

Gebruik van fluorescentie en Green light in de oncologische chirurgie

Alex Vahrmeijer, MD, PhD
WWW.GREENLIGHT.NU



Ziekenhuis test



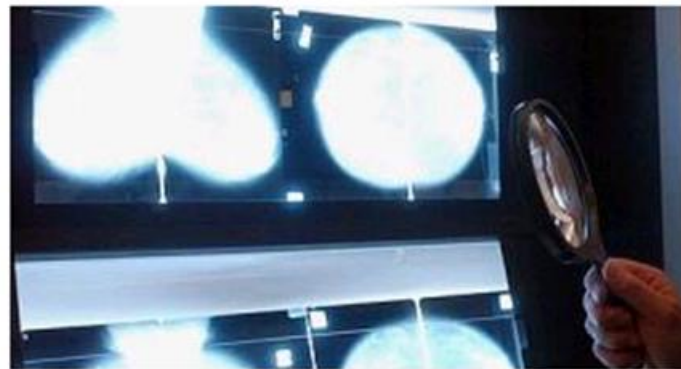
Hoe scoort uw eigen ziekenhuis?

Ziekenhuis Top-100

Te vaak heroperatie borstkanker

Door RONALD VAN GEENEN / KEES WESSELS

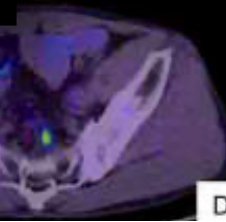
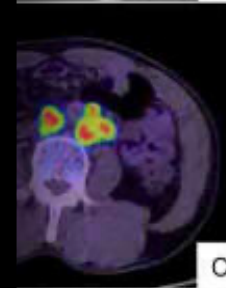
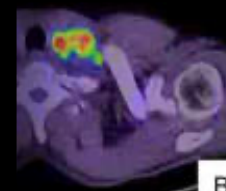
AMSTERDAM - Lichtpuntje voor veel vrouwen is dat chirurgen er tegenwoordig vaak in slagen kleine tumoren te verwijderen zonder dat de borst er af moet. Zo'n operatie slaagt niet altijd in één keer.



Röntgenfoto's van een tumor in de borst. FOTO EPA

Daarom hanteren deskundigen en de Inspectie voor de Gezondheidszorg de gulden regel dat maximaal één op de tien patiënten voor een tweede keer onder het mes mag.

Amper de helft van de ziekenhuizen voldoet aan die kwaliteitseis, blijkt uit onderzoek van deze krant. Bovendien lopen de resultaten



A

D

Waarom image-guided surgery?



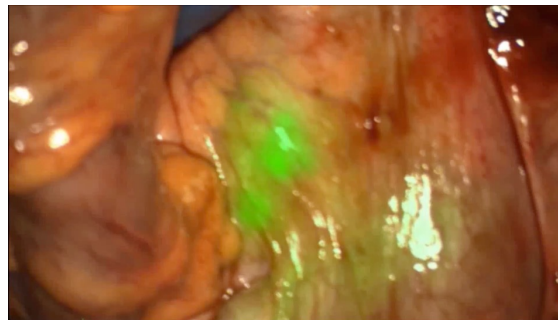
Eerste patiënt in LUMC in 2009

2009 – ICG



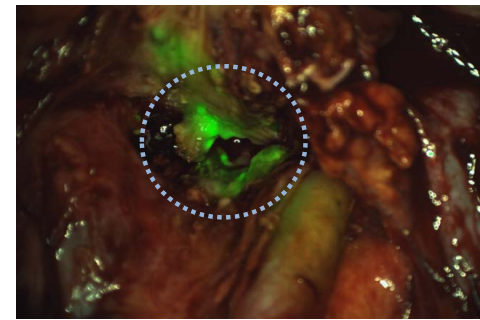
1st patient LUMC
SLN in breast cancer

2014 – tumor specific



650th patient
LN metastasis ovarian cancer

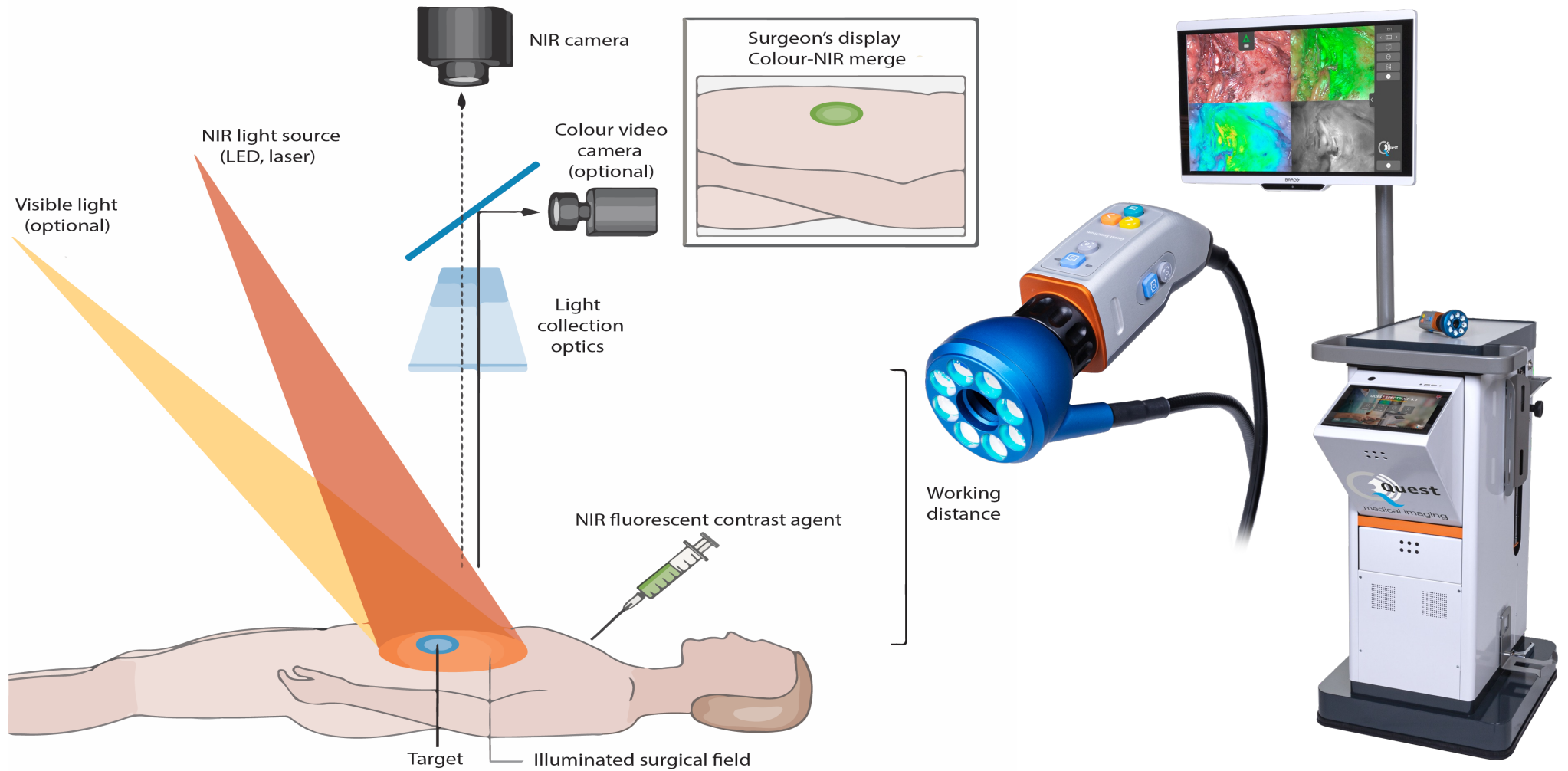
2019 – tumor specific



1000th patient
First in multicenter phase III study



Fluorescentie beeldvorming



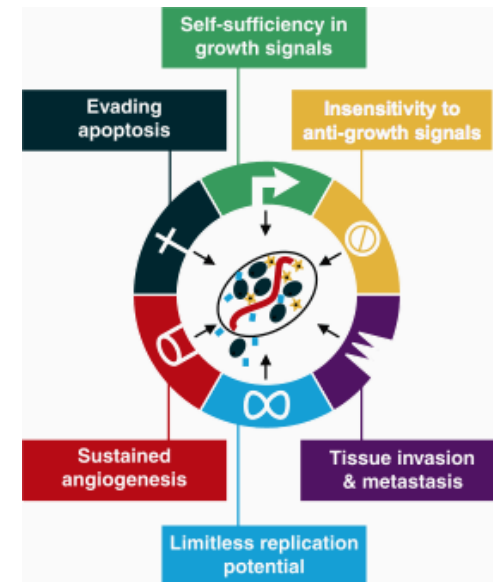
Contrastmiddelen

Klinisch beschikbaar (off label gebruik):

- Indocyanine groen (ICG)
- Methyleen blauw (MB)

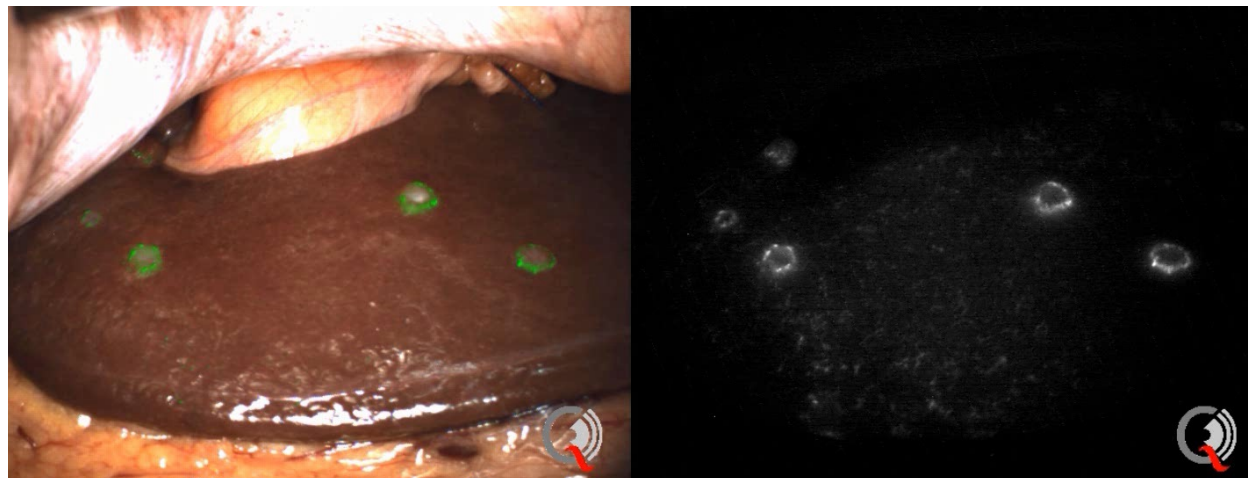
Toekomst: **Academic Pharma**

- Tumor-specifieke contrastmiddelen
- Preklinische ontwikkeling en validatie
- Klinische translatie optimaal in LUMC



Colorectale lever metastasen

- 40% van de patiënten met CRC
- Fluorescentie beeldvorming met ICG
- 1/8 patiënten extra laesie
- Standard-of-care in LUMC



MIMIC Trial: Focus op resectie marge

Minimaal invasieve, Indocyanine-Groen gestuurde
Lever resecties: 186 inclusies nodig

Primaire uitkomst:

- Toename radicale resecties

Secondaire uitkomst:

- Extra leases, recidief,
- Lange termijn uitkomsten



MIMIC Studie Design: focus op resectie marge

Prospectieve multicenter studie: standard-of-care protocol

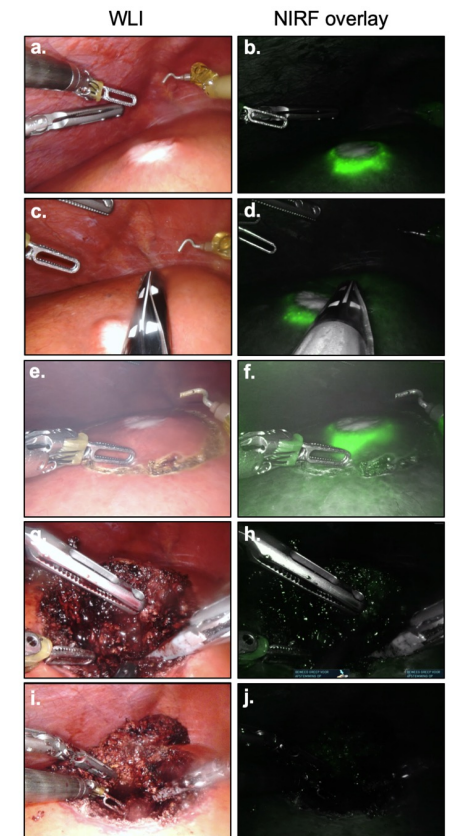
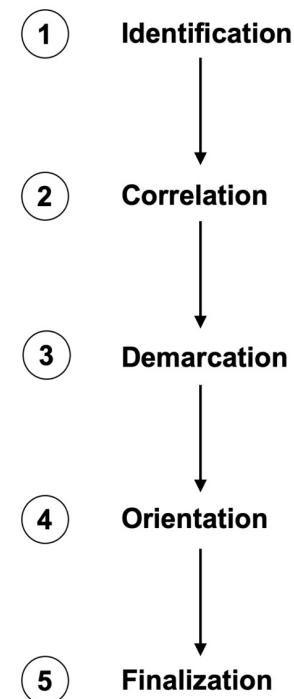
- 24h preoperatief 10mg ICG

