



F. COLLAMATI - 04.07.17

INCONTRO CON I REFEREE INFN - CHIR2

FIRST EX-VIVO VALIDATION OF

β -RGS IN CLINICAL USE CASES



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TECHNIQUE VALIDATION BY MEANS OF EX-VIVO TESTS

- ▶ While waiting for probe **certification**, only ex-vivo tests available
- ▶ Yet a **very important benchmark!** Allows to **check**:
 - ✓ Feasibility of the whole **procedure**
 - ▶ Injection - time lapse - surgery - probe
 - ✓ PET with ^{68}Ga -DOTATOC as a predictor of ^{90}Y -DOTATOC **uptake**
 - ▶ to estimate the activity we expect in the surgery from pre-operative standard imaging
 - ✓ Our ability to project the **performances** of the probe in the real application case
 - ▶ starting from lab measurements + MC simulations
 - ✓ **Radioprotection** issues

FIRST APPLICATION CASE: BRAIN TUMORS

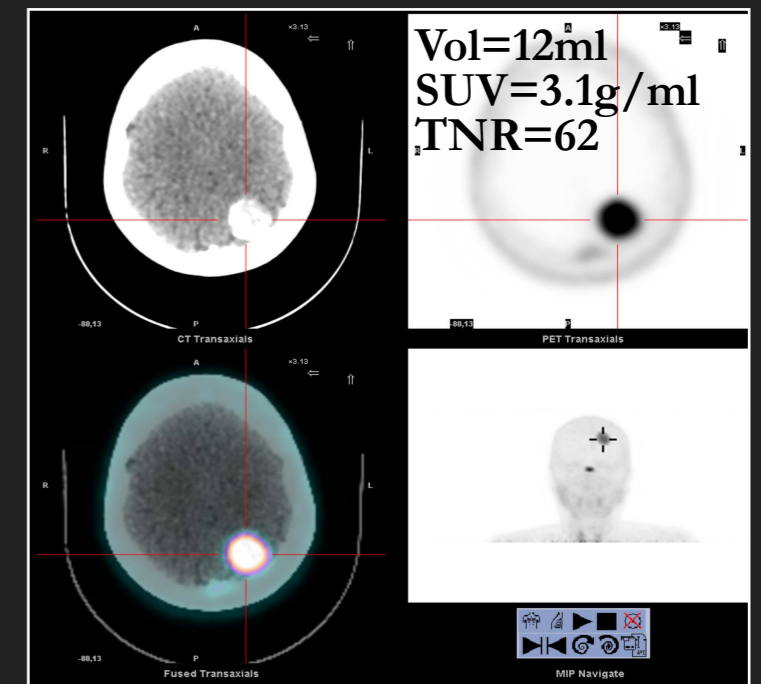
FIRST APPLICATION CASE: BRAIN TUMORS

▶ Glioma:

- ▶ Is a very aggressive, malignant, recurrent and infiltrative tumor that would profit greatly of β^- -RGS
- ▶ “Application case” in brain tumors

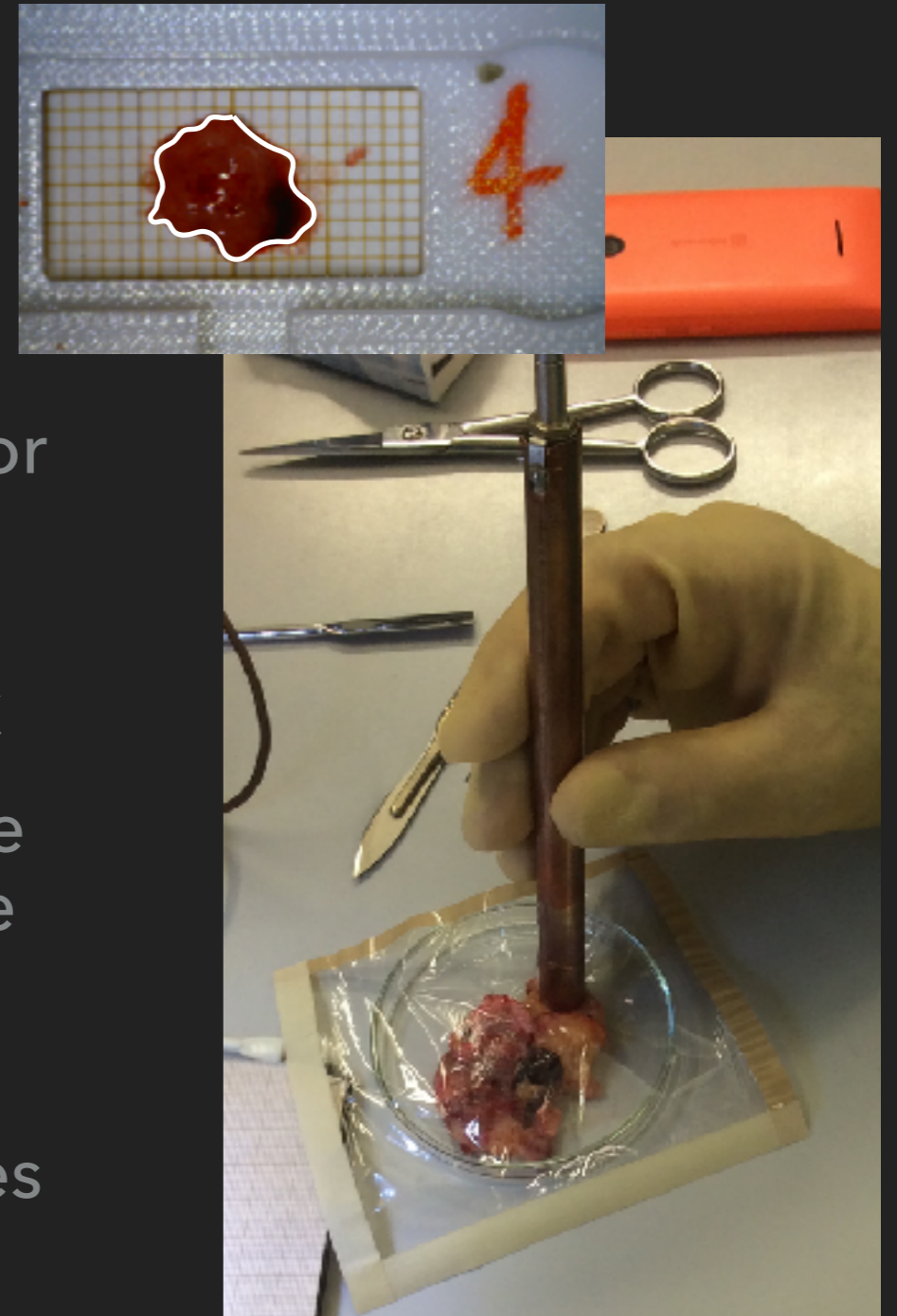
▶ Meningioma:

