Michael H. Weber

New Methods and Laser Technology in Photodynamic Cancer Therapy

Photodynamic therapy (PDT)

- Photodynamic therapy is one of the most interesting and promising approaches in the treatment of various cancers.
- The principle is the stimulation of a light sensitive drug which is injected into the blood and accumulates in cancer cells
- Tumor tissue is subsequently destroyed by irradiation with light of appropriate wavelength according to the absorption spectra of the various photosensitizers
- The basic principle behind this mechanism is the development of radical oxygen species.

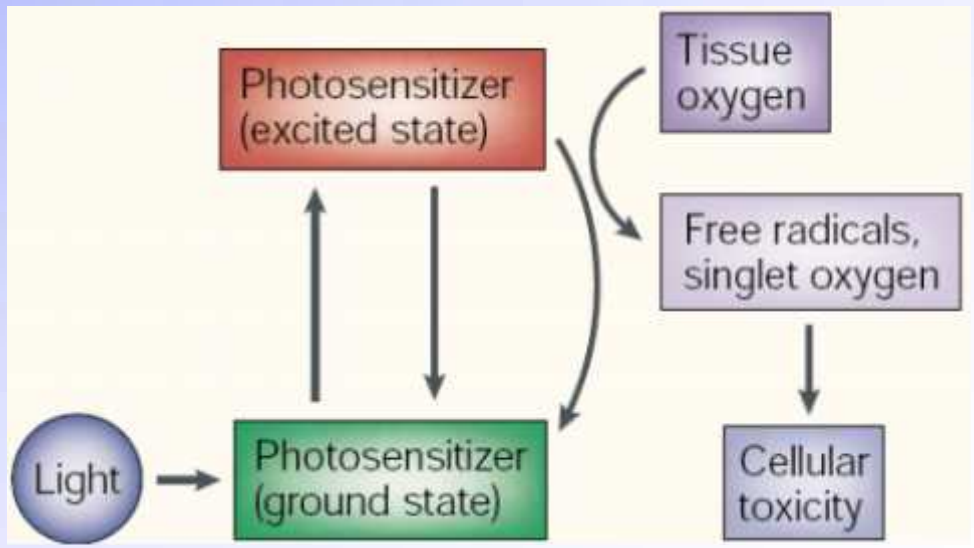
Photodynamic therapy (PDT)

- However up to today PDT was limited to cancer treatment of superficial tumors
- Because we are not able to bring the laser beam in a sufficiant concentration deeper into the body.

Introduction:
Process of Photodynamic Therapy

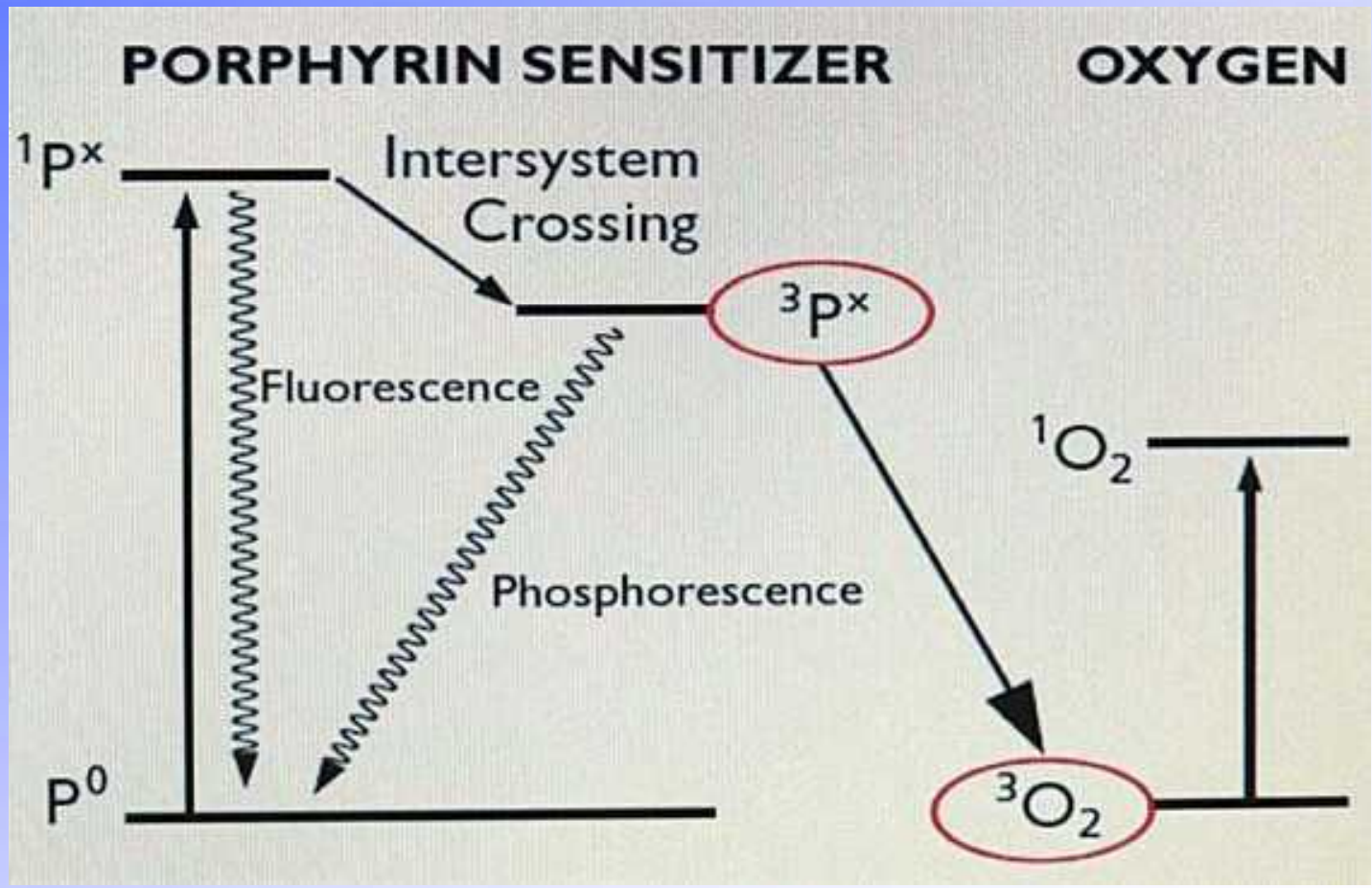
- 2 individually non-toxic components brought together to cause harmful effects on cells and tissues

  - Photosensitizing agent
  - Light of specific wavelength

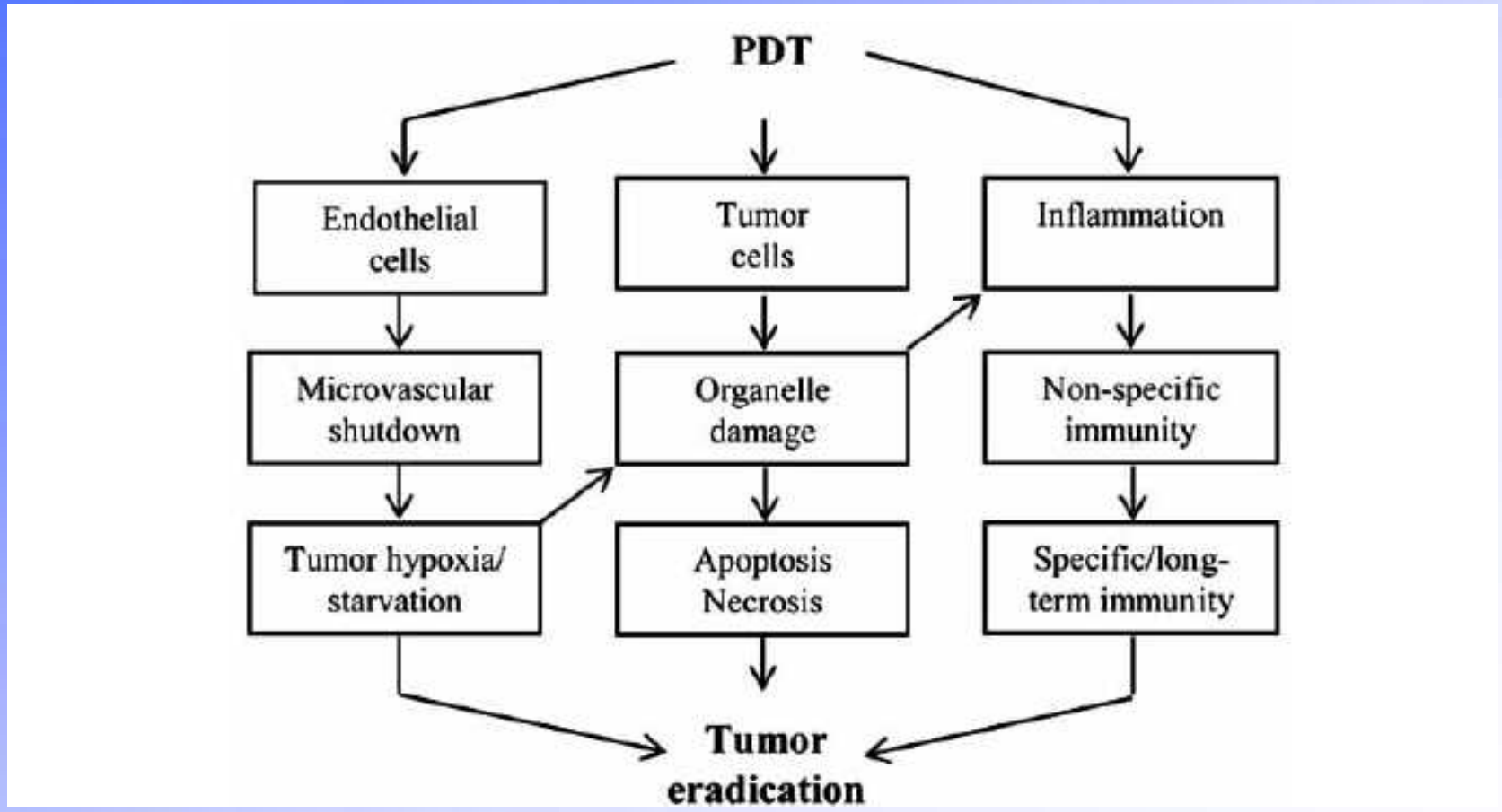


Nature 2003, 3, 380.

Photodynamic Therapy



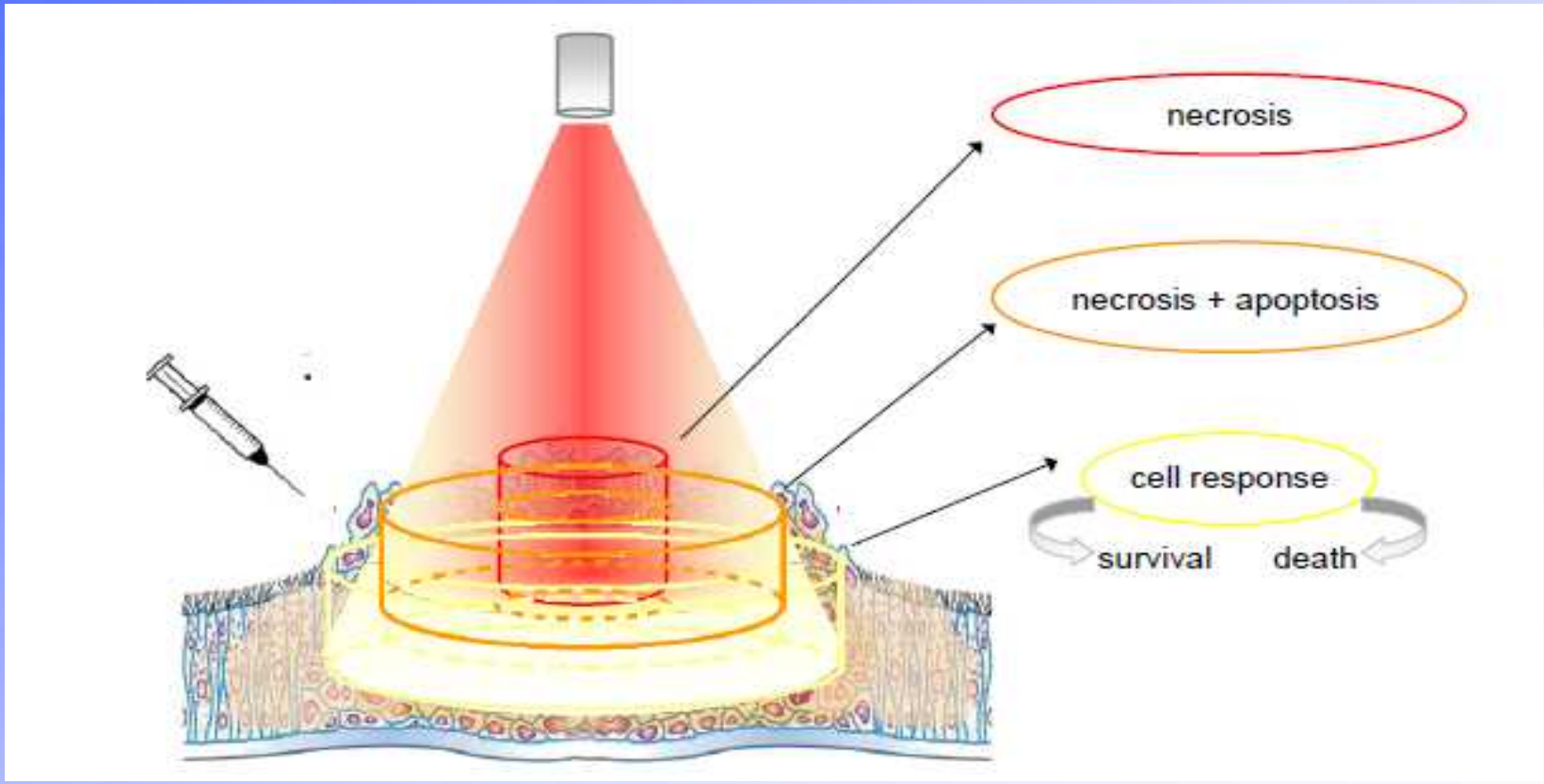
Mechanisms of PDT



Mechanisms of PDT

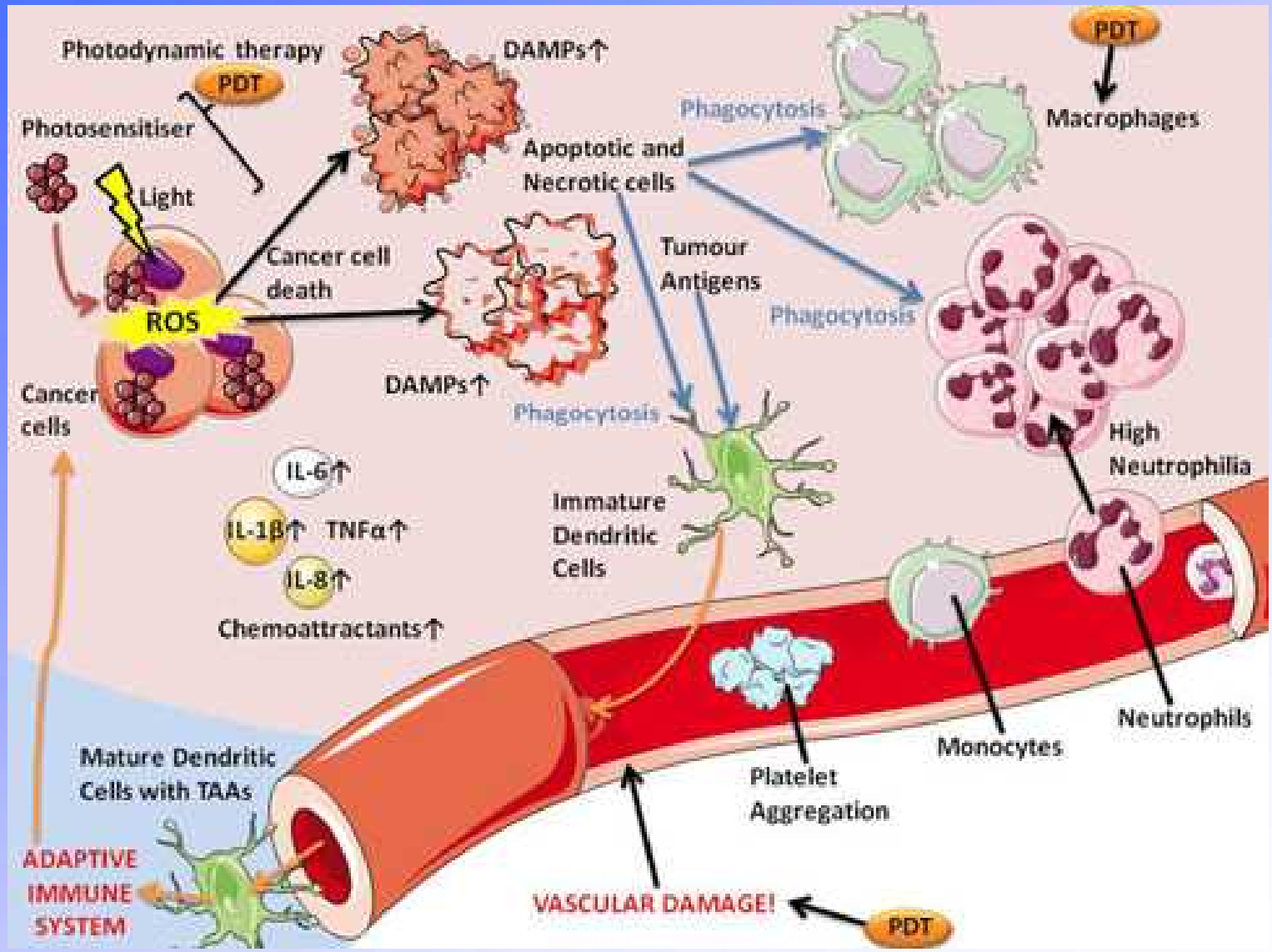
- Selective targeting of tumor cells
- Minimal side effects
- No resistance after repeated treatments
- Tumor vascular shutdown by thrombosis and haemorrhages
- Induction of local inflammation
- Immune activation

The photodymamic reaction



Light distribution and cellular response during PDT

Immunological effects of PDT



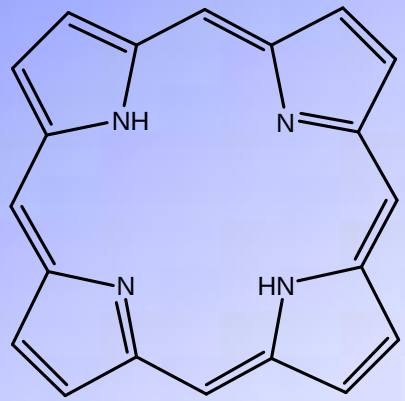
Photosensitizers

Traditional Photosensitizers
(porphyrin derived)

- Haematoporphyrins, HpD

  - Derivatives of Haem

  (Photofrine and others)



- Chlorines
  - Derivatives of Chlorophyll

- Porphycenes
  - Synthetic Porphyrines

Photodynamic Therapy traditional Photosensitizers

Table 1 Currently available photosensitizers.

Platform	Drug	Substance	Manufacturer	Web site
Porphyrin	Photofrin®	HpD	Axcan Pharma, Inc.	www.axcan.com
Porphyrin	Levulan®	ALA	DUSA Pharmaceuticals, Inc.	www.dusapharma.com
Porphyrin	Metvix®	M-ALA	PhotoCure ASA	www.photocure.com
Porphyrin	Visudyne®	Vertiporfin	Novartis Pharmaceuticals	www.visudyne.com
Texaphyrin	Antrin®	Lutexaphyrin	Pharmacylics	www.pharmacyclics.com
Chlorin	Foscan®	Temoporfin	Biolitec Pharma Ltd.	www.bioletcpharma.com
Chlorin	LS11	Talaporfin	Light Science	www.lightsciences.com
Chlorin	Photochlor	HPPH	RPCI	www.roswellpark.org
Dye	Photosens®	Phthalocyanine	General Physics Institute	www.gpi.ru

Photodynamic Therapy
Treatment indications (all superficial)

Photosensitizer	Type of diseases	Country
(*5-ALA*) 5-aminolevulinate	Actinic keratosis, Basal cell carcinoma	U.S., EU
Photofrin	Barrett's displasia	U.S., Canada, EU, UK
Photofrin	Cervical cancer	Japan
Photofrin	Endobronchial cancer	Canada, Most EU Countries, Japan, U.S.
Photofrin	Esophageal cancer	Canada, Most EU Countries, Japan, U.S.
Photofrin	Gastric cancer	Japan
Photofrin	Papillary bladder cancer	Canada
Foscan	Head and neck cancer	EU, Norway, Iceland
Verteporfin	Age-related Macular Degeneration	Canada, Most EU Countries, Japan, U.S.

Photosensitizers approved for therapy

Photodynamic Therapy
New natural derived Photosensitizers

- Chlorin E6 (Red 660 nm)
- Indocyaninegreen liposomal (Infrared 810 nm)
- Hypericin (Yellow 589 nm)
- Curcumin (Blue 447 nm)
- Riboflavin (Blue 447 nm)

Photodynamic Therapy:
new chemodrug derived Photosensitizers

- Doxorubicin, liposomal (447 nm, blue)
- Mitoxantron, (yellow 589nm, red 632nm)
- Paclitaxel, (ultraviolett, 345 nm)
- Cisplatin, (ultraviolett, 345 nm)
- 5-FU, (ultraviolett, 345nm)

Topical photodynamic therapy
5-Aminolaevulinic-acid, (5-ALA Creme)

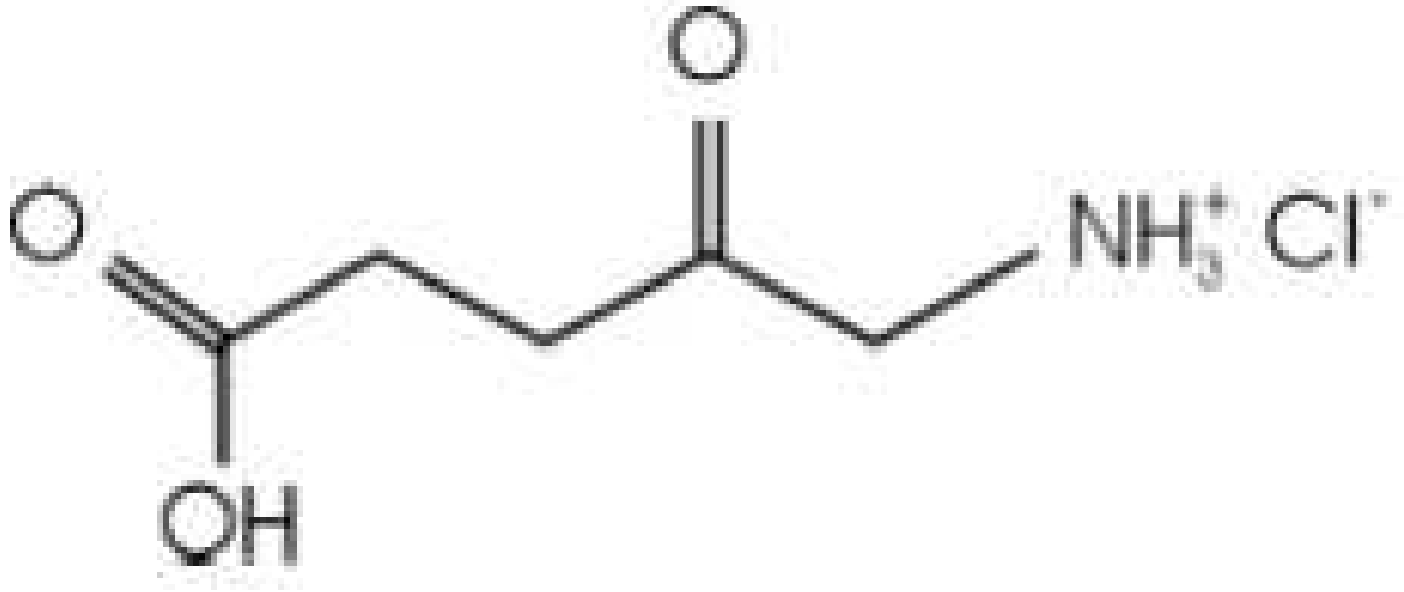
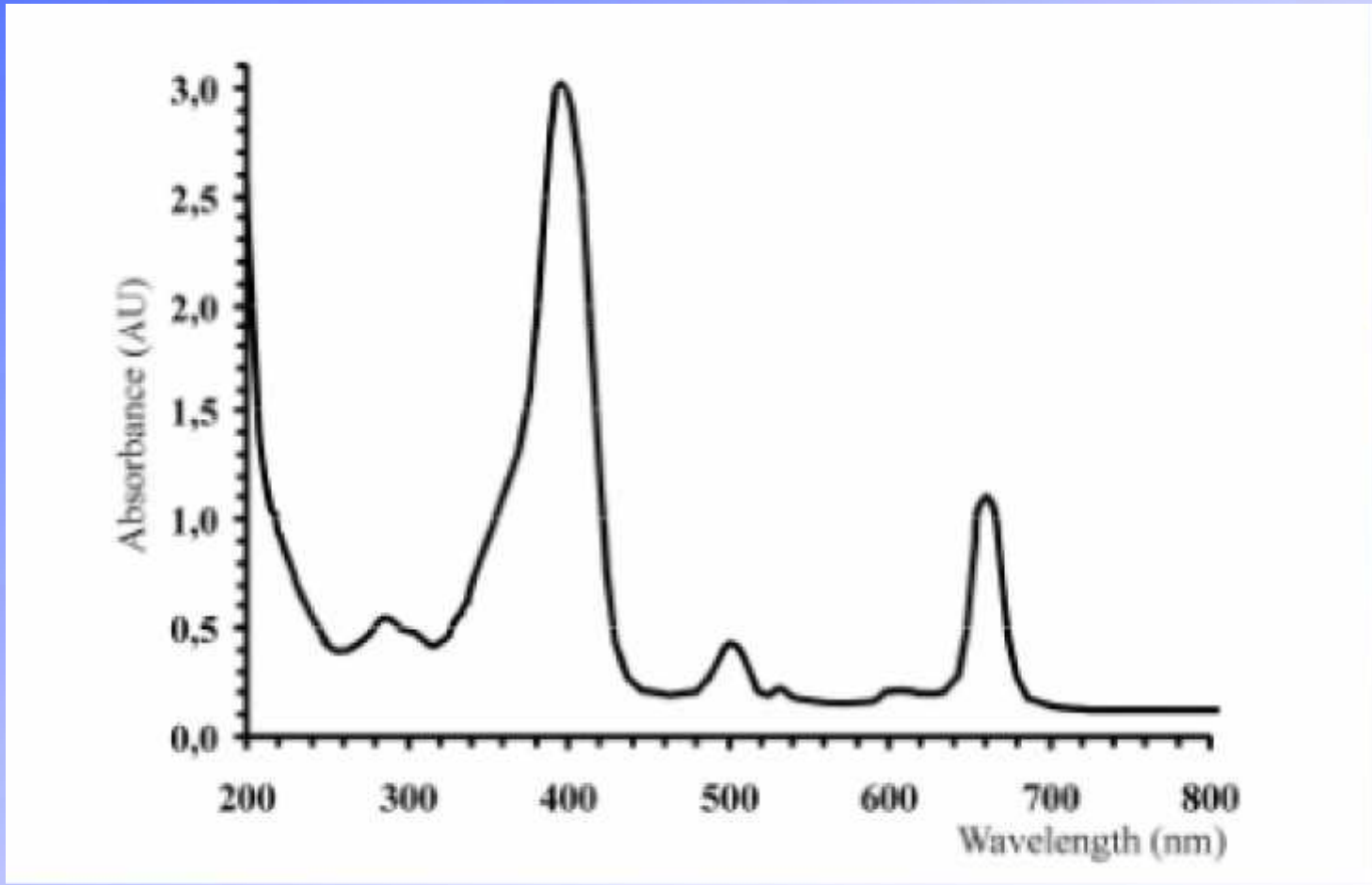


Figure 2 Molecular structure for ALA.