Inclusie: 186 patiënten

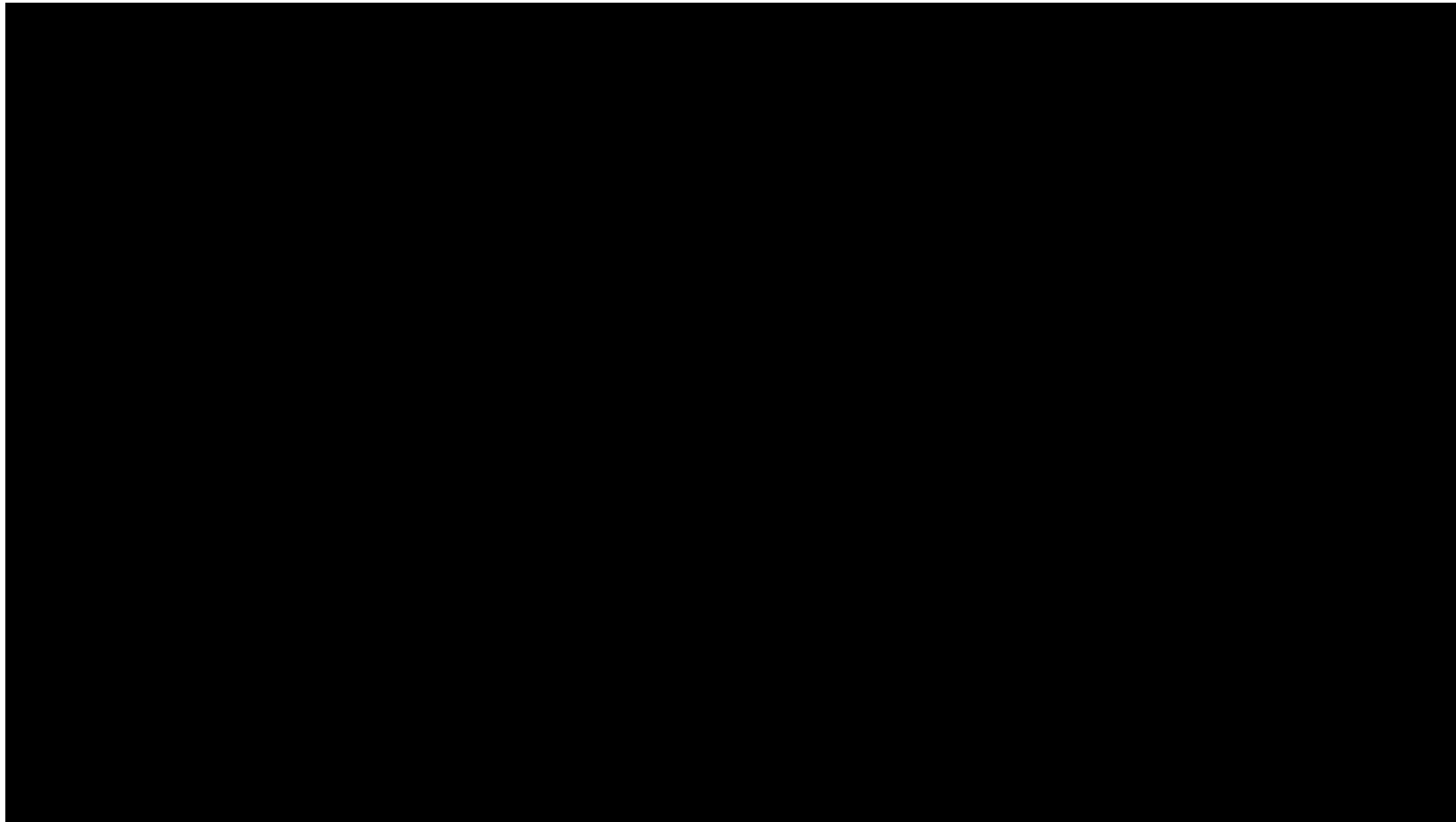
- Minimaal invasieve procedure voor CRLM

Chirurgische workflow:

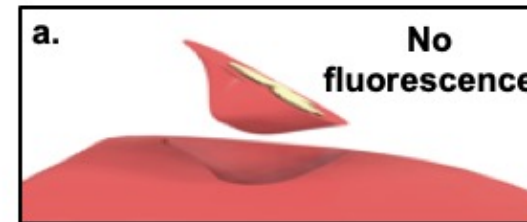
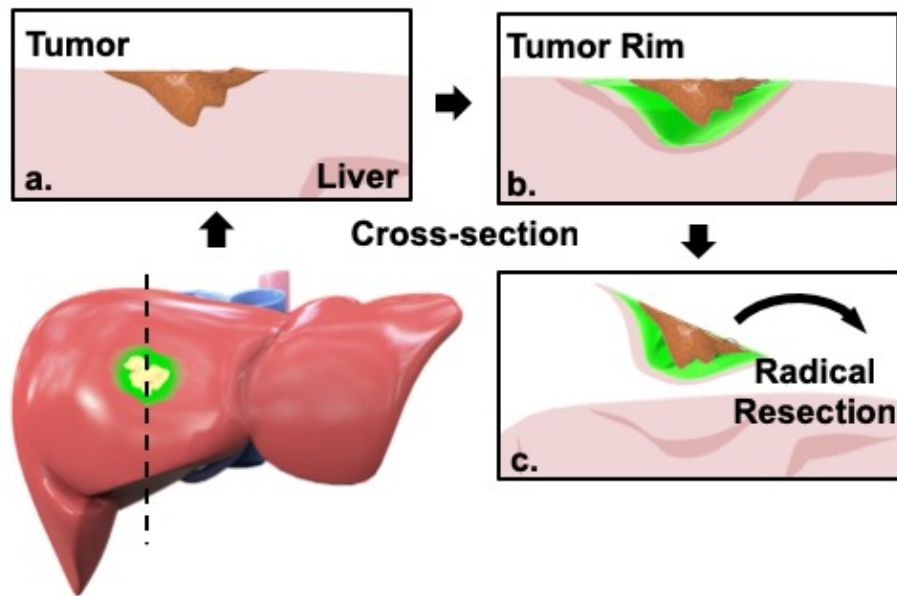
- Inspectie met echo
- Fluorescente inspectie en markeren leasie
- Fluorescentie-geleide resectie
- Correlatie met pathologie



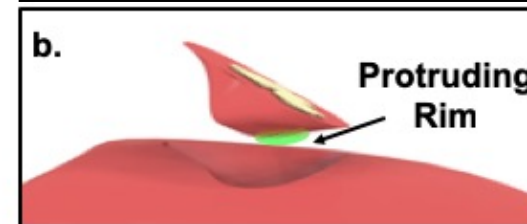
Robot-geassisteerde fluorescentie geleide chirurgie



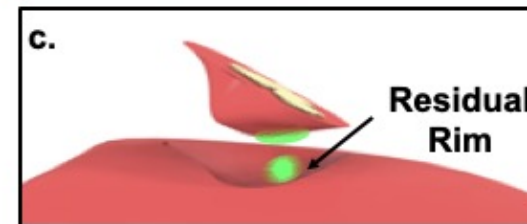
In vivo tumor marge beoordeling – Directe Feedback



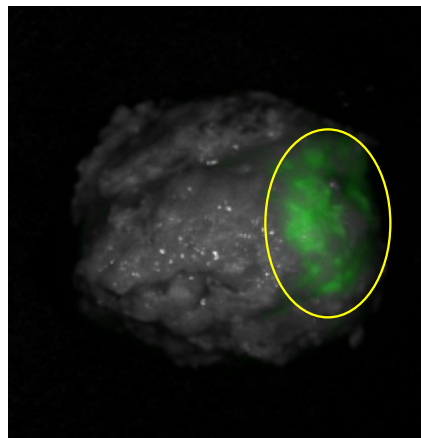
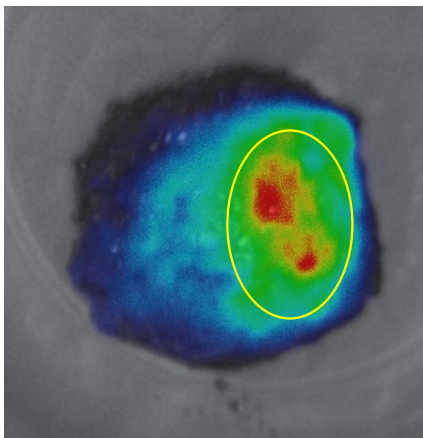
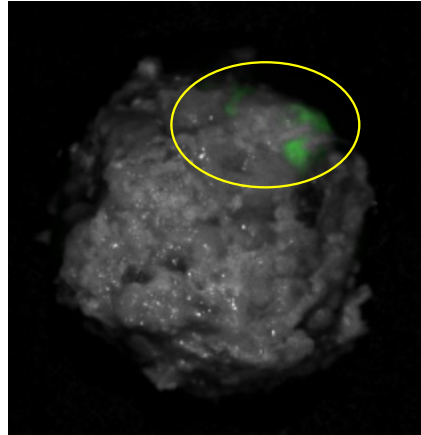
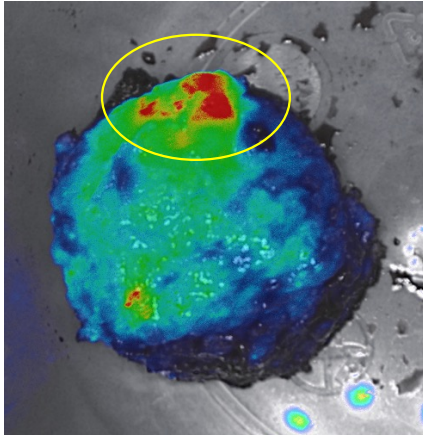
R0



R1



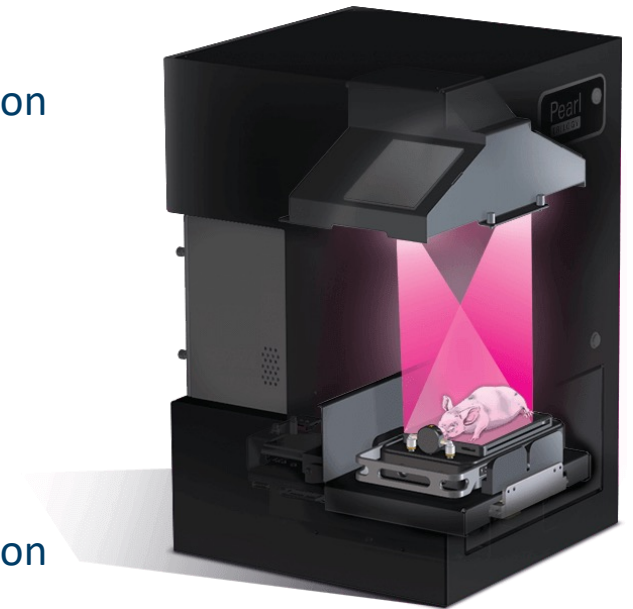
Directe beoordeling op OK



R1 resection

R1 resection

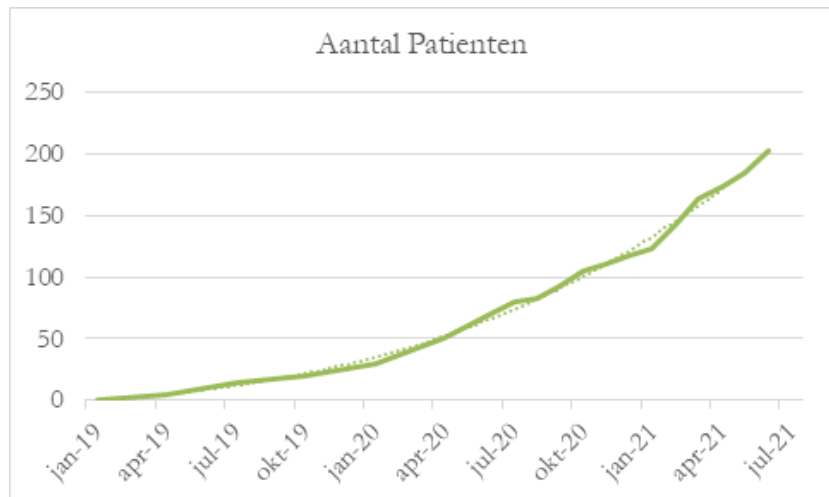
Licor Pearl



Voorlopige resultaten:



Inclusies compleet!

