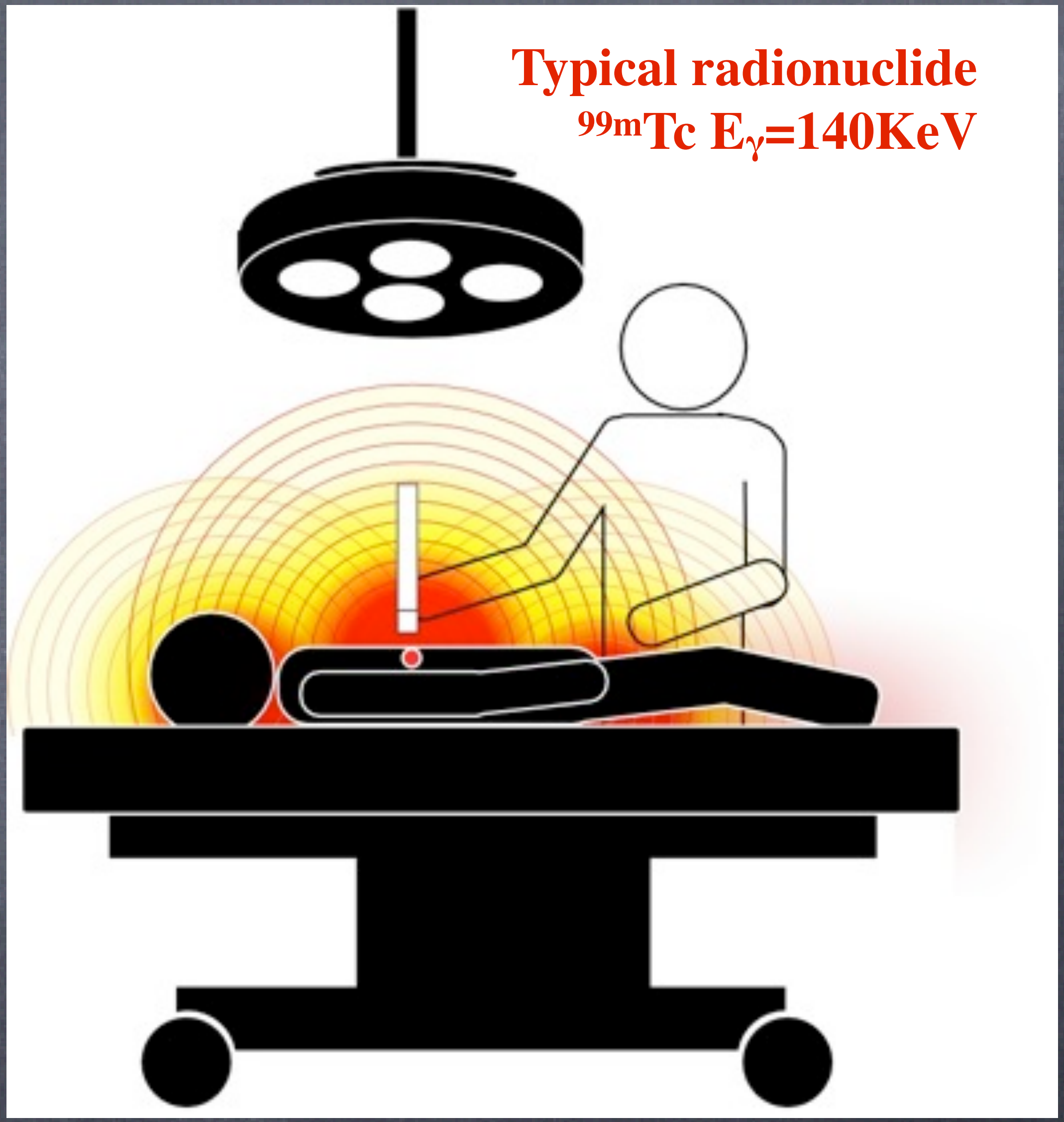
2. **Wait** for the drug to diffuse to the margins of the tumor.
3. **Start operation**
   - Remove the bulk of the tumor
   - Verify with an intraoperative probe that detects the emitted particles the presence of:
     - Tumor residuals
     - Infected lymph node



Radio-pharmaceutical

Basic concepts of Nuclear Medicine:

Injection of radioactive material inside the patient.

If the emitted particles "**escape**" the patient

→ **Diagnostics**: scintigraphy (SPECT), Positron Emission Tomography (PET), Radio-guided surgery (RGS)

- gamma radiation and β^+ decays.
- Low Activity (MBq/kg).
- Life time radionuclide: minutes/hours.

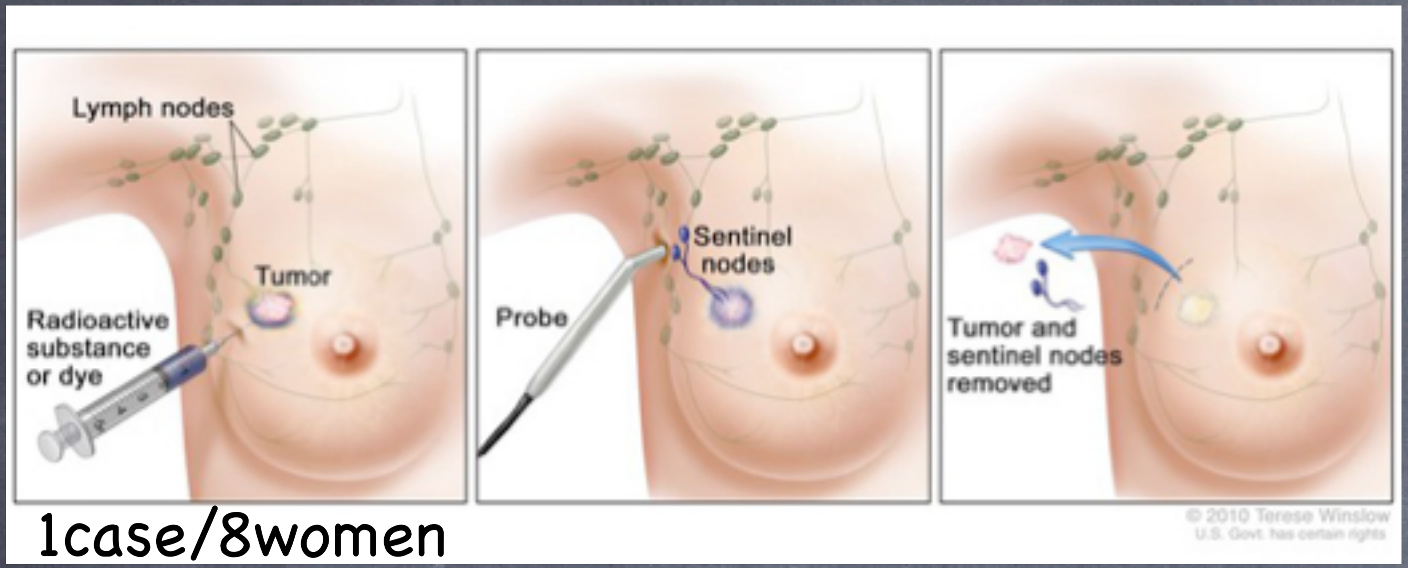
If the emitted particles **interact inside** the patient

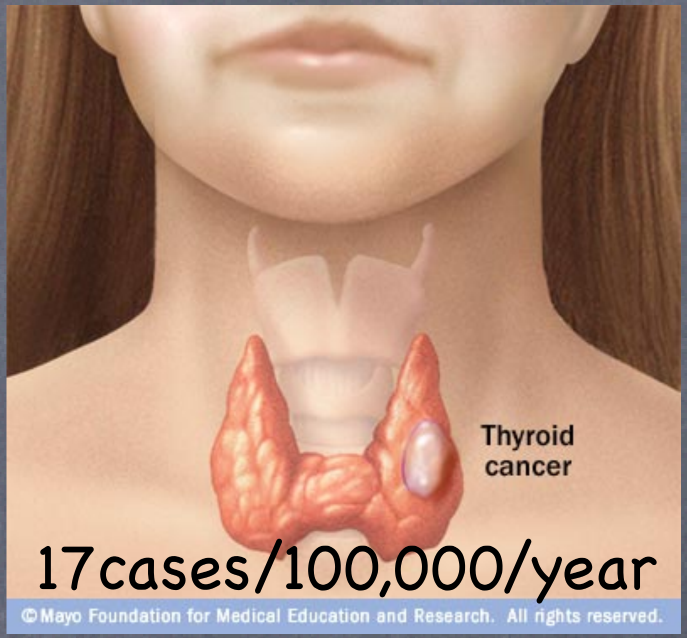
→ **Therapy**: Radio-Metabolic Therapy, Brachitherapy

- β^- decays.
- High Activity (50-100MBq/kg).
- Life time radionuclide: days.

isotope	symbol	Z	$T_{1/2}$	decay	gamma (keV)	positron (keV)
Imaging:						
fluorine-18	^{18}F	9	109.77 m	β^+	511 (193%)	249.8 (97%)[15]
gallium-67	^{67}Ga	31	3.26 d	ec	93 (39%), 185 (21%), 300 (17%)	-
krypton-81m	^{81m}Kr	36	13.1 s	IT	190 (68%)	-
rubidium-82	^{82}Rb	37	1.27 m	β^+	511 (191%)	3.379 (95%)
nitrogen-13	^{13}N	7	9.97 m	β^+	511 (200%)	1190 (100%)[16]
technetium-99m	^{99m}Tc	43	6.01 h	IT	140 (89%)	-
indium-111	^{111}In	49	2.80 d	ec	171 (90%), 245 (94%)	-
iodine-123	^{123}I	53	13.3 h	ec	159 (83%)	-
xenon-133	^{133}Xe	54	5.24 d	β^-	81 (31%)	0.364 (99%)
thallium-201	^{201}Tl	81	3.04 d	ec	69–83* (94%), 167 (10%)	-
Therapy:						
yttrium-90	^{90}Y	39	2.67 d	β^-	-	2.280 (100%)
iodine-131	^{131}I	53	8.02 d	β^-	364 (81%)	0.807 (100%)

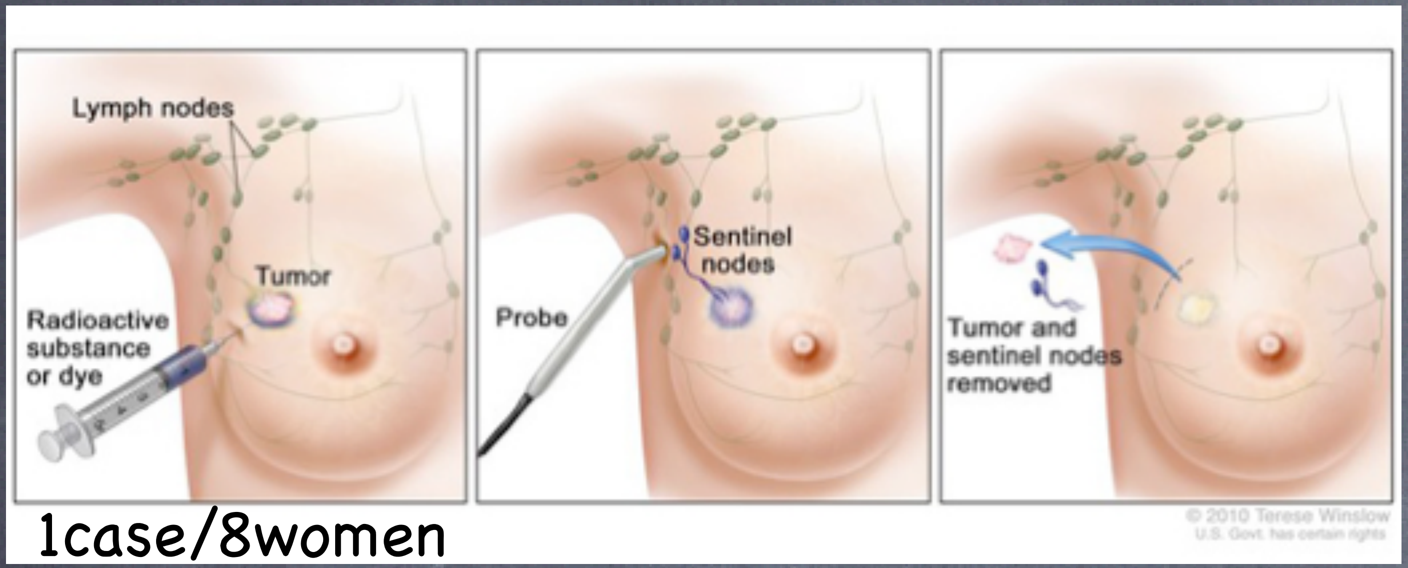
RGS: Clinical Applications

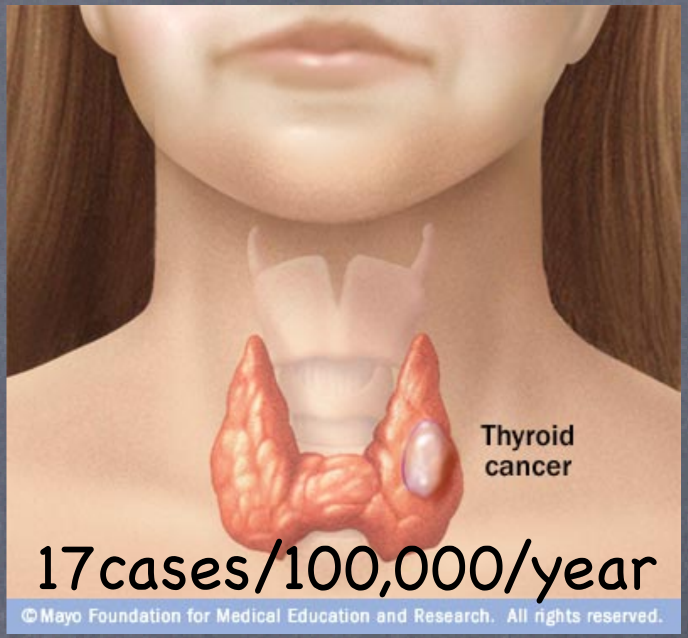




- Many clinical applications:
  - thyroid carcinoma lymph-node recurrence;
  - sentinel-node mapping for breast cancer and melanoma.
- Minimizes the surgical invasiveness.

RGS: Clinical Applications





- Many clinical applications:
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- Minimizes the surgical invasiveness.

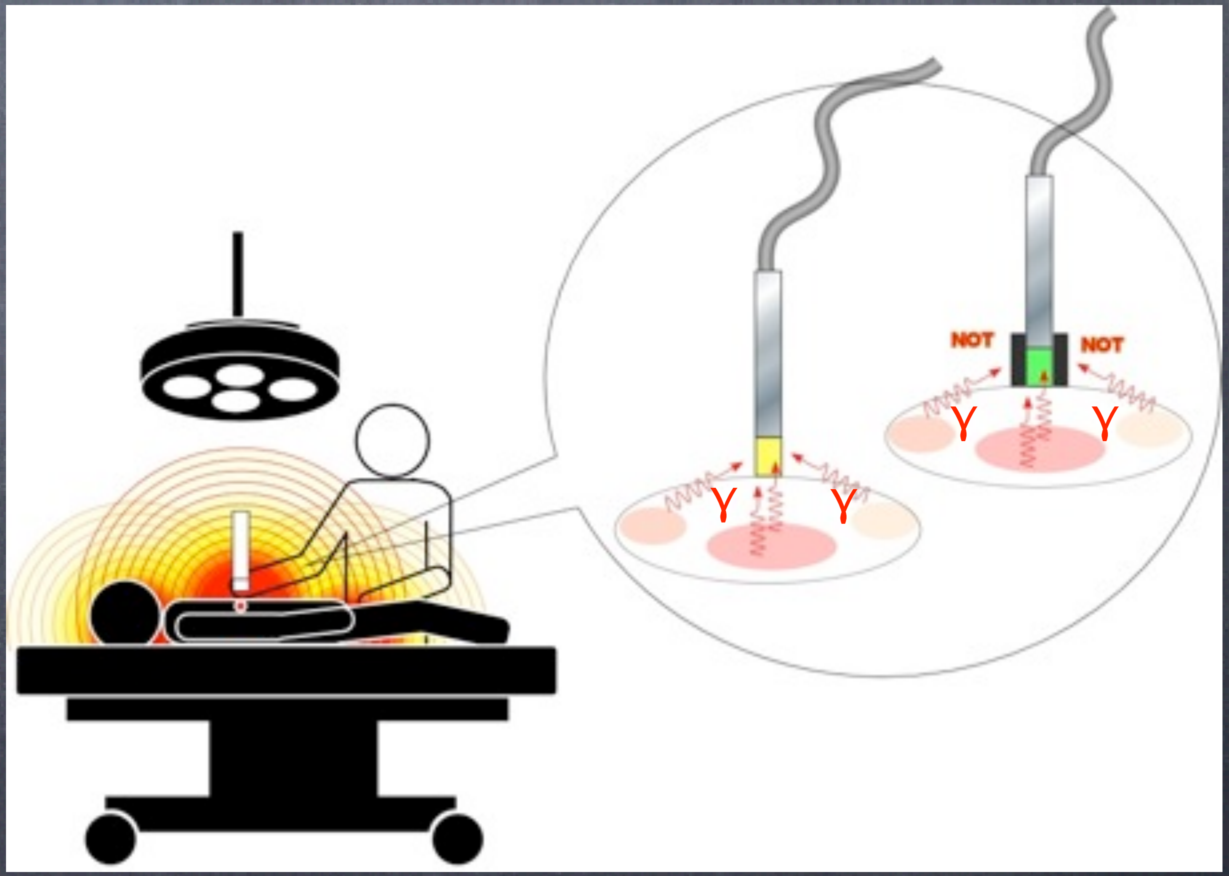
Critical for those tumors where a **complete surgical resection** is the only possible therapy.

Established Technique

γ emitting tracer + GAMMA CAMERA

- Typical radionuclide ^{99m}Tc (E_γ=140KeV)

Gamma decays



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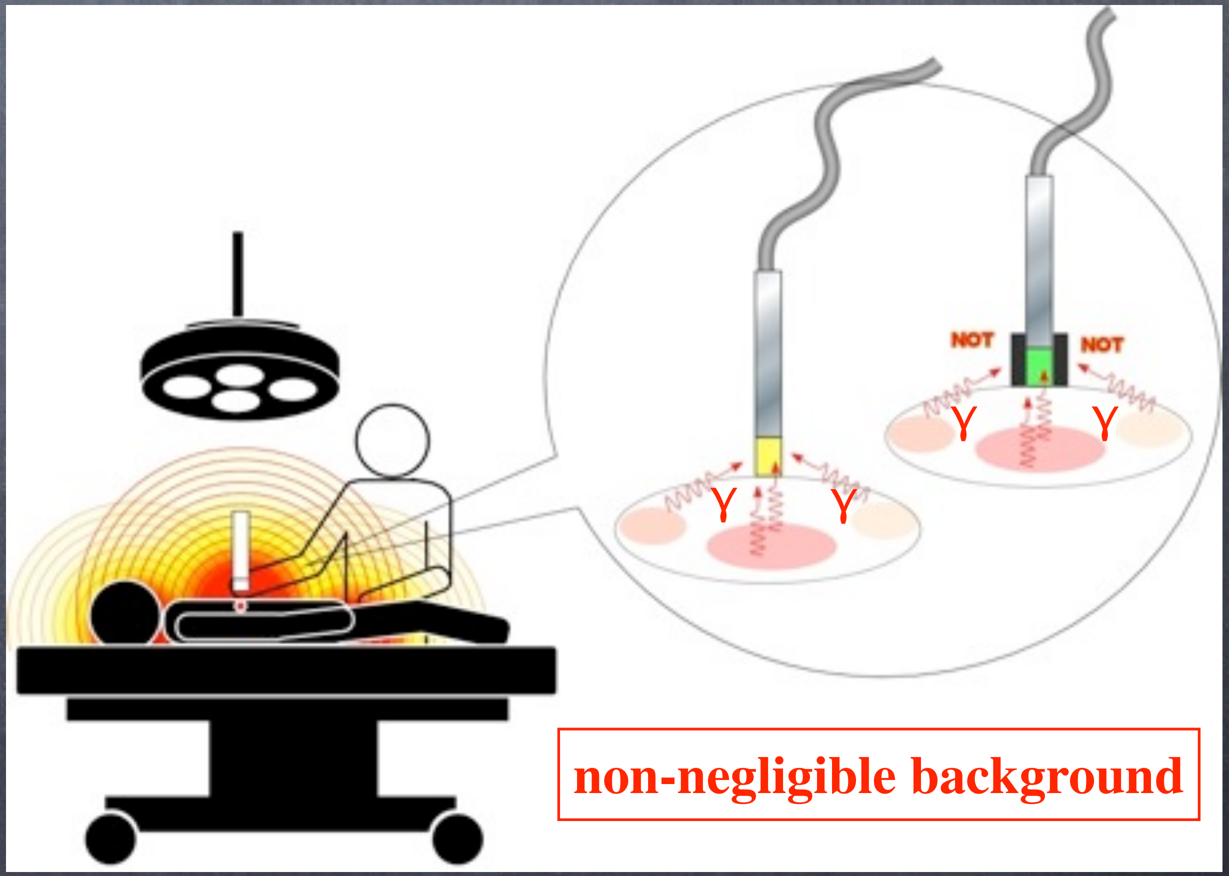
CURRENT LIMITS:

Long range of photons involves

- Exposure of medical personnel.
- Uptake in nearby healthy tissue

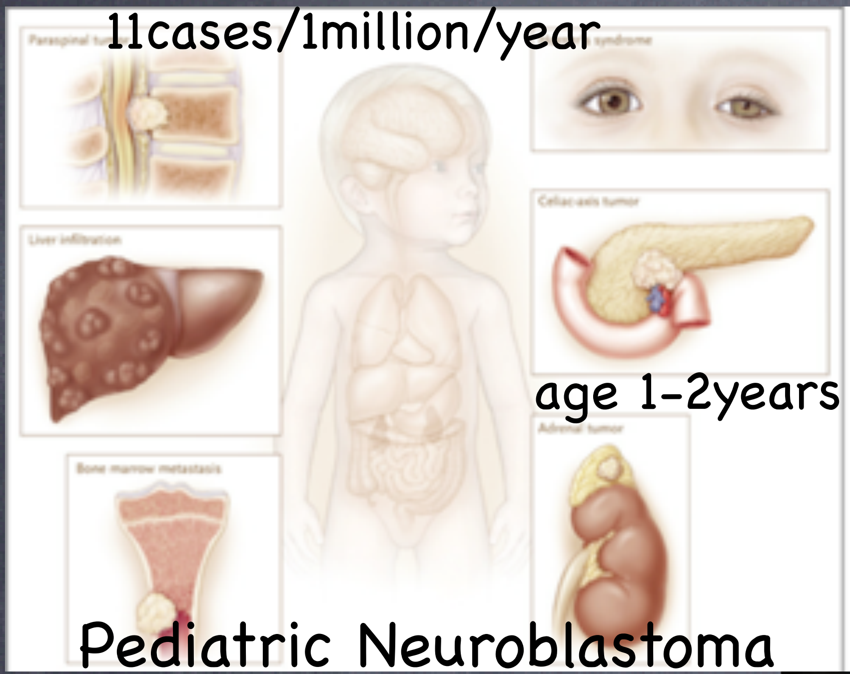
→ non-negligible background.