Photodynamic Therapy

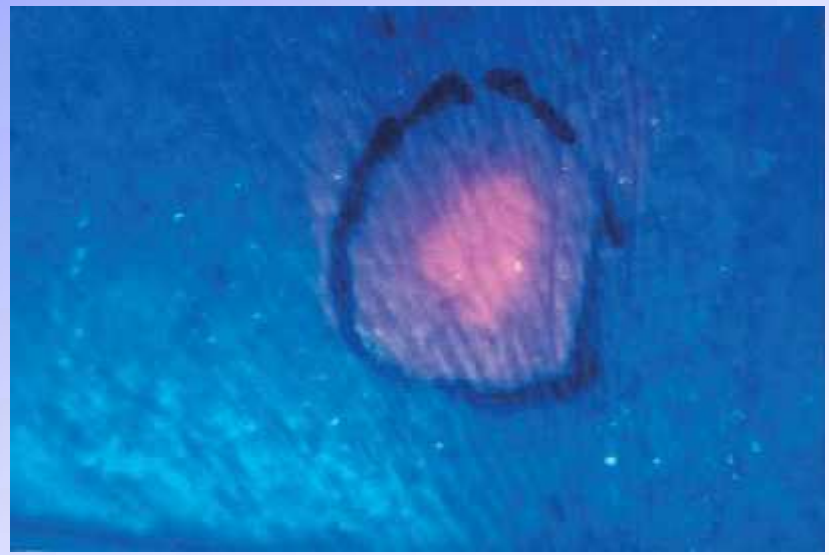
Absorption spectrum of 5-ALA



Photodynamic diagnostics PDD

(Fluorescense diagnostic with blue laser)

Fuselage skin basal cell carcinoma in daylight

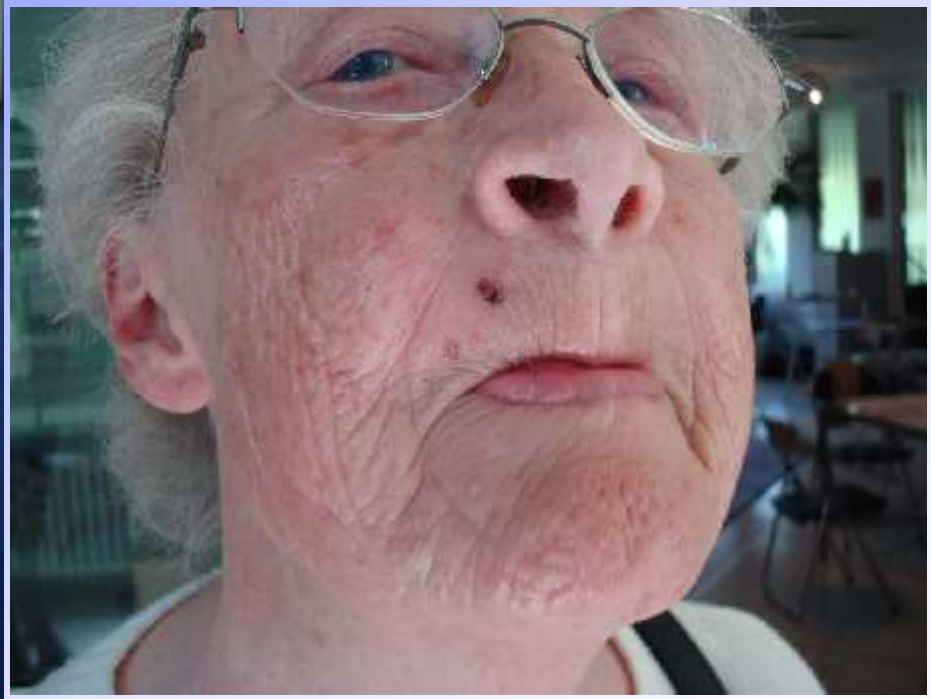


Fuselage skin basal cell carcinoma under wood light

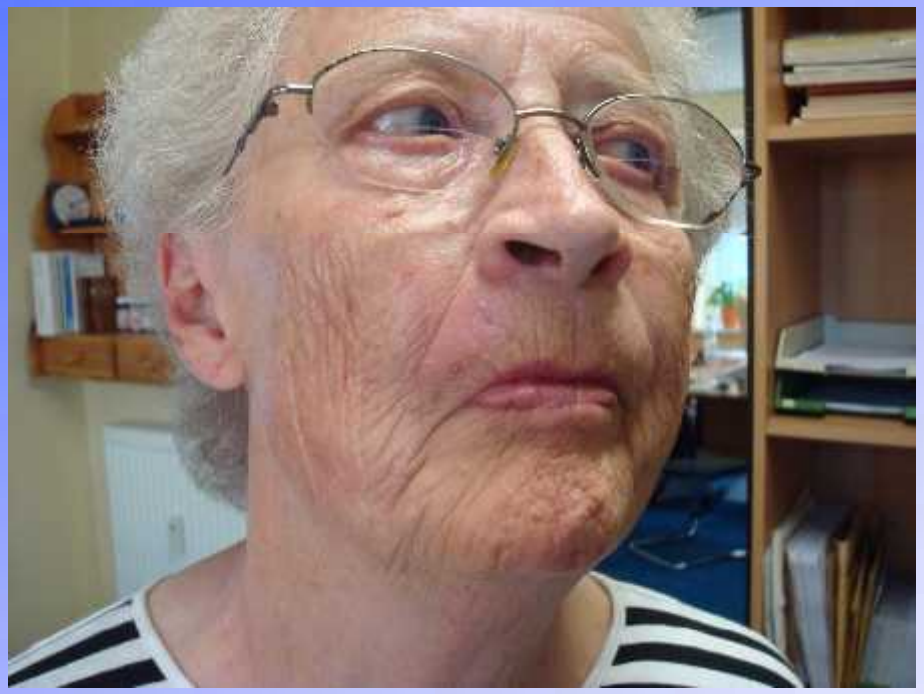
Photodynamic therapy of actinic keratosis

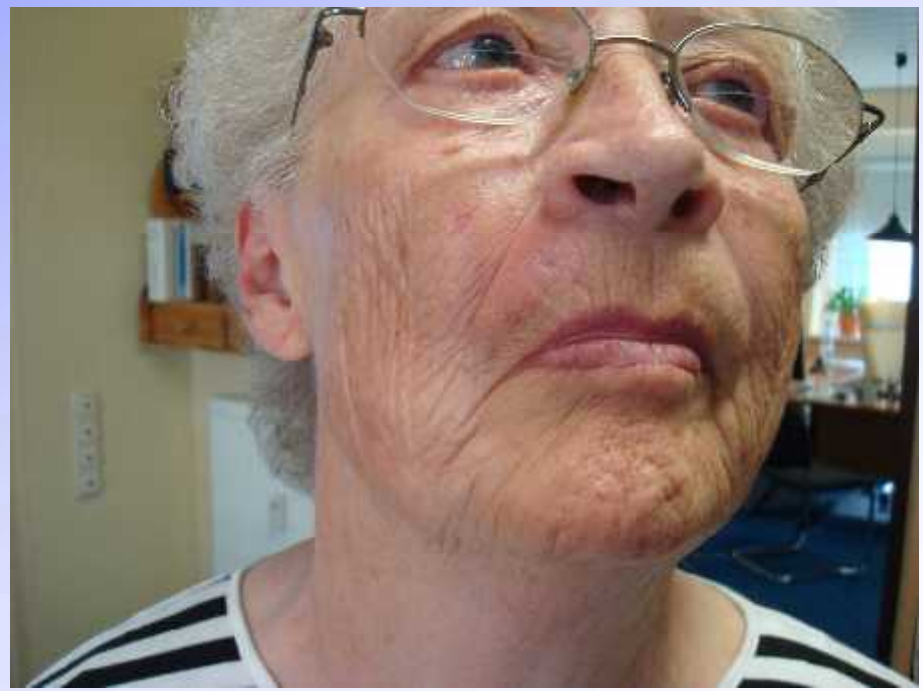
Photodynamische Therapie von Basaliomen und aktinischen Keratosen

Photodynamic therapy of basal cell carcinoma



Photodynamic therapy of basal cell carcinoma





Photodynamic therapy of basal cell carcinoma

Ulcerated basal cell carcinoma before treatment

Findings after 1 treatment PDT

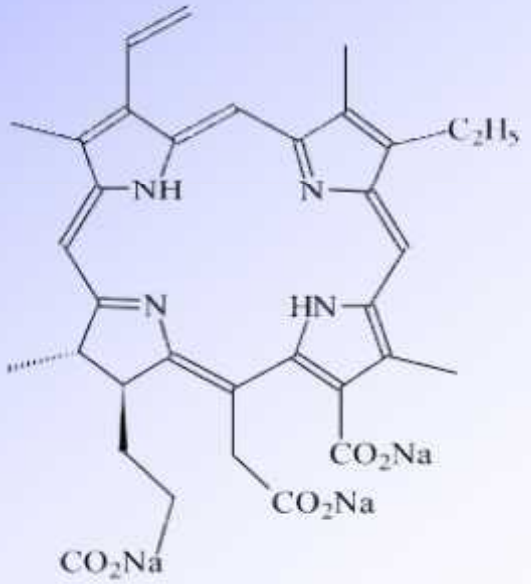
Systemic photodynamic therapy

Fotolone (Chlorin E6)

- Chlorin e6 as photosensitizer
- Indications
- current development status

Chlorin E6
(chemical properties)

- trisodium salt of the „green“ porphyrin
- high solubility in water
- Molecular formula: $C_{34}H_{33}N_4Na_3O$
- High stability of the lyophilized API



APOCARE PHARMA GMBH

Production of Chlorin E6

Natural sources (algae, grass, lucerne etc.)

FDA approved, GAP

inexhaustible availability (different sources/world-market)

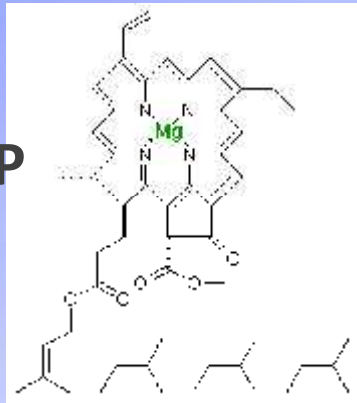
APOCARE PHARMA GMBH

Production of Chlorin E6

GAP

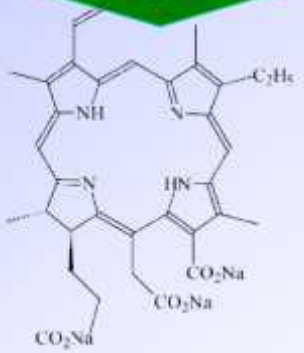
Extraction

In accordance to GMP



Processing

GMP process:
- unique
-Efficient
- highes purity



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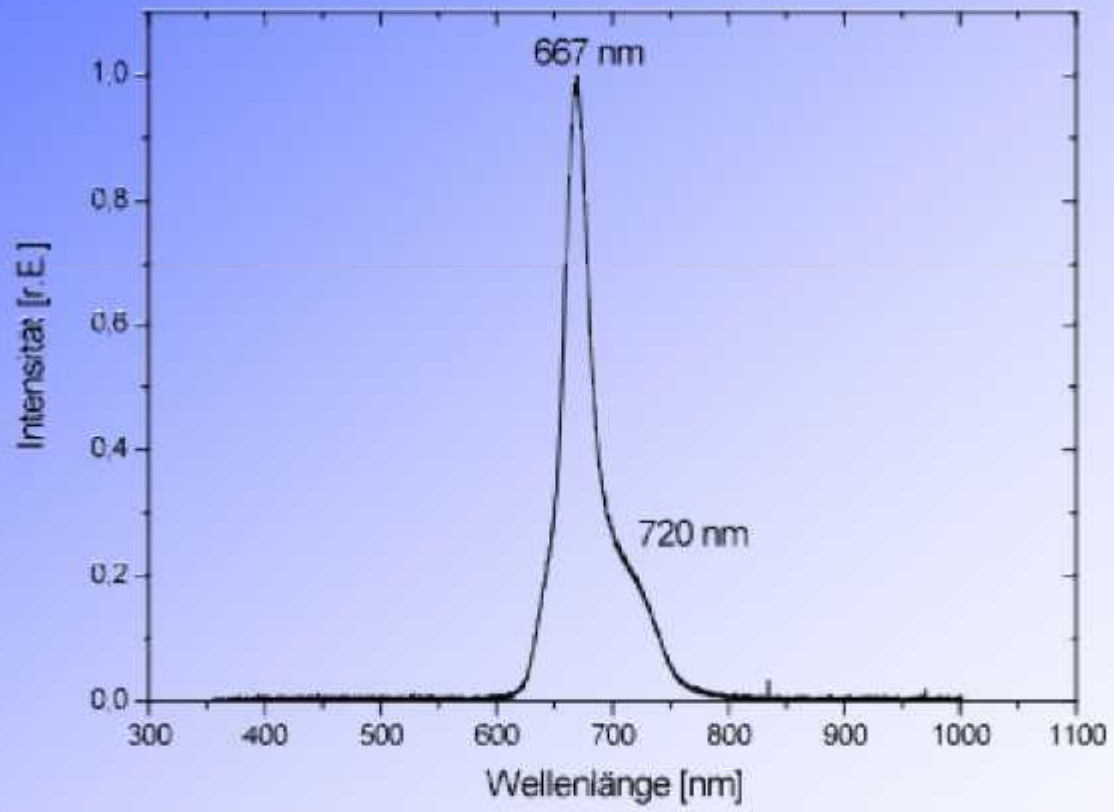
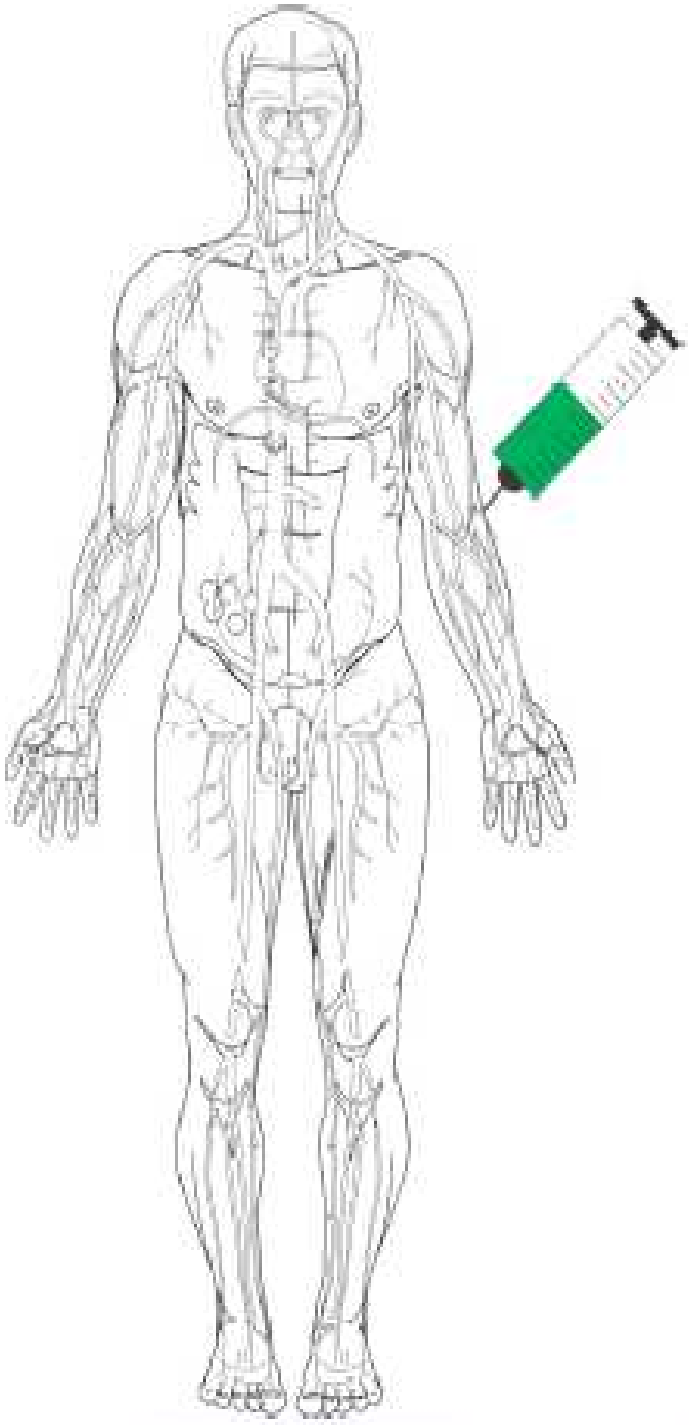
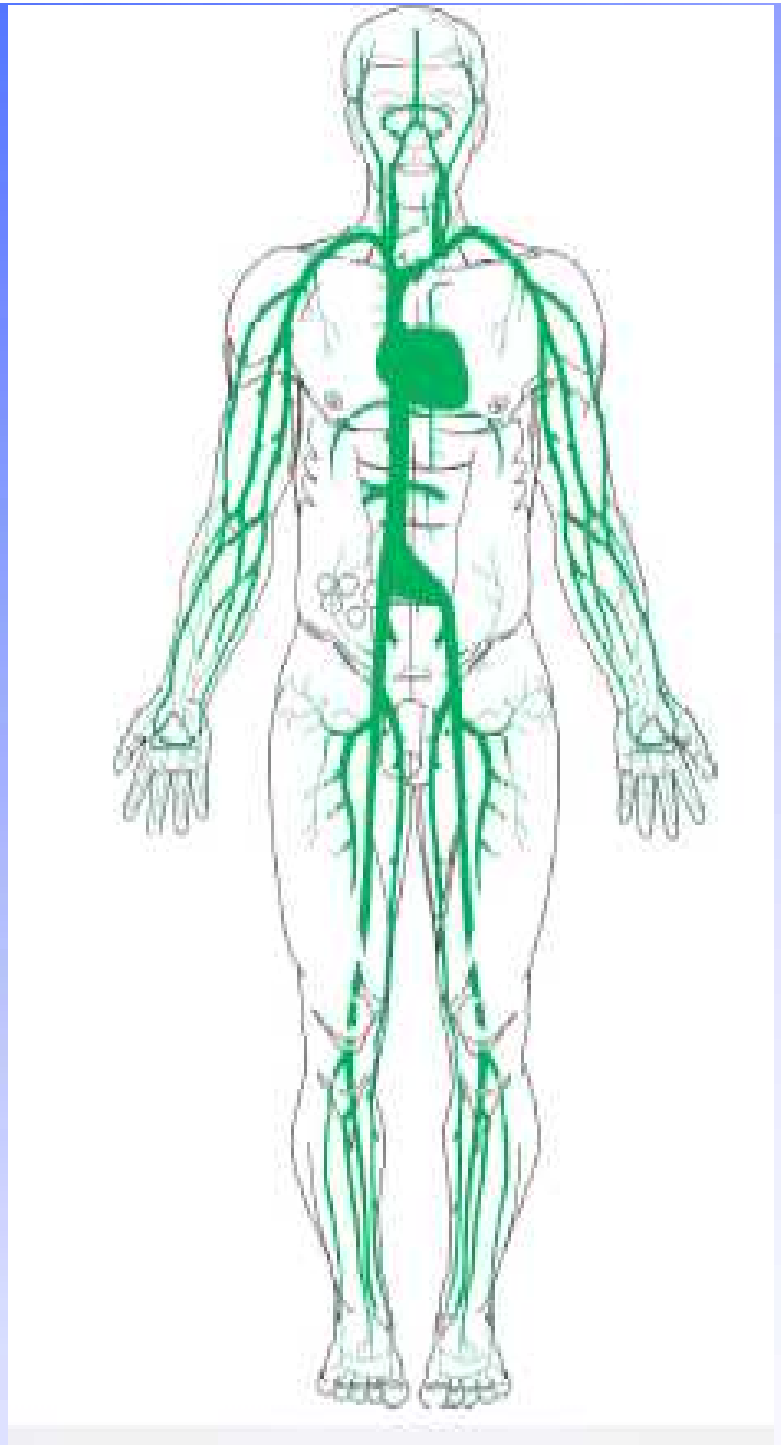
Absorption spectrum of Chlorin E6

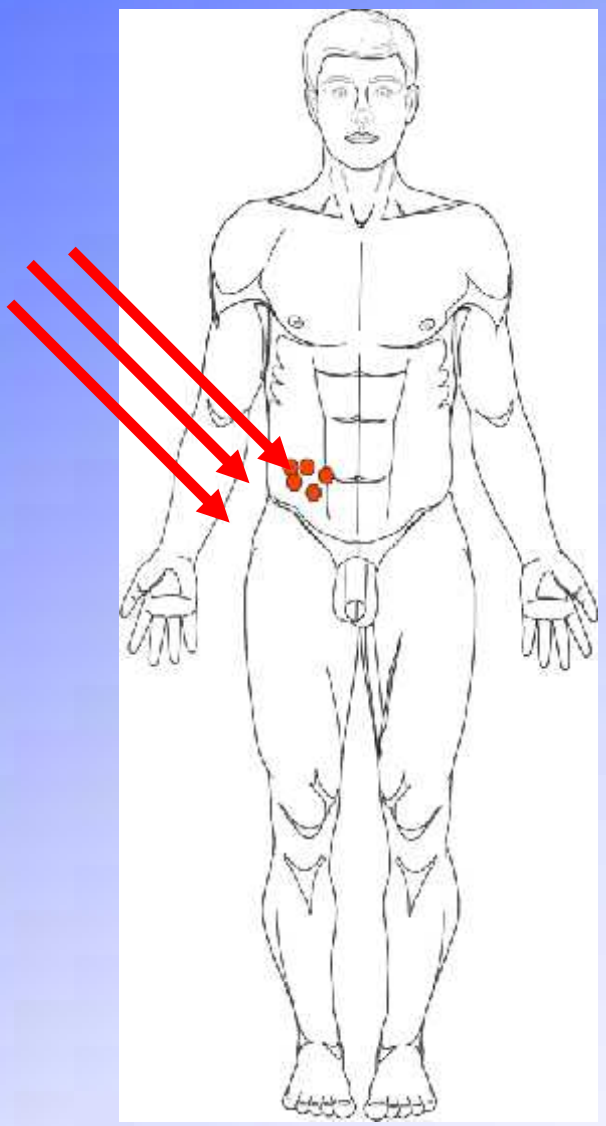


APOCARE PHARMA GMBH





1 – 15 min



PDT

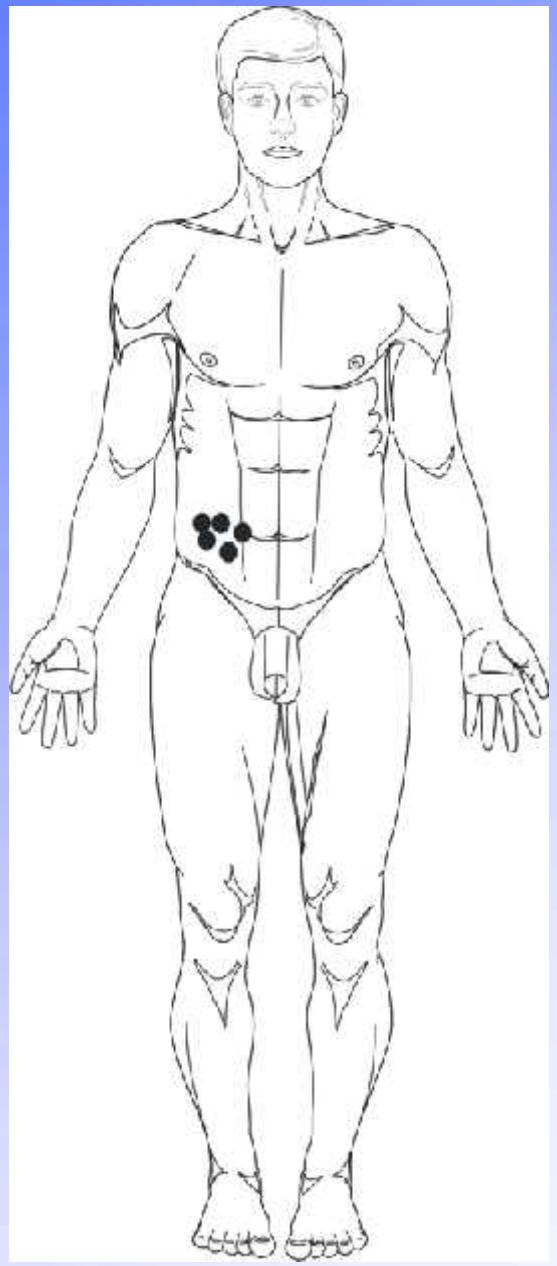
Generation of singlet oxygen

APOCARE PHARMA GMBH

24 – 48 h

- Apoptosis/
  Necrosis

- Elimination
  of Ce6 from blood



PDT

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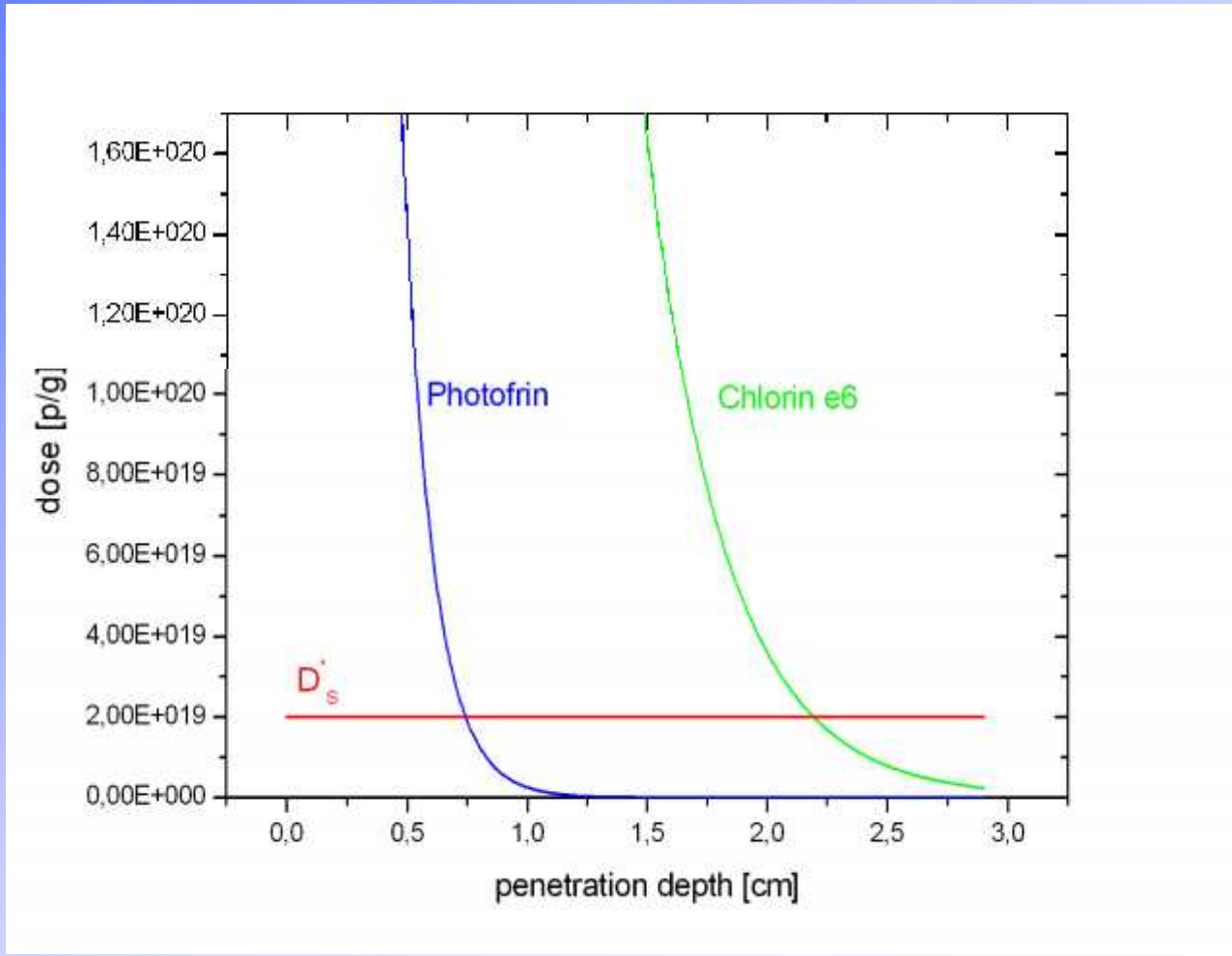
PHARMA GMBH

Problem of all porhyrin derived photosensitizers:

limited penetration depth with red laser and tumor size



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The body shower for superficial tumors with external irradiation