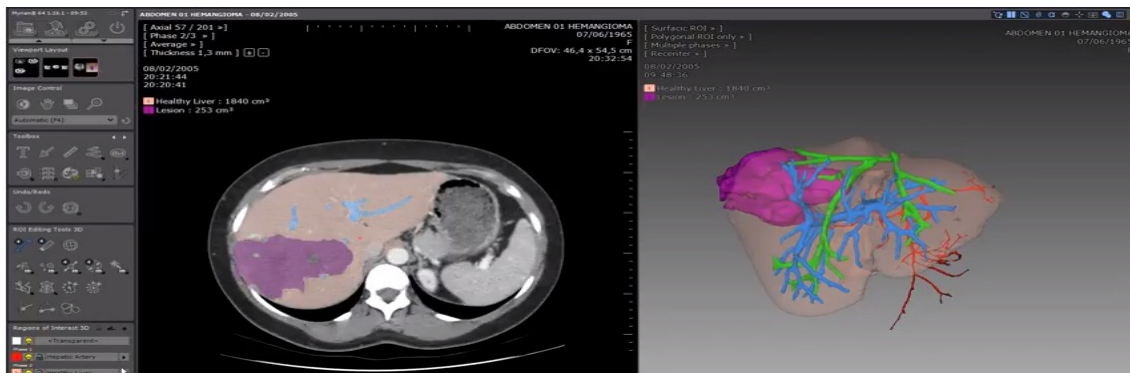


Analyse: Okker Bijlstra

- 30% verandering chirurgisch plan
- 88% R0 (>1mm) resecties na aanpassing (was 82%)

3D Segmentatie voor training en navigatie

- Identificatie van extra laesies (12%)
- Limitatie: oppervlakkige afwijkingen
- Nieuwe techniek: correlatie met preoperatieve CT/MRI scan

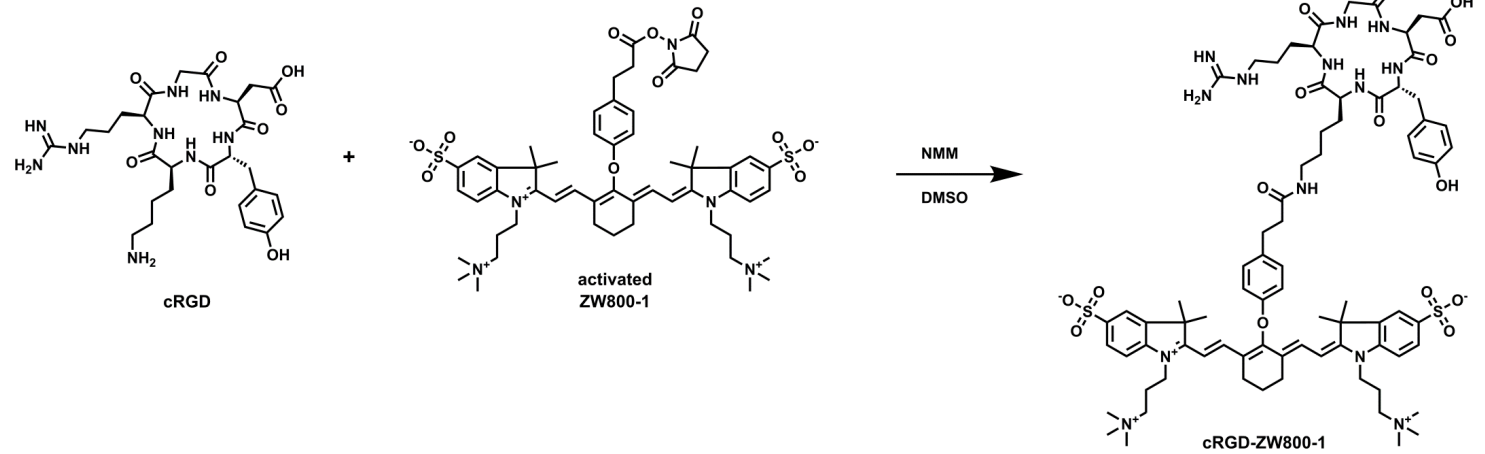
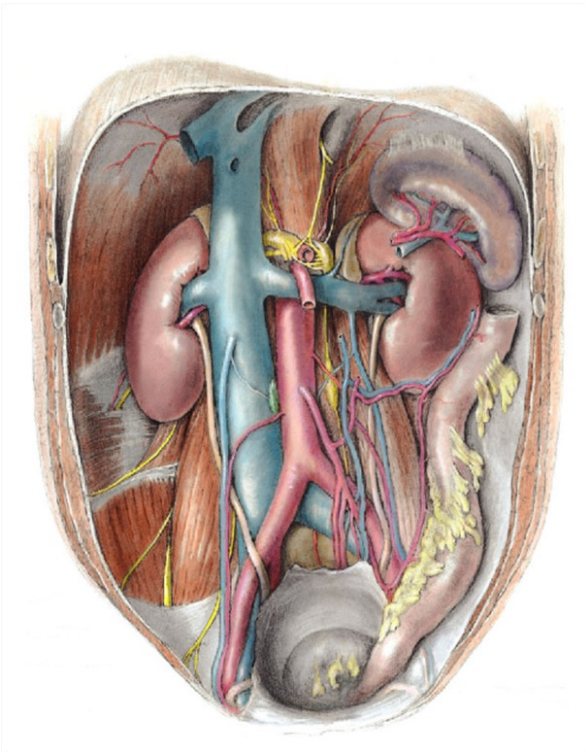


3D reconstructie



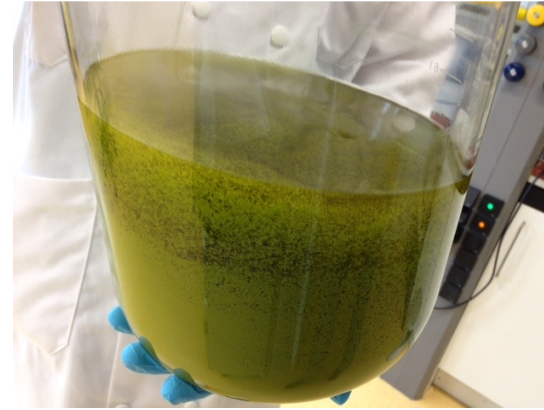
CT navigatie in console

Ureter beeldvorming - cRGD-ZW800-1 / ZW800-1 (cGMP)



synthesis

Purification of ZW800-1
intermediate



Klinische translatie ZW800-1

Development

- cGMP production

Preclinical phase

- Tumor specificity
- Toxicology

Phase 1A, First-in-human

- Safety and pharmacokinetics
- CHDR Leiden

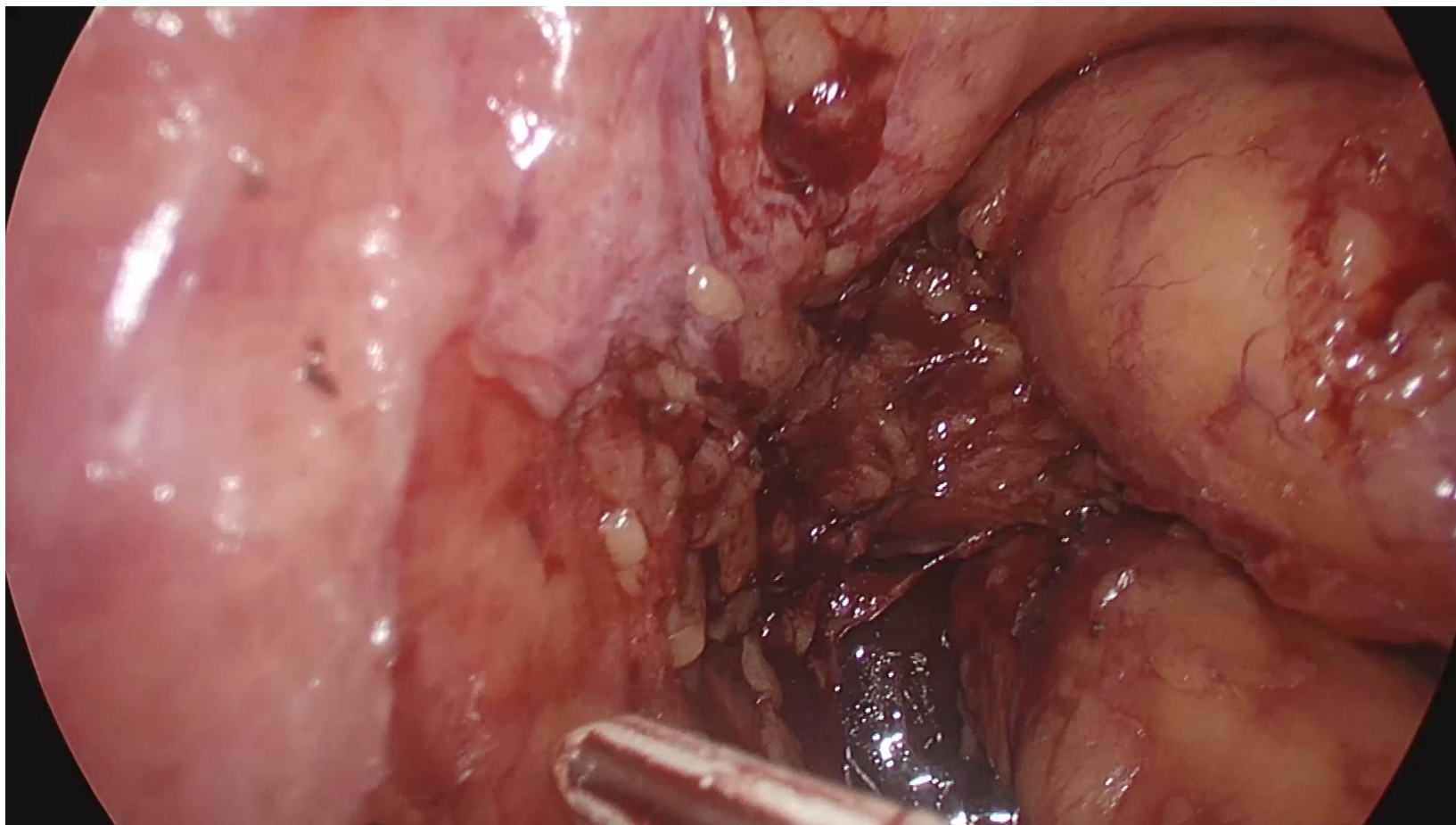
Phase 1B, First-in-patient

- Dose and timing optimization
- Leiden University Medical Center/CHDR

Centre for Human Drug Research



Ureter identificatie – ZW800-1



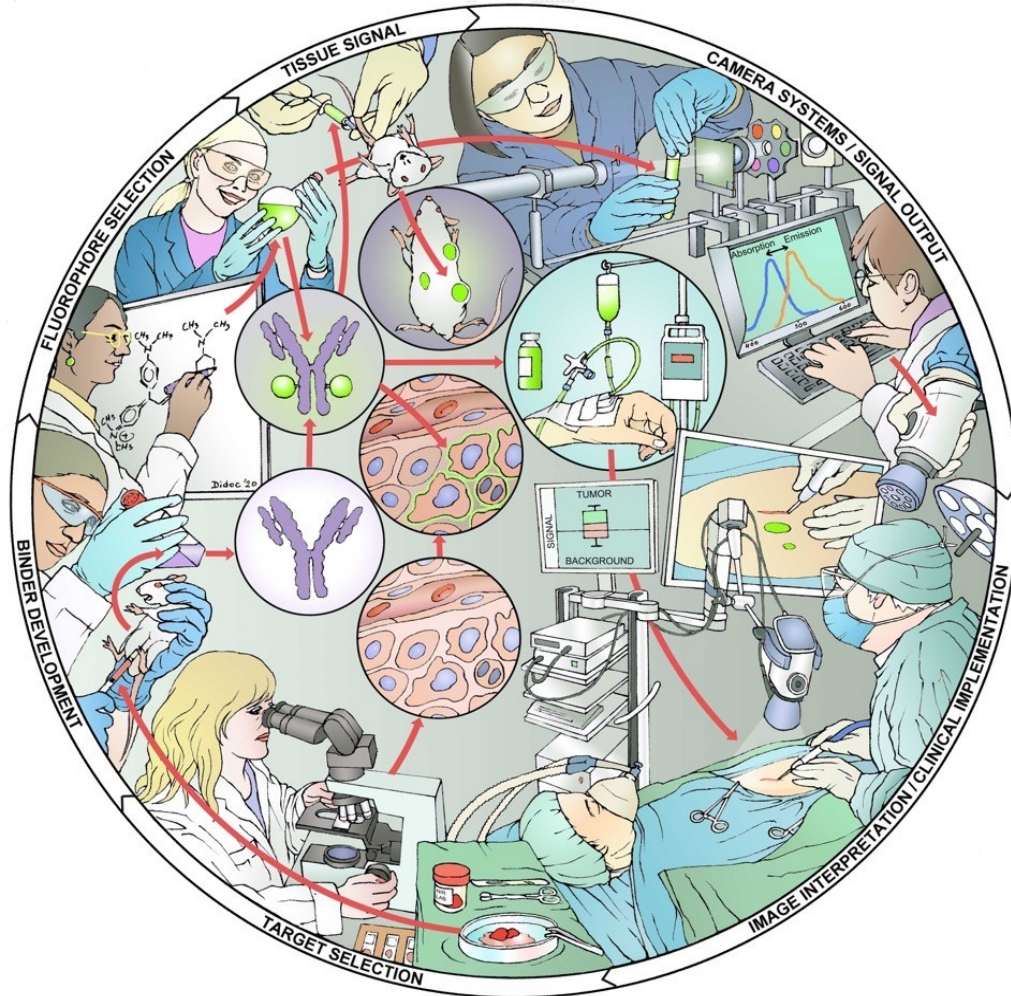
Laparoscopische ureter beeldvorming – ZW800-1



