Mediterranean Thematic Forum
on Advanced Molecular Imaging in Personalized Healthcare

Radio-Guided Surgery with β- radiation: tests on ex-vivo specimens

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on behalf of the **ARPG group**
http://arpg-serv.ing2.uniroma1.it/arpg-site/

Applied Radiation Physics Group

Applied Radiation Physics Group

Collaborations with **medicinal chemists**, **biologists**, **radio-pharmacist**, **nuclear medicine physicians**, **oncologists**, **surgeons**:

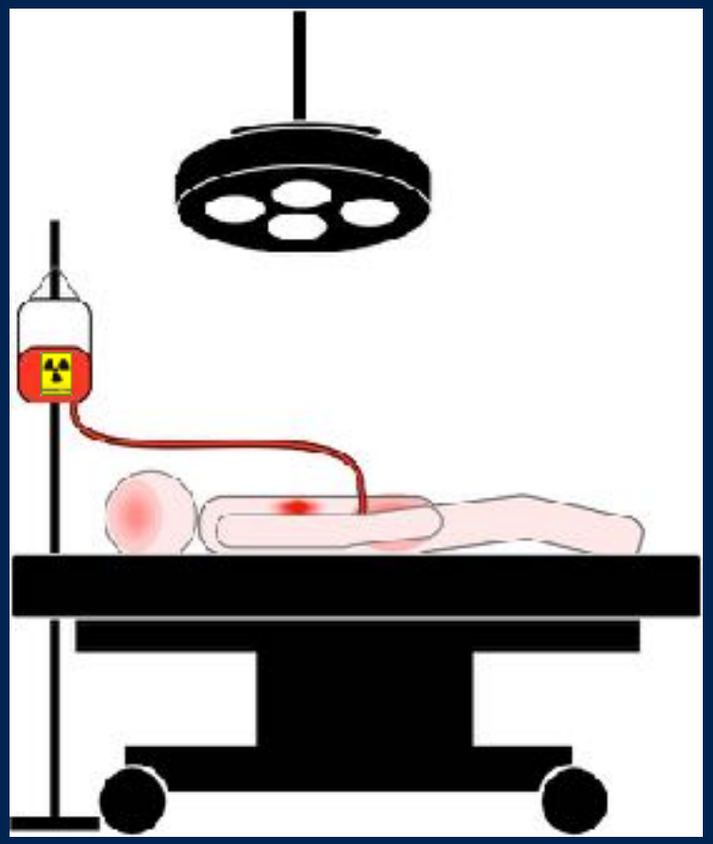
Outline

- The radio-guided surgery (RGS) based on β- radiation
  - Clinical applications of interest;
  - The β- detecting technology;
    - Validation with ex-vivo tests on specimens
      - Meningioma brain tumours.
      - Gastro-entero-pancreatic neuroendocrine tumors (GEP-NET).
    - Method to estimate the minimum injectable activity;
- Conclusion and next steps

Radio-Guided Surgery

GOAL: as much complete as possible tumour resection

RADIOPHARMACEUTICAL



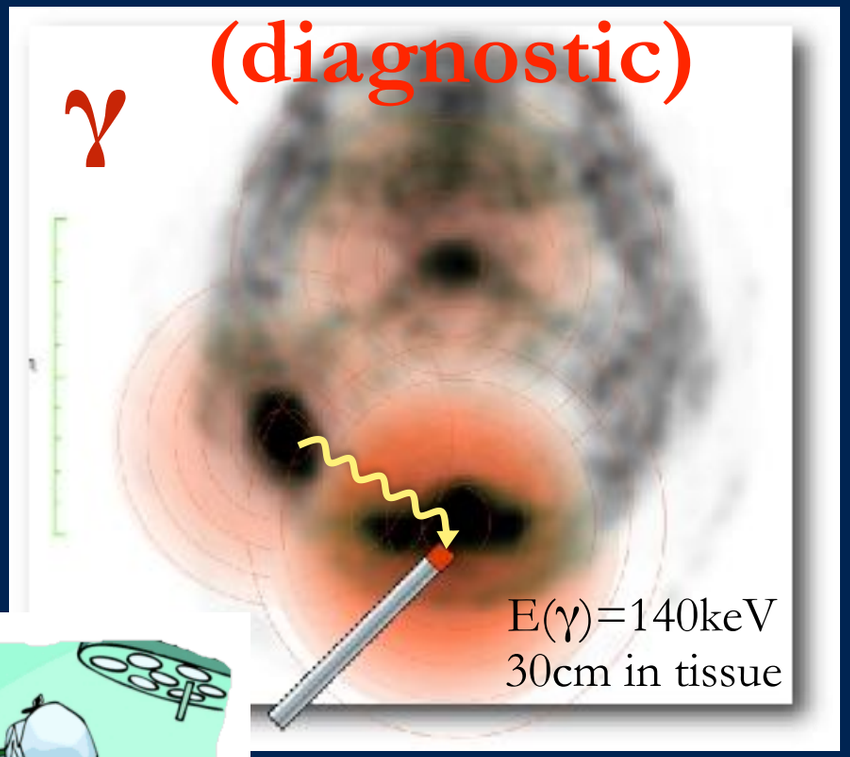
&

INTRAOPERATIVE DETECTING PROBE

RGS is crucial for recurrence-free and overall survival.

RGS based on β- radiation

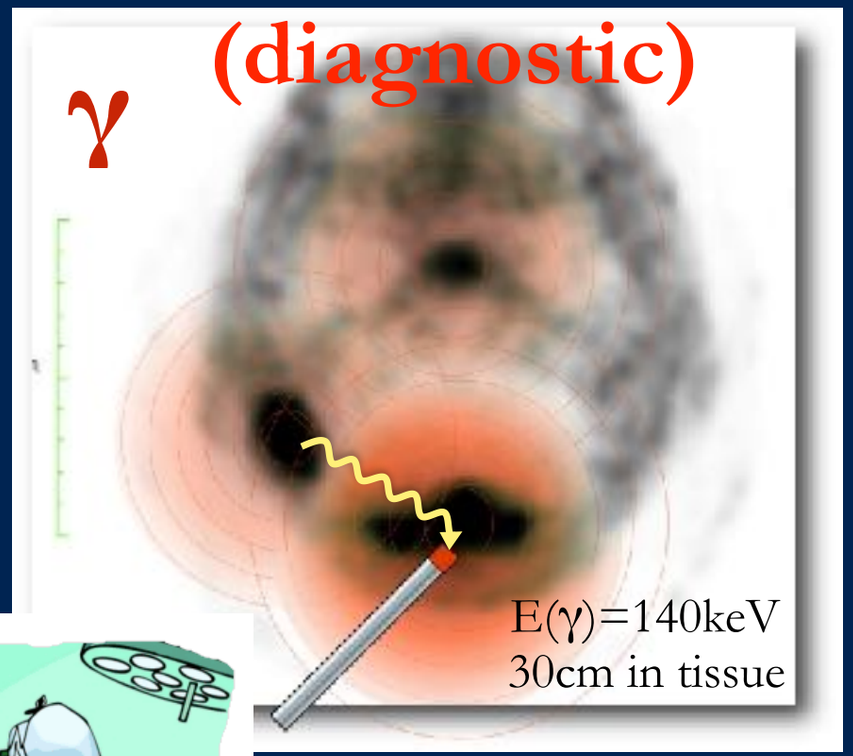
Long Range Radio-tracer



RGS based on β- radiation

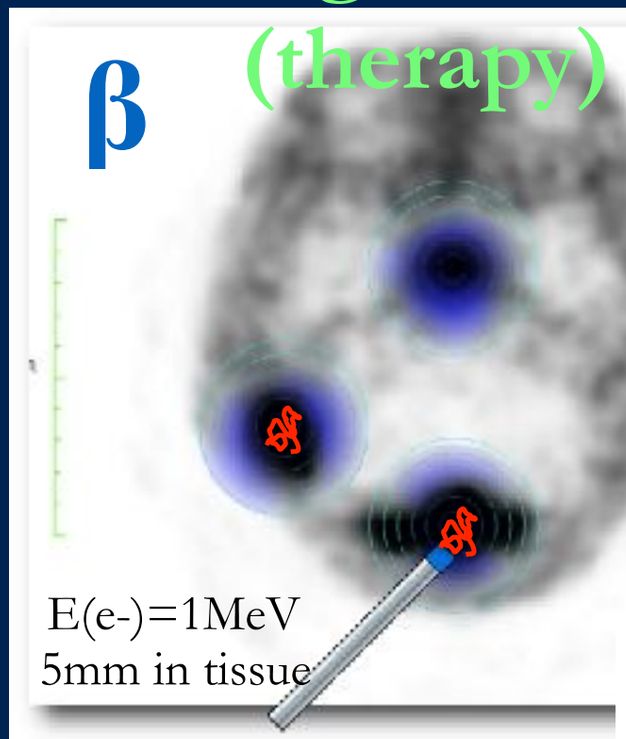
Long Range Radio-tracer (diagnostic)

γ



Short Range Radio-tracer (therapy)

β



RGS based on β- radiation

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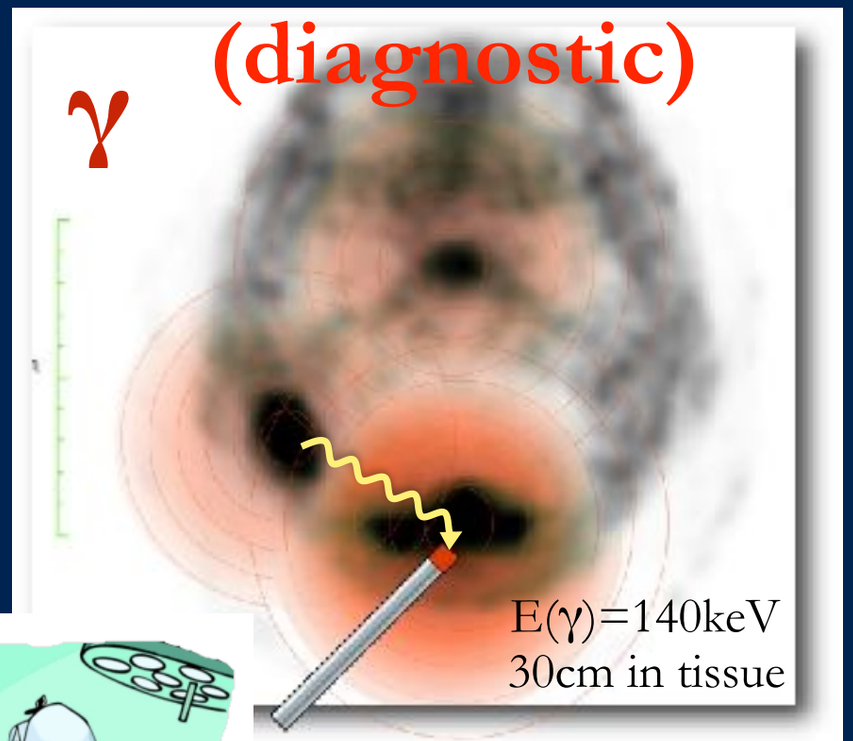

Short Range Radio-tracer (therapy)

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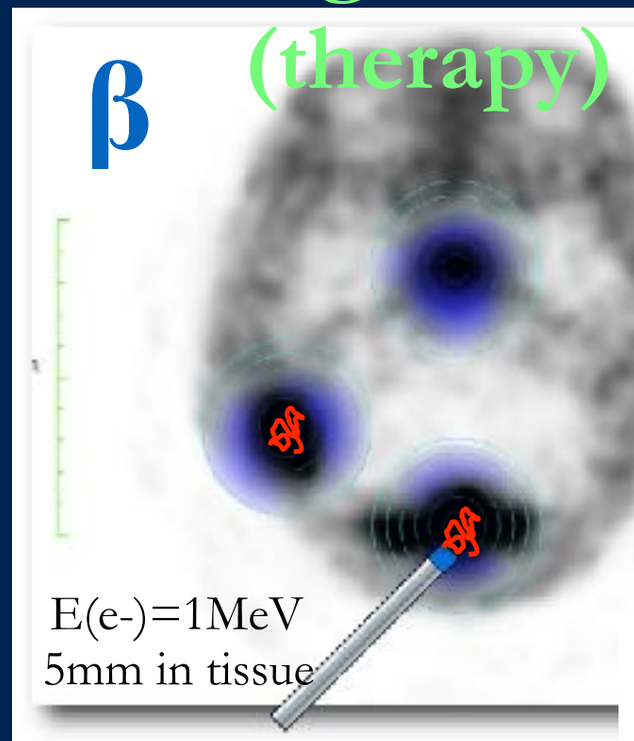
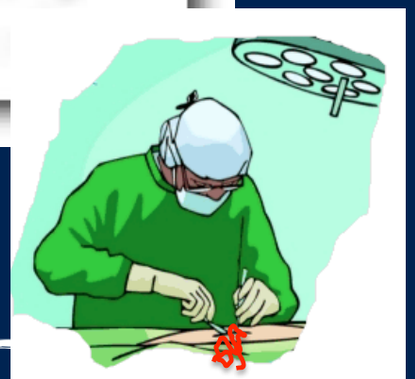




