Opportunities and innovations for local interventions

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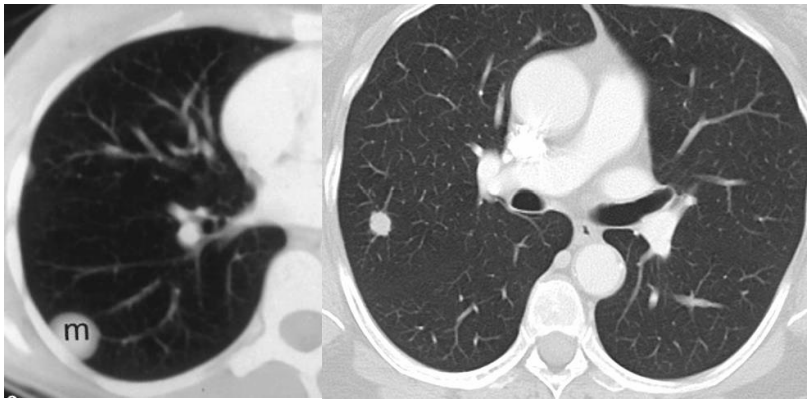
Metastases of soft tissue sarcoma

Typical: lungs



Asymptomatic

No cough, no hemoptysis

Intraparenchymal/subpleural

Detected at follow-up

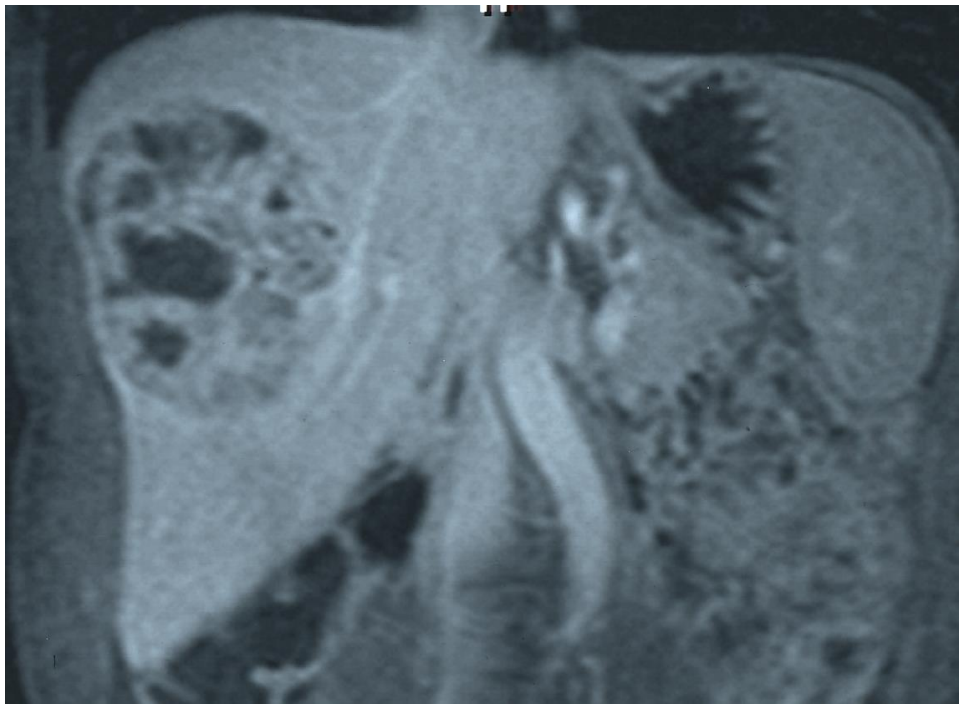
Few (isolated)*

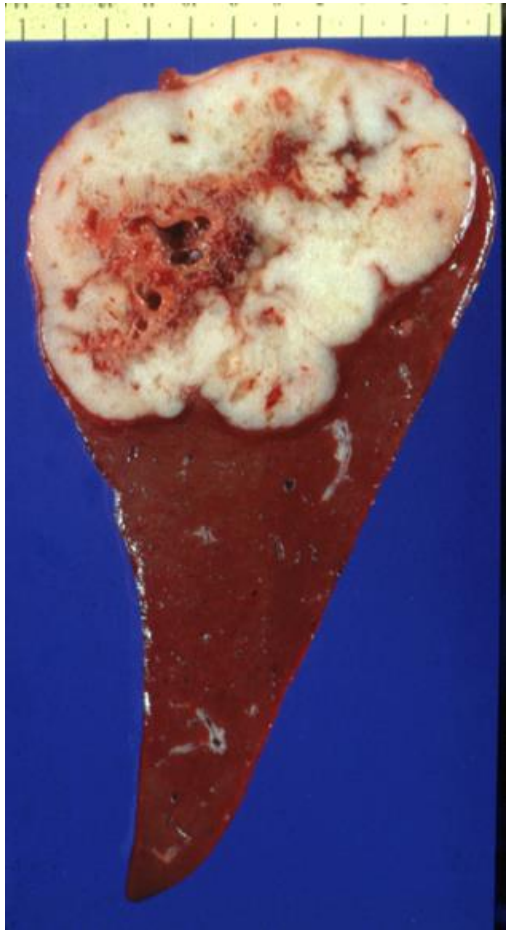
Time interval to primary tumor depends on tumor grade

*Gadd, Ann.Surg 1993

Metastases of soft tissue sarcoma

Not so typical, but if solitary - surgery is the option

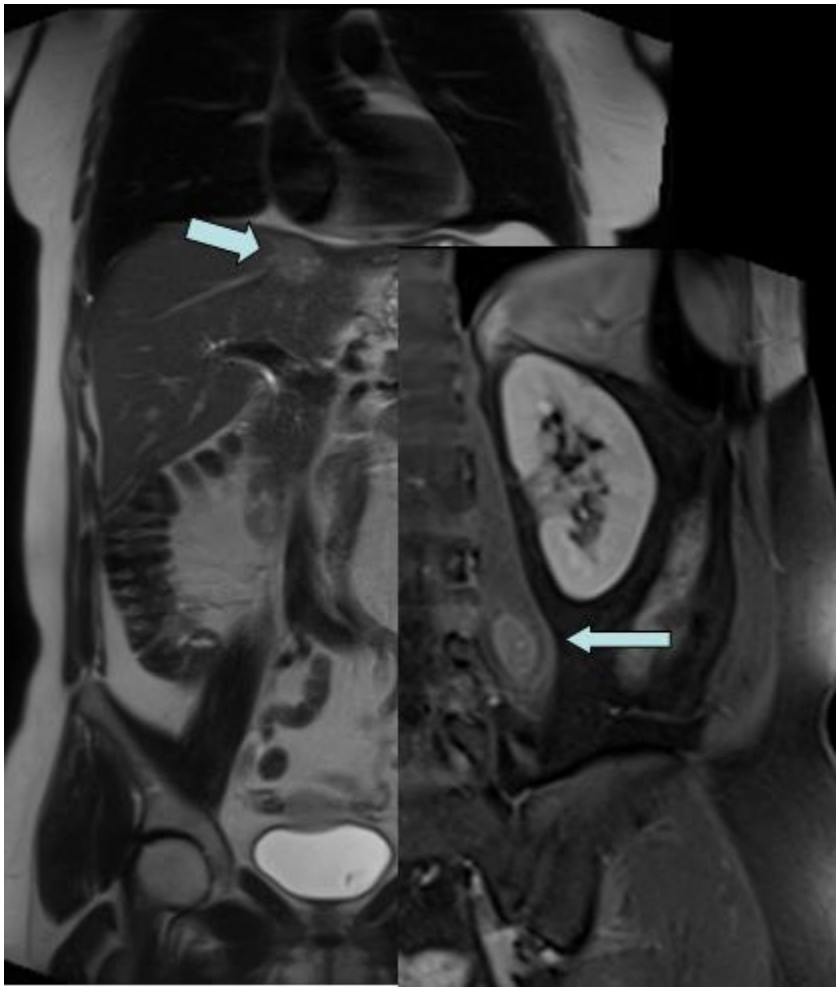




61yr, m, leio-myo thigh, 3 yr earlier

Metastases of soft tissue sarcoma

Not too typical, but different



liver metastasis and

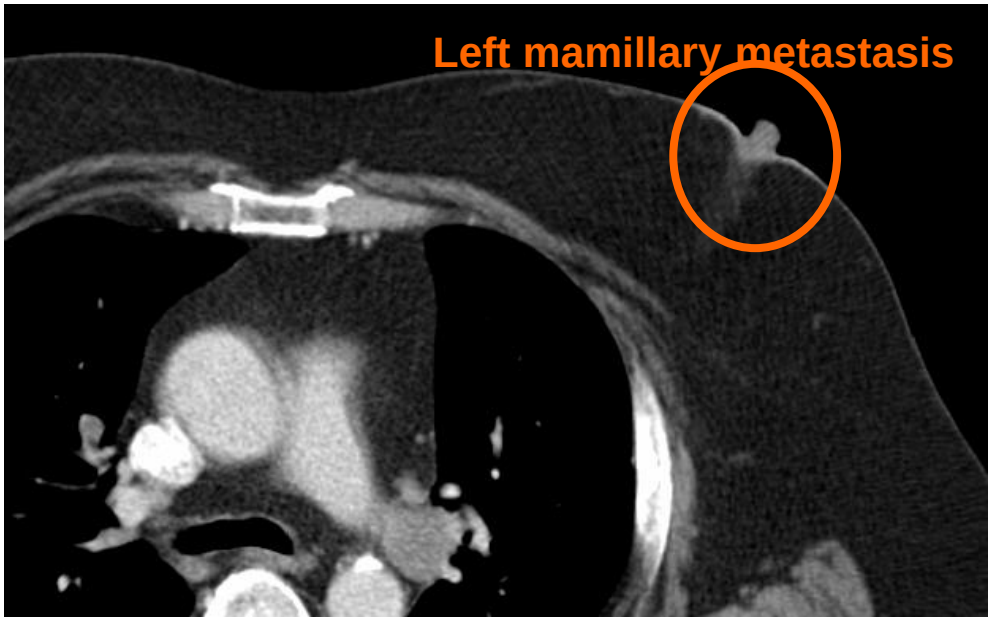
soft tissue met. to psoas

leiomyosarcoma of the ureter
26 months earlier, 43 yr, f

Surgery for ‚single' mets or multifocal metastatic disease requiring chemotherapy ?

Metastases of soft tissue sarcoma

- Unusual: soft tissue met from GIST followed by brain metastases 6 months later
- Symptomatic: surgery



Unusual locations of metastases of STS

- **Lymph node:** epitheloid, clearcell, synovial sarcoma <10%
- **Bone** metastases from myxoid liposarcoma
- **Rate of extrapulmonary metastases**: 4.3%
  346 patients with G3, out of n=3671: n=15

- Usually appear after lung metastases

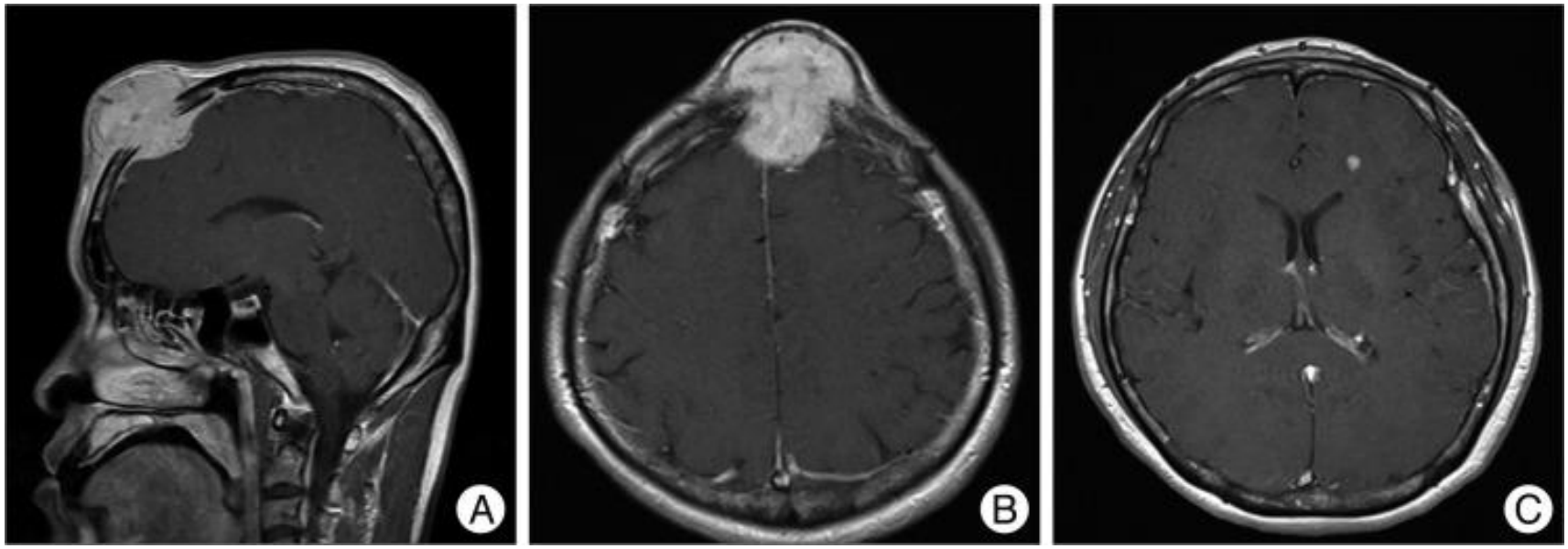
Small bowel met from MRCLS

Ryzewicz, Orthopedics 2008

Unusual locations of metastases of STS

Overrepresented: alveolar soft part sarcoma (ASPS) to the brain ?

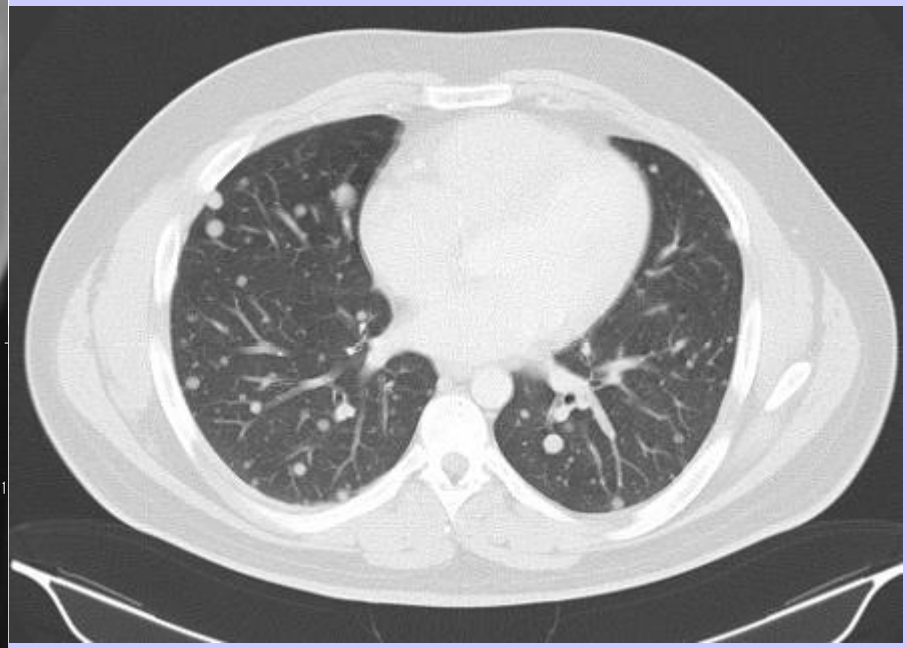
J Korean Neurosurg Soc. 2012 July; 52(1): 55–57.



Overall incidence : < 1%, MSKCC data base n=3829

Espat, Cancer 2002

Indication for surgery (local modalities): NO

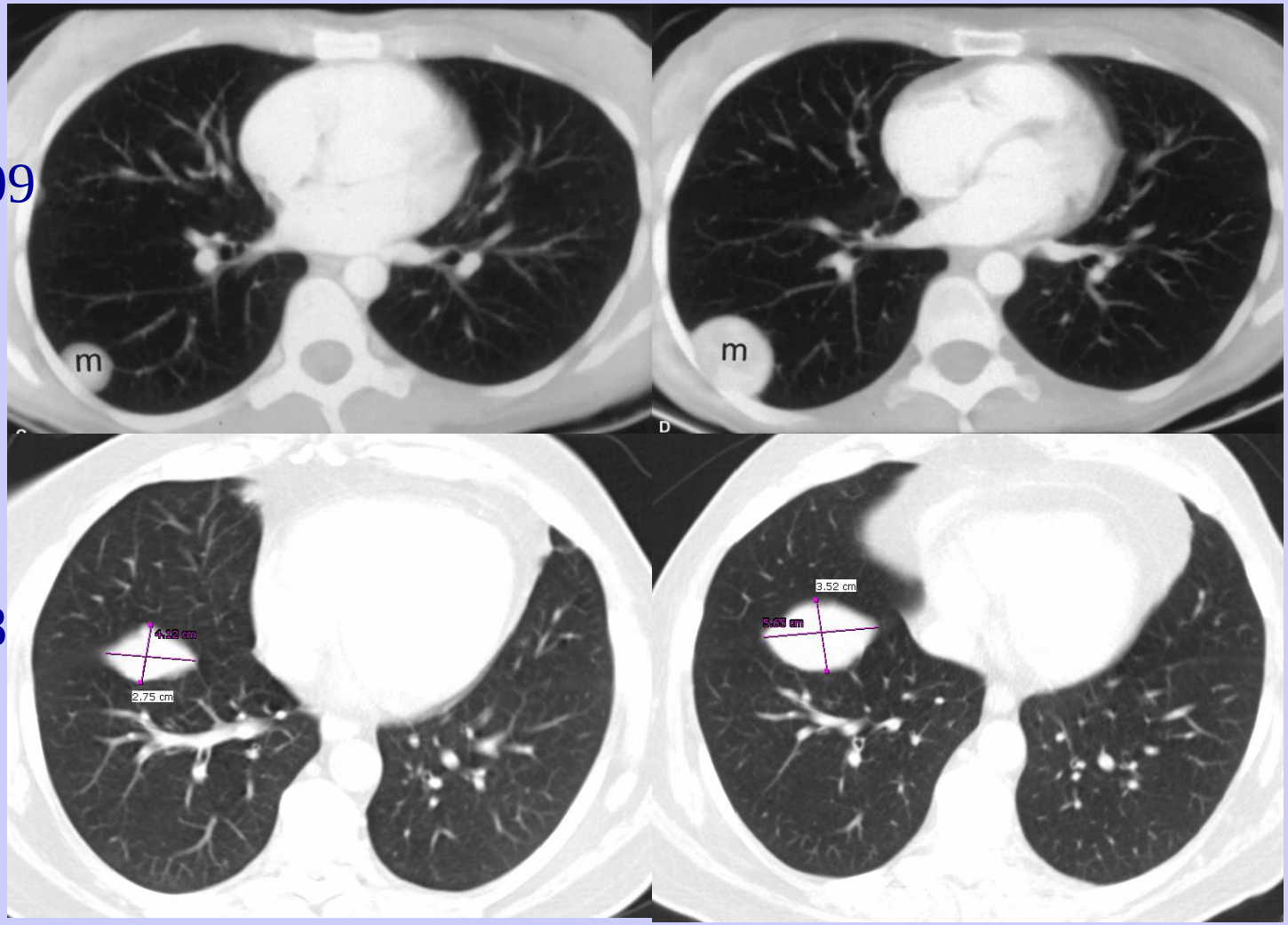


26 yr, m, ASPS

Indication for surgery : YES, but when

March 09

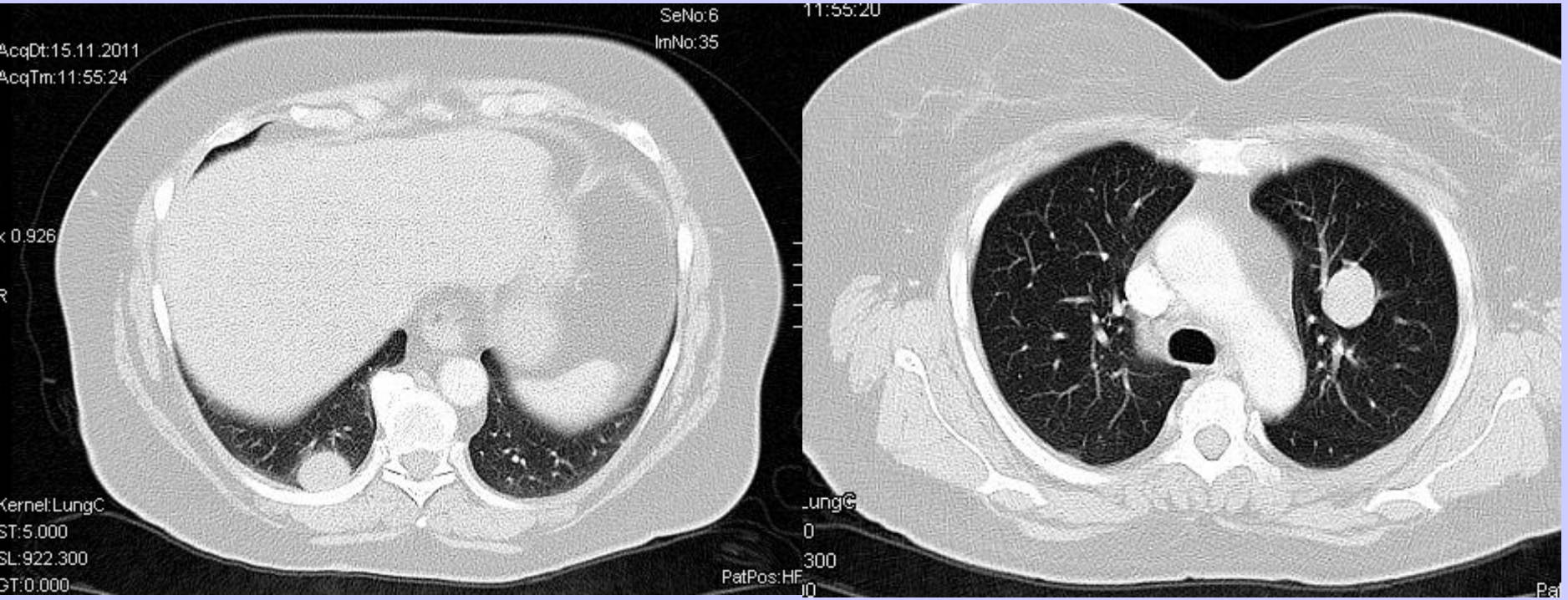
Jan 10



April 08

Dec 08

Indication for surgery (local modalities): in principle, YES



55yr, f, ut-LMS

The concept of oligometastases

- Metastatic stage between localized disease and widespread metastases
- Barney 1939: kidney cancer, M1 lung
  nephrectomy + lung resection: DFS of 23 years
- Surgery of liver metastases from CRC: long-term DF survivors

- Maybe cured by surgery or other local measures

Hellman & Weichselbaum JCO 1995; Corbin, Hellman, Weichselbaum JCO 31, April 10, 2013

Oligometastases and oligorecurrences

- Number of metastases < 5*

- Recurrences at different sites = **oligorecurrence**
- Oligorecurrence might have better prognosis than re-recurrence at the same site
- ‚Intermediate stage of metastases' months later

- Adopted mainly for SBRT in lung and liver metastases

*Niibe, Jpn J Clin Oncol 2010; Treasure, J Roy Soc Med 2012

Oligometastases: mechanism

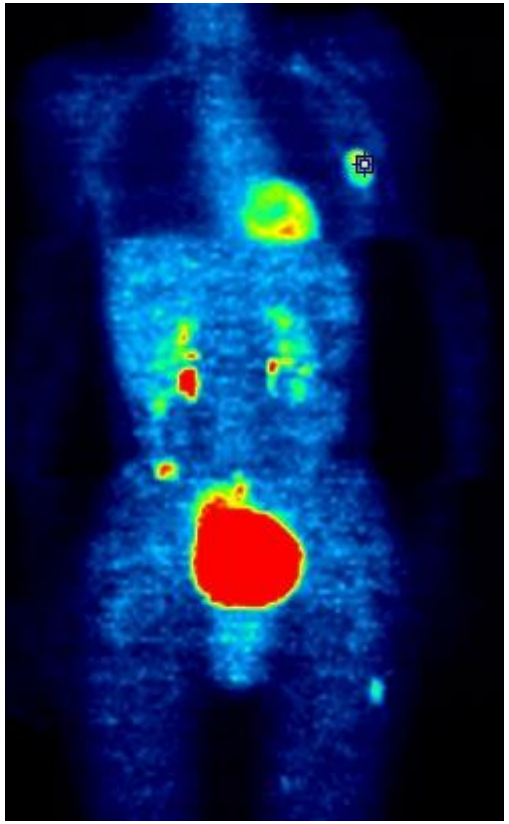
- Controlled primary tumors for success
- Metachronous mets. mainly
- Basis: tumor-host cross talk – allowing site specific metastases only
- Eradication of these might provide long-term disease control

- miRNA-200c linked to oligomets
- PBK, BIRC5, PTTG1 in renal cancer lung mets

Lussier PloSOne (6)12: e28650; Wuttig, Int J Cancer 2009

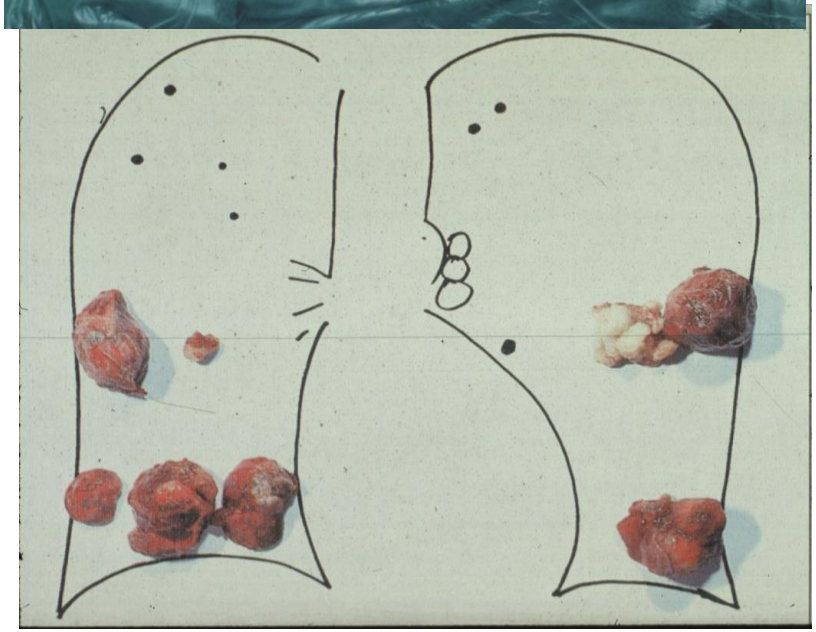
Diagnostic work-up

- High resolution CT
- Make sure that ther are no mets at other ‚unusual' sites
- Whole body MRI
- 18F-FDG PET
  - detected only additional 6% of metastases
  - additional lung mets often missed

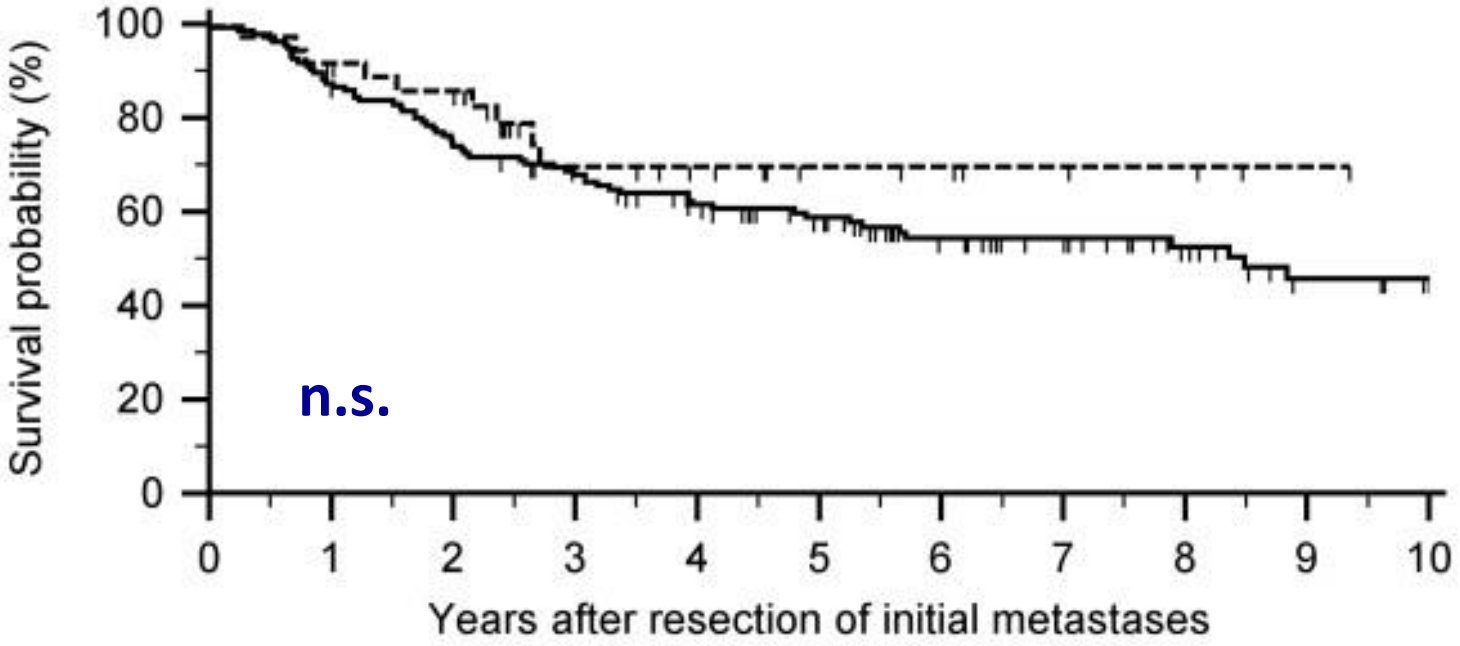


Eary, J.Nucl Med 2011; Roberge Sarcoma 2012

Lung resection of metastases: open or VATS ?



Surgical technique: open vs VATS does not matter: R0 !