Robotic ureter beeldvorming



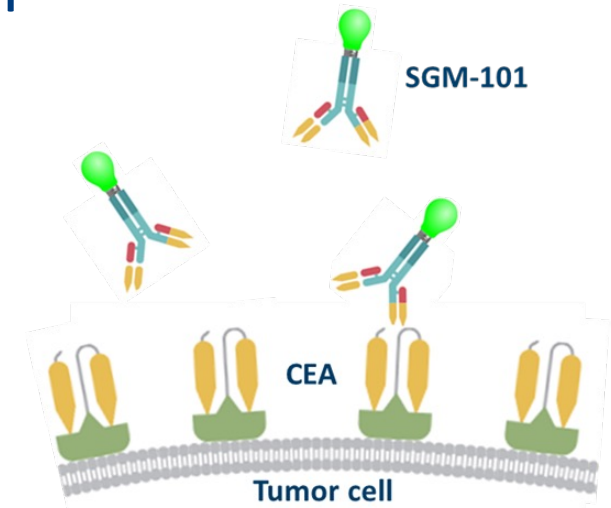
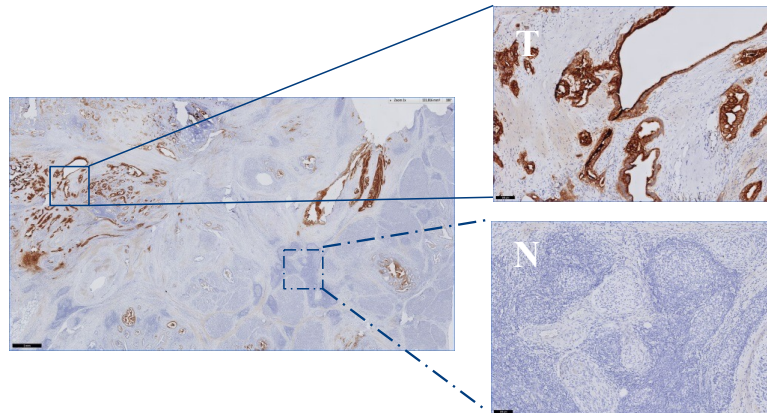
Ontwikkeling Tumor specifieke contrast middelen



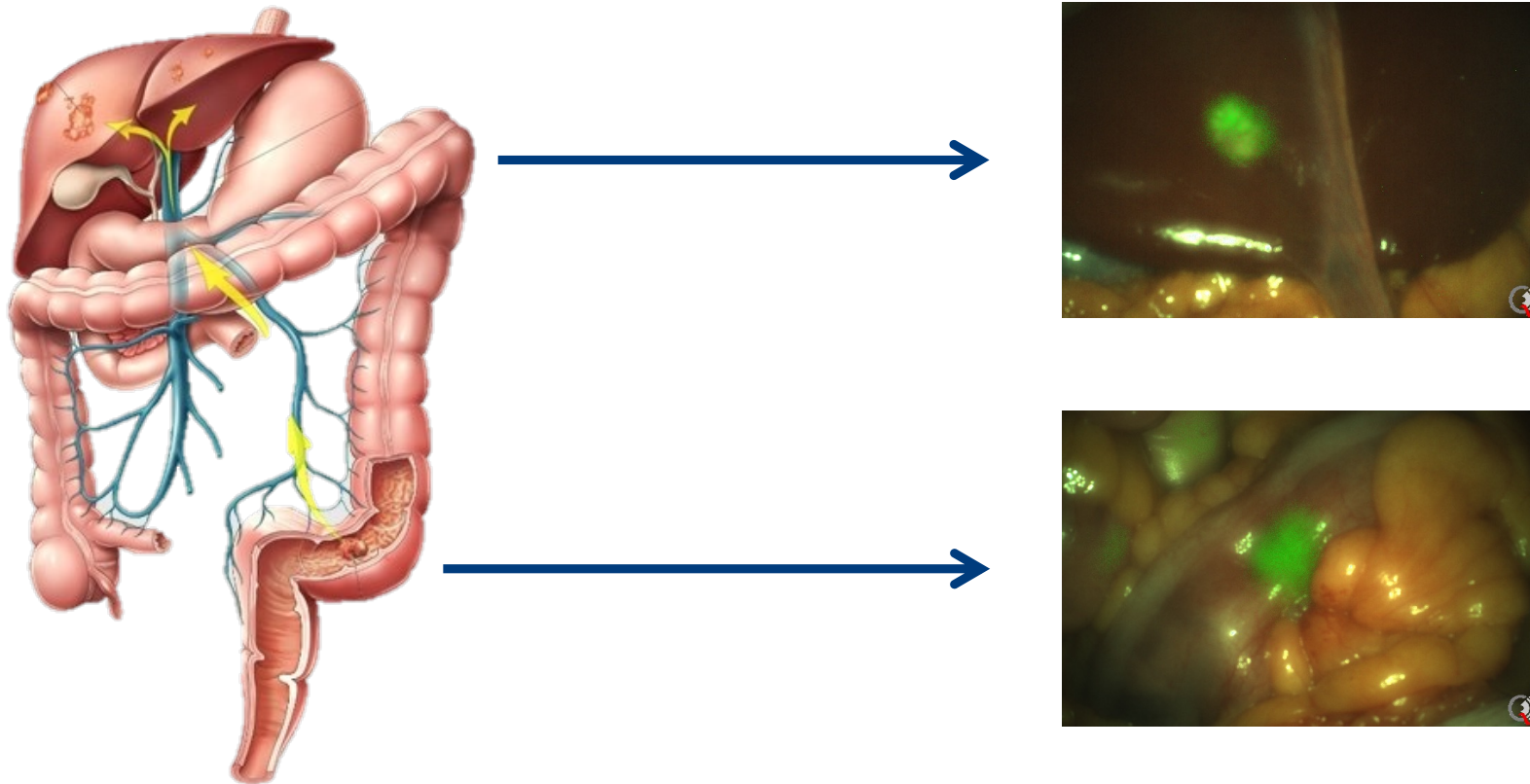
Targeting CEA – Colorectaal carcinoom



- Carcino-embryonal antigen
- Glycoproteïne betrokken bij cel adhesie
- 80-90% overexpressie in dikke / endeldarm kanker
- Expressie niet beïnvloed door RT of CRT