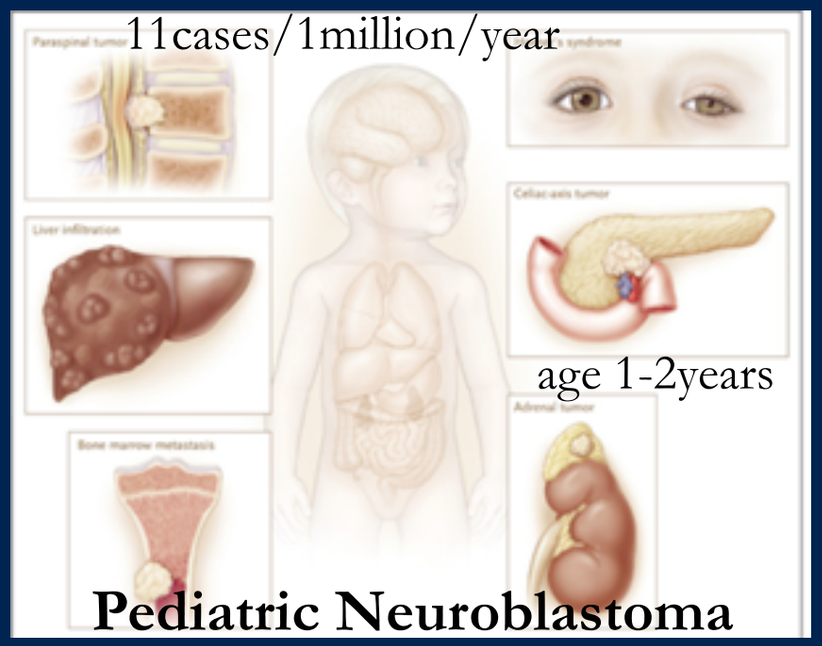
- **Better S/N** → compact and "simple" detector system.
- **Low activity** to detect small remnants.
- **Negligible** medical staff **exposition.**
- BUT **scarce** availability of pure **β- radio-tracers**

Clinical Applications

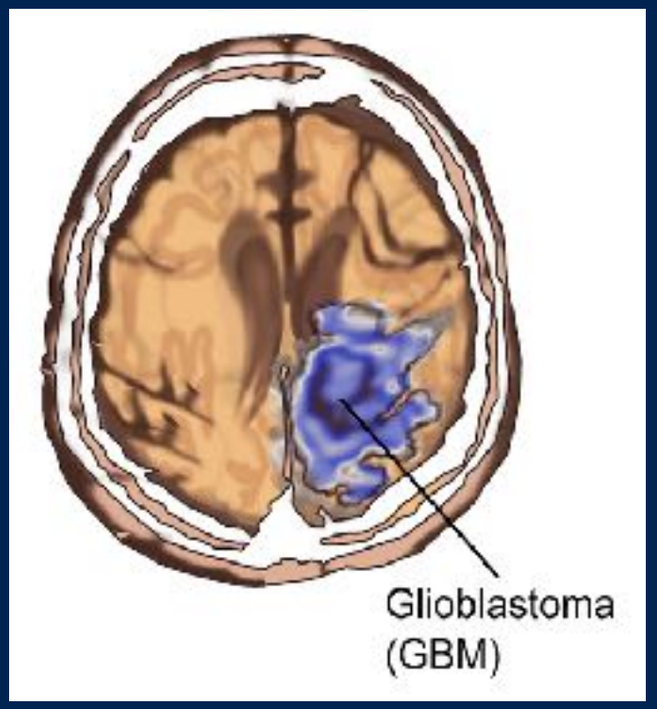
β- radionuclides can extend the range of RGS application

PEDIATRIC TUMORS

11cases/1million/year



Pediatric Neuroblastoma

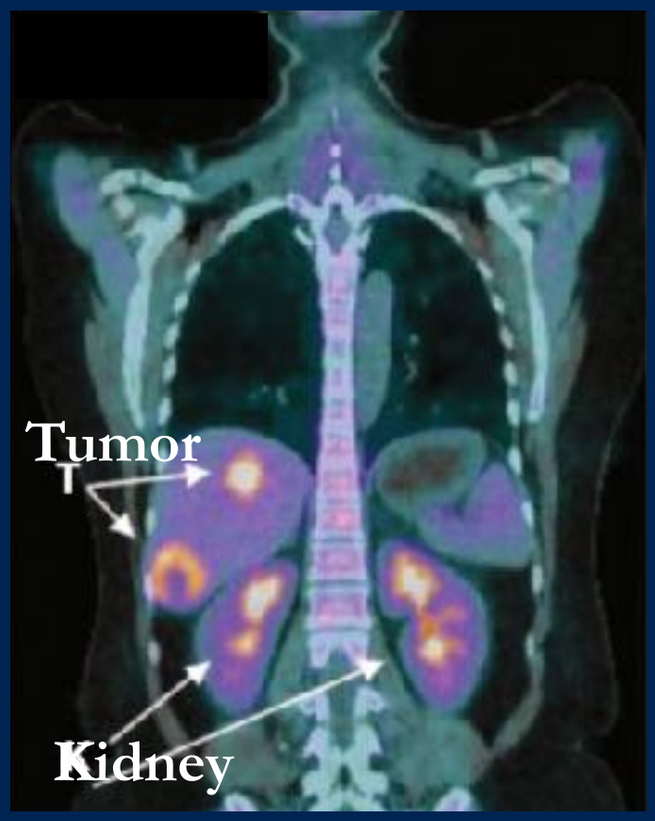


BRAIN TUMORS

RGS would help:

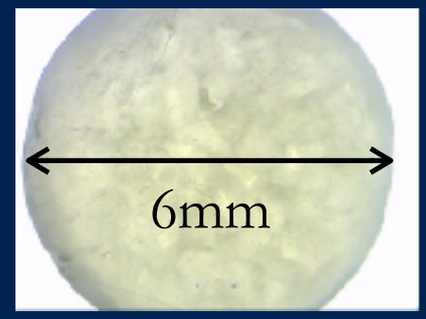
- after the tumor mass removal, brain shape changes with respect to the images acquired before.

ABDOMINAL TUMORS



The β- Detecting System

1. Scintillator: Para-terphenyl
   - High light yield 2*LY(stilbene)
   - Scarce sensitivity to γ (ϱ=1.24g/cm^3)
   - Light attenuation λ~few mm
2. Silicon PhotoMultiplier (SiPM)
   - SensL C-10035 dark current ~15nA
3. Portable electronics read-out, customised to match the surgeon needs



Compatible with a standard sterile covering (e.g. for endoscopic camera)

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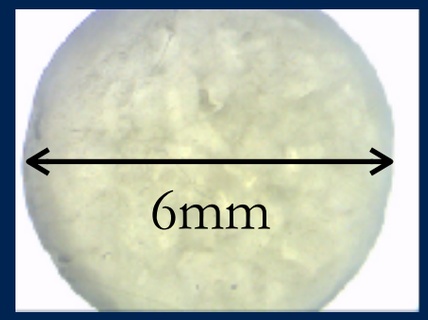
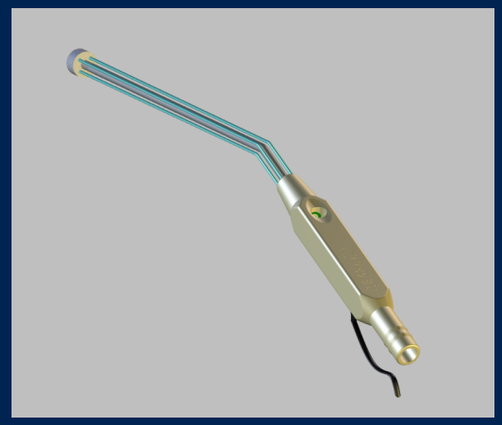


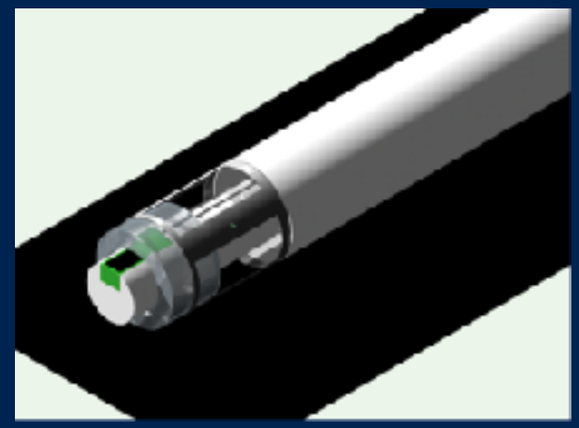
Compatible with a standard sterile covering (e.g. for endoscopic camera)

Able to detect small lesions ≤0.1ml within 1s with activity of ~1kBq/ml.

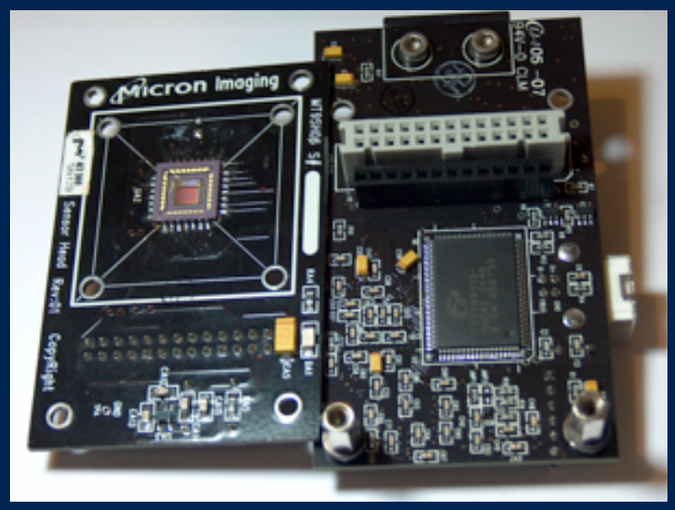
Next Prototypes

- The adopted technology is flexible and can be easily integrated into surgical devices/applications
  - minimally invasive robotic surgery
- Working on two new applications:
  - integration with a frazier surgical suction instrument;
  - endo/laparoscopic tools.





- Also under study CMOS technology as alternative
  - to lower the energy limit
  - better gamma/beta discrimination would open the technique to the most common PET radionuclides (long range)



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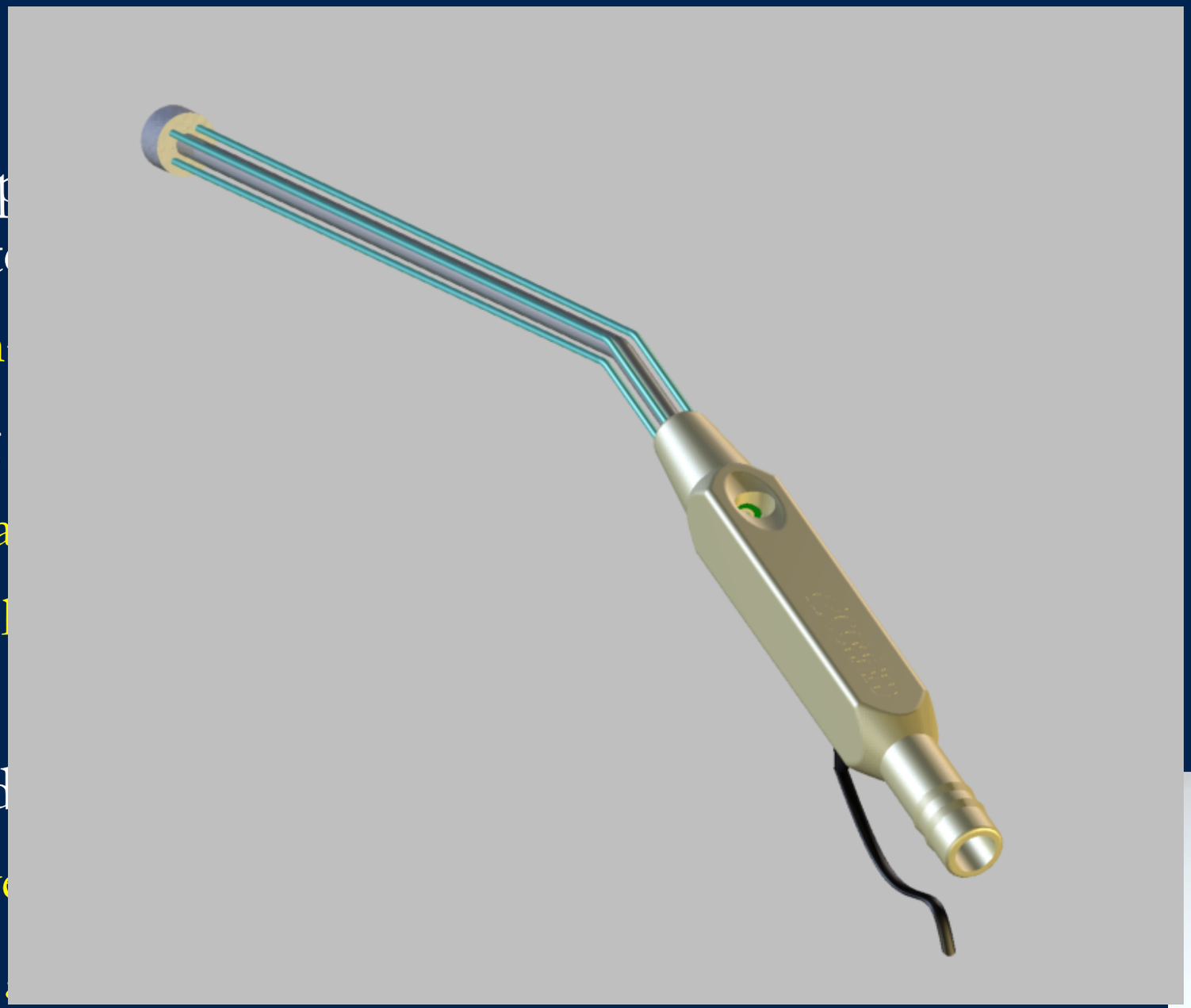