RGS would help

The non-negligible background prevents the γ RGS application:

TUMORS of INFANCY

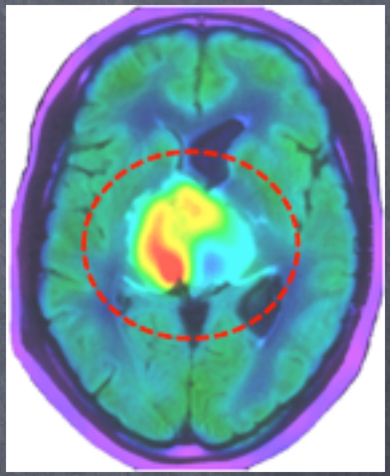


ABDOMINAL TUMORS

BRAIN TUMORS

Despite the resolution of neuronavigation, after the tumor mass removal

- location of the soft cerebral tissue is spoiled;
- brain shape changes with respect to the images acquired before.



RGS is critical for those tumors where a complete surgical resection is crucial both for recurrence-free survival and overall survival.

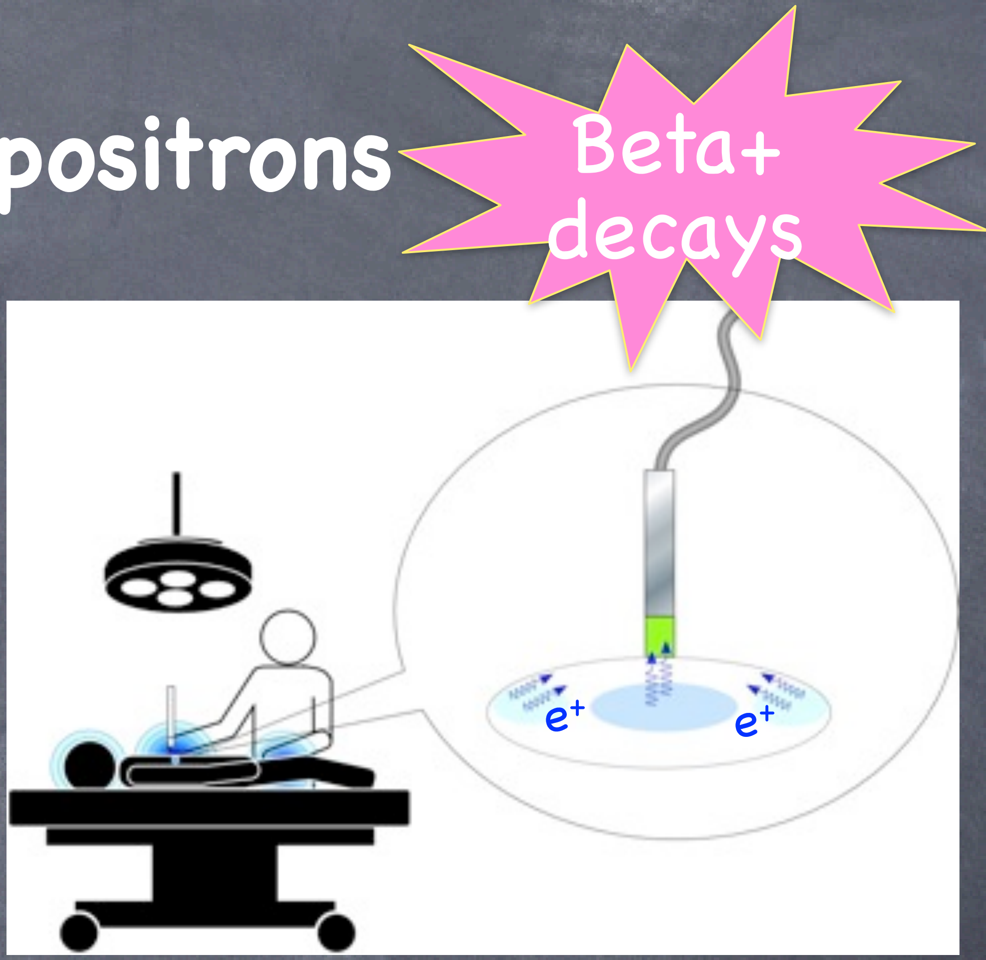
Ongoing Studies

β^+ radio-tracer + PROBE detecting positrons

Beta+ decays

Ongoing Studies

β⁺ radio-tracer + PROBE detecting positrons



PROS

- ✓ Positrons travel 100 times less than gammas.
- ✓ High spatial resolution and sensitivity
  - ➔ clear delineation of radioactive tissue.
- ✓ PET tracers with known protocols can be used.

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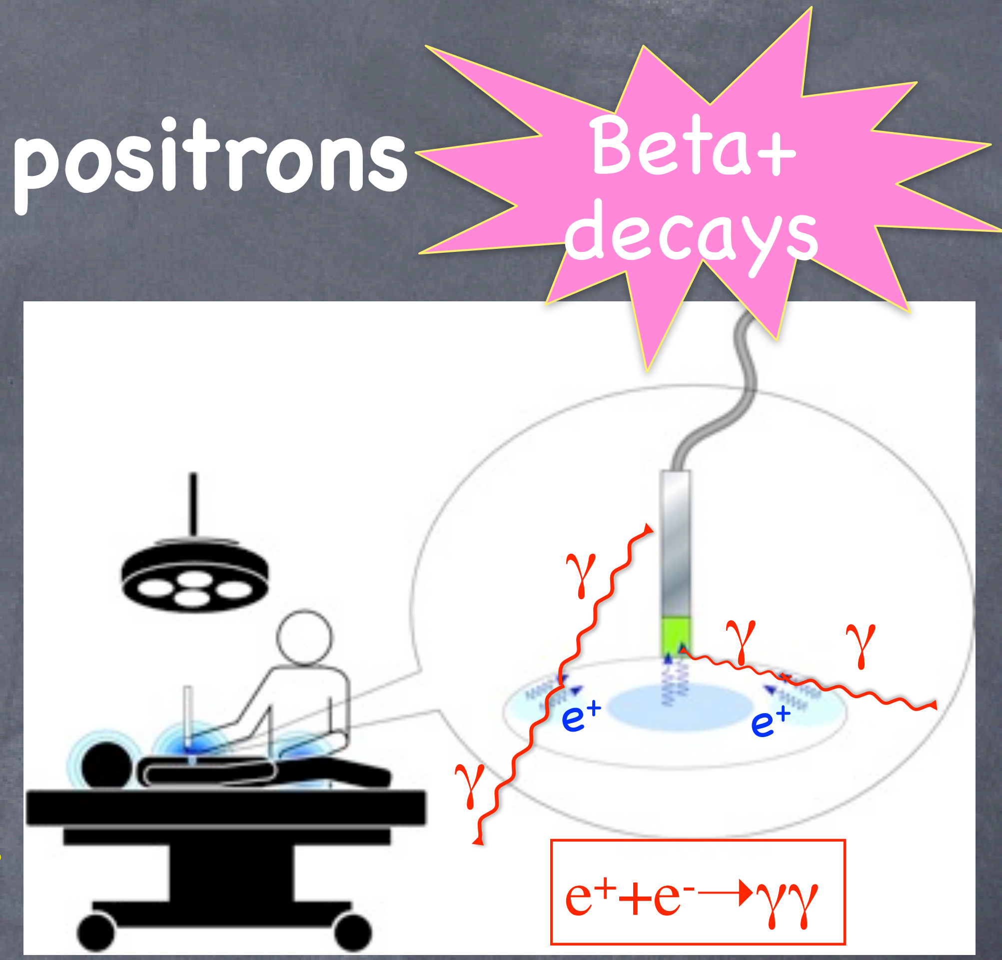

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CONS

- Limited by gamma background $e^+ + e^- \rightarrow \gamma\gamma$
  - Requires dual-mode devices for background subtraction.
  - Slow real-time performance.
  - Still limited range of applications.

Our Proposal

RGS exploiting β^- decays

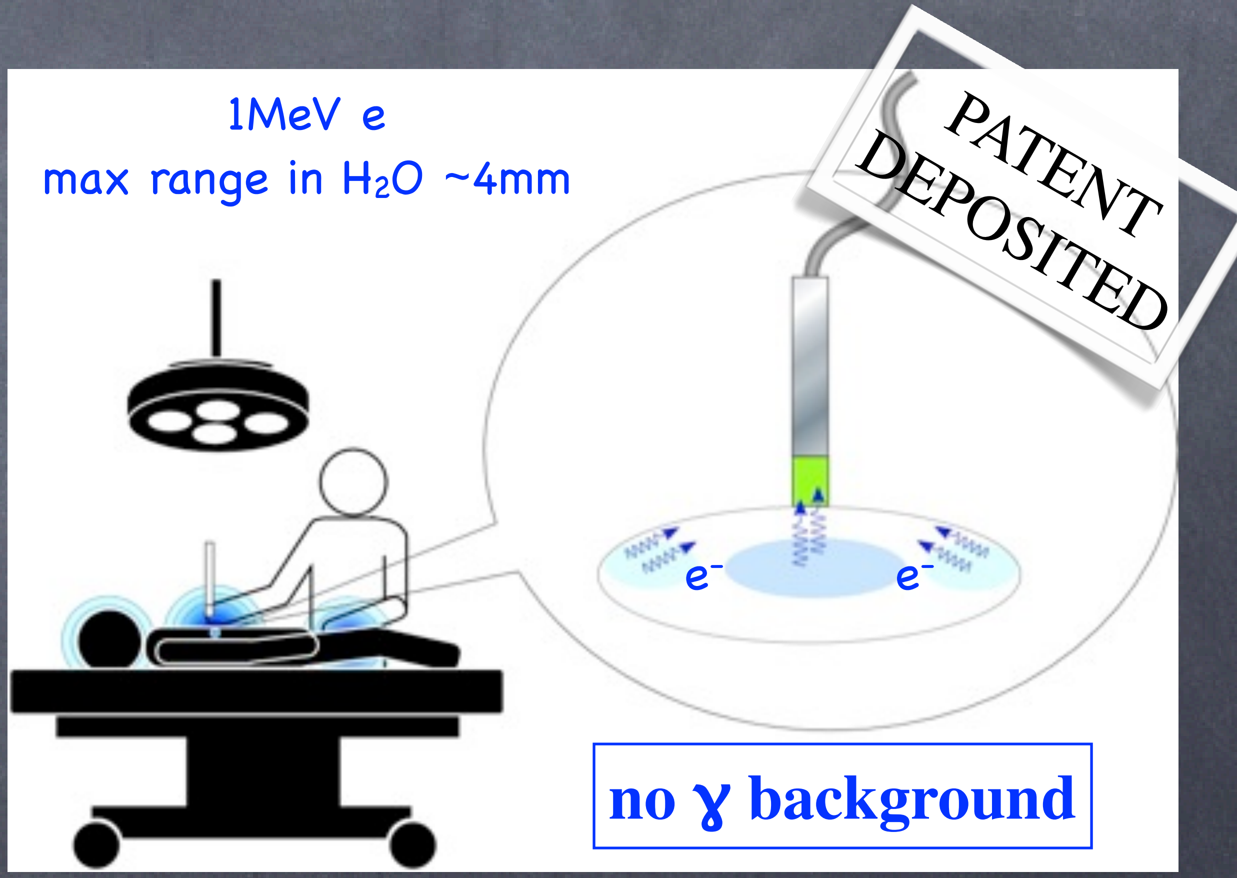
β^- RGS

β^- emitting tracer + PROBE detecting e^-

- Typical radionuclide ^{90}Y (end-point 2.3MeV, $\tau_{1/2}$=64h)

Very low γ background around the lesion:

Beta-decays



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

β⁻ RGS

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Very low γ background around the lesion:

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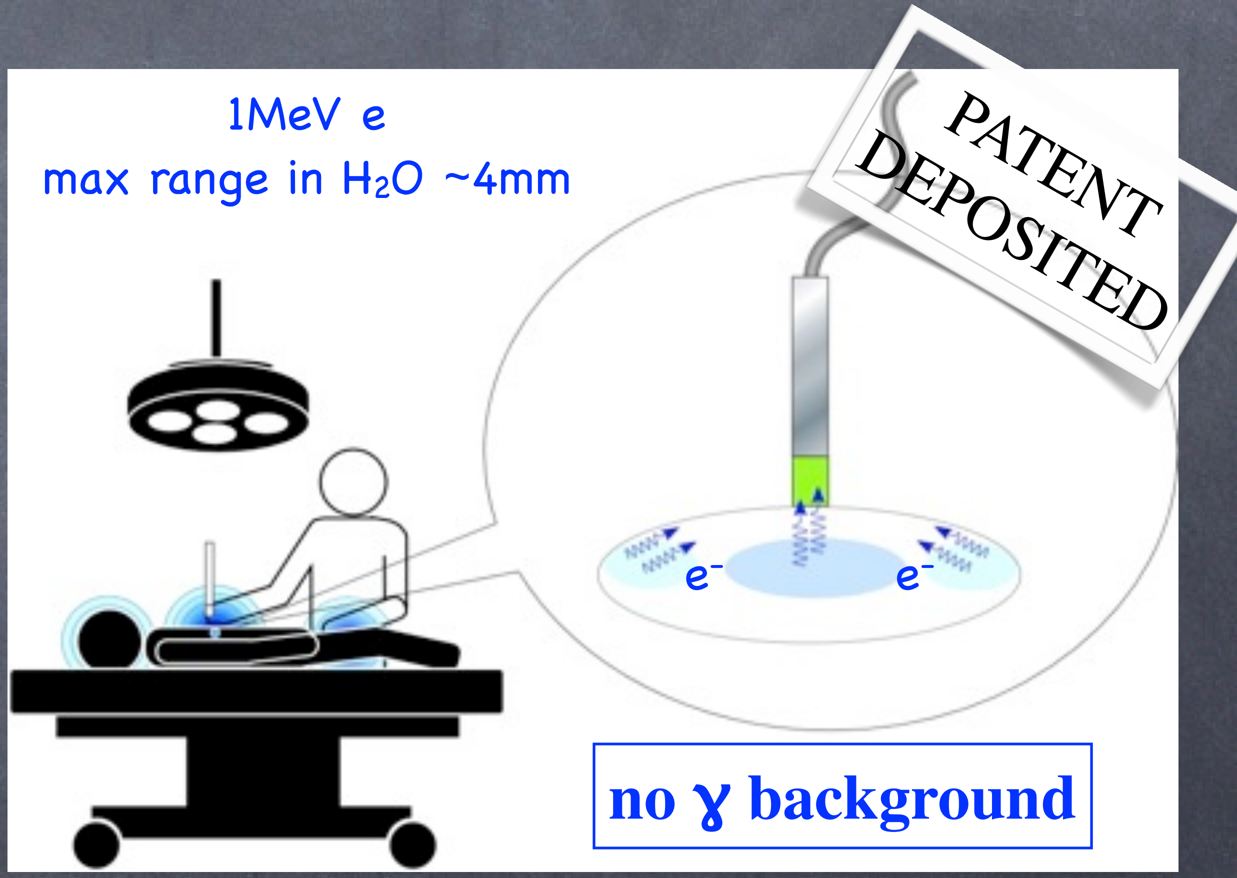
- **low injected activity** to detect tumor remnants;
- **low exposure** to radiation;
- simple and compact device.



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- **low sensitivity to activated tissue in depth** due to short range of electrons.

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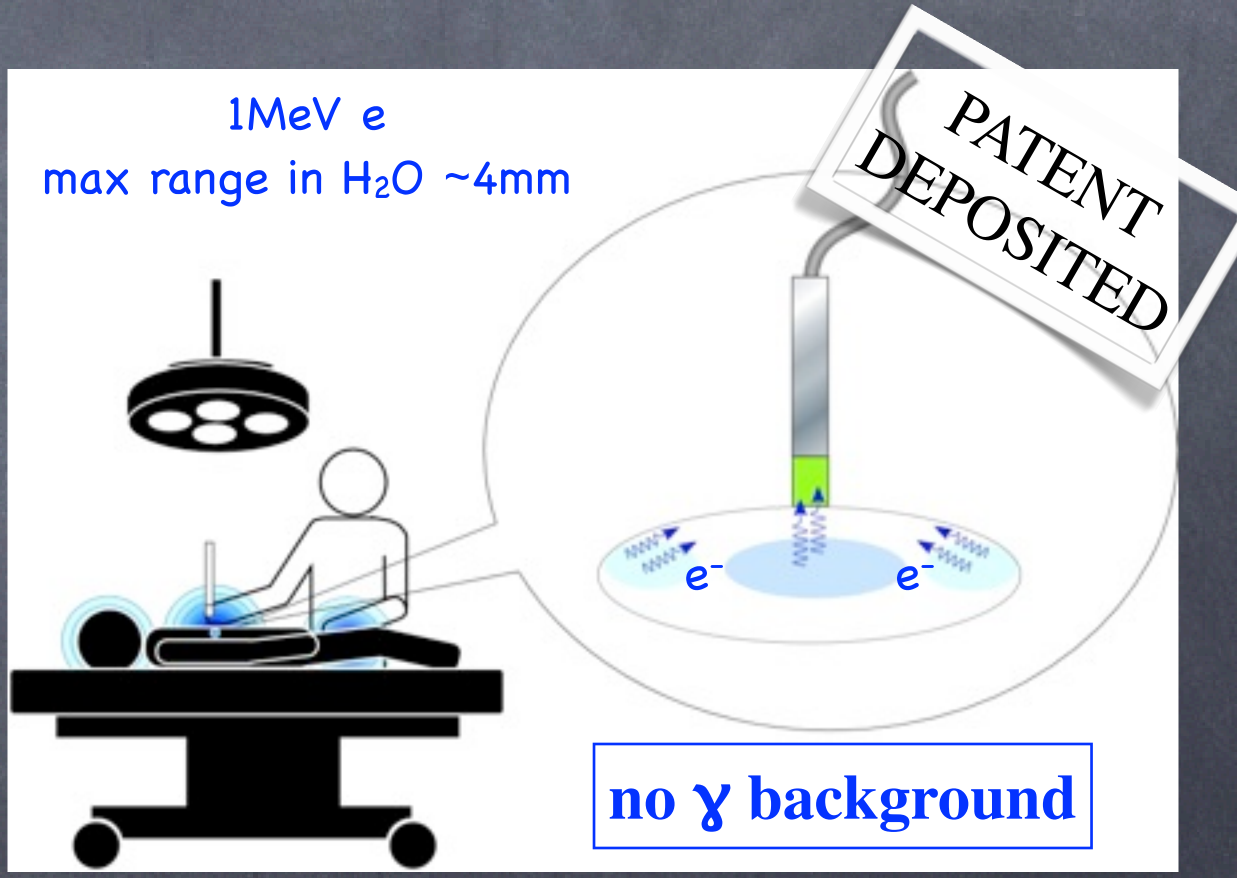

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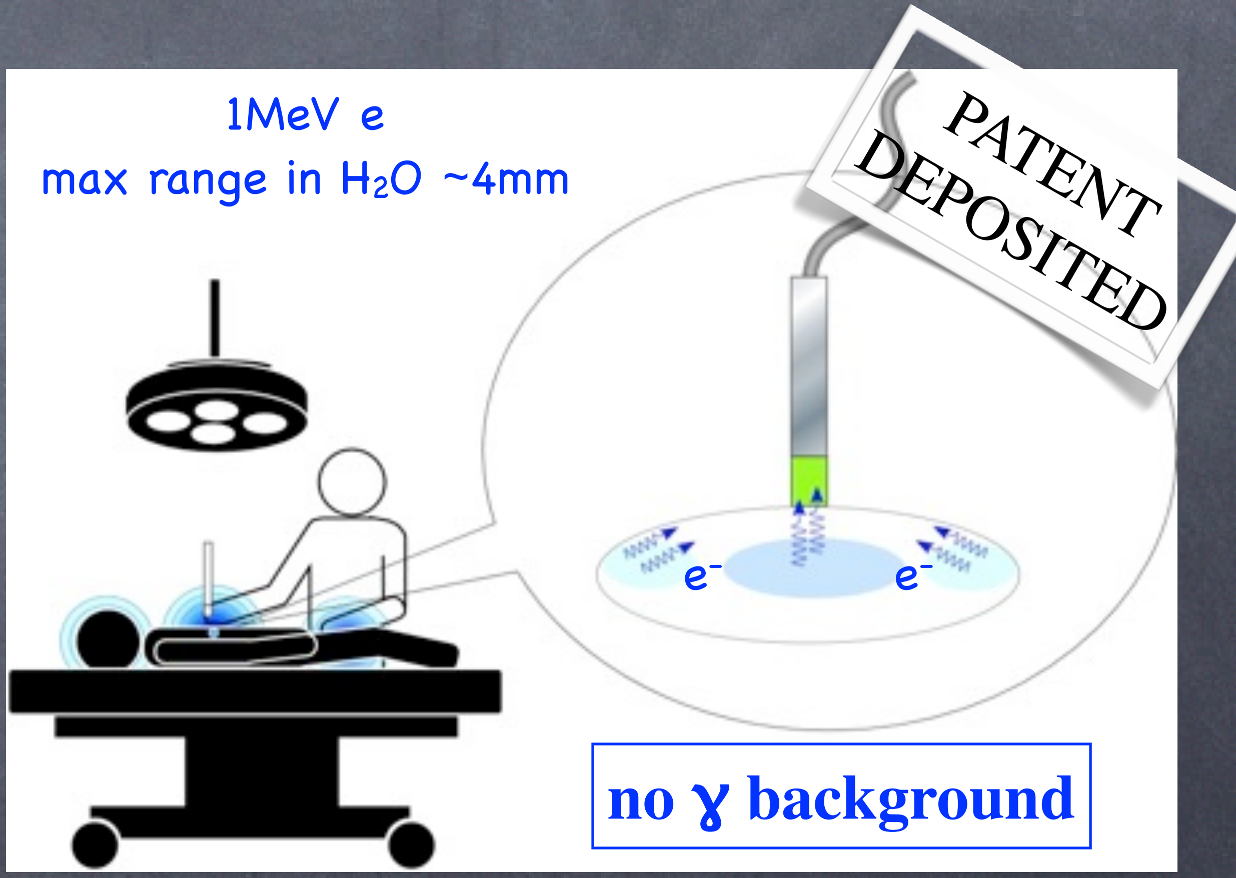

May extend the technique to cases with a large uptake of nearby healthy organs: **abdominal** or **brain tumors**.

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

Applied Radiation Physics Group

CHIRONE

INFN Istituto Nazionale di Fisica Nucleare

SAPIENZA Università di Roma

iit @SAPIENZA

Istituto Italiano di Tecnologia

Collaborations with **bio-engineers**, **medicinal chemists**, **nuclear medicine physicians**, oncologists, **surgeons**:

Politecnico Milano

Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta – Sistema Sanitario Regione Lombardia

Servizio Sanitario Regionale Emilia-Romagna – Azienda Ospedaliera di Reggio Emilia – Arcispedale S. Maria Nuova – Istituto in tecnologie avanzate e modelli assistenziali in oncologia – Istituto di Ricovero e Cura a Carattere Scientifico

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Universitas Catholica Sacri Cordis Iesu Mediolani

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3. Develop new specific medical **devices**.
4. Perform **pre-clinical** and **clinical tests**.