Toekomst: Colorectaal carcinoom & lever uitzaaiingen



Ex-Vivo pathologie beoordeling

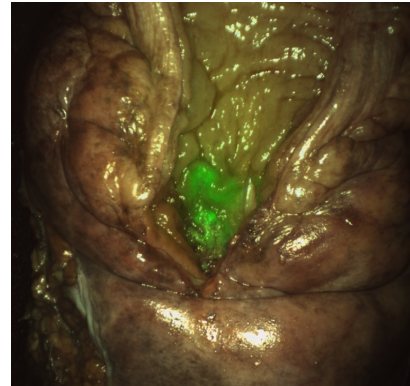
Color



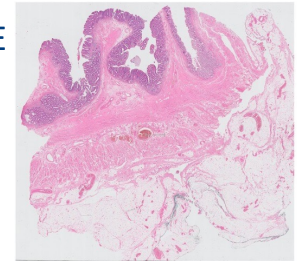
Fluorescence



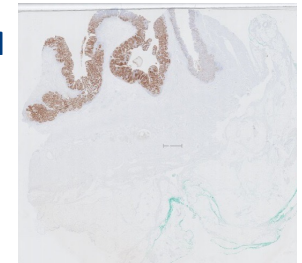
Fusion



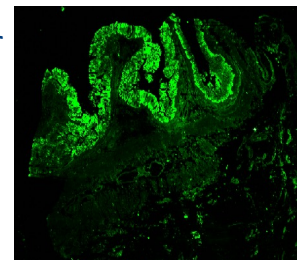
HE



CEACAM

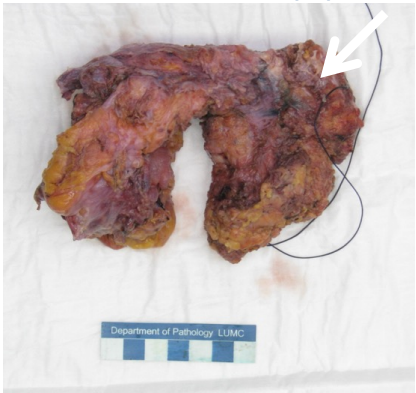


Fluor

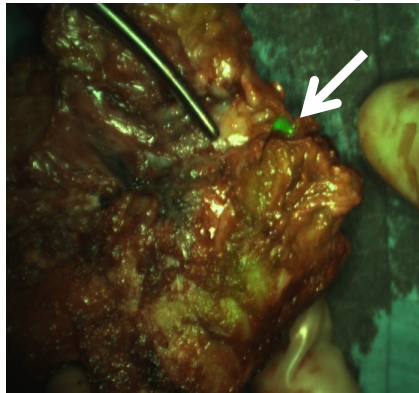


Recidief rectum carcinoom

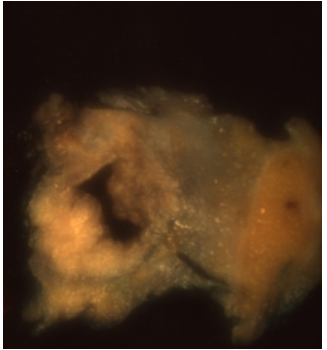
Macroscopy



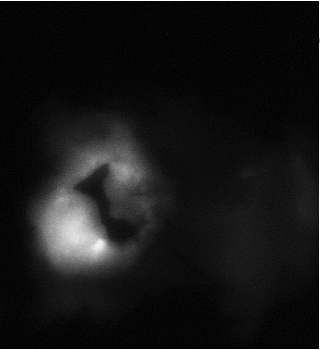
Color-NIR Merge



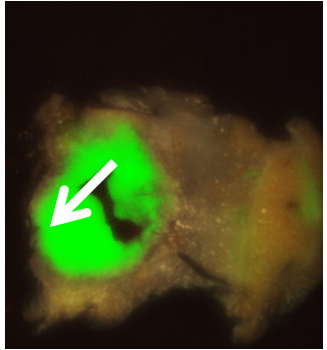
Color



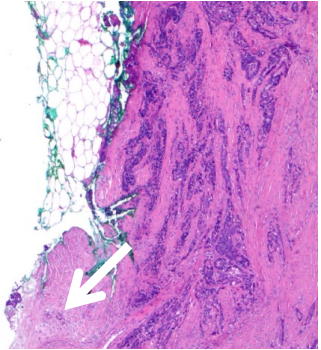
NIR



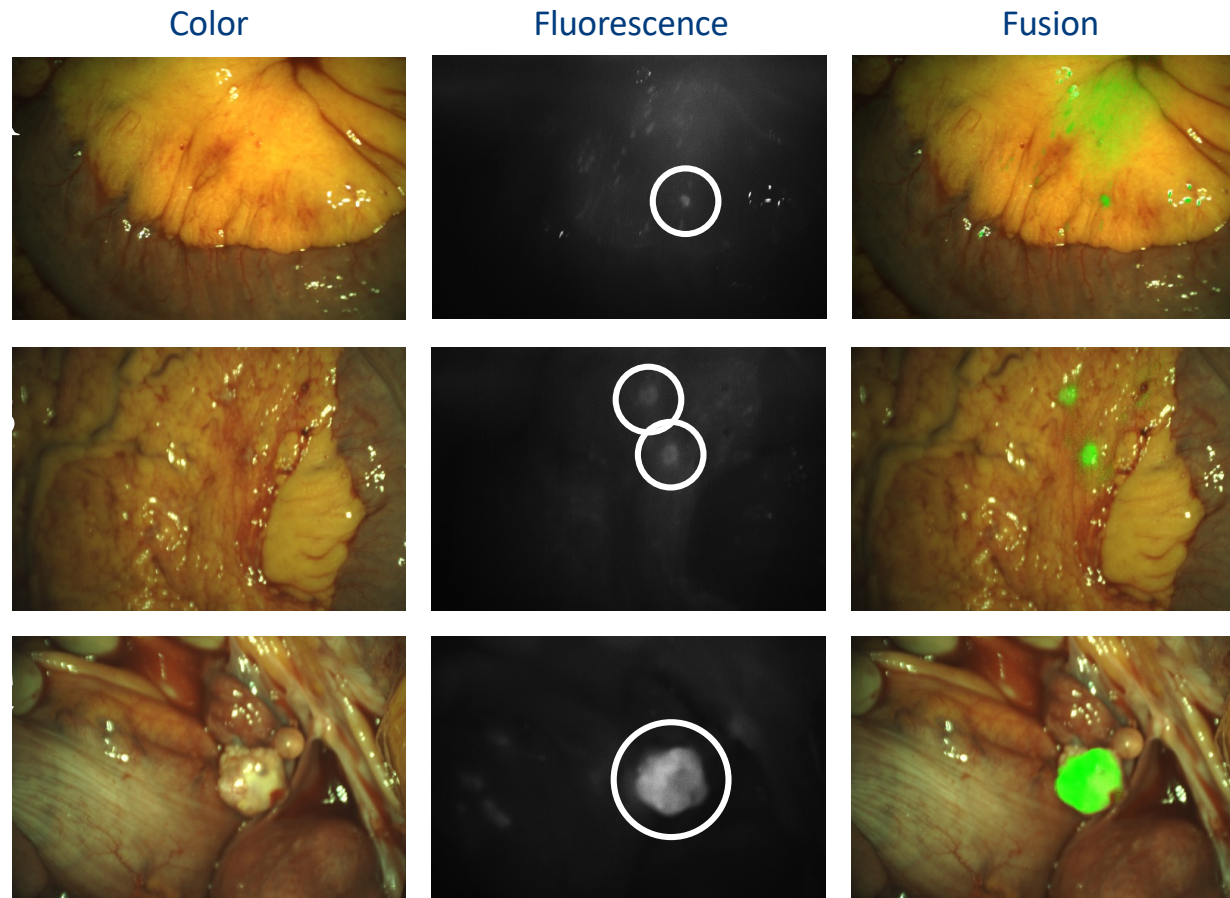
Color-NIR



HE



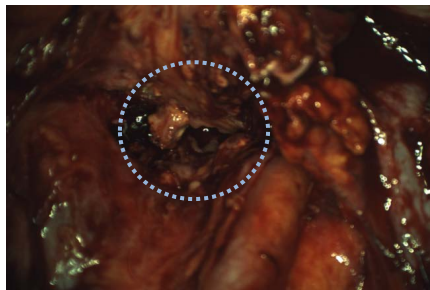
Beeldvorming tijdens HIPEC



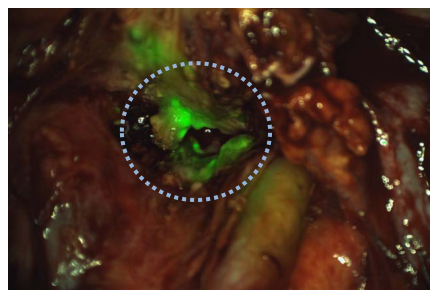
Resultaten SGM-101 Fase II

- 37 patiënten met primair of recidief colorectaal carcinoom
- 8 extra afwijkingen in 6 patiënten
- Verandering van chirurgisch plan in 9 van 37 patiënten (24%)
 - 7 patiënten met extra afwijkingen
 - 2 downstaging behandeling

Voor resectie

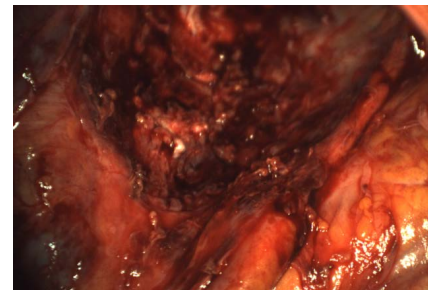


White light

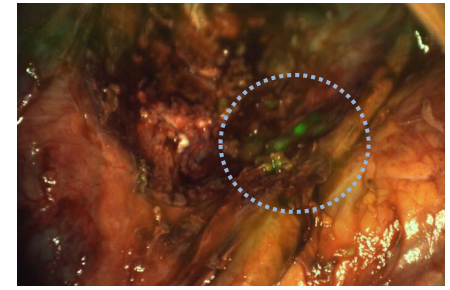


Overlay

Na resectie



White light

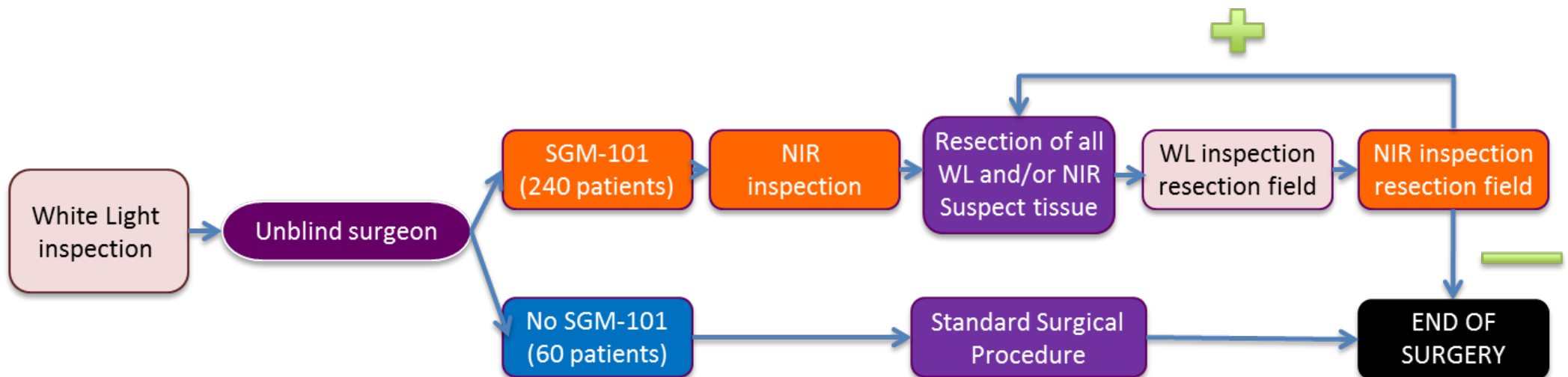


Overlay

FDA Fase III Studie Design: Chirurgische Procedure

Totaal of 300 patiënten

Grootste uitdaging: Blinderen chirurg



Fase III: Sponsor SurgiMab (>150 Patiënten Geïnccludeerd)

- Gestart in 2019
- 10 centra

USA:

- University of California San Diego Medical Center
- Massachusetts General Hospital
- UMASS
- University of Pennsylvania
- Cleveland Clinic

Italy:

- Policlinico San Matteo di Pavia – Fondazione IRCCS

Germany:

- University of Göttingen

The Netherlands:

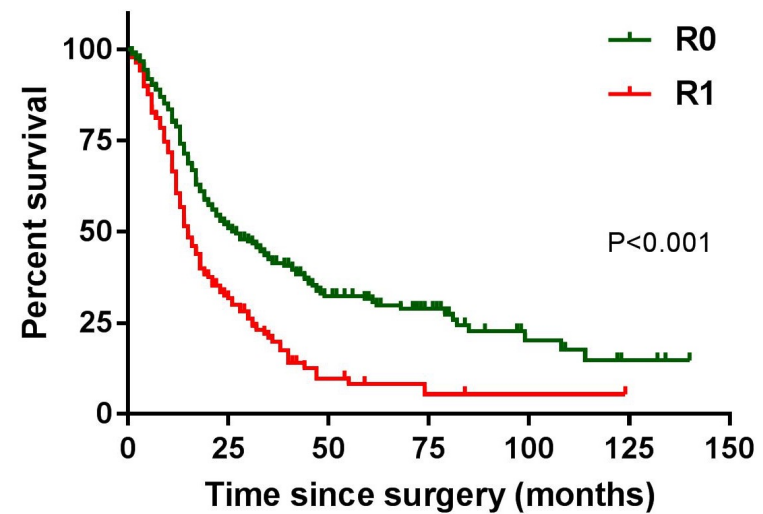
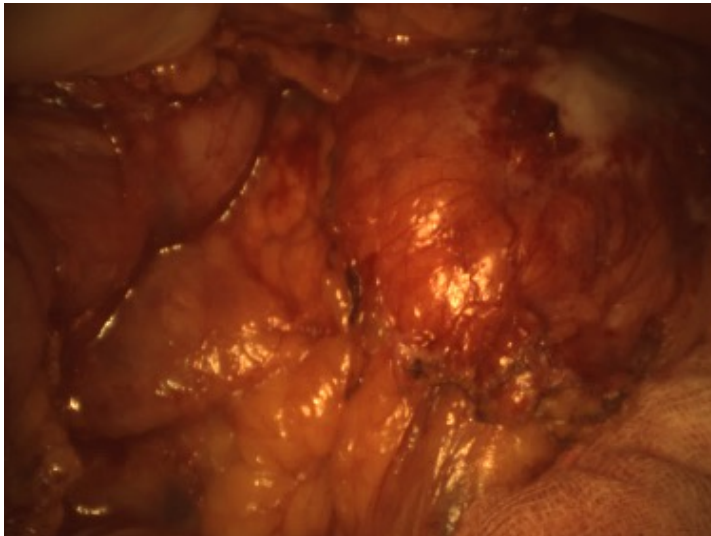
- Erasmus University Rotterdam
- Catharina Hospital Eindhoven
- Leiden University Medical Center

Pancreas Cancinoom

Belang van een complete resectie

65% niet radicaal

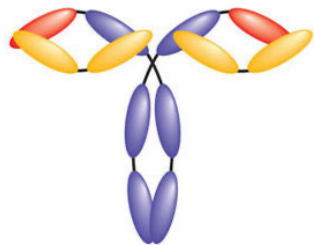
Slechte prognose





Ontwikkelen van een optische beeldvorming

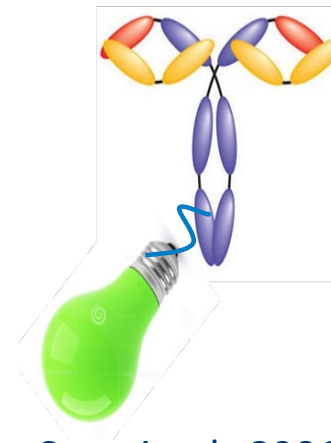
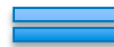
- Cetuximab; IgG1 monoclonal antibody against EGFR
- Approved for human use by FDA; Erbitux[®]



Cetuximab

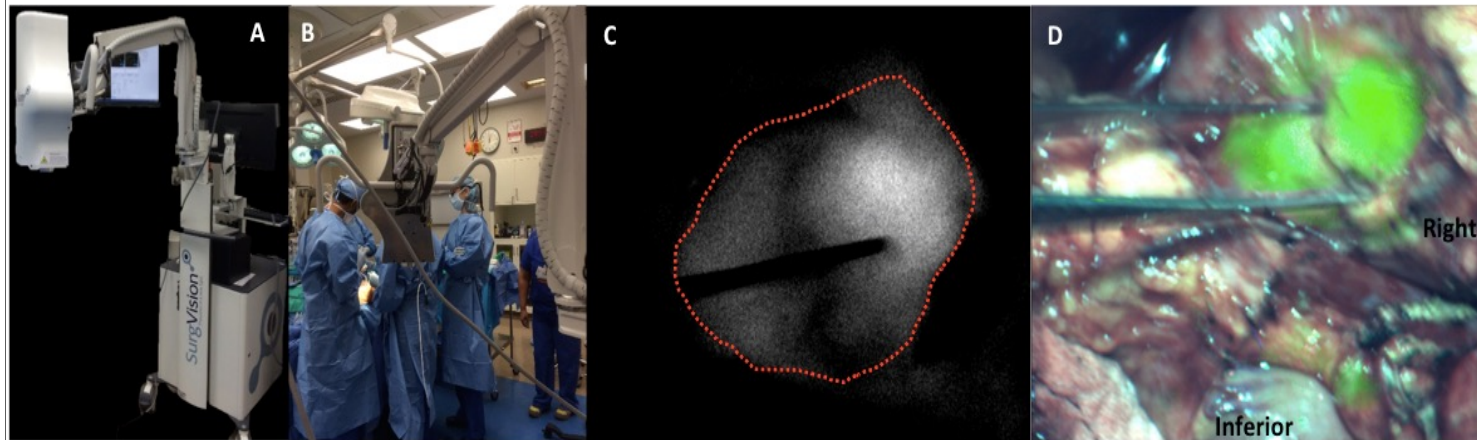


IRDye 800CW



Cetuximab-800CW

Eerste resultaten in 6 patiënten tijdens Whipple

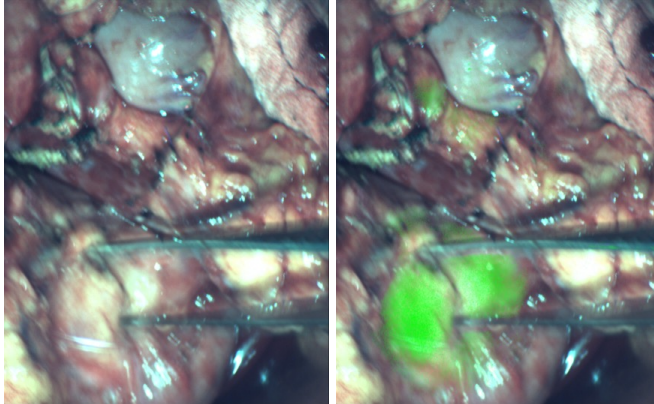


= **Cetuximab-IRDye800 (50 mg)**
i.v. 2 dagen voor de operatie

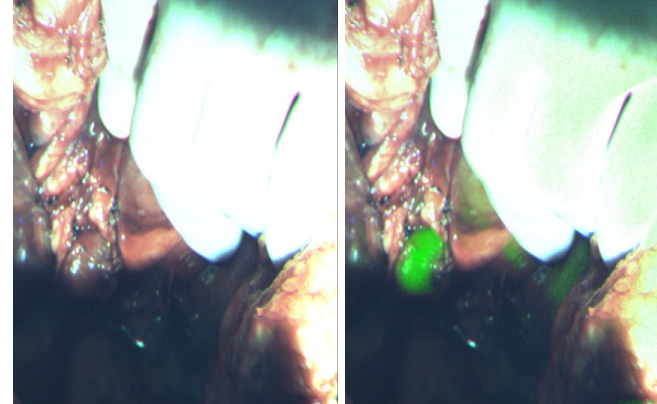
Tummers, Swijnenburg, Vahrmeijer (LUMC)
Gambhir, Poultides, Rosenthal (Stanford)