Insertion of laser-needles with different wavelengths into a special shower head

External PDT of lymph metastases

Potential overdosing with skin burn

Interstitial photodynamic therapy of liver metastases

Eur Radiol (2004) 14:1063–1073
DOI 10.1007/s00330-004-2290-8

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and Interventional Radiology,
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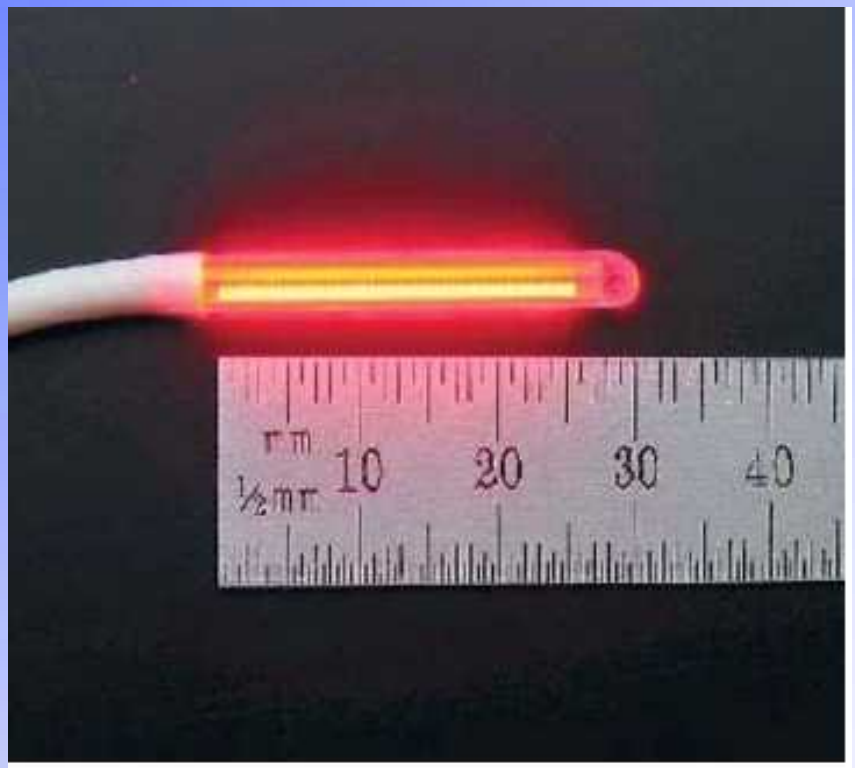
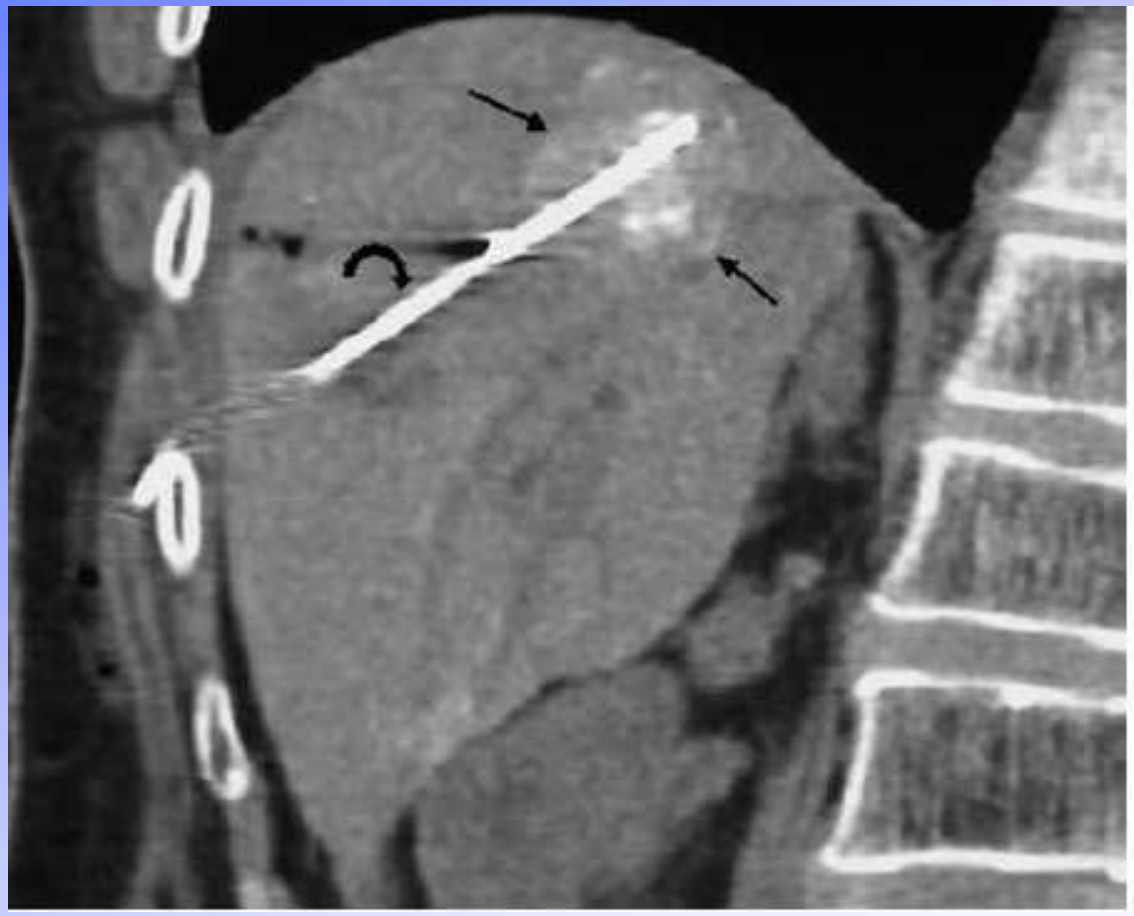
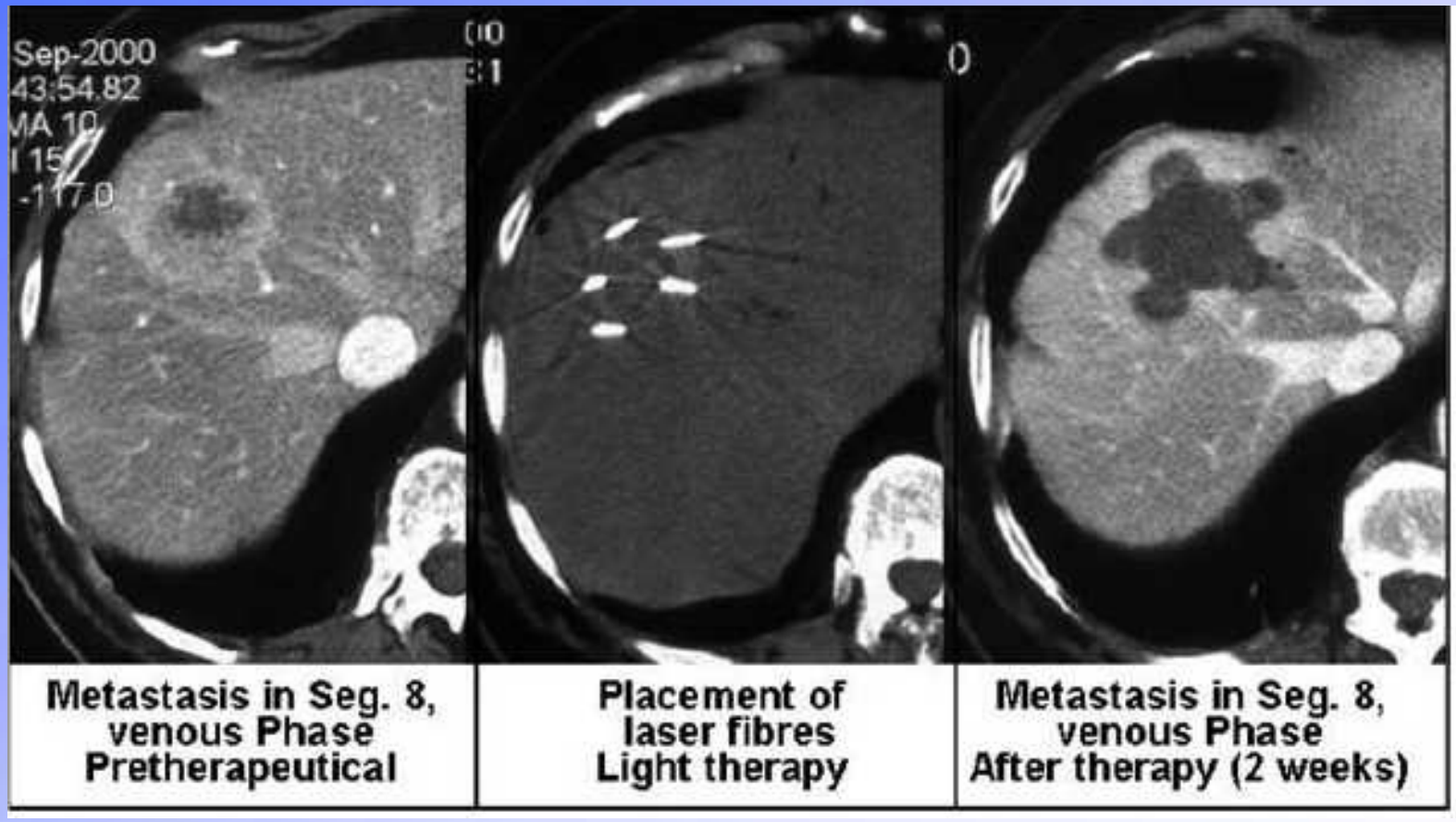


Interstitial photodynamic therapy of liver metastases

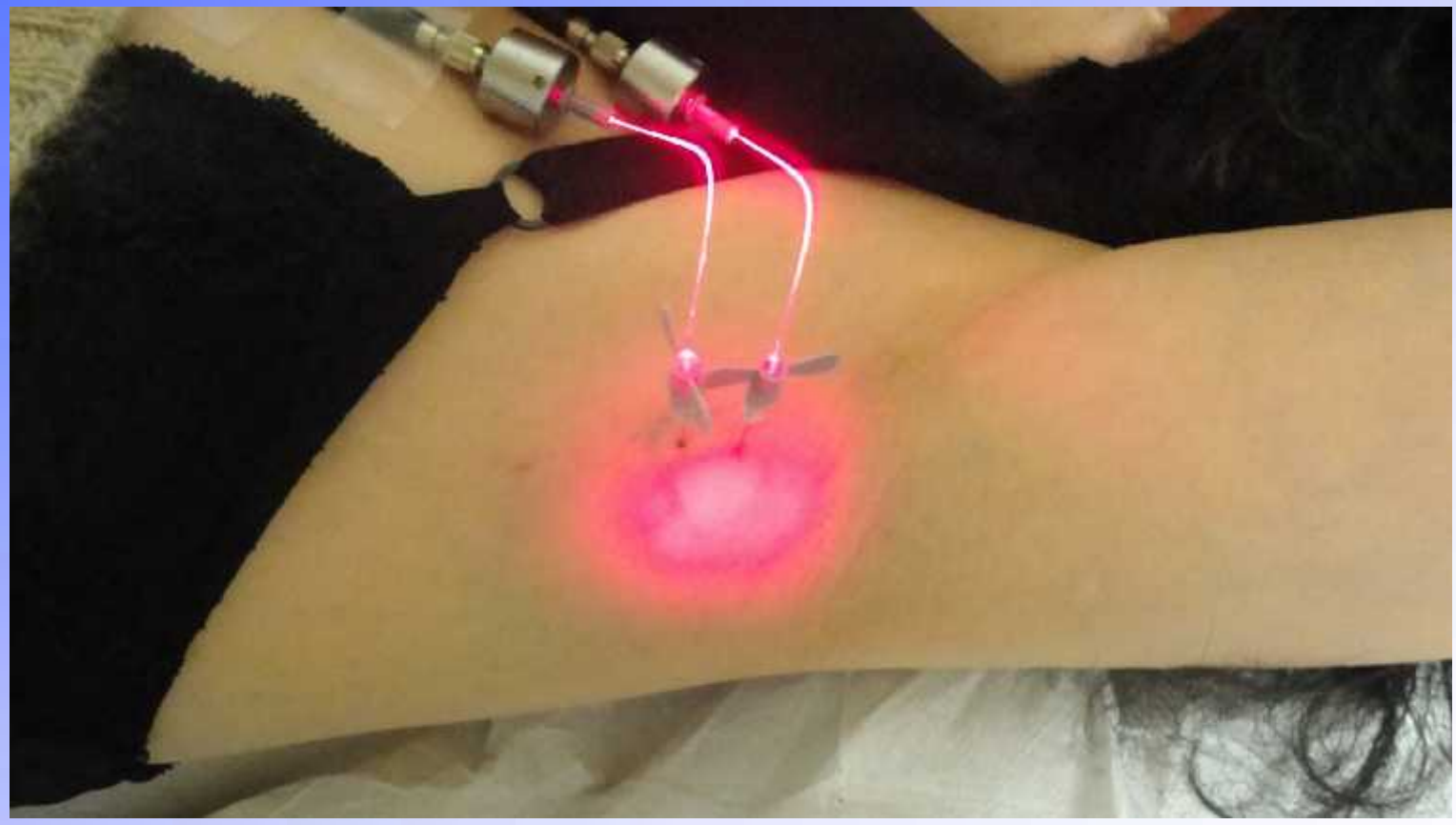


Interstitial photodynamic therapy of liver metastases

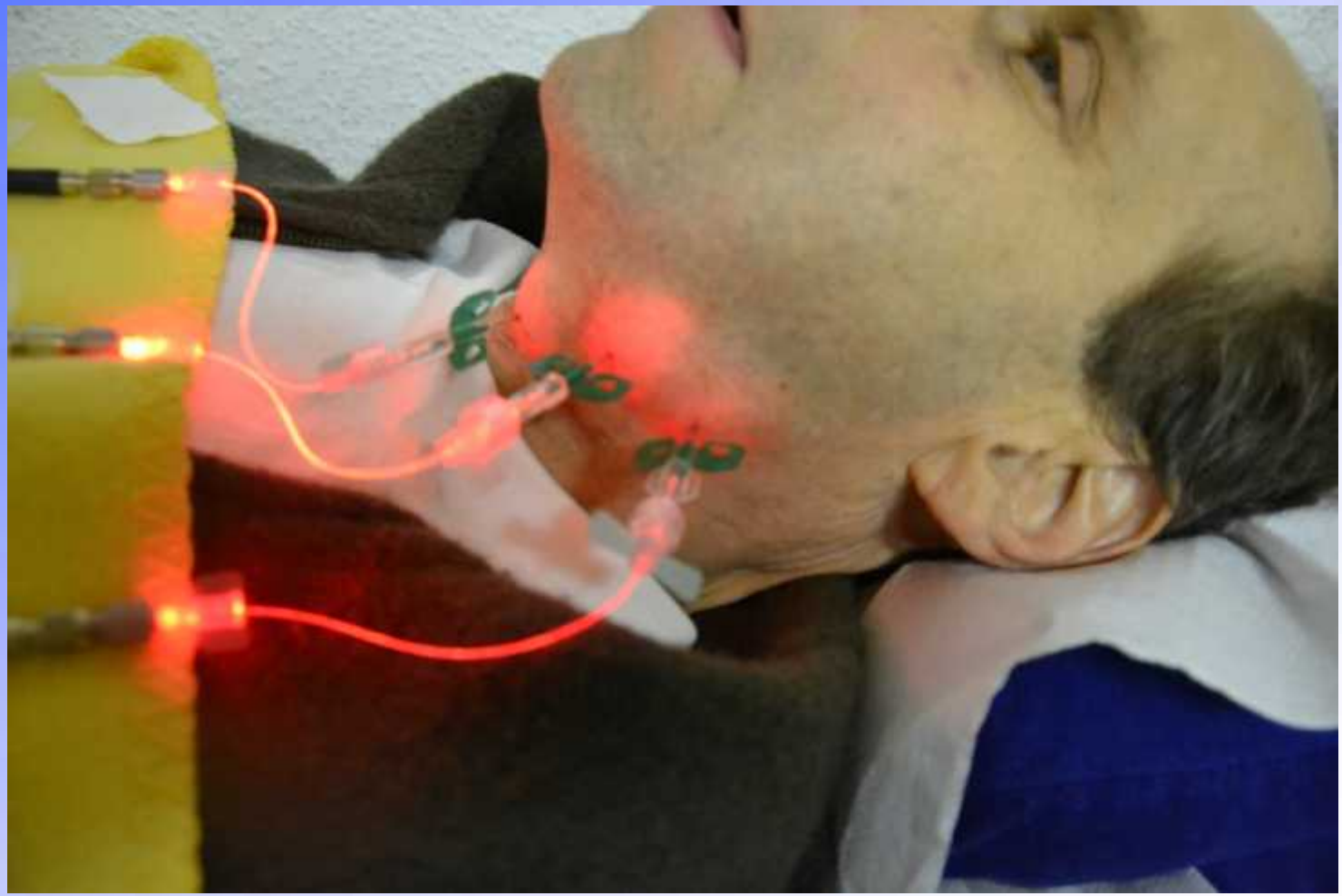


Interstitial PDT of lymph metastases

Interstitial PDT of lymph metastases



Interstitial PDT of squamous cell carcinoma



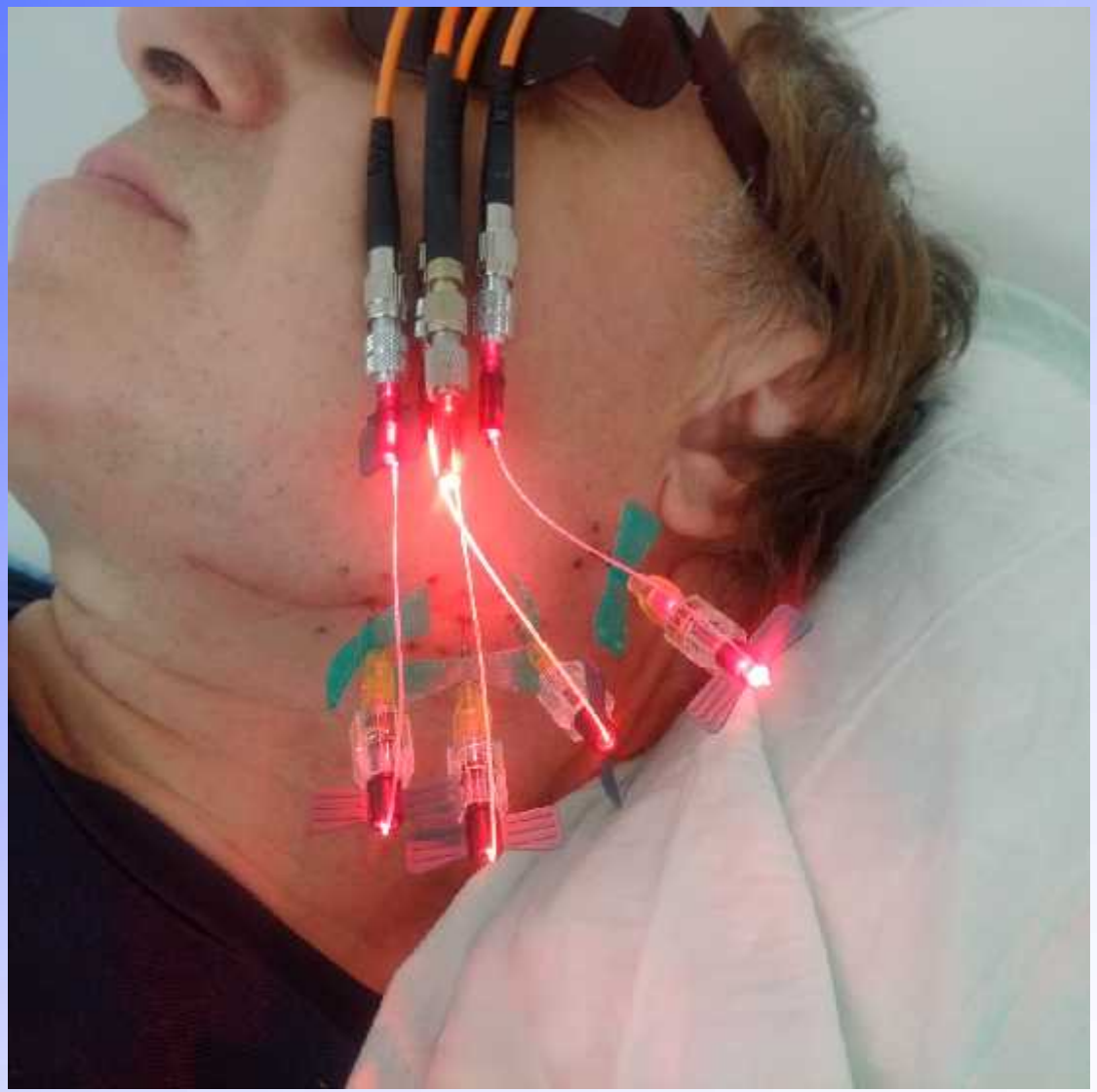
Mouth bottom cancer with lymph nodes

Larynx cancer, spreading in the neck

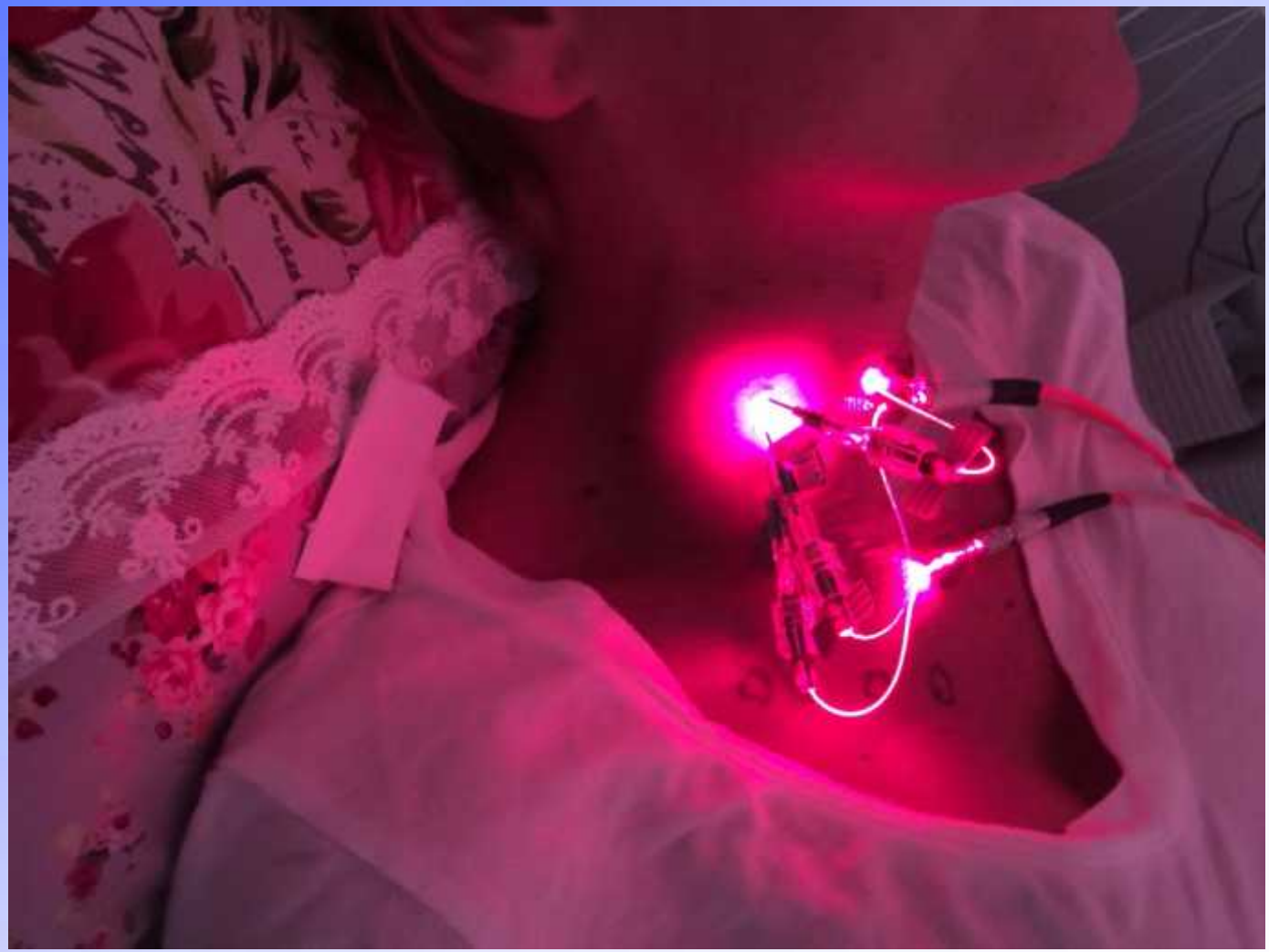
Larynx cancer

Larynx cancer

Interstitial laser therapy of neck lymph nodes



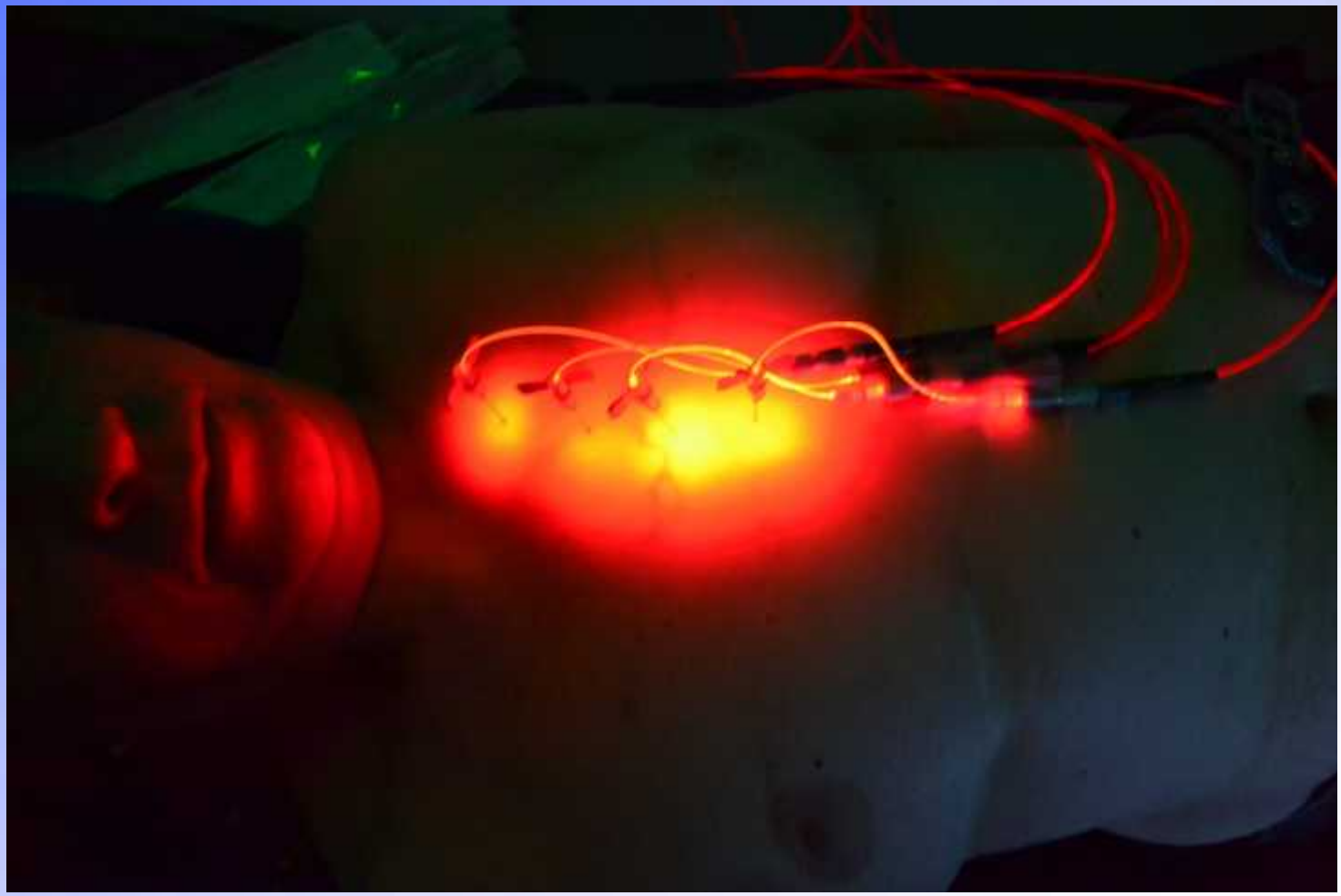
Interstitial PDT for neck lymph nodes



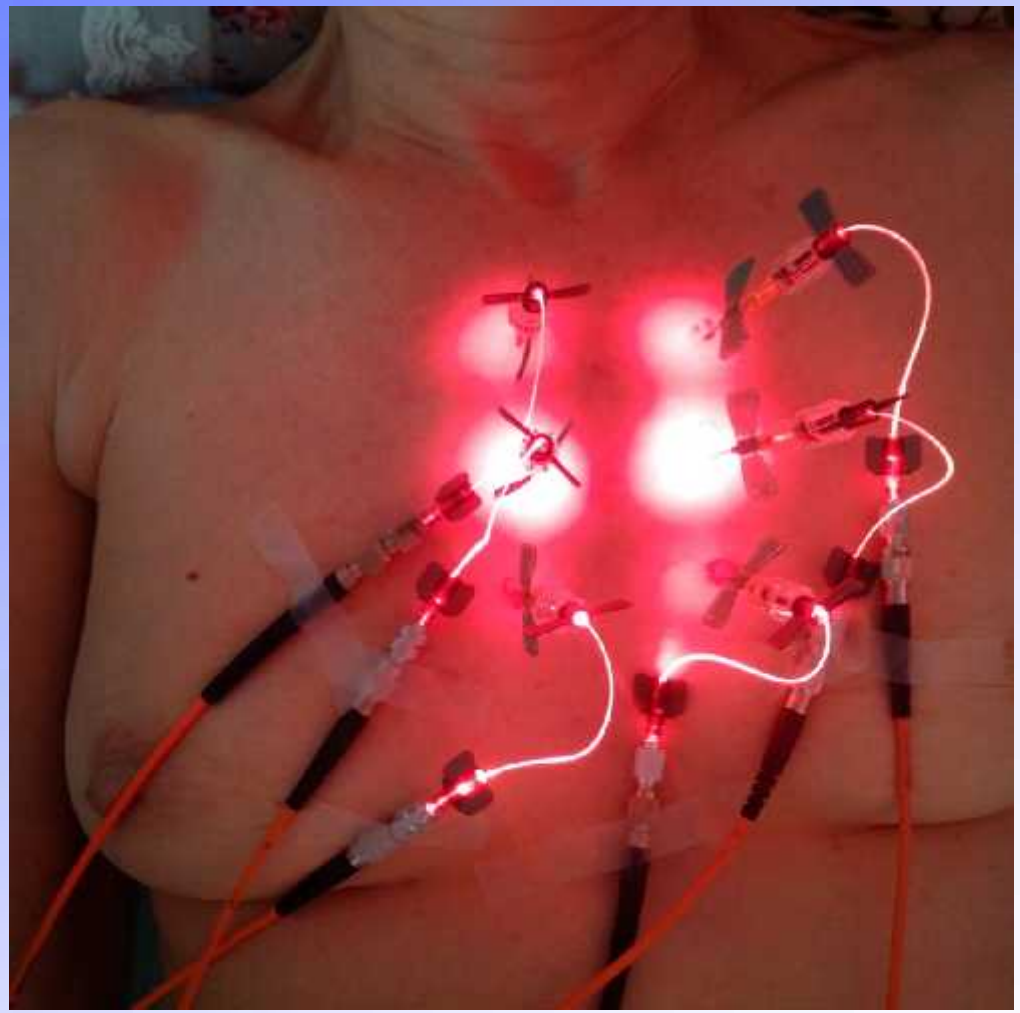
Interstitial PDT for thyroid cancer

Interstitial PDT of breast cancer with mediastinal lymph metastases

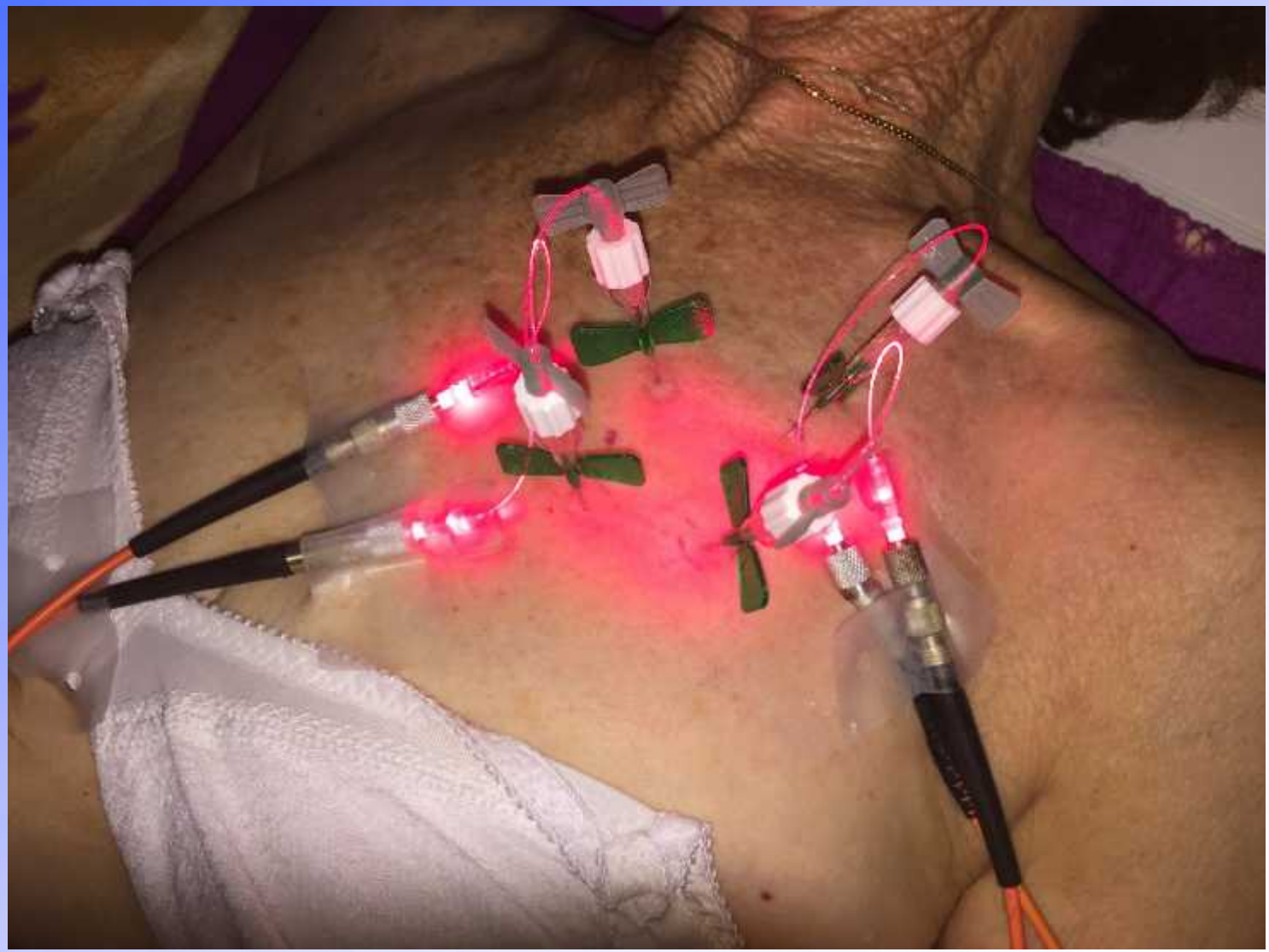
Interstitial PDT of breast cancer with mediastinal lymph metastases