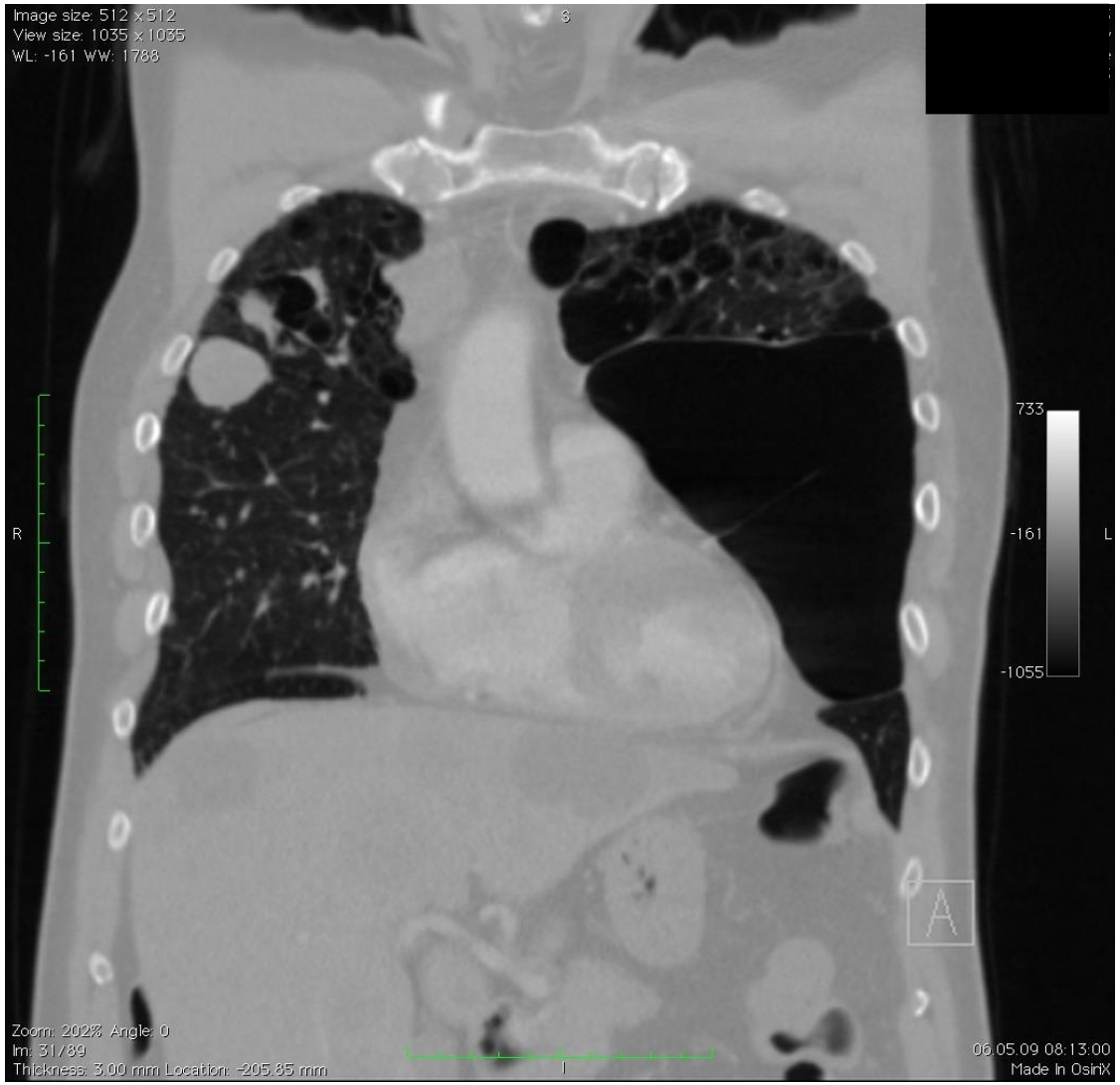


Number at risk

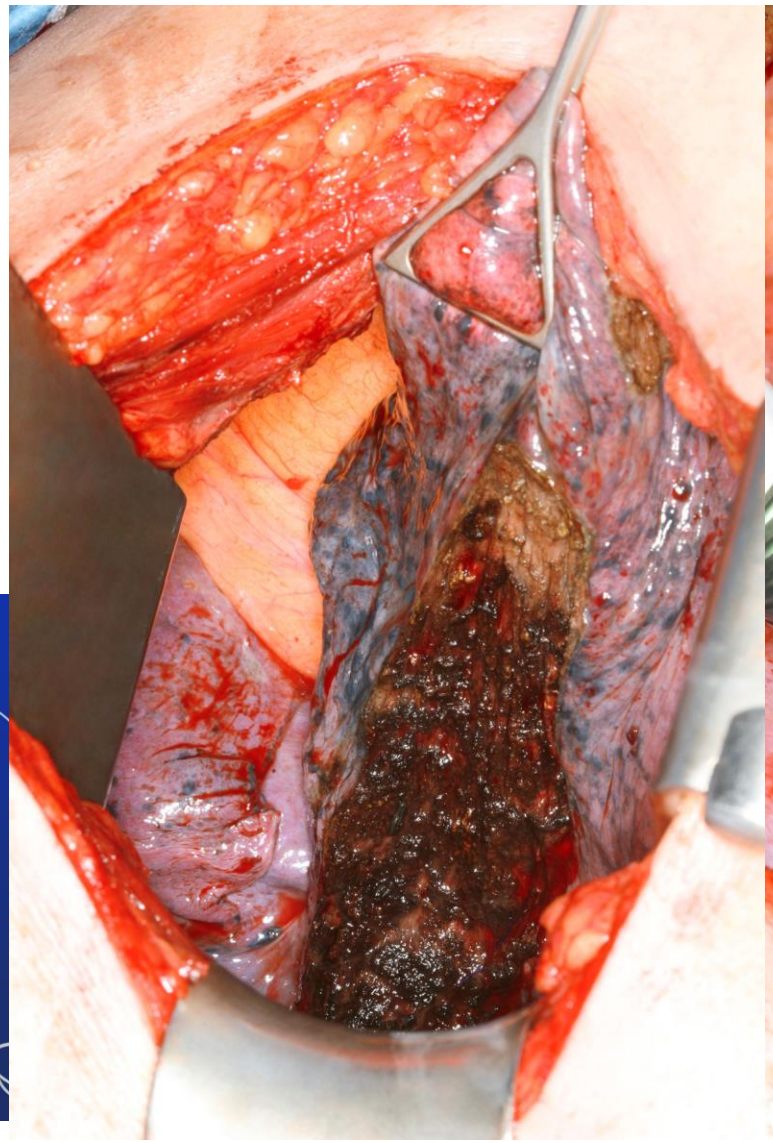
Group: OPEN (solid line)										
135	117	99	88	73	61	45	38	28	18	14
Group: VATS (broken line)										
36	32	29	14	11	7	6	4	3	1	0

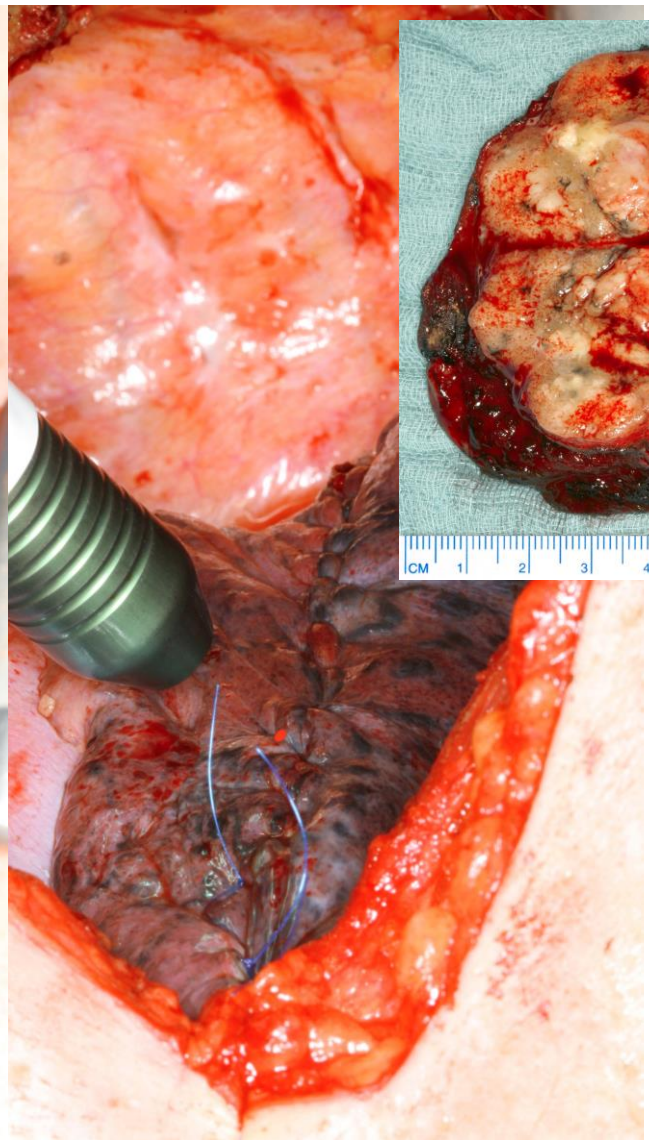
Carballo J Cardiothor Surg 2009

Surgical technique: laser resection

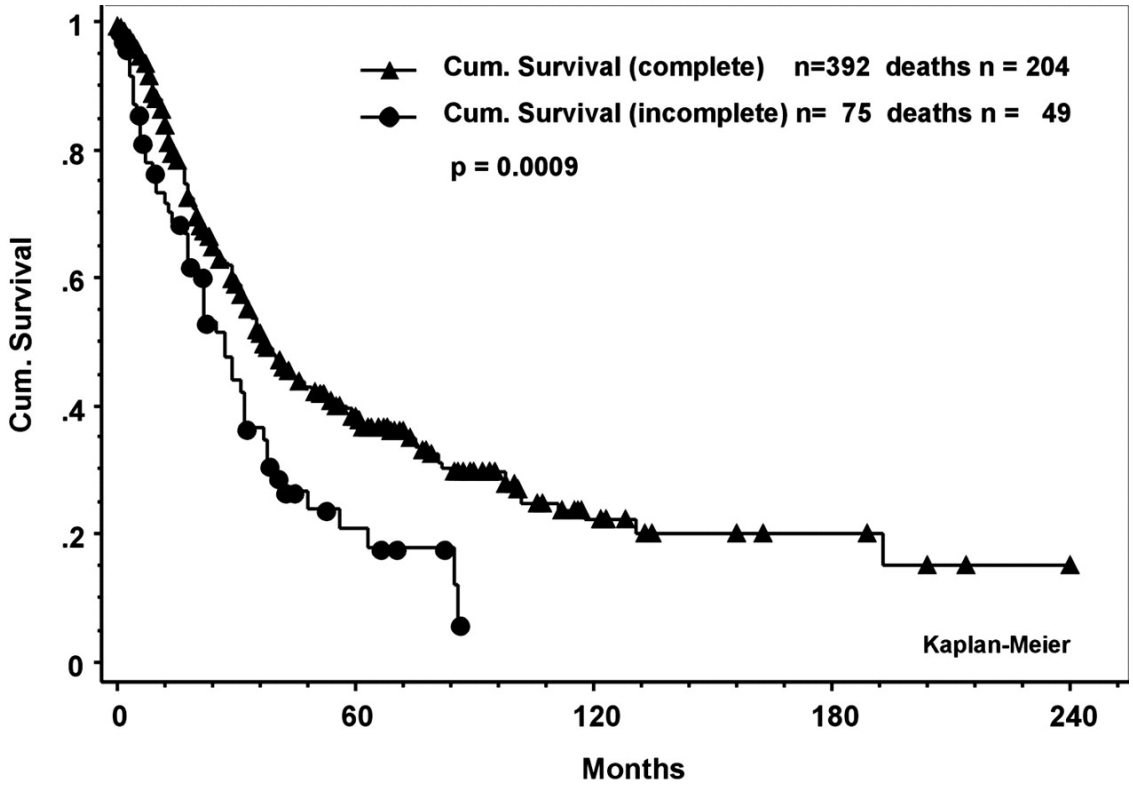


Surgical technique: laser resection





R0 vs R1 resection : p = 0.0009



	5 - year surv.	5 - year at risk	10 - year surv.	10 - year at risk	15 - year surv.	15 - year at risk	median
complete	38%	82	22%	15	20%	5	37m.
incomplete	18%	7					25m.

Friedel G. et al.; Eur J Cardiothorac Surg 2006;22:335-344

Prognostic score after resection of lung metastases

Metastases number : 1 vs 2- 3 **vs. >4**

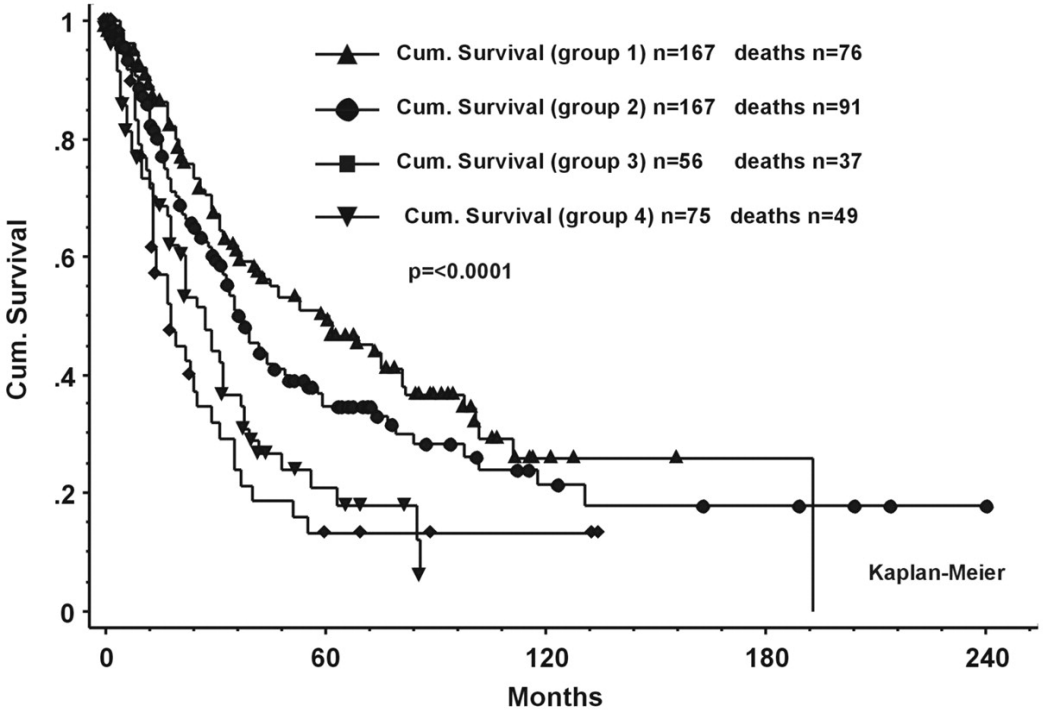
time interval : < 1 yr vs. > 1 yr vs. > 2 yr

Resektion margin : R0, R1, R2

Registry of Lung Metastases, J.Thorac.Cardiovasc.Surg. 1997: 113; 37

Friedel G. et al.; Eur J Cardiothorac Surg 2006;22:335-344

Prognostic score after resection of lung metastases



	5 - year surv.	5 - year at risk	10 - year surv.	10 - year at risk	15 - year surv.	15 - year at risk	median
Group 1 (no risk factor)	50%	47	26%	5	26%	1	59 m.
Group 2 (1 risk factor)	35%	31	21%	8	18%	4	36 m.
Group 3 (2 risk factors)	13%	4	13%	2			18 m.
Group 4 (incomplete res.)	18%	7					25 m.

Friedel G. et al.; Eur J Cardiothorac Surg 2006;22:335-344

Prognostic score after resection of liver metastases

Ann. Surg. • September 1999

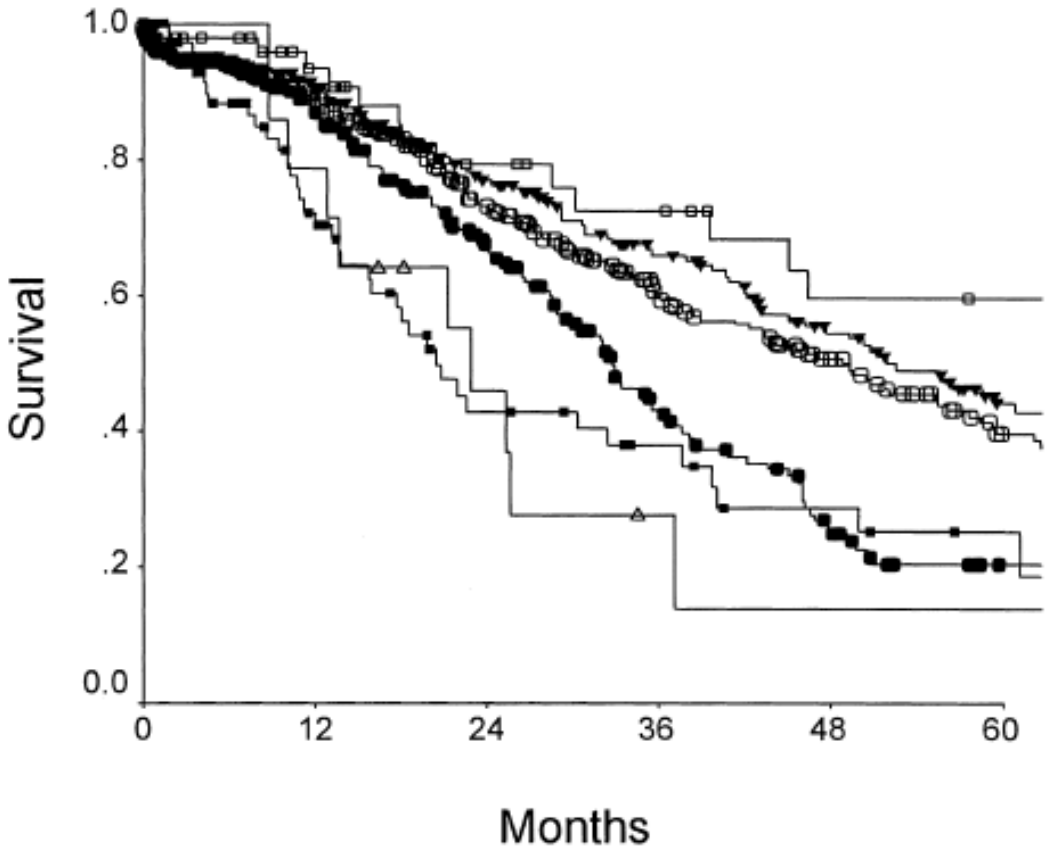


Figure 3. Survival after hepatic resection as related to clinical risk score. Open box: score = 0 (n = 52); filled triangle: score = 1 (n = 262); open circle: score = 2 (n = 350); filled circle: score = 3 (n = 243); filled box: score = 4 (n = 80); open triangle: score = 5 (n = 14). $p < 00001$.

Fong Ann Surg 1999

Long term survival

Time interval :		survival after 5 years	survival after 10 years
<12 mon.	n = 1384	33%	27%
12-35	n = 1662	31%	22%
36+	n = 1416	45%	29%

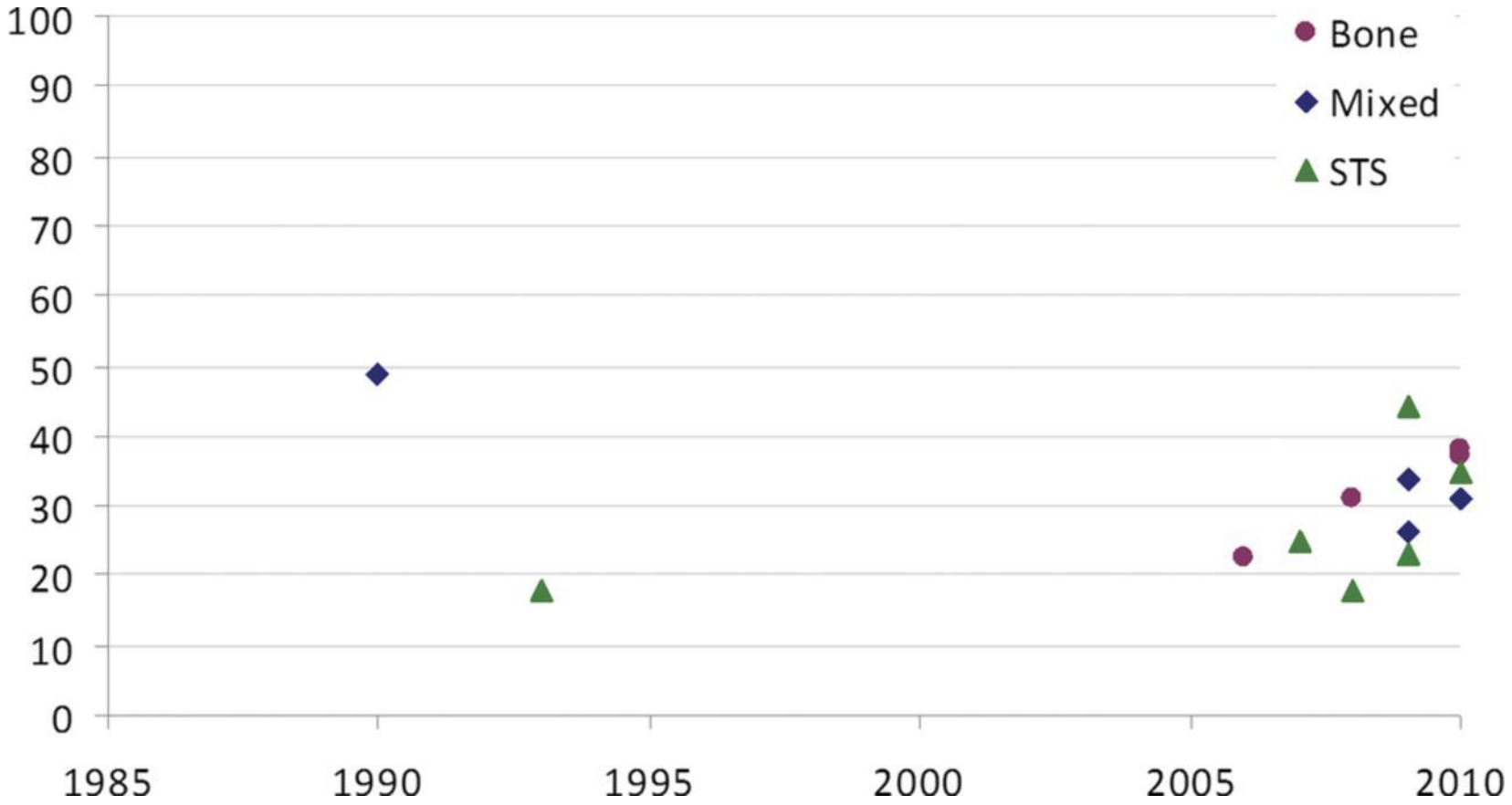
Friedel G. et al.; Eur J Cardiothorac Surg 2006;22:335-344

Systematic review of pulmonary metastasectomy for sarcoma

- 1980 – 2006, n= 1357
- N=1196: 1ry resection, 43% re-resection
- **up to 10 thoracotomies**
- **5 year survival: 34% for STS, 25% for bone**
- **Better survival for fewer mets and longer time interval**
- Beats the expected survival for M1 sarcoma patients in the Thames Cancer Registry

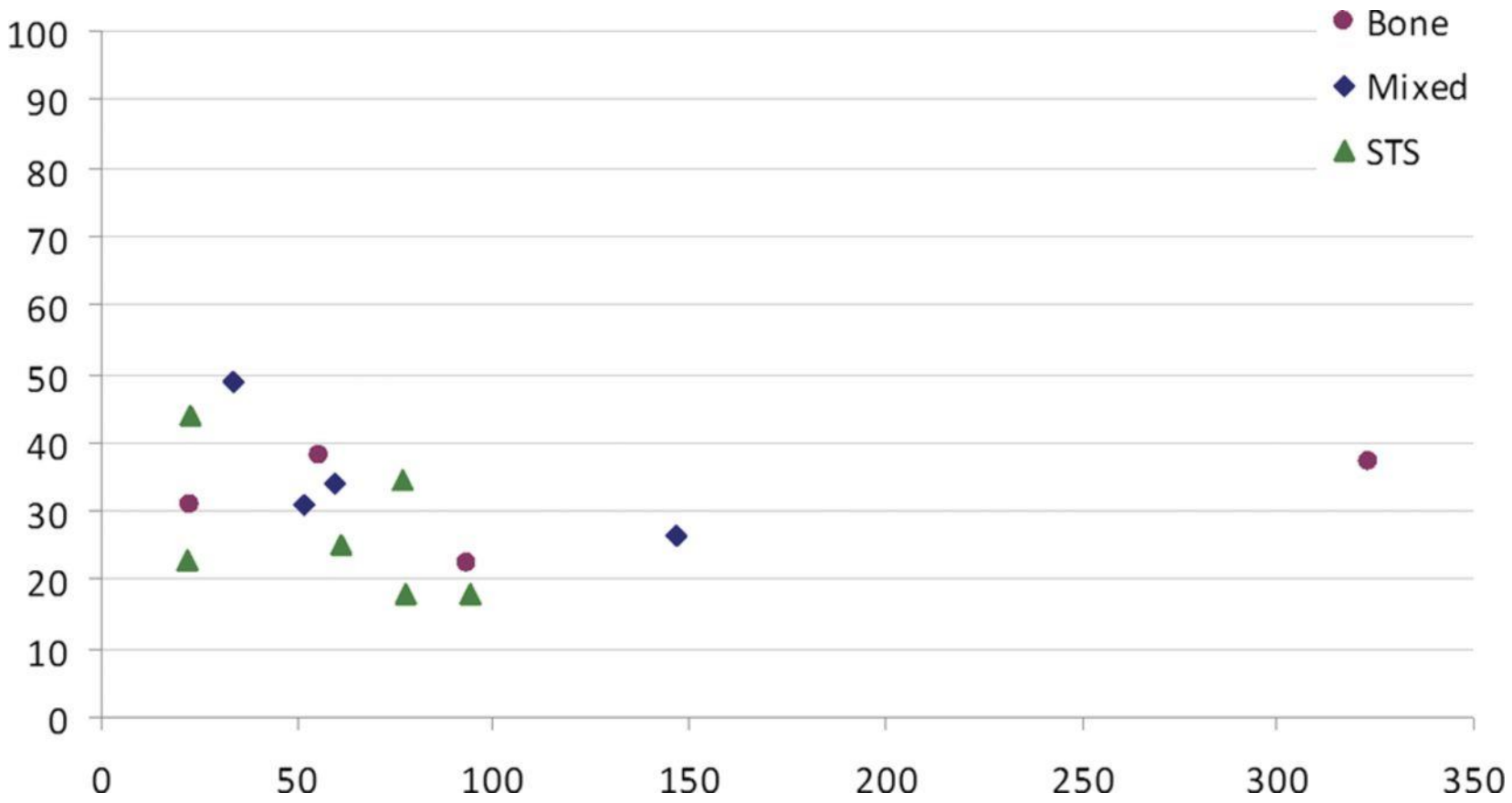
Treasure T, BMJ Open 2012; 2: e001736

Five-year survival rates plotted against the publication date.



Treasure T et al. BMJ Open 2012;2:e001736

Five-year survival rates plotted against the size of the series.



Treasure T et al. BMJ Open 2012;2:e001736

Systematic review of pulmonary metastasectomy for sarcoma

We can reasonably deduce that

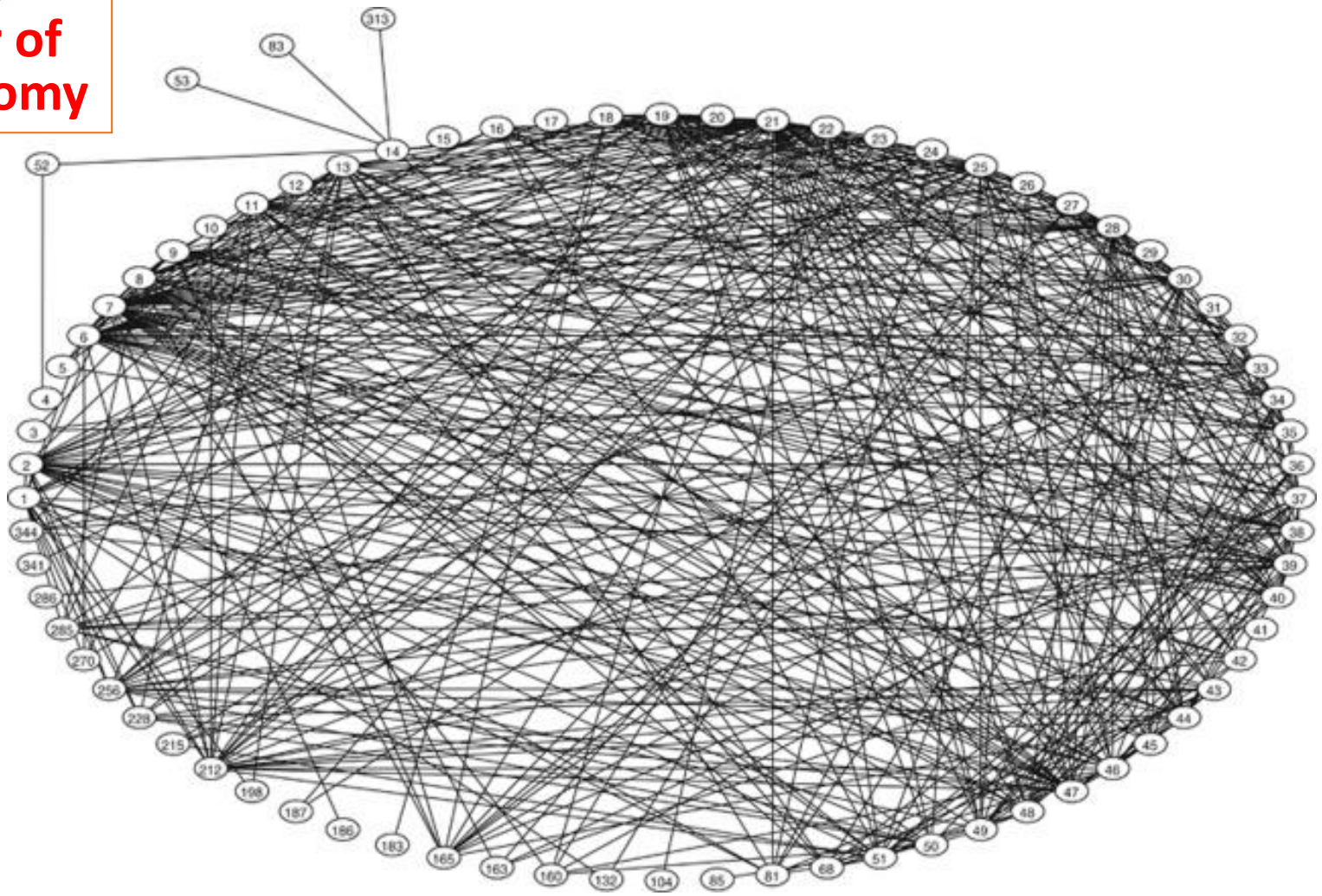
- Five-year survival does not equate to cure since there are 5-year survivors with metastatic disease.
- But at 10 years many of those patients still are alive
- **Given the *lack of effective systemic therapies*, PM remains the only potentially curative treatment for STS lung metastases as long as all known disease can be completely resected with negative margins**.
- We demonstrate that after repeated metastasectomies, a subset of patients can be cured.