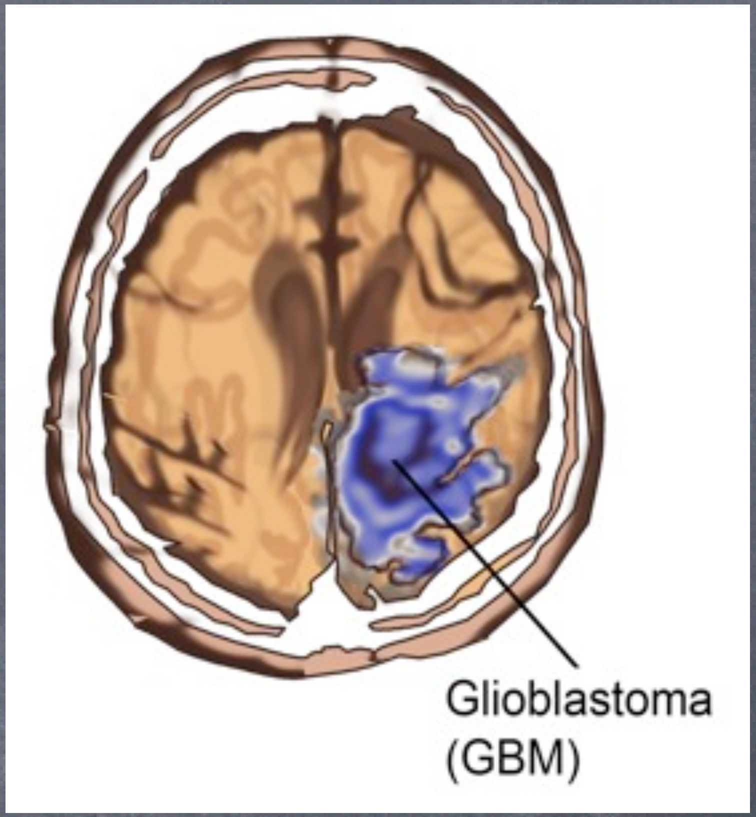
Clinical Case Candidates: Brain Tumors

FONDAZIONE I.R.C.C.S. ISTITUTO NEUROLOGICO CARLO BESTA
Sistema Sanitario Regione Lombardia

Fondazione IEO
Istituto Europeo di Oncologia

GLIOBLASTOMA MULTIFORME

- The most common and most aggressive malignant primary brain tumor
  - rare: 2-3 cases/100,000/year in Europe and North America.
- Complete resection of neoplastic cells is crucial to raise the patient outcome.
- FDG (the most common tracer) is useless, due to great glucose avidity of normal brain tissue → very high γ background



^{18}F-FDG-PET scan

Large uptake in healthy cerebral tissue.

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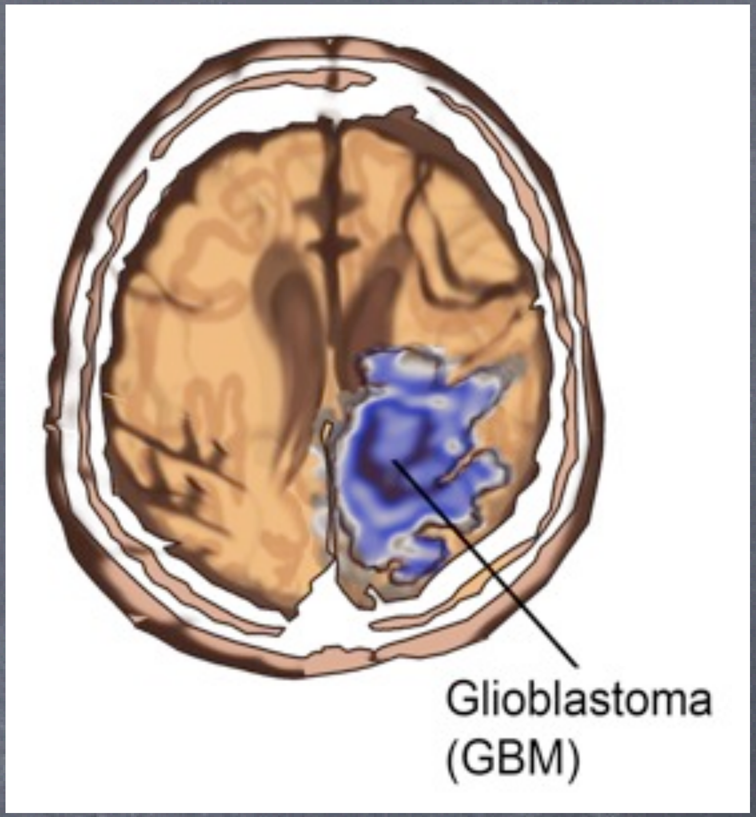
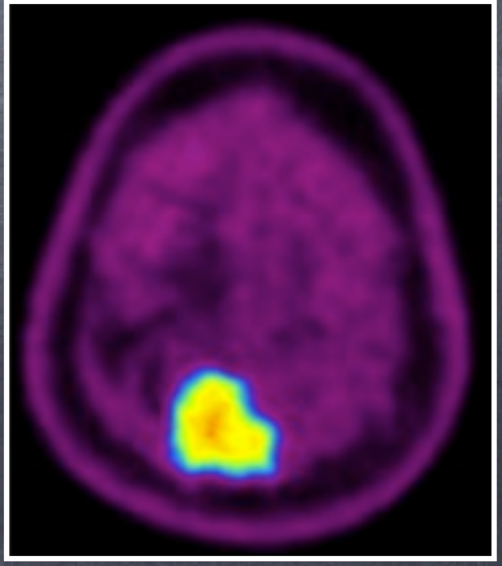


▸β^- RGS

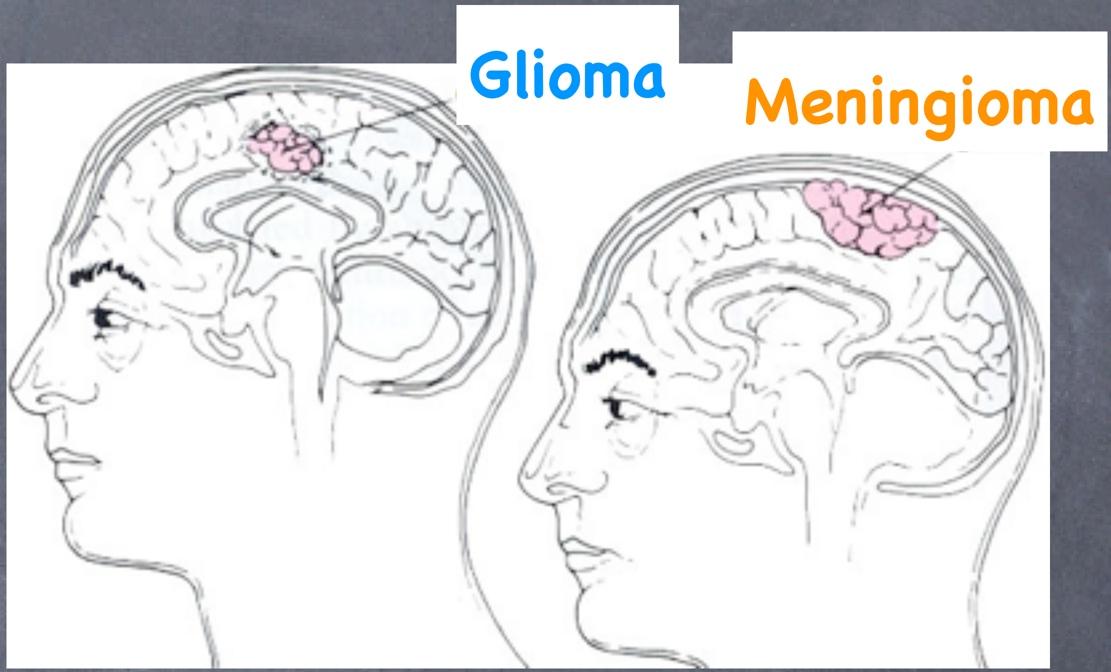
- pure β^- radionuclide ^{90}Y bounded to DOTATOC (synthetic somatostatine analogue) is much more specific.



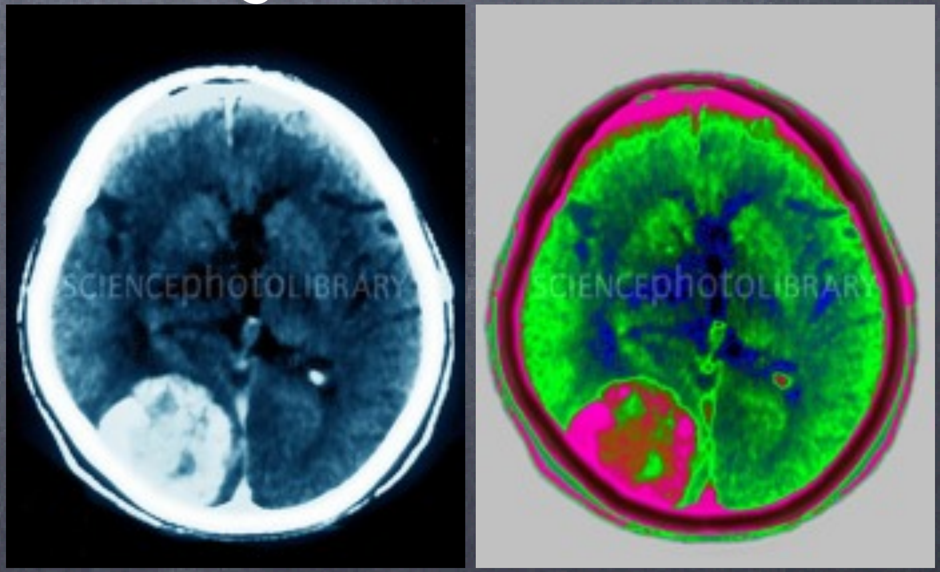
<u>^{68}Ga-DOTATOC-PET scan</u>

MENINGIOMA "proof-of-principle"

- Set of tumors arising from the meninges, usually benign
  - 20 cases/100,000/year more frequent in women
- Can cause symptoms depending on the size and location.
- Best candidate to validate the technique
  - **large uptake for ^{90}Y-DOTATOC and well known since it is administrated for radio-metabolic treatment.**



Meningioma: PET-CT scan



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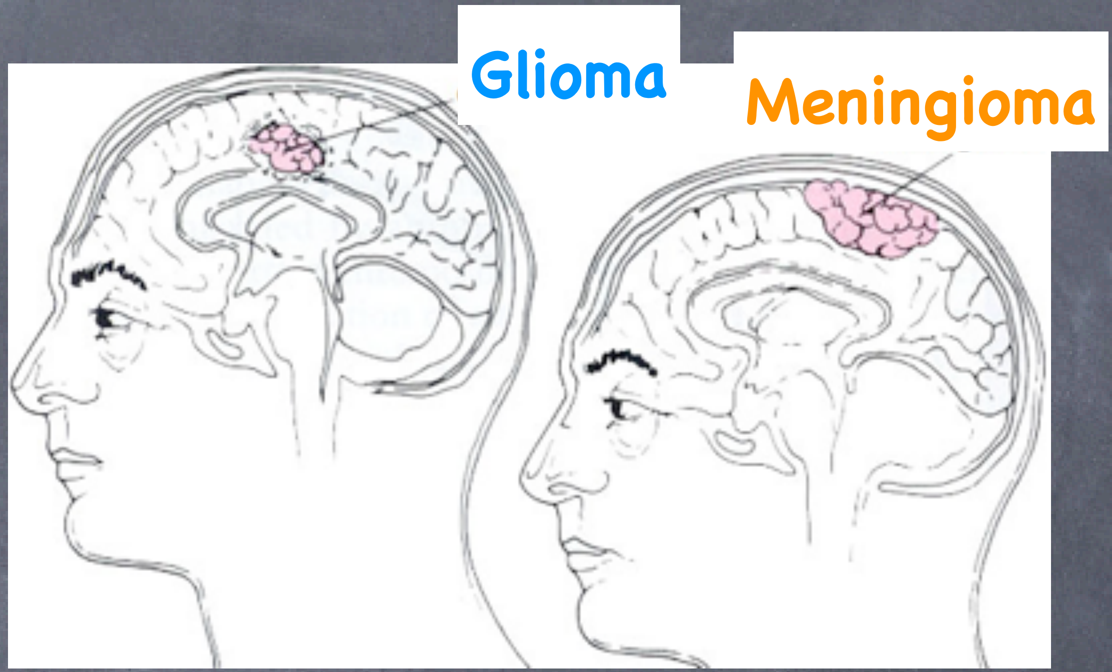

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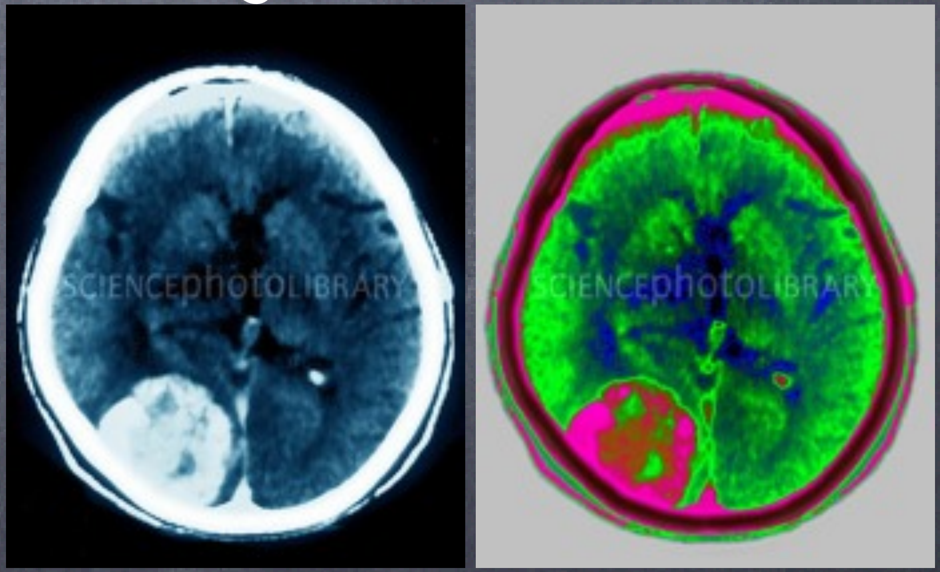
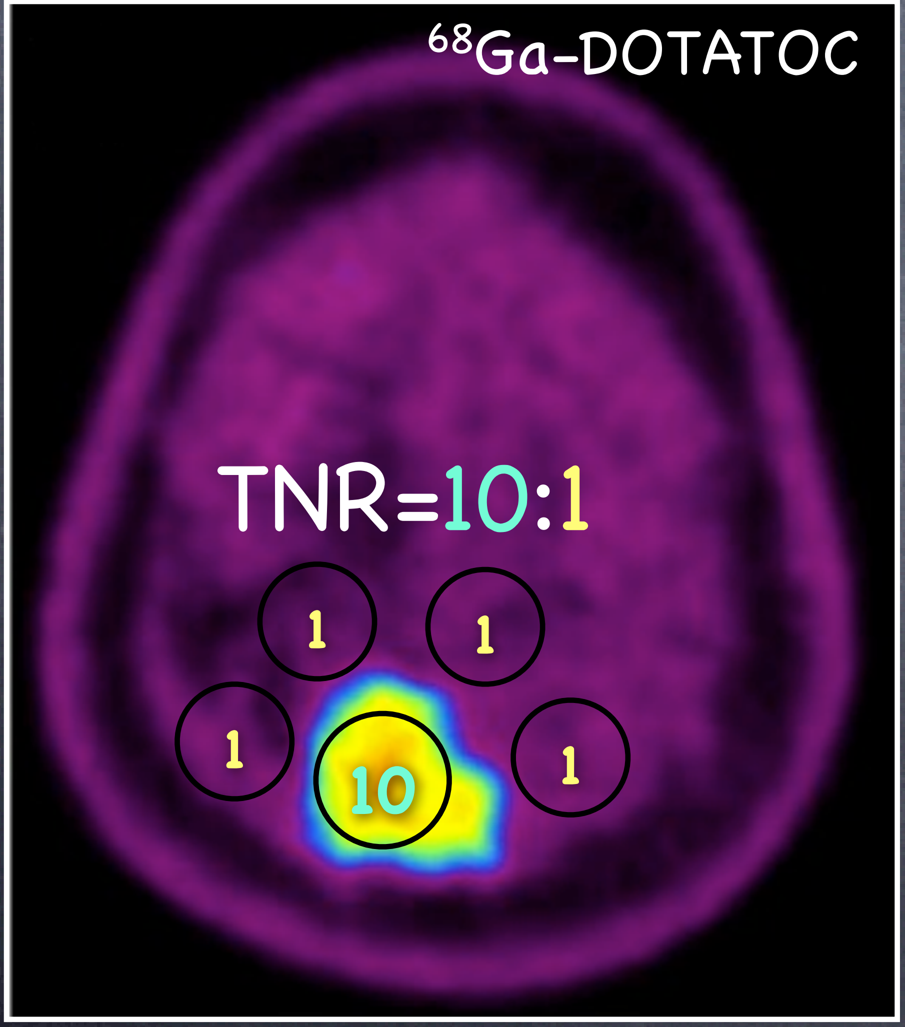


After considering the different tracer uptakes, the results of meningiomas will allow prediction on glioblastoma.

Applicability of β⁻ RGS

Diagnostic imaging exams allow us to quantify the uptake to the tracer from the **tumor** with respect to the **healthy tissue** around the lesion.

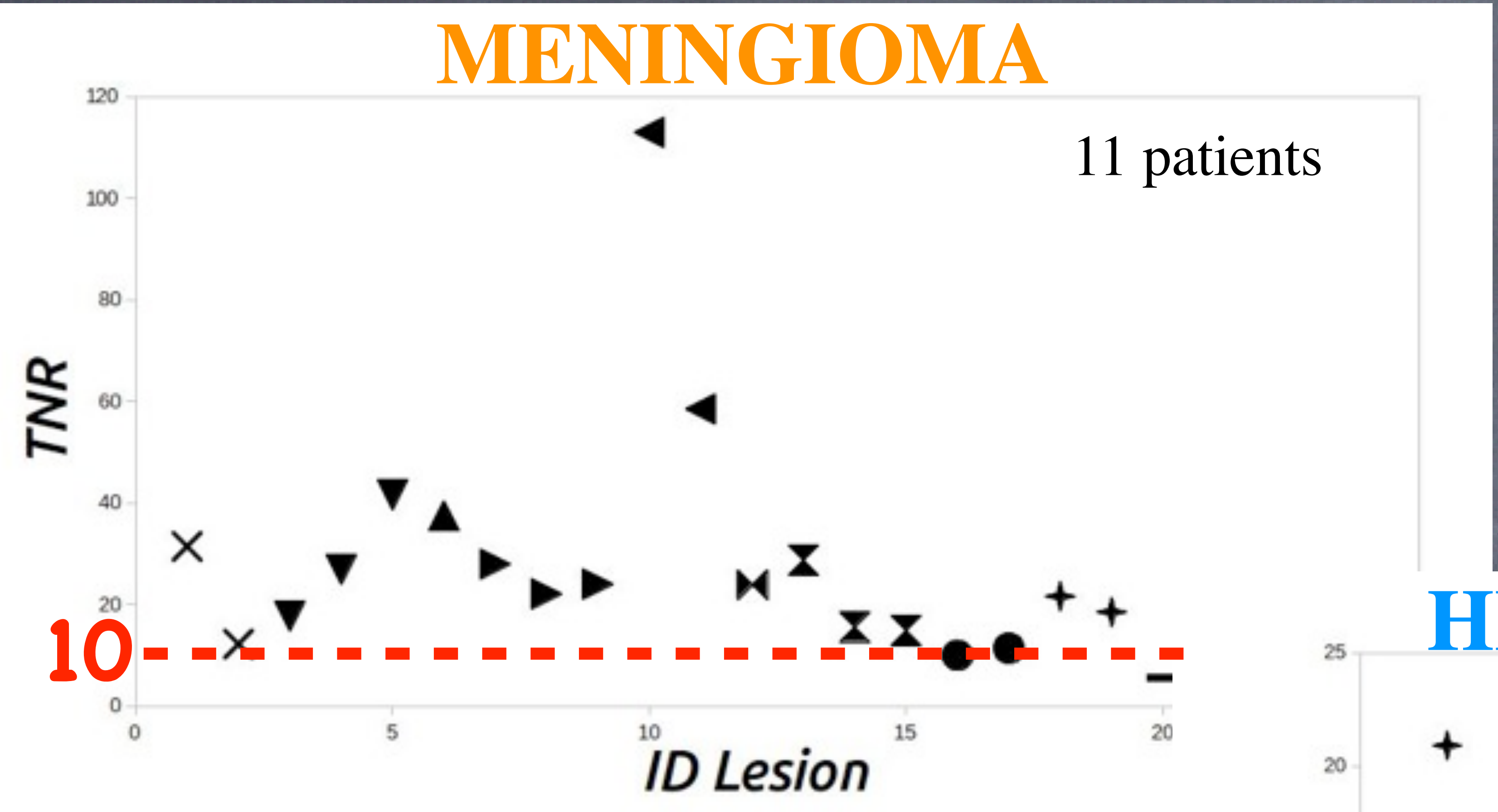
Meningioma: PET exam

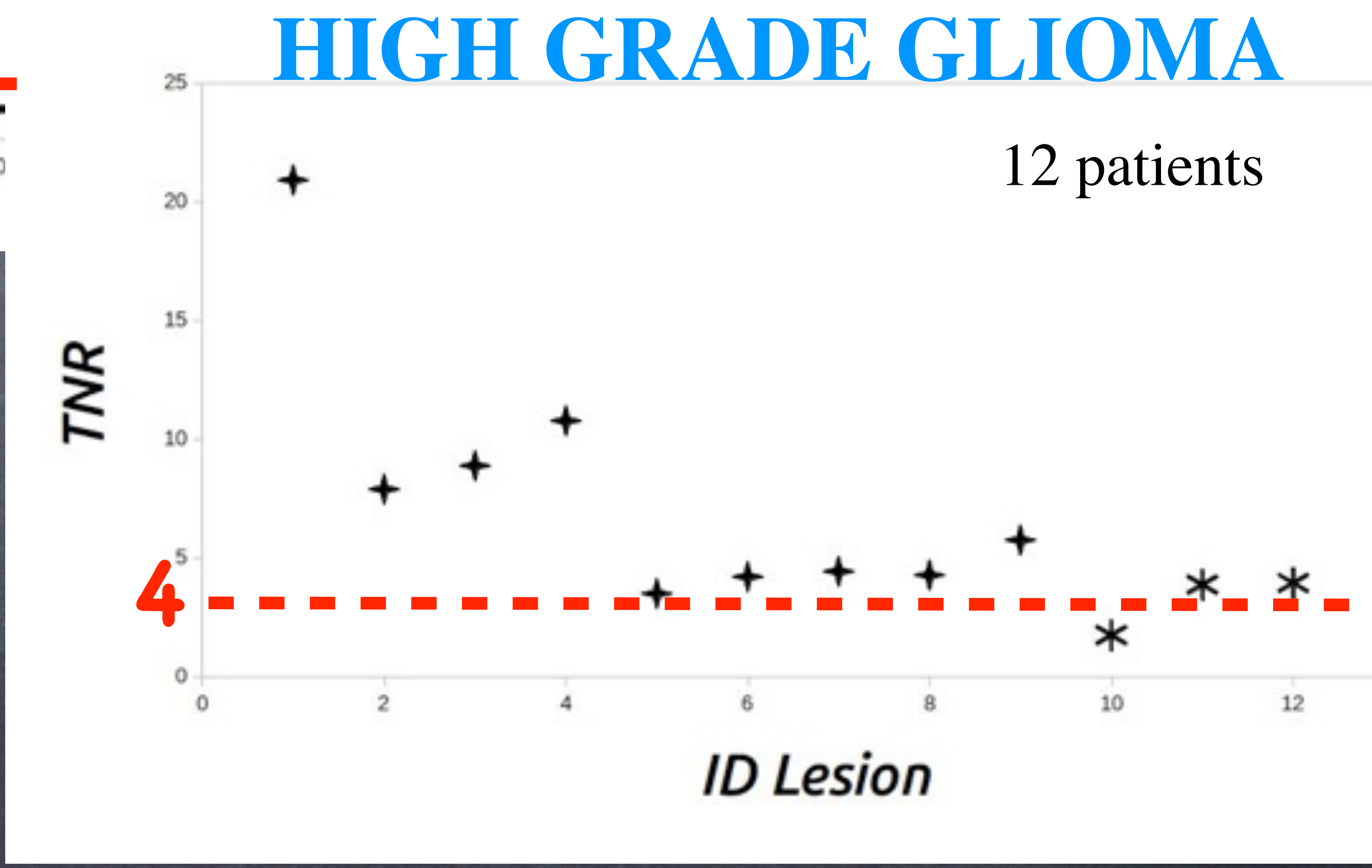


TNR:
Target-to-Noise
specific activity Ratio

DICOM
Digital Imaging and Communications in Medicine is a standard for handling, storing, printing, and transmitting information in medical imaging.
DICOM data object consists of patient's attributes (name, ID, etc.) and special attributes containing the image pixel data (e.g. activity per voxel).