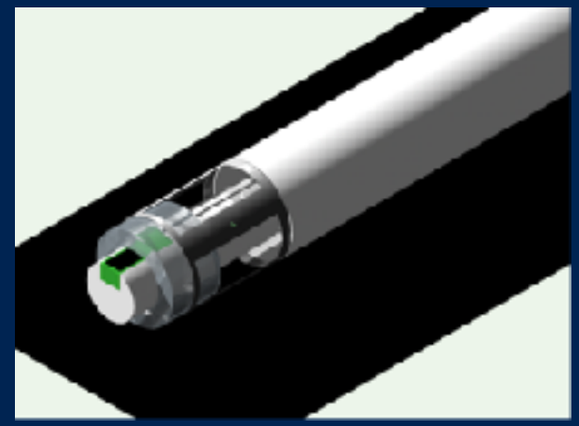

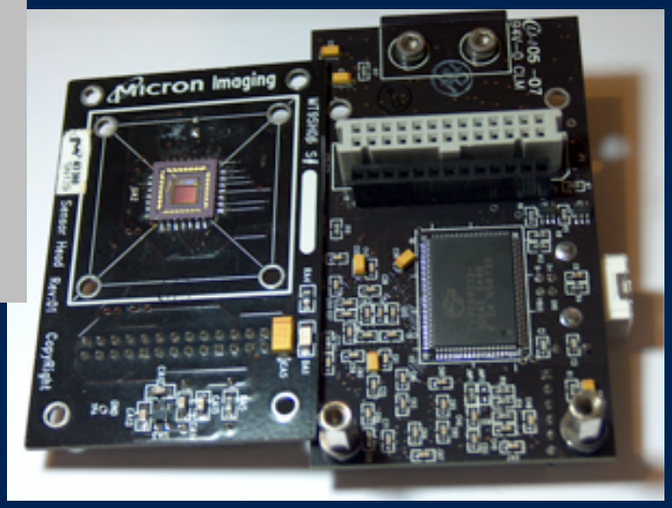

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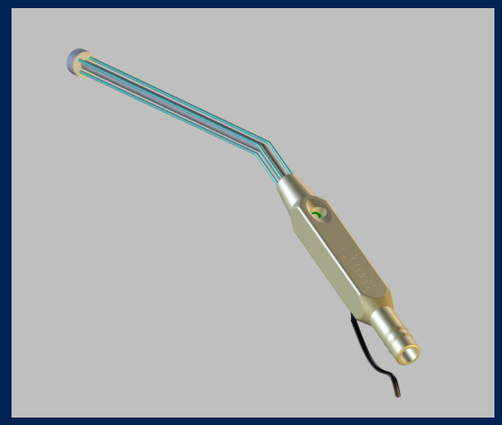

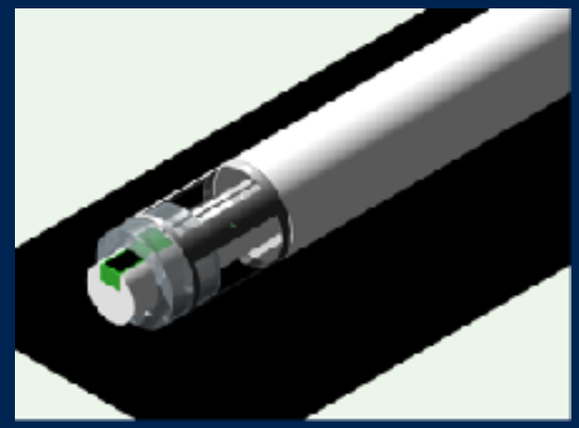

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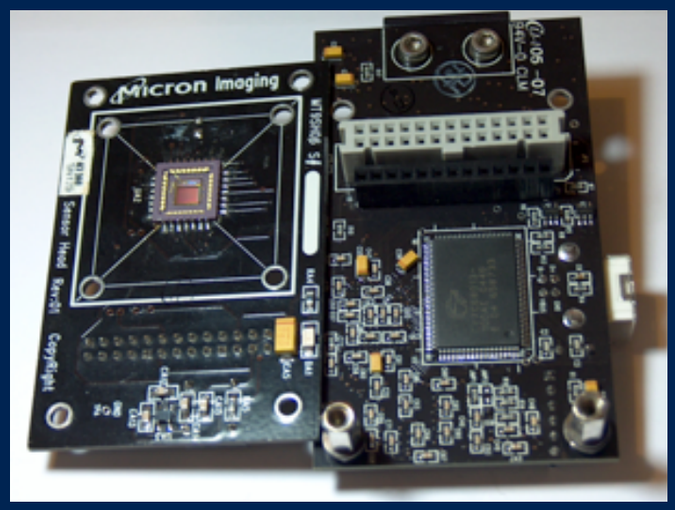

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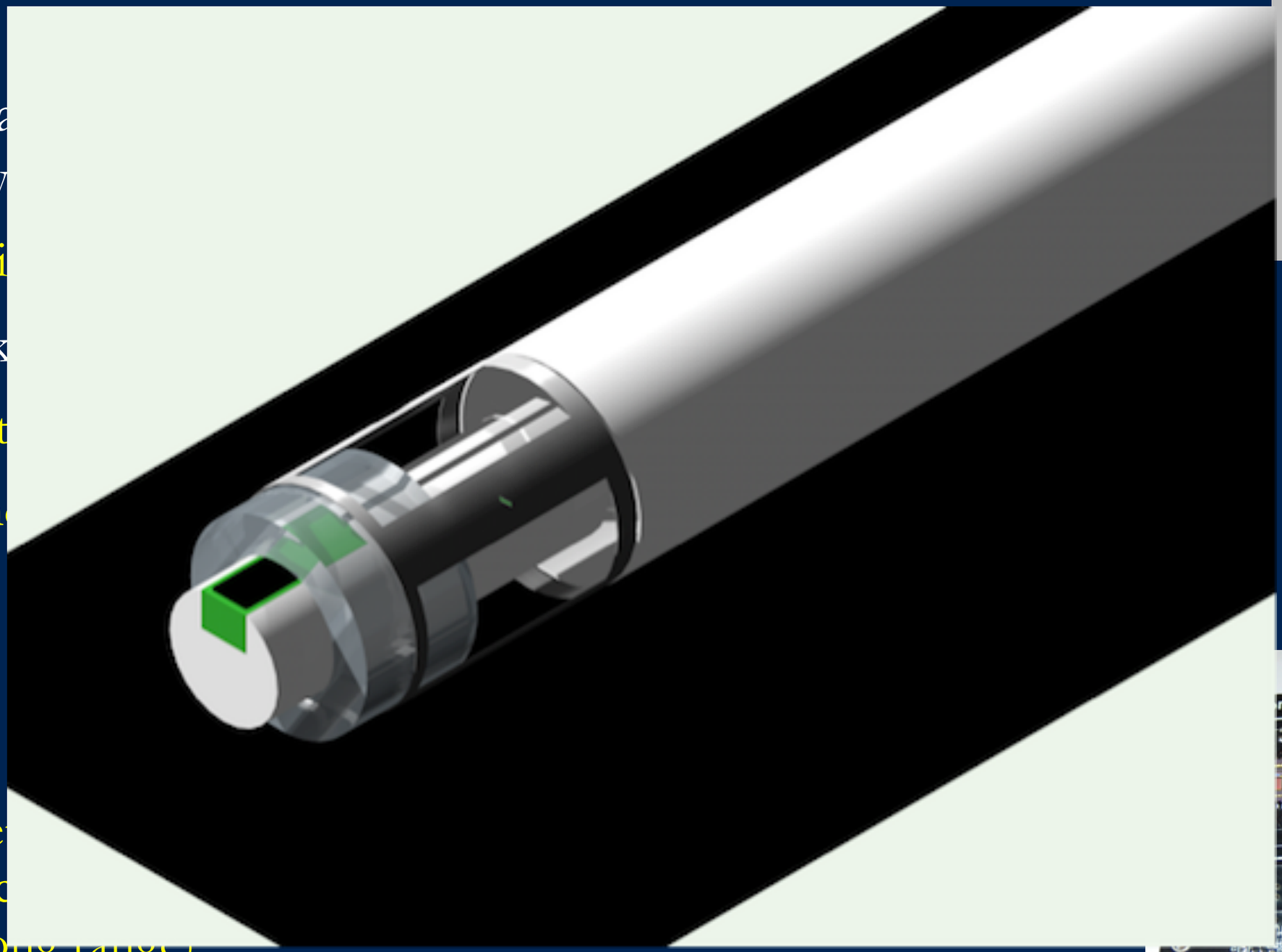

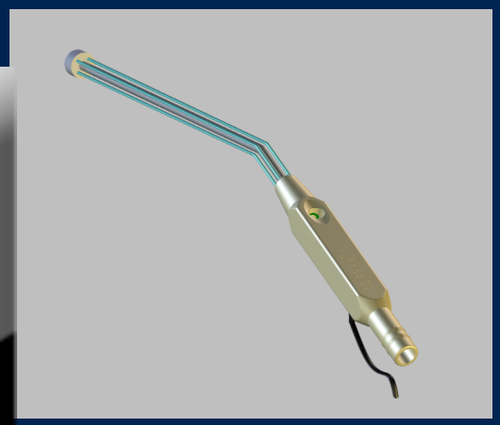

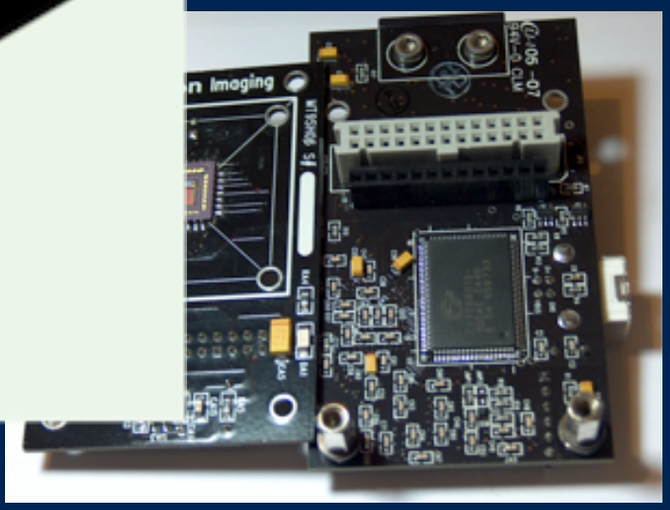

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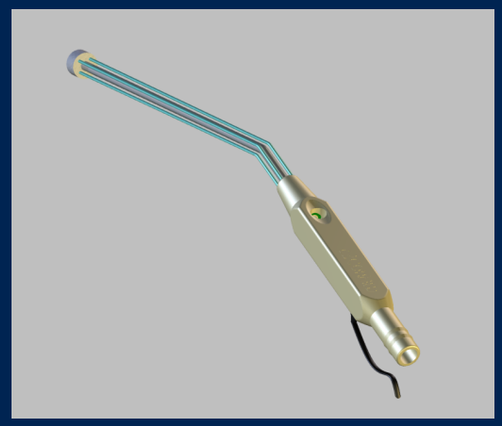

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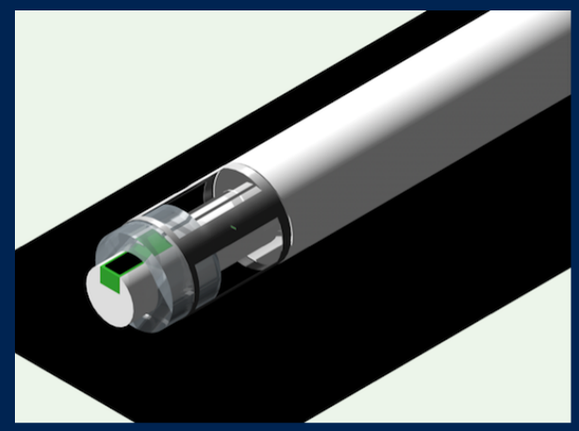

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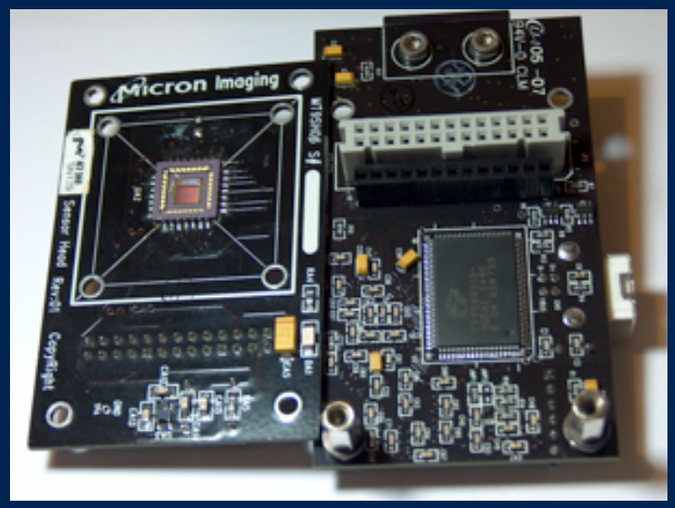