Level of evidence:

- No randomized study
- Comparison : surgery for oligometastases vs. standard of care (chemotherapy) missing

Level of evidence: Clinical reports of pulmonary metastasectomy for colorectal cancer: **a citation network analysis**

4 Studies not in favor of metastasectomy

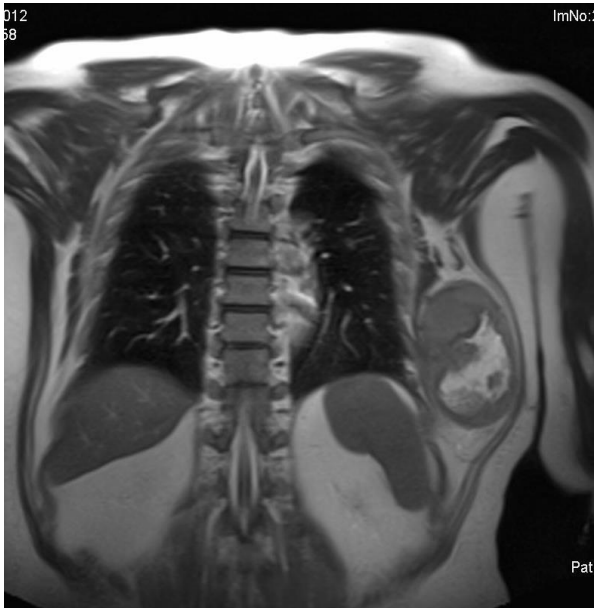


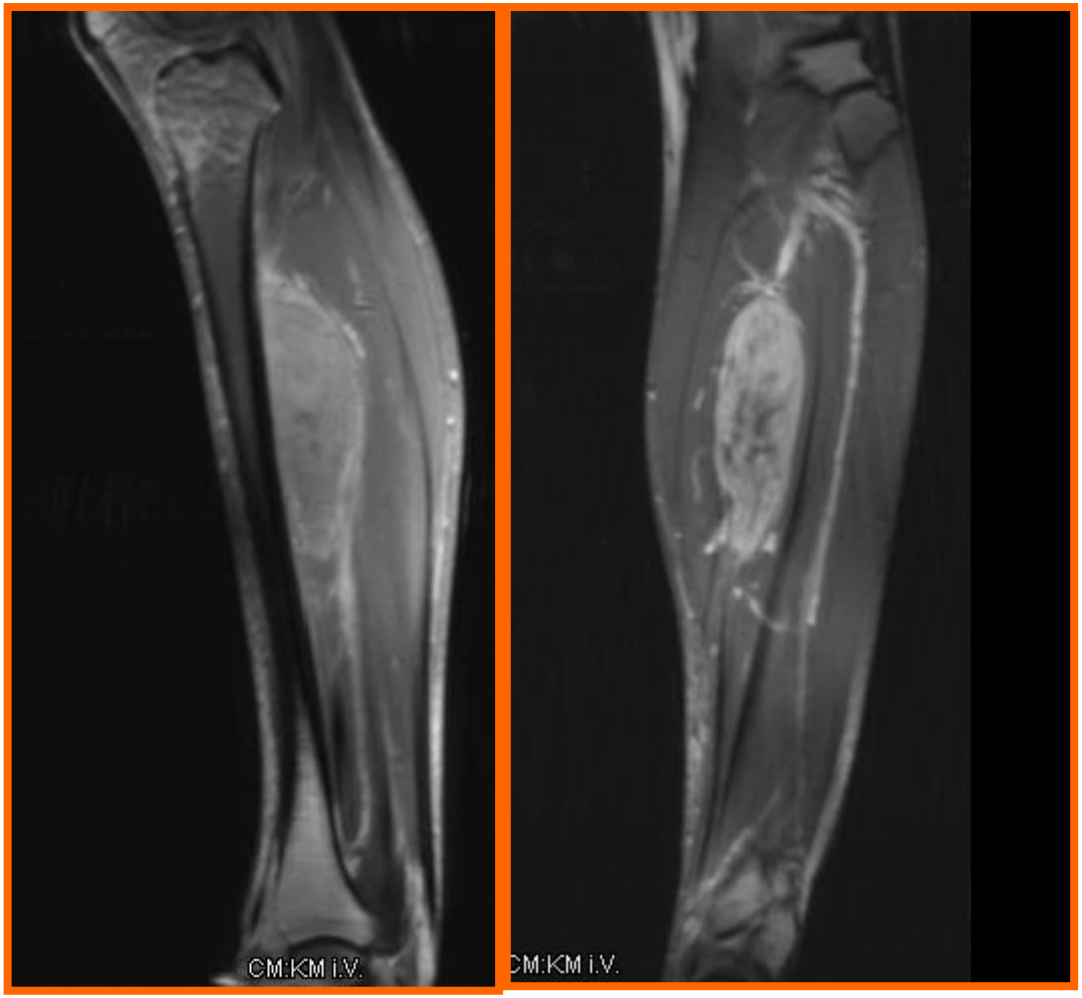
Fiorentino F, Vasilakis C, Treasure T. ; Br J Cancer. 2011 Mar 29;104(7):1085-97

Criteria for local treatment measures in M1 patients

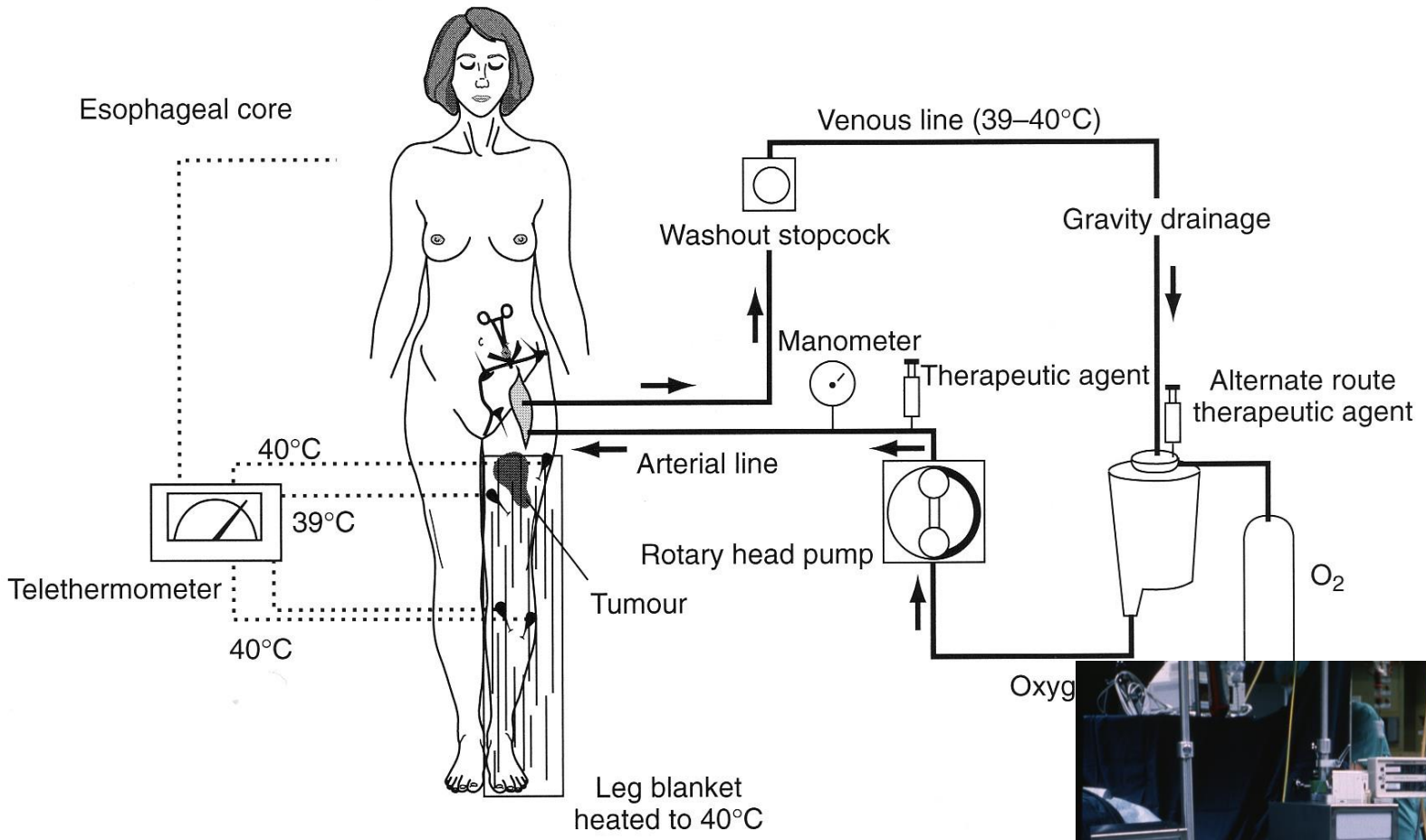
- Technically feasible
- R0 resection locally possible
- Expected morbidity low
- Removal of all metastases can be achieved
- Limited number of M1 lesions
- Not just a few weeks after the last surgery
- Better not in an NOS, grade 3 sarcoma of 14 cm initial size, presenting with skip metastases

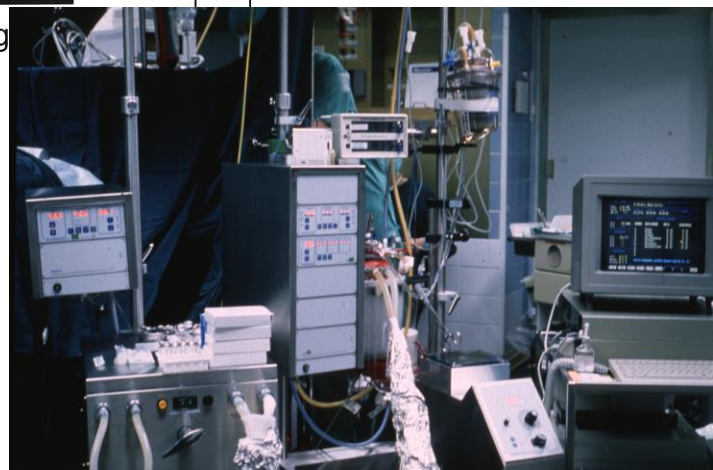
Other locations of metastases



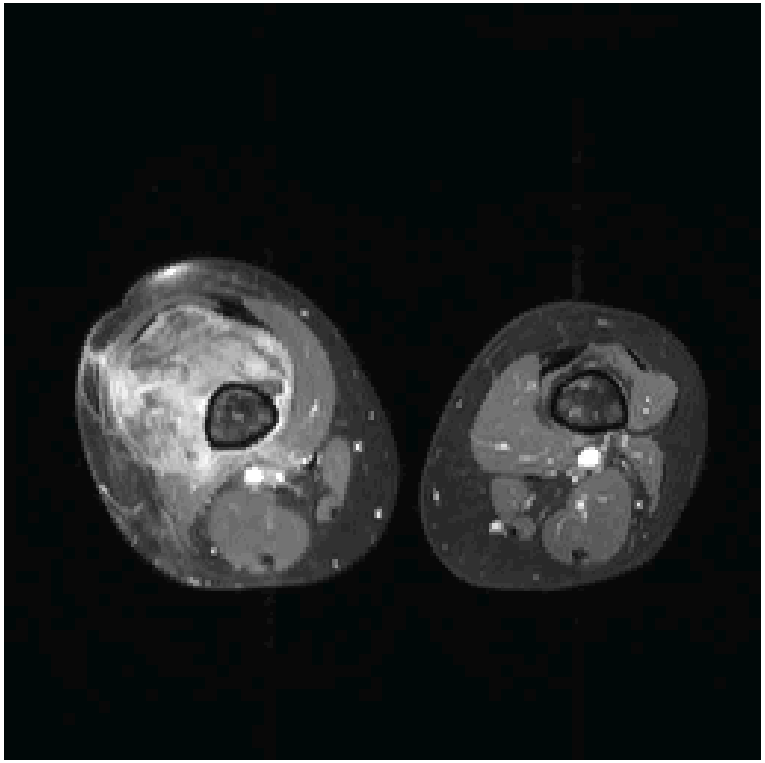


Isolated limb perfusion

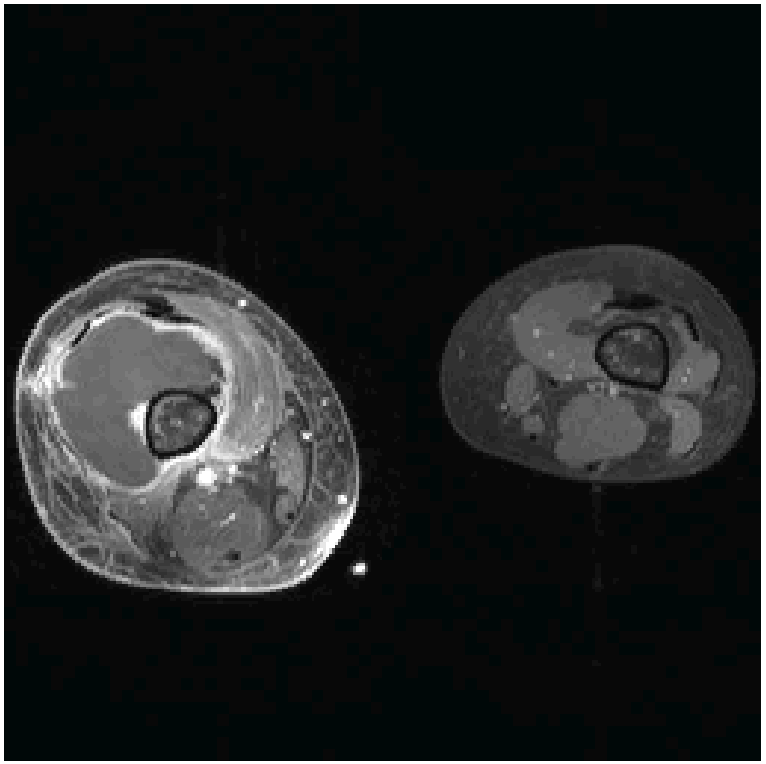




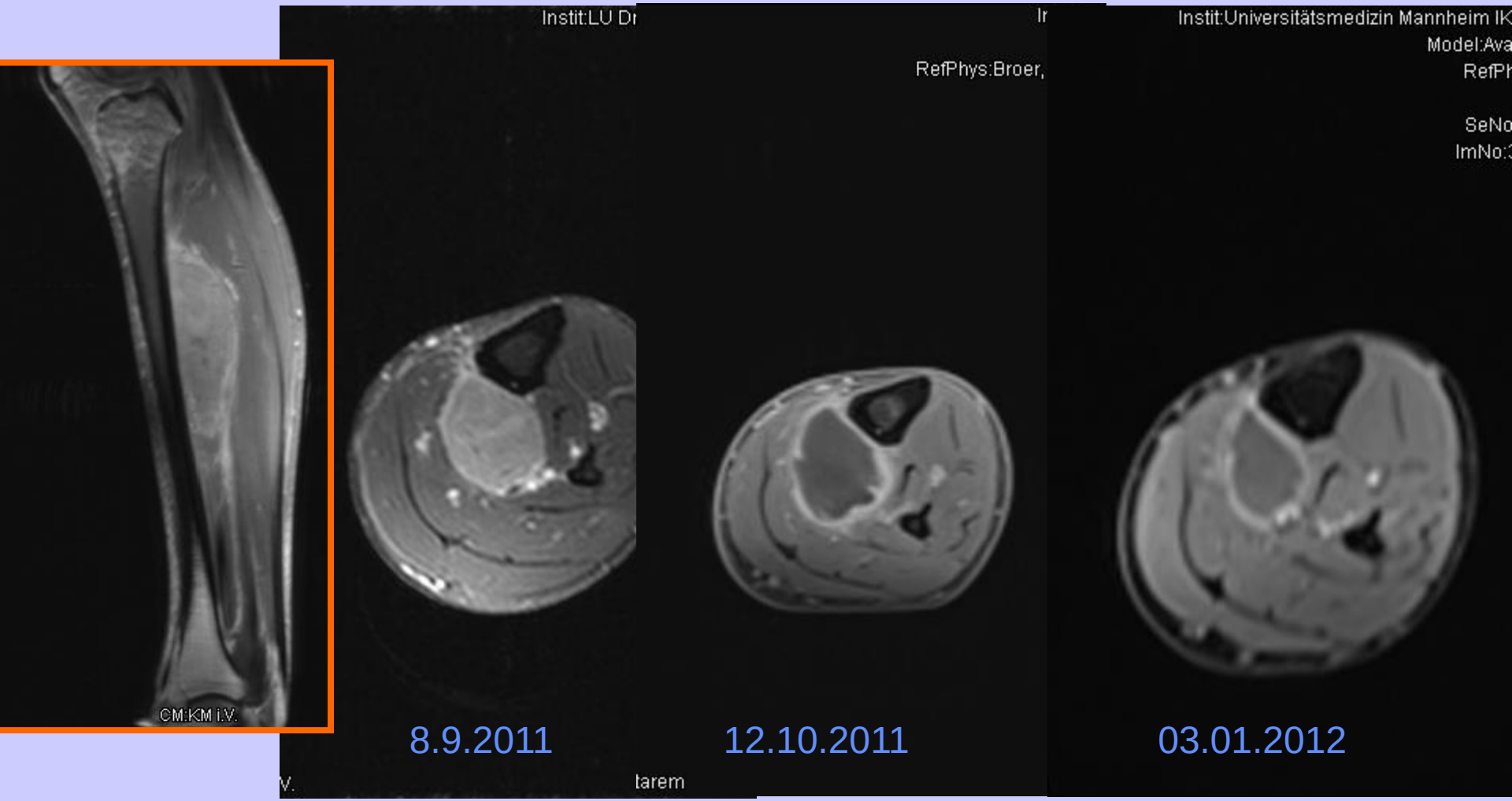
Pre-ILP



post ILP



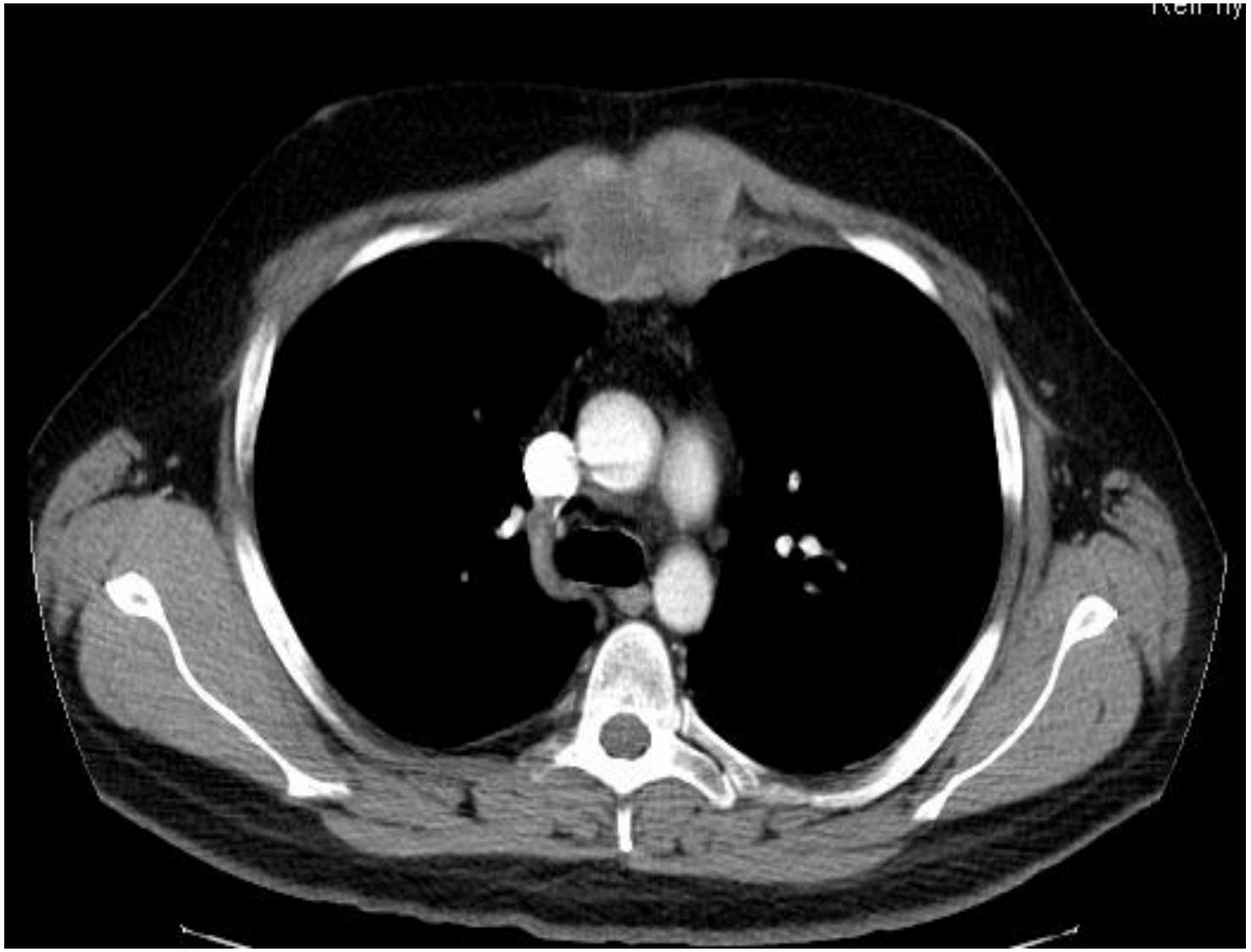
Soft tissue met. of osteosaroma after brain metastasis resection



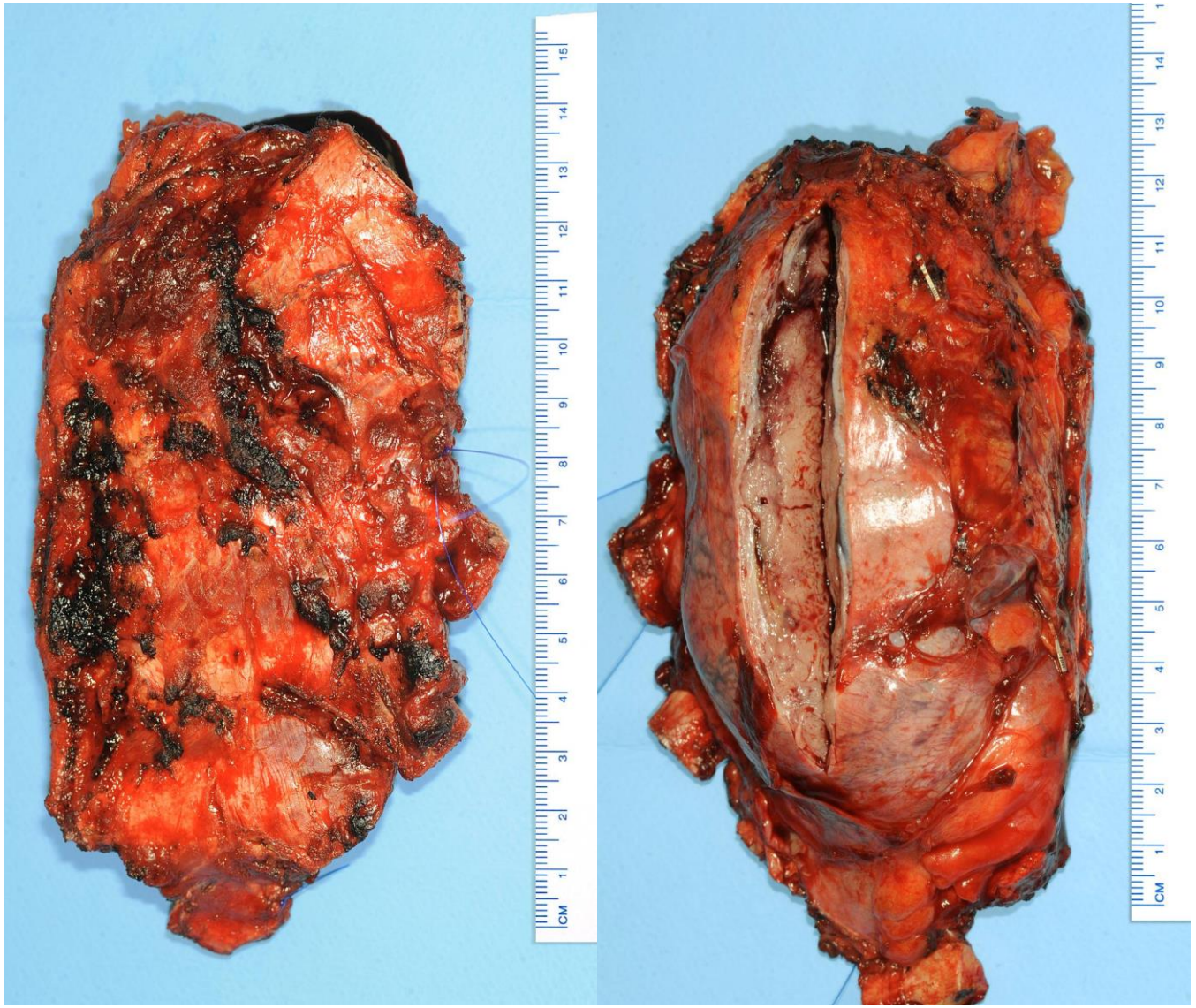
Final illustrating case

- Patient: 57 yr, f
- Uterine leiomyosarcoma, locally advanced involving left ureter, TAH+BSO in **Nov 2006**
- Retroperitoneal recurrence, multivisceral resection, incl. nephrectomy **Aug 2008**
- Regional recurrence to the right retroperitoneum and rectum, resection, IORT + adj RT of 50.4 Gy, **February 2010**
- Sternal metastasis March **2012**

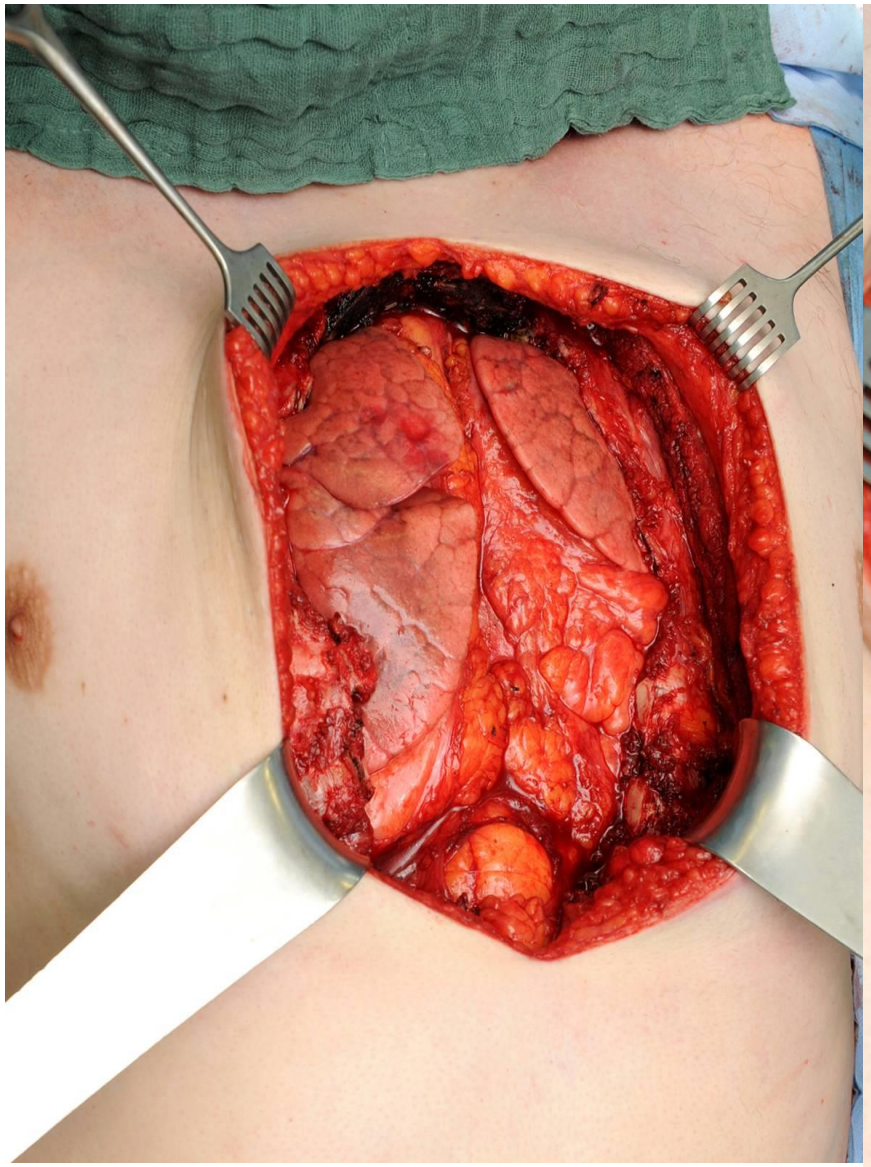
Sternectomy, titanium strut reconstruction

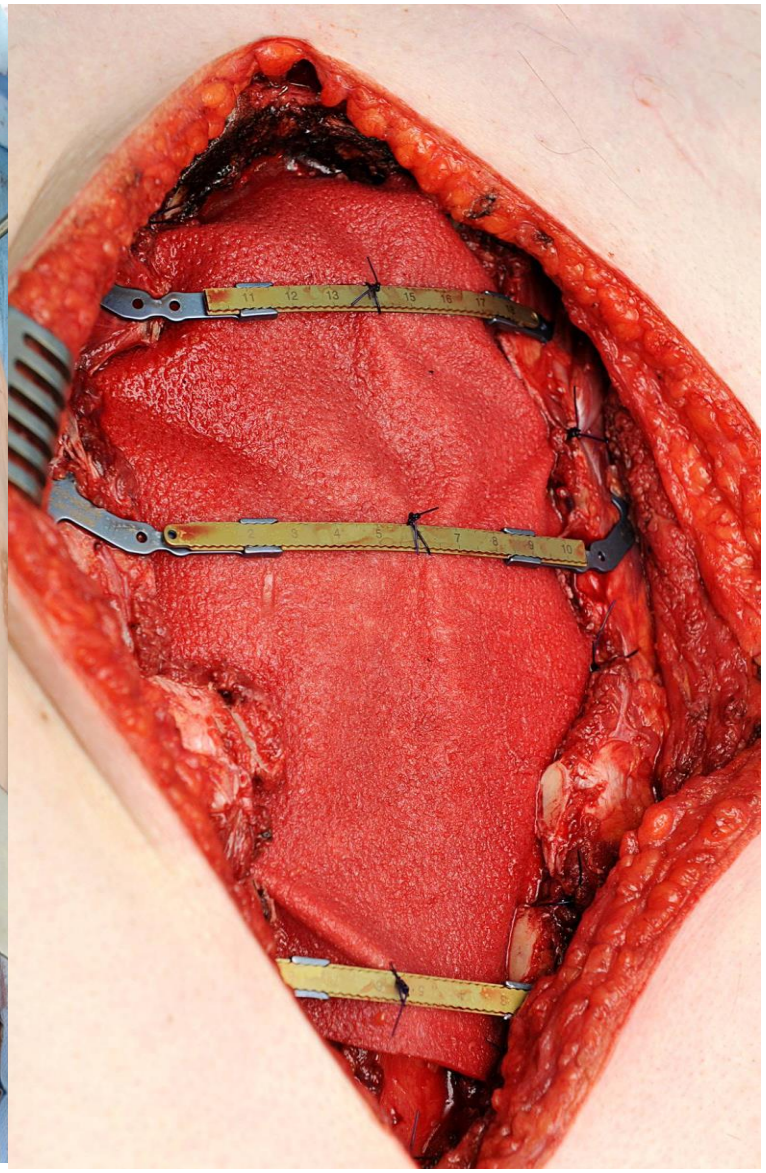


Sternectomy, strut reconstruction



Sternectomy, struts, human dermal implant





Sternectomy, struts, human dermal implant + 4 mos.

Final illustrating case

- Patient: 57 yr, f
- Uterine leiomyosarcoma, locally advanced involving left ureter, TAH+BSO in **Nov 2006**
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- Sternal metastasis March **2012**
- **Lung metastasis, April 2013**
- **Still alive with drug therapy for M1 in 2019!**

Key points

- Patients suffering from an oligometastatic or oligo-recurrent disease progression, have a certain potential for a curative approach by local treatment measures.
- Surgery and radiotherapy remain the two main treatment approaches to gain a high local tumor control rate
- This is also the case of a metastasized disease with a limited number of metastases in the lungs or at other sites.

Key points – contin‘d

- **R0 resection/complete tumor destruction is a must, there is no room for debulking**
- **This is not removal of residual tumor after preoperative chemotherapy of widespread disease**
- These highly selected and sophisticated measures should only be agreed upon in an interdisciplinary sarcoma board
- Shared decision-making with the patient is mandatory as the (slim and often transient) chance of disease relief must be weighed against the risks of the treatment.