Target-to-Noise Ratio





F. Collamati et al, accepted by Jour. Nucl. Med. (2014)

Clinical Case Candidates: Abdominal Tumors

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
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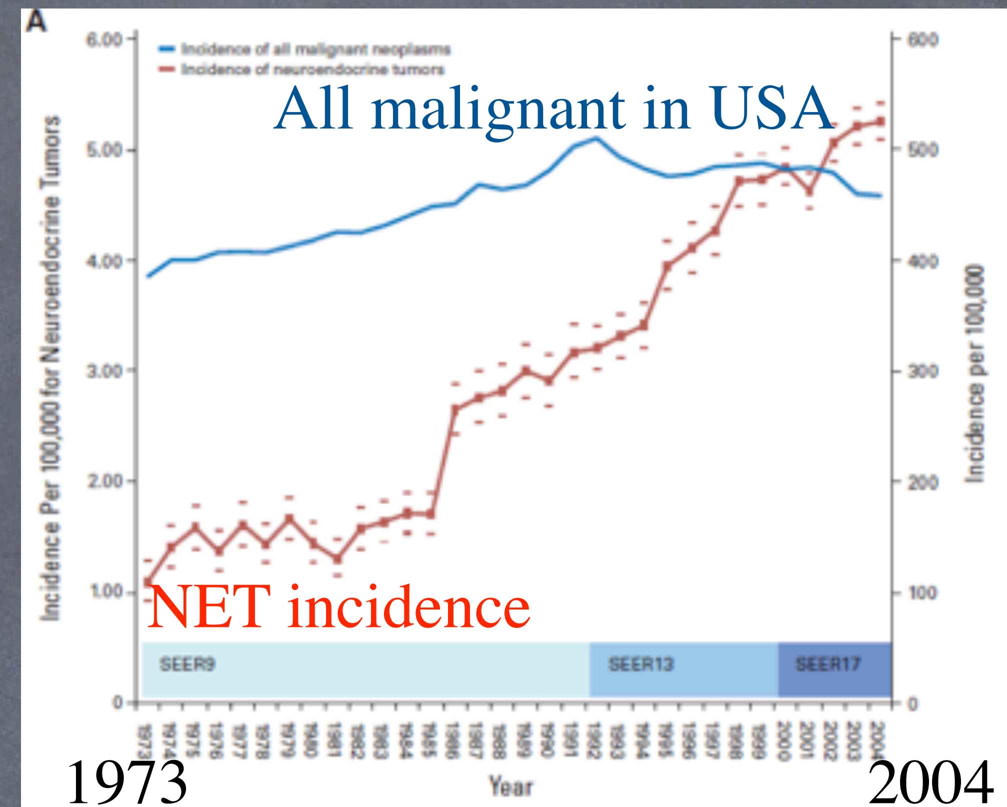
Istituto Europeo di Oncologia

UNIVERSITAS CATHOLICA SACRI CORDIS JESU MEDIOLANI

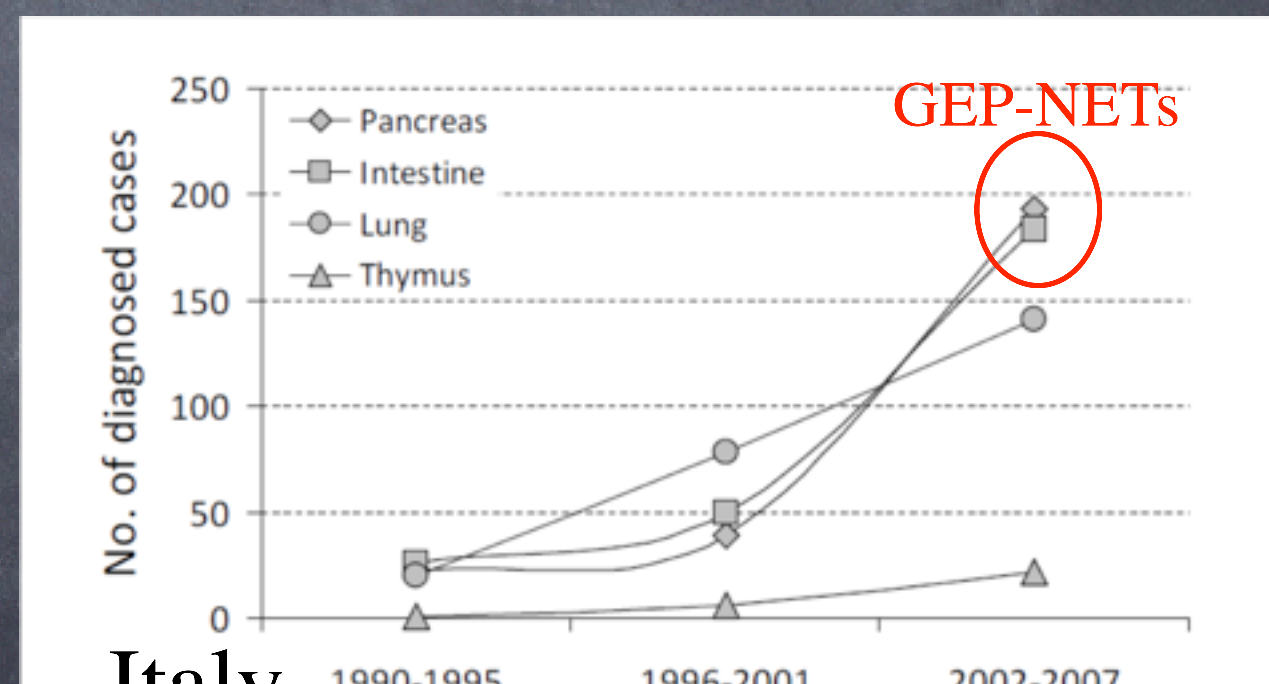
Neuroendocrine Tumors

- NETs arise from cells of the endocrine (hormonal) and nervous systems; commonly occur in the intestine but also in the rest of the body.
- Rare but incidence increases over time
  - >5 cases/100,000/year (USA 2004).
- Surgery is the main treatment.
- Radio-marked by ^{90}Y-DOTATOC.



Year	Incidence (95% CI)
1973	1.09 (0.92 to 1.28)
1974	1.40 (1.22 to 1.61)
1975	1.58 (1.39 to 1.78)
1976	1.37 (1.20 to 1.56)
1977	1.61 (1.42 to 1.81)
1978	1.43 (1.27 to 1.62)
1979	1.66 (1.48 to 1.86)
1980	1.44 (1.28 to 1.63)
1981	1.30 (1.14 to 1.48)
1982	1.57 (1.40 to 1.76)
1983	1.63 (1.46 to 1.83)
1984	1.71 (1.53 to 1.91)
1985	1.70 (1.53 to 1.90)
1986	2.65 (2.42 to 2.88)
1987	2.76 (2.53 to 3.00)
1988	2.82 (2.59 to 3.06)
1989	3.00 (2.76 to 3.24)
1990	2.91 (2.68 to 3.15)
1991	3.17 (2.94 to 3.41)
1992	3.21 (3.01 to 3.41)
1993	3.31 (3.11 to 3.51)
1994	3.41 (3.21 to 3.62)
1995	3.95 (3.74 to 4.17)
1996	4.11 (3.89 to 4.33)
1997	4.27 (4.05 to 4.49)
1998	4.71 (4.49 to 4.95)
1999	4.73 (4.50 to 4.96)
2000	4.84 (4.68 to 5.01)
2001	4.63 (4.47 to 4.79)
2002	5.06 (4.90 to 5.23)
2003	5.21 (5.04 to 5.38)
2004	5.25 (5.09 to 5.42)

Yao JC et al
J Clin Oncol 26 (2008)



Faggiano A et al. 2011

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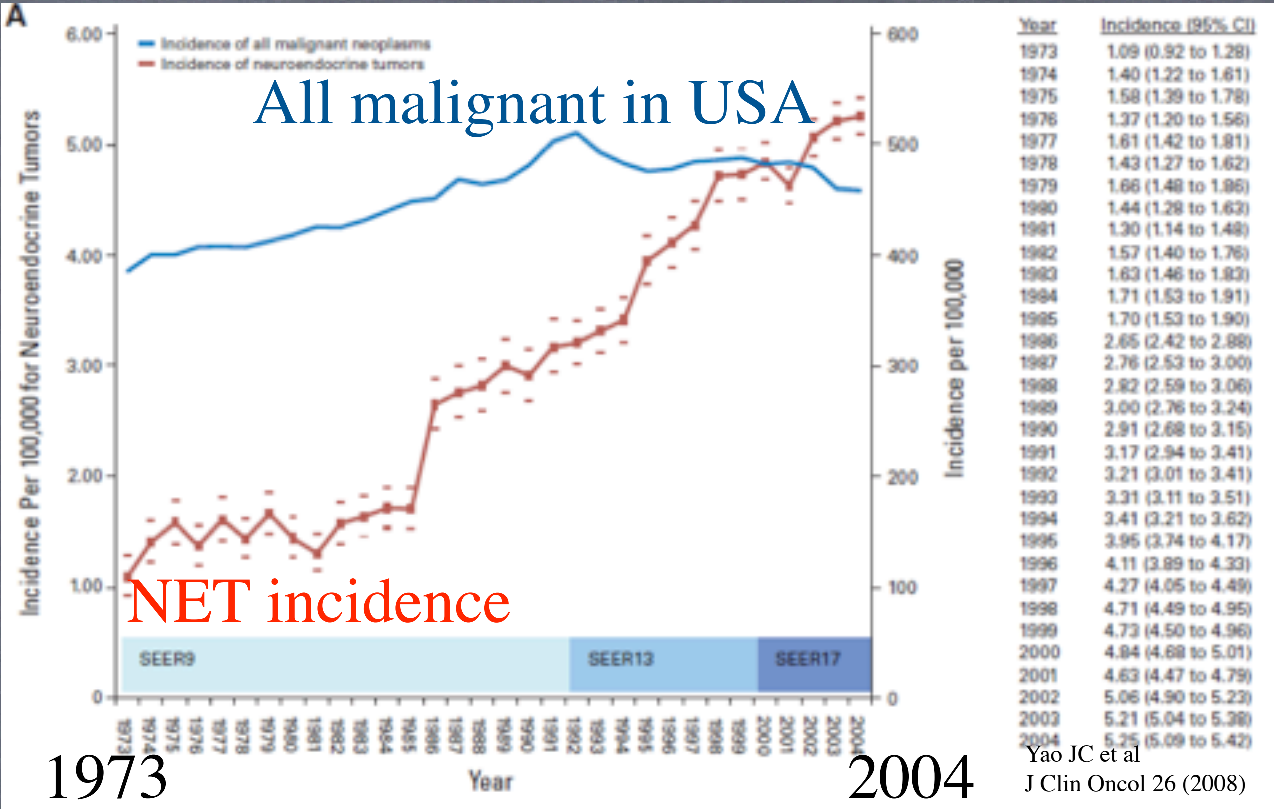
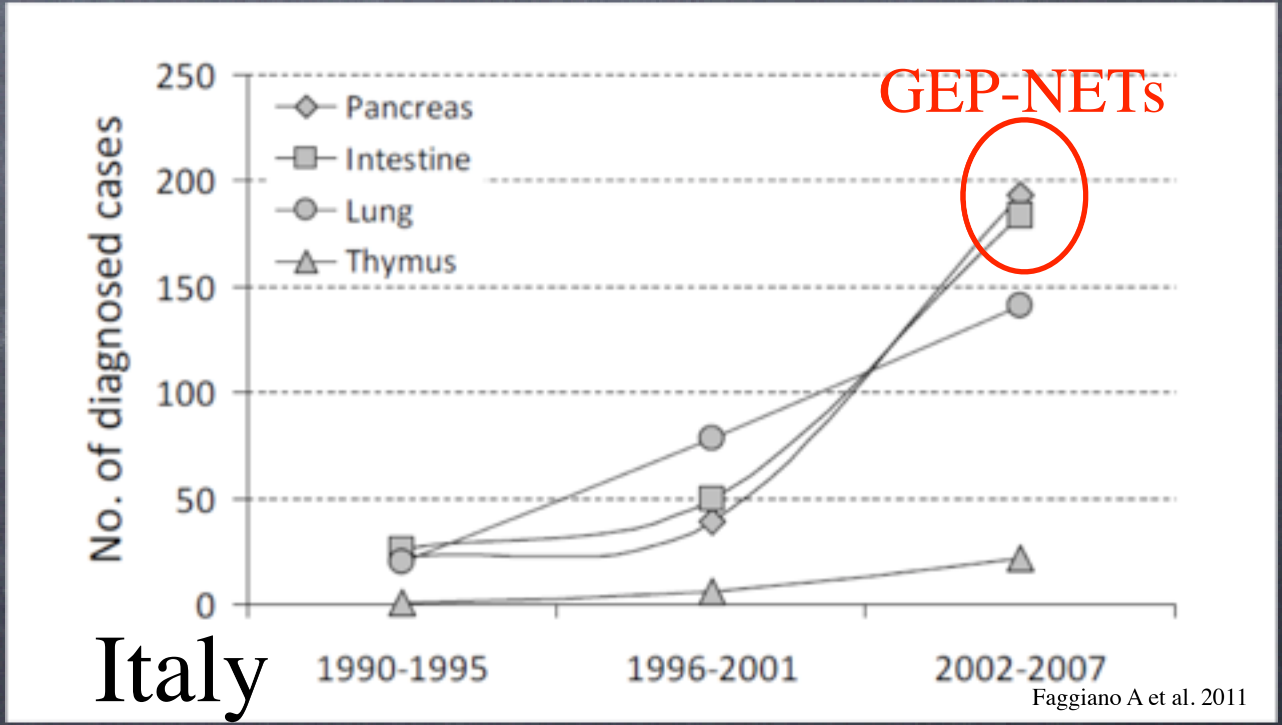
- Surgery is the main treatment.
- Radio-marked by ^{90}Y-DOTATOC.
- **β⁻ RGS** would allow research and detection of
  - Non visible liver metastases and involved lymph nodes from NETs.
  - Gastro-entero-pancreatic neuroendocrine tumors (GEP-NET) difficult to be localized except by symptoms
    - pancreatic insulinoma;
    - colorectal bowel cancer.



Yao JC et al
J Clin Oncol 26 (2008)