Ex-vivo Tests on Meningioma

Clinical trial EUDRACT 2013-004033-32

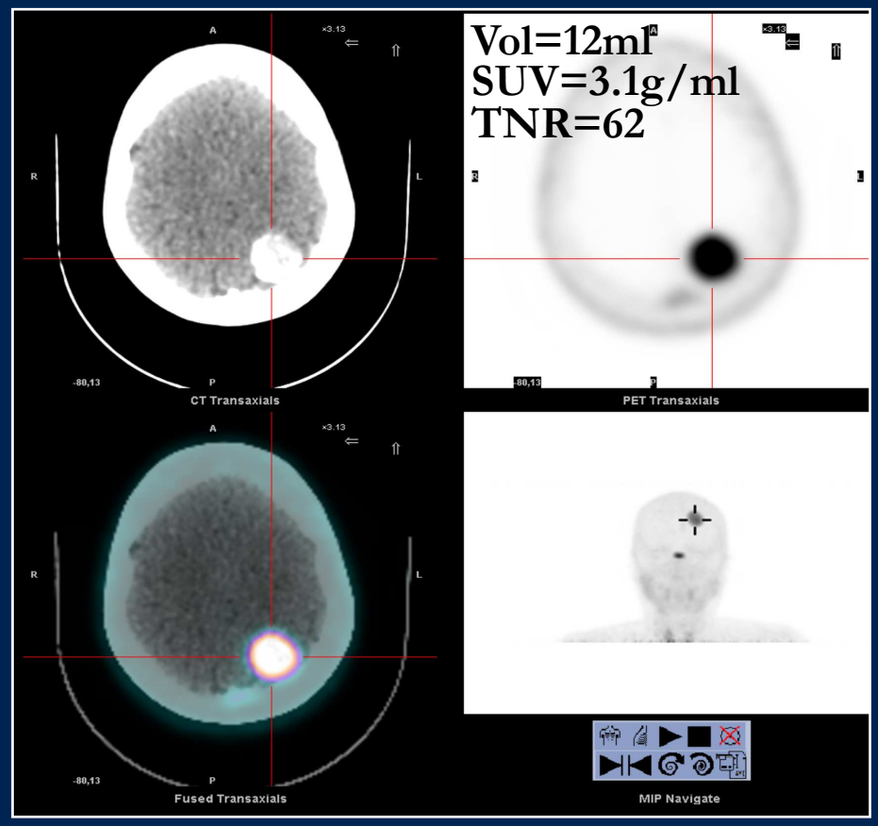
IEO Istituto Europeo di Oncologia

Fondazione IRCCS Istituto Neurologico Carlo Besta — Sistema Sanitario Regione Lombardia

Patient Enrolment

- **MENINGIOMA**
  - high uptake to a β- radio-tracer **^{90}Y-DOTATOC** (synthetic somatostatin analogue)
- From ^{68}Ga-DOTATOC PET images:
  - standardised uptake value **SUV>2g/ml**
  - tumor/non-tumor **TNR>10**
- According to a previous feasibility study:
  - **0.1ml** tumor residue detectable in **1s** with administration of **~1MBq/kg**

156MBq ^{68}Ga-DOTATOC PET/CT



Patient	V_T [ml]	$\overline{SUV}$ [g/ml]	SD(SUV) [g/ml]	TNR	A_{adm} [MBq]	W [kg]	A_{est} [kBq/ml]
1	18.3	4.3	1.1	26	167	104	5.4
2	11.9	3.1	0.9	62	111	77	3.4
3	21.5	2.8	1.2	92	93	65	3.0

Expected Activity for Lesioned Specimens

At the time of surgery:

$A_{est}[kBq/ml] = A_{inj}[MBq/kg] * SUV[g/ml] * 2^{(-\Delta t/\tau_{1/2})}$

Injected activity

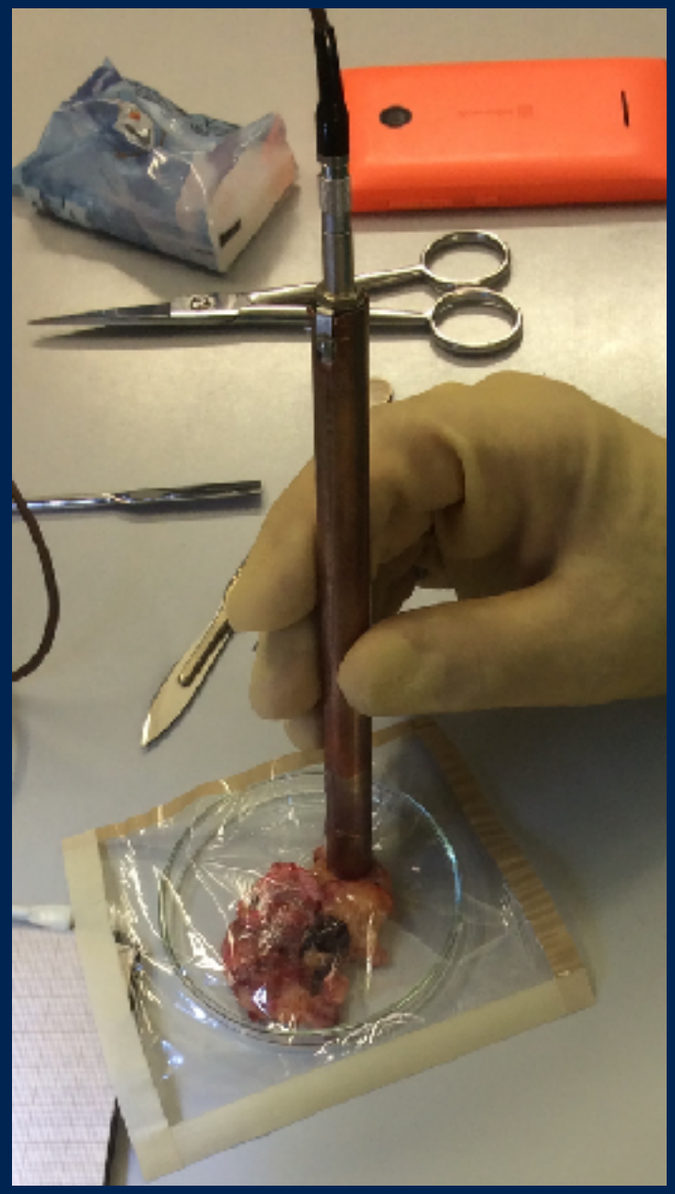
SUV of the primary lesion estimated from ^{68}Ga-PET

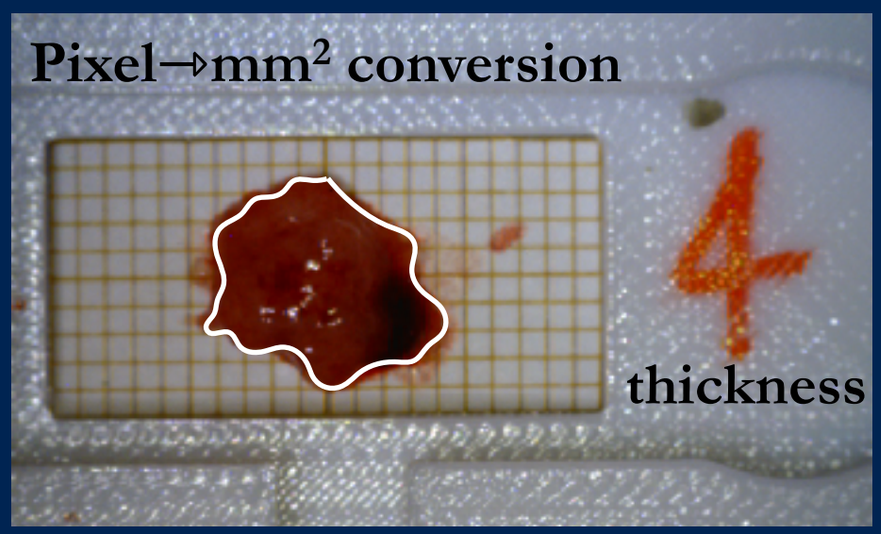
Assuming that the bio-distribution depends on the drug delivery mechanism and is not affected by the labelling radionuclide.

Clinical Protocol

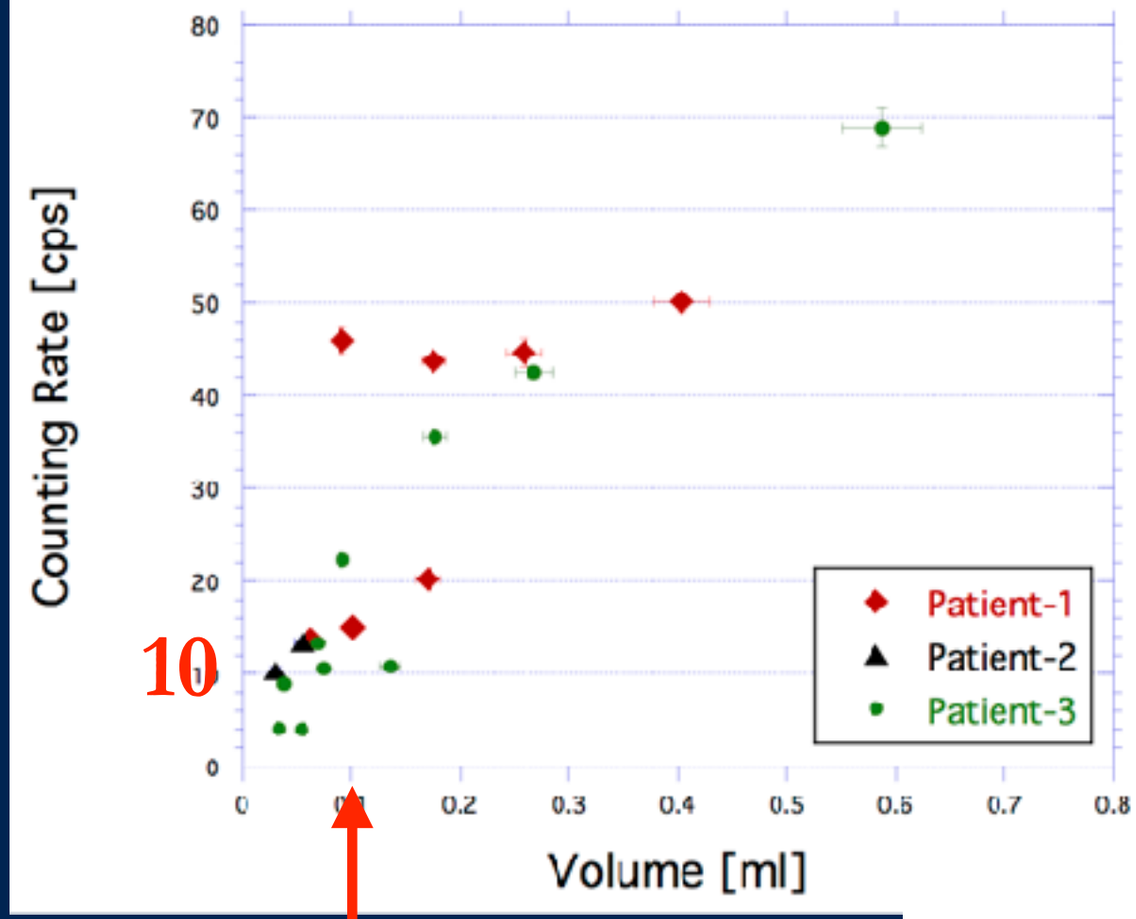
1. ^{68}Ga-DOTATOC PET/CT scan (2 weeks prior).
2. Voluntary patients gave written informed consent.
3. ^{90}Y-DOTATOC injection.
4. Wait 24 hours for bio-distribution and wash-out from healthy organs ➔ optimal TNR.
5. Tumor bulk removal by neurosurgeon.
6. Quantification of β- probe response on small (~0.1ml) samples.
7. Specimen classification by anatomo-pathologists.

Patients received the kidney protection (aminoacid solution) as in Peptide Receptor Radionuclide therapy (PRRT)