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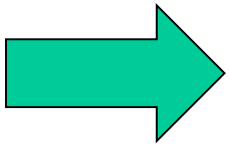
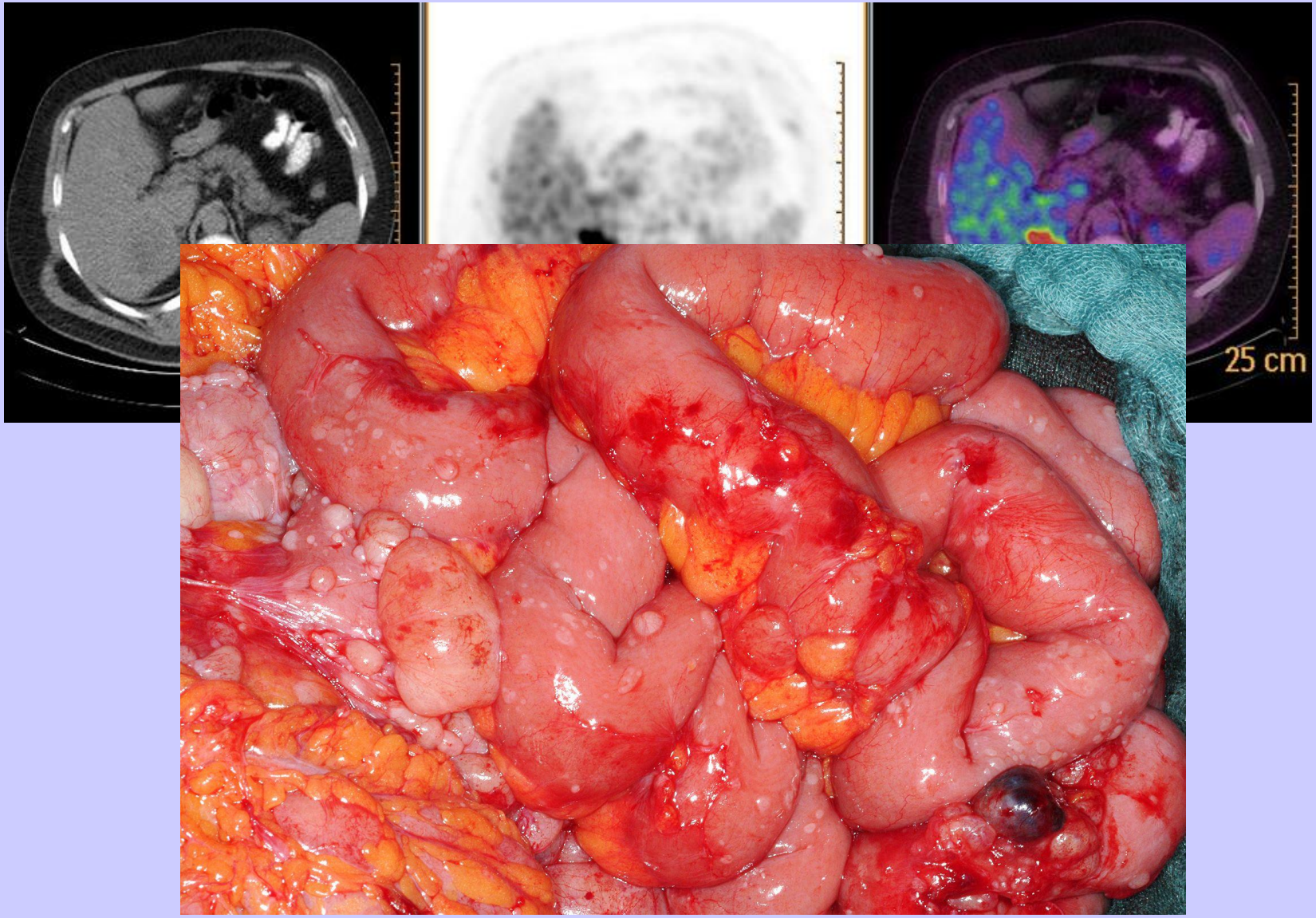
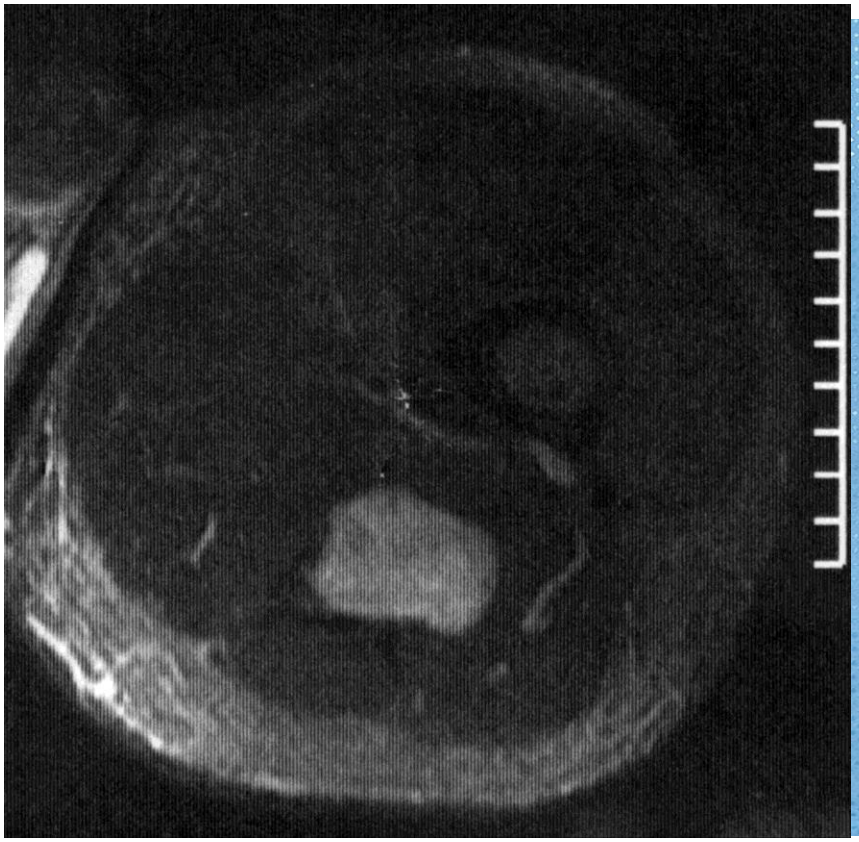


Specific interventions

GIST: liver and peritoneal metastases = typical

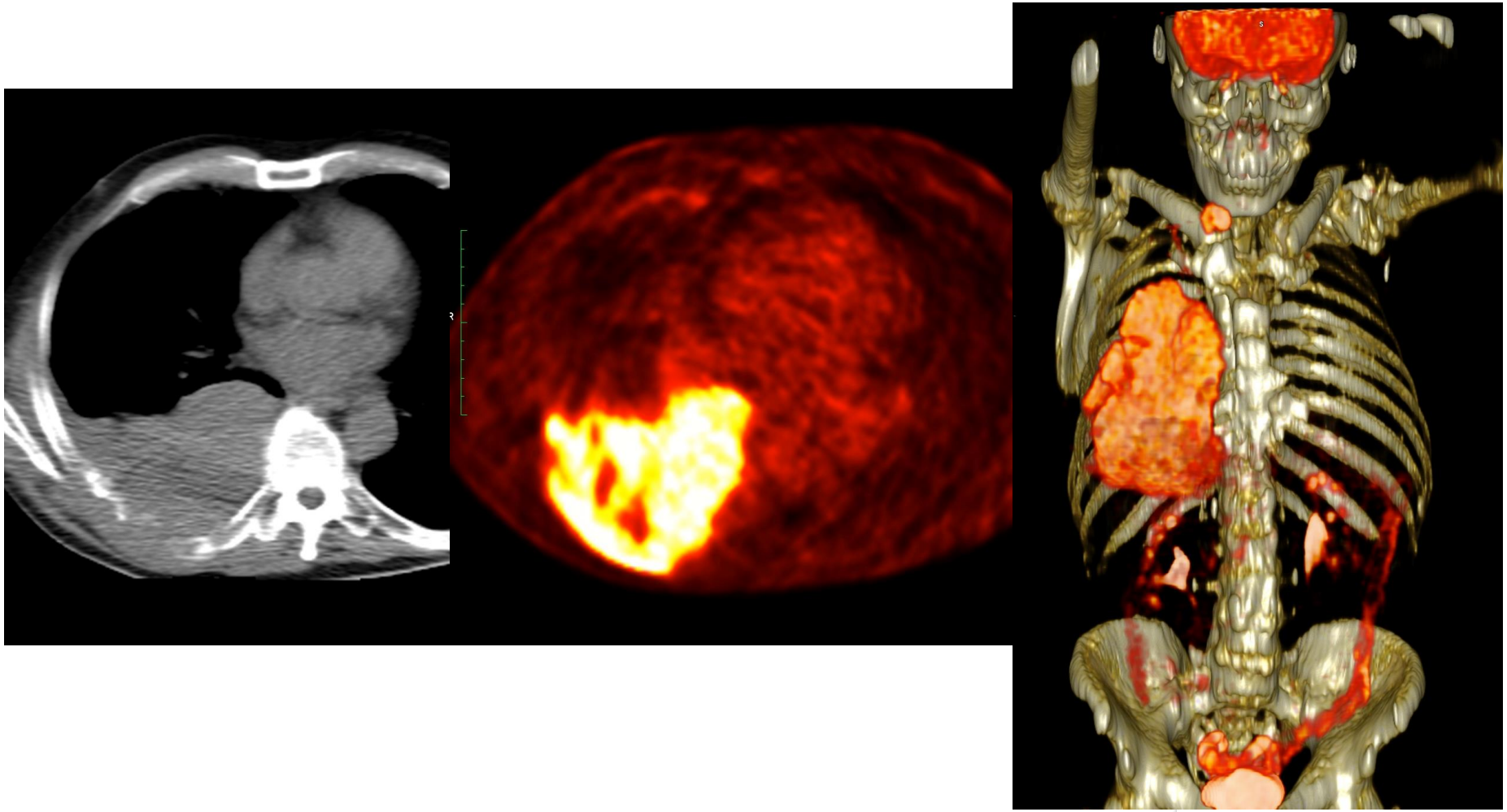


Unusual location of metastases
patient entered EORTC 62005 in 3/2001, exon 11

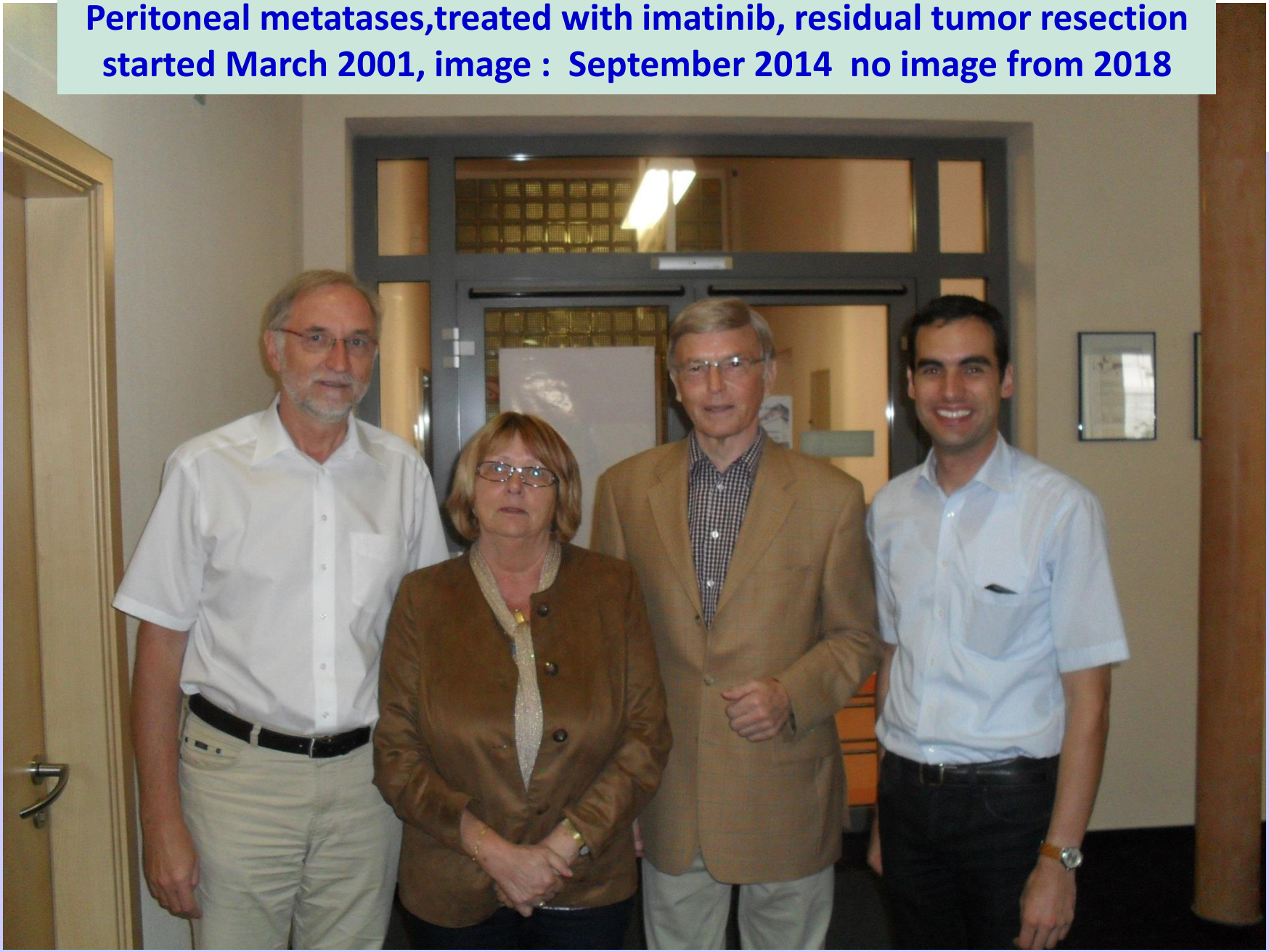


Right leg in 2007 and left leg in 2009

Unusual location of metastases
first: exon 11, then exon 13, now exon 17 mutation

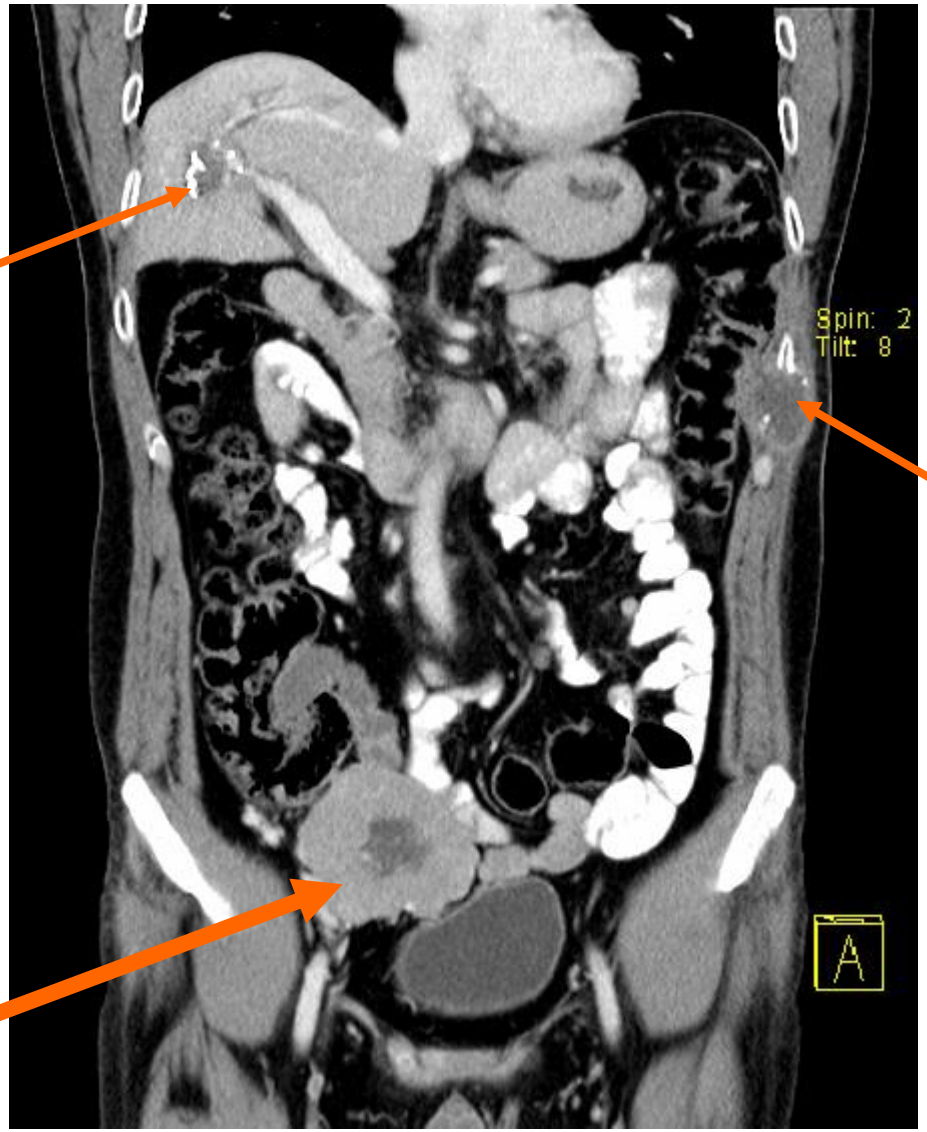


Peritoneal metatases,treated with imatinib, residual tumor resection started March 2001, image : September 2014 no image from 2018



GIST multifokale Metastasen, m, 40yrs
first diagnosis 2002

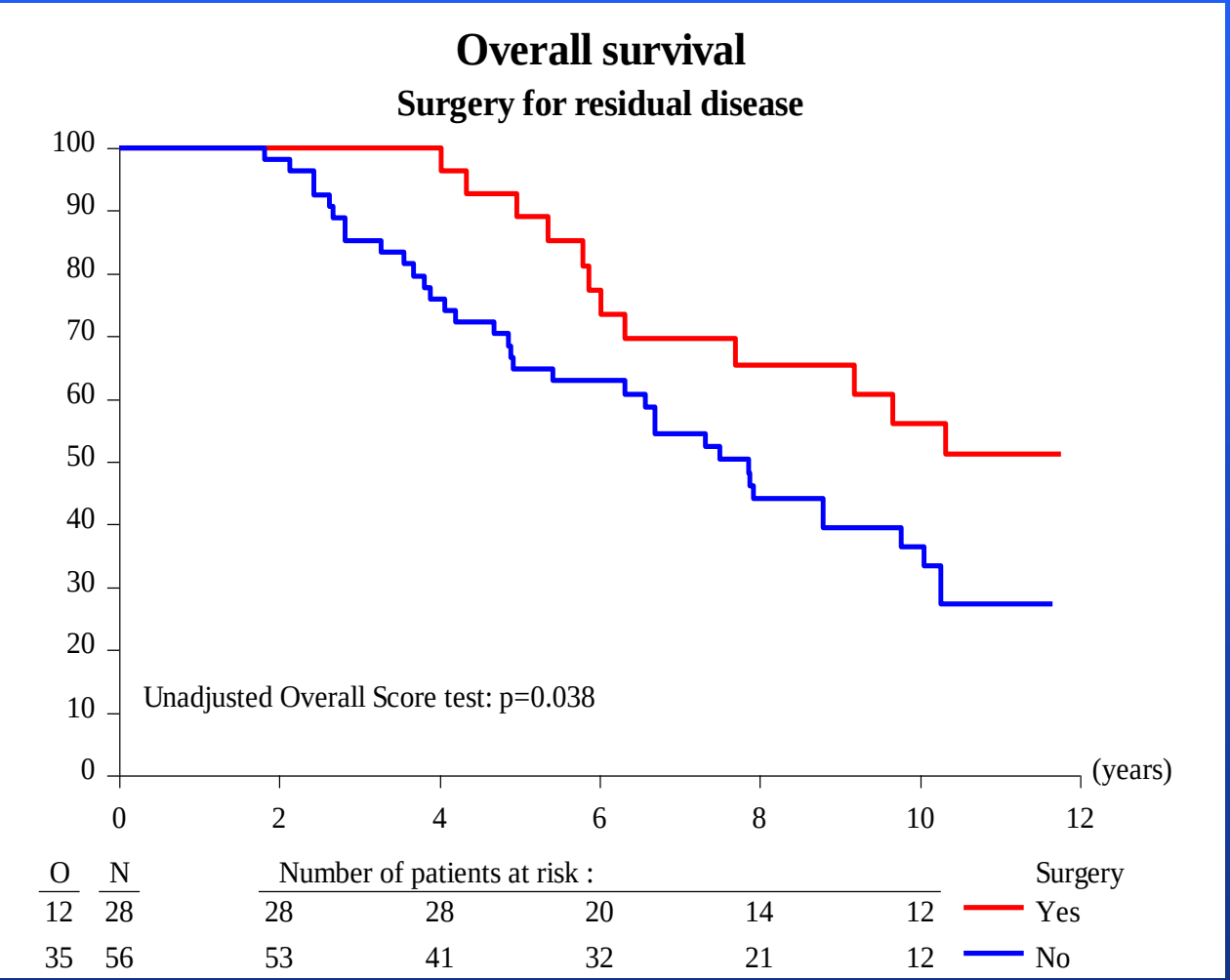
Surgery,
later RFA



Irradiation

neu

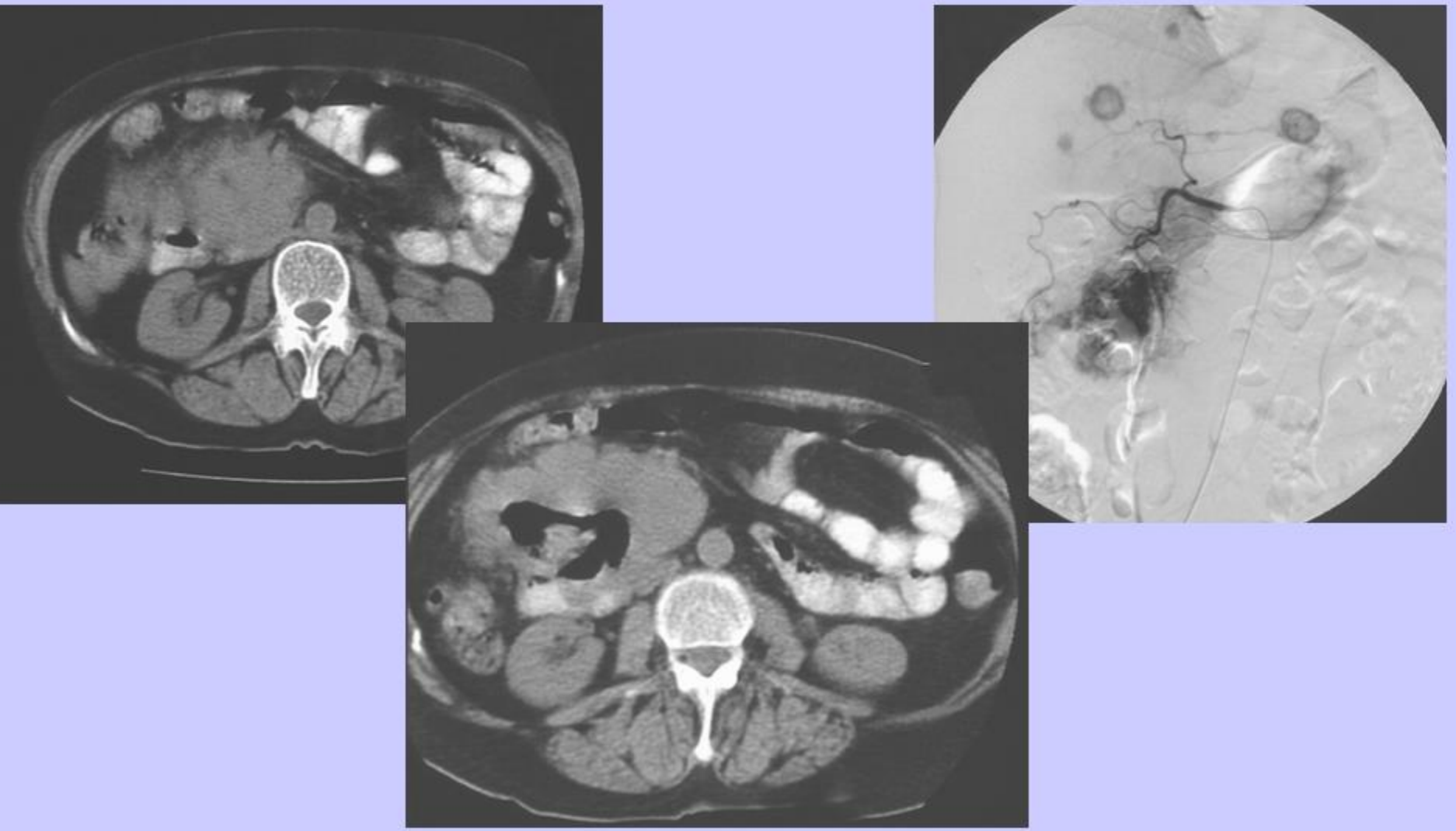
Post-surgery PFS (residual disease)



EORTC The future of cancer therapy

Hohenberger et al. 2016; EurJ Cancer (accepted)

GIST metastases by angiogram



Local treatment for liver metastases: TACE

Hepatic Artery Chemoembolization for 110 Gastrointestinal Stromal Tumors

Response, Survival, and Prognostic Factors

Katsuhiro Kobayashi, MD[1]
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Jonathan C. Trent, MD, PhD[2]
Jean-Nicolas Vauthey, MD[3]
Savitri Krishnamurthy, MD[4]
Joe Ensor, PhD[5]
Kamran Ahrar, MD[1]
Michael J. Wallace, MD[1]
David C. Madoff, MD[1]
Ravi Murthy, MD[1]
Stephen E. McRae, MD[1]
Marshall E. Hicks, MD[1]

85 patients:
PR 12 (14%), SD 63 (74%), PD 10 (12%)

PFS-liver rates:
31% at 1 year
8% at 2 years
5% at 3 years

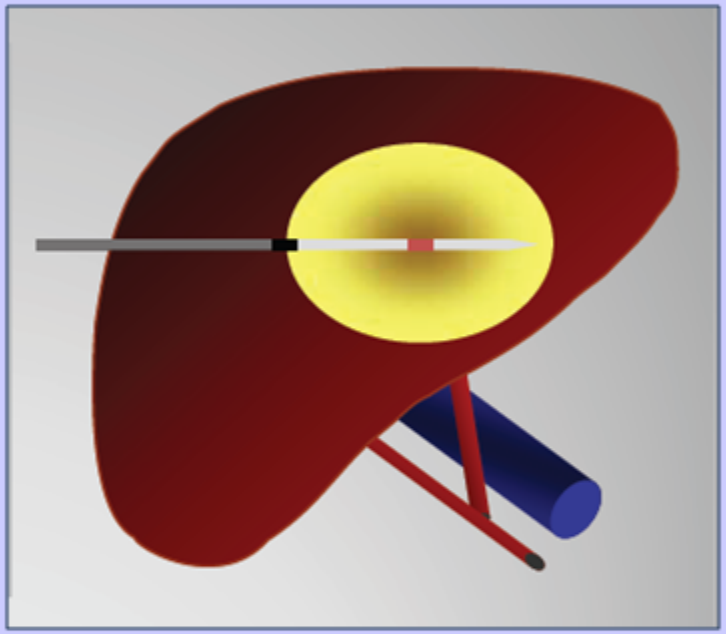
median PFS time:
8.2 months

OS rates:
62% at 1 year
32% at 2 years
20% at 3 years

median OS time:
17.2 months

Cancer 2006; 107: 2833

Local treatment for liver metastases: **RFA**



GIST	n=36
Leiomyosarcoma	n=18
Sarcoma	n=12

Resection +/- RFA, RFA alone

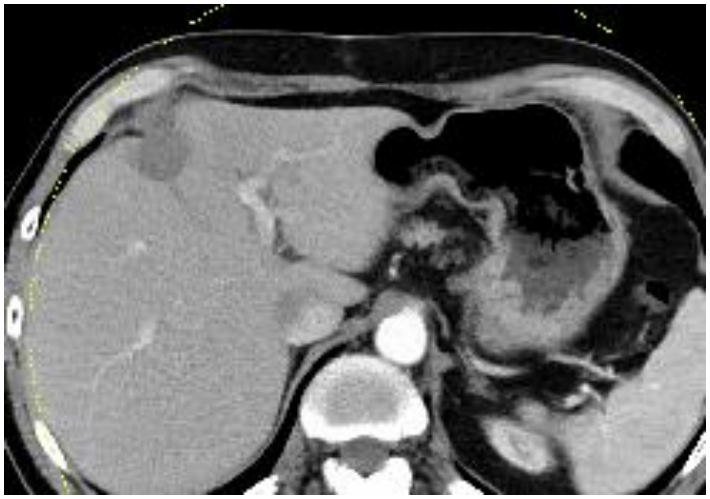
Results of a Single-Center Experience With Resection and Ablation for Sarcoma Metastatic to the Liver

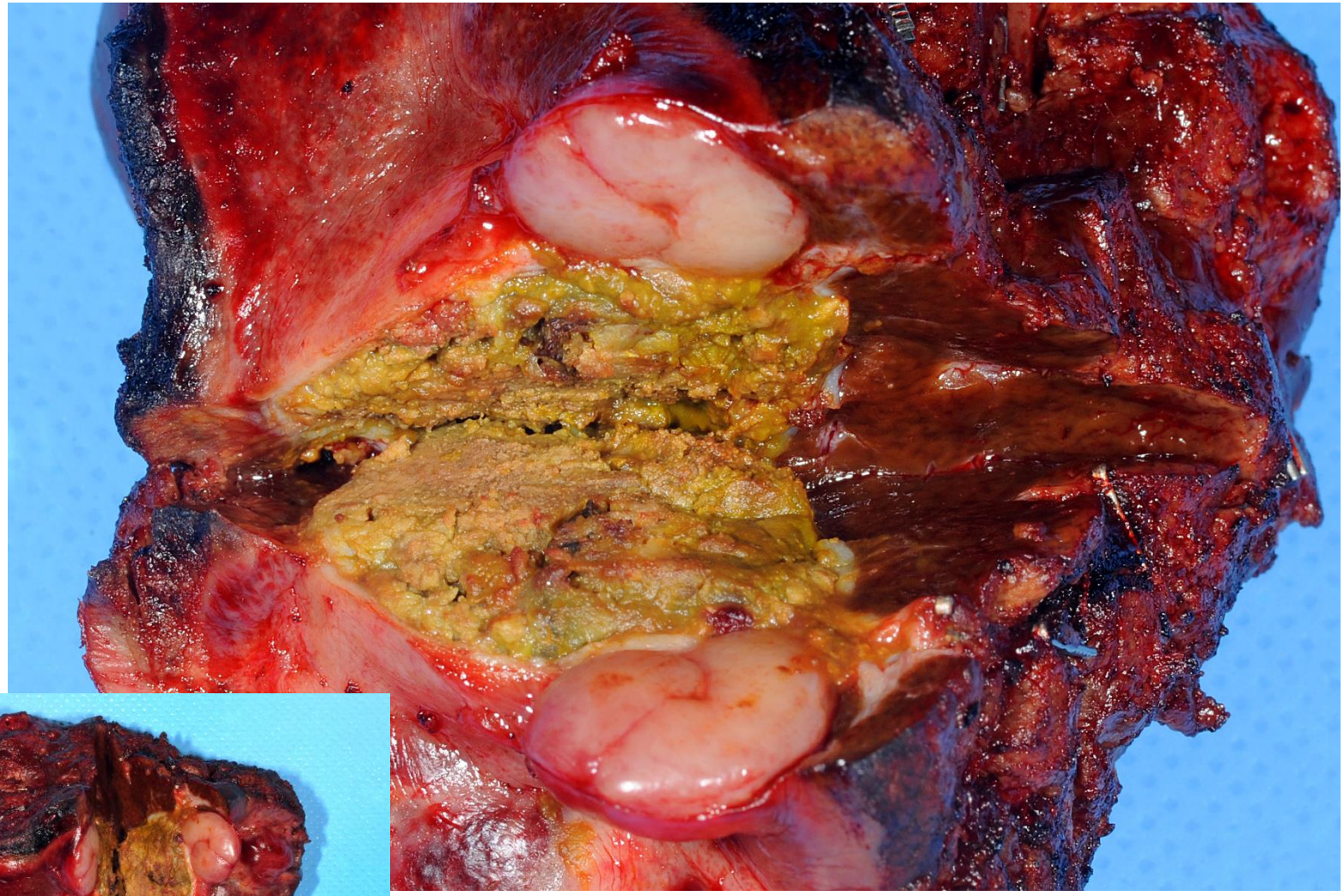
Timothy M. Pawlik, MD, MPH; Jean-Nicolas Vauthey, MD; Eddie K. Abdalla, MD; Raphael E. Pollock, MD, PhD; Lee M. Ellis, MD; Steven A. Curley, MD

Pawlik, Arch Surg 2006; 141: 537

Different:

Surgery in M1 GIST: **Peri-RFA Progression**






CM
1
2
3
4
5
6
7
8
9

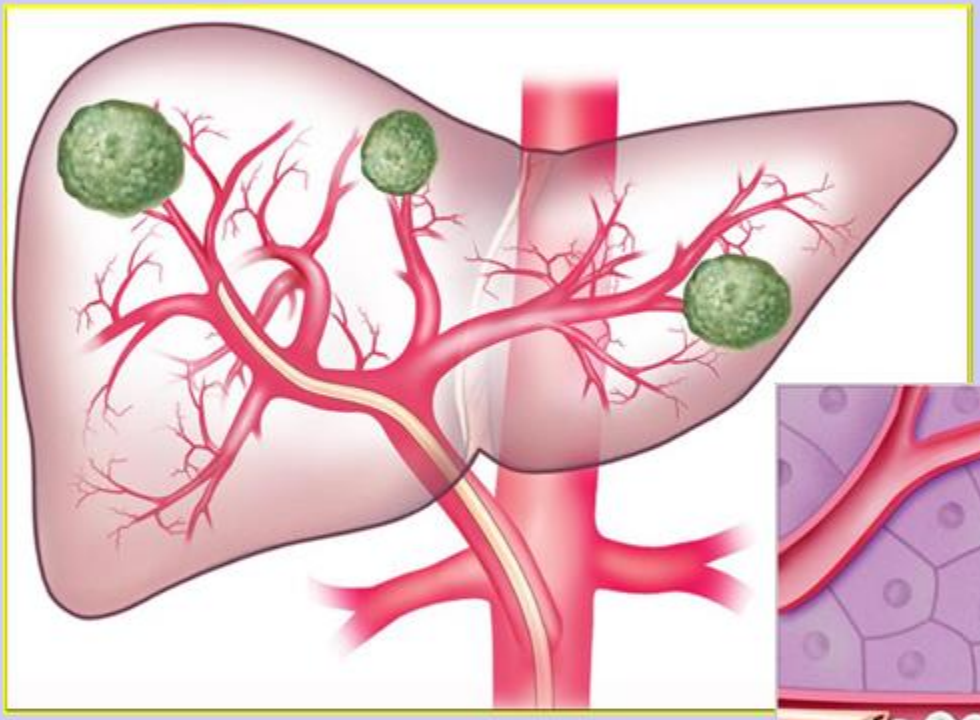
Local treatment for liver metastases: RFA

DFS at 1 yr	52%
DFS at 3 yrs.	16%
DFS of resection	18 months
DFS of RFA +/- resection	7.4 months
OS at 1 yr	91%
OS at 5 yrs.	27%
Recurrence rate of RFA alone	84%

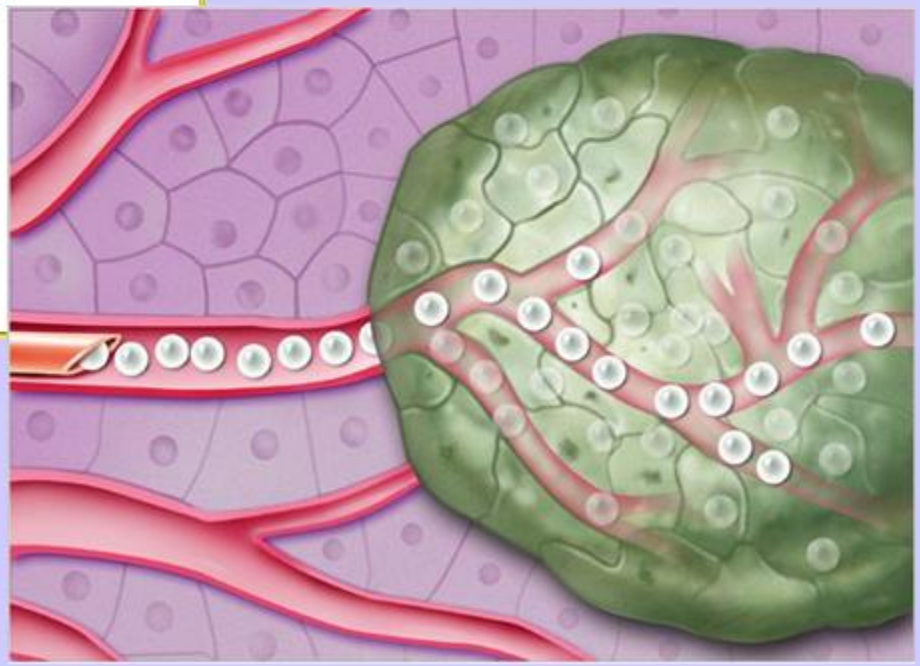
> **Continuation of TKI treatment is absolutely crucial**

Pawlik, Arch Surg 2006; 141: 537

Locoregional therapy for multiple liver mets: **SIRT**
(Selective Internal Radiation Therapy)



Liver- supplied by two blood vessels:
more arterial vessels within the tumor ratio - 3:1



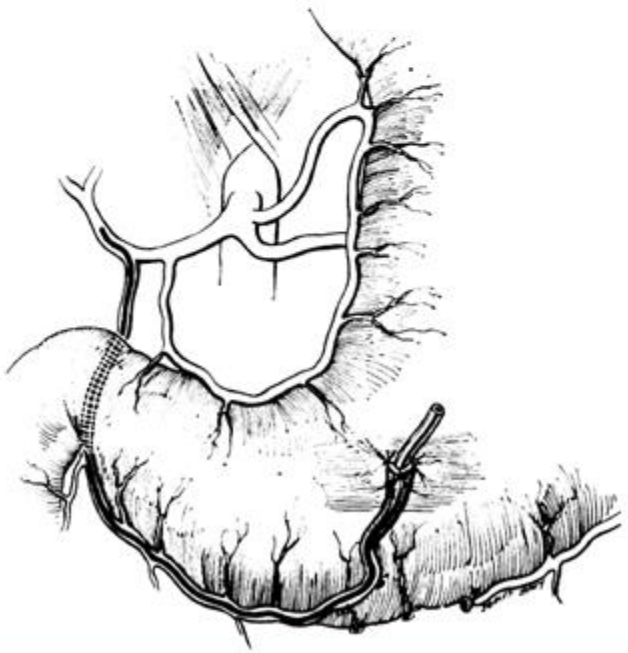
- normal liver tissue > 75% portal vein

Locoregional therapy for multiple liver mets: **SIRT**

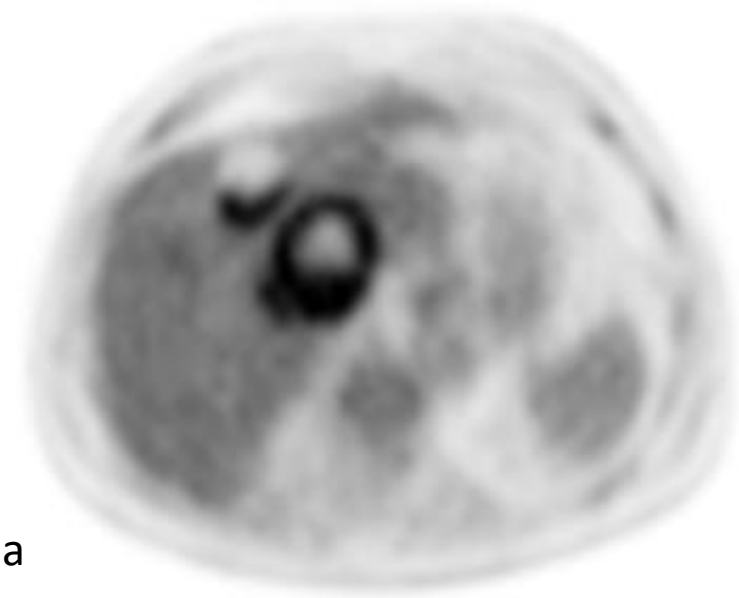
Treatment of Inoperable Primary Pancreatic and Liver Cancer by the Intra-Arterial Administration of Radioactive Isotopes (Y^{90} Radiating Microspheres) *

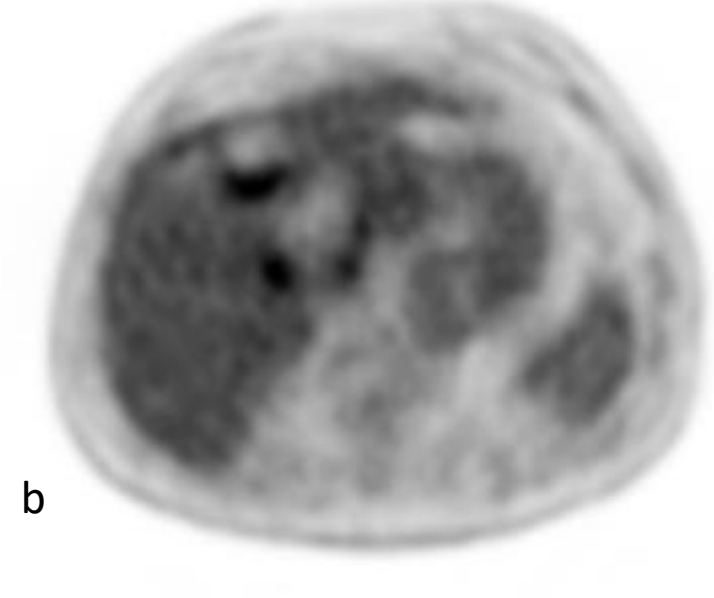
IRVING M. ARIEL, M.D., F.A.C.S.

From the Pack Medical Foundation, and the Division of Radioactive Isotopes, Department of Radiation Therapy, Hospital for Joint Diseases, New York, New York

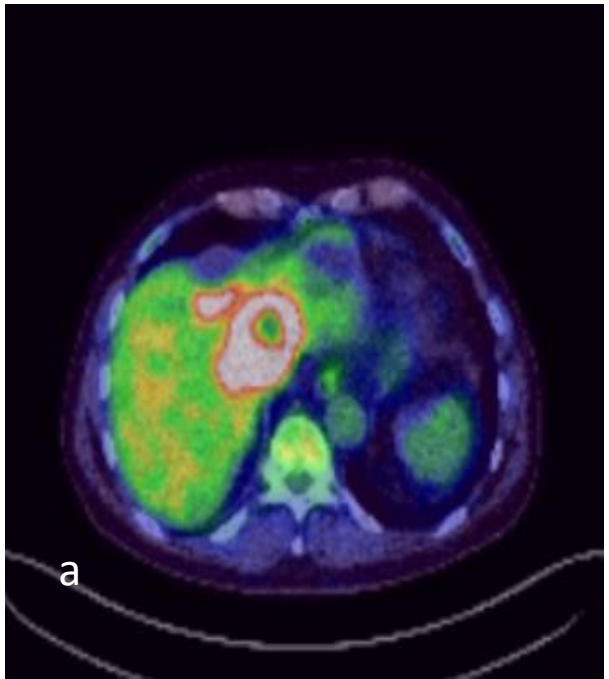


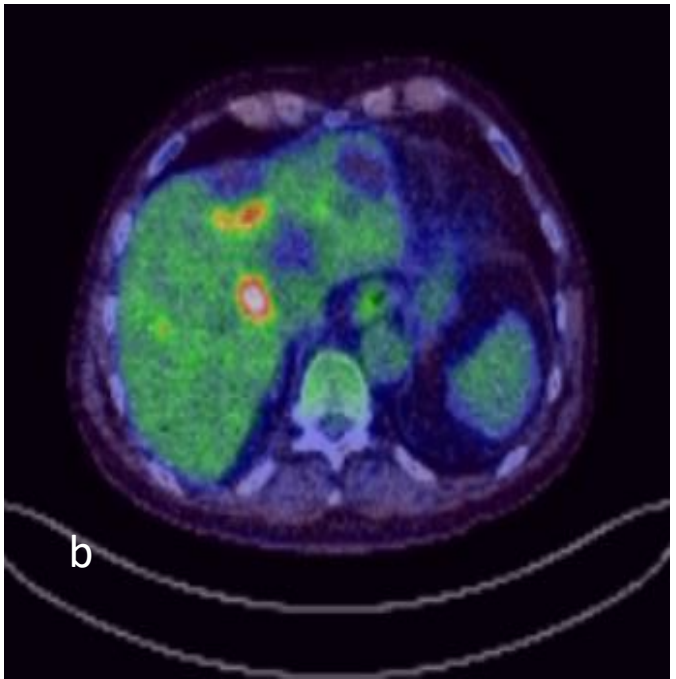
Ariel IM. 1965 Aug; *Ann Surg* 162: 267 - 278





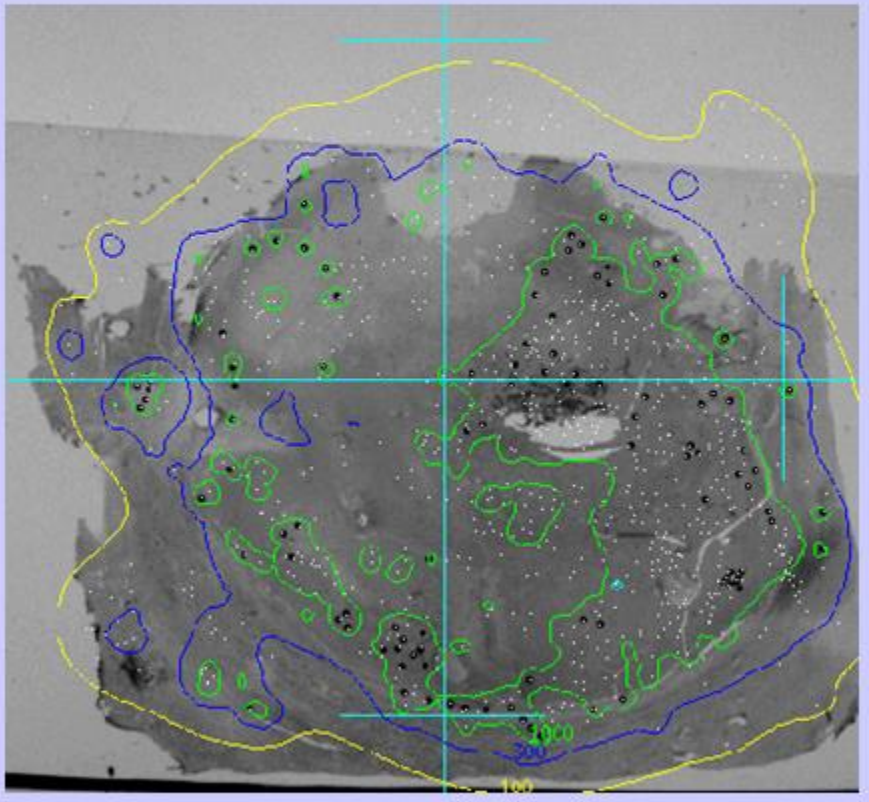
Patient #7 PET CT a) pre SIRT, b) Partial Response 11 months post SIRT with reduced SUV of the lesions.





Locoregional therapy for multiple liver mets: **SIRT**

- Radiation dose locally 120 Gy
- Steep dose decline < 100 Gy
- Up to 4mm outside of tumor
- Ø significant hepatitis



Courtesy of A. Kennedy, MD

SIRT: Result in GIST

June 14, 2009

Sep 9, 2010

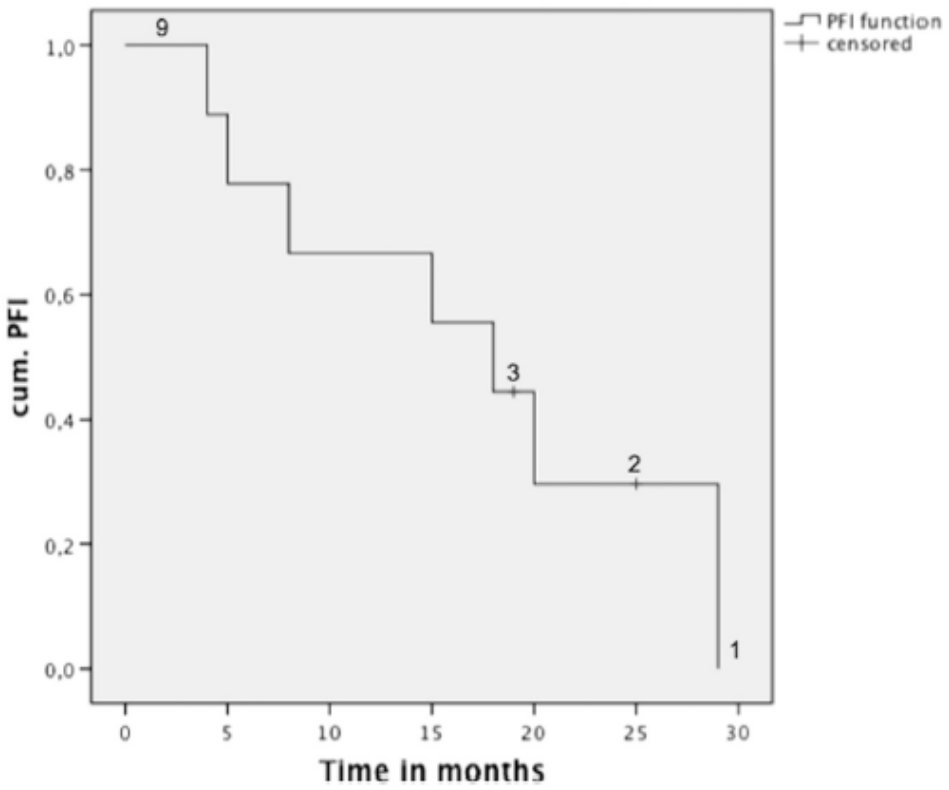
SIRT and GIST: University Medical Center Mannheim

Patient	Initial diagnosis	Therapy pre SIRT	Therapy post SIRT
1. f 34y.o.	06/99	IM, IM 600 + RAD-001, sunitinib	sunitinib, nilotinib, Regorafenib
2. f 52y.o.	09/06	IM, IM 600 + RAD-001, sunitinib	IM 800, nilotinib, Sorafenib
3. m 73y.o.	05/05	IM, IM 800, sunitinib, nilotinib	sorafenib, everolimus
4. m 55y.o.	09/03	IM, IM 600, IM 800	sunitinib, IM 600 + RAD-00s
5. m 55y.o.	07/07	IM, IM 800, IM 1000, sunitinib	sunitinib, nilotinib, sorafenib
6. m 61y.o.	03/07	IM, sunitinib, sorafenib	IM 800
7. m 58y.o.	06/08	IM, sunitinib	sorafenib
8. m 48y.o.	12/04	IM, IM 800, sorafenib	nilotinib
9. m 74y.o.	08/11	IM, sunitinib	pazopanib

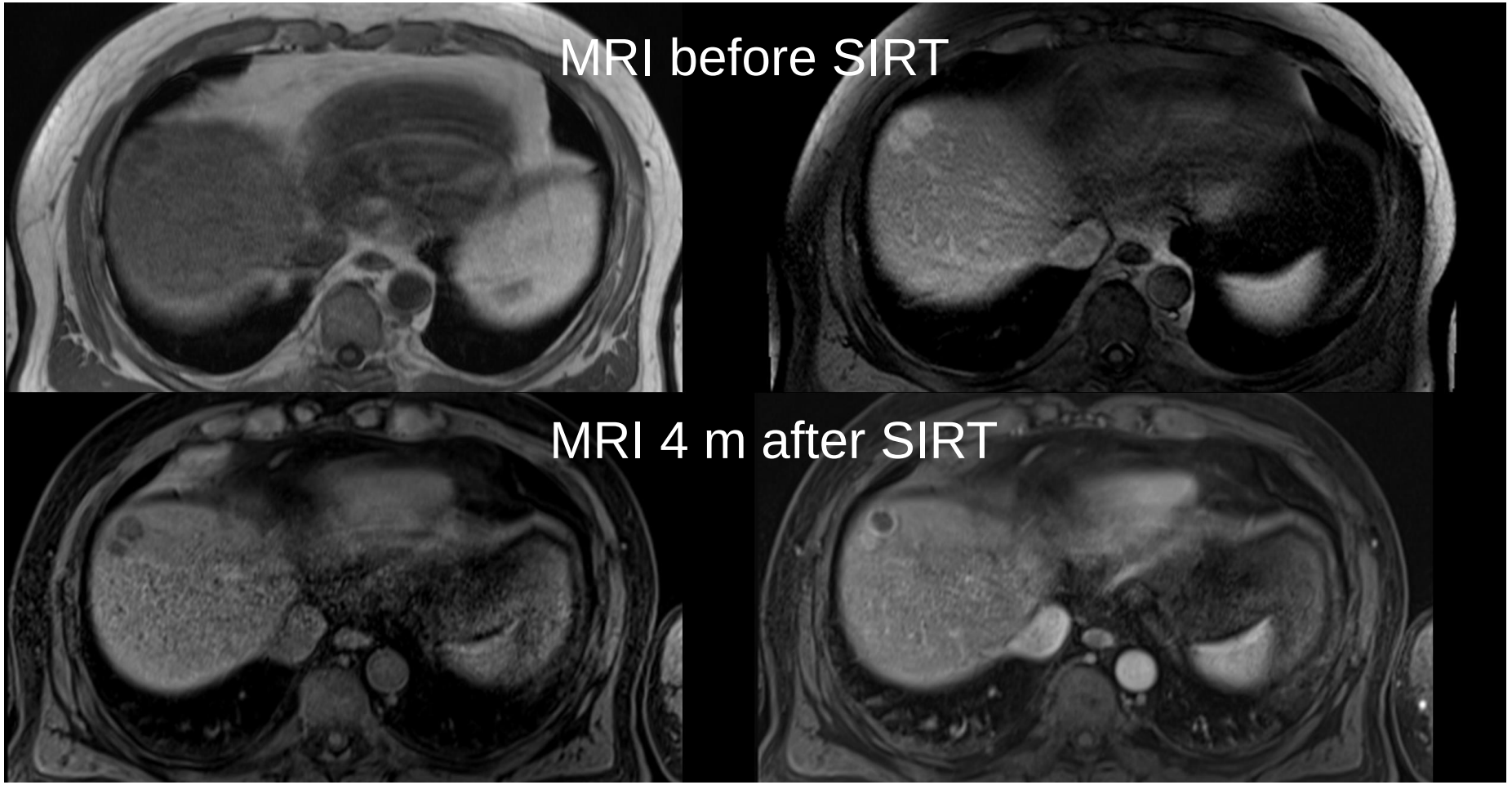
Radioembolization in Patients with Progressive Gastrointestinal Stromal Tumor Liver Metastases Undergoing Treatment with Tyrosine Kinase Inhibitors

Nils Rathmann, MD, Steffen J. Diehl, MD, Dietmar Dinter, MD, Jochen Schütte, MD, Daniel Pink, MD, Stefan O. Schoenberg, MD, and Peter Hohenberger, MD

J Vasc Interv Radiol 2015; 26:231–238



Hepatic-Progression free survival: mean 19.5 mos



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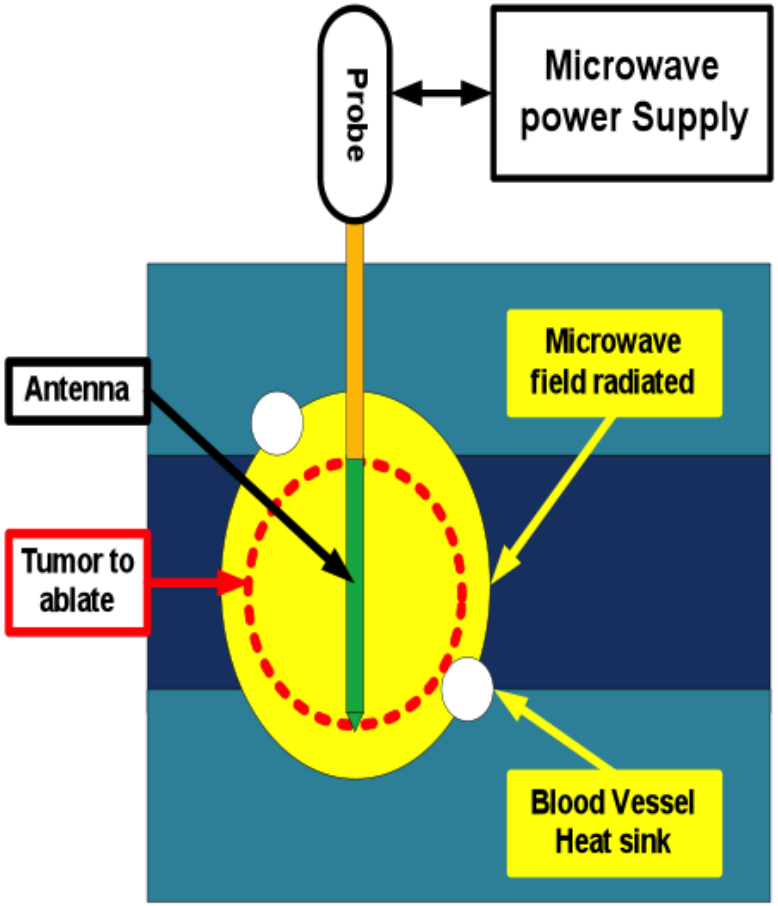
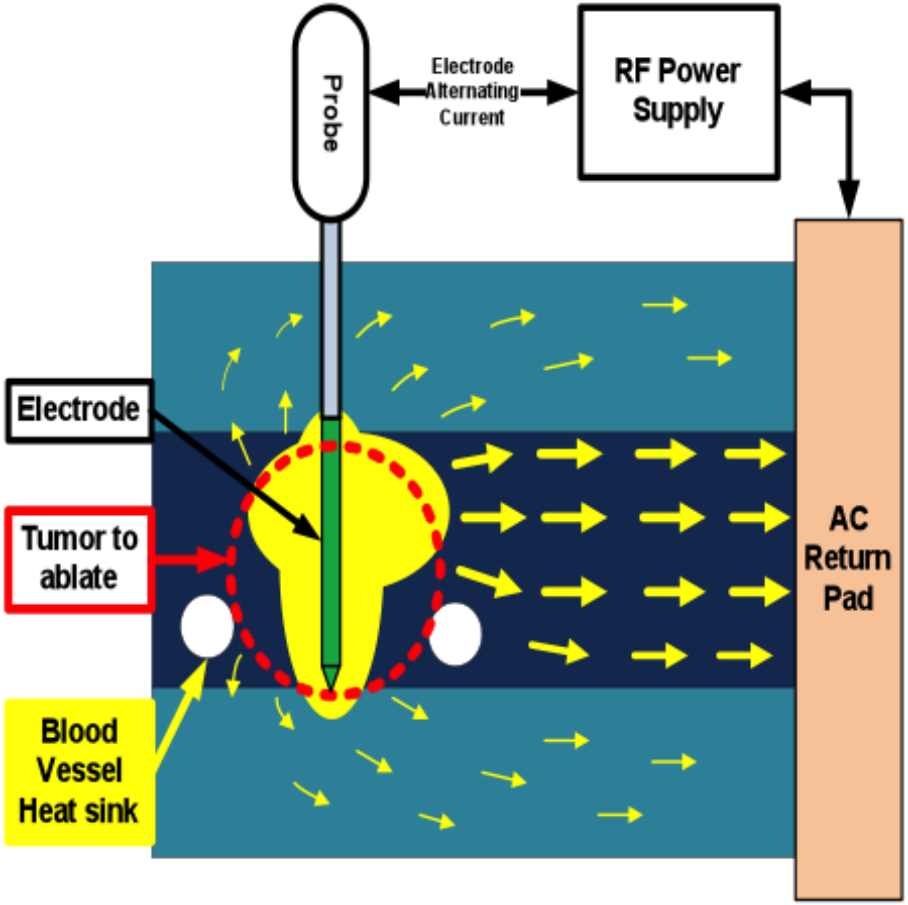
Percutaneous Ablation

Microwave (MW)



Radiofrequency (RF)

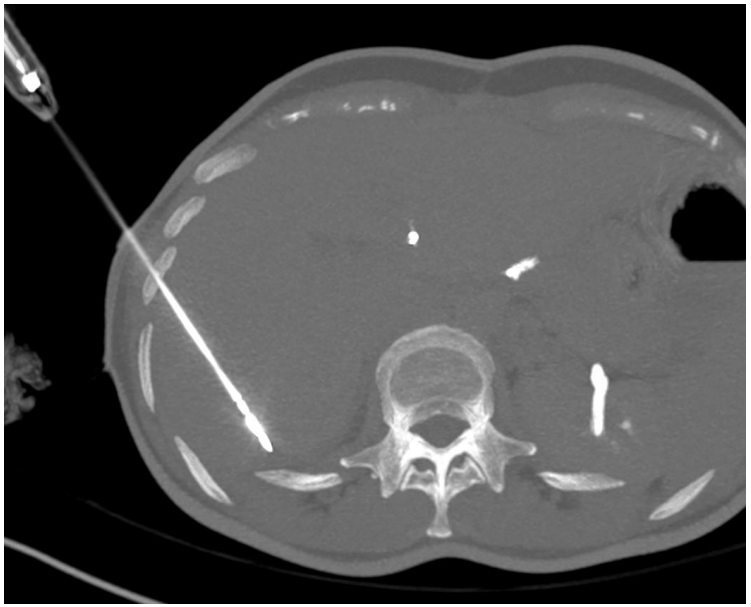


67 years, male, GIST liver metastasis, CT before SIRT

67 years, male GIST liver metastasis, PET before SIRT

67 years, GIST liver metastasis, PET after SIRT

67 years, GIST liver metastasis



PET after SIRT/MWA

Irreversible Electroporation (IRE)

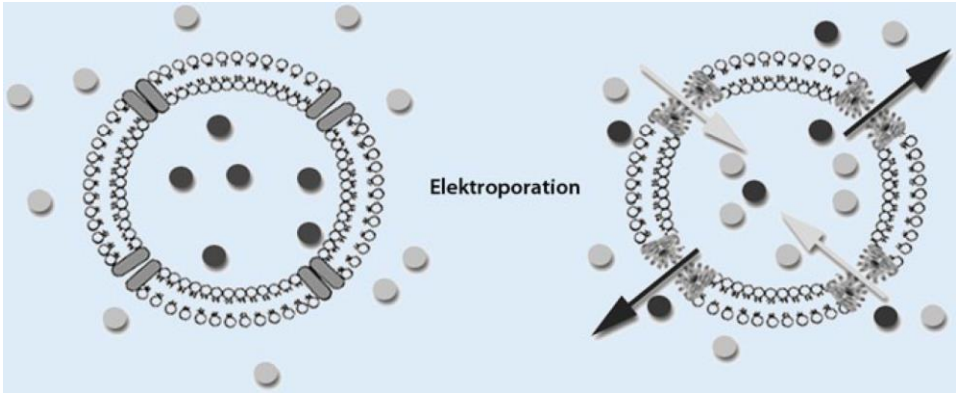
Short-pulse electric fields

Destruction of cell membrane

Apoptosis induction

Advantages: No destruction of blood vessels and connective tissue therefore less vascular complications and new application

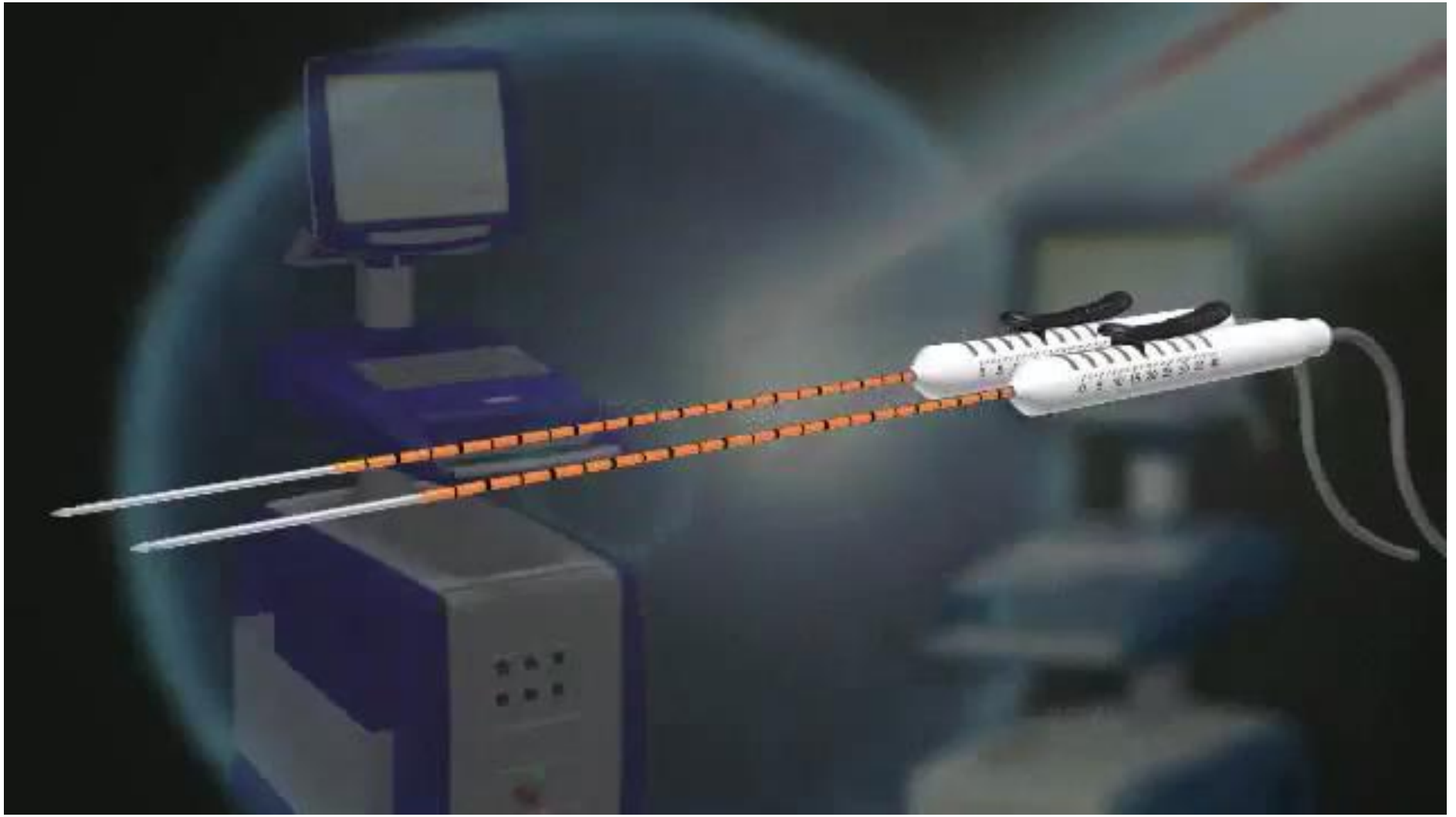
Disadvantages: time-consuming and general anaesthesia required



What is IRE?