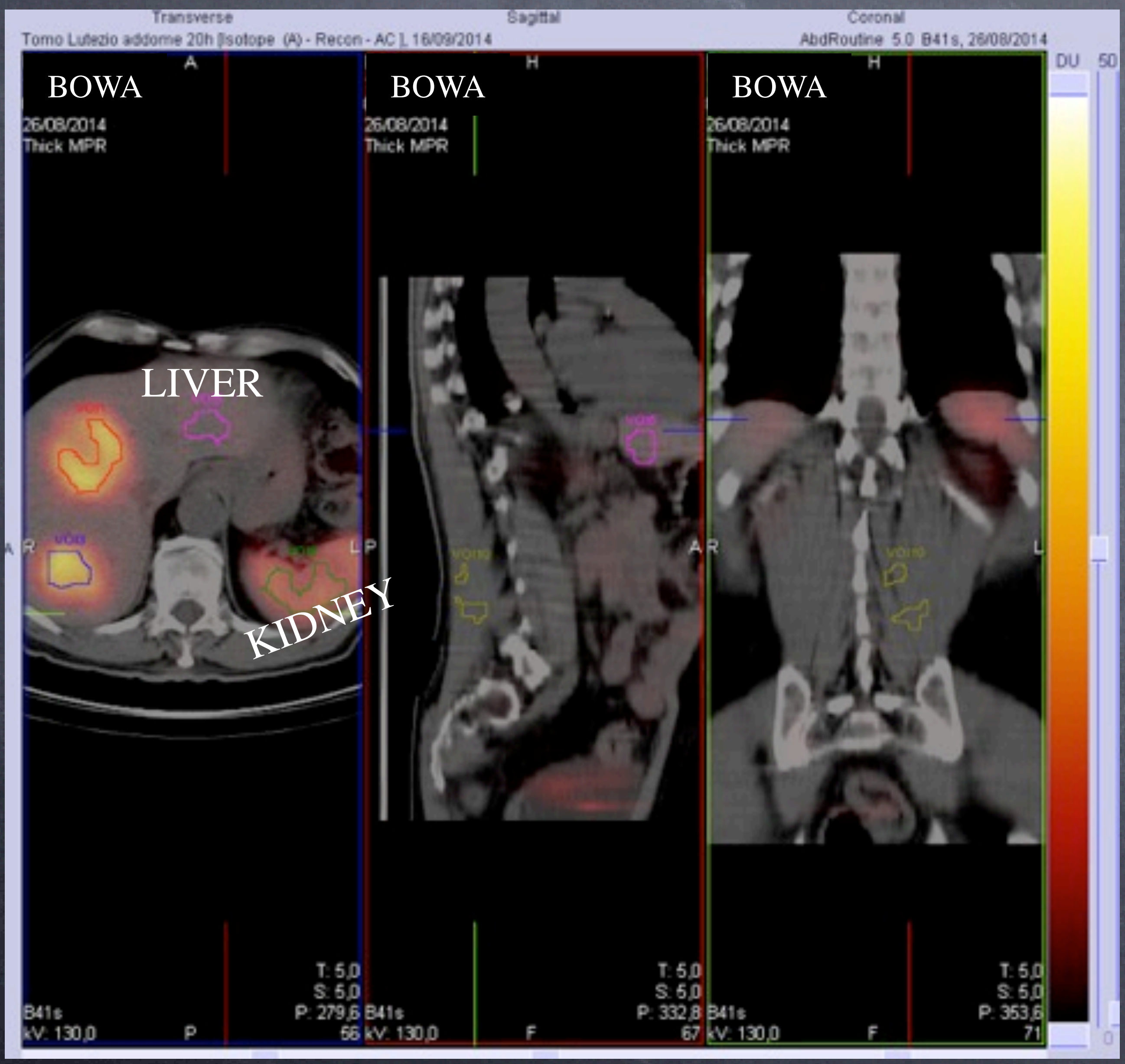


Faggiano A et al. 2011

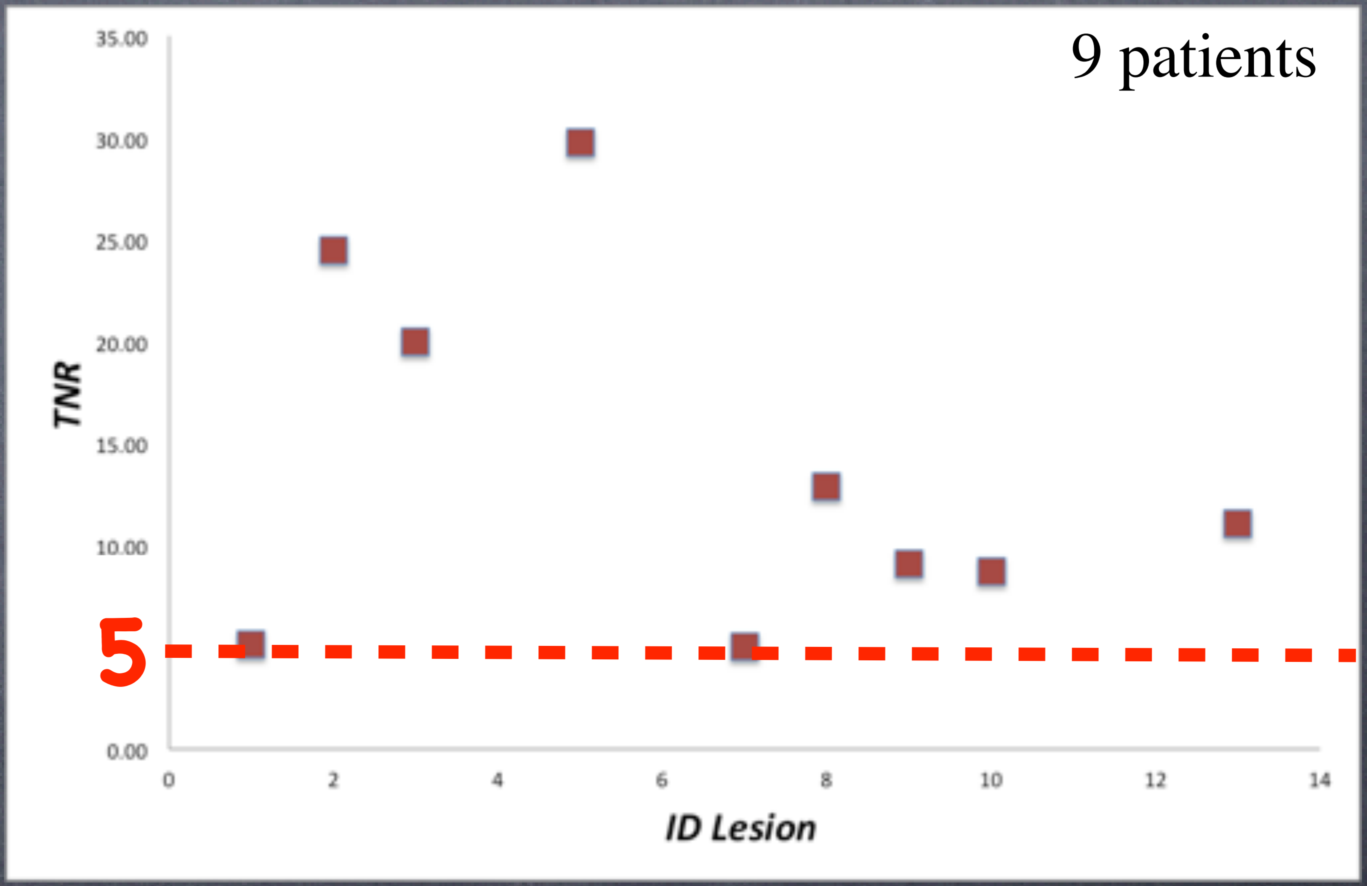
Applicability to NETs

Patients affected by **hepatic metastases** from NETs

^{177}Lu-DOTATOC-SPECT scan

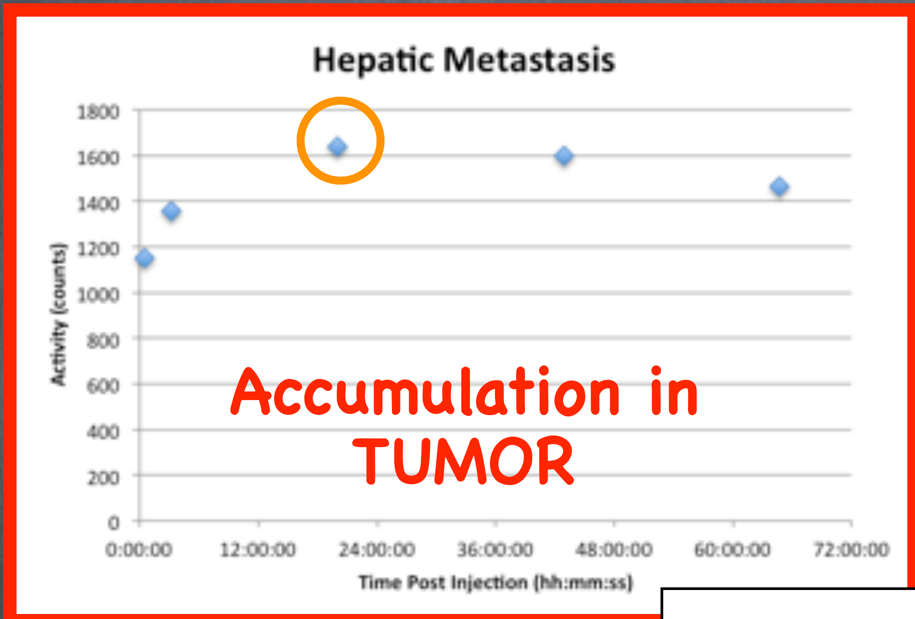


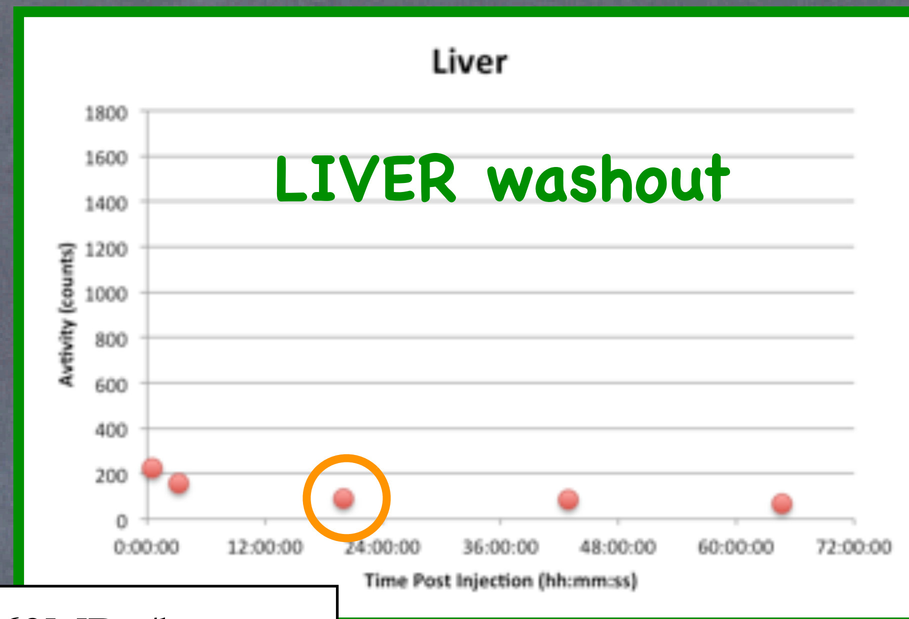
NET Target-to-Noise Ratio



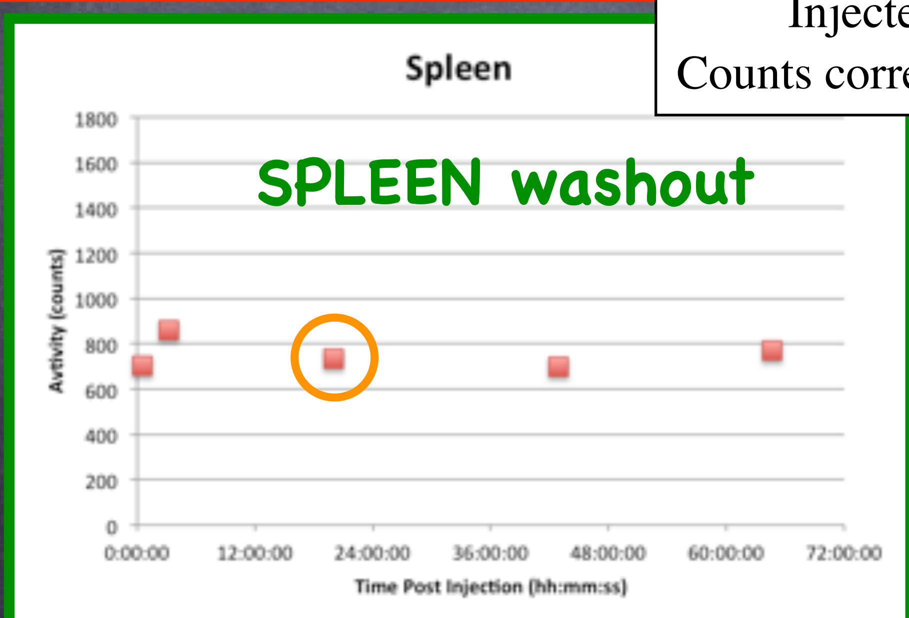
TNR: Evolution in Time

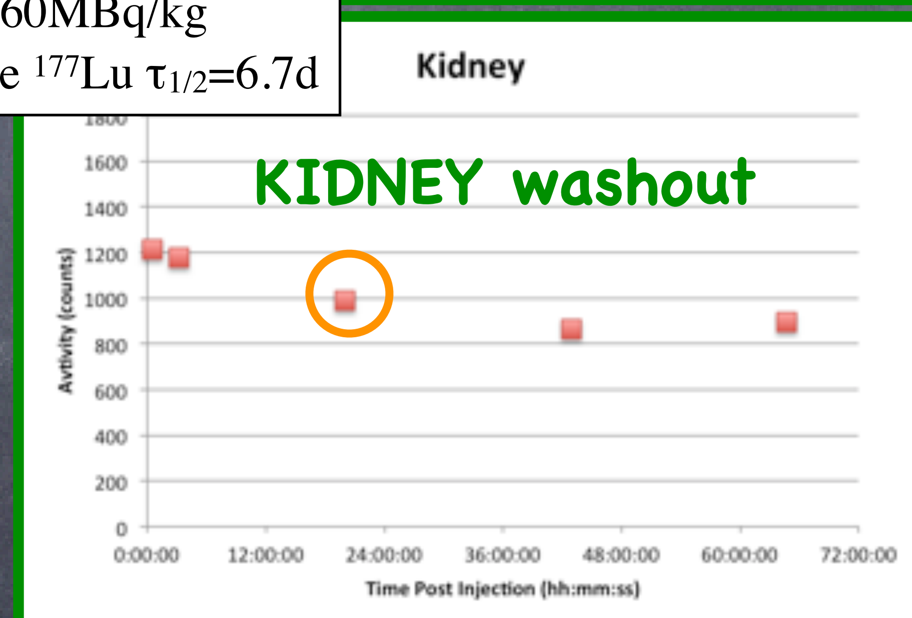
Study on the radio-tracer accumulation in tumor and washout from the healthy organs for 72h after injection:





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



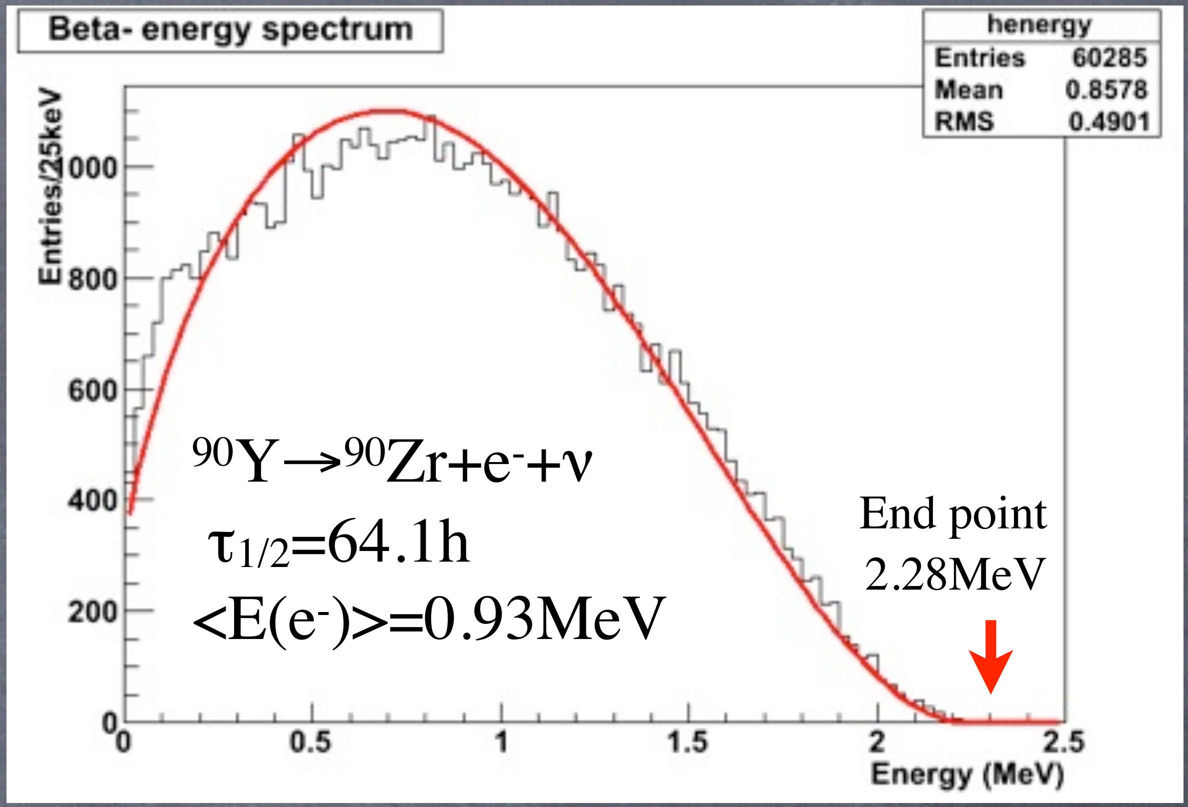


TNR is maximized after 24h → best moment for RGS

Intraoperative
β^- Probe

Detector Development

- Requirements:
  - maximal reduction of injected activity
    - high sensitivity and fast response;
  - handy tool for the surgeon
    - compactness and small size.



M.Angelone et al. IEEE Trans. on Nucl. Sci. 61, 3 (2014)

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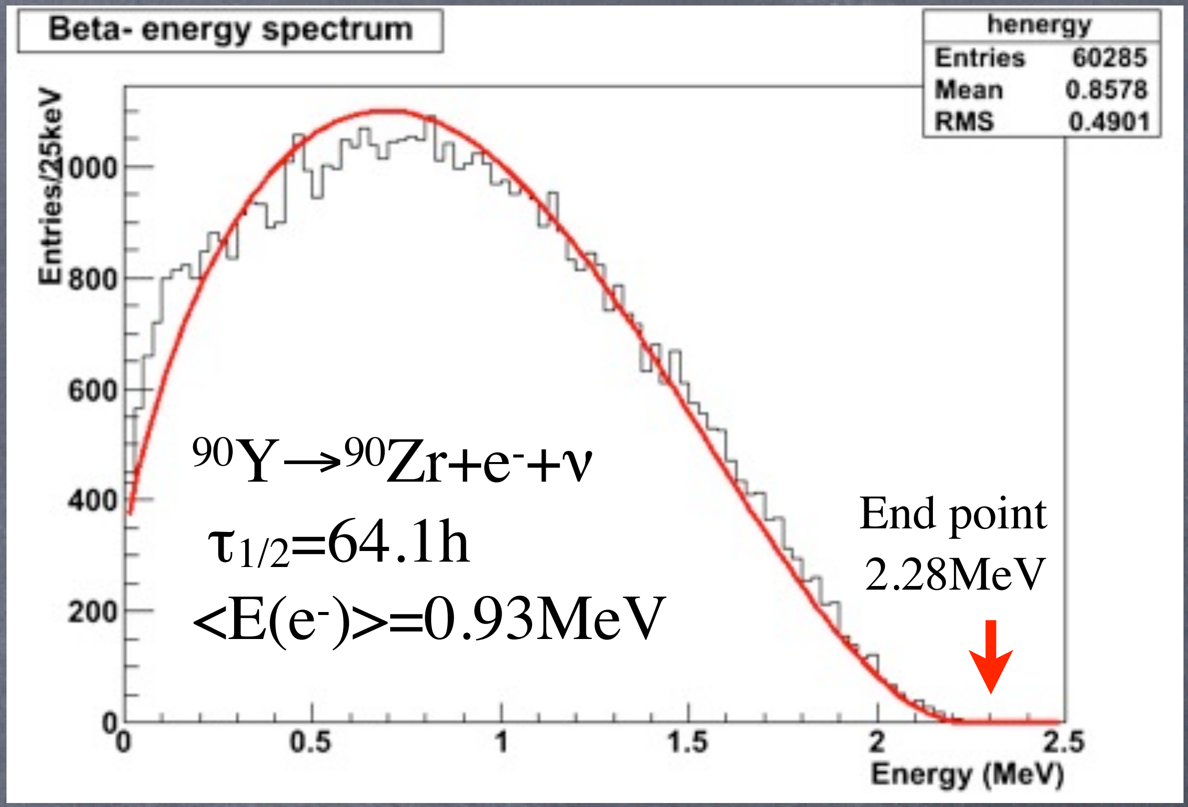
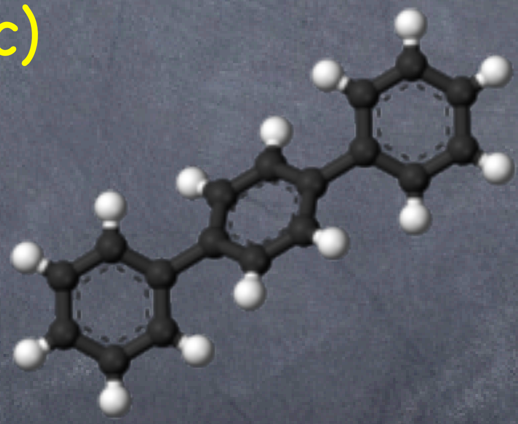


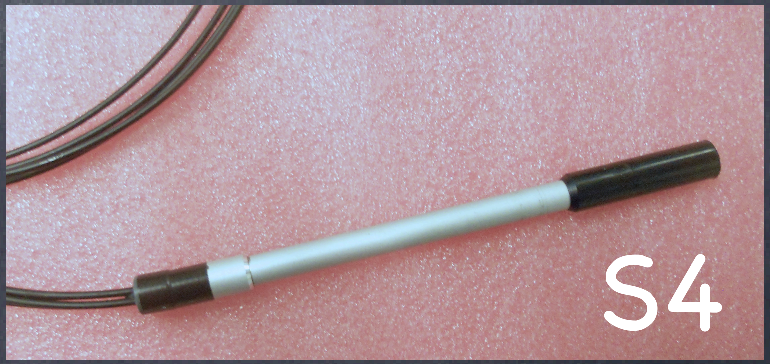
- Our best candidate: **para-terphenyl**
  - Mechanically robust (non-hygroscopic)
  - Light material (low ρ=1.24g/cm^3)
    - scarce sensitivity to γ.
  - High signal
    - Light Yield 3.5 times larger than typical organic scintillators.
  - suitable for detection of non-penetrating low energy radiation
    - Light Attenuation Length λ ~5 mm



aromatic hydrocarbon isomer $C_{18}H_{14}$

M.Angelone et al. IEEE Trans. on Nucl. Sci. 61, 3 (2014)

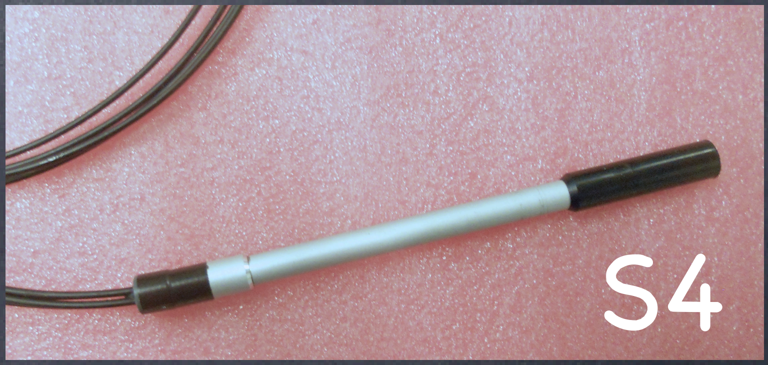
β^- Probe Prototypes



Compatible with a standard sterile covering of sub-millimetric film for surgical environment.

β- Probe Prototypes

- Core: cylindrical scintillator of p-terphenyl
  - S1 d=2.1mm, h=1.7mm
  - S4 d=5mm, h=3mm
  - SiPM d=10mm, h=3mm



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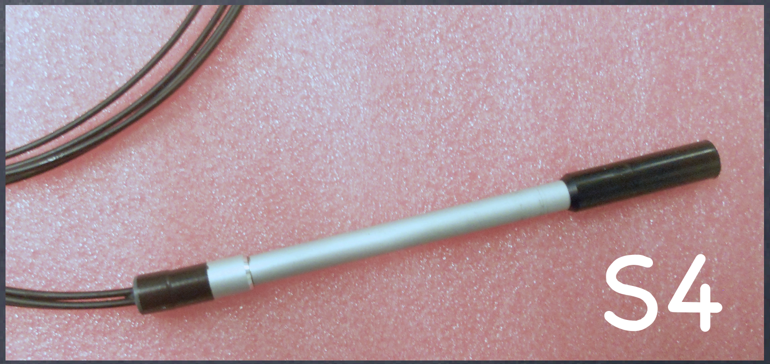
- Light detector:
  - optical fiber connected to a photo-multiplier tube
    - PMT Hamamatsu H10721-210
  - directly coupled to a Silicon photo-multiplier
    - SiPM sensL B-series 10035



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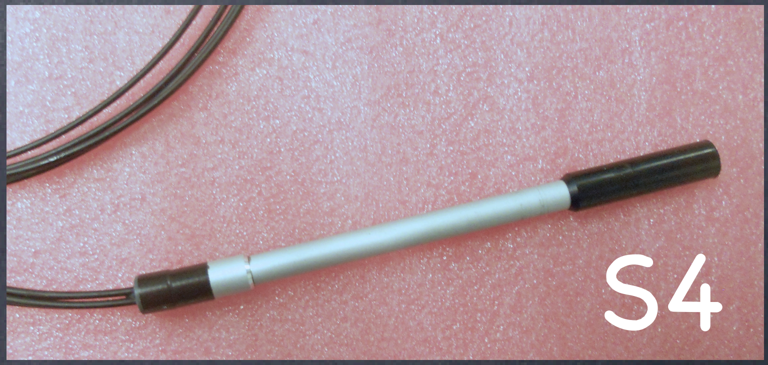
  - directly coupled to a Silicon photo-multiplier
    - SiPM sensL B-series 10035
- Probe mechanical:
  - Entrance window: 10μm Al sheet ensures the light-tightness.
  - Tip: PVC ring to be shielded against radiation from the sides;
  - Body: a thin aluminum body for easy handling;
  - Mass: 50-150g



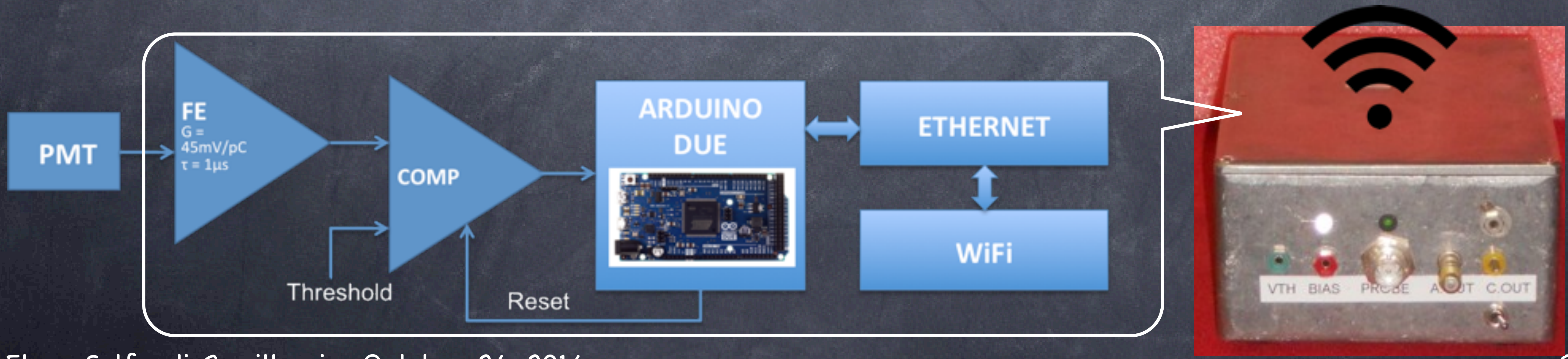
Compatible with a standard sterile covering of sub-millimetric film for surgical environment.

Electronics Read-out

Electronics read-out is portable and customized to match the surgeon needs

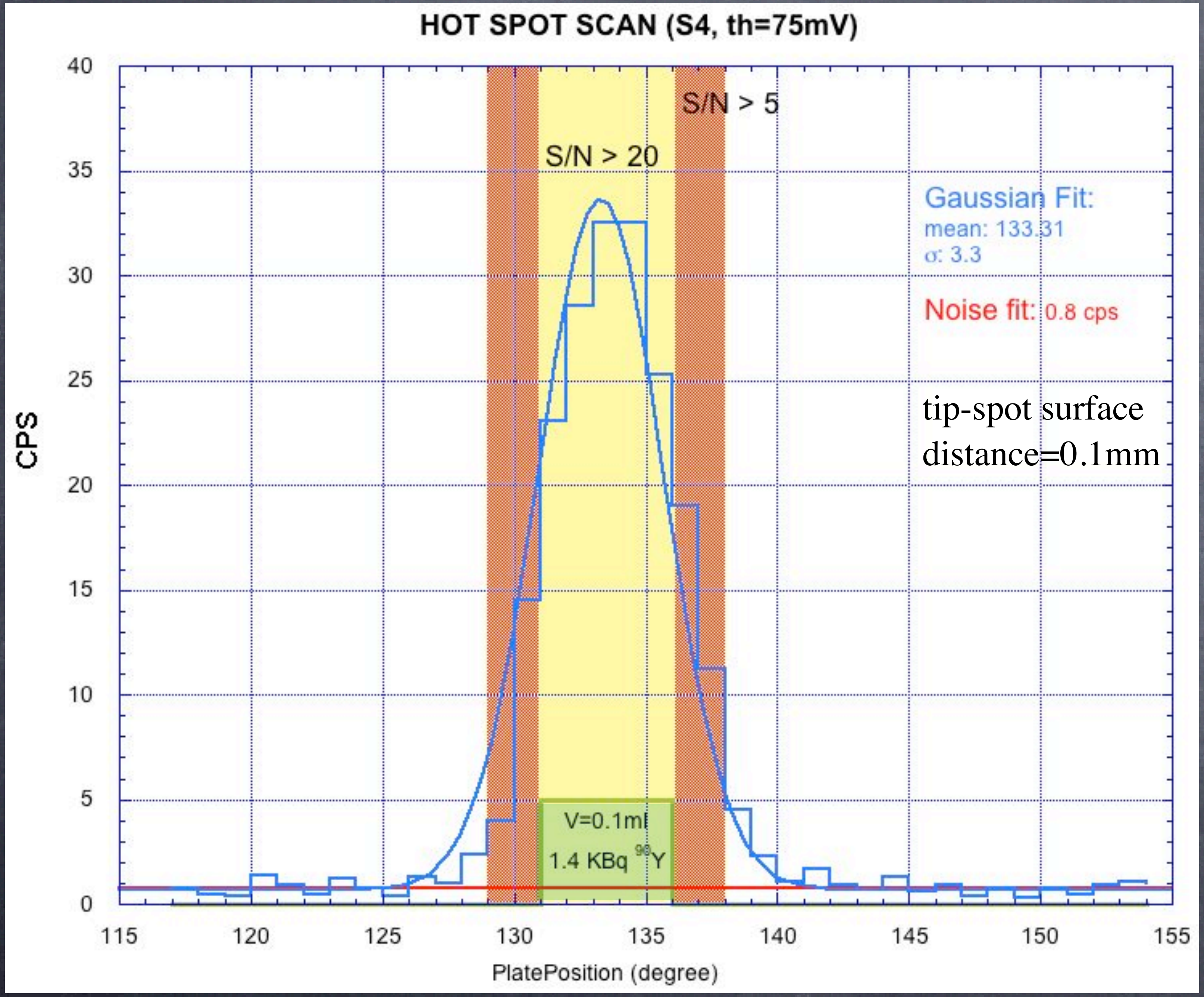
- time to take a decision ~1s;
- acoustic and visual alarm;
- wireless data transfer;
- user interface available both for PC or tablet.