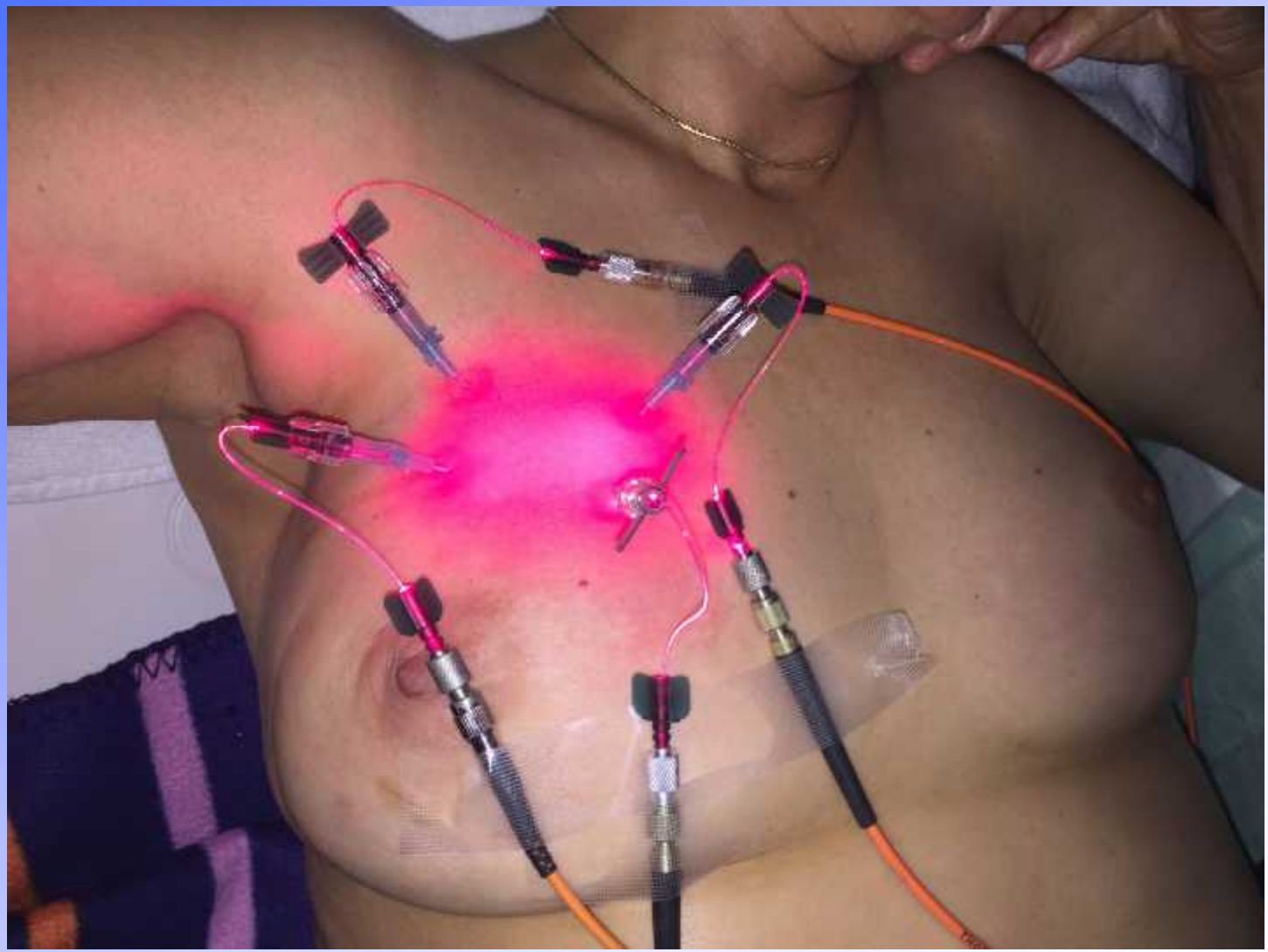
Interstital therapy for mediatinal metastases



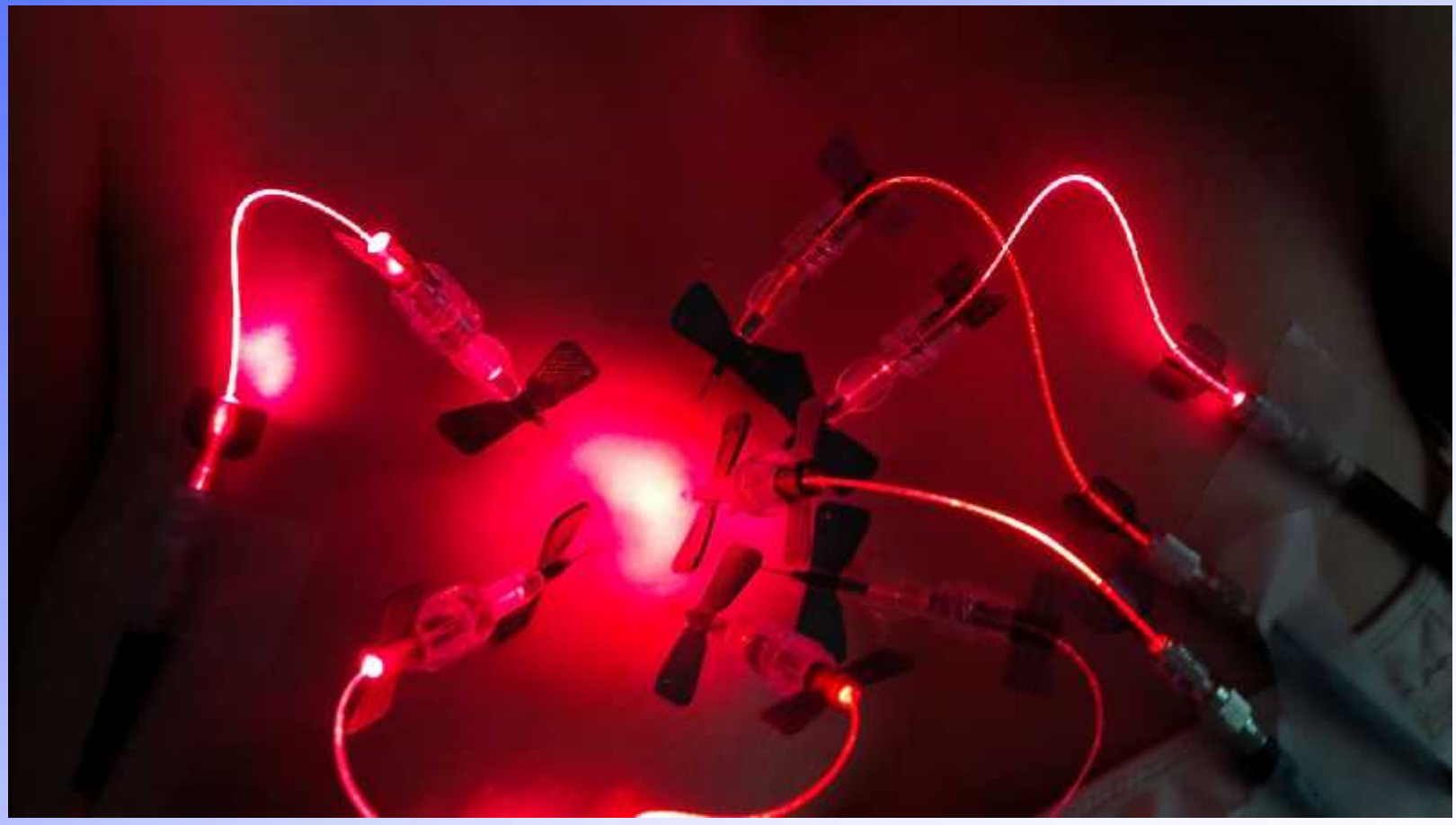
Lung cancer (needles on pleura)