- Irreversible Elektroporation (IRE) is a minimally-invasive tissue ablation technique
- Selective destruction of tumor areas

- Strong, but locally limited electric fields.
- FDA and CE approved
- No big prospective studies
- Structures like blood vessels are not damaged



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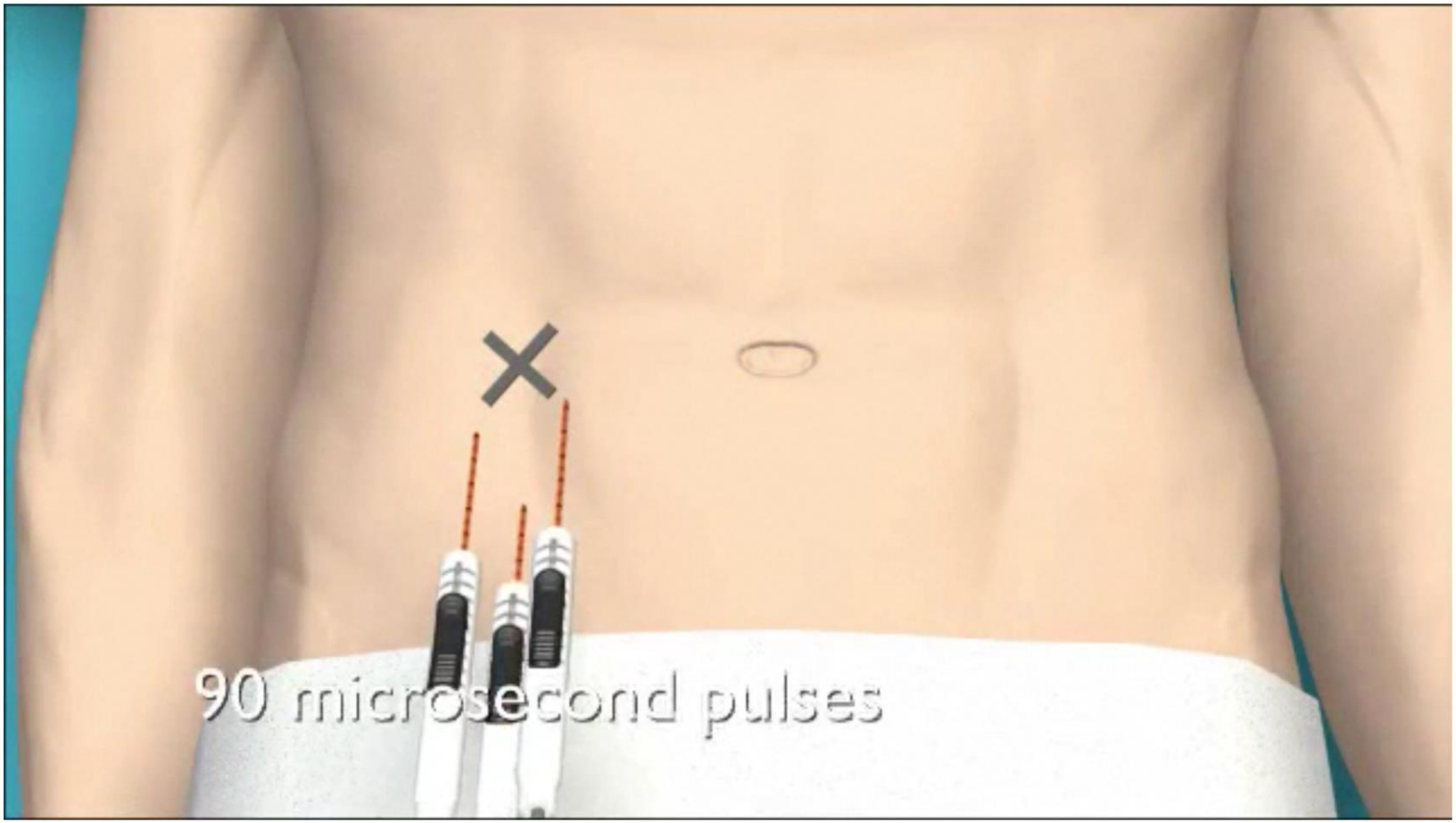
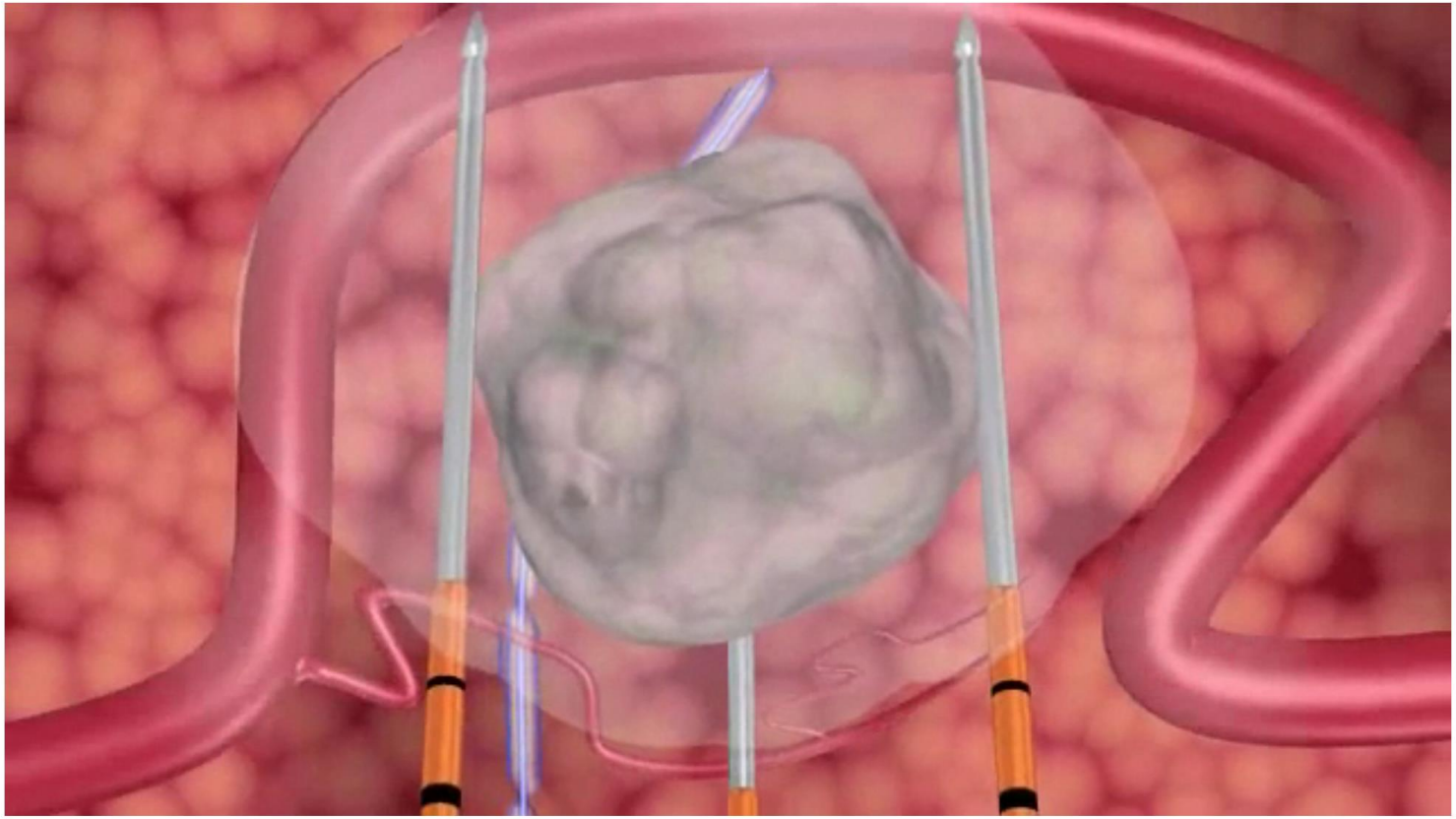
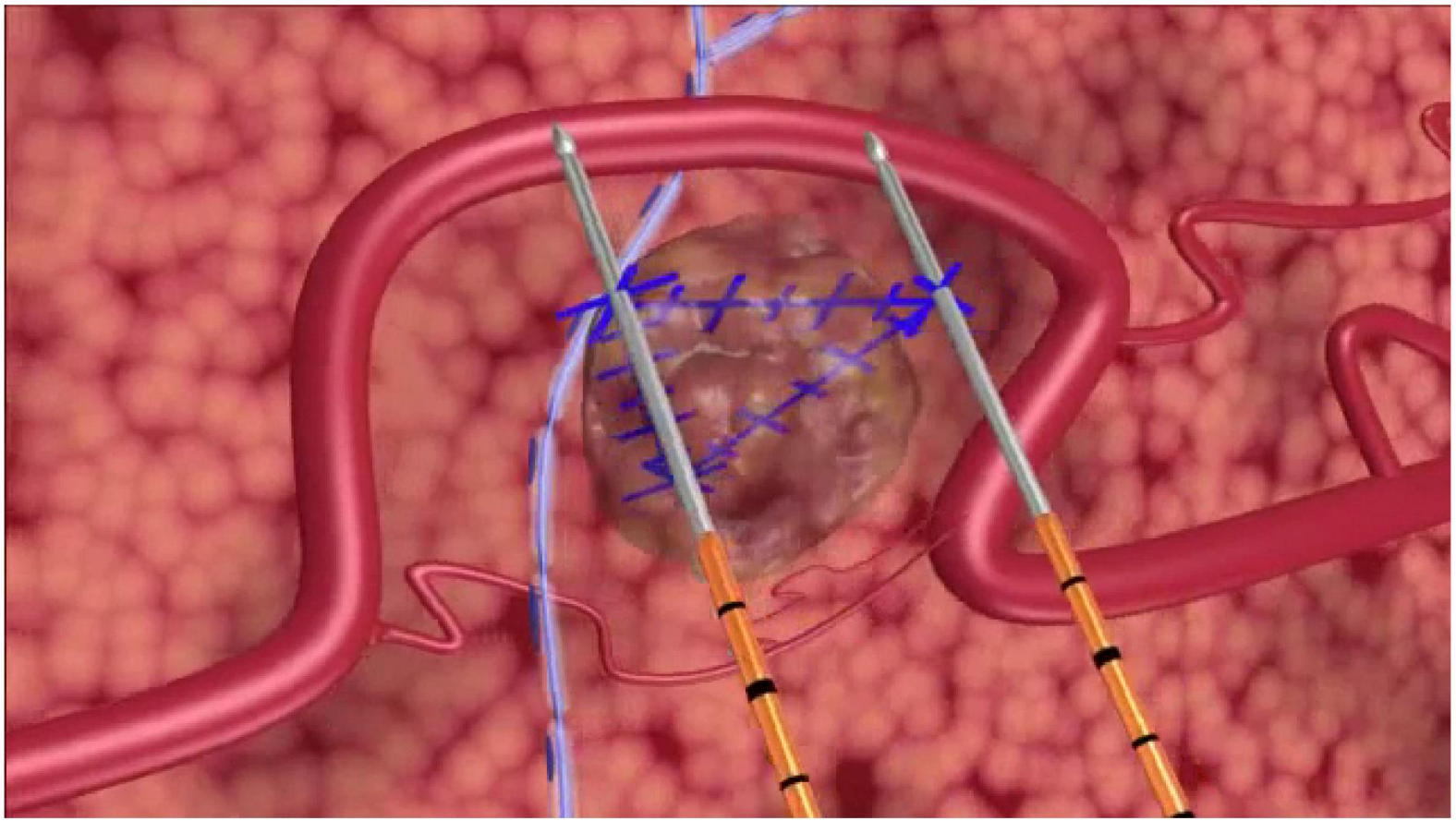
Irreversible Electroporation (IRE)



Irreversible Electroporation



Irreversible Electroporation



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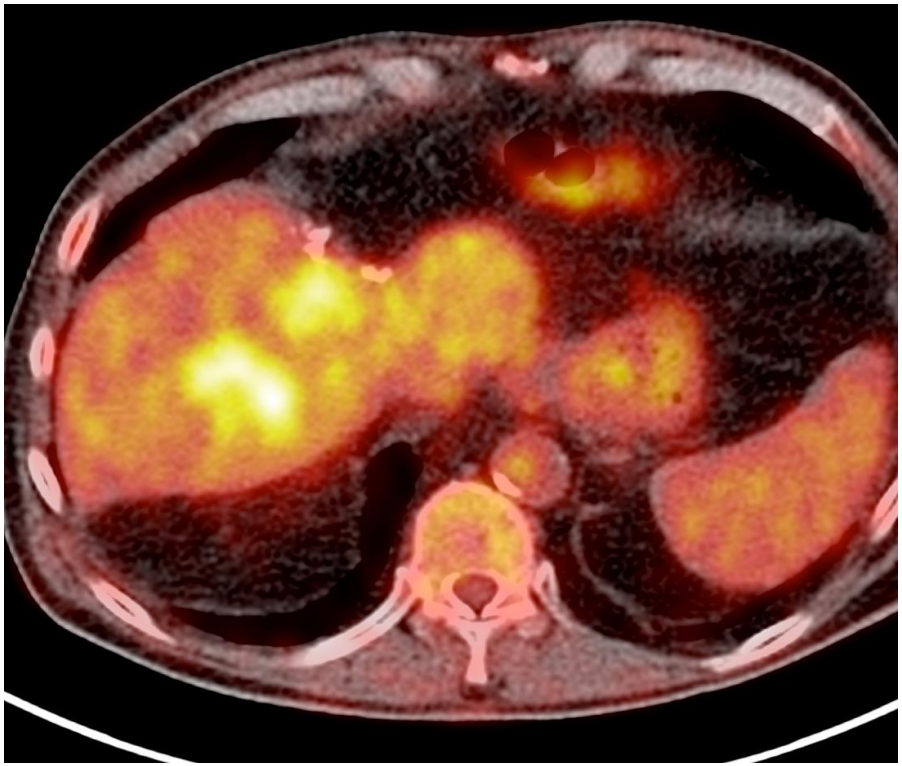
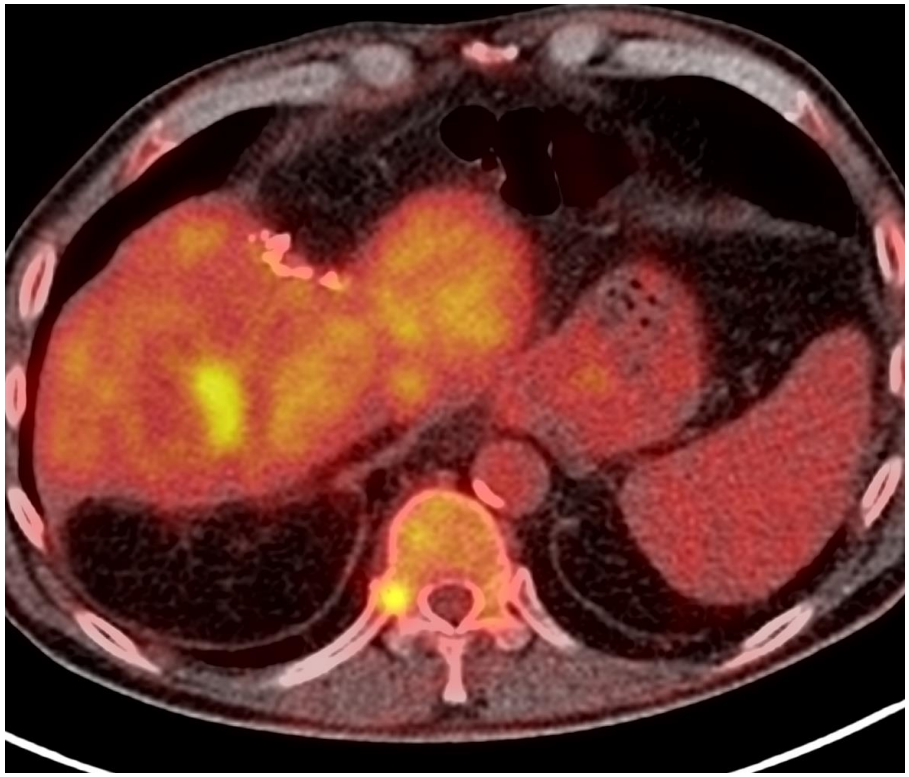
Case:

58 y.o. male, c.a. GIST of stomach, c.a. liver resection, recurrent liver metastases after several TKIs



PET-CT before SIRT



PET-CT after SIRT

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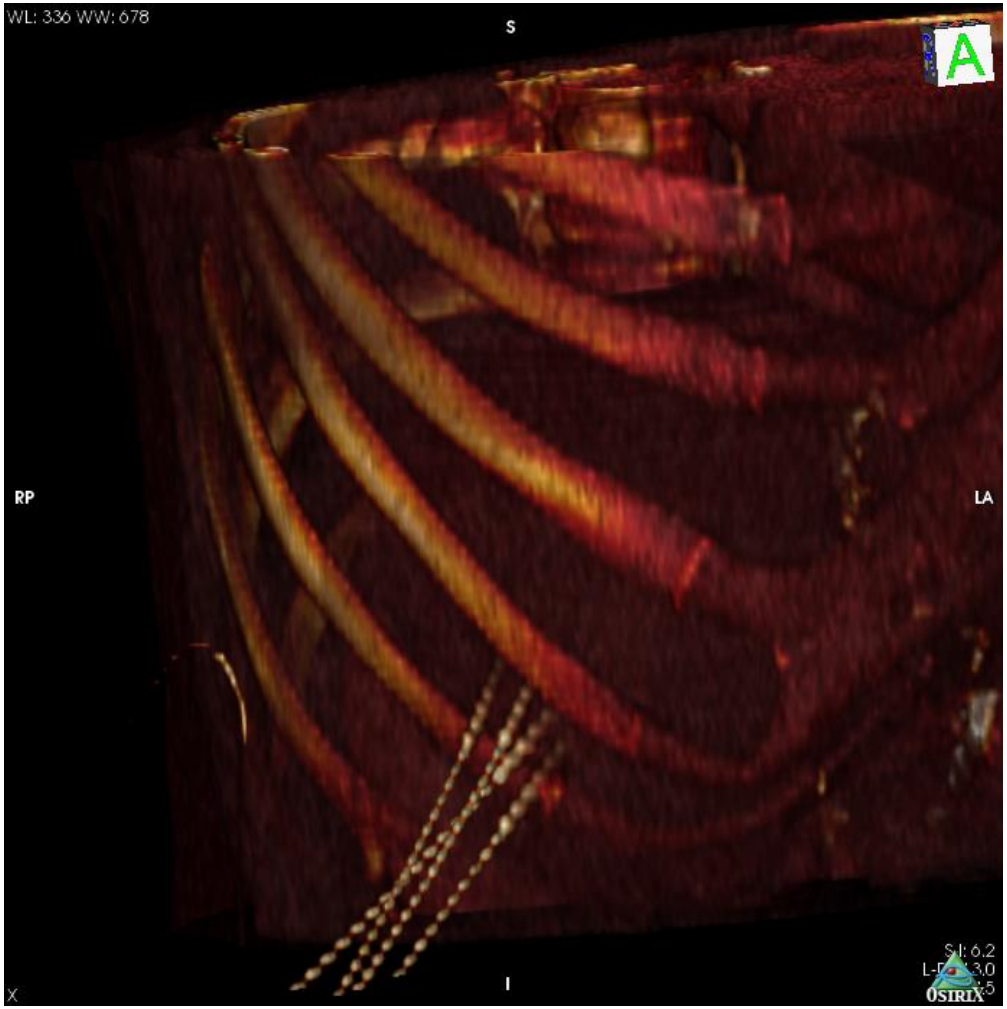
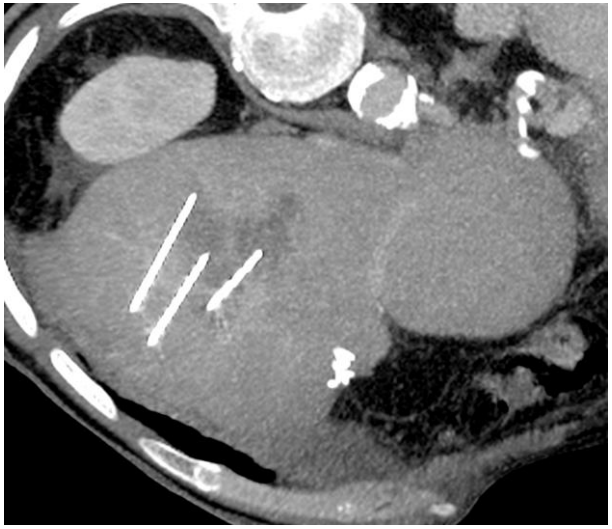
Irreversible Electroporation

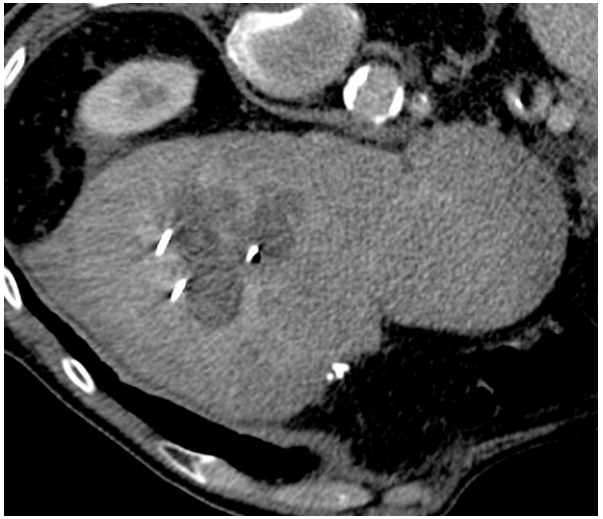
Control CT scan
3D Volume IRE plan



Irreversible Electroporation



1.

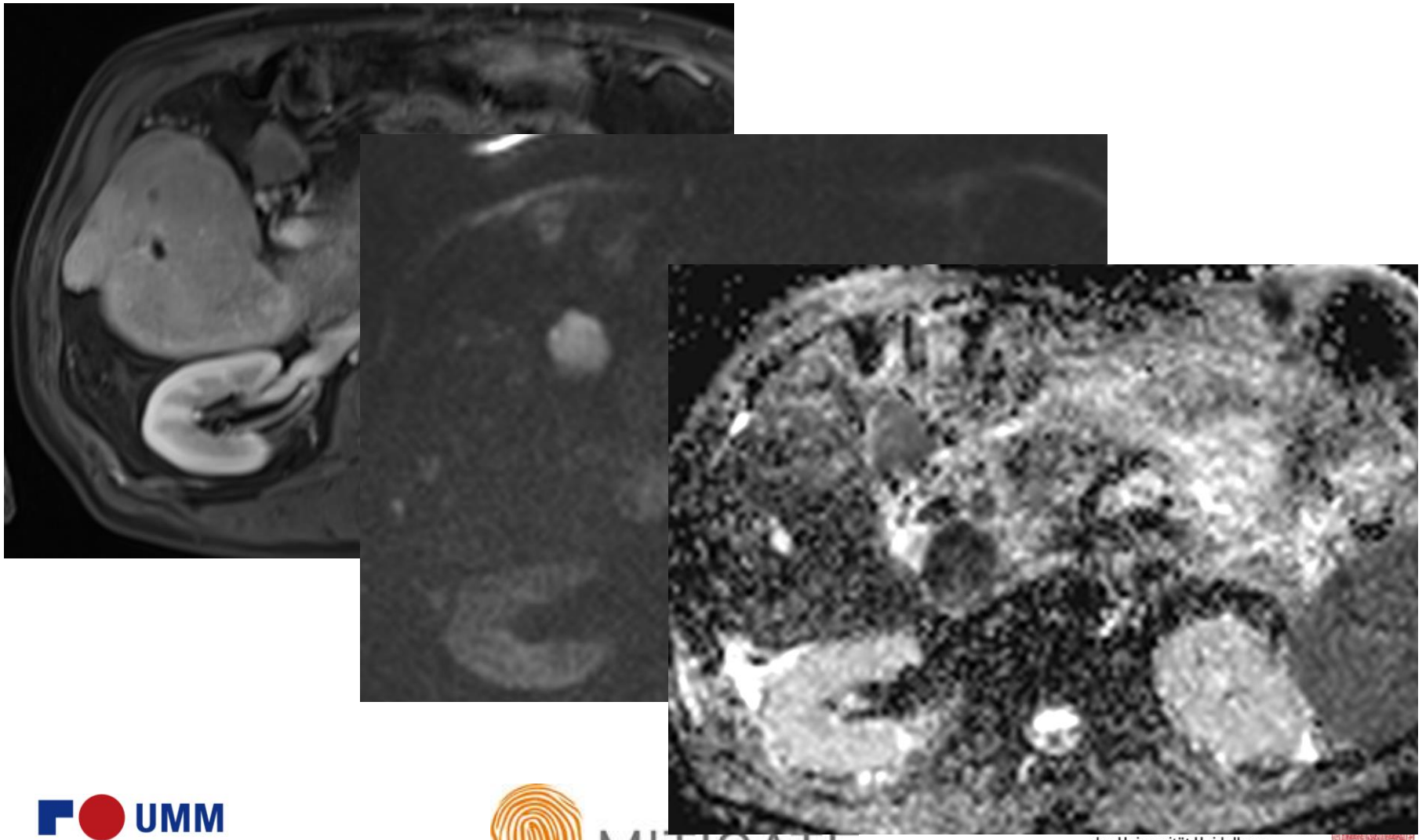


2.

3.

Control scans during procedure (1. and 2.) and follow up scan (3.)