No Danger of electric discharge on patient



Performance of the Probe

Sensitivity to active spot

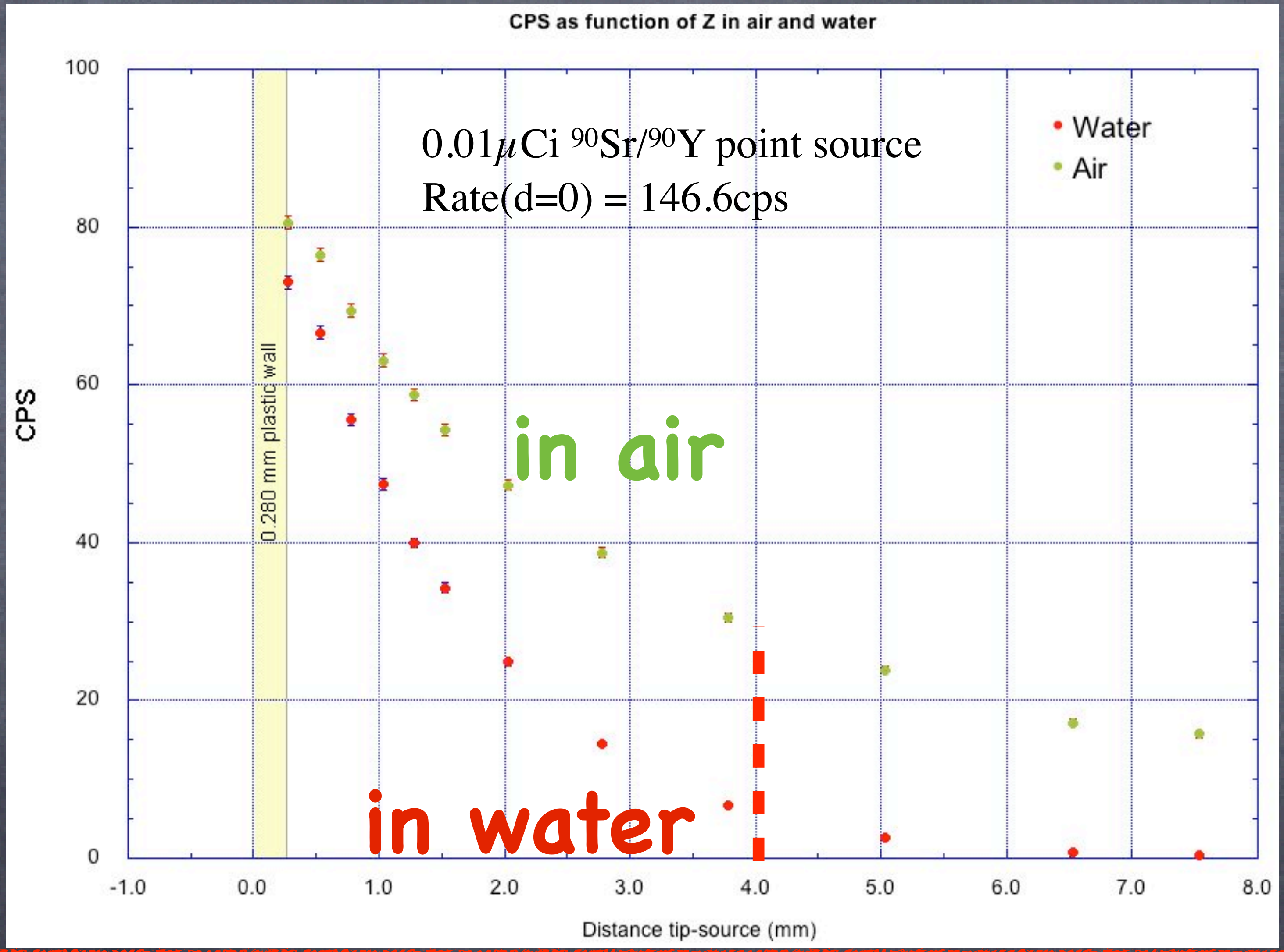


- Sensitivity to β:
  - $3.8 \cdot 10^5$ counts/s/MBq
  - ε_β=40% E_β>300keV
- Good sensitivity to active spot of V<0.1ml.
- Very directional and local view.

Performance in water

Probe in water to test the sensitivity in environment equivalent to the body

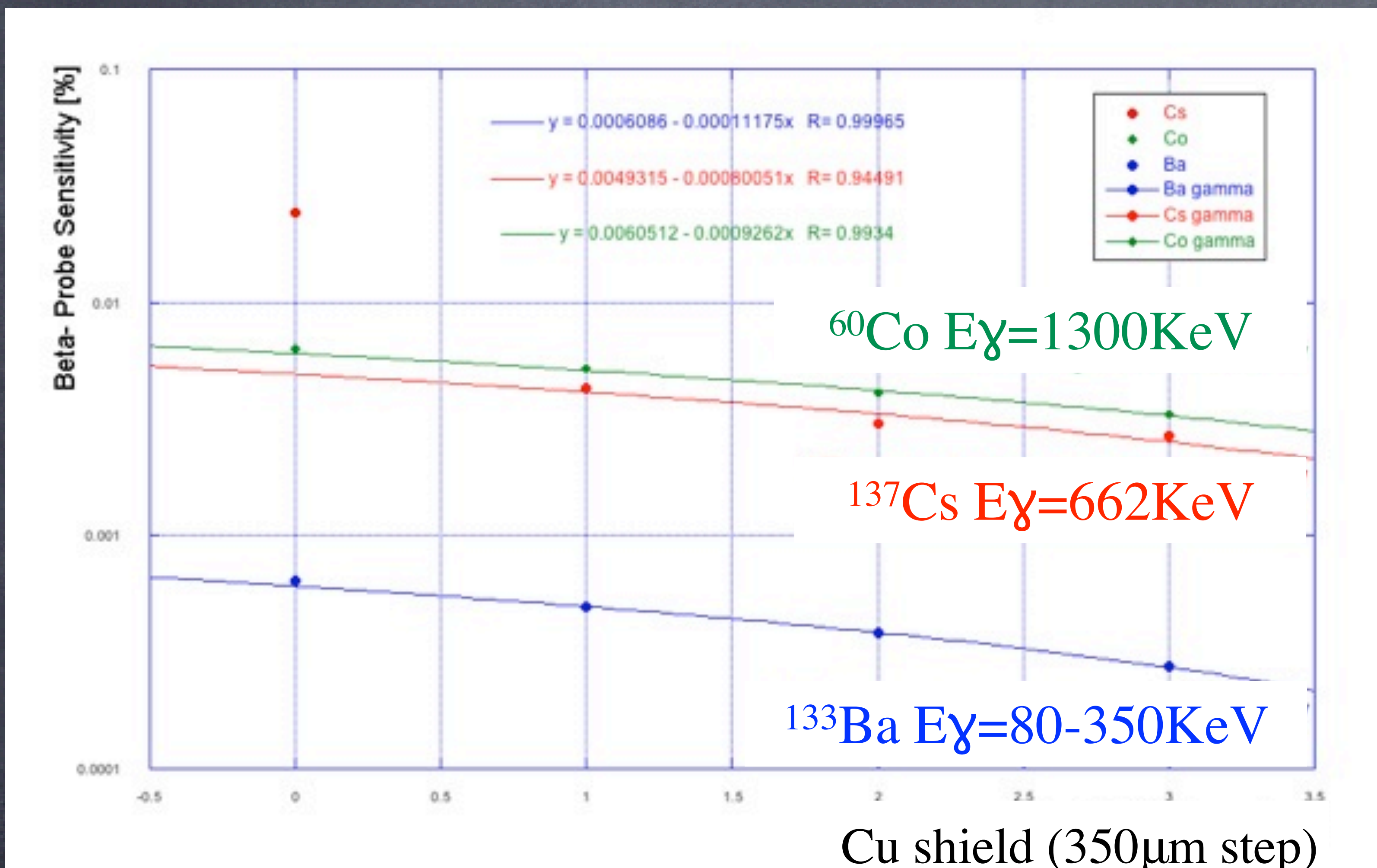
Sensitivity vs tip-source distance

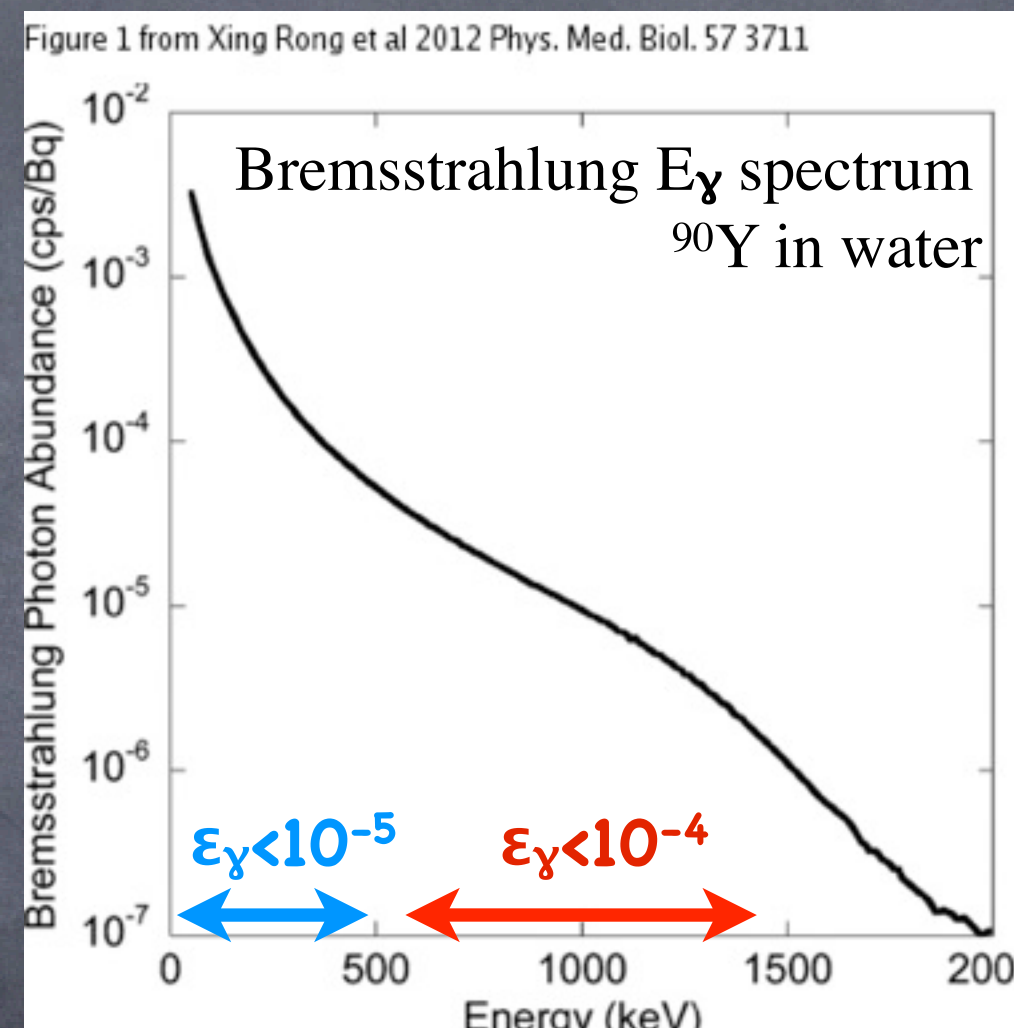


➡sensitive until to 4mm depth (=maximal path of 1MeV electron in water).

Photon Transparency

GOAL: evaluation of the γ background from Bremsstrahlung





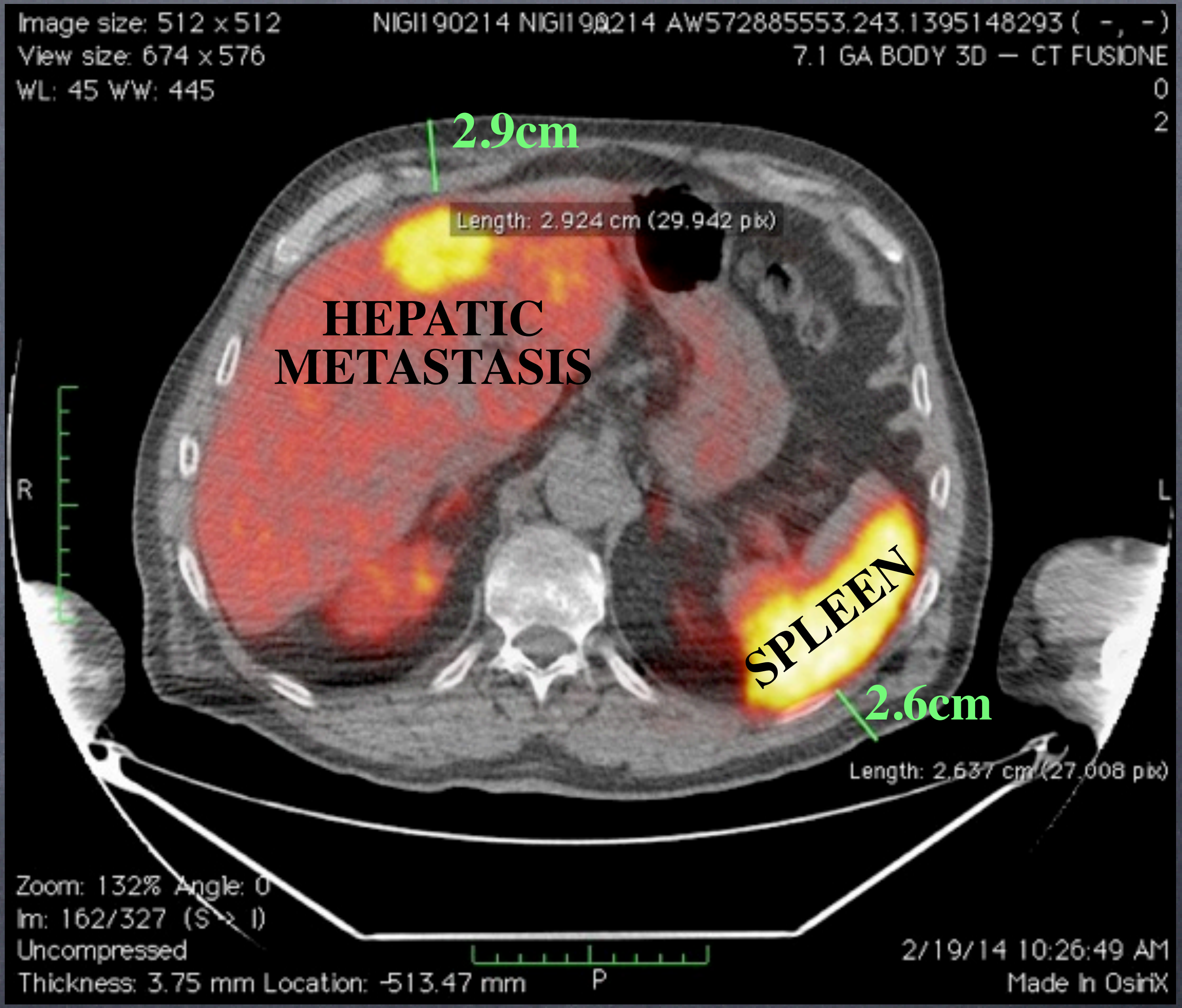
➡Very low sensitivity to photons

Patient

also in a real case of Bremsstrahlung background

NIGI

- Injected activity (24h before)
  - ^{90}Y-DOTATOC 54mCi
  - 21MBq/kg therapeutic treatment
- Lesion of interest:
  - **Hepatic metastasis from neuroendocrine tumor**



β- Probe on Patients

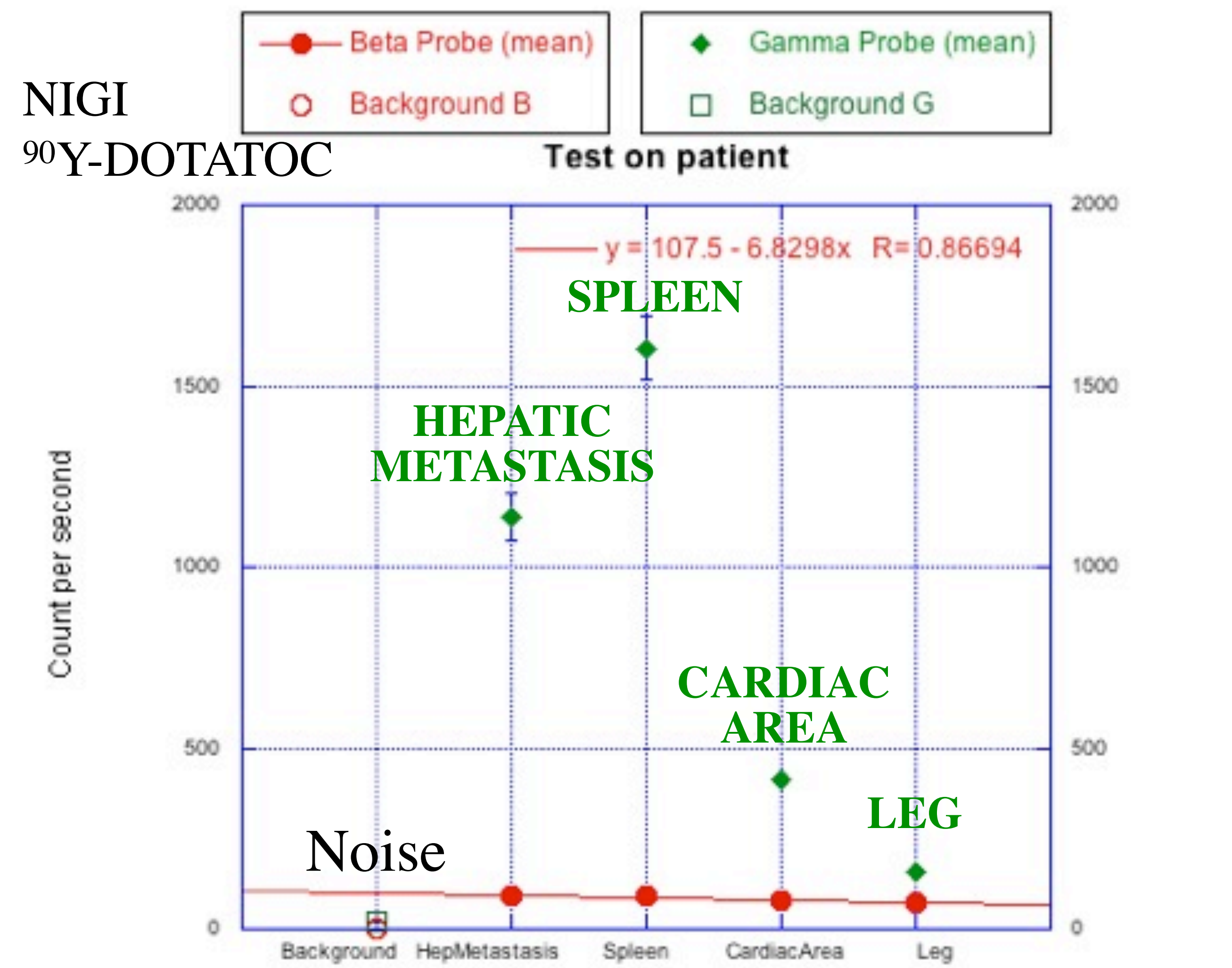
GOAL: first look to the real Bremsstrahlung background and cross-check with a commercial γ-probe

SiPM prototype

VS

Neoprobe® GDS Gamma Detection Probe

Comparable sensible area ~1cm^2



Not surgery, probes outside the body!

- ✓Detected activity is related to electrons emitted in superficial tissue.
- ✓Verified transparency to photons from Bremsstrahlung.
- ✓Uptake by healthy organs around the lesion does not affect the count rate.

Personnel Exposure

PATIENT: ^{90}Y-DOTATOC Activity for therapy, after 24h: ~500MBq

Direct reading dosimeter (Δt=15min) close to the patient:

	Distance from patient	Skin Dose [μSv]	Depth Dose [μSv]
Doc1	10cm	29	2
Doc2	1.5m	3	0
Doc3	1.5m	2	0

Indication that exposure in the surgical environment and with activity for diagnostic will be almost negligible.