Interstitial PDT of breast cancer

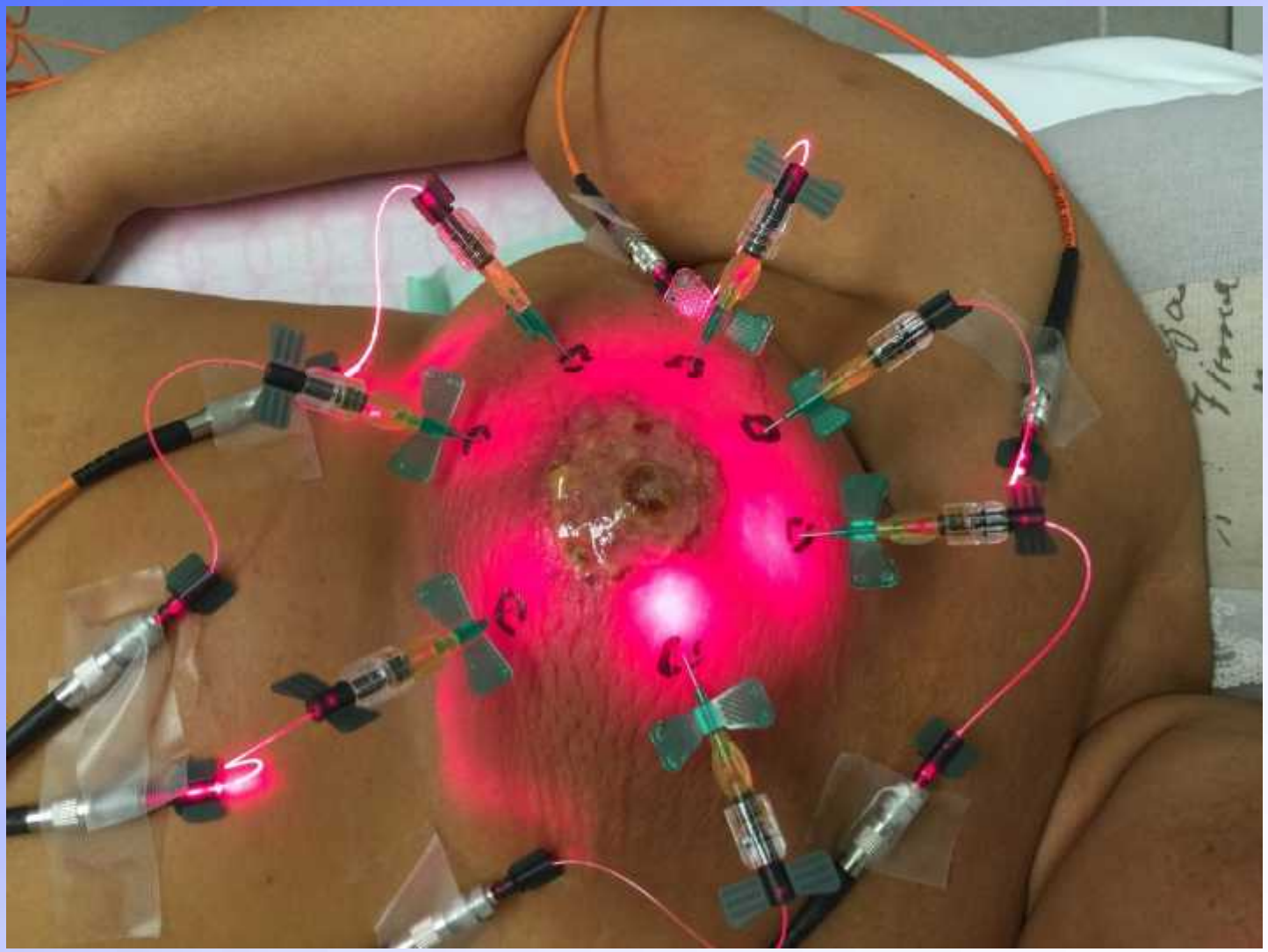


Interstitial breast cancer treatment

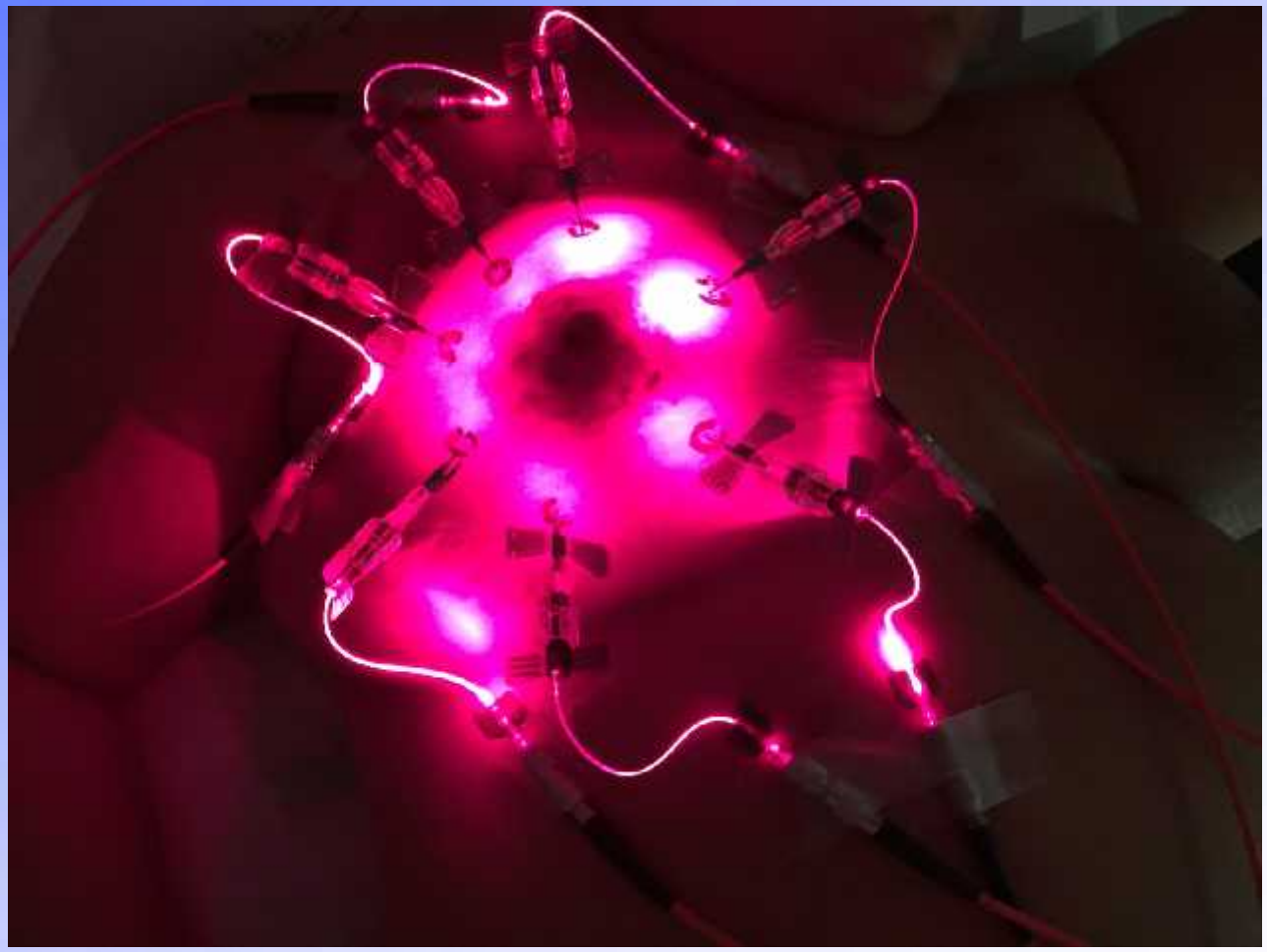


Interstital PDT of breast cancer

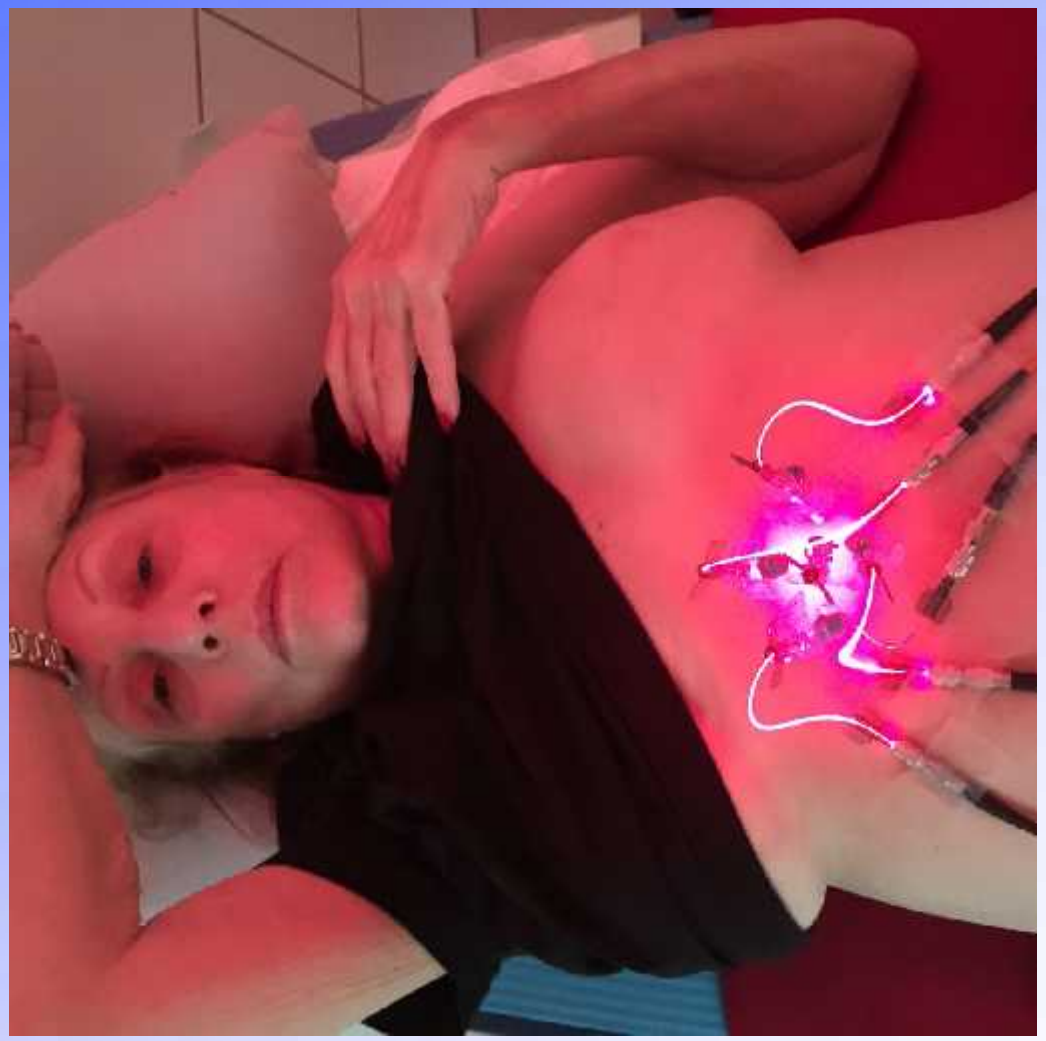
Interstital PDT of breast cancer



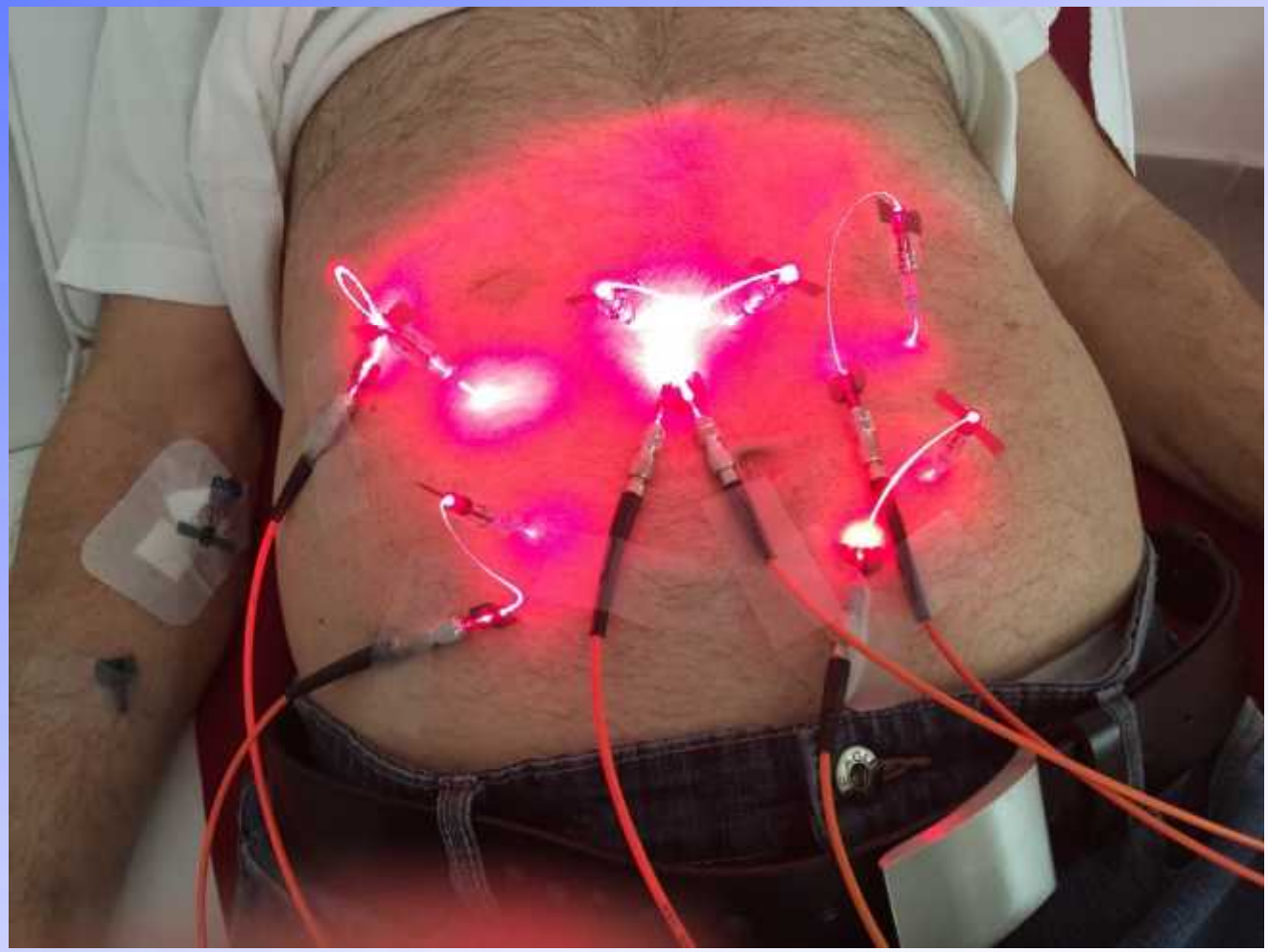
Interstital PDT of breast cancer



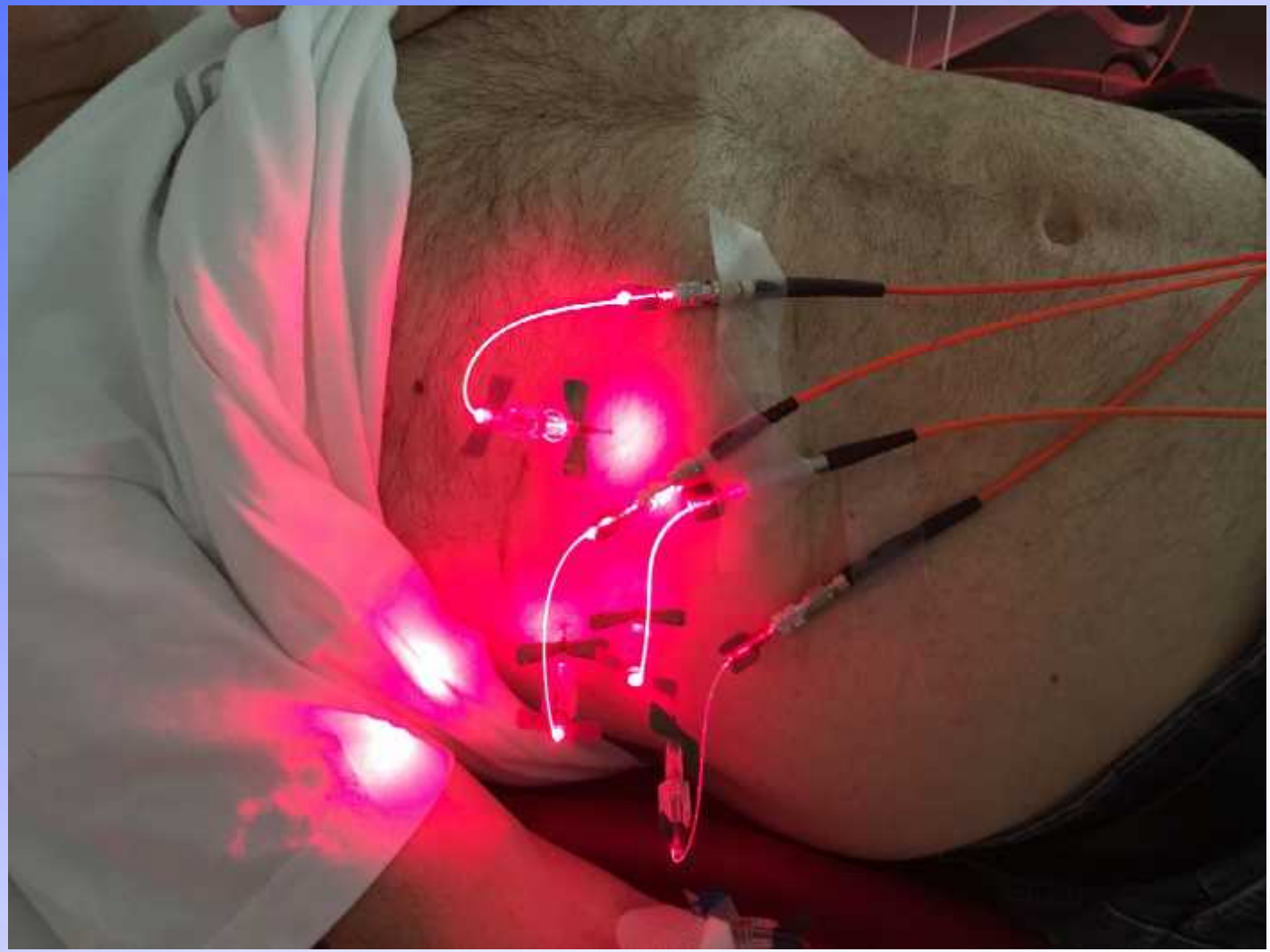
Interstitial PDT for pancreatic cancer



Peritoneal carcinosis



Liver metastases

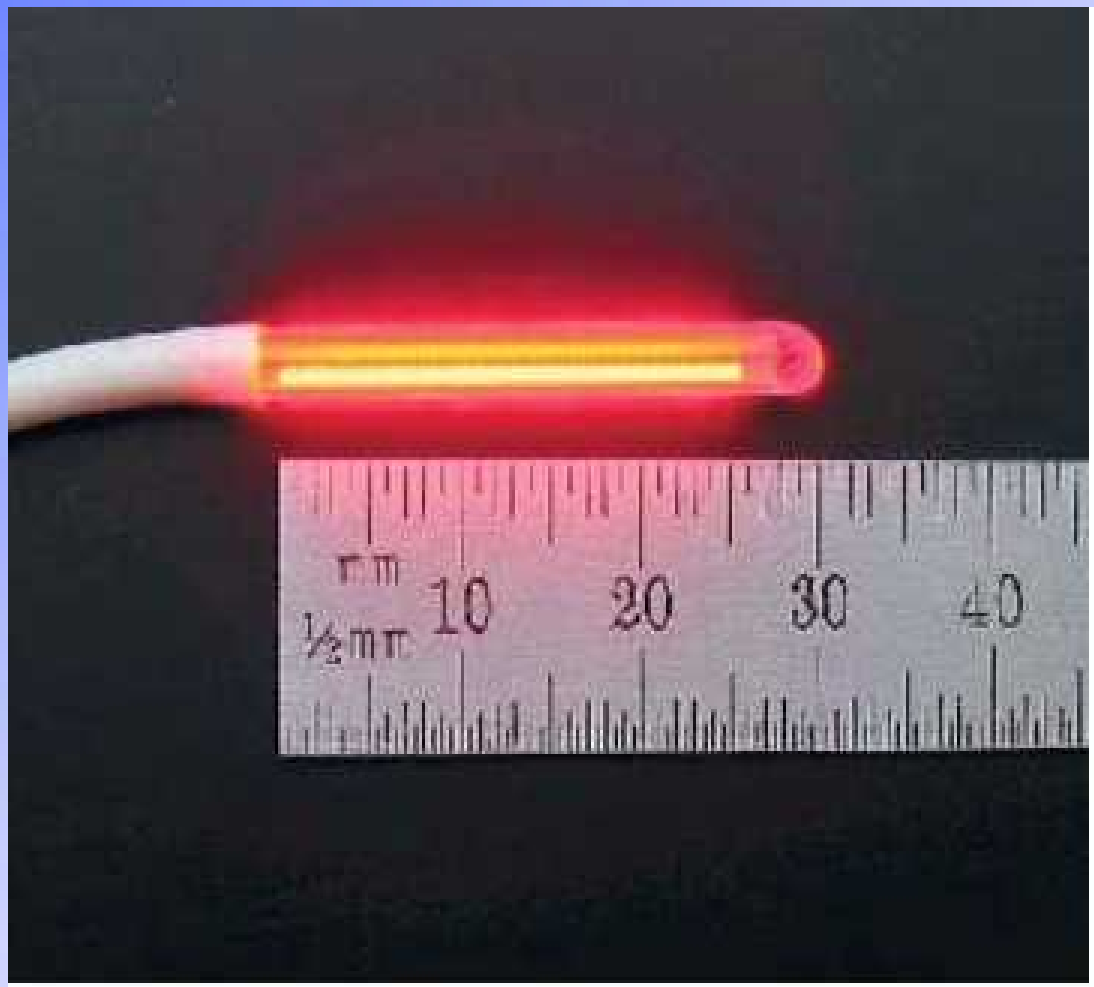


PDT in Urology

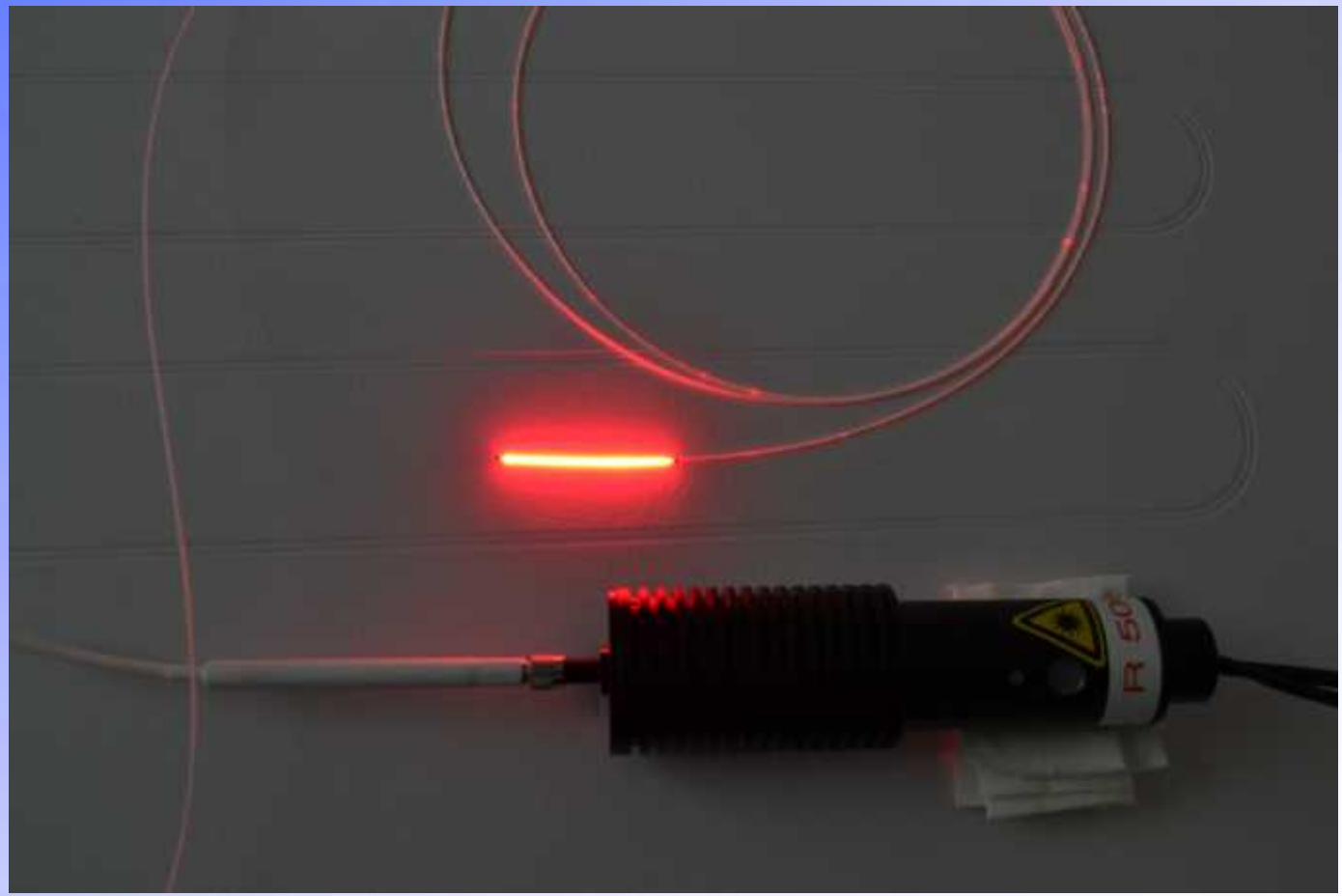
PDT in urology

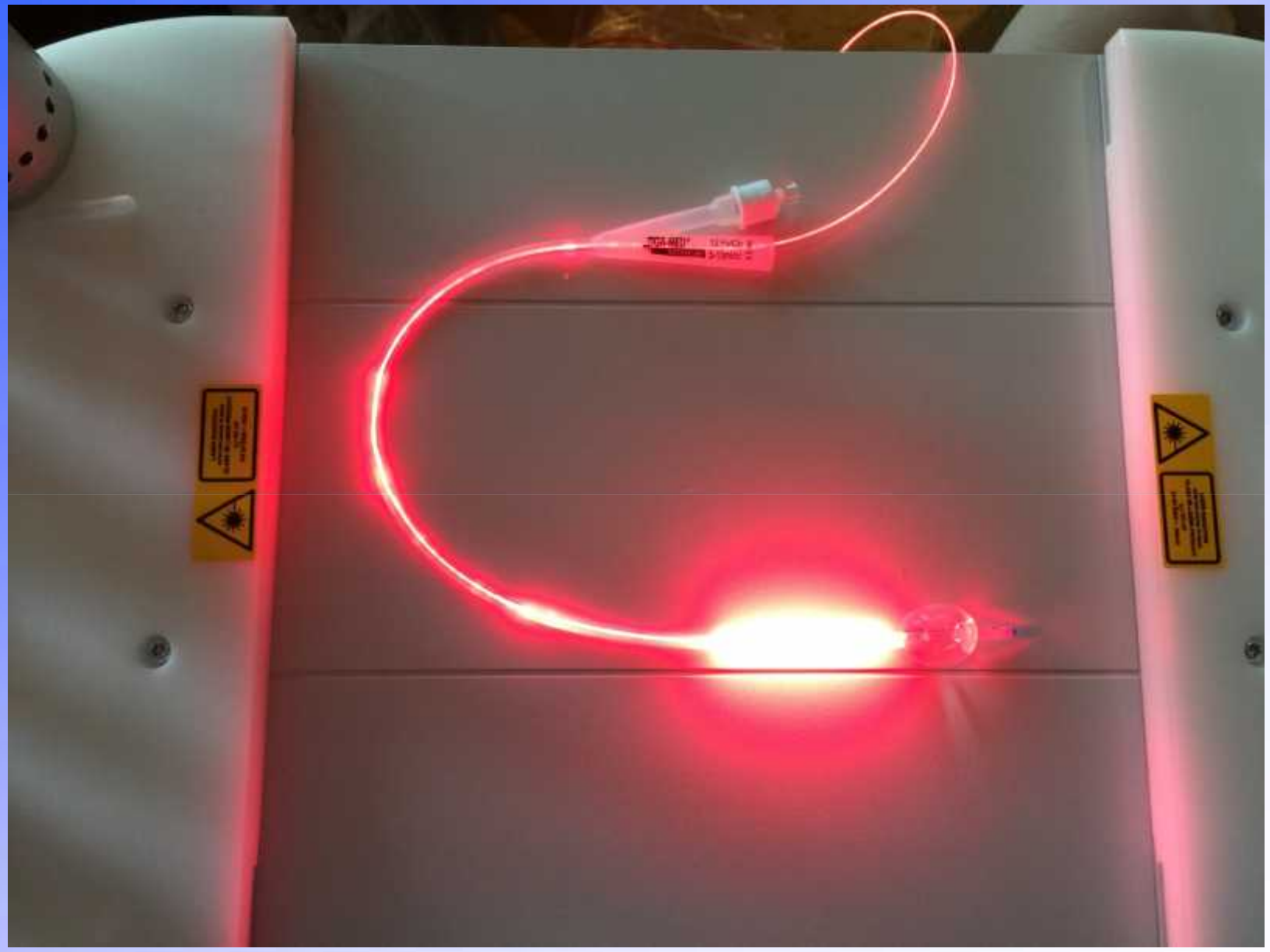
Fiberoptic catheter with circular irradiation (for prostate cancer)

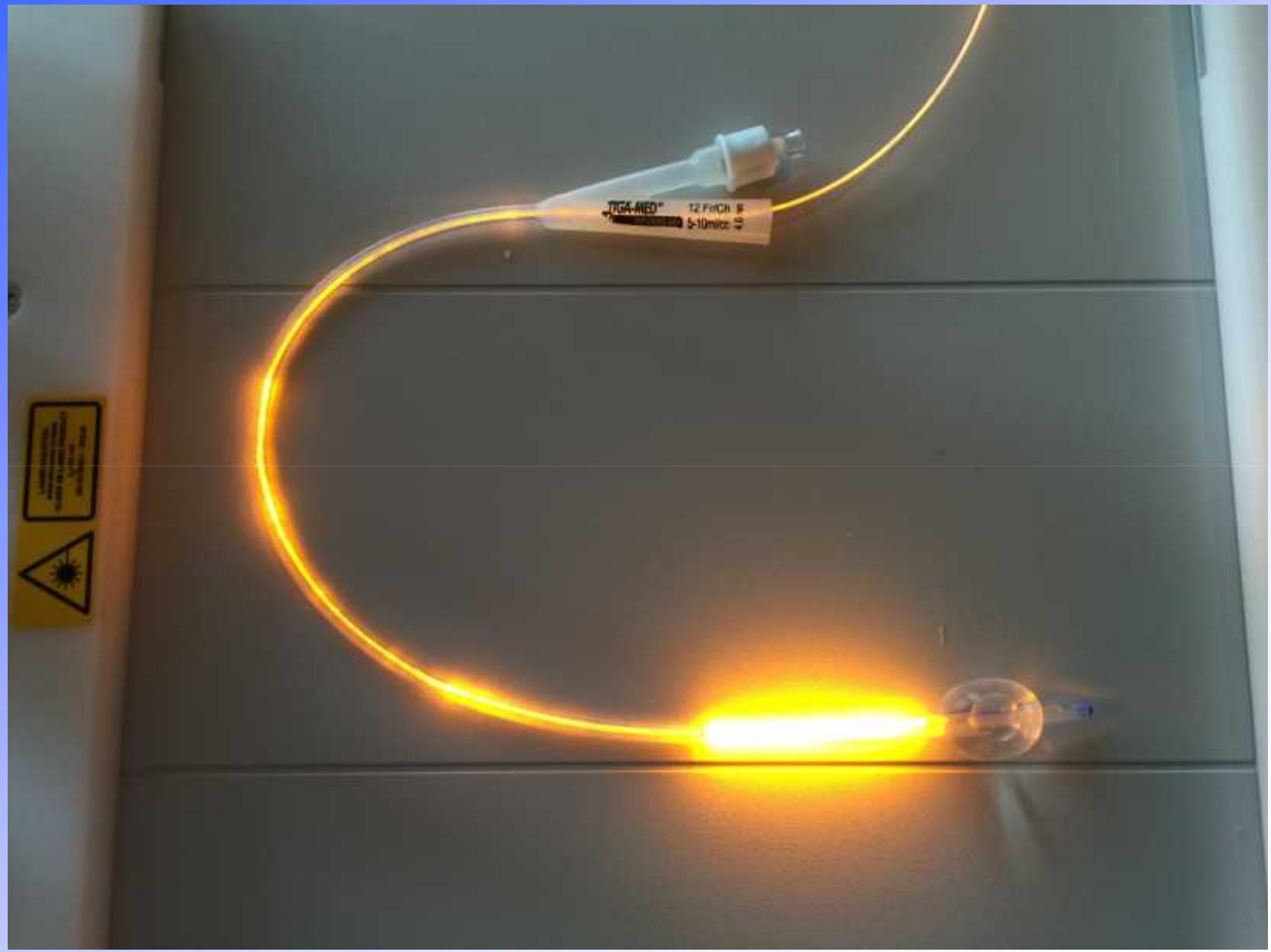
New catheter for bladder and prostate cancer