- ▶ Is a (mostly) benign tumor, (mostly) easy to identify and remove completely, low recurrence rate
- ▶ Would not profit much of β^- -RGS, but it is a very good “use-case” to assess the technique’s applicability in brain tumors:
 - ▶ It shows documented high uptake for DOTATOC, the radio tracer we would like to use!



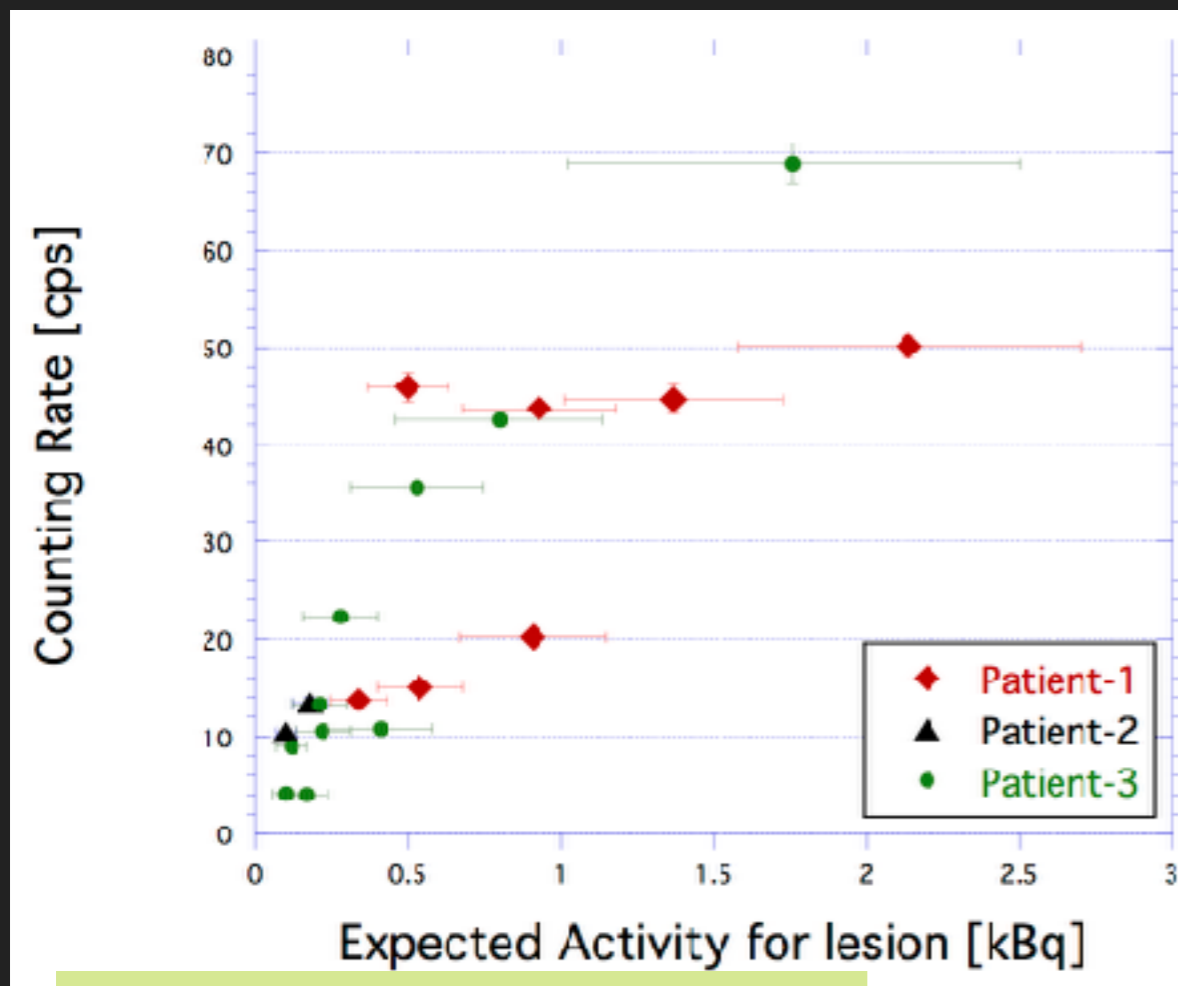
EX-VIVO TESTS ON MENINGIOMA SAMPLES

- ▶ Collaboration protocol with IEO and Besta Institute (Milano)
 - ▶ We enrolled **4 patients** affected by meningioma with demonstrated uptake for DOTATOC (pre-op PET)
 - ▶ Patients were **injected** ~24h before surgery with a PET-like dose of DOTATOC
 - ▶ **Surgery** was performed **normally**, and we had the opportunity to test with the probe the counts on excised samples (tumor, healthy tissue nearby...)
 - ▶ Our findings were compared with the ones from anatomo-pathologists



EX-VIVO TESTS ON MENINGIOMA SAMPLES

- ▶ Starting from pre-operative PET imaging, we are able to foresee the activity in the tumor at the time of surgery and to correlate it with probe counts:



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

- ➔ **All tumor samples were recognised as malignant**
- ➔ Correlation factor > 80%
 - ➔ Ability to evaluate the minimal activity to be injected to reveal a residual within 1s
 - ➔ **Room to lower the dose**
- ➔ Radiation exposure:
 - ➔ **Personnel**: almost negligible
 - ➔ **Patient**: ~22mSv (almost 2x standard PET)

E. Solfaroli, R. Faccini et al, Physica Medica 32 (2016)

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

SECOND APPLICATION CASE: NEURO-ENDOCRINE TUMORS (NET)

SECOND APPLICATION CASE: NEURO-ENDOCRINE TUMORS

- ▶ Neuro-endocrine tumors:

- ▶ Are **rare**:

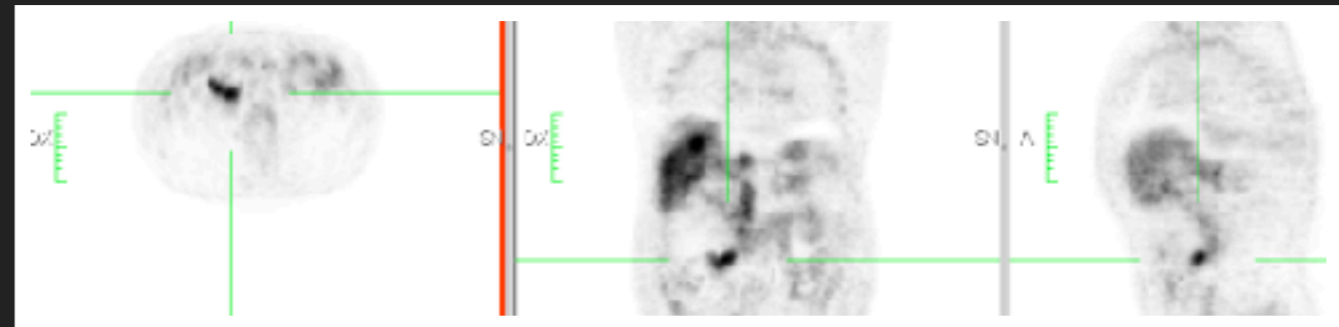
- ▶ Low incidence (~8/100k) but high prevalence (35/100k) due to long survival

- ▶ Can have several localisations:

- ▶ Pancreas, liver, intestine, lung...

- ▶ Due to slow growing are often **discovered late** and when already spread

- ▶ They show good uptake for DOTATOC



RADIO-GUIDED SURGERY IN NEUROENDOCRINE TUMORS

- ▶ **Surgery** is the gold-standard treatment for NETs (even if metastasised)
 - ▶ **Complete asportation** crucial for outcome → RGS!
- ▶ Today, **γ-RGS** is used in NET, also for:
 - ✓ Lymph node discrimination
 - ✓ Hidden lesions identification
 - ✓ Recurrent operations
 - ✓ Infiltrations identification

guided surgery leads to a change in the management in 50% of patients. Visually, it was not possible to differentiate the pathologically enlarged, tumor infiltrated lymph nodes from the nonpathologically enlarged/inflammatory lymph nodes. On palpation also, none of the lesions showed signs of tumor infiltration.³¹ In patient 4,