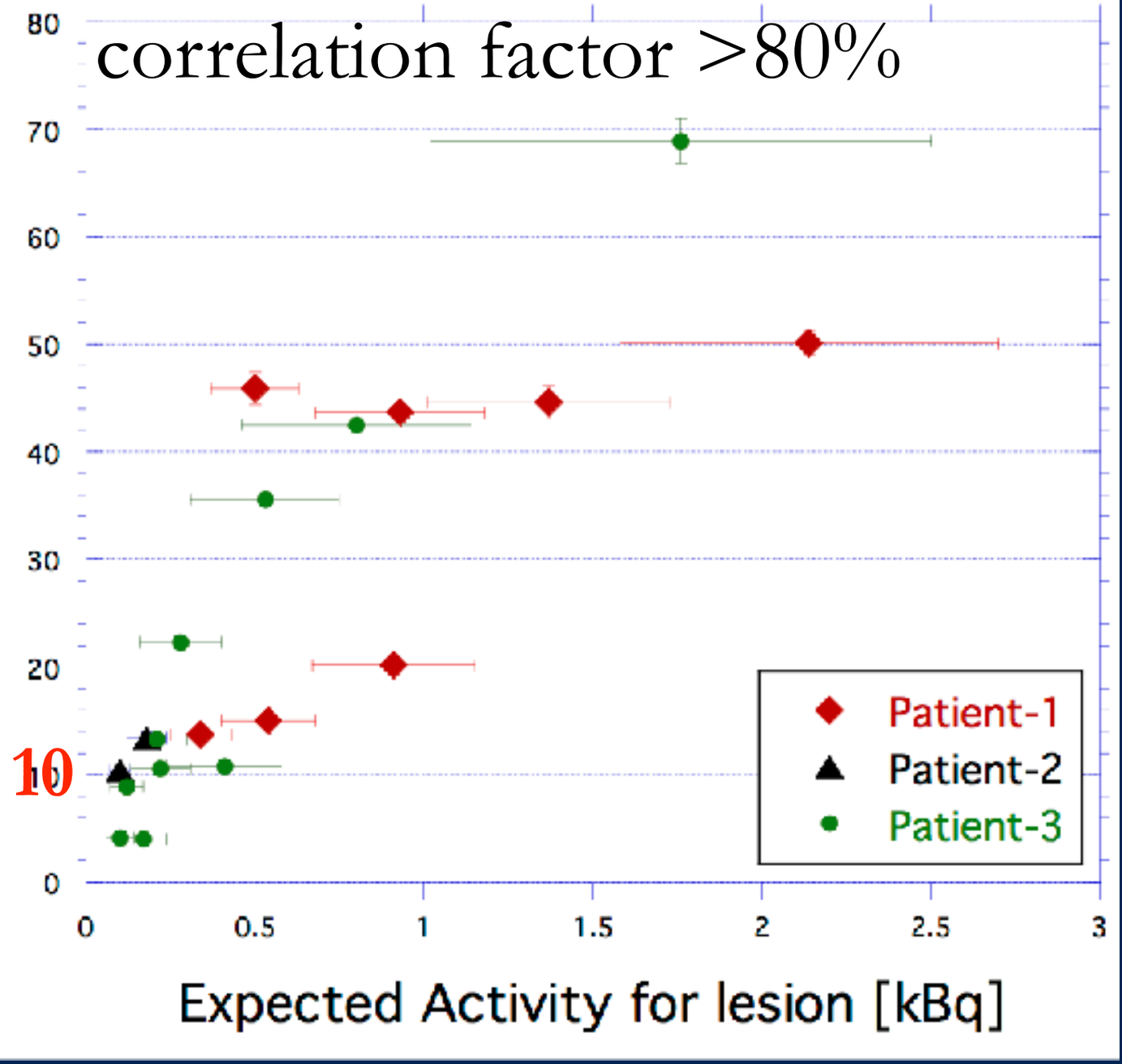




Ex-vivo Meningioma specimens

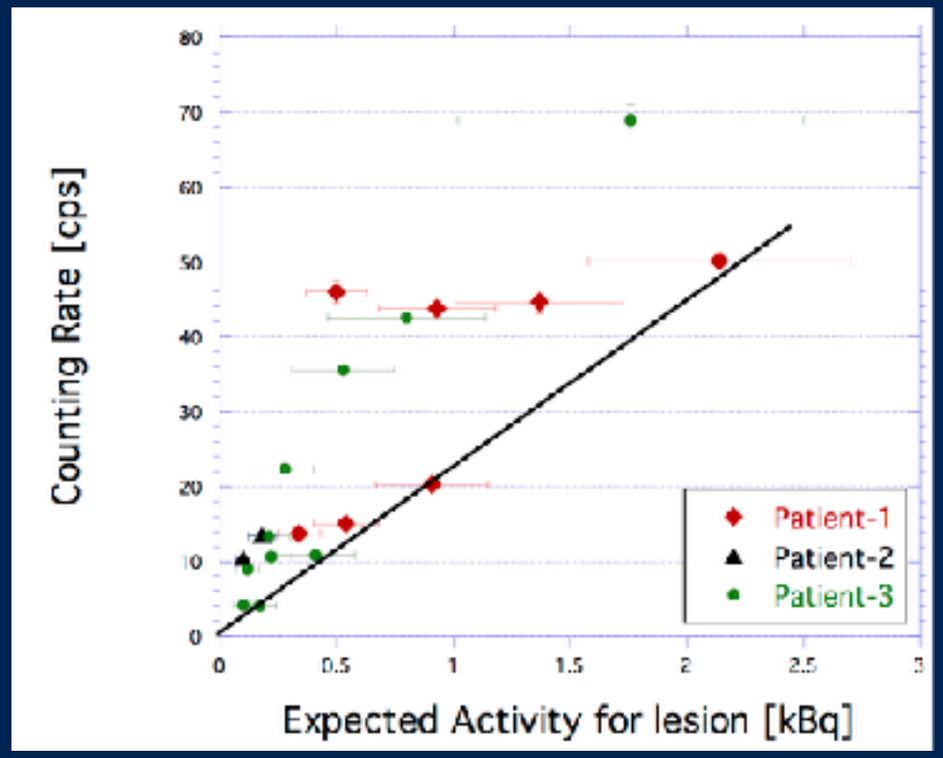


Expected background 1cps



Histological exams confirmed the tumoral nature of the specimens.

The Minimum Injectable Activity



SUV and TNR from ^{68}Ga-PET :

- R_{min}: minimum counting rate to detect a **0.1ml** sample in **1s** with probability of
  - false positive <1%
  - false negative <5%
- A_{min}: minimum activity of a tumor residual of 0.1ml

A. Russomando, M. Schiariti et al, submitted to J Nucl Med (2017)

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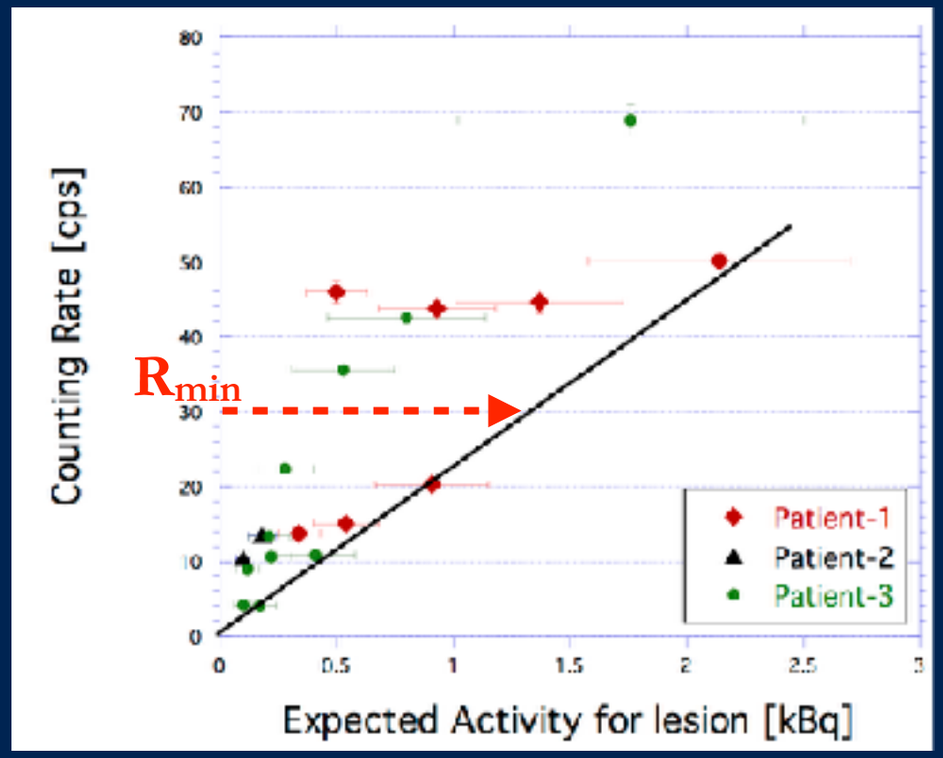

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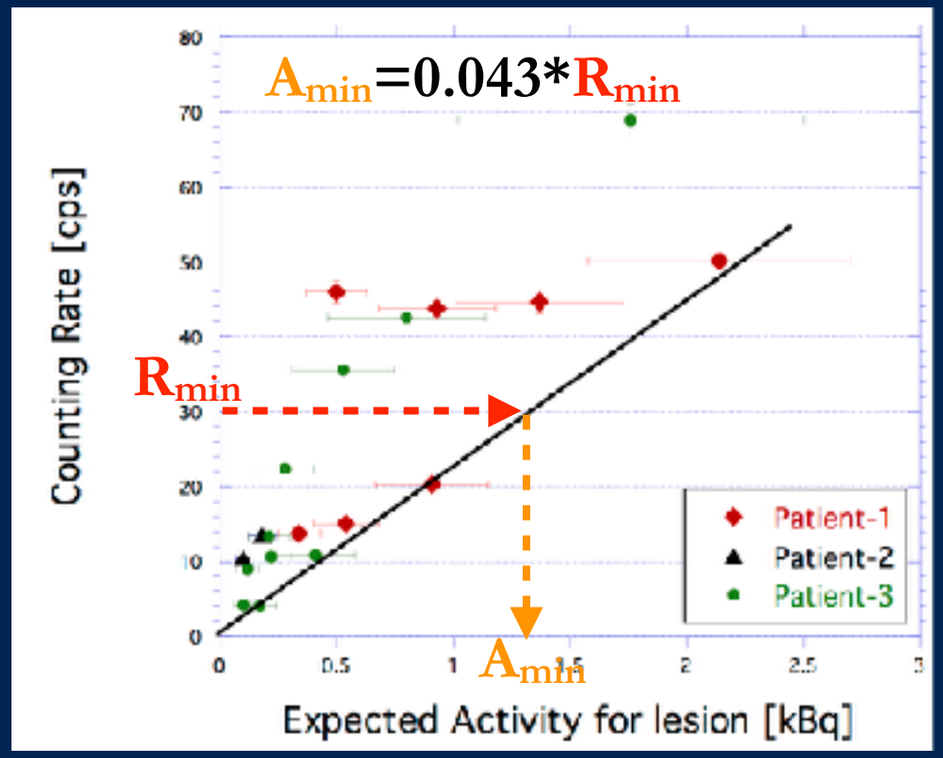

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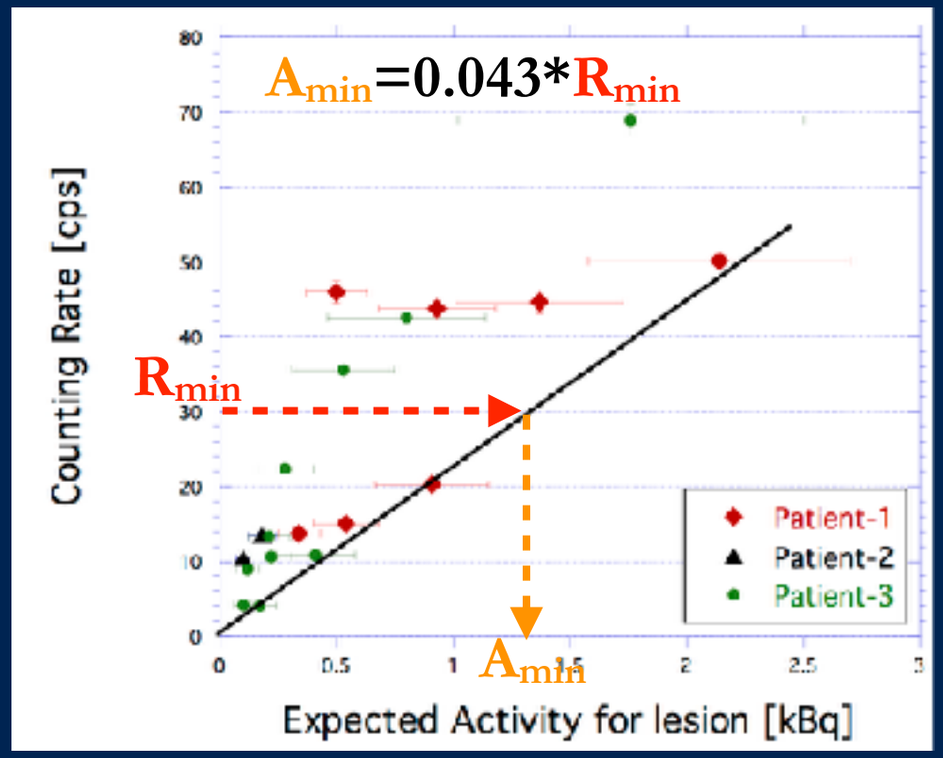

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$$A_{inj}[MBq/kg]=(A_{min}/0.1ml)/SUV$$

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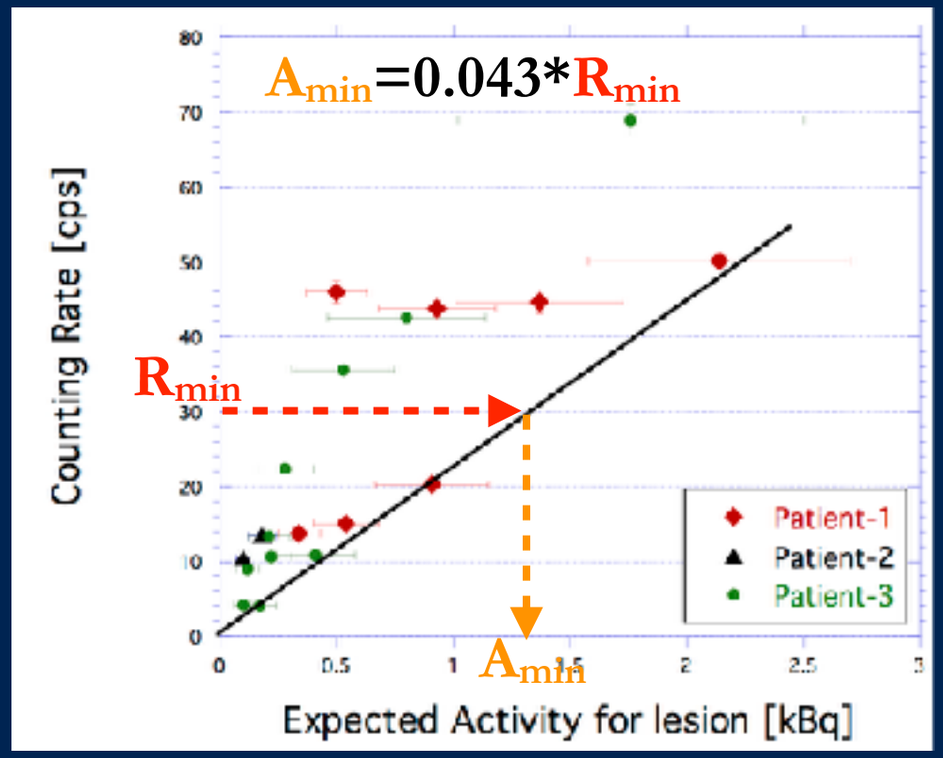

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$$A_{inj}[MBq/kg]=(A_{min}/0.1ml)/SUV$$

- For Patient-1:

  SUV=4.3g/ml, TNR=26 ➔ R_{min}=8cps and A_{min}=0.34kBq

  ➔ **0.1ml** detectable in **1s** by administering **0.8MBq/kg**.