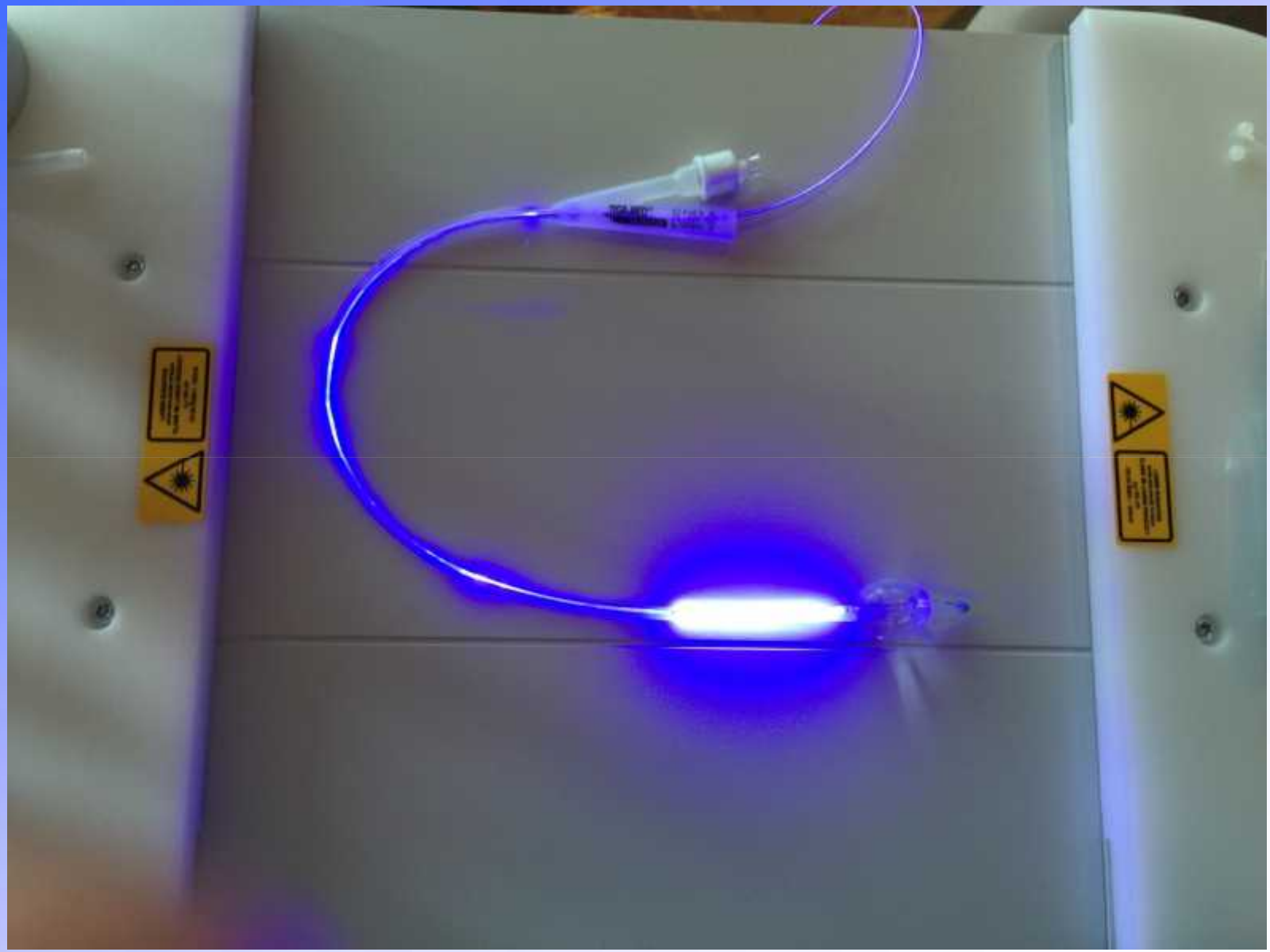


500 mW Red laser 658 nm

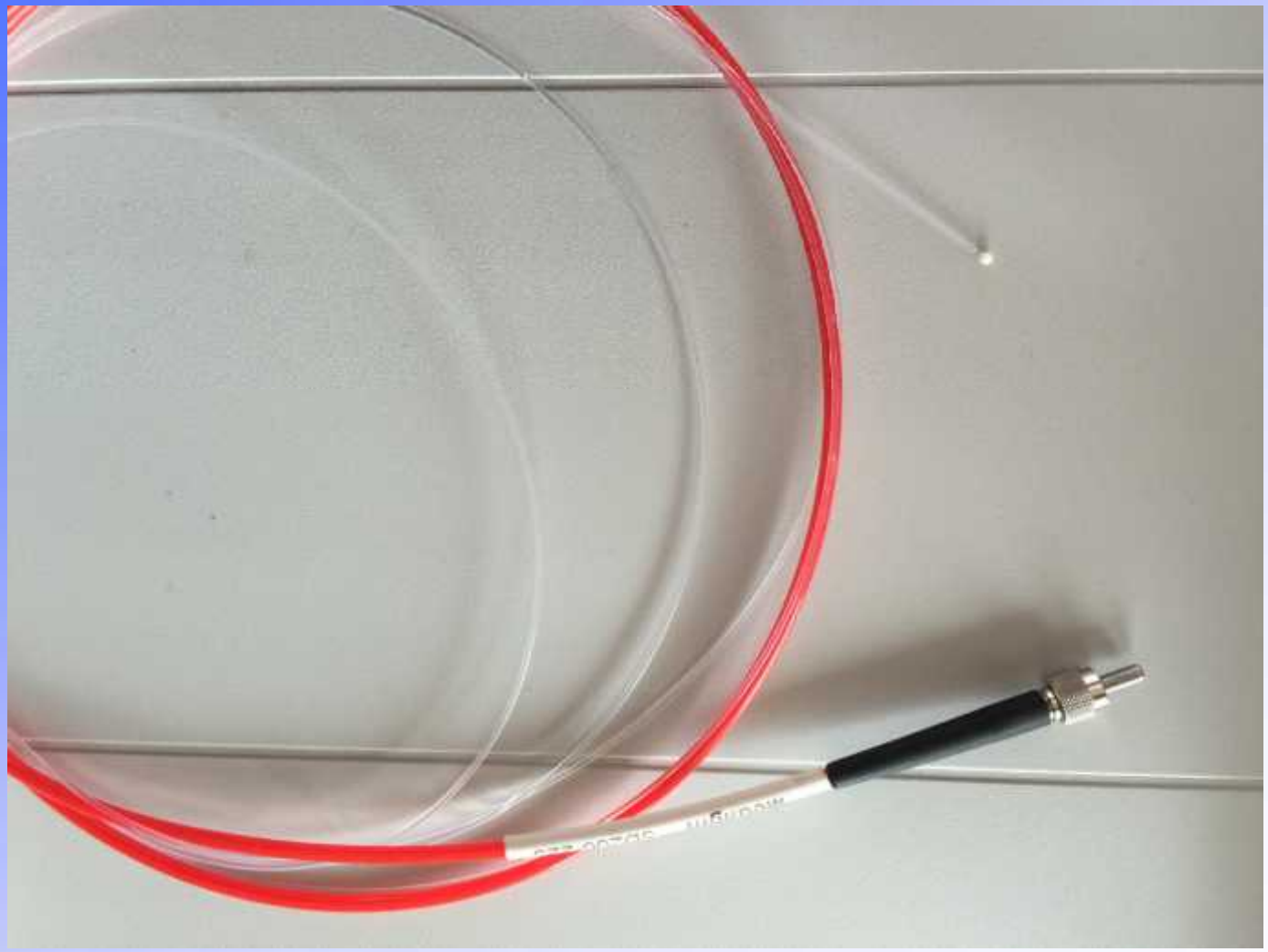


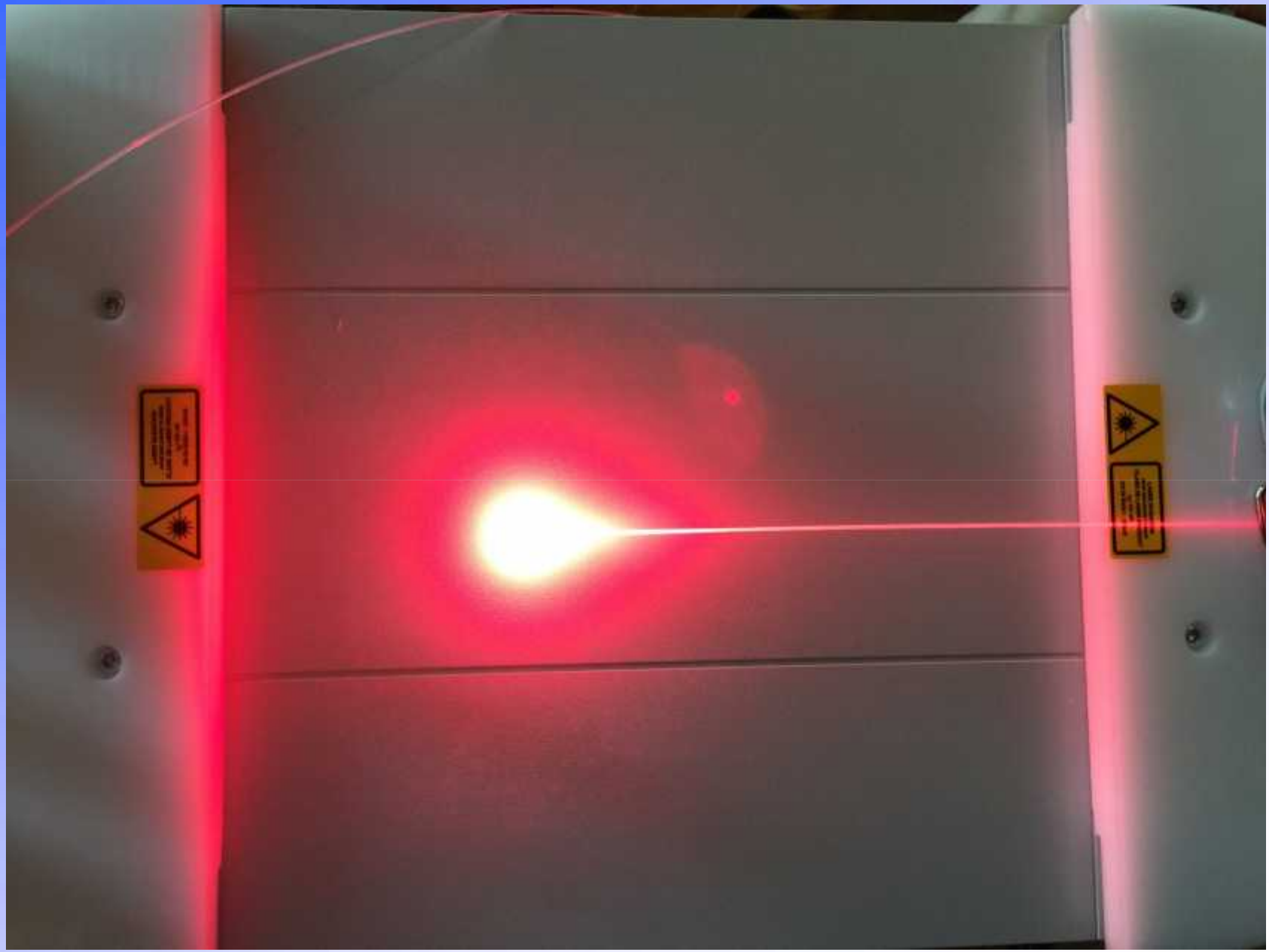


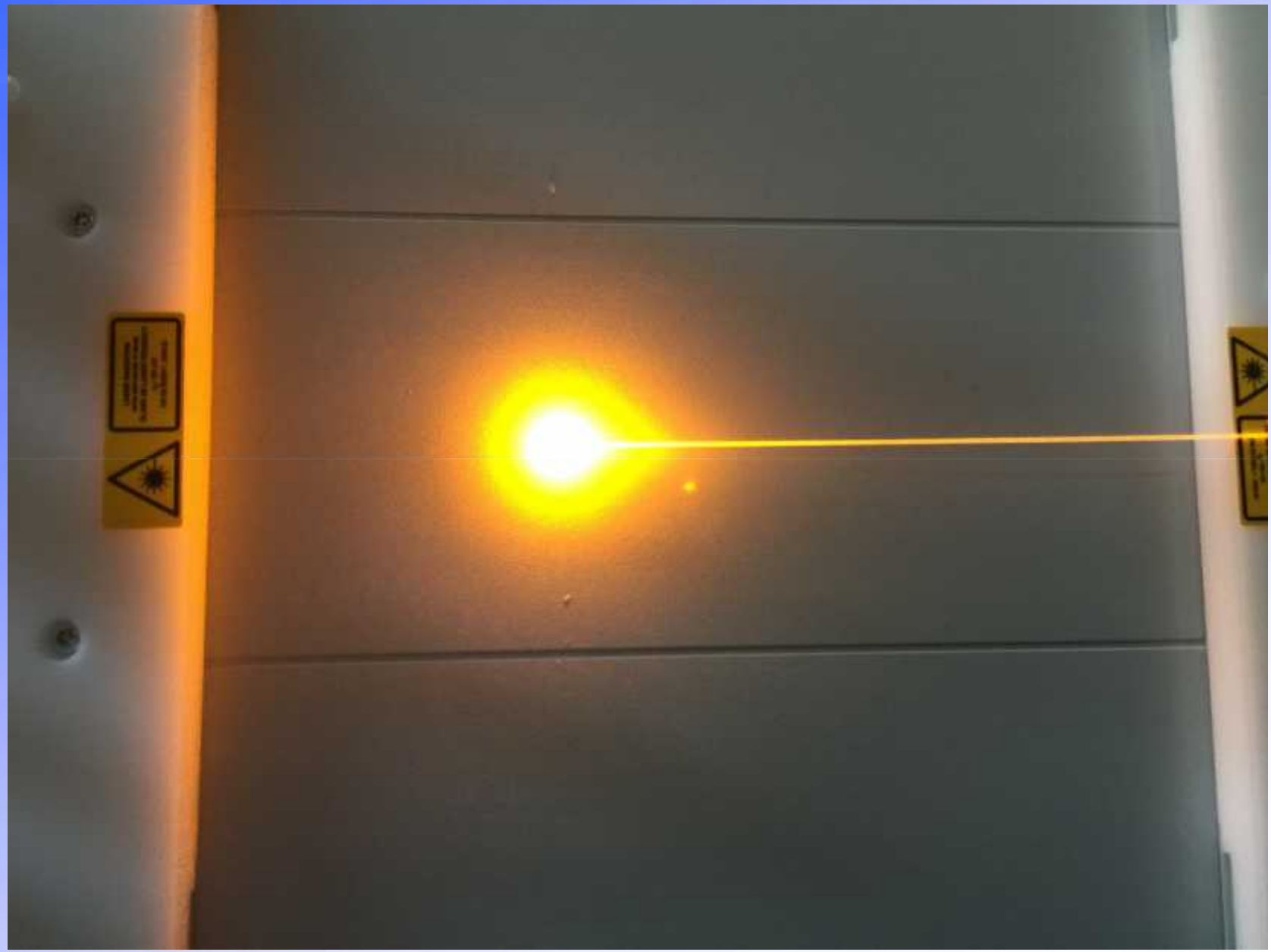

TIGA-MED
12 Fr/Ch
5-10ml/cc

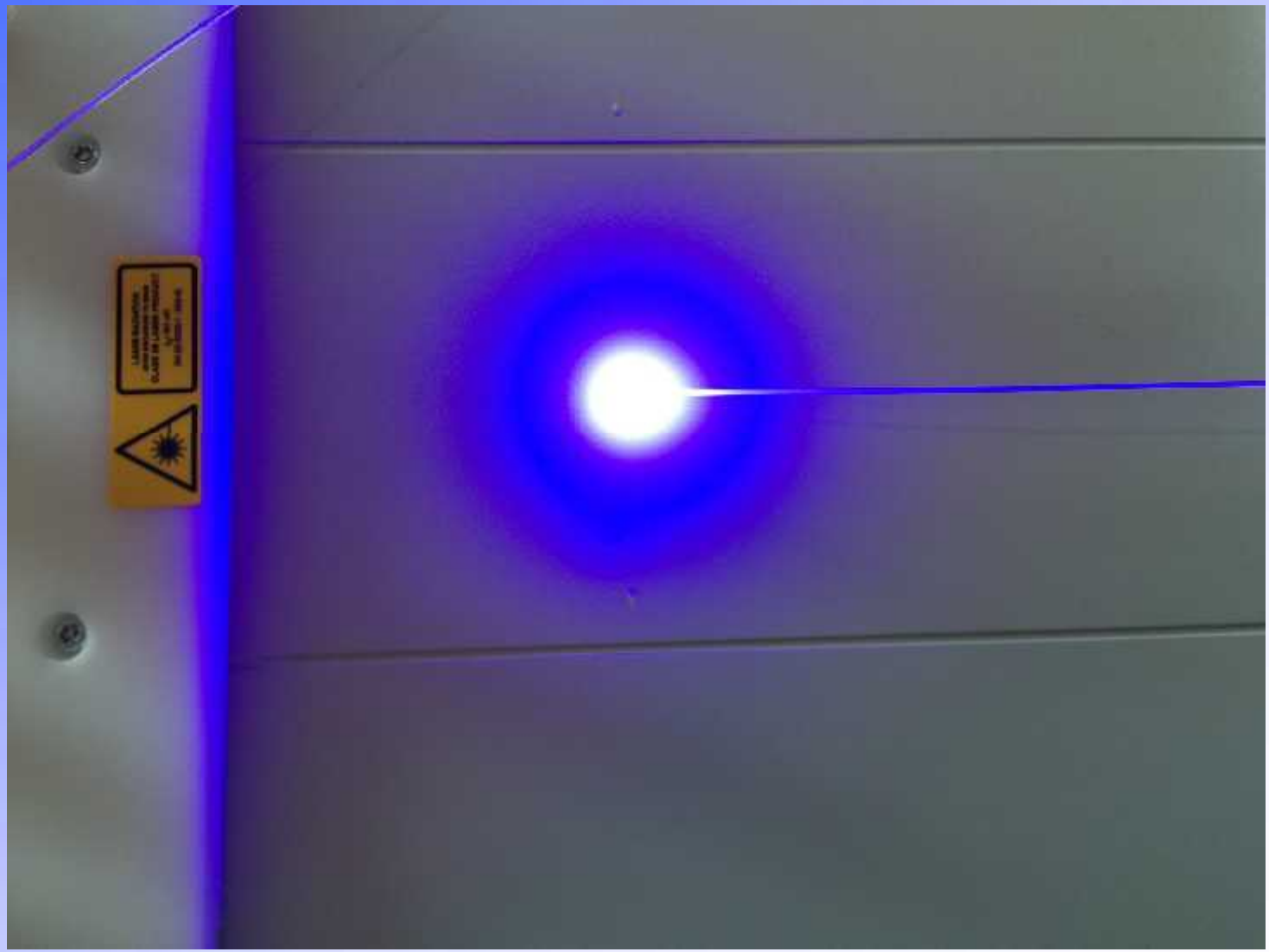


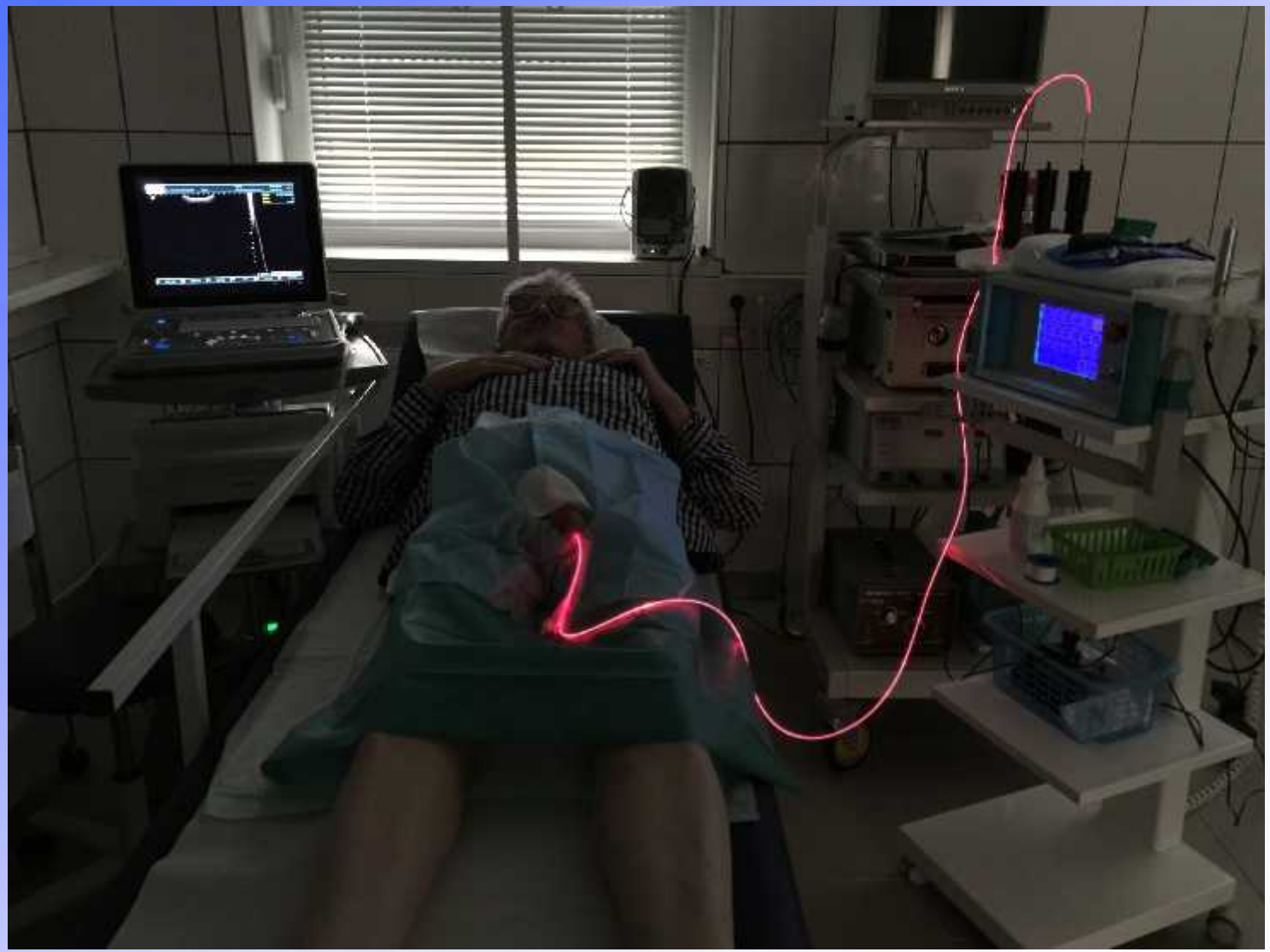
Fiberoptic catheter with spheric irradiation for bladder cancer

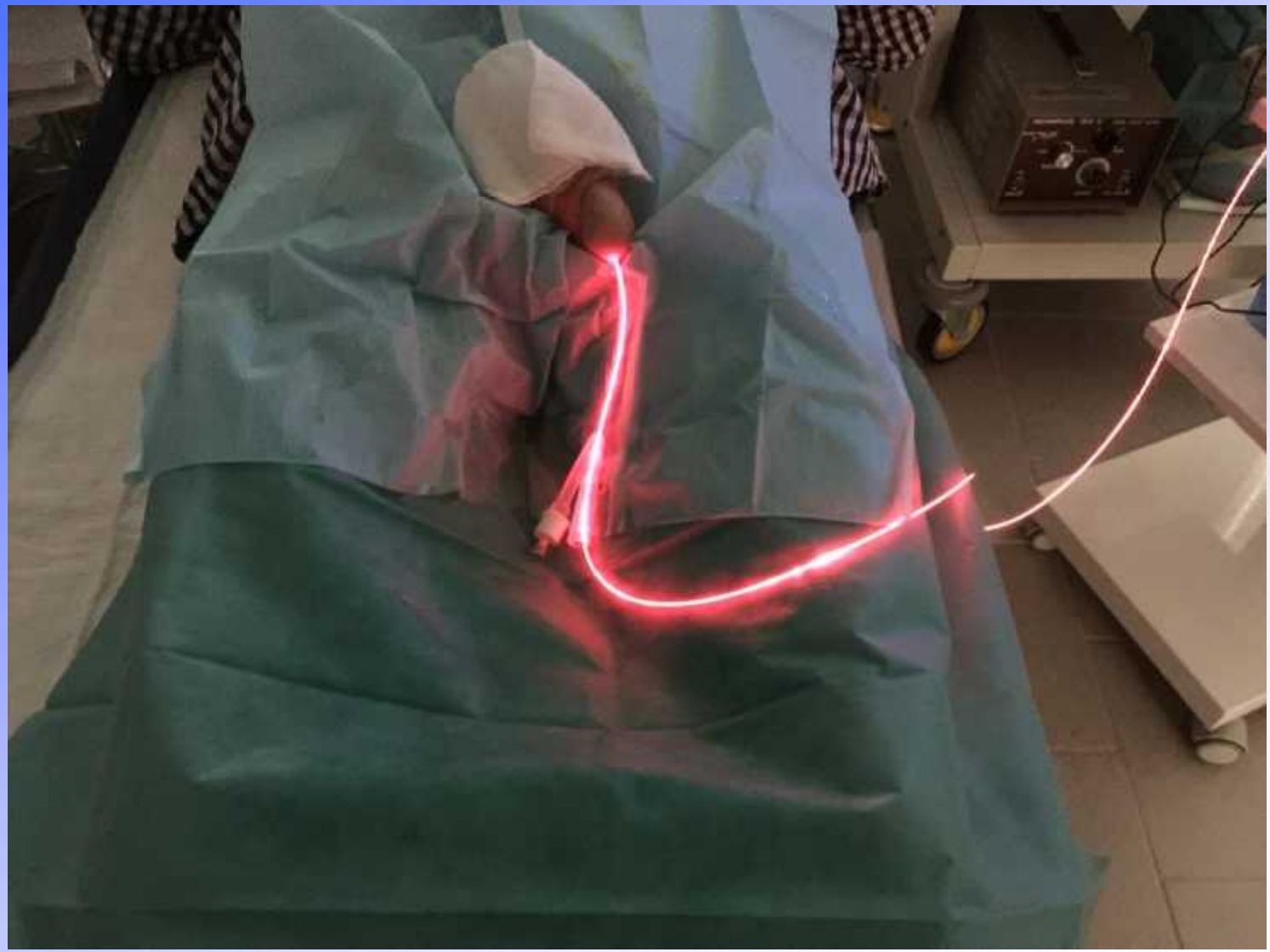




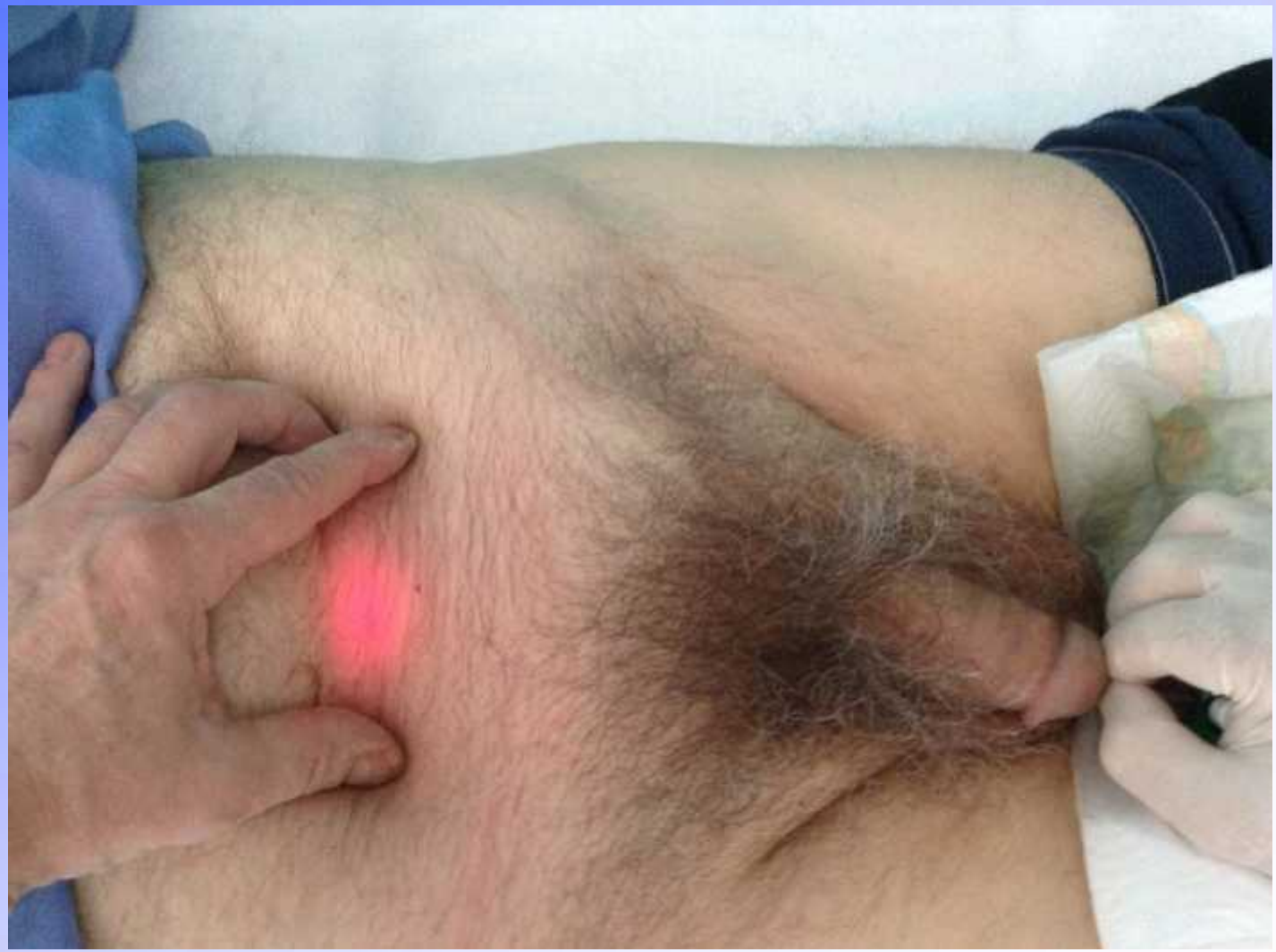








Bladder Cancer

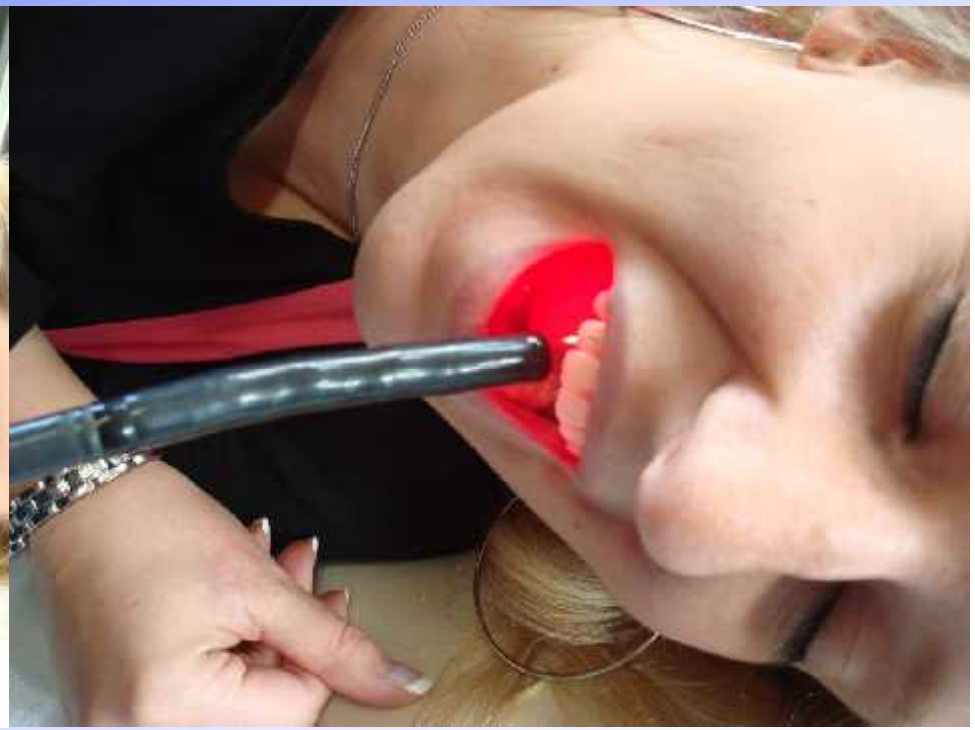


Bladder cancer PET 10/2014 before treatment

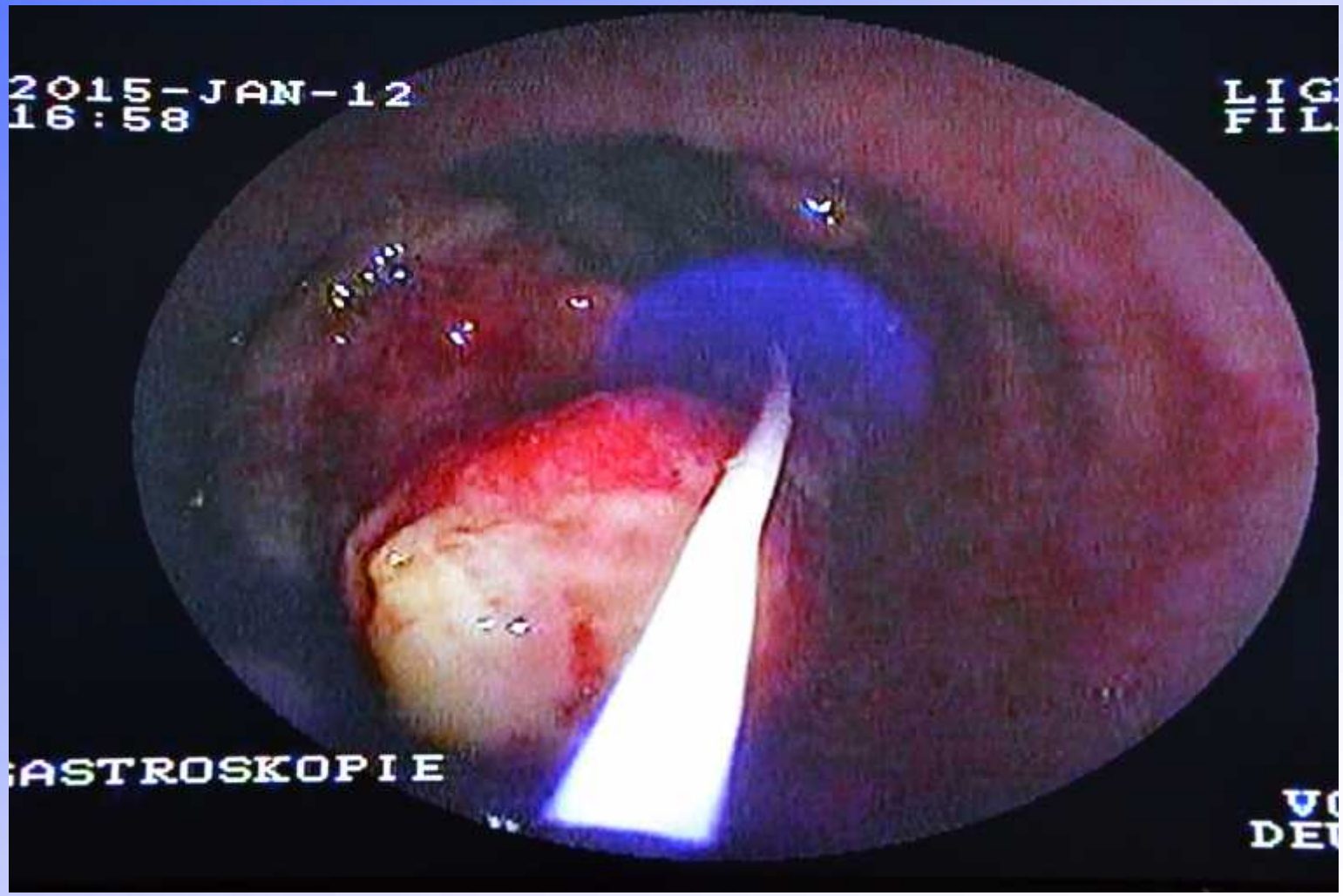
Bladder cancer 2/2015 after PDT

Endoscopic PDT

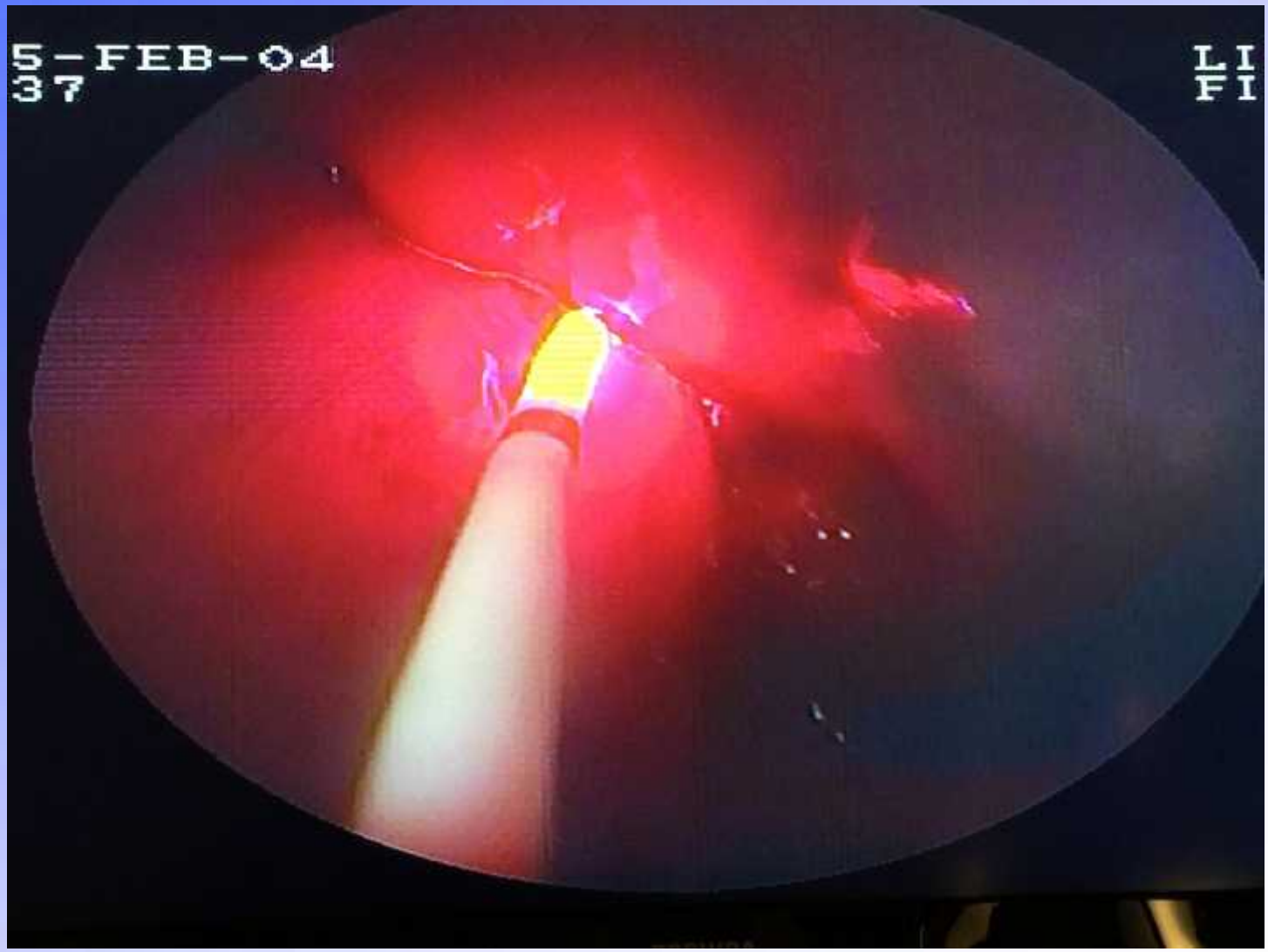
Endoscopic PDT



Endoscopic PDT



Endoscopic PDT



The big problems of red laser photosensitizers still remain:

- Limited succes by using red laser only
- Limited penetration depth (max. 2,5 cm)
- Limited tumor size: max 2,5 cm
- Burning and ulceration with overdosage
- Light sensitivity
- No good success with liver metastases
- Limited success for bone metastases
- No success in treatment of brain tumors

The solution: liposmal Indocyanine Green

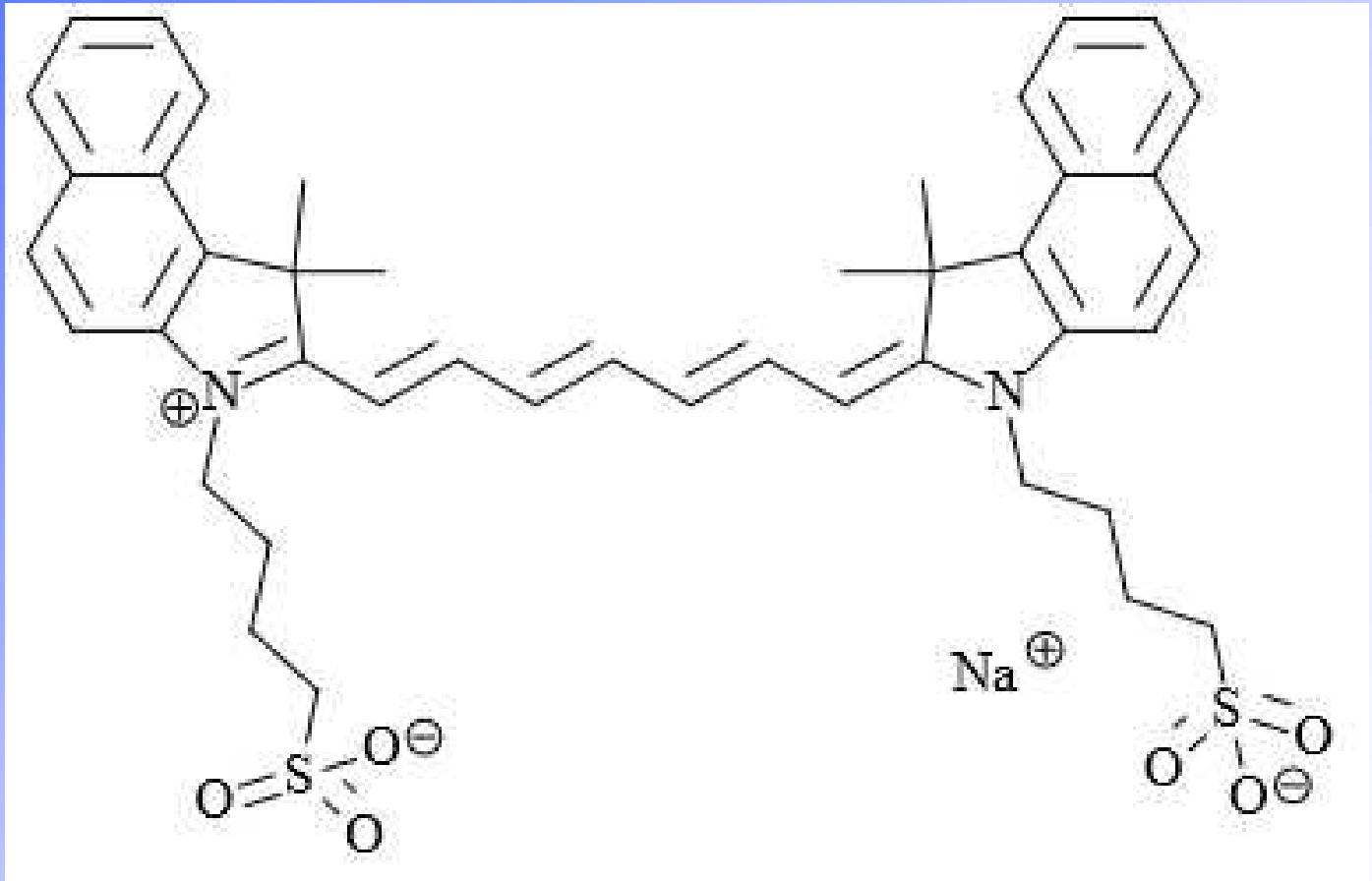
- **Indocyanine Green** is a fluorecent green dye and absorbs light in the infrared range (810 nm)
- It is applied intravenously
- Indocyanine Green is an approved drug used for fluorescense diagnostics (blood flow in eyes, liver heart) even FDA approved in the USA