Irreversible Electroporation
Mesenteric Lesions in GIST Patients



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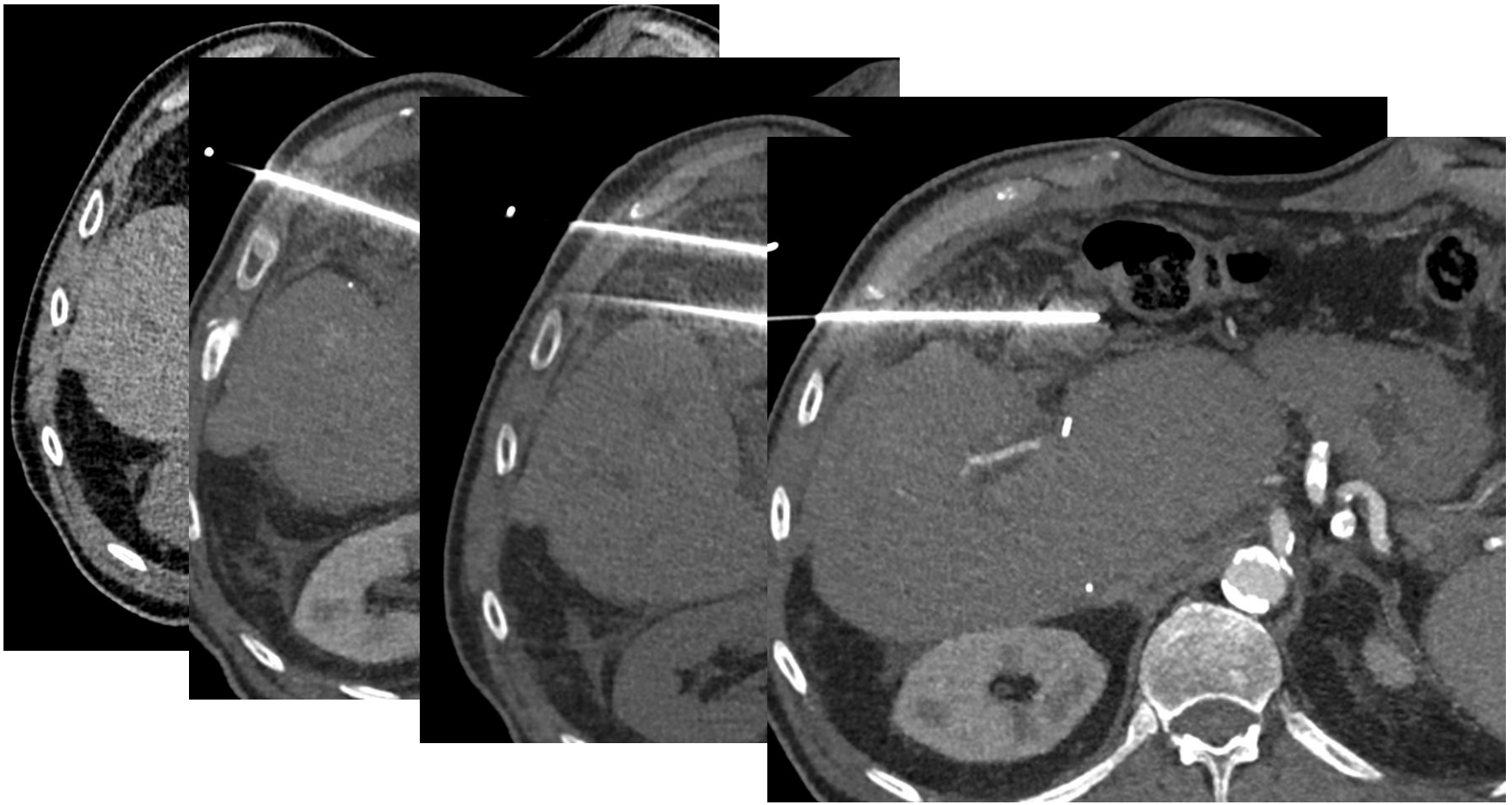
Irreversible Electroporation
Mesenteric Lesions in GIST Patients



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Irreversible Electroporation
Mesenteric Lesions in GIST Patients

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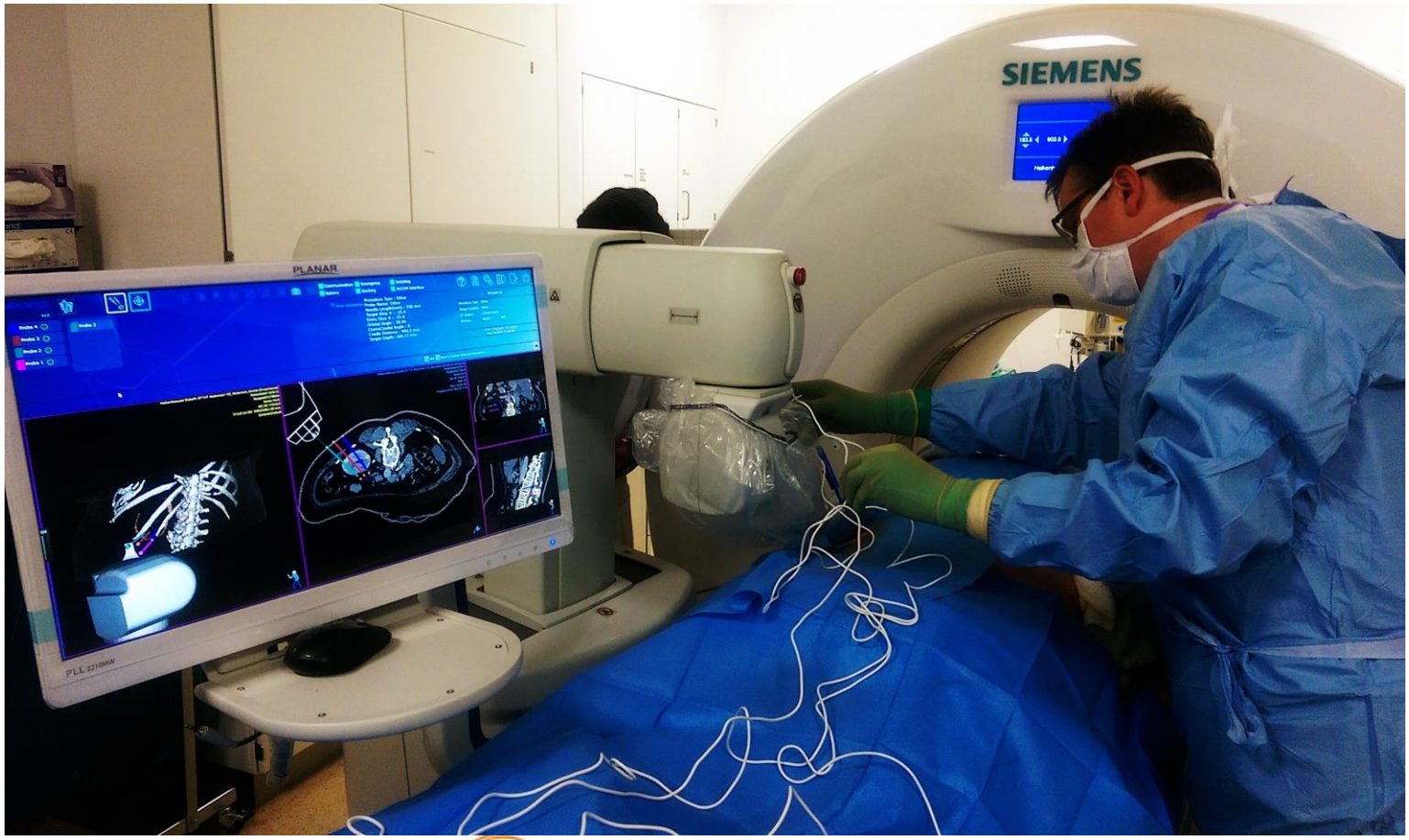
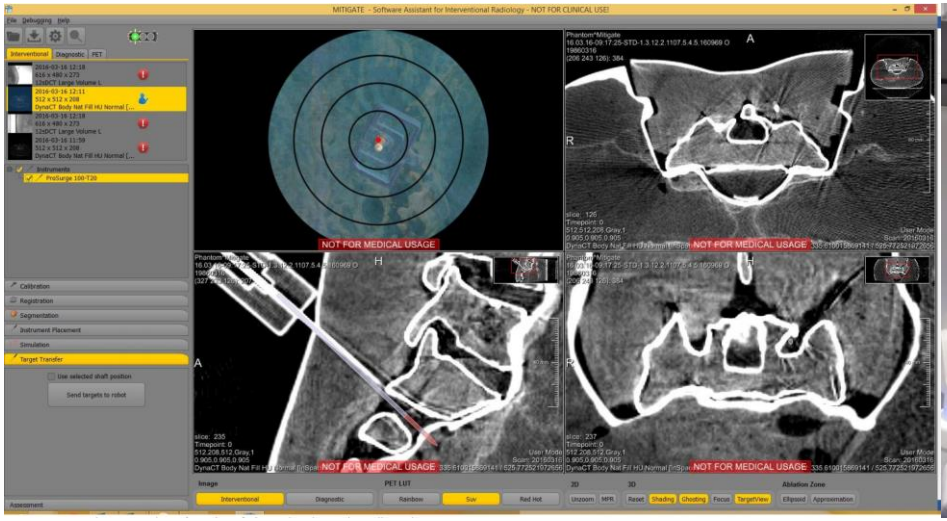
Ablation and Robotic Assistance

MAXIO, Perfint healthcare, India, Software Version 2.1

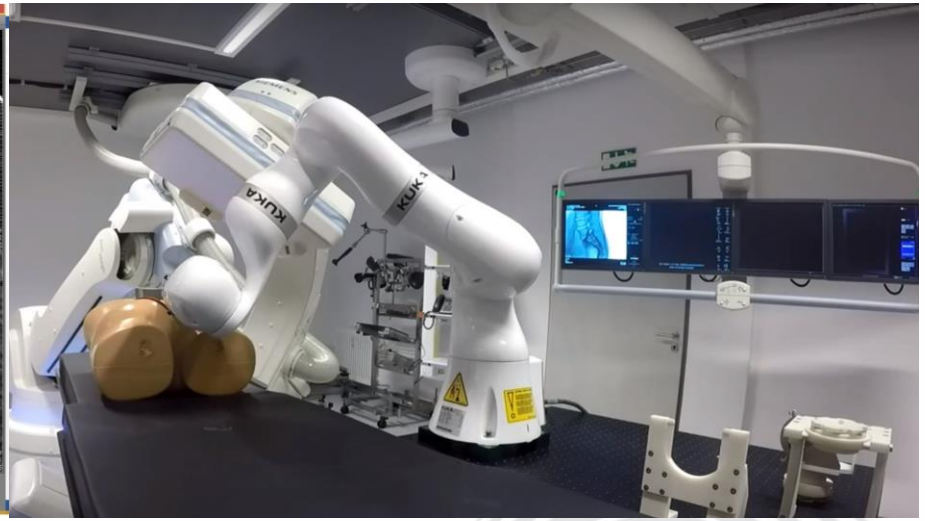


Assisting Device: Technology Concept

Robot Assistant with imaging feedback



1.Planning software



2. Prototype performing intervention on phantom

In cooperation with Fraunhofer IPA

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no 602306.

Performance of a Robotic Assistance Device in Computed Tomography-Guided Percutaneous Diagnostic and Therapeutic Procedures

Arman Smakic[1] · Nils Rathmann[1] · Michael Kostrzewa[1] · Stefan O. Schönberg[1] · Christel Weiß[2] · Steffen J. Diehl[1]

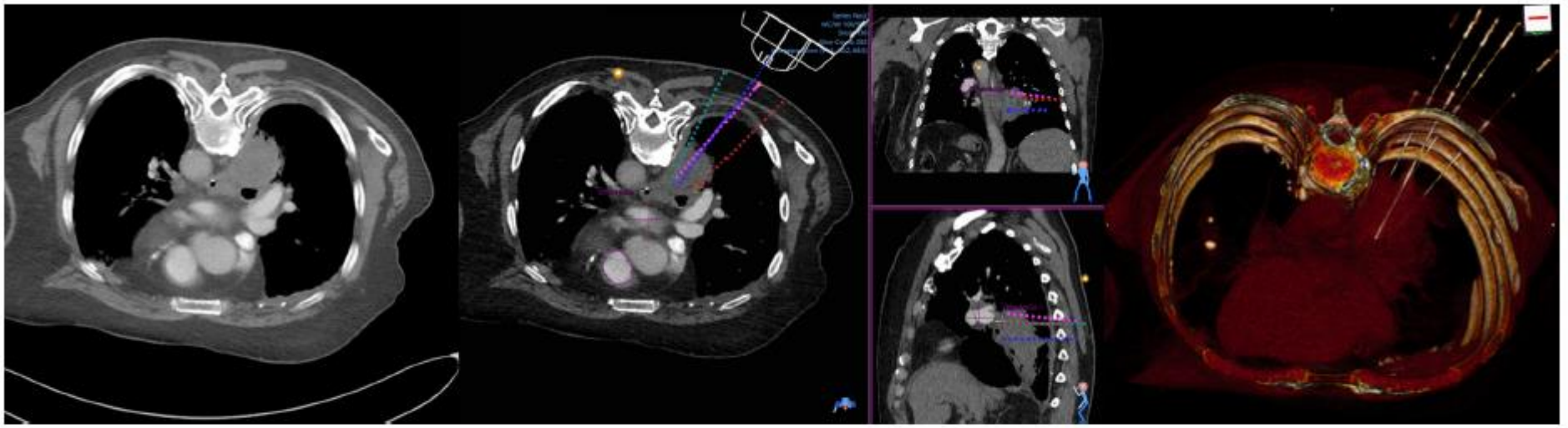


Fig. 1 Robotic assistance procedure. Intervention planning scan (left), planned needle paths (middle) and volume rendering of the verification scan (right) of an IRE tumor ablation in the lung using the navigation system for needle placement (Size 1747 × 470)

Target and patients' characteristics	Group		*p* value
	Navigation system	Control	
Mean target size (mm)	29.6 ± 1.7	25 ± 1.0	0.7
Mean target depth (mm)	100.5 ± 5.2	76.6 ± 2.7	0.6
Mean patient age (years)	65 ± 10.9	66 ± 8.5	
Patient sex (female, male)	43, 46	64, 37	
Number of biopsies	18	55	
Number of MWA	20	26	
Number of IRE	17	20	

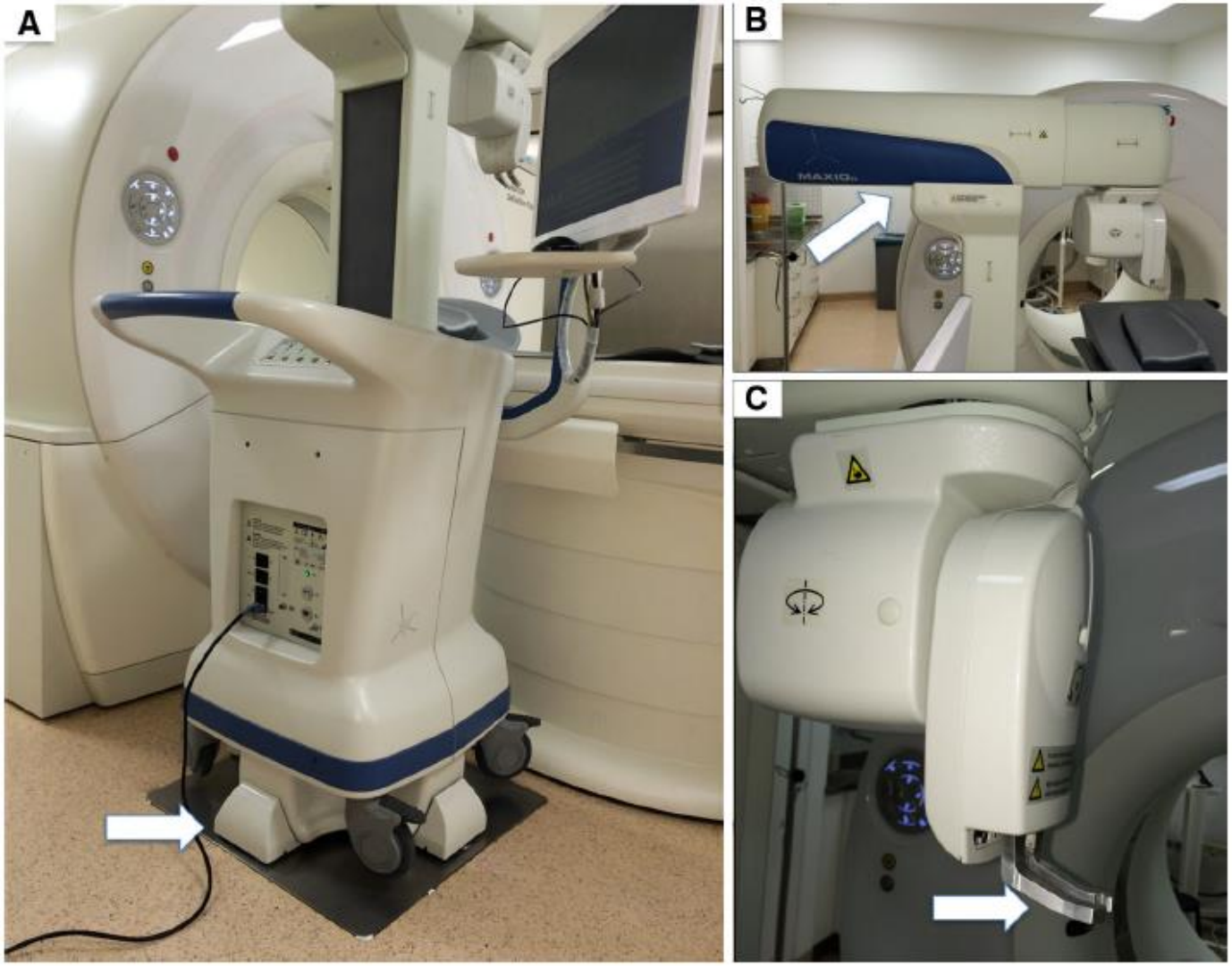


Fig. 2 Setup of the robotic assistance device: **A** Device attached next to CT table on registration plate (arrow). **B** Robotic arm of the navigation system (arrow). **C** Needle holder of the robotic arm (arrow) (Size 1710 × 1346)

Table 2 Mean deviation from the planned target in the navigation system group and the comparison group within the subgroups anesthesia method and puncture plane with regard to targets displaceable and not displaceable on breathing

Subgroup analysis	Mean deviation form planned target (mm)		*p* value
	Navigation system group	Comparison group	
All performed punctures	1.2 (± 1.6)	2.6 (± 1.1)	< 0.001
Anesthesia method			
General target displaceable on breathing	0.7 (± 0.8)	2.2 (± 1.1)	< 0.001
General target not displaceable on breathing	0.5 (± 0.9)	1.9(± 1.3)	< 0.001
Local target displaceable on breathing	2.5 (± 1.5)	3.4(± 1.1)	0.001
Local target not displaceable on breathing	1.5 (± 1.5)	3.2 (± 1.0)	< 0.001
Puncture plane			
Out-of-plane target displaceable on breathing	1.3 (± 1.1)	3.4 (± 1.2)	< 0.001
Out-of-plane target not displaceable on breathing	1.1 (± 1.0)	3.1 (± 1.1)	< 0.001
In-plane target displaceable on breathing	1.2 (± 1.1)	1.8 (± 1.0)	0.03
In-plane target not displaceable on breathing	1.0 (± 0.8)	1.5 (± 1.4)	0.04

Table 3 Number of replacements needed to insert the probe until the target was reached

Procedure	Group		*p* value
	Navigation system	Control	
All punctures	0.3 ± 0.4	1.8 ± 0.7	< 0.001
Number of replacements in-plane punctures	0.22 ± 0.6	1.56 ± 1.0	< 0.001
Number of replacements out-plane punctures	0.35 ± 0.6	2.3 ± 0.7	< 0.001

Table 4 Mean DLP in the navigation system and control group in in-plane and out-plane punctures

Procedure	Group		*p* value
	Navigation system	Control	
Mean DLP all punctures (mGy × cm)	139.5 ± 111.3	103.1 ± 72.2	0.093
Mean DLP in-plane punctures	113.7 ± 69.7	96.2 ± 53.2	0.2
Mean DLP out-plane punctures	157.1 ± 123.1	124.8 ± 79.9	0.13

Exploitation and impact

Exploitable product

Imaging probe based on a GLP2 peptide conjugated to a chelate agent for targeting GLP2 receptors

Exploitation strategy

- Application for patent protection after in vivo validation assays
- Submission of a manuscript to high impact factor journal
- Licensing of the products to pharmaceutical companies for large scale distribution

Impact for MITIGATE project

GLP-2 receptor is highly expressed in imatinib-resistant cells and human GIST samples. The synthesis of an imaging probe targeting GLP2-R is crucial for improving GIST diagnosis.

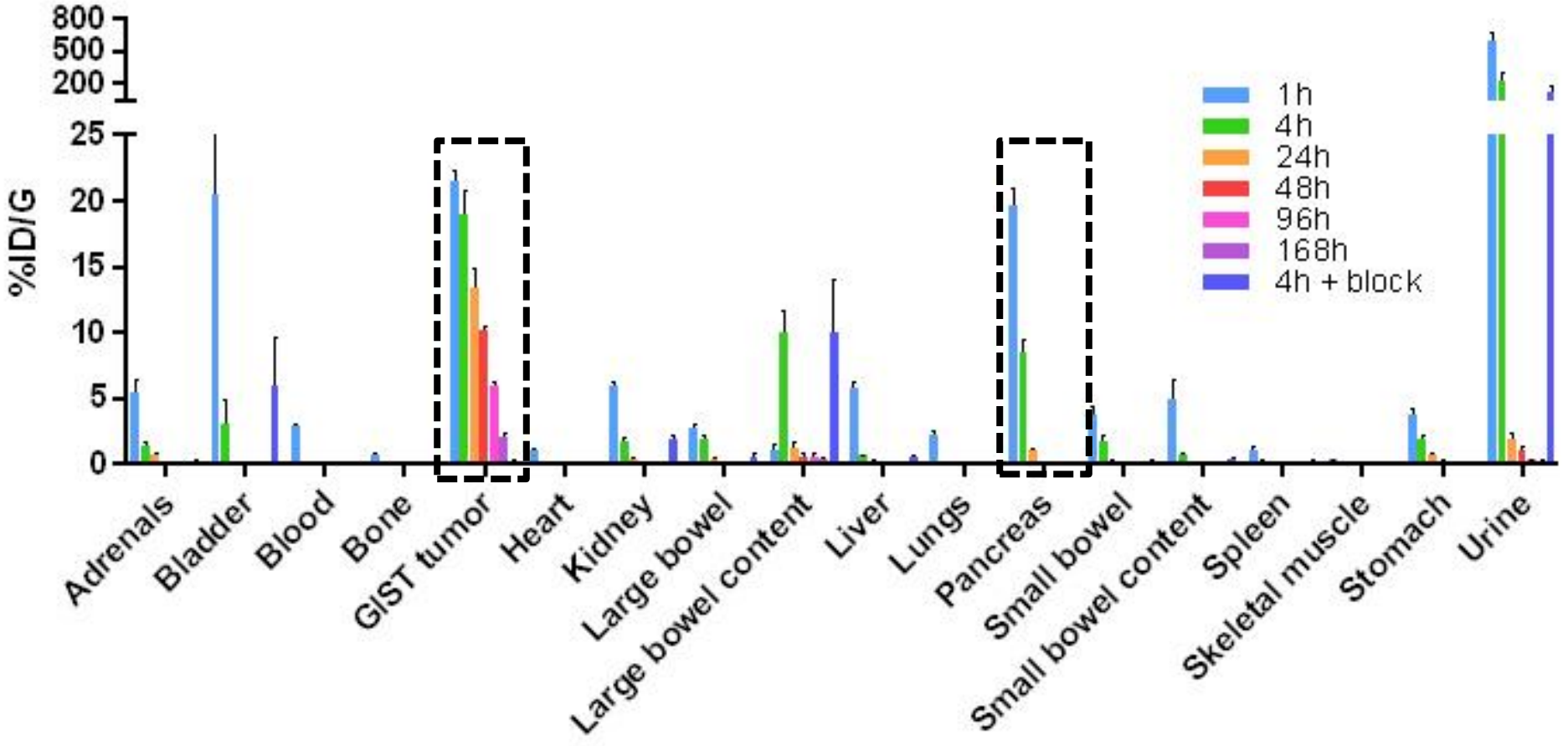
The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no 602306.

[^{68}Ga]NeoBOMB1 gegen GRP-2

- **Internalization to the cellular space:**
  NeoBOMB1 is internalized via active transport receptor-mediated internalization or endocytosis
- **Affinity to receptors:**
  NeoBOMB1 binds to a well-defined targeting receptor (GRPR) with a well-defined affinity.
- **Binding site:**
  NeoBOMB1 binds to cell membrane receptors

^{177}Lu-NeoBOMB1 biodistribution in GIST models

Biodistribution in GIST-882 bearing animals after iv injection of ^{177}Lu-NeoBOMB1
→ nice correlation with data obtained on PC-3 model



The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no 602300. www.mitigate-project.eu

Task 6.3 (lead MUI): First in human clinical trial

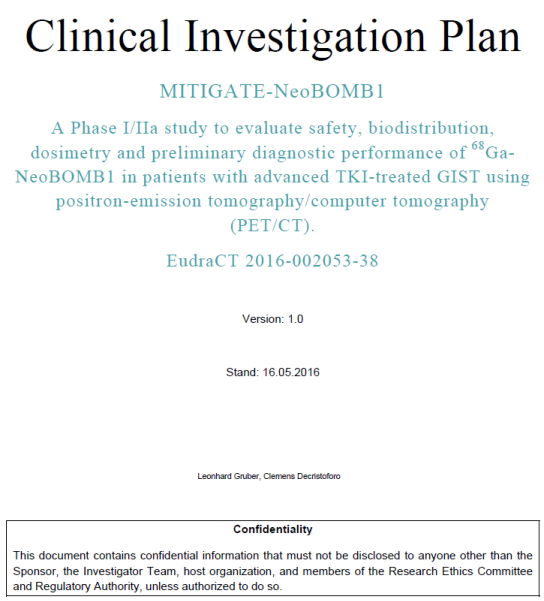
10-12 study participants

Part 1: Focus on safety, tolerability and pharmacokinetics for PBPK-modelling (~5-6 patients) **(Phase I)**

Part 2: Focus on GIST imaging with a focus on GRP-receptor affinity, demonstration of tumour targeting (~5-6 patients)

Confirmed GRP receptor expression

(Phase I/IIa)



Clinical Investigation Plan

MITIGATE-NeoBOMB1

A Phase I/IIa study to evaluate safety, biodistribution, dosimetry and preliminary diagnostic performance of ^{68}Ga-NeoBOMB1 in patients with advanced TKI-treated GIST using positron-emission tomography/computer tomography (PET/CT).

EudraCT 2016-002053-38

Version: 1.0

Stand: 16.05.2016

Leonhard Gruber, Clemens Decristoforo

Confidentiality

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organization, and members of the Research Ethics Committee and Regulatory Authority, unless authorized to do so.

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no 602306.

Task 6.2 (AAA, MUI, UHEI) Preclinical studies for translation of radiopharmaceutical development into the clinic

Kit for the preparation of ^{68}Ga-NeoBOMB1- AAA

- A pilot industrial batch of the lyophilized vial (CT00516001) was manufactured in **March 2016** (1000 vials scale)
- First GMP batch of the lyophilized vial (CT00516002), at a scale of 2000 vials, was manufactured in **May 2016** → **used for stability evaluation only**
- Second GMP batch of the lyophilized vial (CT00516003), at a scale of 2000 vials, was manufactured in **July 2016** → **used for radiolabeling testing at the hospital**
- Third GMP batch of the lyophilized vial (CT00516004), at a scale of 3000 vials, was manufactured in **Nov. 2016** → **currently in use for clinical study**
- **Long term stability** of the lyophilized vial up to 18 months and at three different storage temperatures (2-8° C, 25° C and 40° C) is ongoing
- **Current product shelf-life**: **12m @ 2-8 ° C**

Next steps :

→ product shelf-life extention (18m) depending on the ongoing stability program results

→ New GMP batch manufacturing of the lyophilized vial (CT00517001) in mid Sept 2017

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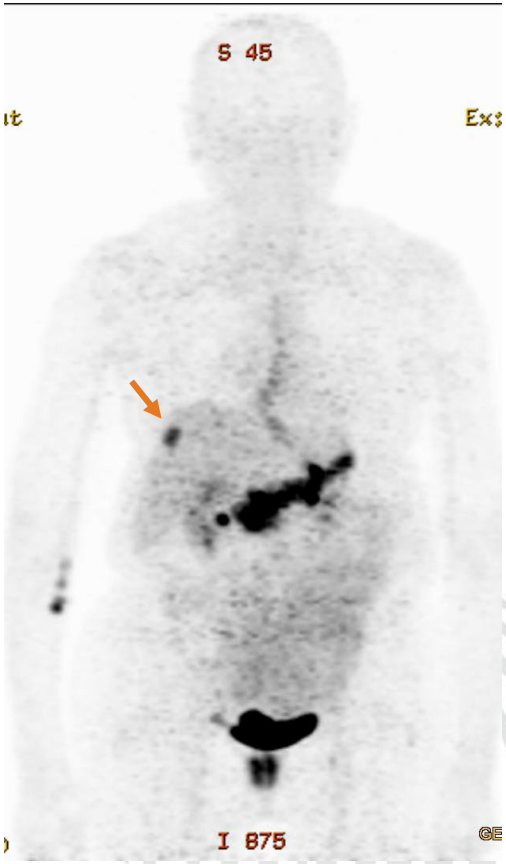
^{68}Ga-NeoBOMB1 Phase I/II study

MIP – images from PET/CT

60min

120min



180min

EudraCT No. 2016 002053-38

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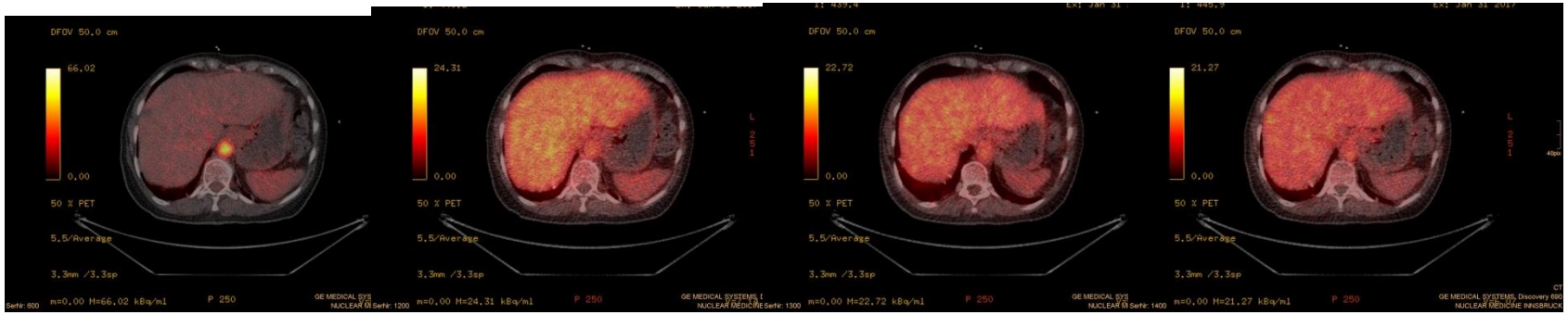
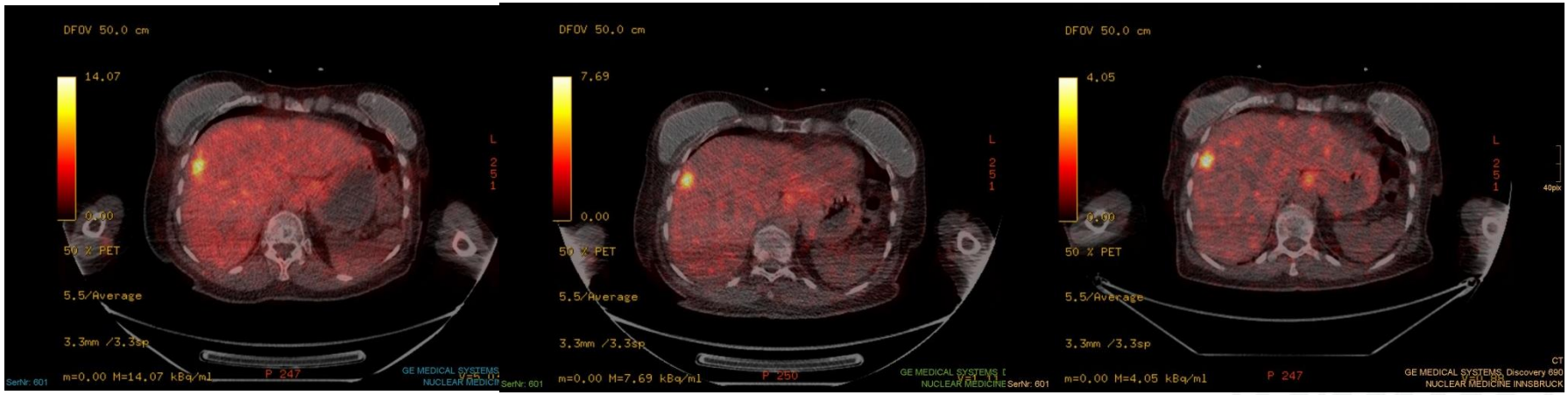
Liver metastasis- Patient 1

5min 10min 15min 20min

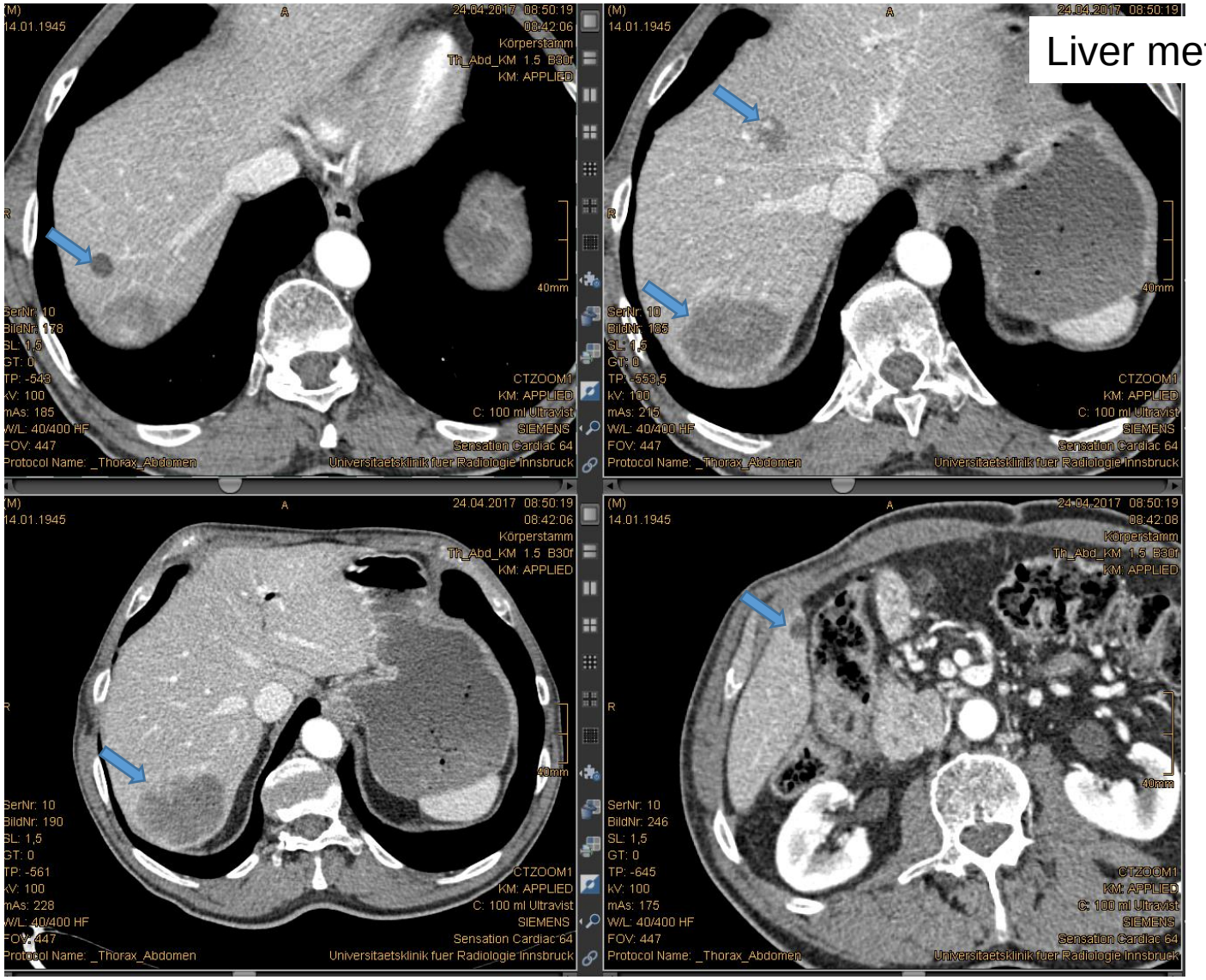




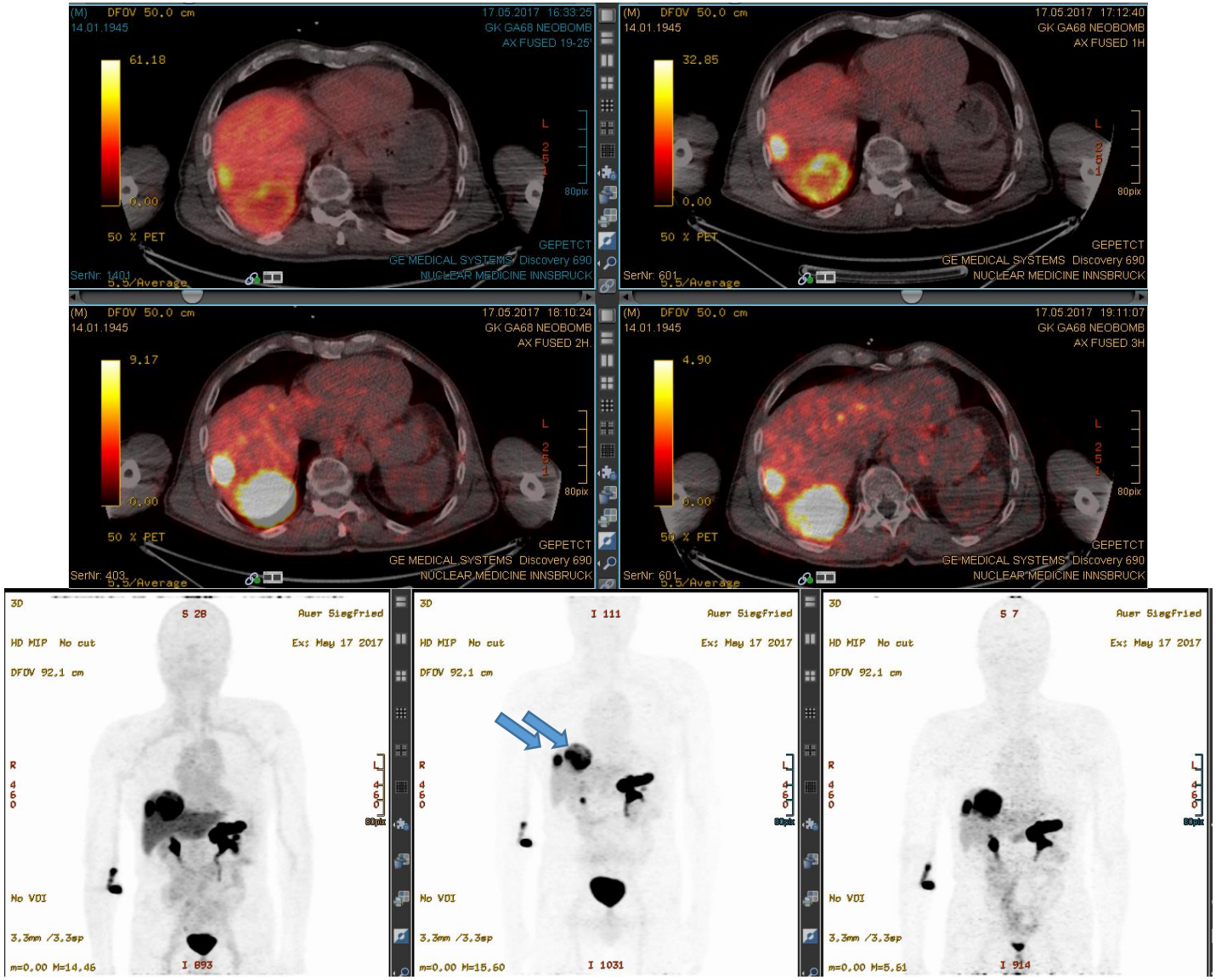
60min 120min 180min

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no 602306.