A. Russomando, M. Schiariti et al, submitted to J Nucl Med (2017)

Exposure

^{90}Y-DOTATOC injected Activity 1.4MBq/kg

Personnel

- total effective dose to staff and dose to surgeon's hands **<40 µSv** (detector sensitivity)

Patient

- total effective dose **~22mSv** (OLINDA)
- comparable with a PET/CT scan with ^{18}F-FDG.
- Surgical wastes and patient urine packs in 1 cm thick methacrylate boxes

Trial in progress

Ex-vivo Tests on GastroEnteroPancreatic NET

Clinical trial EUDRACT 2015-005202-10

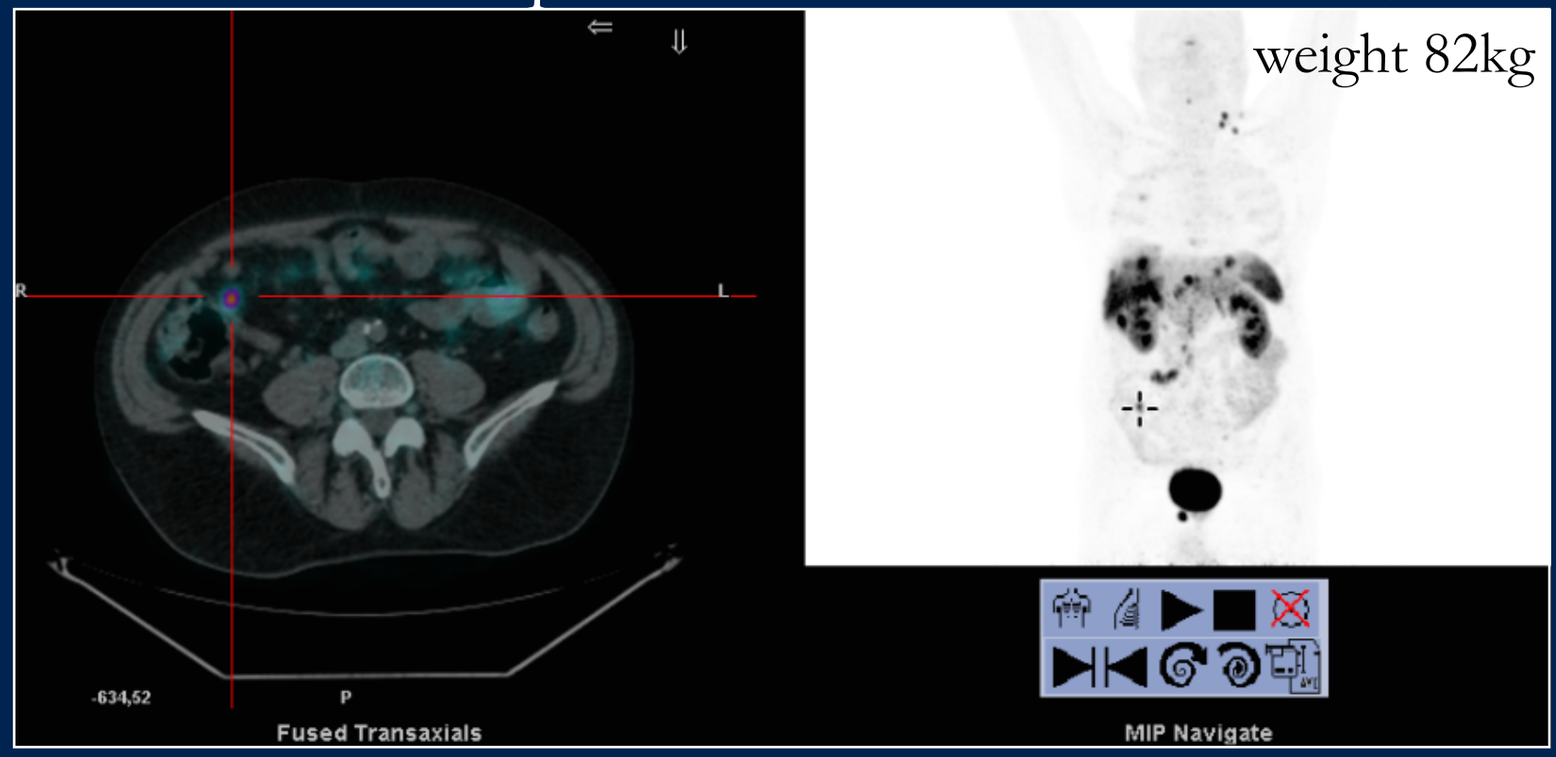
IEO
Istituto Europeo di Oncologia

Small Bowel NET

ILEAL LESION
Primary lesion 1ml
SUV=7.6g/ml
TNR=22

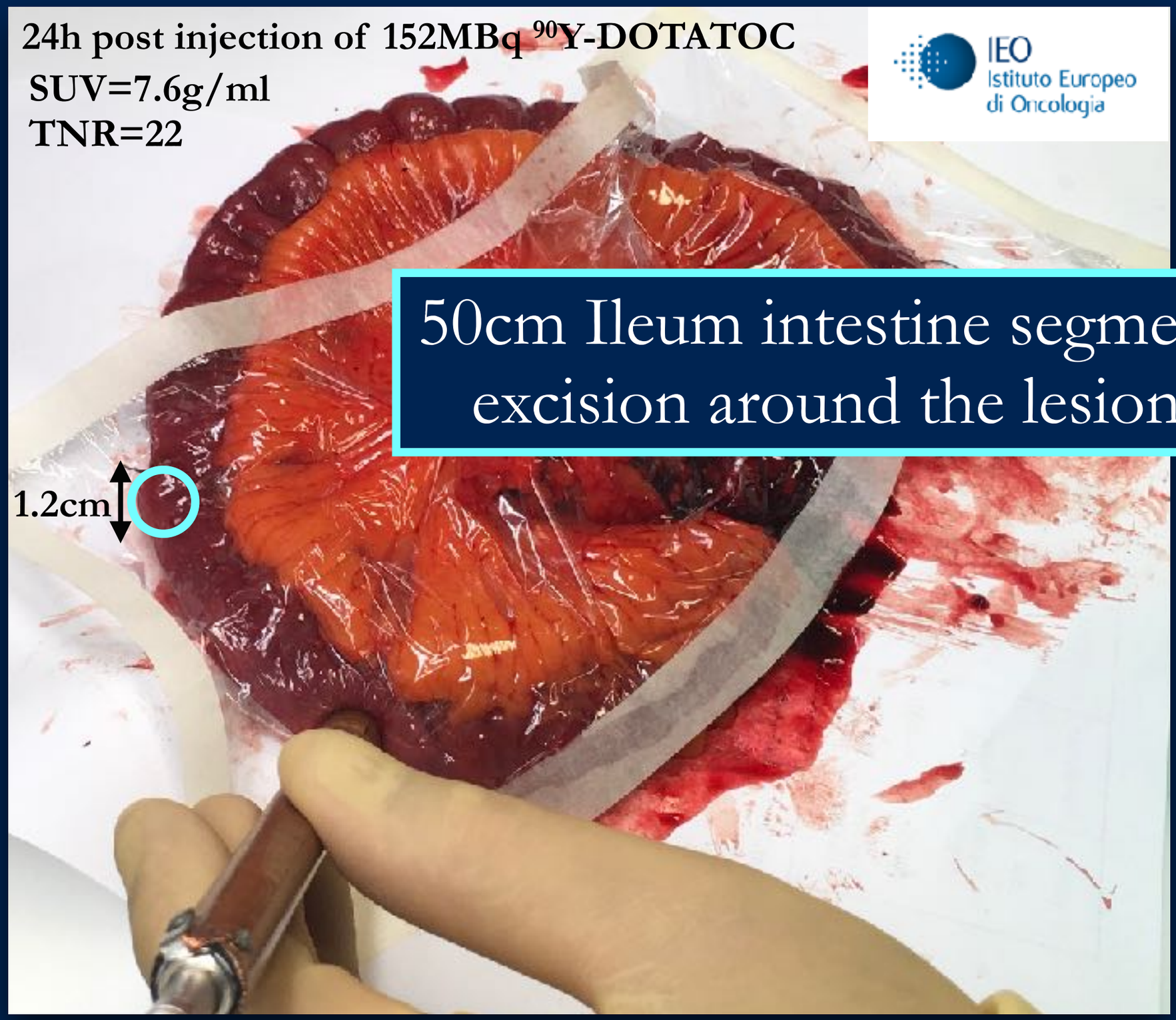
MESENTERIC
Lymph-nodes 4ml
SUV=5.5g/ml
TNR=15

107MBq ^{68}Ga-DOTATOC PET/CT

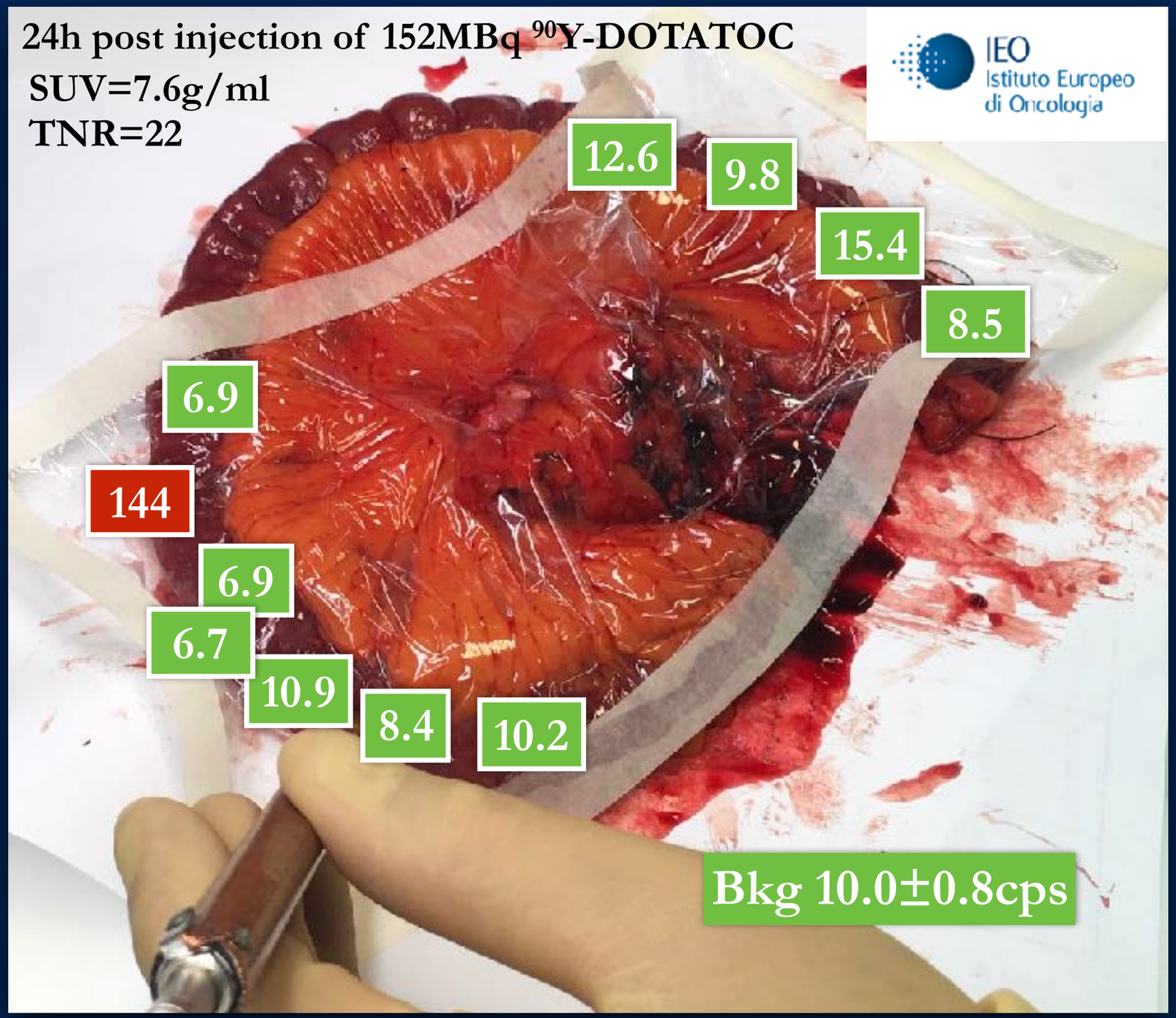


Patient enrolment and clinical protocol similar to those for meningioma tests.