Indocyanine Green liposomal as a new photosensitizer

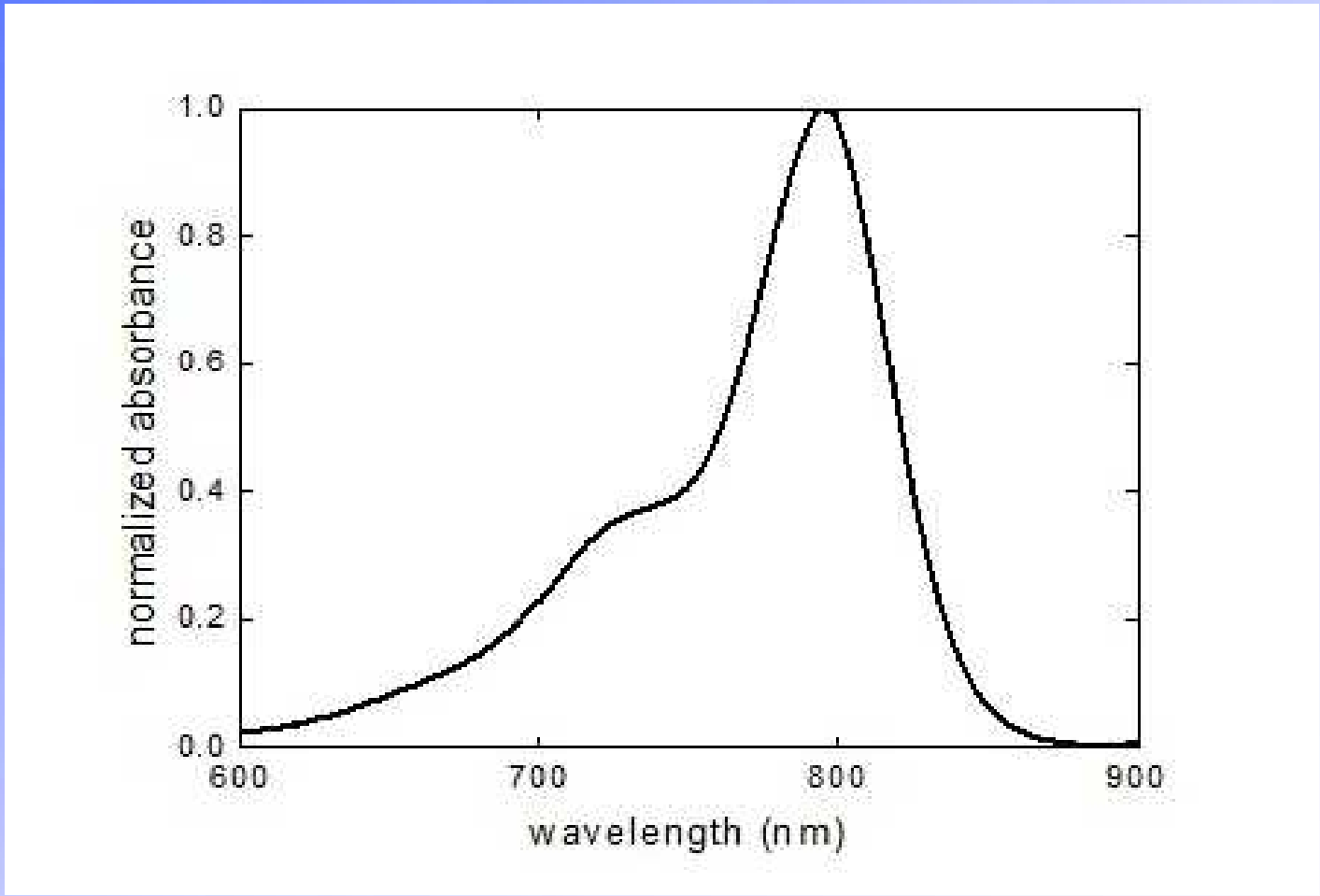
- Pure Indocyanine Green binds to plasma proteins and is removed from the body in about 30 minutes and cannot be used as photosensitizer

- In liposomale form however it will be in integrated in tumor cells and can so be used for PDT with infrared laser

Indocyanine Green, chemical structure



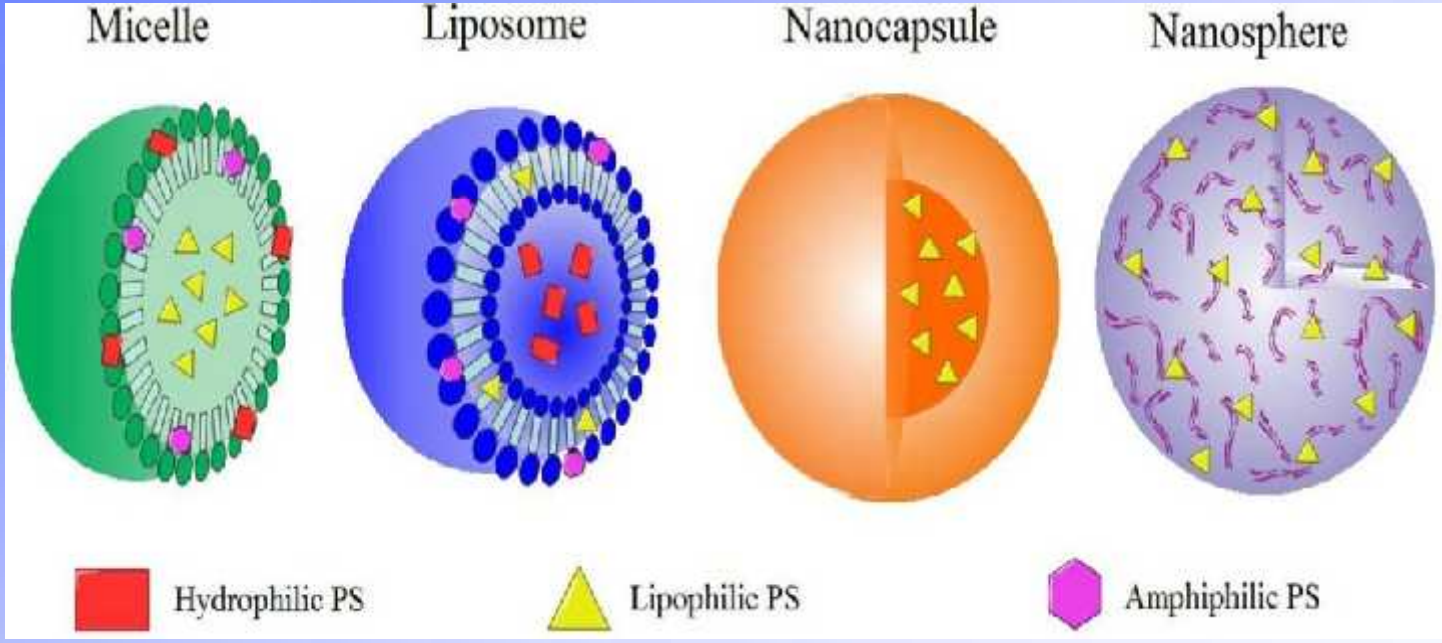
Indocyanine Green, absorption spectrum



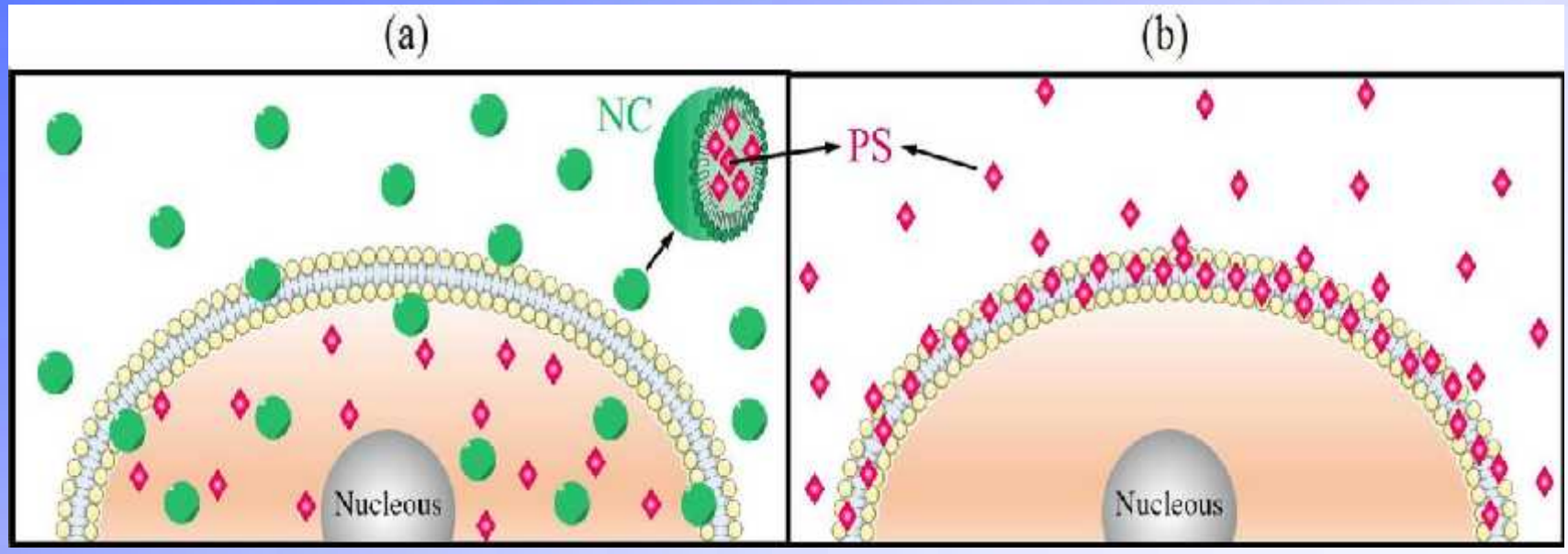
Indocyanine Green as photosensitizer

A new option for improved tumor targeting and uptake is the formulation of ICG in nanopartikels like liposomes .

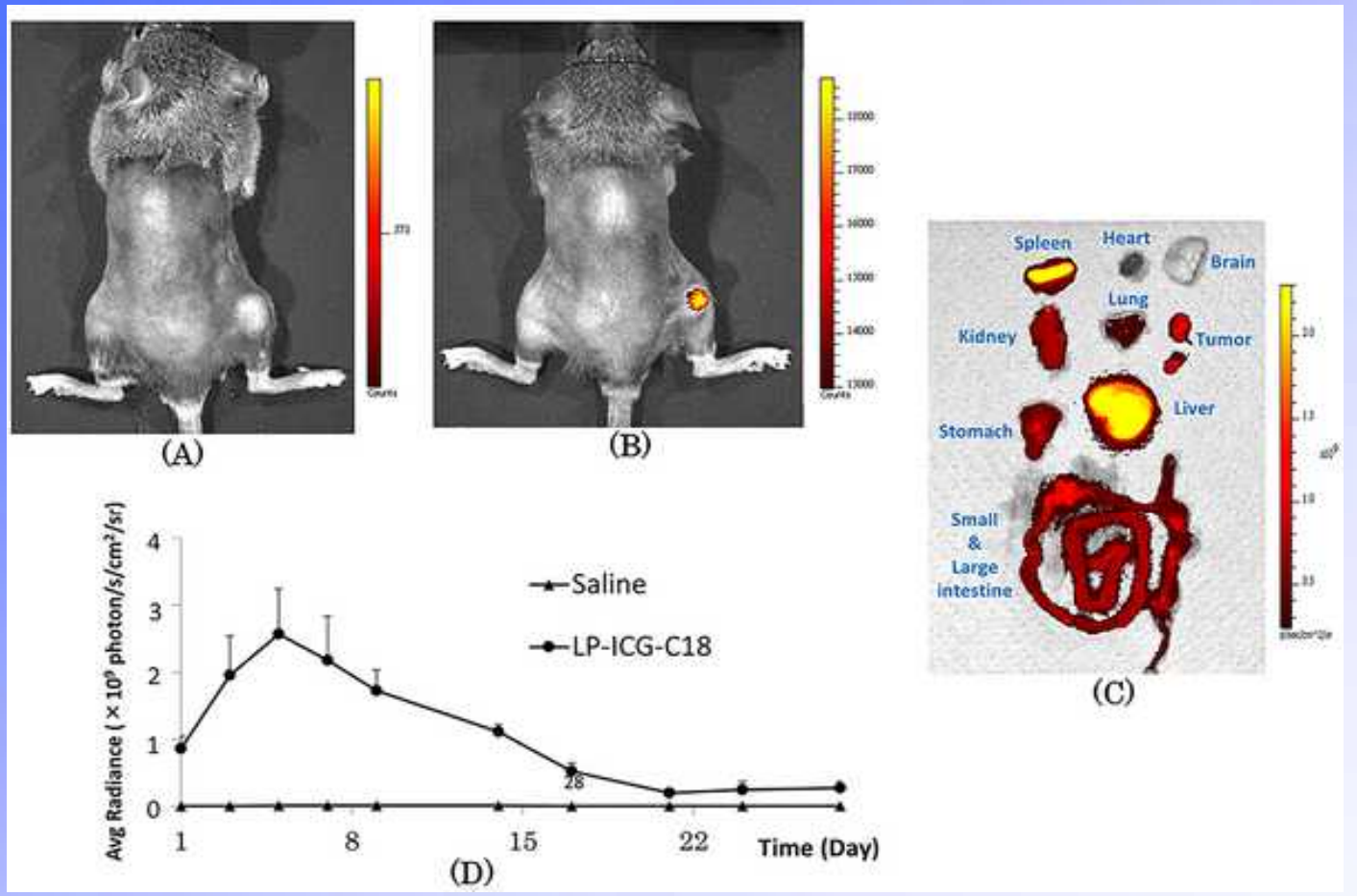
Nanoparticles for transport of photosensitizers



Cellular integration of a lipophile photosensitizer



Pharmacokinetic of Lip-ICG



NIR fluorescence images of tumor bearing mice 24 hours after injection of (A) saline and (B) LP-ICG-C18. (C) NIR fluorescence images of the organs 24 hours after injection of LP-ICG-C18. (D) Photon count of tumor bearing mice.

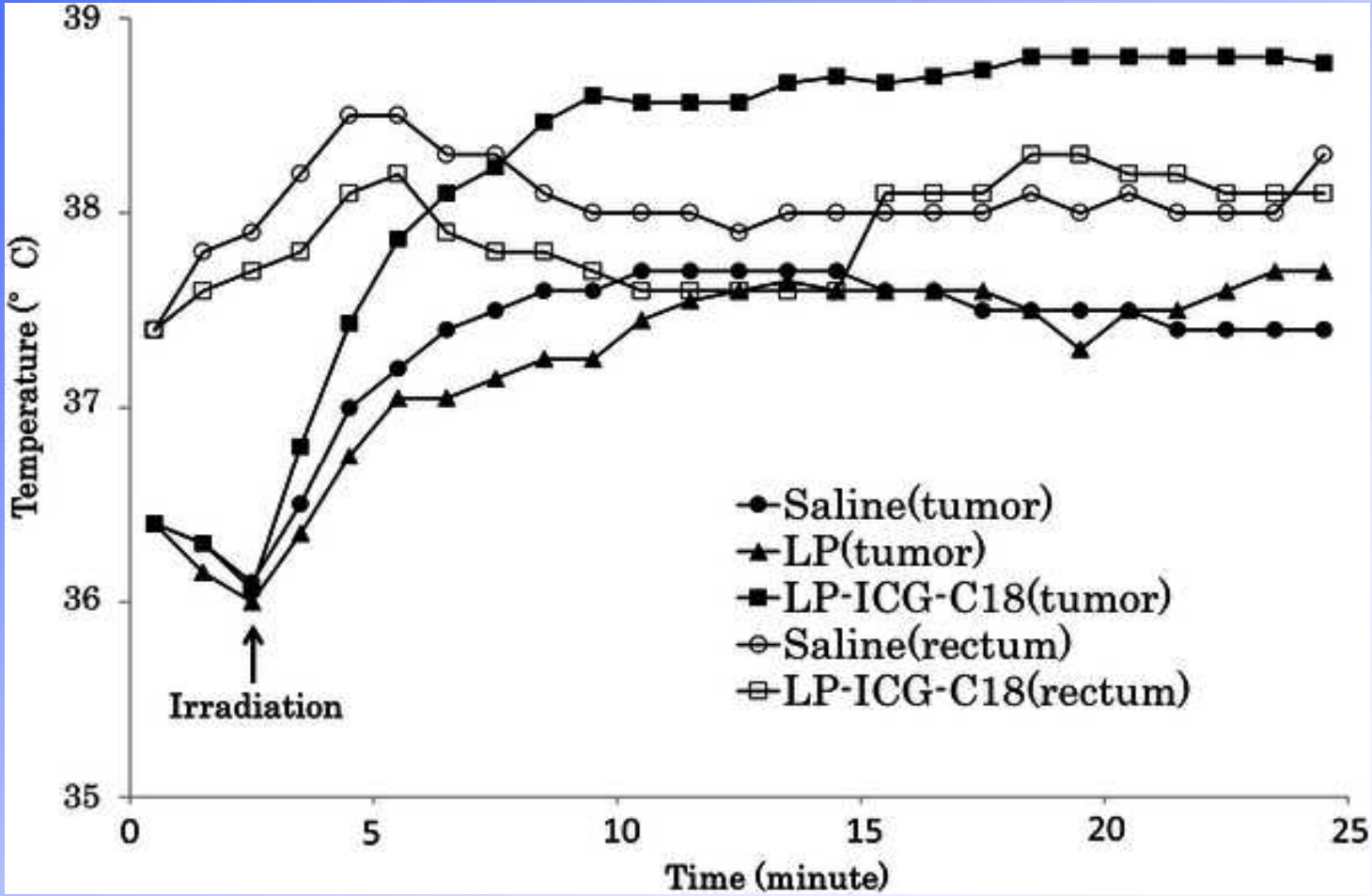
Maruyama T, Akutsu Y, Suganami A, Tamura Y, Fujito H, et al. (2015) Treatment of Near-Infrared Photodynamic Therapy Using a Liposomally Formulated Indocyanine Green Derivative for Squamous Cell Carcinoma. PLoS ONE 10(4): e0122849. doi:10.1371/journal.pone.0122849
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0122849

Selective "Over-heating" of tumor tissue by infrared stimulated Indocyanine Green

- ICG absorbs infrared light 810 nm.
- Infrared light has the highest penetration depth in the tissue. Besides activation of the ICG with production of **singlet oxygen** tumor tissue will be warmed up

  (**overheating effect**) and so supports the photodynamic reaction without damage of surrounding healthy tissue.
- The combination of overheating and PDT leads to an improved reaction with „tumor melting",
- We can call it **„Photothermodynamic therapy (PTDT)"** or **„Photothermoablation"** of tumor tissue**.** [21]

The transition of temperature in the tumor and rectum during irradiation.



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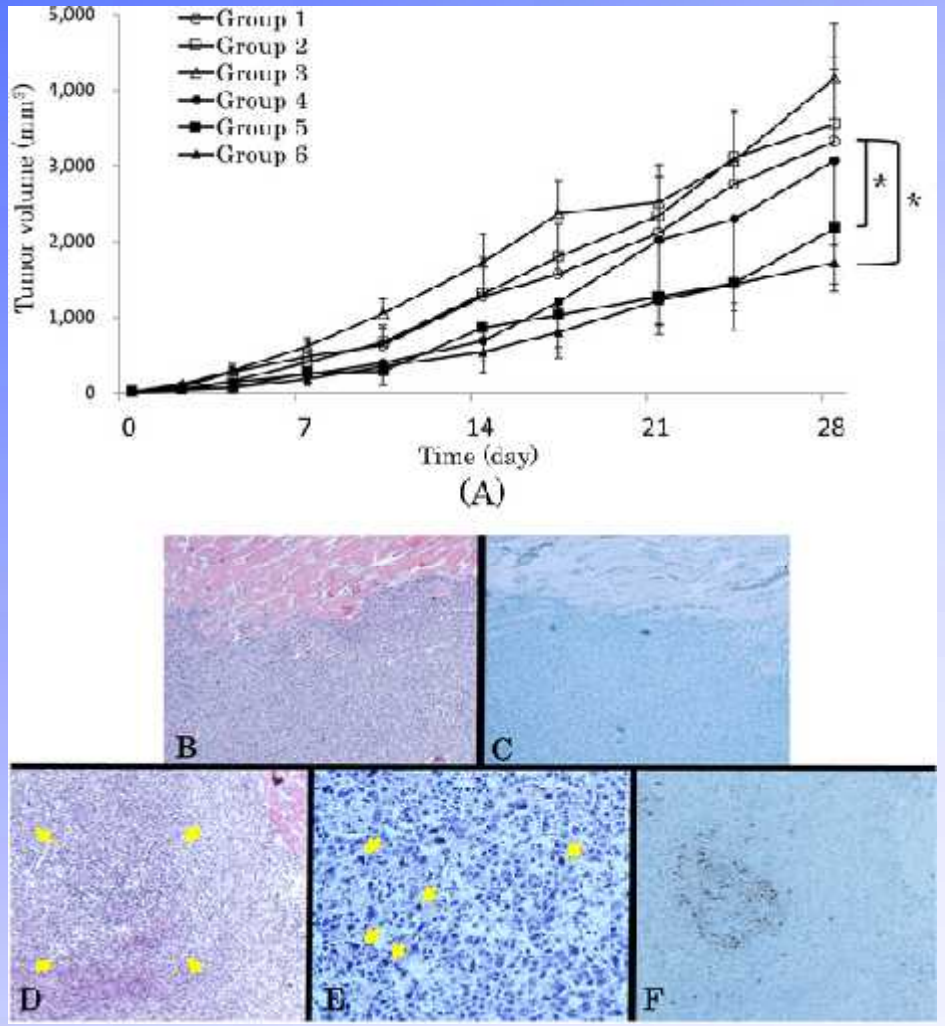
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0122849

PLOS | ONE

Antitumor effect of LP-ICG-C18 in SCCVII subcutaneous mice model.



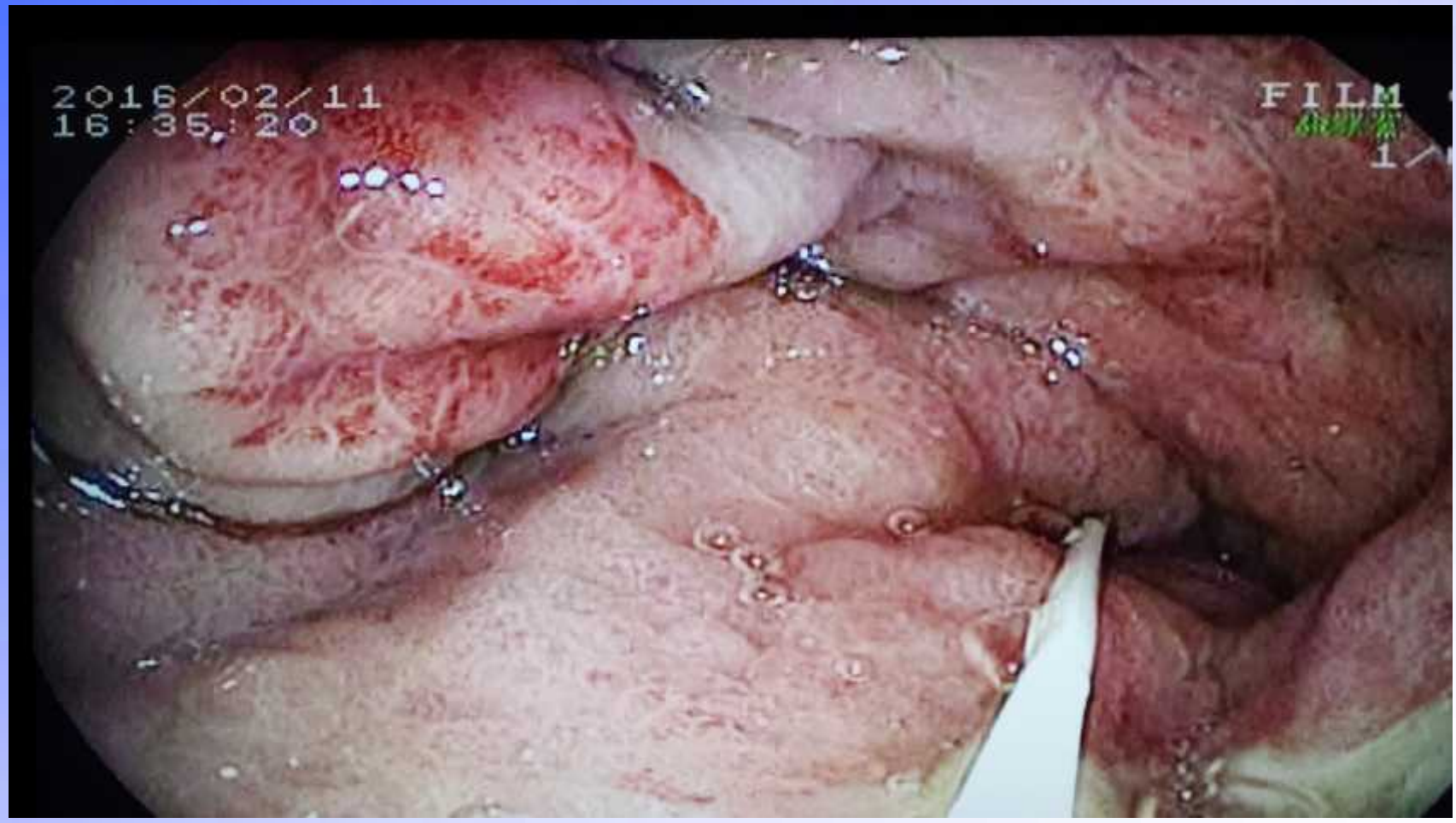
Maruyama T, Akutsu Y, Suganami A, Tamura Y, Fujito H, et al. (2015) Treatment of Near-Infrared Photodynamic Therapy Using a Liposomally Formulated Indocyanine Green Derivative for Squamous Cell Carcinoma. PLoS ONE 10(4): e0122849. doi:10.1371/journal.pone.0122849
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0122849