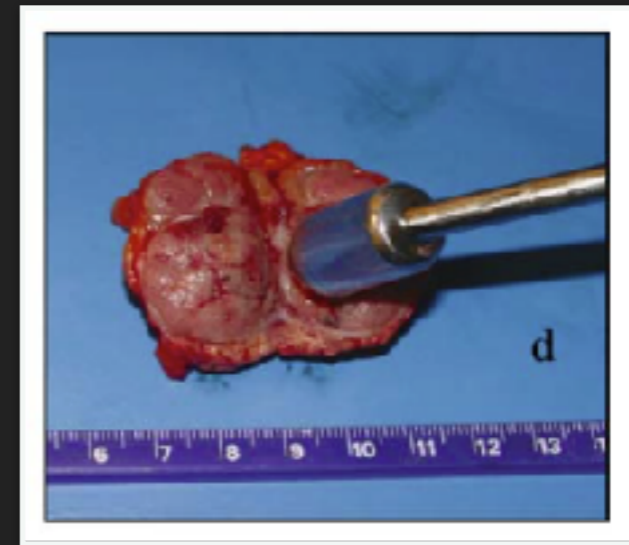
could not be localized are still insufficient. From our experience, it is not possible to localize the tumour in about 25% of cases (5). The Institute for General Surgery in Pavia (Italy) has published one case report, and the Institute

live surgery can be considered in all patients in whom 90% of the tumors can be removed.⁷ The challenge for the surgeon intraoperatively, is to differentiate malignant from scarred and inflammatory tissue in patients with advanced tumor disease and recurrent laparotomies. The

of tumor involvement is known. From the naked eyes, it is very difficult to differentiate tumor tissues from non-tumor margins and this differentiation is possible only through pre-/perioperative imaging.²⁸ It is known that emergency surgery precludes a complete and negative margin resection and constitutes a risk factor for

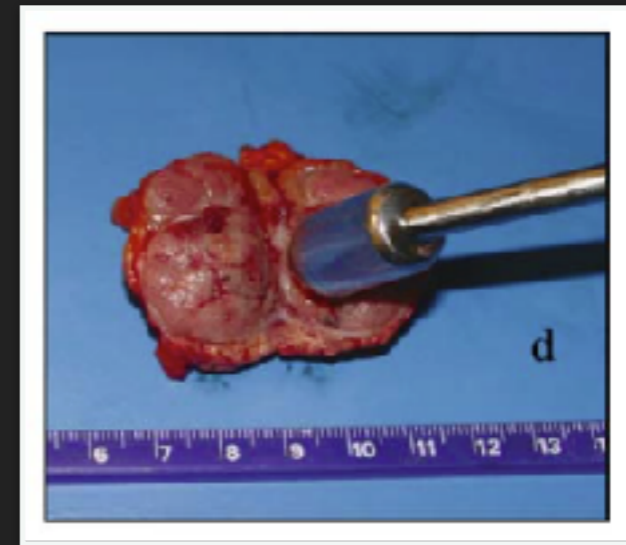
RADIO-GUIDED SURGERY IN NEUROENDOCRINE TUMORS

- ▶ Common characteristics of today NET **γ -RGS**:
 - ▶ Detector:
 - ▶ Commercial gamma probe
 - ▶ Radio pharmaceutical:
 - ▶ Somatostatine analogues marked with In, I, Tc
 - ▶ One recent attempt to use ^{68}Ga (β^+ decay)
 - ▶ Approach:
 - ▶ Search of the known lesions + "systematic scan" to look for possible unknown ones
 - ▶ Results and limitations:
 - ▶ Very good capability of **discovering hidden lesions** (i.e. in stomach and small bowel)
 - ▶ Reduced utility in areas with greater physiological **background**:



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physiological
DOTANOC
uptake

- ▶ Reduced utility in areas with greater physiological **background**:

We found that lesions in the pancreas and peripancreatic lymph nodes were difficult to detect with the probe as a result of high relative background counts. In such cases,

helpful in confirming the location of a single lesion with a TBR of 43.6 (WHO grade 1 insulinoma). We did not find that the probe was helpful for detecting liver lesions: in 3 patients with liver metastases found on ^{68}Ga -DOTATATE PET/CT, the background count for the liver was high, with an average of 499.7 ± 89.0 , and target lesions therefore could not be distinguished. Resection was guided by ultrasound.

EX-VIVO TESTS ON NET SAMPLES

- ▶ Collaboration protocol with IEO (Milano)
 - ▶ We are enrolling 5 **patients** affected by Neuro Endocrine Tumor with demonstrated uptake for DOTATOC (pre-op PET)
 - ▶ Patients are **injected** ~24h before surgery with a PET-like dose of DOTATOC
 - ▶ **Surgery** is performed **normally**, and we have the opportunity to test with the probe the counts on excised samples (tumor, healthy tissue nearby...)
 - ▶ Our findings are compared with the ones from anatomo-pathologists