Ileal Lesion

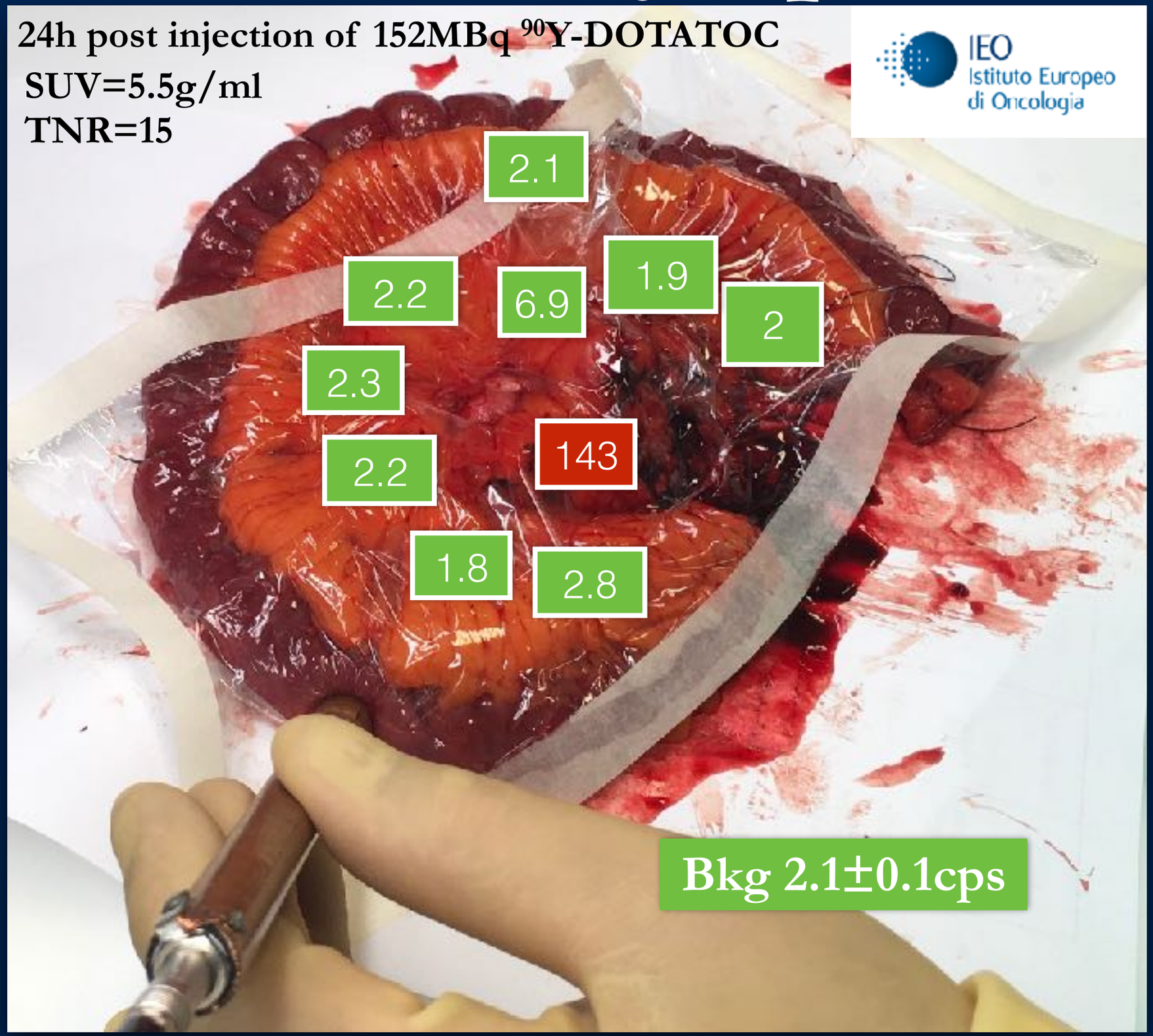


Ileal Lesion



Tumoral bulk embedded in the healthy tissue

Mesenteric Lymph-nodes



Conclusions

- **RGS based on β- radiation is under development:**
  - **Ex-vivo tests confirmed the β- RGS potentialities.**
  - **Short range radio-tracer** (normally used for therapy) **can be adopted for RGS with low activity ~1MBq/kg.**
  - **A method to estimate the minimum activity for detection of 0.1ml tumour in 1s has been proposed.**
  - **Negligible exposure of personnel was demonstrated.**
- **Next steps:**
  - **New β- RGS applications (including endo/laparoscopic application) are under investigation;**
  - **R&D of β- RGS with different radio-tracers and radionuclides other from ^{90}Y.**

Promising Radionuclides

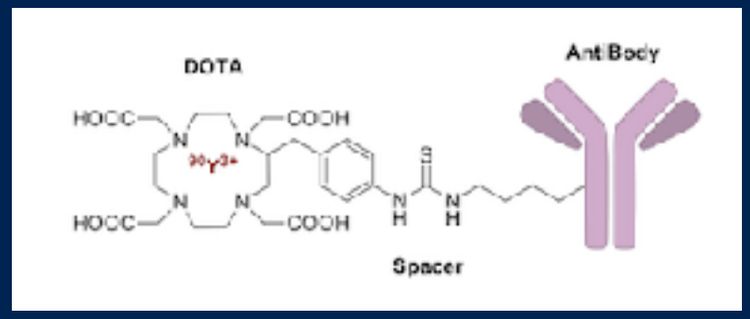
Isotope	$T_{1/2}$(h)	E_g(keV)	I_g(%)	EP_b(keV)	I_b(%)	T_{min}*(s)	Dose@1m(μSv/h)
^{18}F	1.8	511	194	633.5	97	>25	38
^{68}Ga	1.1	511	178	1899	88	0.7	38
^{31}Si	2.6			1491	100	0.4	$27*10^{-3}$
^{32}P	343			1710	100	0.3	$27*10^{-3}$
^{67}Cu	62	93/184	16/48	377/468/56	22/20/99	>25	4.8
^{83}Br	2.4			935	99	0.9	0.29
^{90}Y	64			2280	100	0.5	$27*10^{-3}$
^{97}Zr	17	743	93	759	88	0.8	6.1
^{131}I	192	365/637	82/7	334/696	7/90	>25	16
^{133}I	20.9	530	87	1227	83.4	2.8	
^{153}Sm	46	103	29	635/704/80	31/49/18	3.1	5.0
^{177}Lu	160	112/208	6/10	500	79	>25	1.6
^{188}Re	17	155	15	1962/ 2118	25/72	0.4	2.3

* **T_{min} = Time needed to detect a 0.1ml activated residual with FN<5% FP<1% if 3MBq/kg are administered and SUV=4, TNR=8**

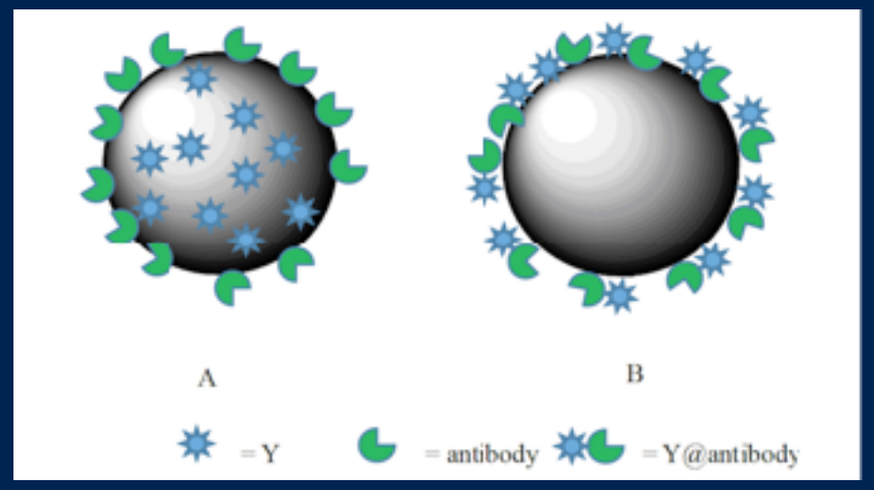
C. Mancini-Terracciano et al, submitted to Physica Medica (2017)

R&D of Tracers with 90Y

- Synthesis of new radio-tracers labeled by 90Y based on
  - Humanized monoclonal **antibodies** for EGFR receptors
    - NIMOTUZUMAB for head and neck carcinoma
  - **PET/SPECT tracer** just replacing the radionuclide
    - MIBG used for scan of neuroblastoma in childhood



- Development of tumor targeting **nanoscale** carriers composed of polymers, antibody and 90Y
  - could be injected locally



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   F. Collamati et al, J Nucl Med 56, 1-6 (2015) PRESS RELEASE January 2015 doi:10.2967/jnumed.114.145995
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   A. Russomando et al, IEEE TNS 63, 5 (2016) doi:10.1109/TNS.2016.2600266
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8. First Ex-Vivo Validation of a Radioguided Surgery Technique with β- Radiation
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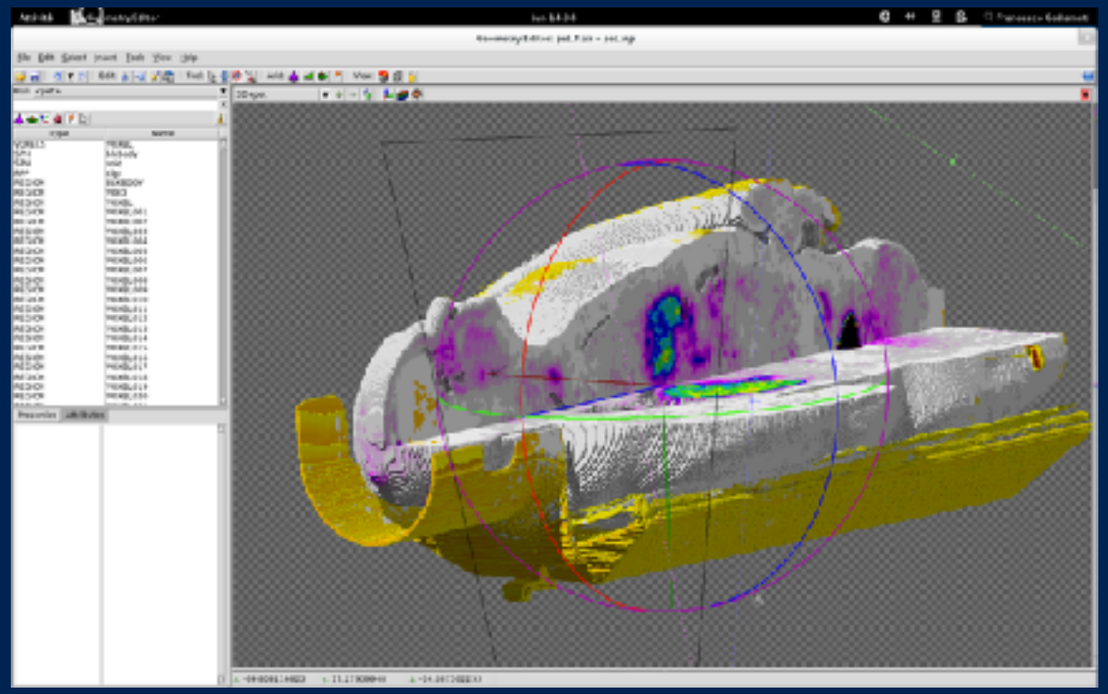
    A. Russomando et al, submitted to JNM (2017)

Back-up Slides

Monte Carlo Simulation

DICOM imported in FLUKA



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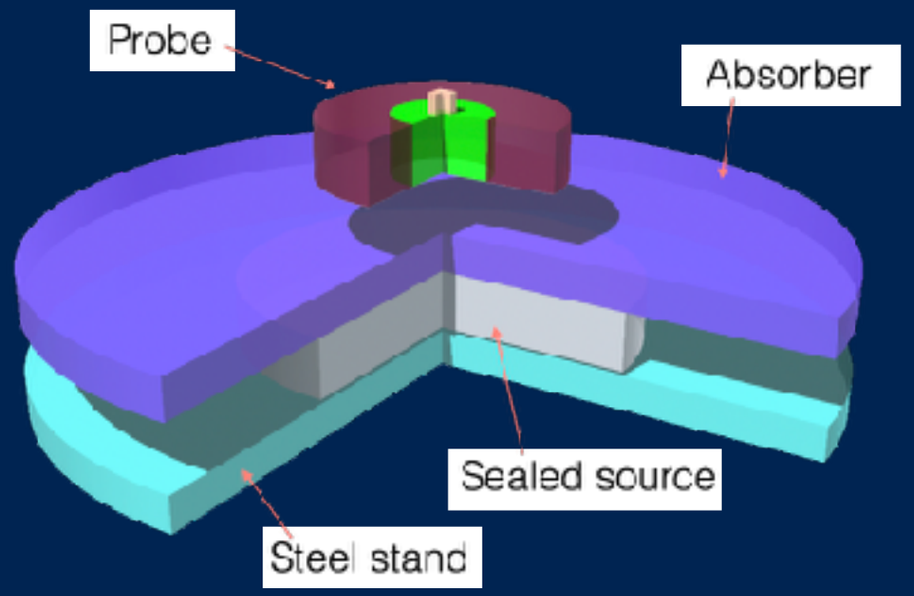
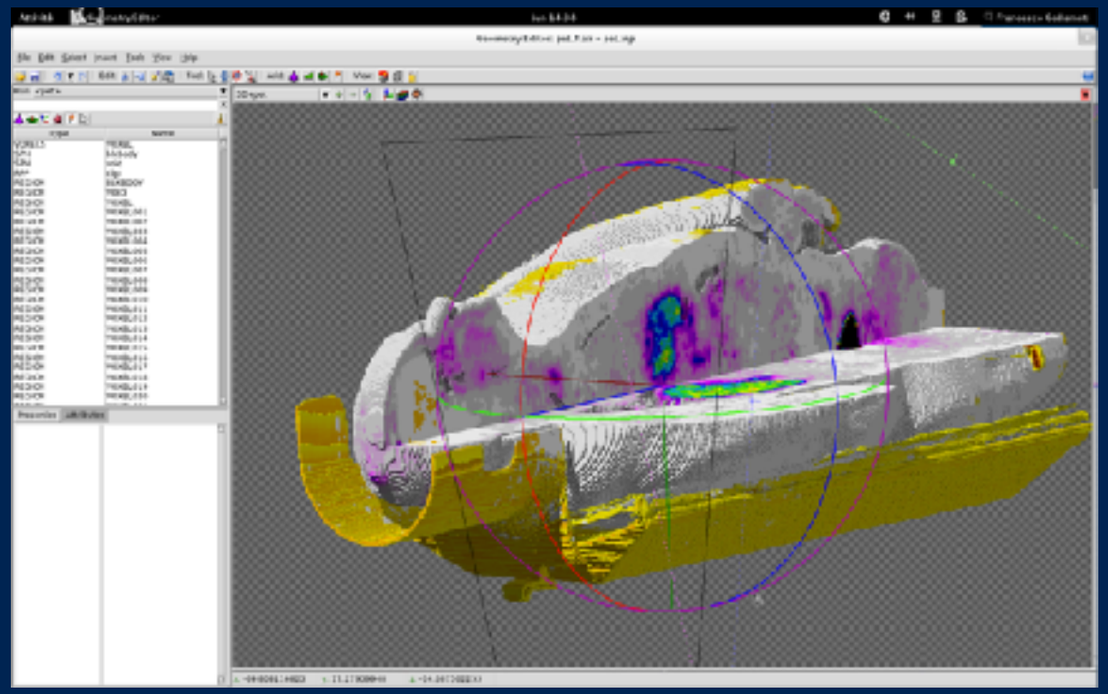
Detector simulation