Intra-operatieve beeldvorming – Resultaten & Conclusie

- Tumor duidelijk zichtbaar in 4/6 patienten
 - Mean tumor-to-background ratio (TBR) primary tumor = 2.3
 - Mean TBR tumor-positive lymph nodes = 6.3



Primary tumor



Tumor-positive lymph node

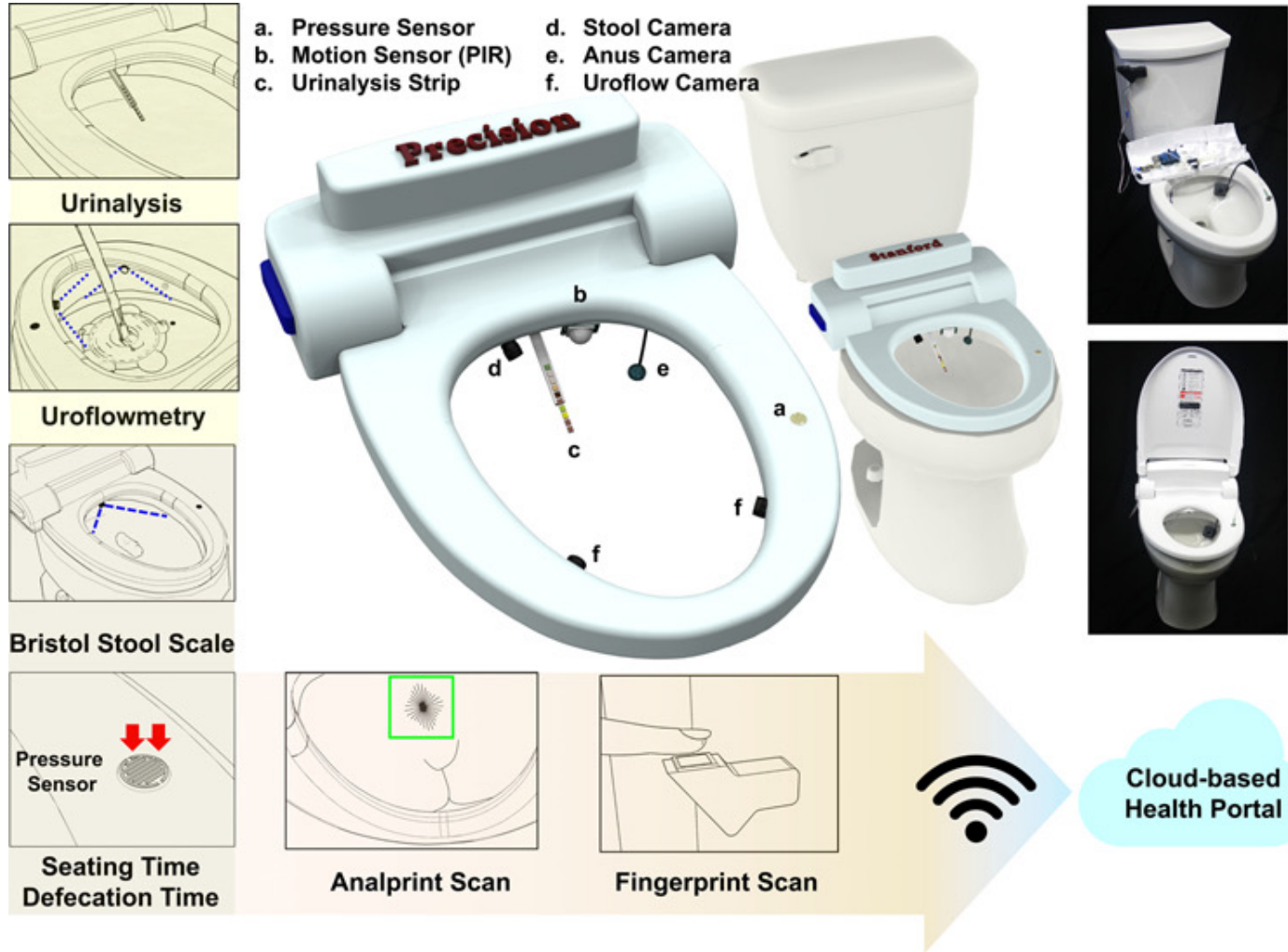
Stanford – Bontius – Prof Sam Gambhir



200 k€ voor translatie nieuwe probe
voor detectie pancreas carcinoom

Nature Biomedical Engineering 2020

Lg Nobel mechanical engineering prize



Cystine Knot Peptides for $A_v\beta_6$ PET Imaging



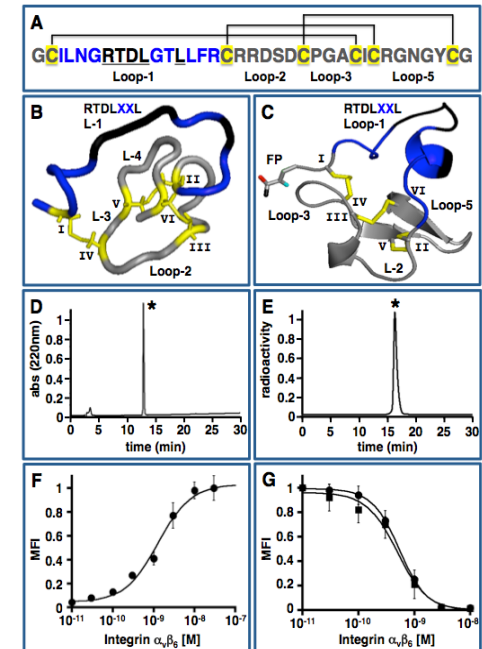
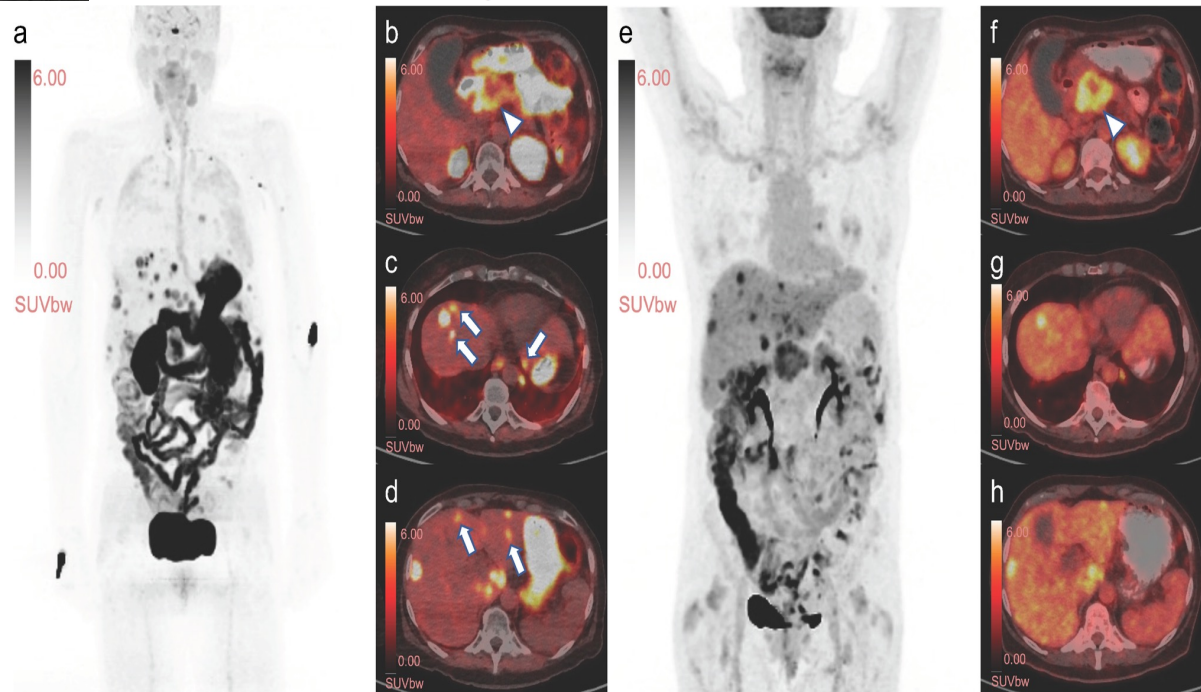
Prof. Sam Gambhir
Director Molecular
Imaging Program

^{18}F -Fluorobenzoate-Labeled Cystine Knot Peptides for PET Imaging of Integrin $\alpha_v\beta_6$

Benjamin J. Hackel^{1,*}, Richard H. Kimura^{1,*}, Zheng Miao¹, Hongguang Liu¹, Ataya Sathirachinda¹, Zhen Cheng¹, Frederick T. Chin¹, and Sanjiv S. Gambhir^{1,2}

¹Department of Radiology, Molecular Imaging Program at Stanford, Canary Center for Cancer Early Detection, Stanford University, Stanford, California

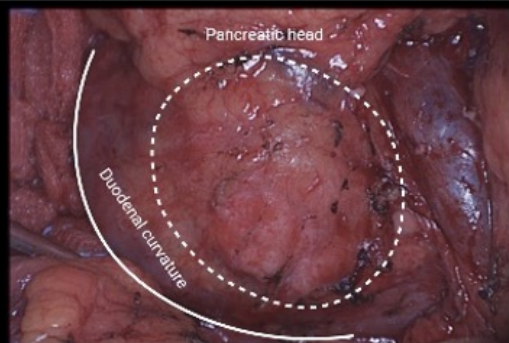
²Department of Bioengineering, Department of Materials Science and Engineering, Stanford University, Stanford, California



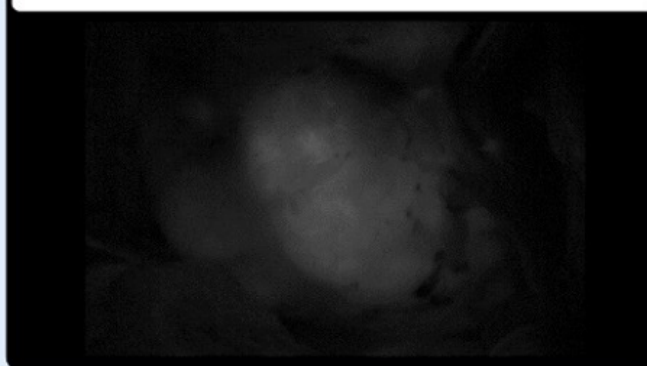
Patienten voorbeeld intra-operatief

In-vivo imaging

Color



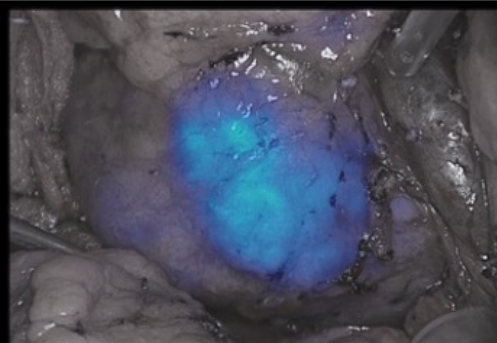
Fluorescence



Overlay



Signal-Intensity map



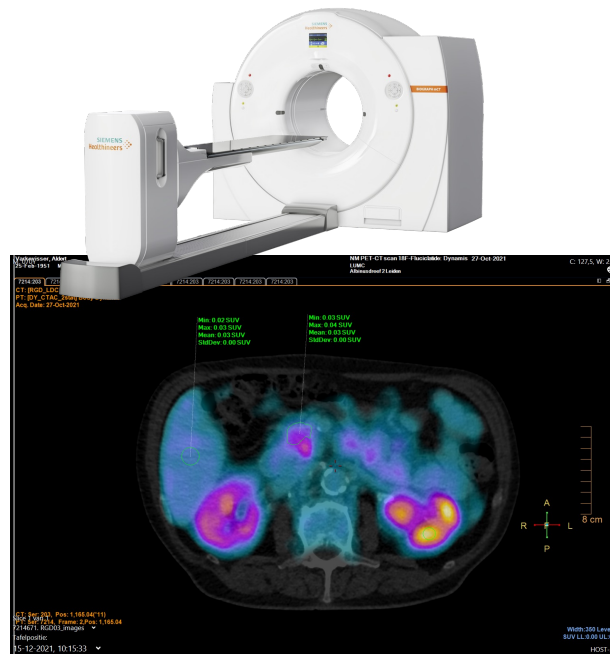
Integrine - targeting – Academic Pharma

Protein structure: cRGD – cyclic pentapeptide (*Arginylglycylaspartic acid*)