Trial in progress



Trial in progress

EX-VIVO TESTS ON NET SAMPLES

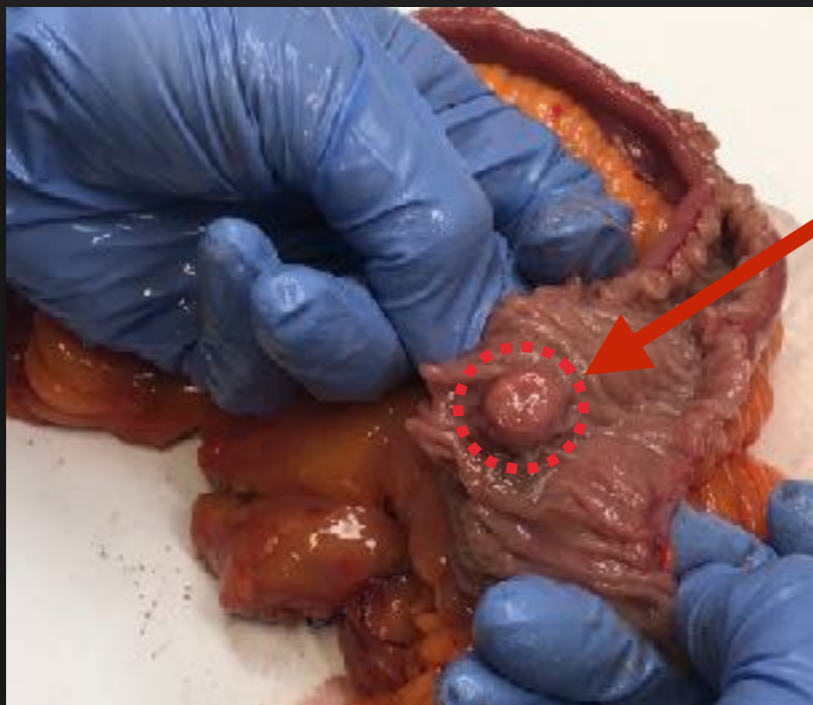
- ▶ With respect to the meningioma ex-vivo tests, we are now in a more realistic situation
 - ▶ In these kind of surgery, a ~50cm segment of ileum is usually excised
 - ▶ We are thus in a ~ **signal + background** configuration!



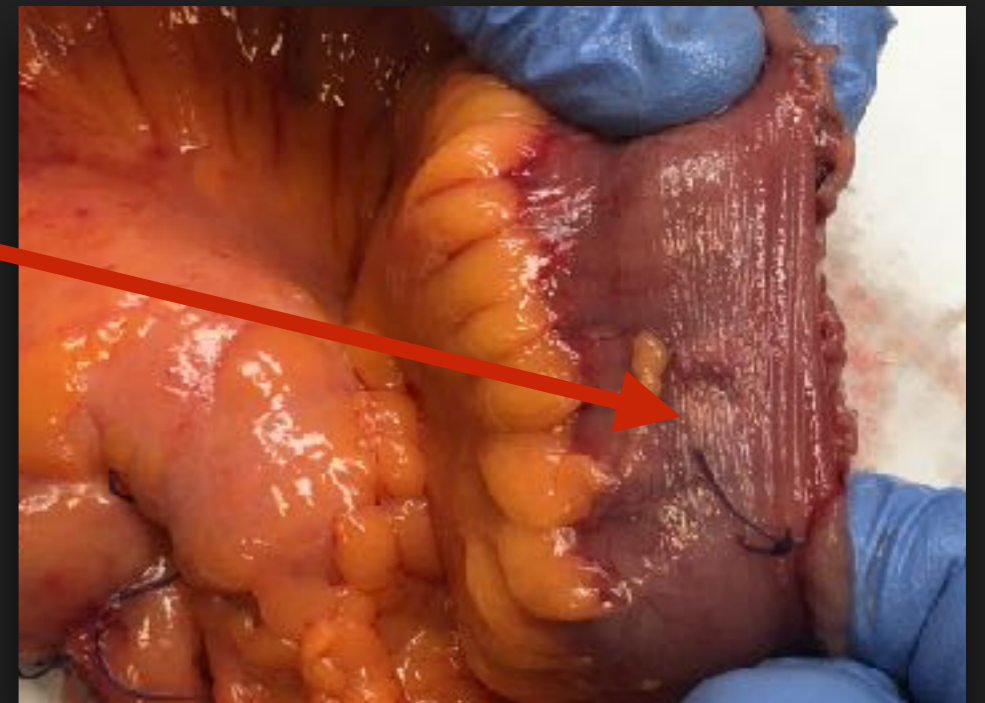
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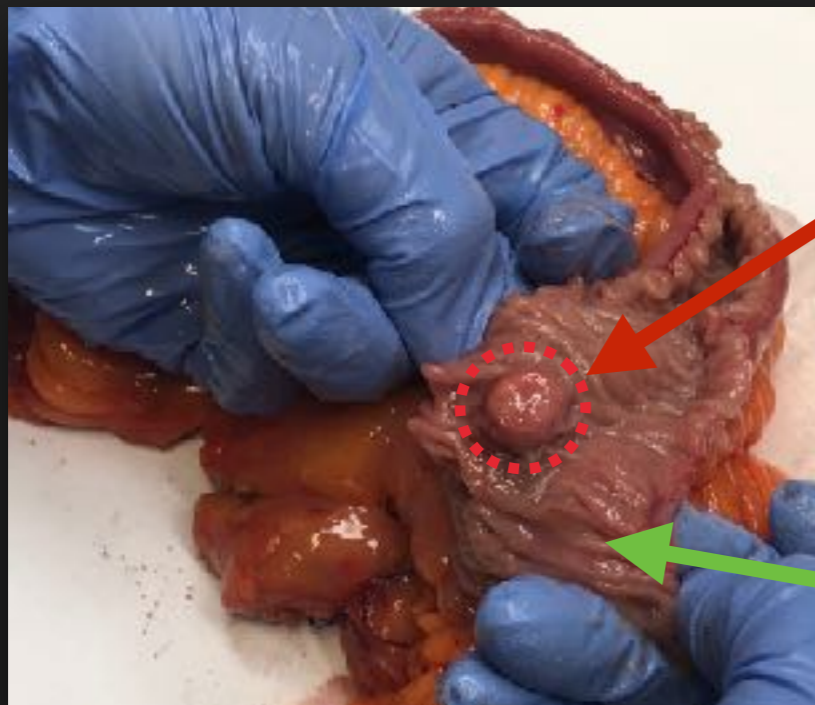
Main lesion