Simulation using FLUKA code allows us to achieve:

Monte Carlo Simulation

DICOM imported in FLUKA



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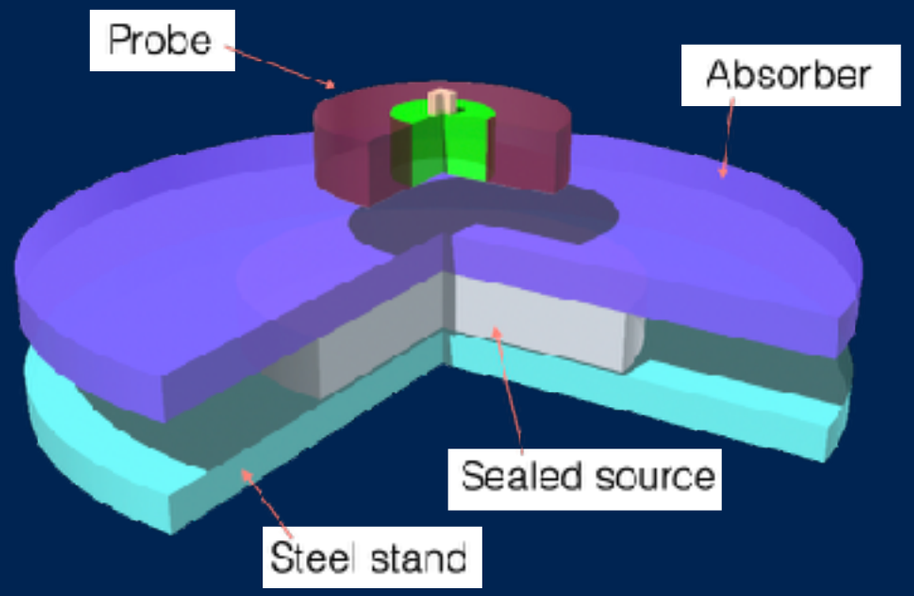
Detector simulation

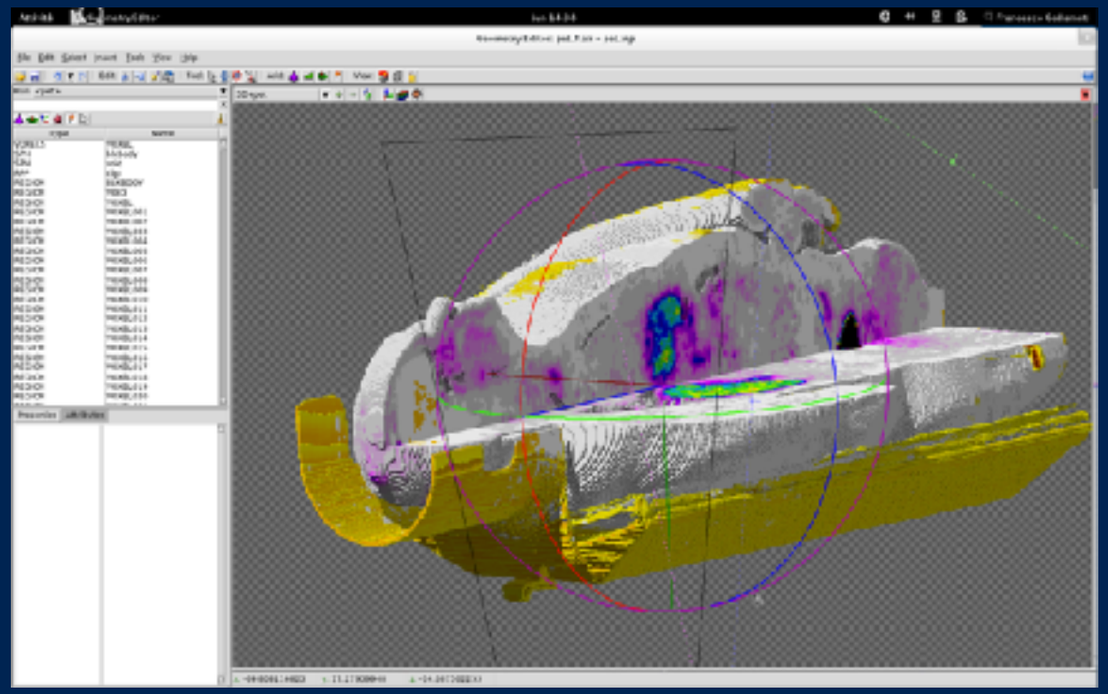


Simulation using FLUKA code allows us to achieve:

- R&D of the **Probe**: technology, geometry and detector shielding.

Monte Carlo Simulation

DICOM imported in FLUKA



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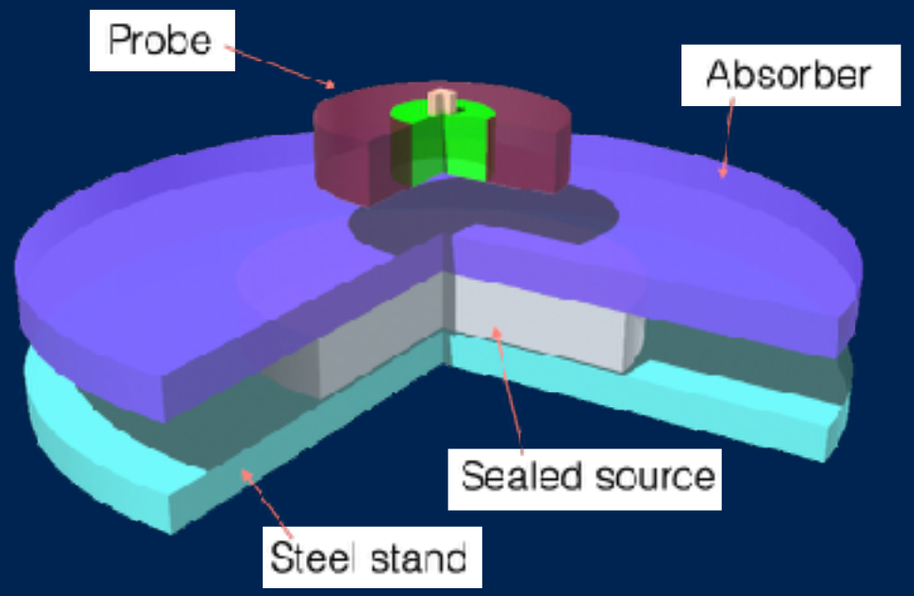
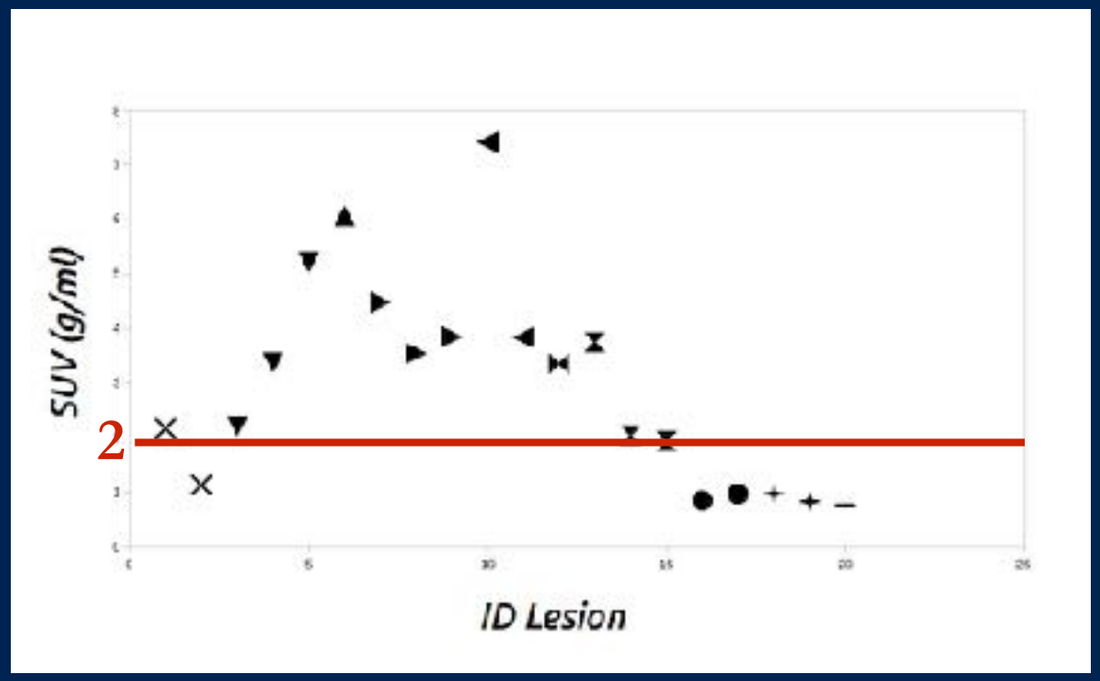
Detector simulation

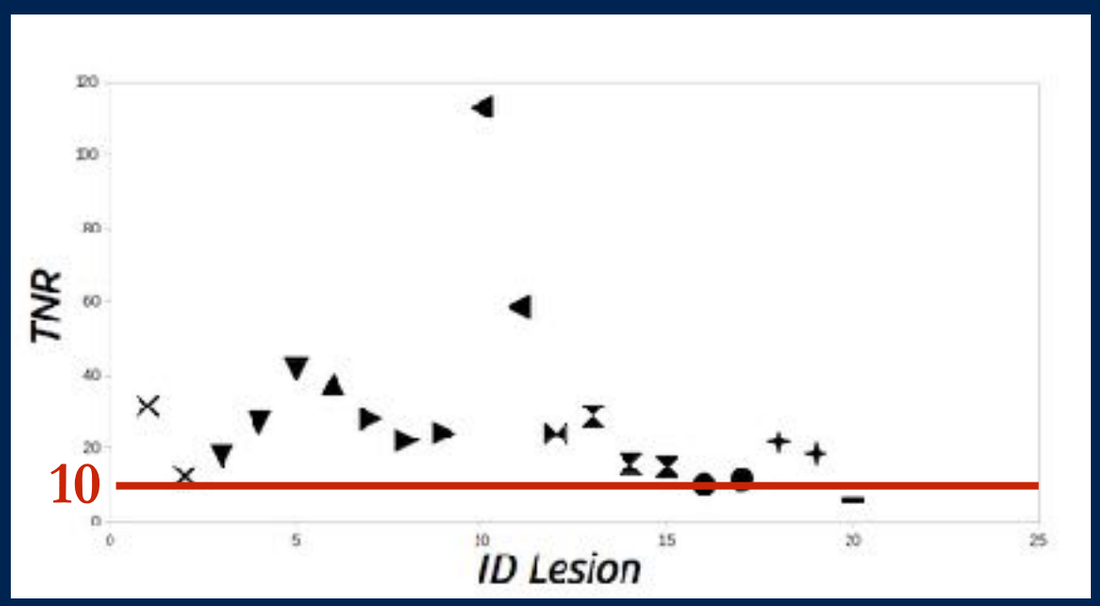


Simulation using FLUKA code allows us to achieve:

- R&D of the **Probe**: technology, geometry and detector shielding.
- Performances of the **β- RGS** in terms of minimum detectable activity, probe counting rate, dose delivery
  - Feasibility studies for **meningioma** and **glioma**, **neuroendocrine** tumors.
  - RGS potentialities with **other radionuclides** different from 90Y.

β- RGS on Meningioma: Feasibility Study





- ^{68}Ga-DOTATOC PET images of 11 patients (20 lesions)
  - SUV > 2g/ml (70%)
  - TNR>10 (90%)
- 0.1ml detectable in 1s with administration of ~1MBq/kg ^{90}Y-DOTATOC with
  - false positive <1%
  - false negative <5%

$$FP = 1 - \sum_{N=0}^{th-1} \mathcal{P}_{\mu_b}(N)$$

$$FN = \sum_{N=0}^{th-1} \mathcal{P}_{\mu_s}(N).$$

F. Collamati et al, J Nucl Med 56, 1-6 (2015) doi:10.2967/jnumed.114.145995

MC simulation: the background

- We imported a PET/CT (DICOM file) in FLUKA
- Hounsfield Units (HU) are converted into density and elemental composition

- spatial distribution of the primaries is sampled using the FDG-PET, thus assuming the same uptake as the FDG
- 50 replicas of the probe were simulated