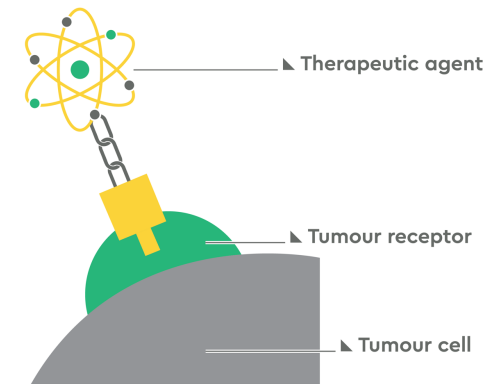
Fluorescence Imaging



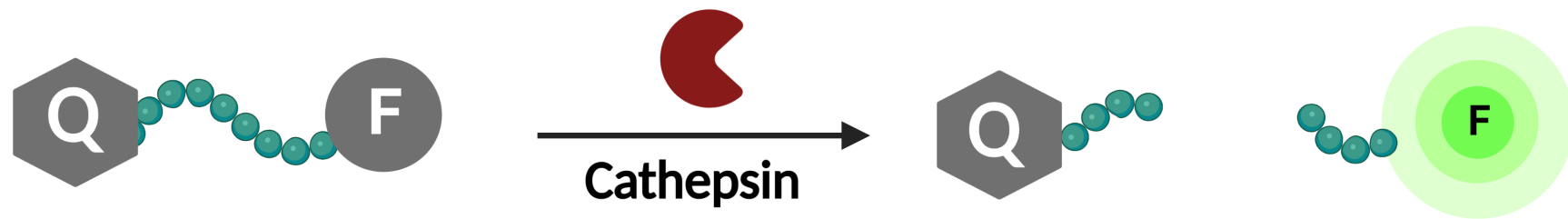
PET/CT Imaging



Theranostics & Drug delivery



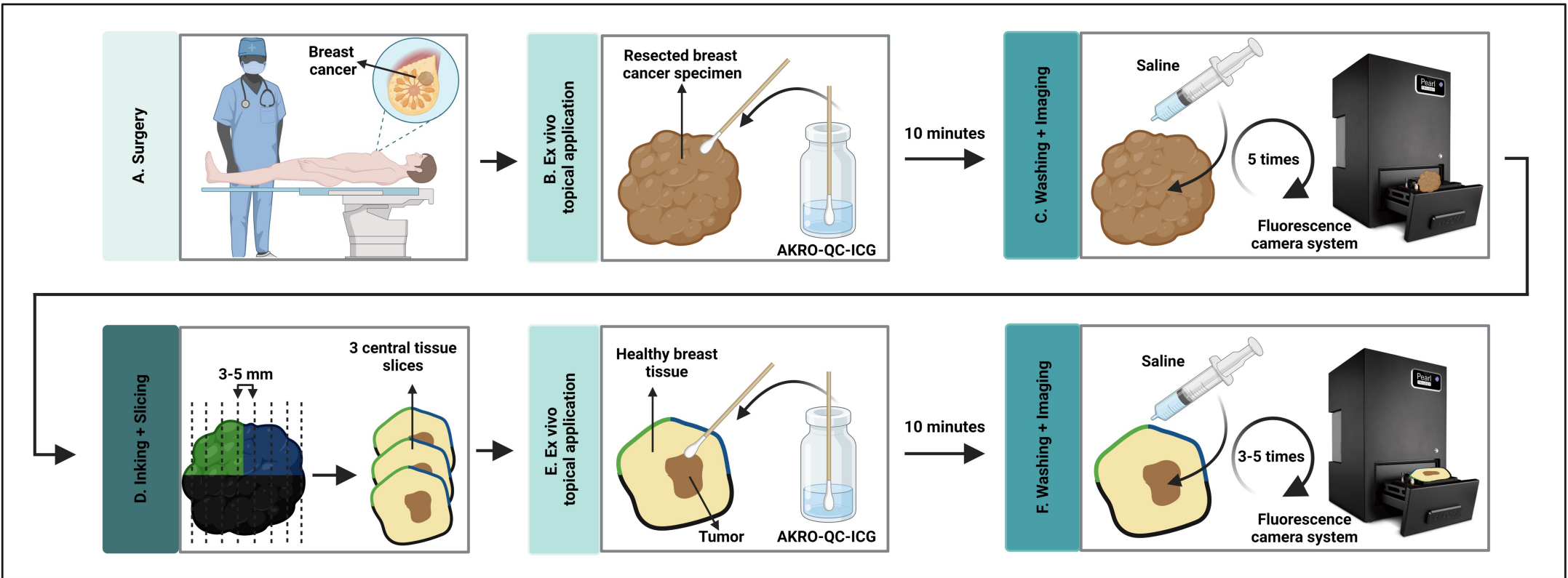
AKRO-QC-ICG: Topische toepassing, quenched, cathepsine-geactiveerde probe



- Cathepsine (proteolytische enzymen) zijn opgereguleerd in diverse tumor typen, waaronder borst kanker
 - Snel (< 10 min), “real-time” beeldvorming of tumor gedurende de operatie

AKRO-QC-ICG: *Ex vivo* proof-of-concept studie in borst tumoren

Studie uitgevoerd in HMC



AKRO-QC-ICG: *Ex vivo* proof-of-concept studie in borst tumoren

Studie uitgevoerd in HMC

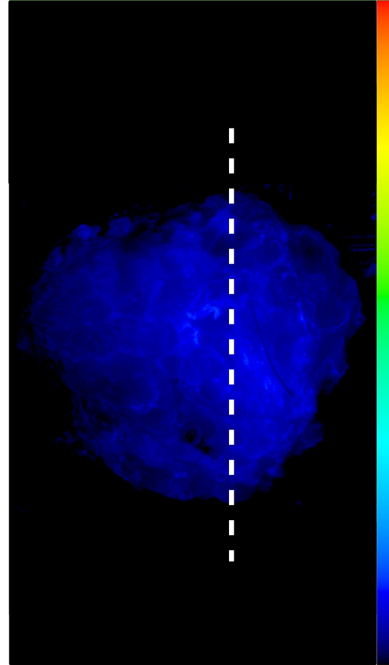
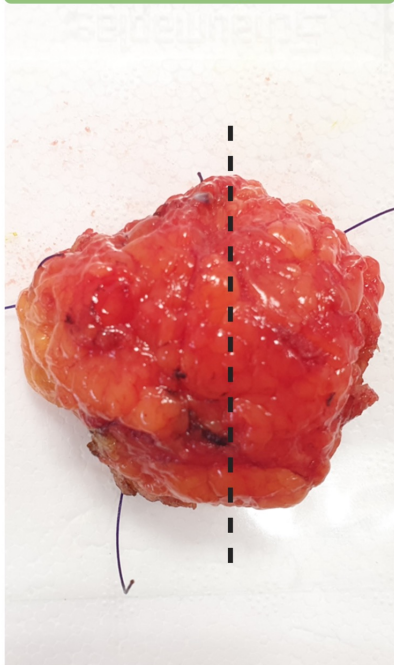
Tumor-negatieve resectie marge

Macroscopic evaluation

(A) Resection plane

Visible Light

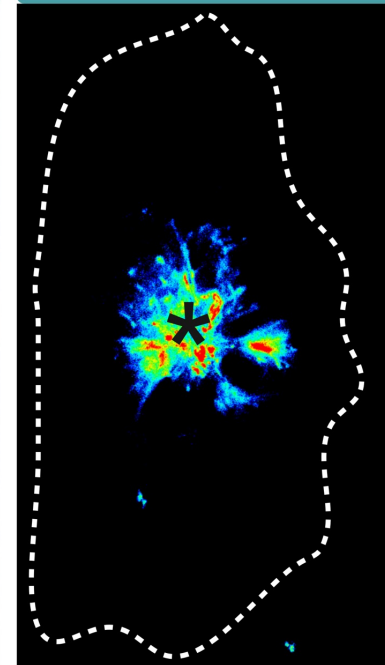
NIR Fluorescence



(B) Tissue slice

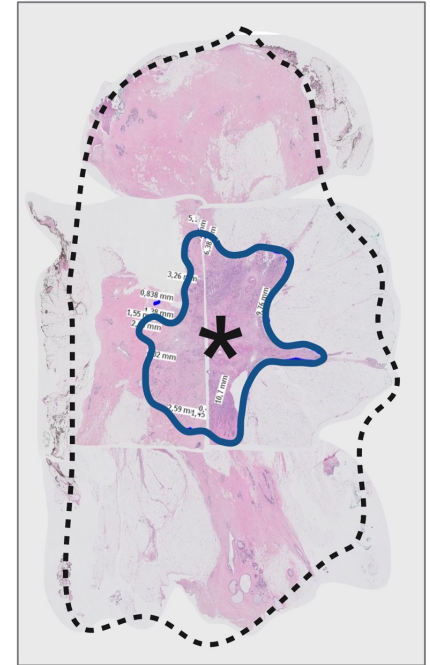
Visible Light

NIR Fluorescence



Microscopic evaluation

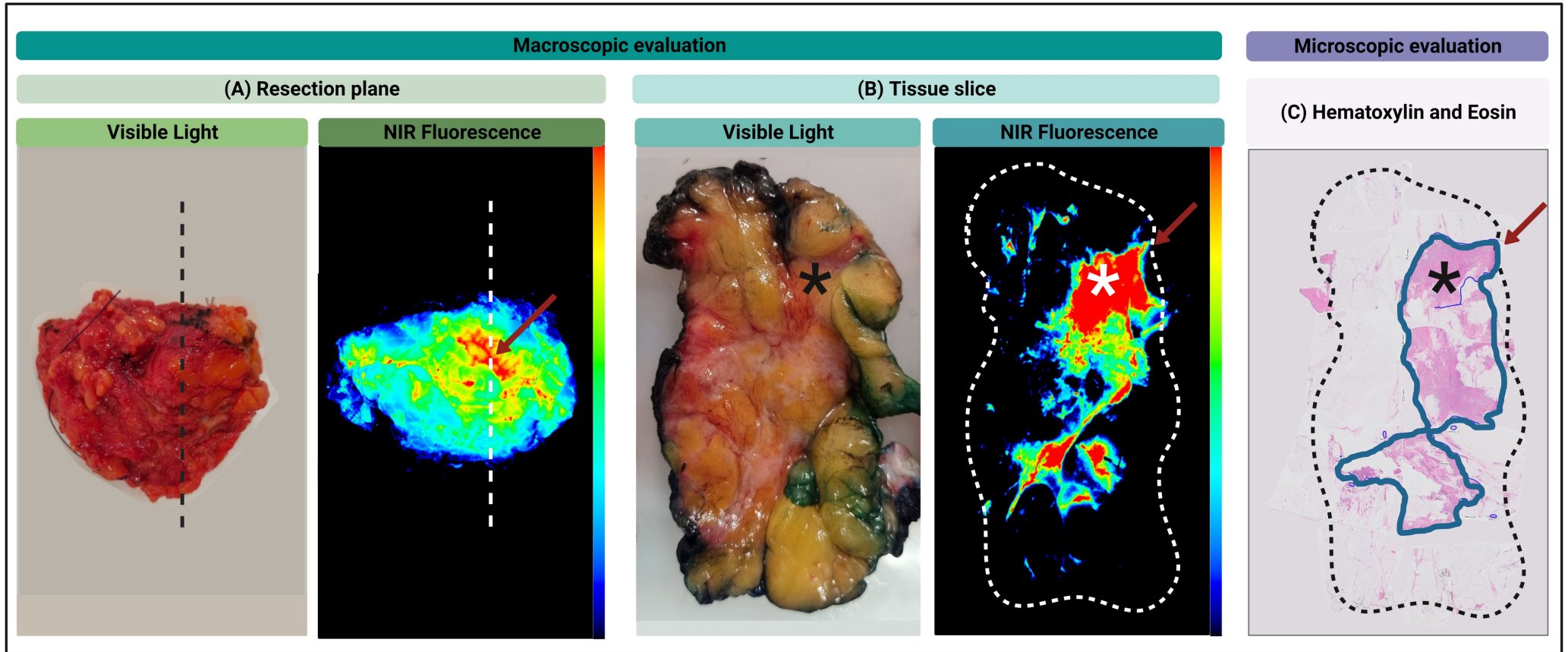
(C) Hematoxylin and Eosin



Ex vivo proof-of-concept studie in borst tumoren

Studie uitgevoerd in HMC

Tumor-positieve resectie marge



Team - NIH



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James Basilion
Ethan Walker



Koos Burggraaf
Robert Rissmann



Matt Bogyo



Alex Vahrmeijer
Daan Linders
Peter Kuppen




Hans Marten Hazelbag
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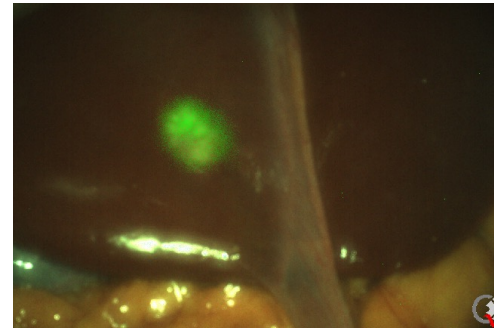
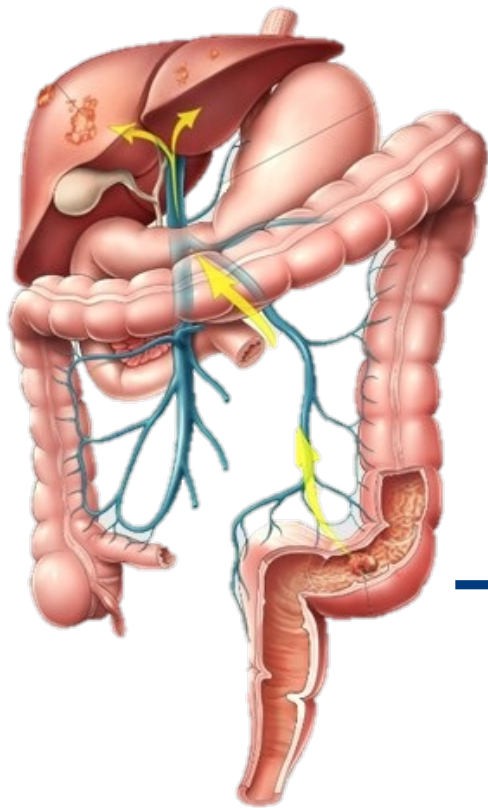
Taryn March
Rob Valentijn
Martin Pool