Realization of "Ad-hoc" Phantoms

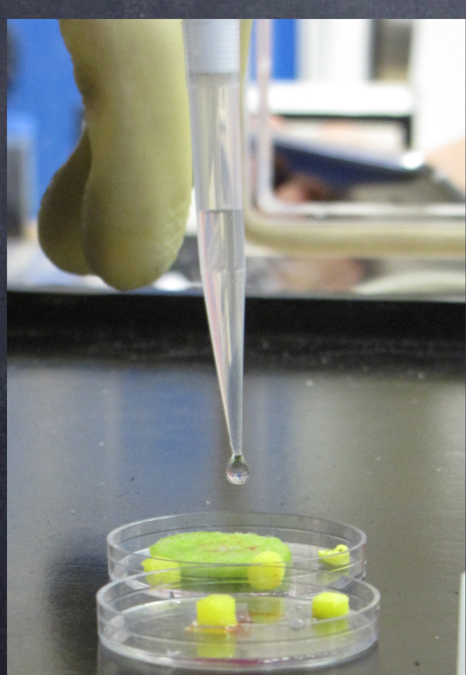
Phantom Factory

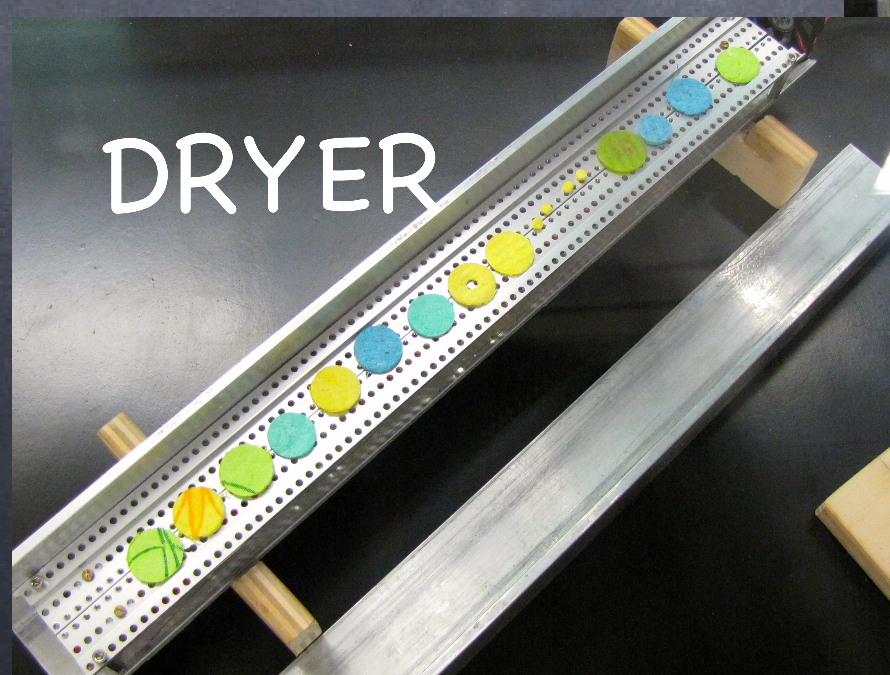
GOAL: **Phantoms simulating tumor remnant pattern embedded in healthy tissue.**

PHANTOM SAMPLES

^{90}Y in saline solution with different dilutions

β^- decays allow to realize a clean and radio-protected box in INFN lab.





Procedure and its reproducibility well tested.

"Ad-hoc" Phantoms (I)

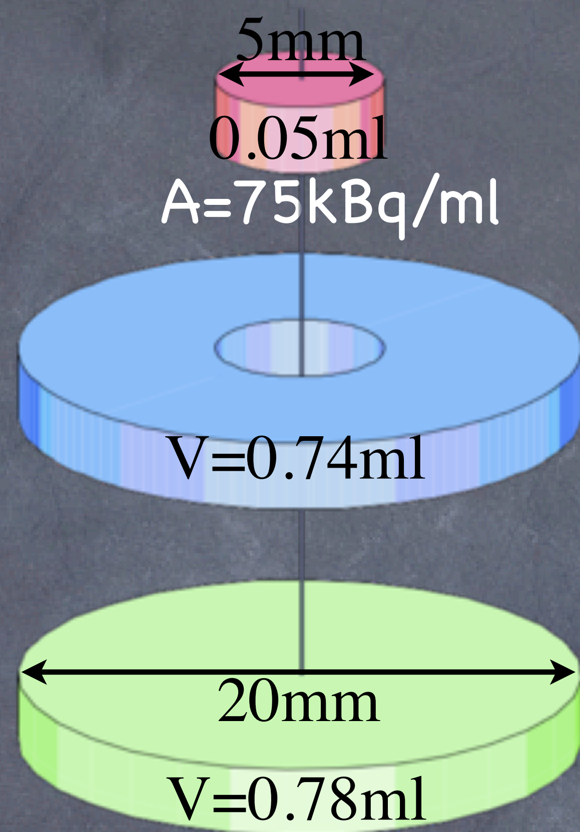
To simulate tumor remnant embedded in healthy tissue.

Tumor residual

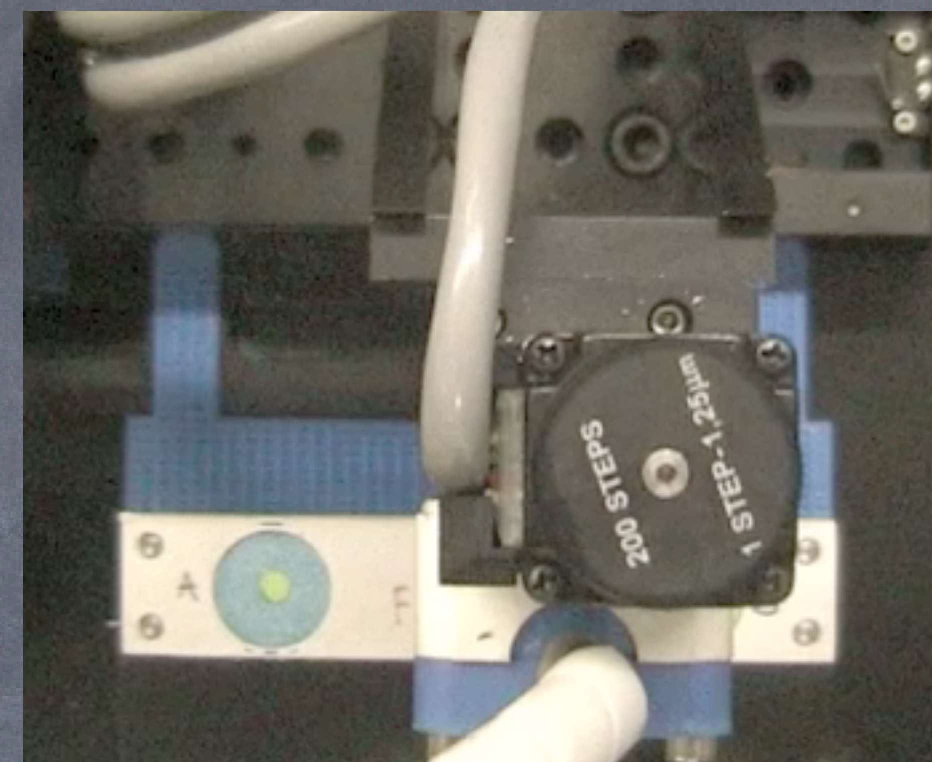
V=0.05ml

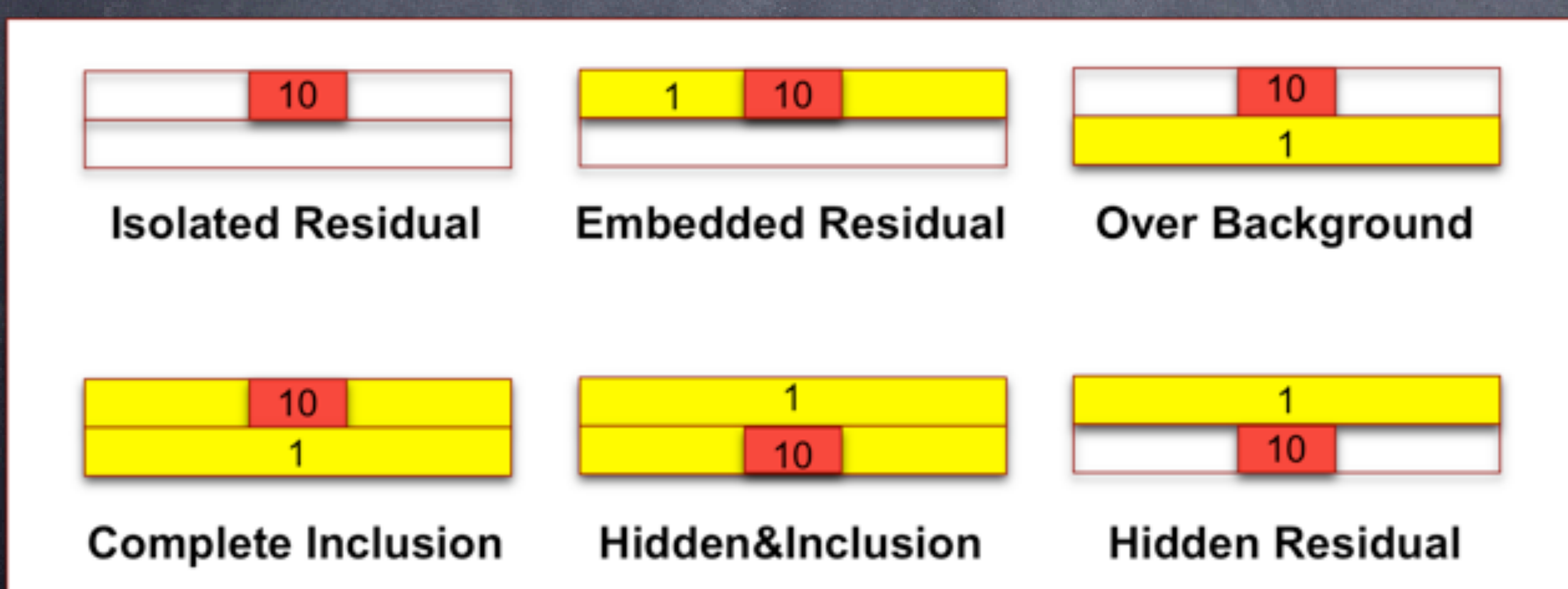
embedded in

tissue with A/10



Motorized scans with S4-Probe

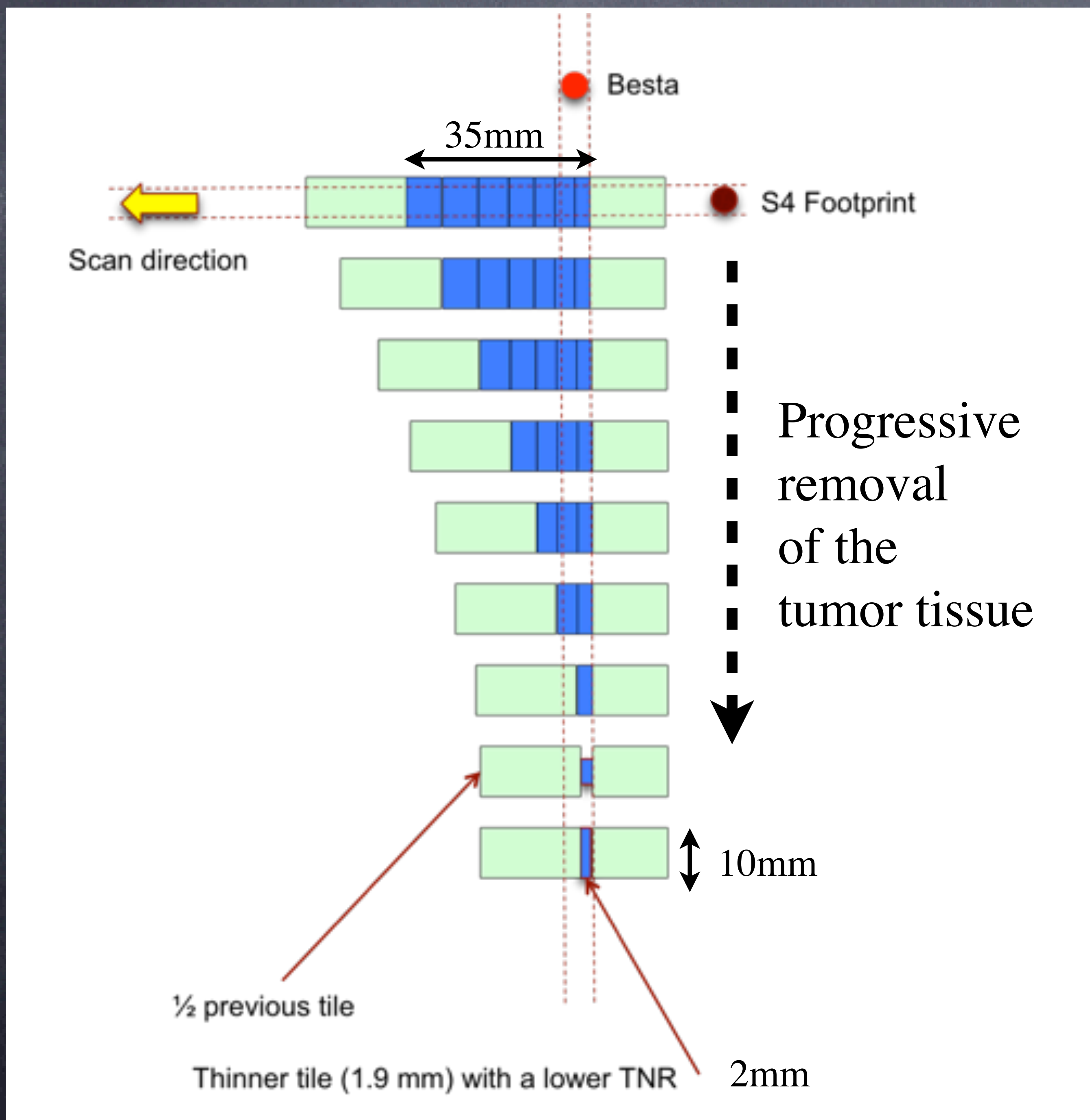


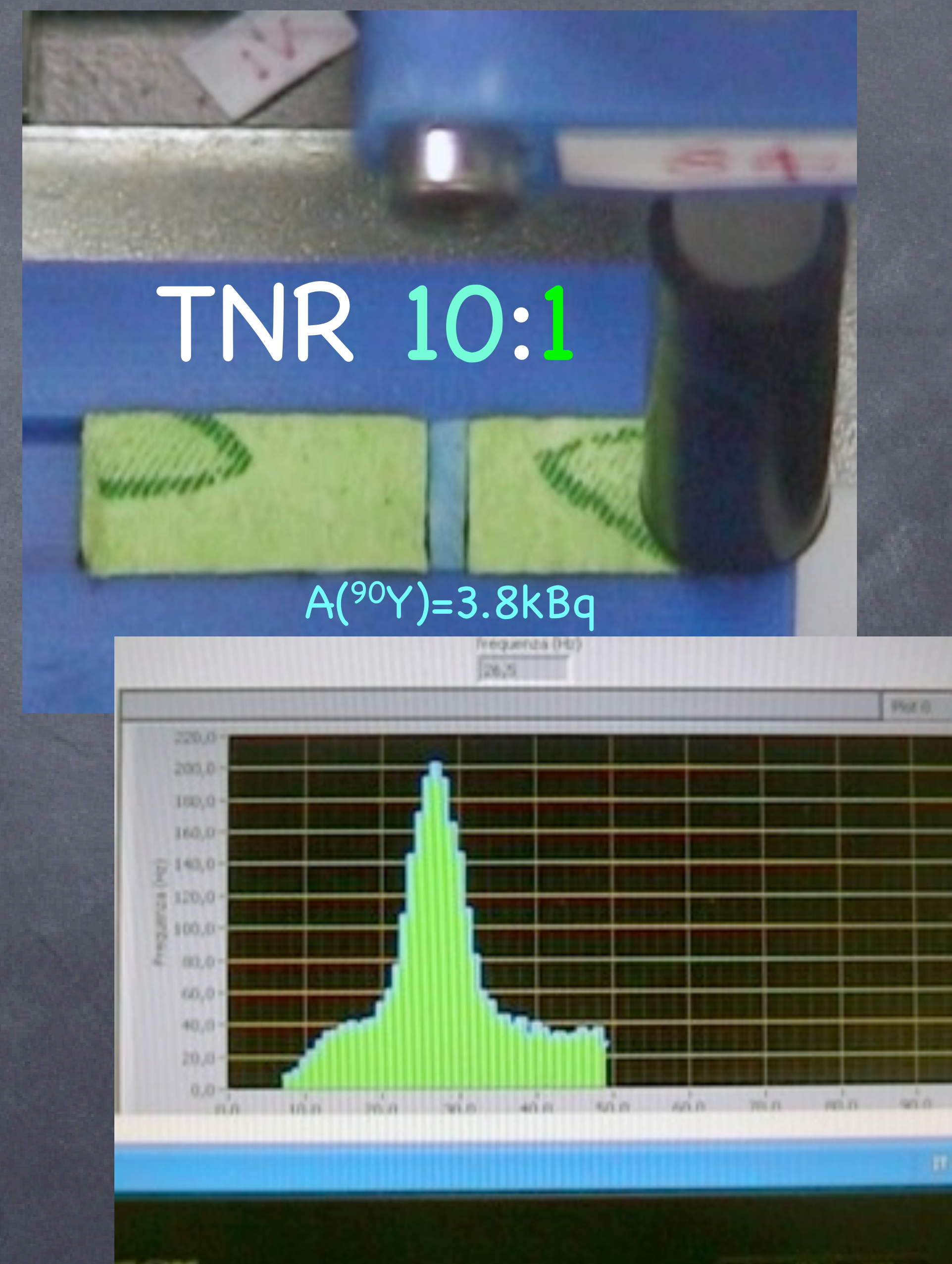


Possible configurations of tumor residual embedded in healthy tissue.

"Ad-hoc" Phantoms (II)

To test the discovery potential of the β⁻ probe in a "surgical cavity" after tumorous bulk removal





Counts stored in 10s per position

Human Factor

To include the human factor in the test colleagues were asked to simulate the surgeon:

Phantoms simulating tumor remnants embedded in healthy tissue with different TNRs

All people required at least 4-5 seconds per position to take a decision.

Next Steps for β^- Probe

- Optimization of the light collection to increase the probe sensitivity.
- Integration with surgical system:
  - surgical devices (e.g. aspirator, scalpel);
  - endoscopic and/or laparoscopic tools;
  - minimally invasive robotic "da Vinci" Surgical System;
- Multichannel probe for higher spatial resolution and directionality.

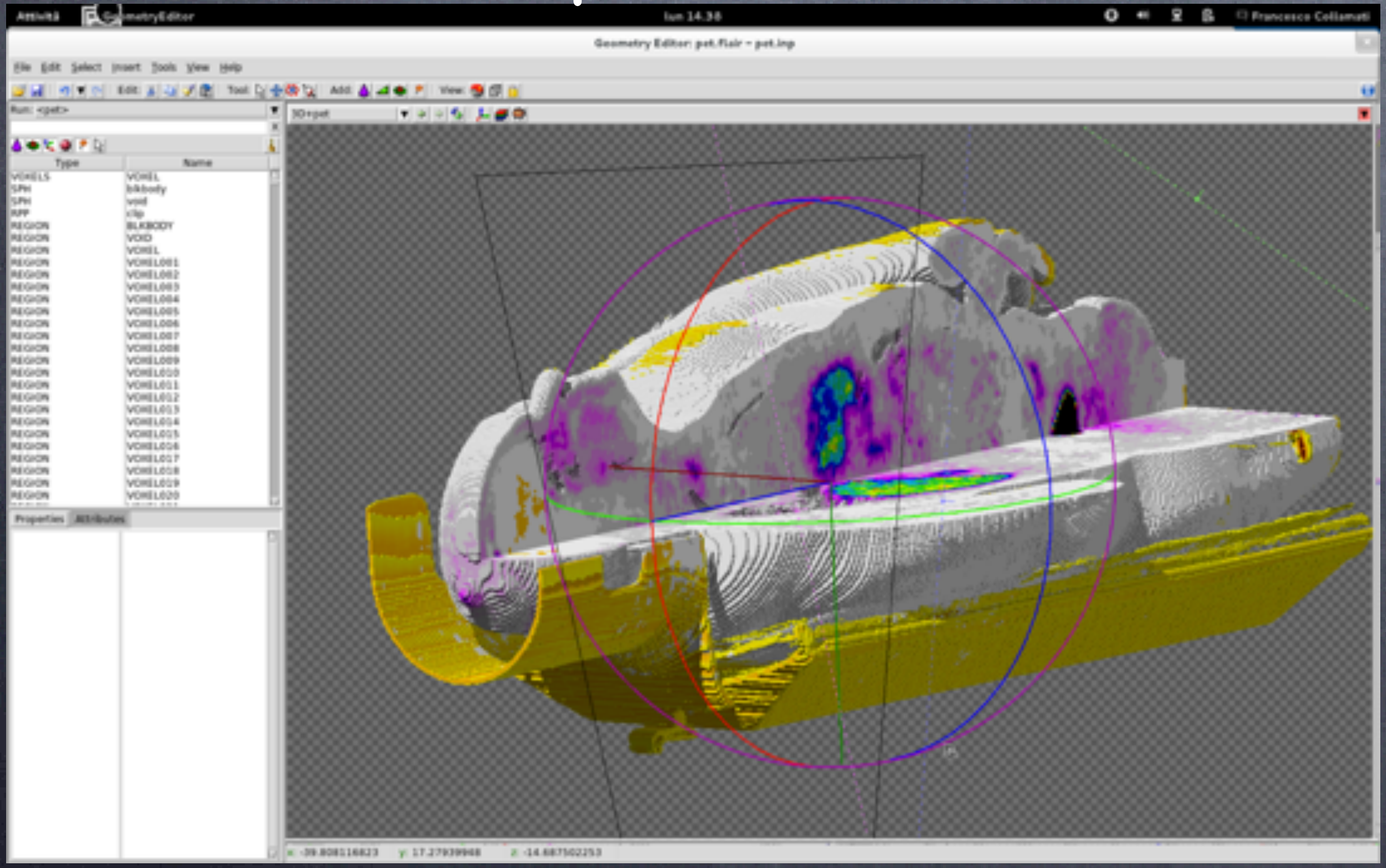
Predictions for the β^- RGS

Monte Carlo Simulation

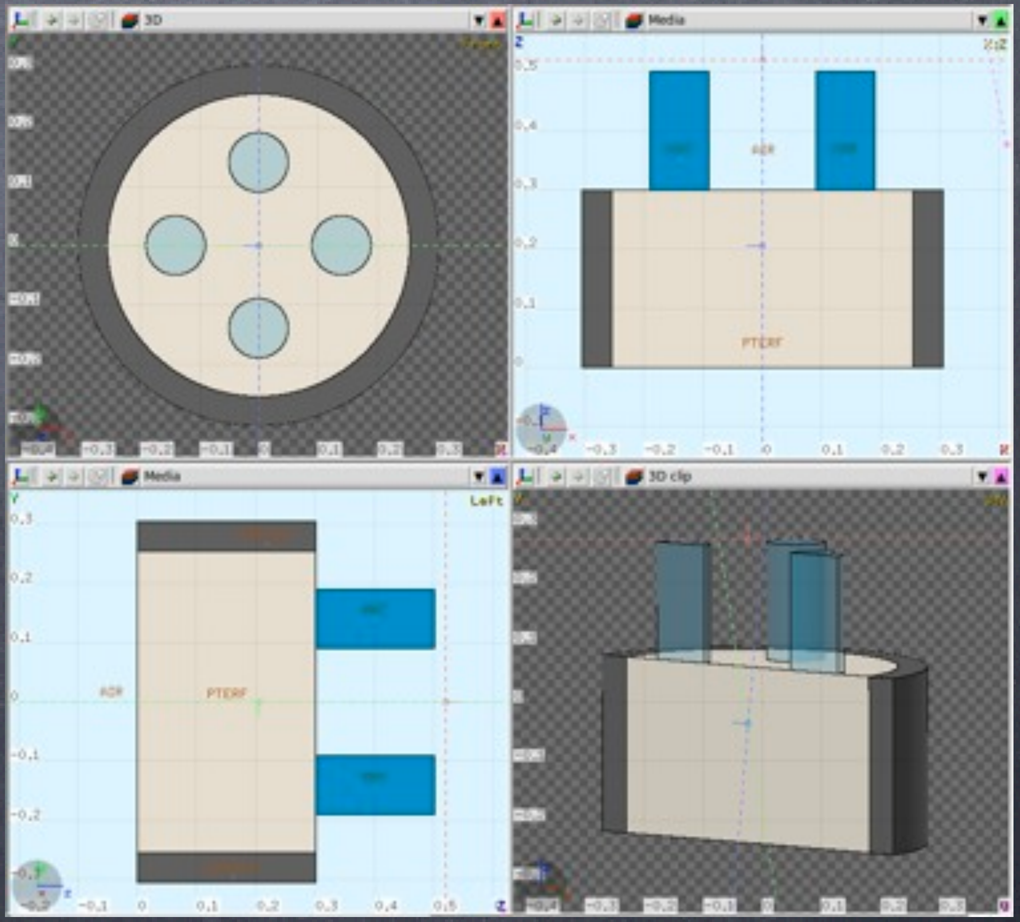
Simulation using FLUKA code allows us to achieve:

- **Probe** prototype's geometry and detector shielding optimization.
- Estimation of the potentialities of **β^- RGS.**
- Predictions of **dose delivered** to surgeon.