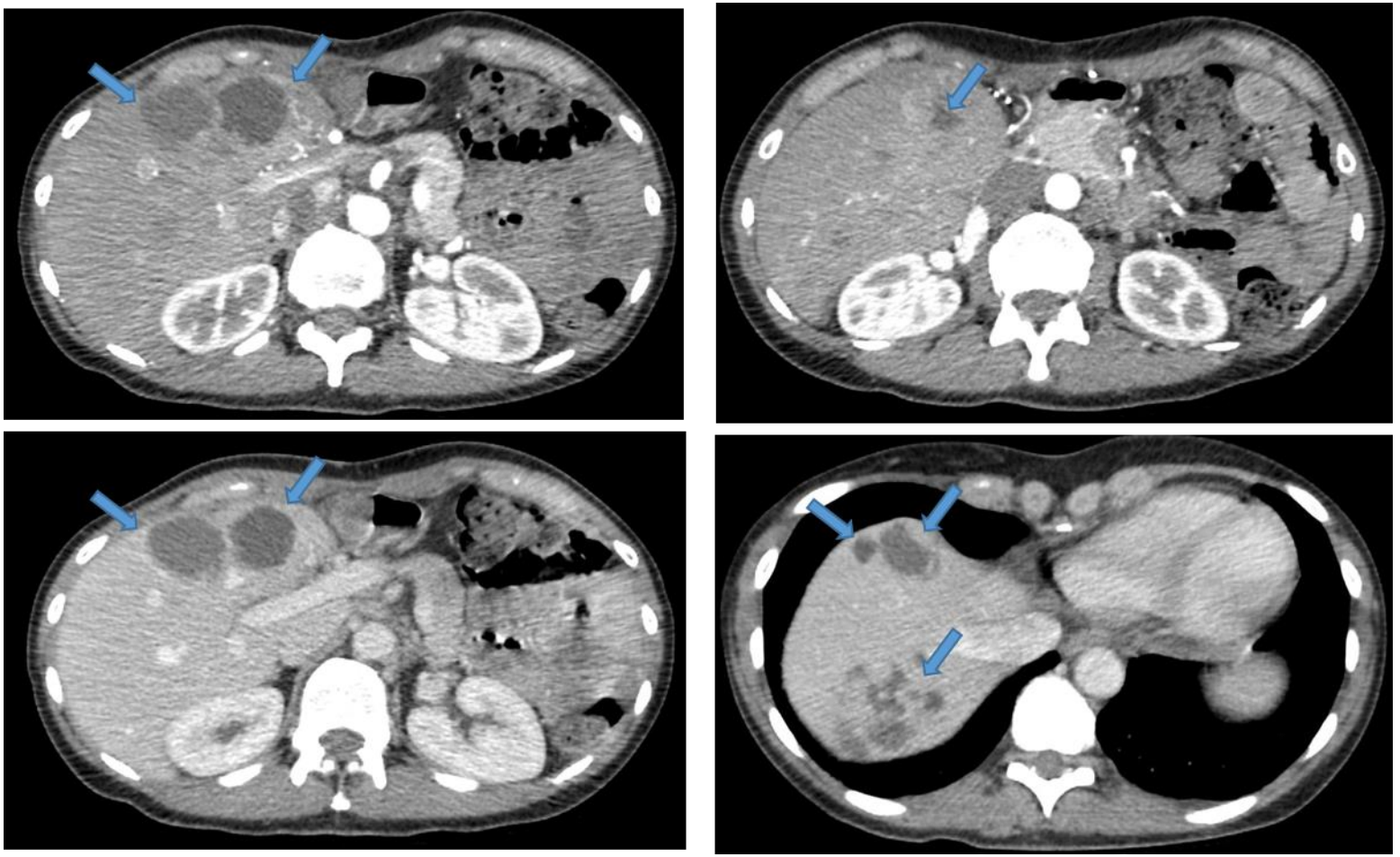
Patient 3 – Liver metastases



Patient 3 – Liver metastases

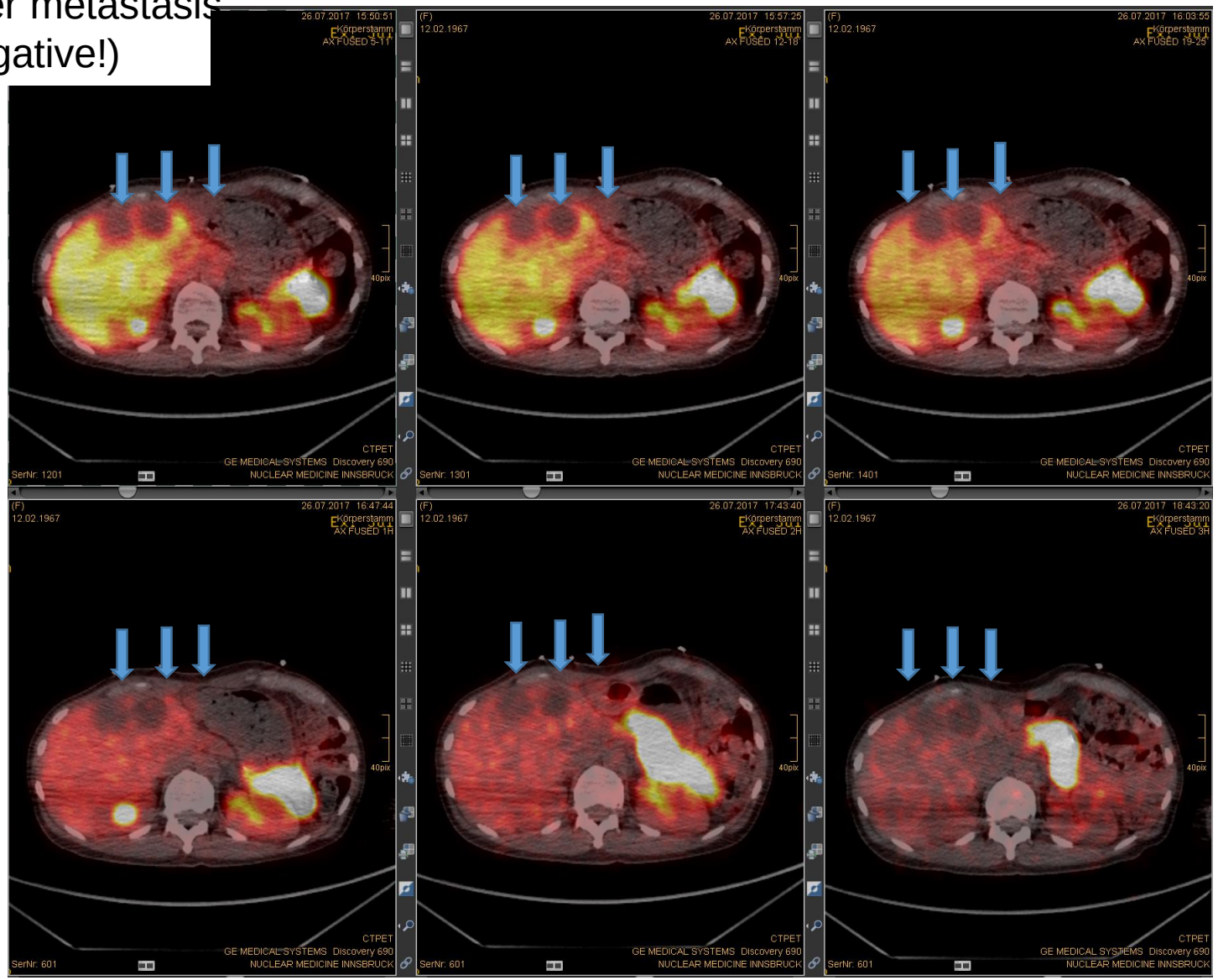


Patient 5- Gastric origin, multiple liver and peritoneal mets



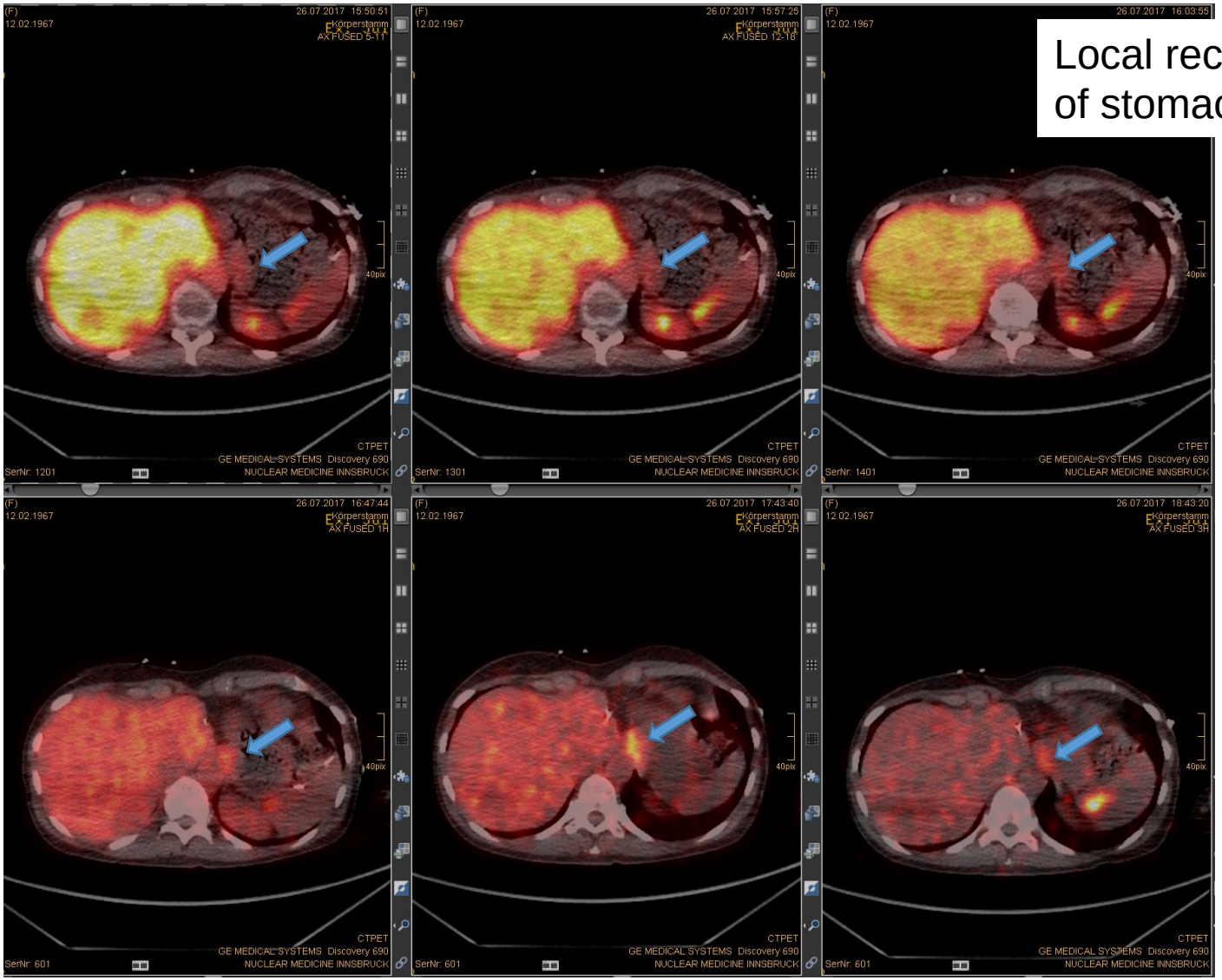
Patient 5 – Liver metastases

Liver metastasis (negative!)



Patient 5 –Stomach

10min 20min 30min



60min 120min 180min

- **Tissue analytics through light**

Diffuse reflectance spectroscopy of human liver tumor specimens - towards a tissue differentiating optical biopsy needle using light emitting diodes

ALINA KELLER,[1,*] PIOTR BIALECKI,[1] TORSTEN JOHANNES WILHELM,[2,3] AND MARCUS KLAUS VETTER[1,3]

[1]*Department of Embedded Systems and Biomedical Engineering, Hs Mannheim, University of Applied Sciences, 68163 Mannheim, Germany*

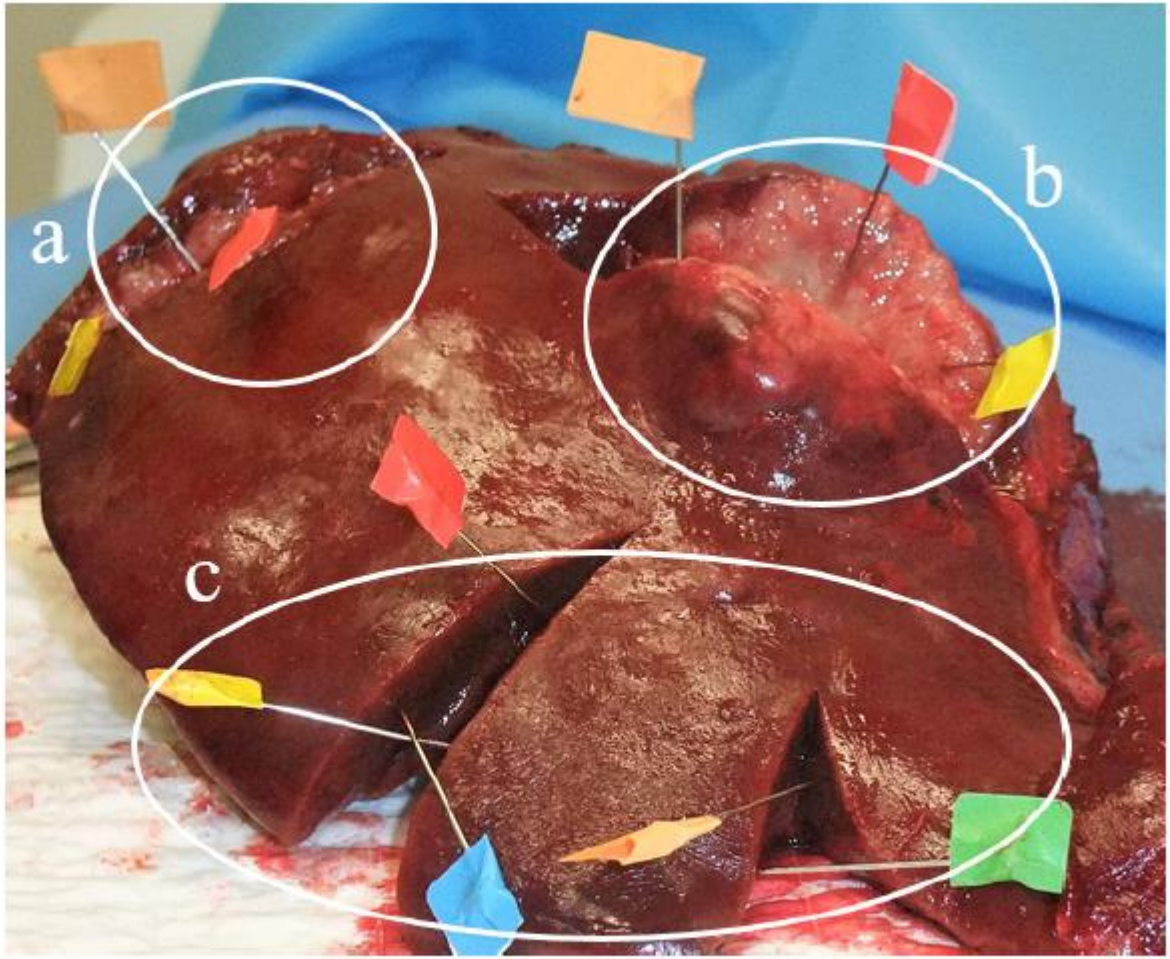


Fig. 2. Representative example of a resected liver with two malign lesions which are metastases from rectal cancer. The colored markers in a and b describe the 6 measurement sites on tumorous tissue. The remaining measurement sites in c are defined on liver parenchyma.

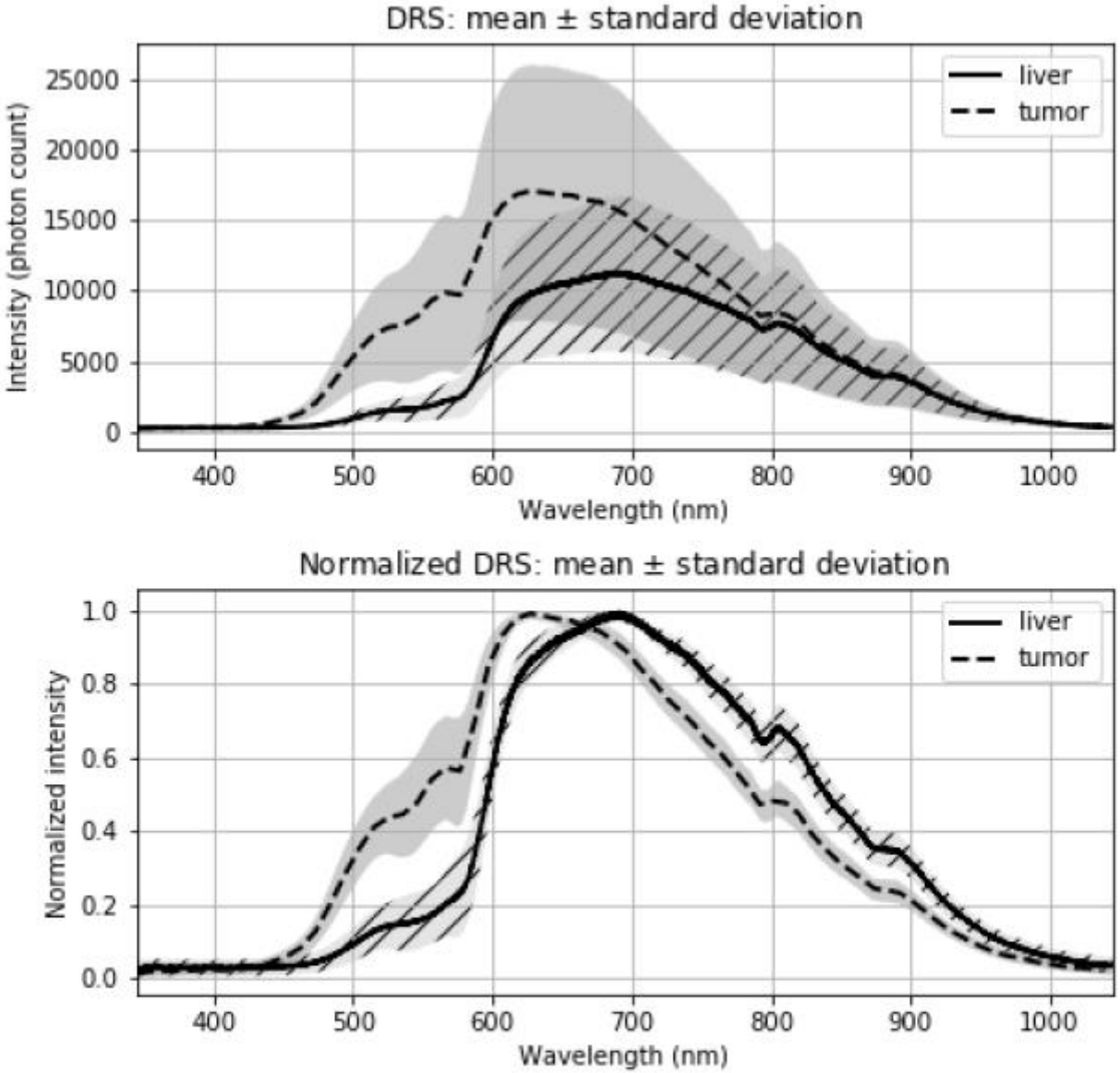


Fig. 3. Mean diffuse reflectance spectra of liver parenchyma (solid line) and tumorous tissue (dashed line) using a broadband light source in the VIS and NIR spectral range before (top) and after (bottom) normalization. The hatched (liver parenchyma) and grey (tumor) areas indicate the standard deviation of each type of tissue.

Table 1. Specification of liver tumors

	Tumor type	Number of patients
Primary tumor	HCC	7
	CCC	2
Secondary tumor	Rectal	10
	Colon	7
	GIST[a]	3
	Others[b]	3

[a]gastrointestinal stromal tumors; [b]chronic lymphoid leukemia, lung carcinoid tumor, renal cell carcinoma

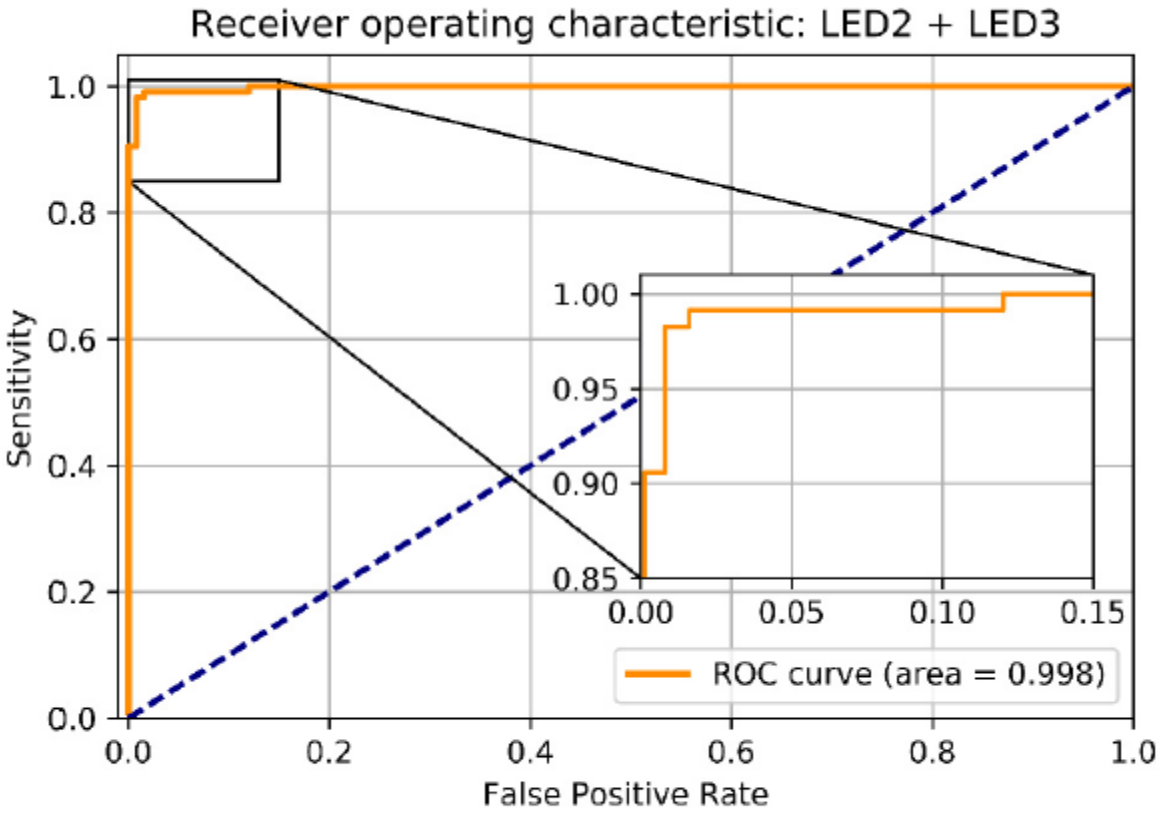


Fig. 6. Receiver operating characteristic curve of discriminating results based on integrated reflectance spectra values of LED02 and LED03. area: area under ROC curve

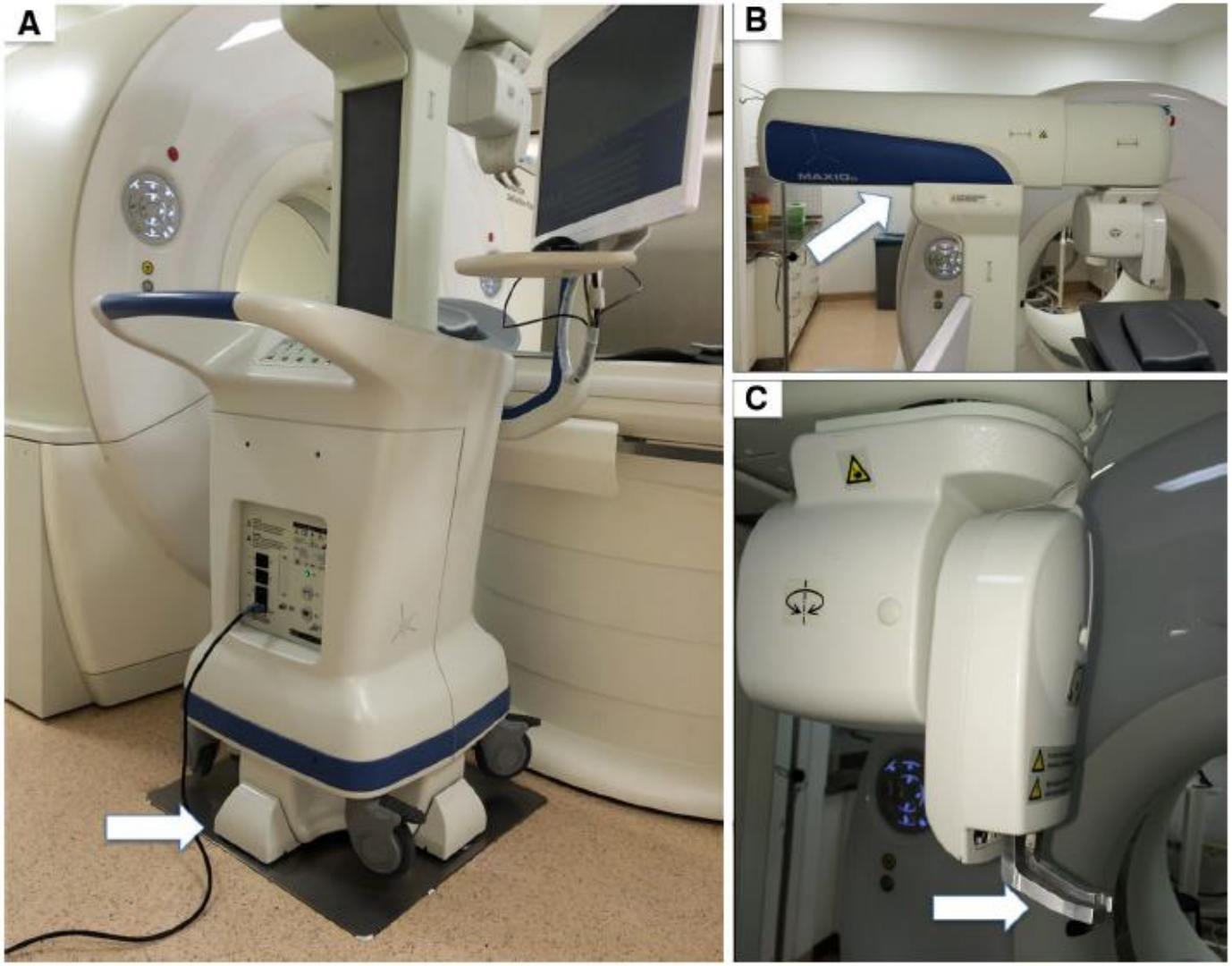


Fig. 2 Setup of the robotic assistance device: **A** Device attached next to CT table on registration plate (arrow). **B** Robotic arm of the navigation system (arrow). **C** Needle holder of the robotic arm (arrow) (Size 1710 × 1346)

Schlussbemerkung

- Operation in der Metastasierung ist eine individuelle Entscheidung.
- Residualtumor Operation ist sicher und morbiditätsarm
- RFA, Embolisation, IRE, SIRT, stereotaktische Strahlentherapie können einzelne Tumorareale zerstören
- Verfahren ist von Zentrum zu Zentrum verschieden
- Es gibt keine Daten die die Überlegenheit eines Verfahrens belegen
- Radiaoaktive Rezeptortherapie ist ganz neue Option

- Gewebeanalytik durch Licht
- Robotische Steuerung von Interventionen