Trial in progress

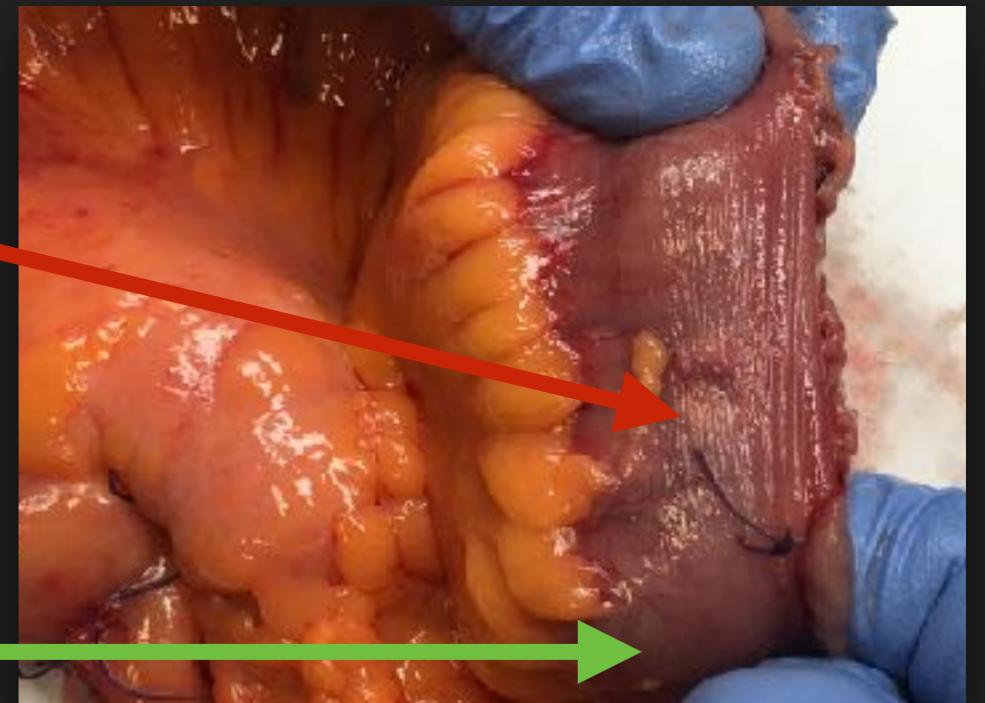
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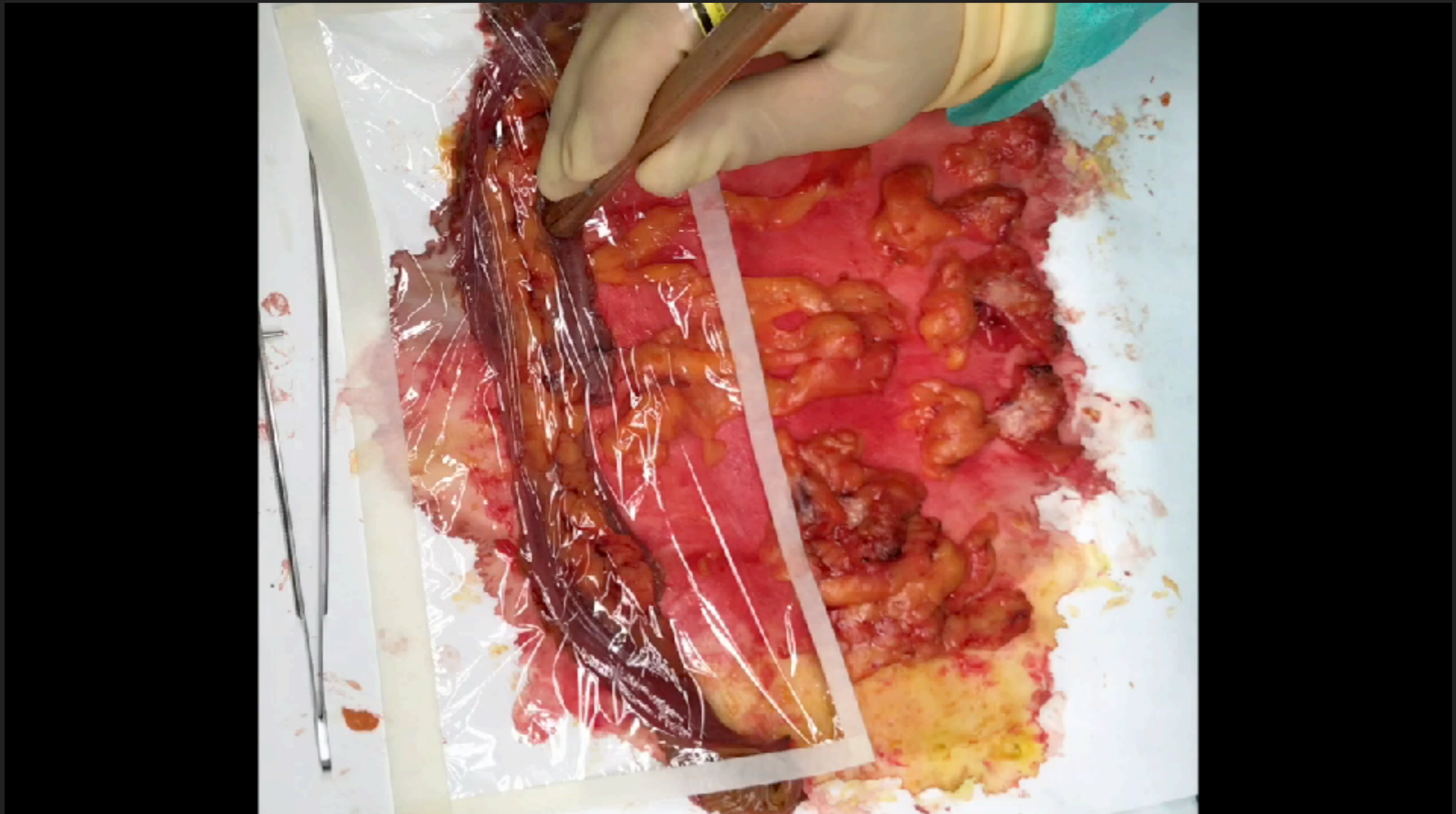