DICOM imported in FLUKA



Probe S4 simulation



Expected Performance

Including in FLUKA simulation

- ✓ TNR from PET/SPECT DICOM images
- ✓ performance of the probes measured in lab tests

we can predict performance of the **β⁻ RGS**:

- t^{min}_{probe} minimum time needed by the probe to identify a 0.1ml tumor residual after administration of 3MBq/kg of radio-tracer
  - **0.1ml** is the minimal residual well identified by diagnostic imaging
  - ➔ useful as reference during further clinical tests
  - **3MBq/kg** is comparable with activity for diagnostic (PET exam).

at 95% C.L.

- > Probability of False Positive FP<1%;
- > Probability of False Negative FN<5%.

Predictions for β^- RGS

Predictions for β- RGS

MENINGIOMA

TNR>10

Good sensitivity to residuals <0.1ml within **1s** with an administered activity smaller than those for PET-scans (**<3MBq/kg**).

Medical Team Exposure

Equivalent dose for surgeon	β^--RGS (^{90}Y) FLUKA simulation	γ-RGS (^{99m}Tc)
hands	<1 μSv/h	24 μSv/h
total body	<0.1 μSv/h	6 μSv/h

Predictions for β⁻ RGS

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HIGH GRADE GLIOMA

TNR>4

At least **5-6s** to detect residuals <0.1ml with administered activity of **3MBq/kg**.

To reduce the time, increase of the probe sensitivity would allow to avoid a larger activity administration.

Predictions for β⁻ RGS

MENINGIOMA

TNR>10

Good sensitivity to residuals <0.1ml within **1s** with an administered activity smaller than those for PET-scans (**<3MBq/kg**).

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Equivalent dose for surgeon	β^--RGS (^{90}Y) FLUKA simulation	γ-RGS (^{99m}Tc)
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HIGH GRADE GLIOMA

TNR>4

At least **5-6s** to detect residuals <0.1ml with administered activity of **3MBq/kg**.

To reduce the time, increase of the probe sensitivity would allow to avoid a larger activity administration.

HEPATIC METASTASIS from NET

TNR>5

At least **4s** to detect residuals <0.1ml with administered activity of **1MBq/kg**.

NEXT STEP:
"Ex-vivo" Tests

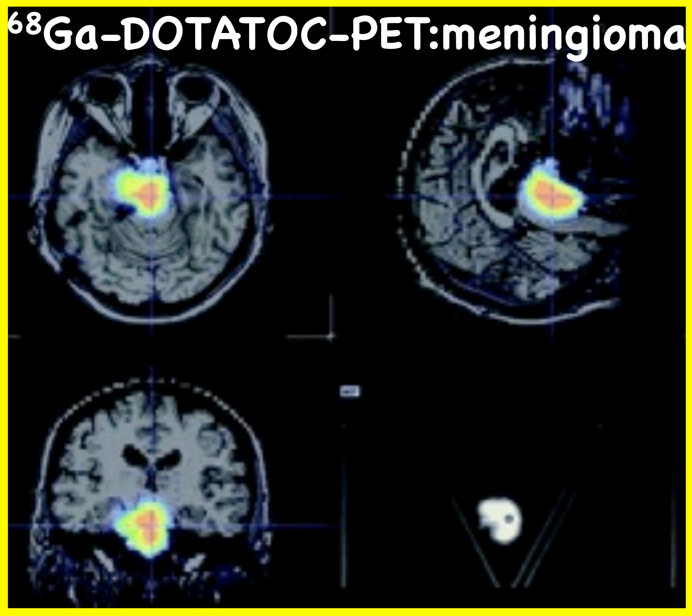
ISTITUTO NEUROLOGICO CARLO BESTA

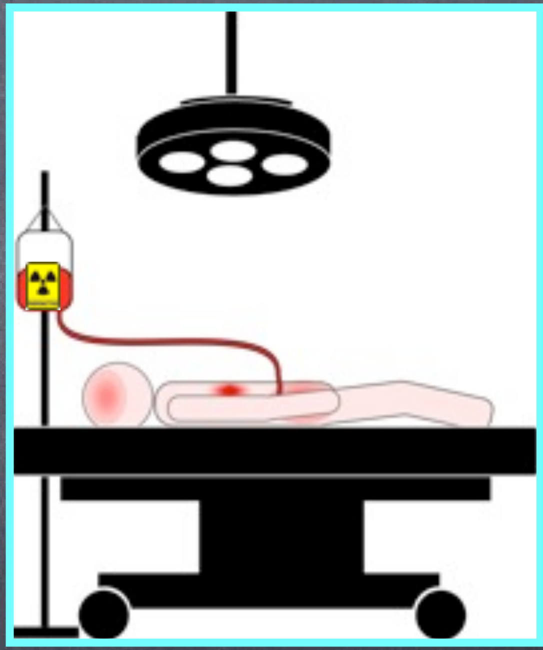
Fondazione IEO
Istituto Europeo di Oncologia

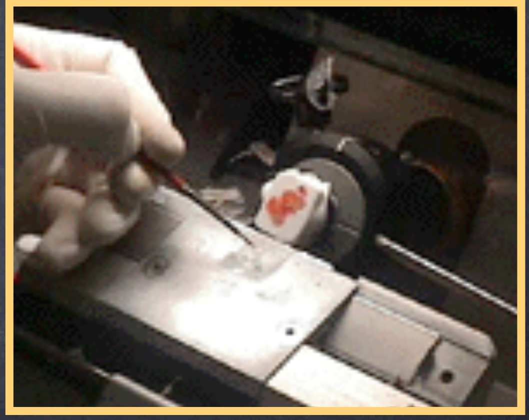
Authorized by Ethic Commitment

"Ex-vivo" Tests

To validate the whole chain of the technique we are going to perform "ex-vivo" test on volunteer patients affected by meningioma:







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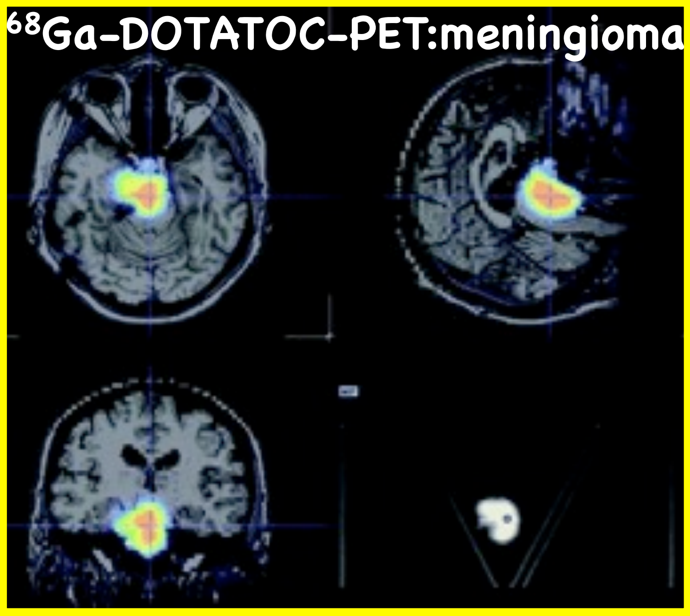

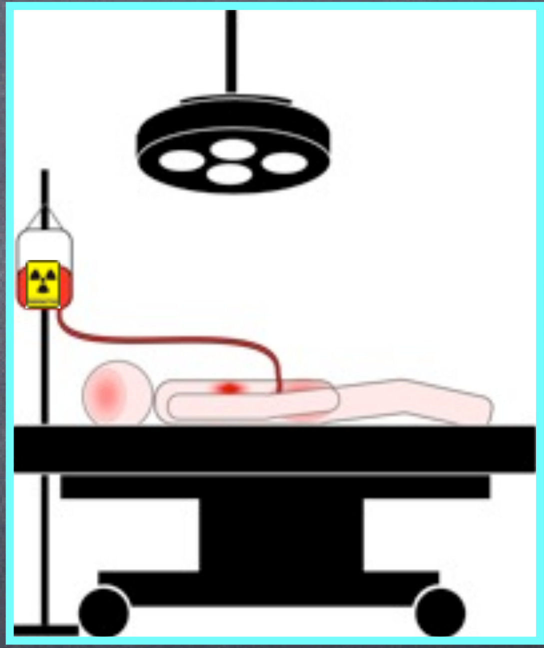

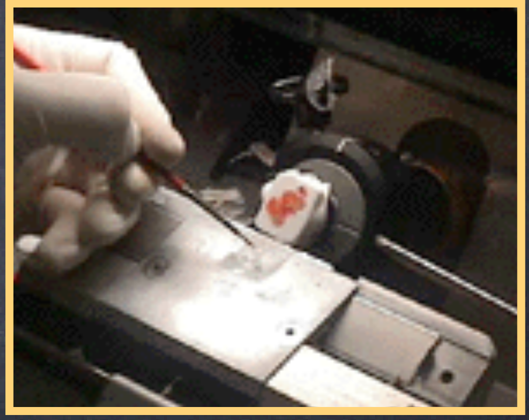

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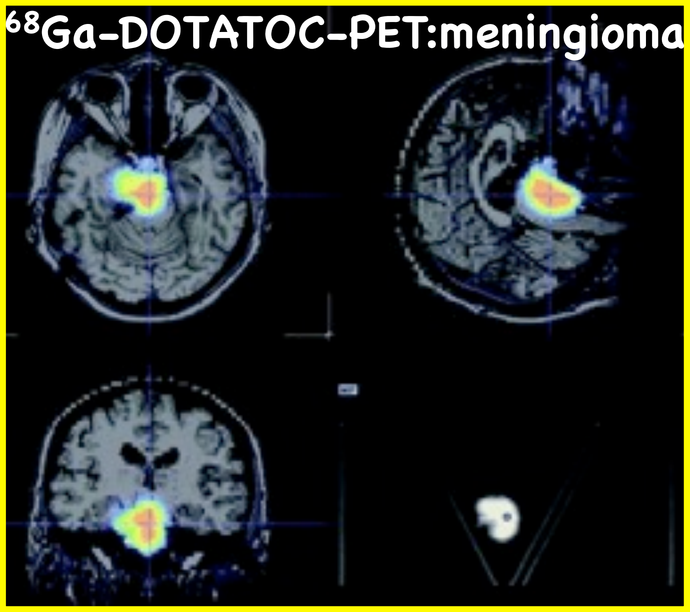

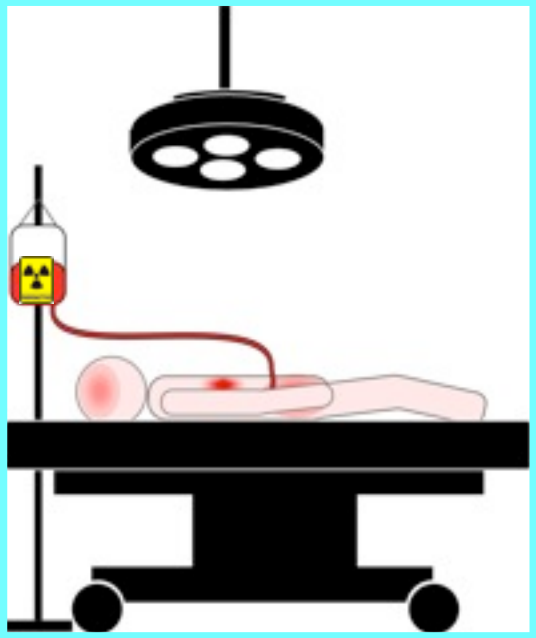

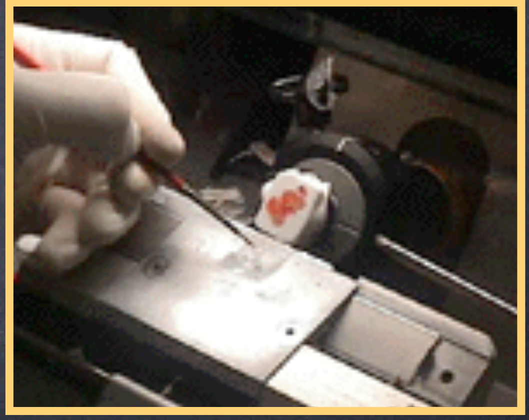

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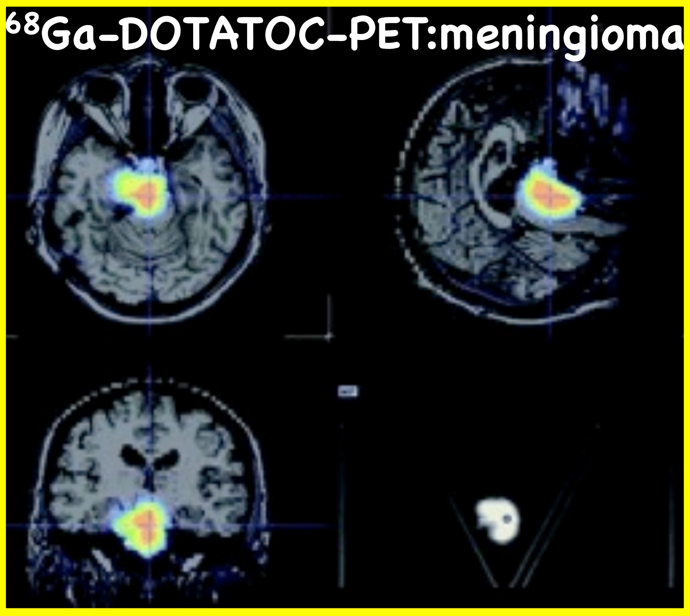

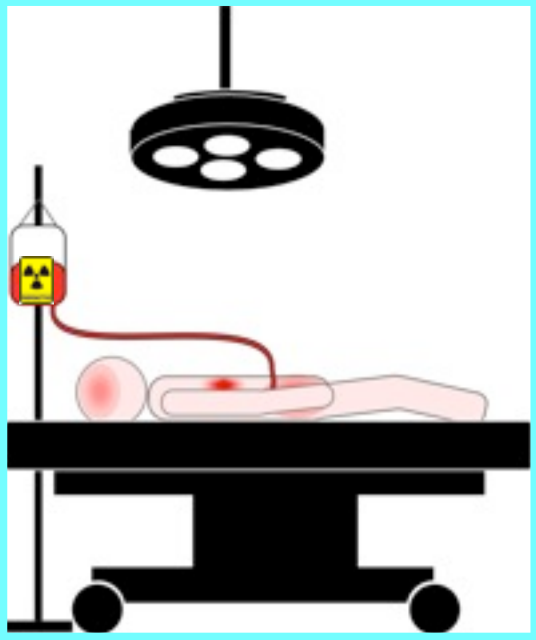

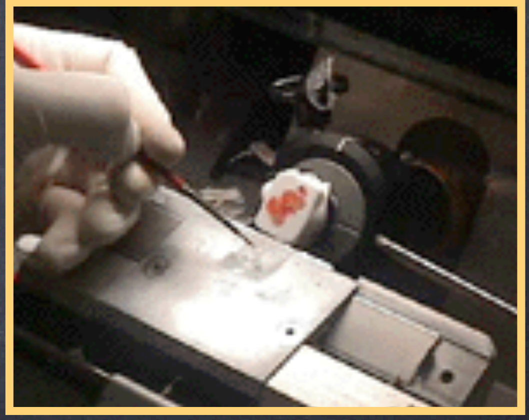

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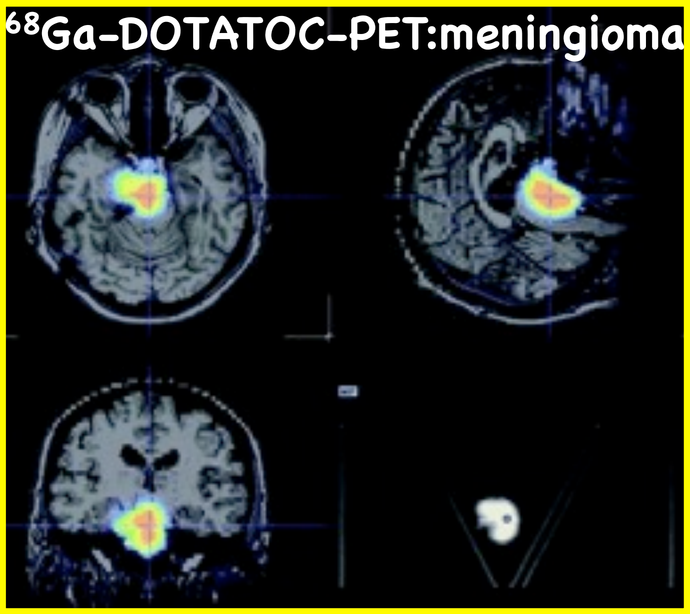
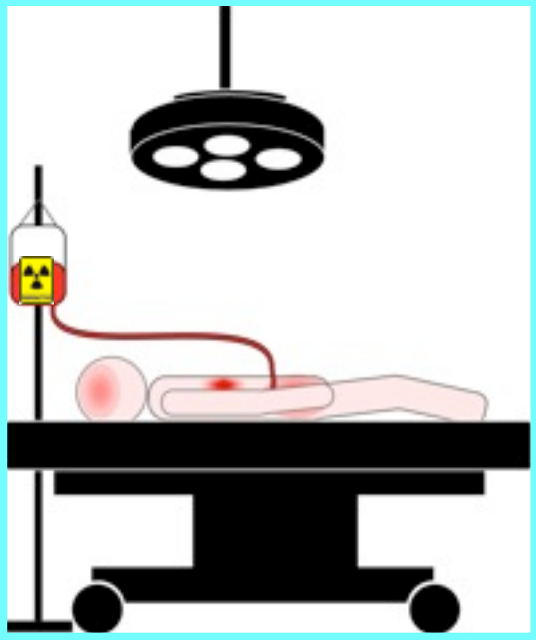
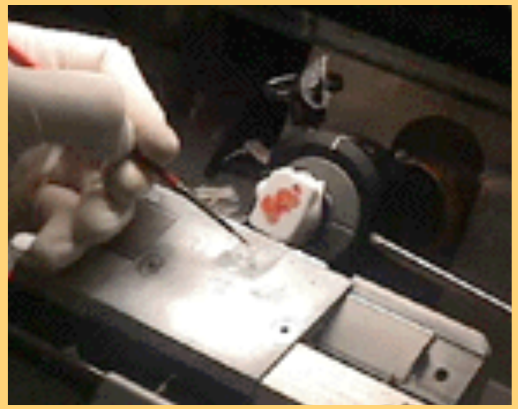
3. During surgery, extraction of small portions from both tumor and healthy tissue (normal prevention already present in protocols).
4. Measurement of the activity of "ex-vivo" specimens with the β^- probe prototype and comparison with the anatomo-pathological tests for cross-check.







NEXT STEP: Developments In Radio-Chemistry

SAPIENZA
UNIVERSITÀ DI ROMA

UNIVERSITAS CATHOLICA SACRI CORDIS IESU MEDIOLANI

New Radio-Tracers

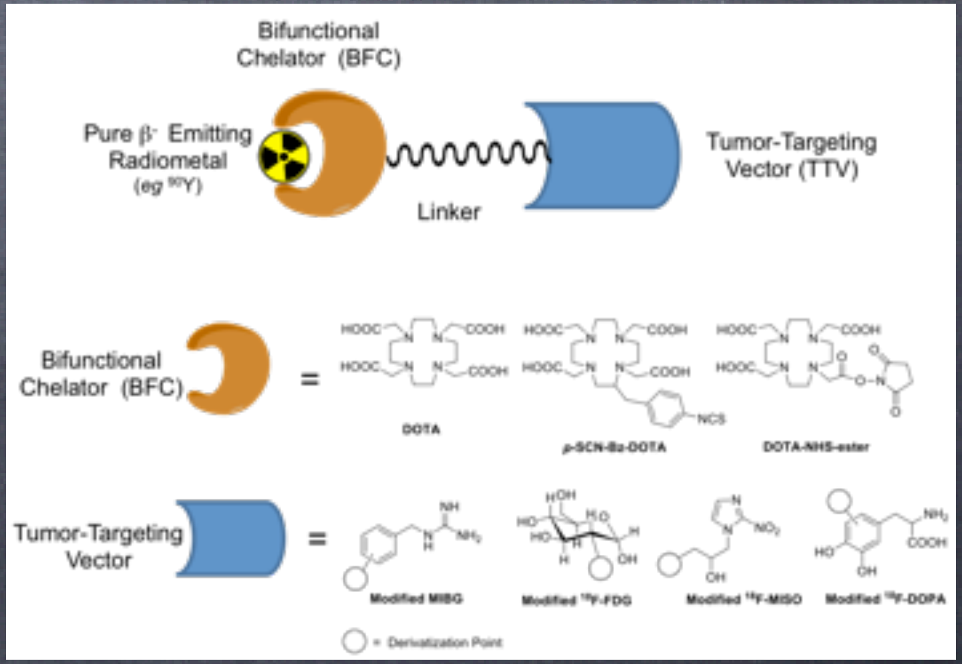
To extend the range of application for β^- RGS

- Collaboration with chemists and biomedical engineer to develop new tracers has just started

➡ To evaluate the possibility of replacing radio-nuclide in PET/SPECT tracer with ^{90}Y (or suitable β^- emitters)

  - e.g. Is it possible to append ^{90}Y to MIBI or sestamibi commonly marked with ^{99m}Tc for SPECT scans?

Isotope	½-life	Pure?
^{90}Y	64h	Y
^{89}Sr	50d	Y
^{49}Sc	1hr	Y
^{31}Si	2hr	Y
^{69}Zn	1hr	Y
^{42}K	12h	N
^{153}Sm	46h	N
^{131}I	8d	N



Possible β⁻ RGS Candidates

- **Parathyroid disease** and micro-metastases from **Head&Neck cancer:**
  - Treatment: parathyroidectomy (less invasive than traditional surgery) to remove the abnormal gland.
  - γ radio-tracer for RGS: ^{99m}Tc-sestamibi
- **Pheochromocytoma** (2-8/million/year) and **Paraganglioma (rare):** neuroendocrine tumor originating from neural crest tissue
  - Treatment: surgical resection with the affected adrenal gland(s)
  - γ radio-tracer for imaging: ^{123}I/^{131}I-MIBG or ^{99m}Tc-sestamibi
- **Neuroblastoma** (11/million/year): the most common extracranial solid tumor in childhood, originates in the adrenal medulla or the paraspinal sites where sympathetic nervous system tissue is present
  - Treatment: generally curable but aggressive therapy has to be considered in children
  - γ radio-tracer for imaging: ^{123}I/^{131}I-MIBG

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- Project in prototyping and proof-of-principle stage.
- Next steps
  - "ex-vivo" tests on meningioma cases;
  - PROBE: different solutions for different clinical applications;
  - development of new specific radio-tracers (and radionuclides).

Master and PhD students are welcome

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