Future perspectives: Planning – Training - Guidance

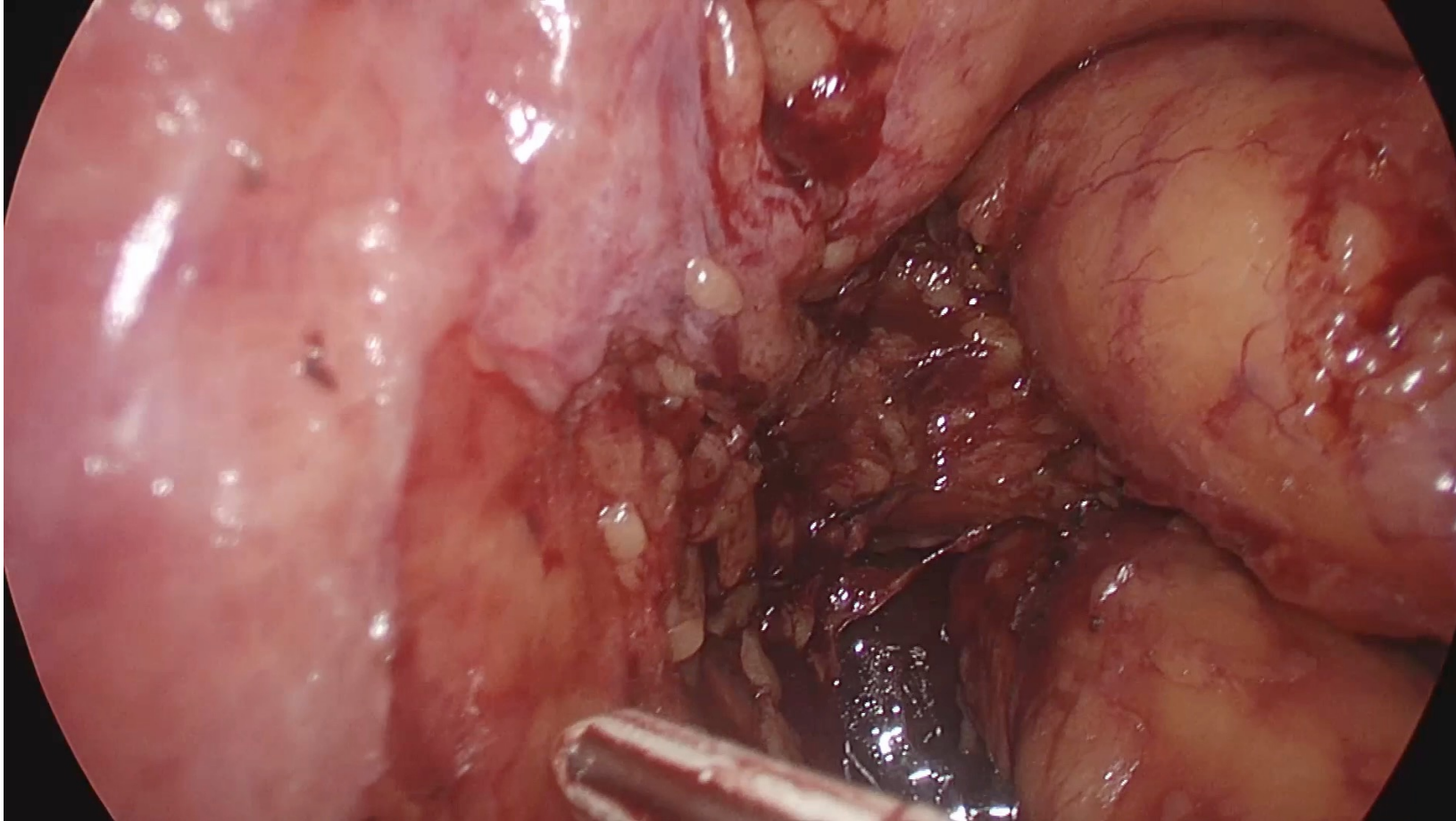
- 
- An iceberg floating in the ocean, with a small portion above the water and a much larger, more complex structure below. The background is a blue sky and sea. The iceberg is white and blue, with a jagged top and a large, irregular shape below the water line.
- Toolbox for Surgeons for real Time Guidance
 - Short Training Cycle by Direct Feedback
 - Novel tracers (EpCAM / cMET / integrins / EGFR / VEGF)
 - Personalized tumor imaging
 - Expanding indications (more tumor types, nerves, etc)
 - Dual-channel imaging
 - Multimodal imaging
 - AI & Quantification
 - Drug delivery

Future of Surgery: SGM-101 / ZW800-1 / ICG

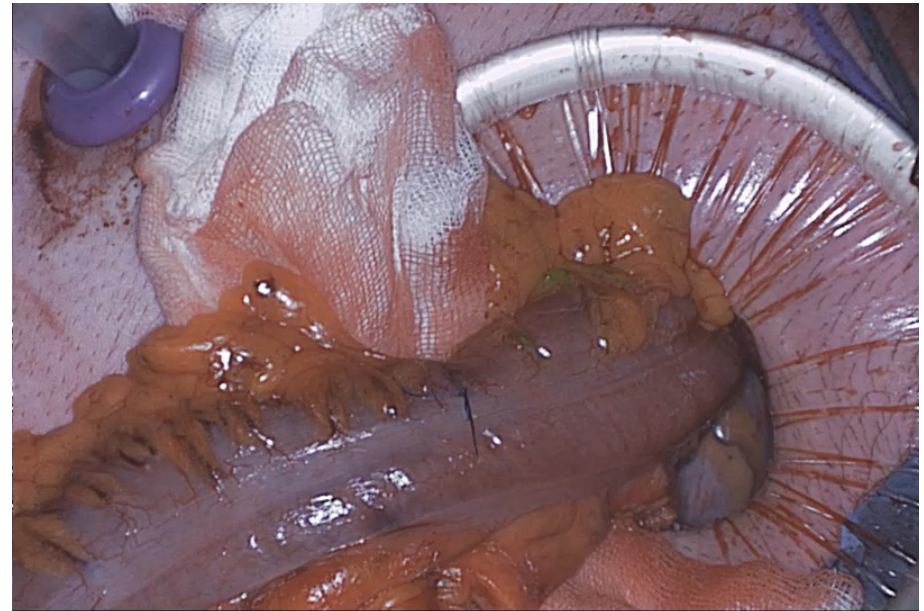
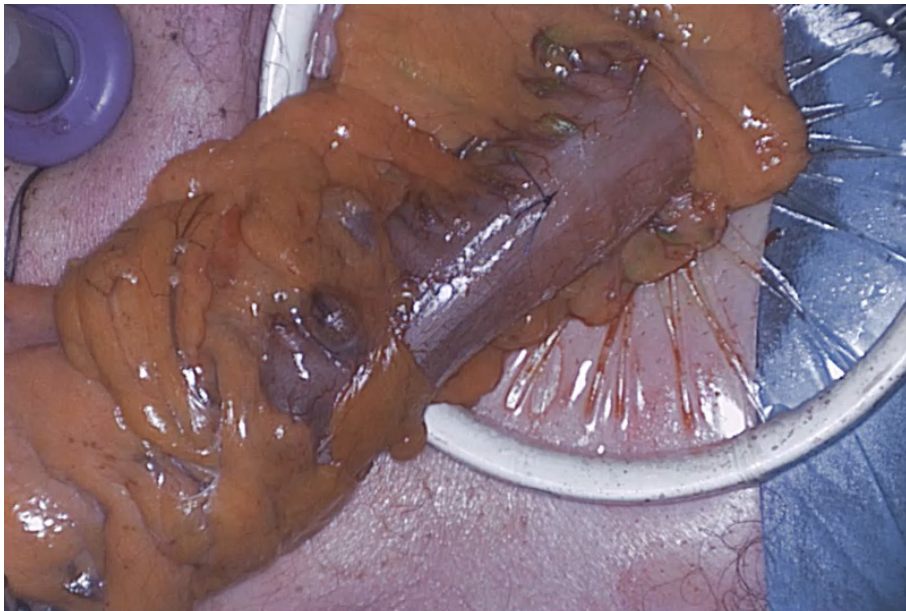
Direct Feedback



Ureter identificatie – ZW800-1



Perfusie beoordeling met ICG en Quest Spectrum



Expanding Expertise → Transfer Knowledge → Training

MIMIC Trial

- 9 centers
- 200 patients
- Colorectal liver

AVOID Trial

- 8 centers
- **RCT**
- 1000 patients
- Tissue perfusion
- Colorectal anastomoses

DIEP Trial

- 2 centers
- **RCT**
- 280 patients
- Perfusion DIEP
- Reconstructive breast surgery
- Wound

SGM-101 (anti-CEA)

- 10 centers
- **Phase III RCT**
- 300 patients

Building a network for future studies





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for the benefit of cancer patients



ESSO Course on
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Surgery
2 & 3 June 2024



LUMC

Chairs

Sven Mieog,

Leiden University Medical Center, NL

Karol Polom,



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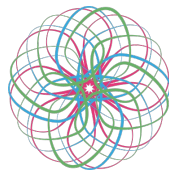
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Olympus Nederland

Tim Laagland



CHDR



OLYMPUS



Geschiedenis van klinische translatie van beeldvorming

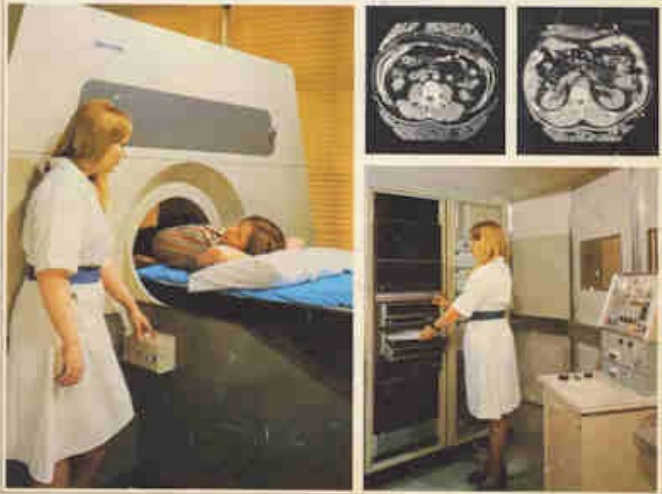
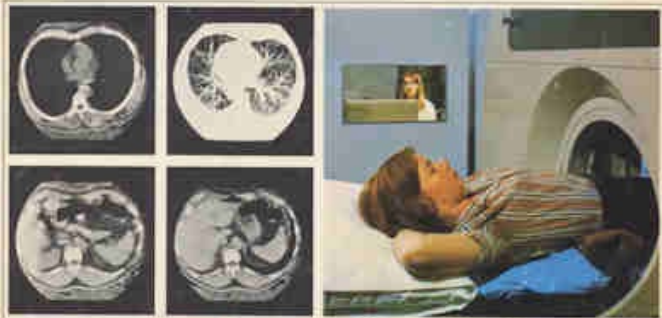
“What we learn from history is that people don't learn from history.” Warren Buffett

<u>Modality</u>	<u>First Patient</u>	<u>Clinical Acceptance</u>	<u>Lag</u>
PET	1953	≈ 2003	≈ 50 years
Plain Films (X-rays)	1895	≈ 1920s	≈ 25 years
SPECT	≈1963	≈ 1985	≈ 23 years
US	≈1940s	≈ 1960s	≈ 20 years
MRI	1970	≈ 1985	≈ 15 years
CT	1967	≈ 1975	≈ 7 years
NIR Optical (-Contrast)	1998	? ?	25+ years
NIR Optical (+Contrast)	1999	? ?	24+ years

Gemiddeld 23 jaar; Mediaan = 22 yrs

EMI-Scanner CT5000 EMI

A major advance in body tissue examination



Godfrey N. Hounsfield
Nobel prize medicine 1979

Leiden University Medical Center

Thank you for your attention

Center for Human Drug Research

www.greenlight.nu



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