Main lesion

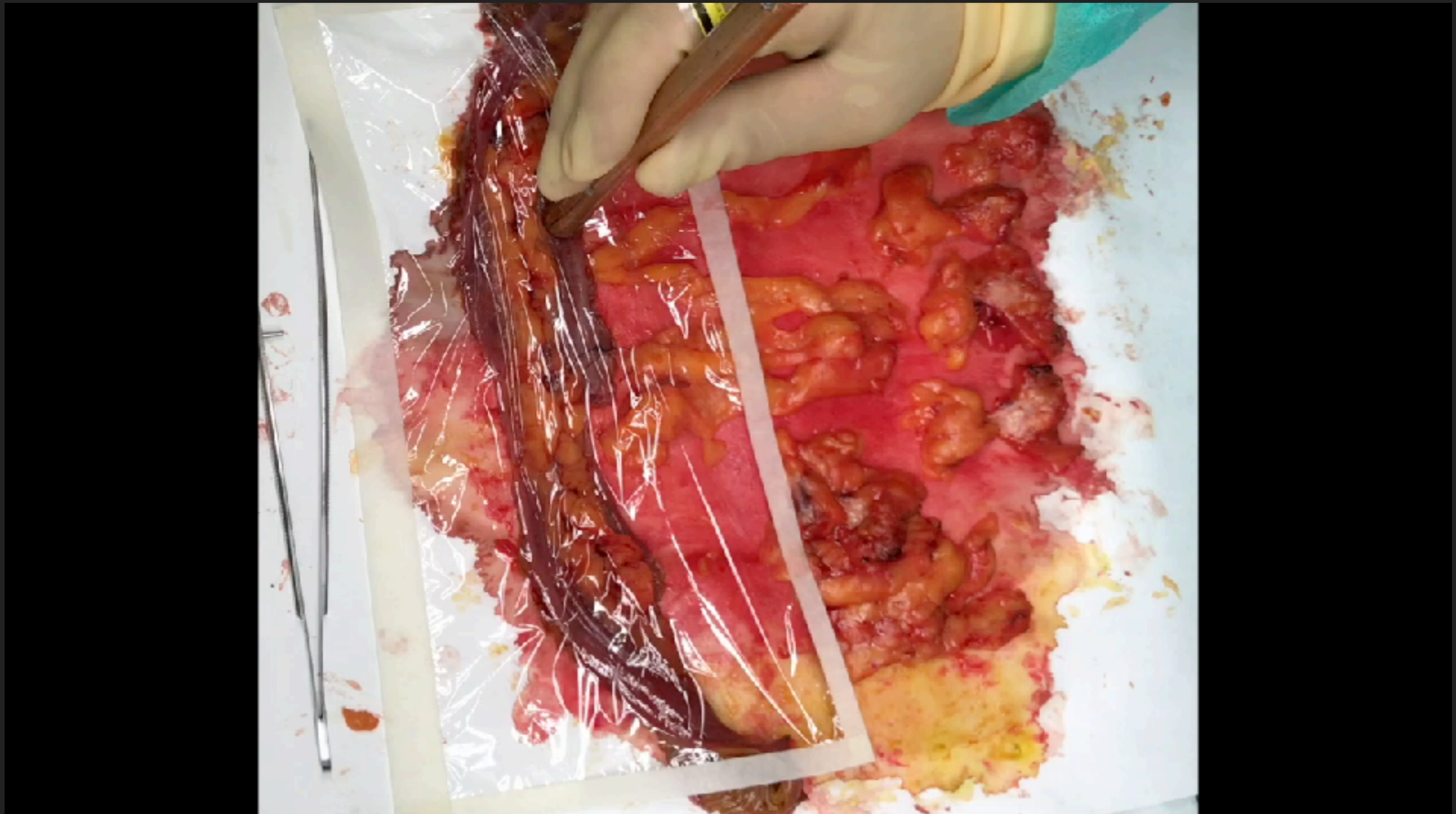
Healthy intestine



EX-VIVO TESTS ON NET SAMPLES



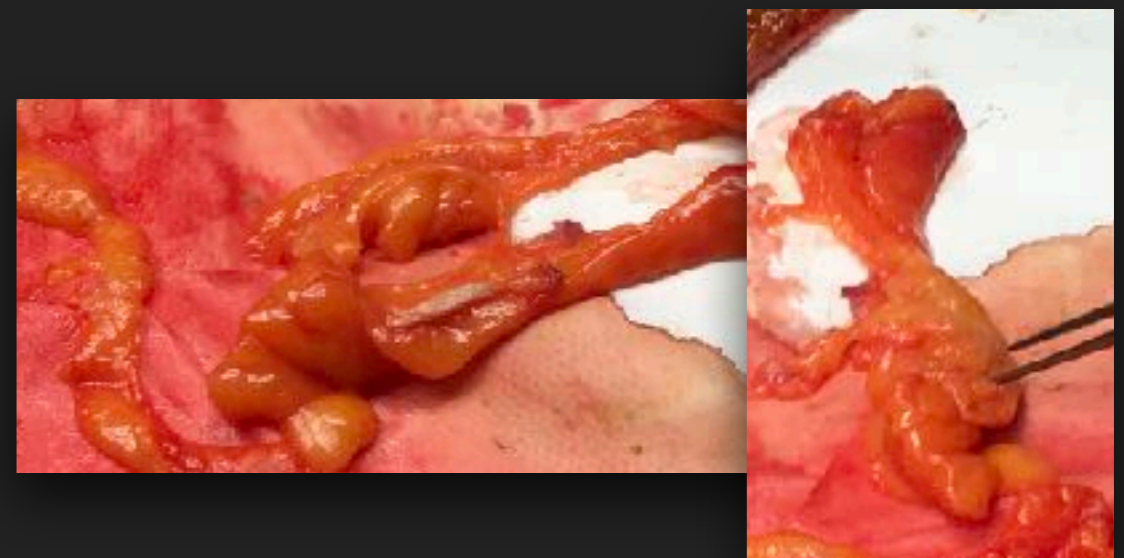
EX-VIVO TESTS ON NET SAMPLES



Trial in progress

EX-VIVO TESTS ON NET SAMPLES

- ▶ Goals of the test:
 - ▶ Ability to **identify** known lesions, and look for unknown (e.g. lymph nodes)
 - ▶ Extract "cut-off" values (cps) for possible RGS application
 - ▶ Assess the behaviour of the probe in a \sim **S+B** configuration
 - ▶ Counts on lesion
 - ▶ Counts on background
 - ▶ D.I.Y. **real application case**: hiding a part of tumor under healthy tissue



SUMMARY

- ▶ So far, we identified **two** possible **application cases** in which ^{90}Y -DOTATOC RGS could give a remarkable contribution
 - ▶ **Gliomas** and **Neuro-Endocrine Tumors**
- ▶ First ex-vivo tests on **Meningioma** were fundamental to assess the **feasibility** of the whole procedure, the **radio protection** impact and the **probe performances**
 - ▶ Their success also contributed to **trigger enthusiasm** in medical staff that led to the starting of the second collaboration protocol
- ▶ Ex-vivo tests on **NETs** have already started and are planned to last for the next months
 - ▶ They will be fundamental to test the technique in an almost realistic scenario
- ▶ Next step:
 - ▶ **In-vivo** tests: ongoing contract with **Nucleomed** for probe certification
 - ▶ Collaboration with Sant'Orsola hospital (BO) to use ^{68}Ga -PSmA in **prostatic cancer** (**laparoscopic approach**)

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