PLOS | ONE

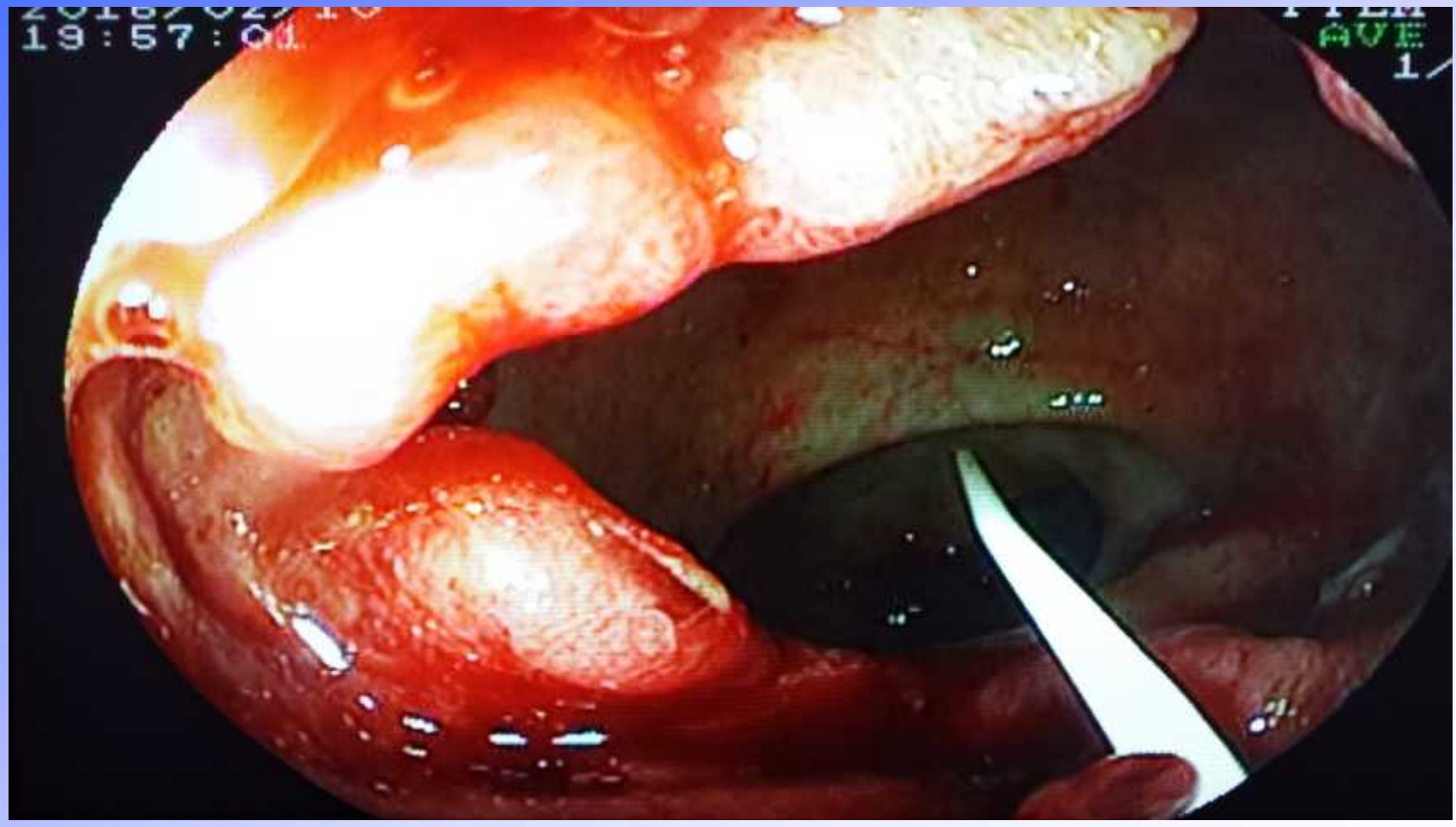
Indozyanine green liposomal

Indozyanine green liposomal

Lip-ICG-PDT: Rectal Cancer

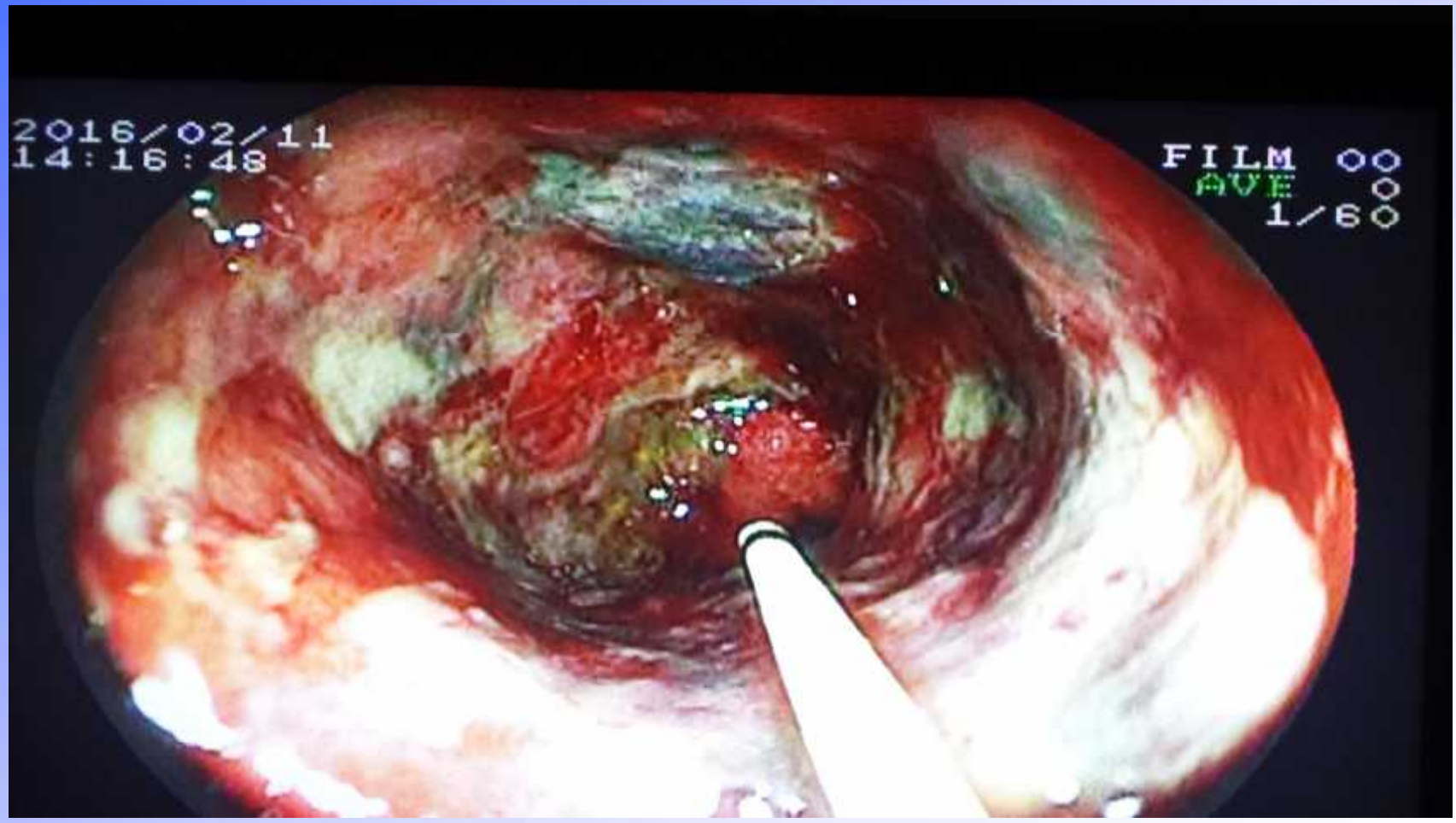


Lip-ICG-PDT: Rectal Cancer



Lip-ICG-PDT, Rectal Cancer

Lip-ICG-PDT: Rectal Cancer

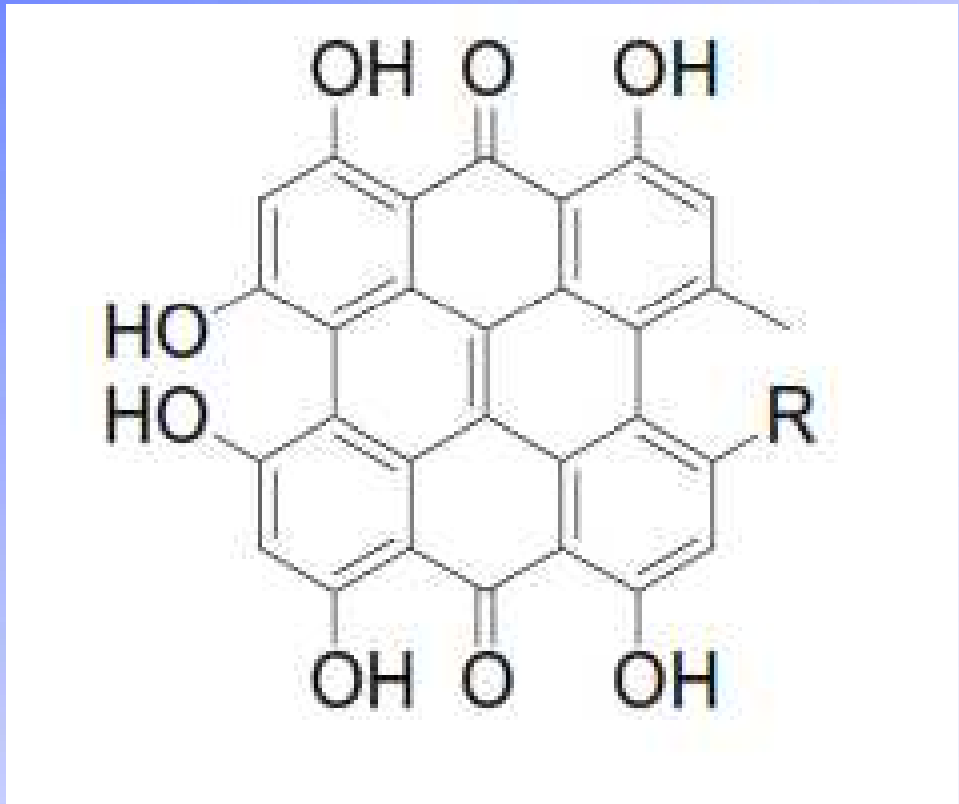


Other natural photosensitizers

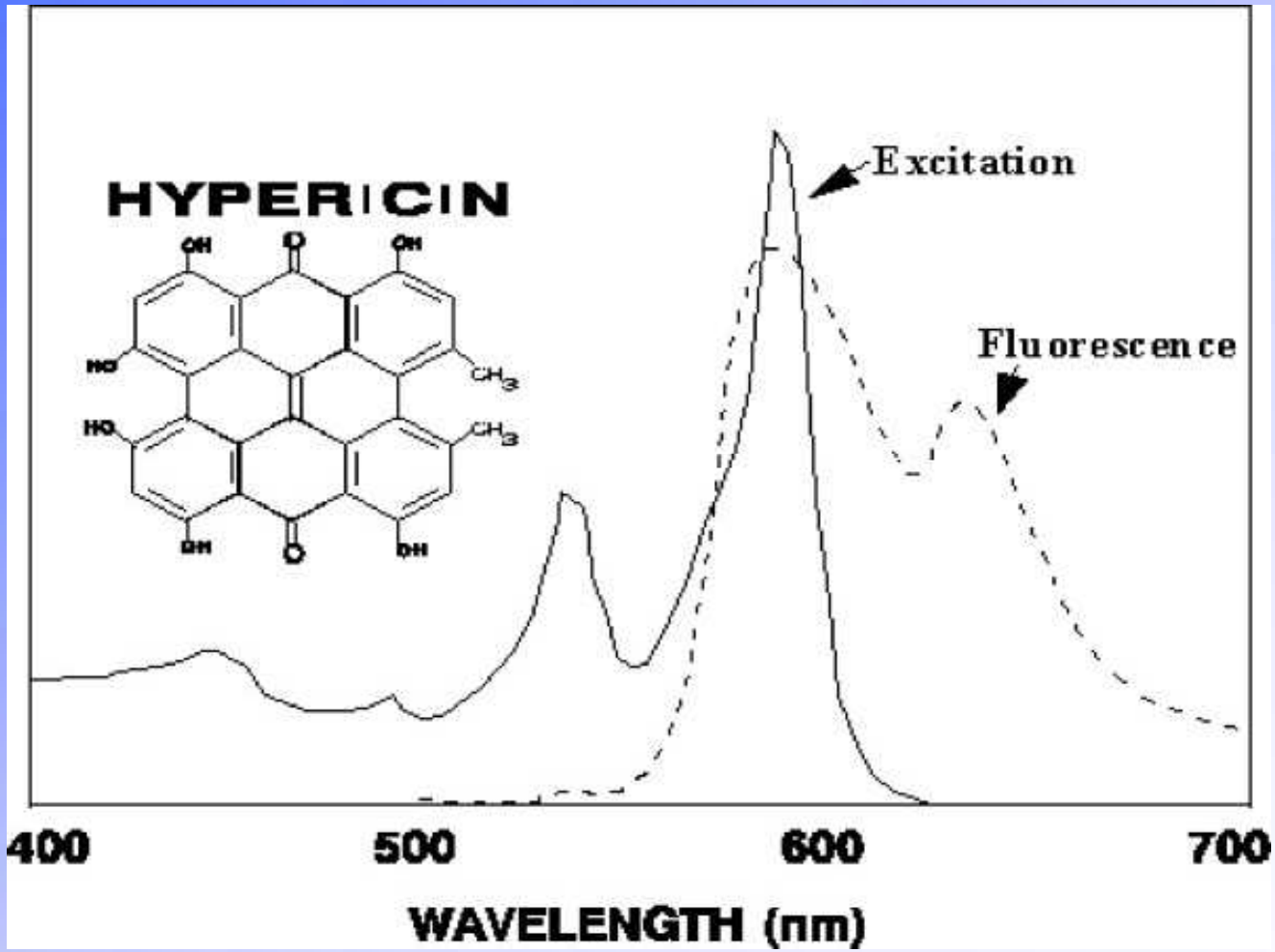
Hypericin as photosensitizer

St. John‘s wart plant

Hypericin as photosensitizer



Hypericin as photosensitizer




G-5%
250 ml
BIBRAUN

Hypericin as photosensitizer in combination with yellow laser therapy

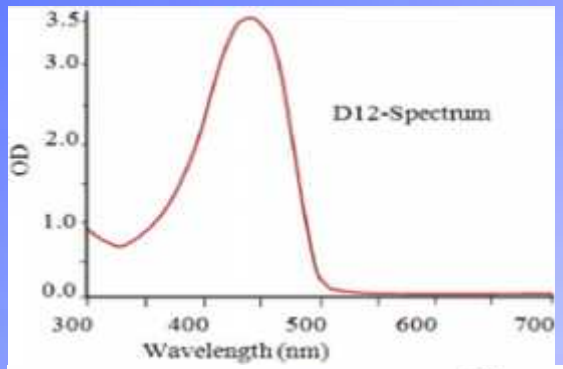
Hypericin as photosensitizer

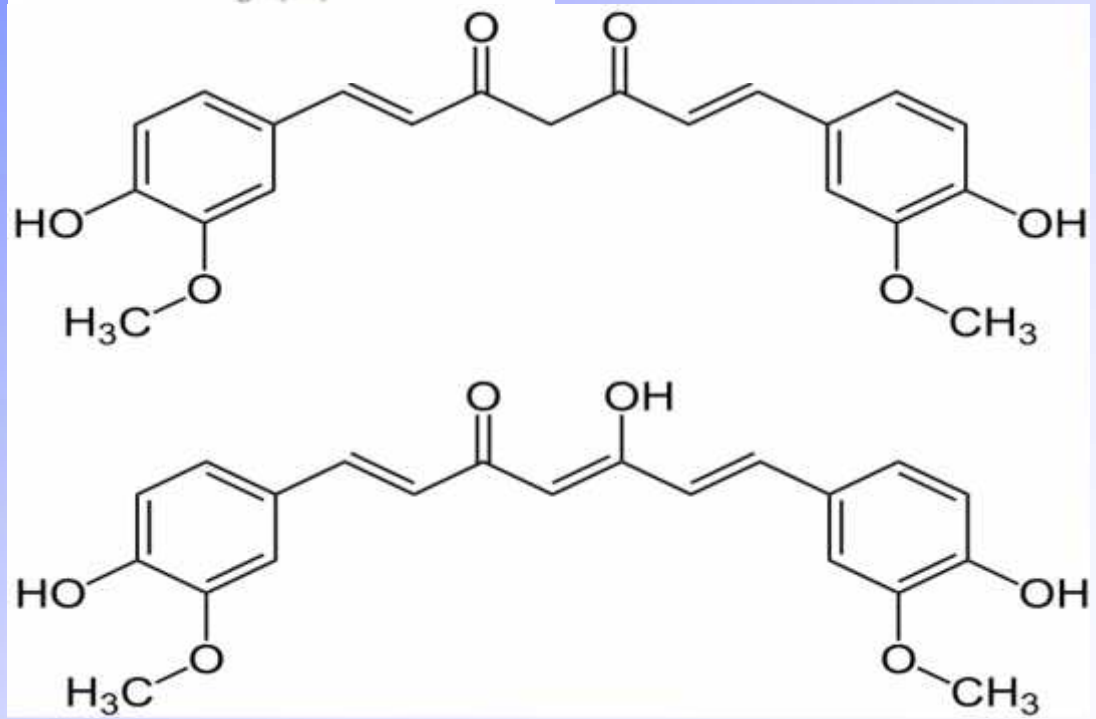
Interstitial PDT of breast cancer

Curcumin as photosensitizer

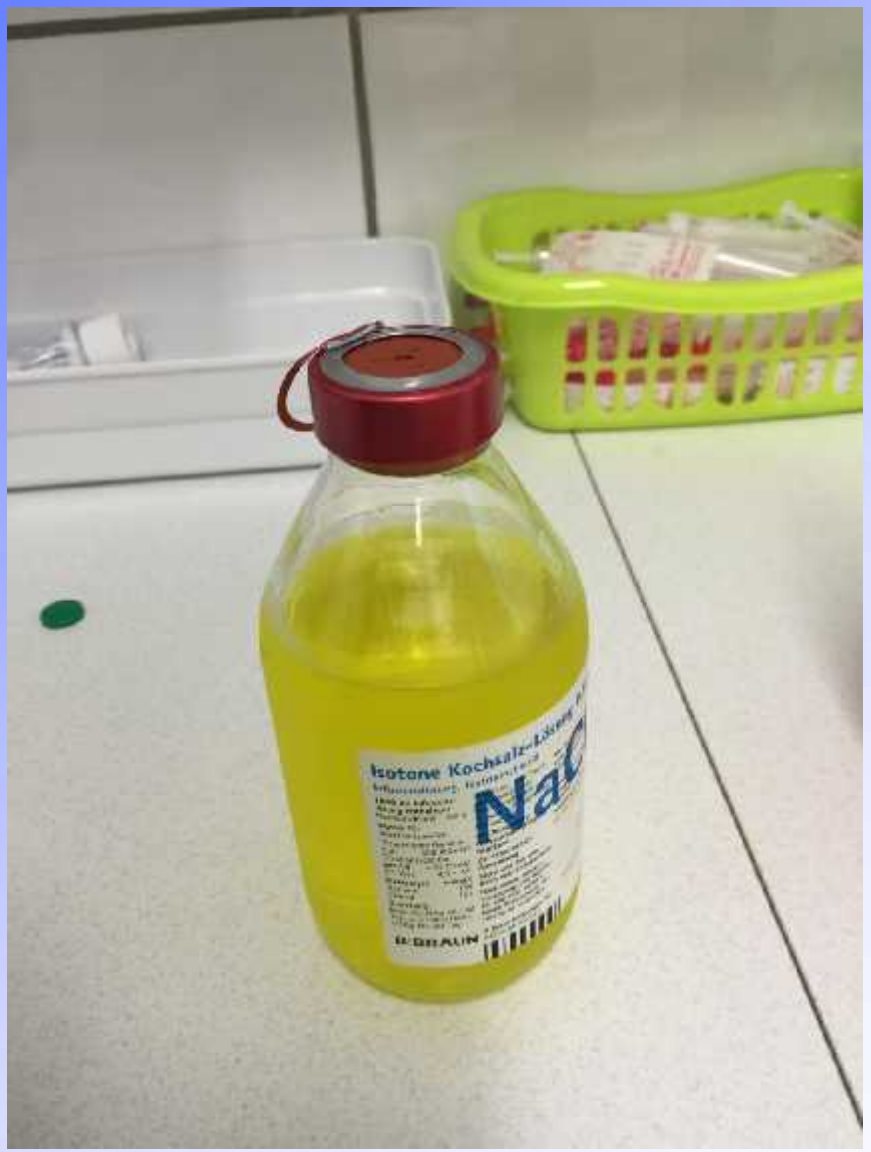
Curcuma powder

Curcumin

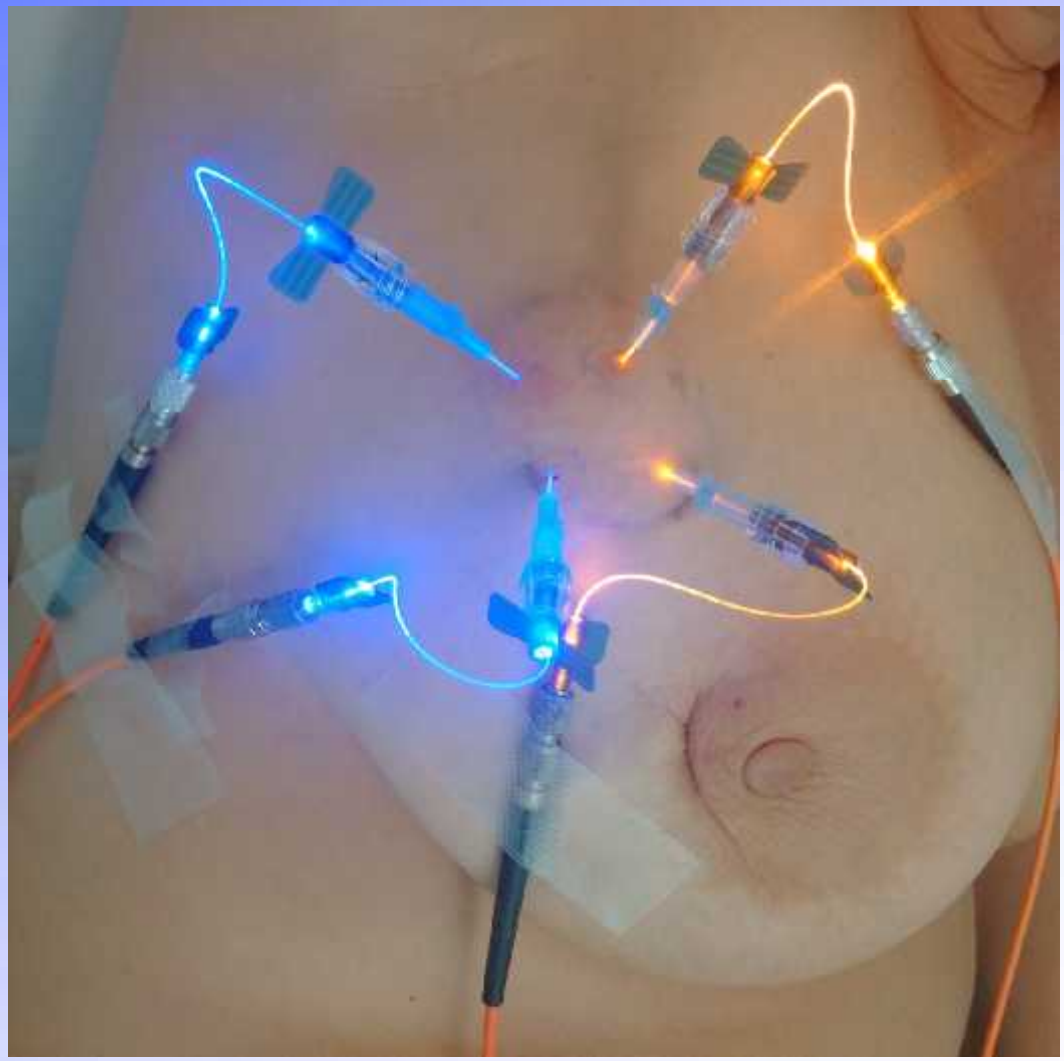

D12-Spectrum
OD
3.5
3.0
2.0
1.0
0.0
300
400
500
600
700
Wavelength (nm)


O
O
HO
OH
O
H3C
O
CH3
O
OH
HO
OH
O
H3C
O
CH3

Curcumin



Interstitial PDT combination after Hypericin and Curcumin



Absorption spectra of different phtotosensitizers

- Chlorin E 6 absorbs 660 nm red laser
- Indocyanine Green absorbs 810 nm infrared laser
- Hypericin absorbs 589 nm yellow laser
- Curcurmin absorbs 447 nm blue laser
- Riboflavin absorbs 447 nm blue laser

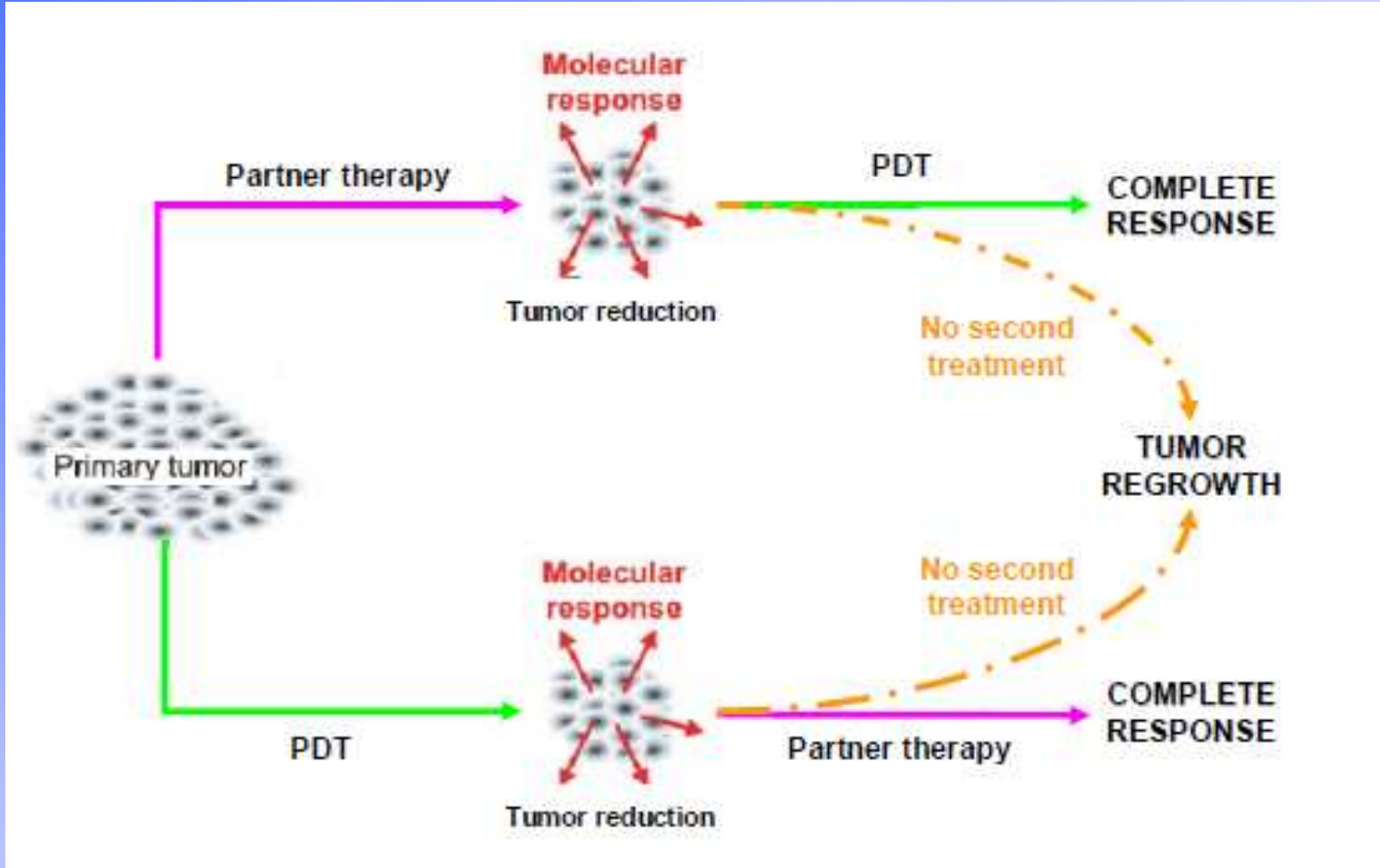
Cancer combination therapy

- Small single tumors are ideal for PDT treatment alone
- **PDT alone is not effective in**

- big tumors
- widely spreading tumors
- multiple metastases

Here we need combination of PDT with other anticancer drugs and methods.

Cancer combination therapy



Cancer combination therapies

1. Combination with traditional chemotherapy
2. **Combination with light sensitive chemodrugs**

   (using chemodrugs as photosensitizers)
3. **Combination with sonodynamic therapy (*using photosensitizers and chemodrugs as sonosensitizers)***
3. Combination with antioxidants
4. Combination with antiangionesis inhibitors
5. Combination with Cox-2 inhibitors
6. Combination with antibodies
7. Combination with different natural compounds
8. Combination with immunotherapy

5-Fluorouracil as a Phosensitiser

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ANGELA STAICU1, BENONE CARSTOCEA2 and RUXANDRA ANGELA PASCU2

1National Institute for Lasers, Plasma and Radiation Physics,
Laser Department, P. O. Box MG-36, Bucharest – Magurele;
2Central Military Hospital, Ophthalmology Clinic, Bucharest, Romania

Abstract

5-FU exhibits a high fluorescence after irradiation with UV-vis light. An enhancement of the cytostatic activity of 5-FU under UV-vis irradiation was observed on an in vivo experimental model.

The tautomeric forms of 5-FU

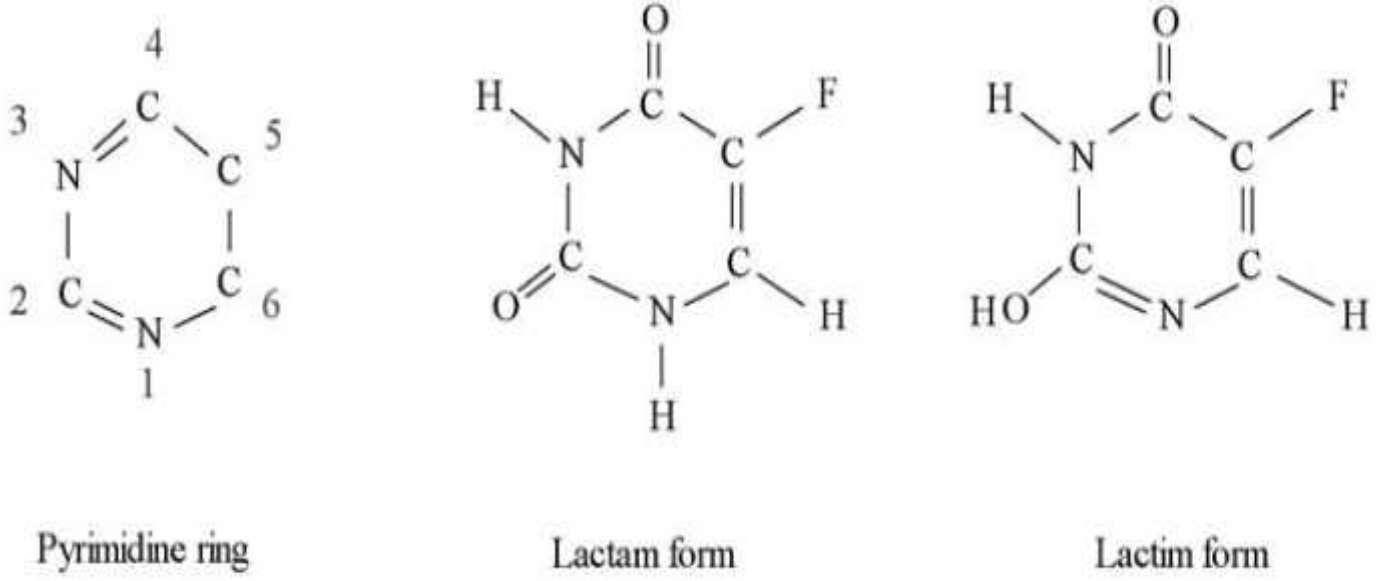


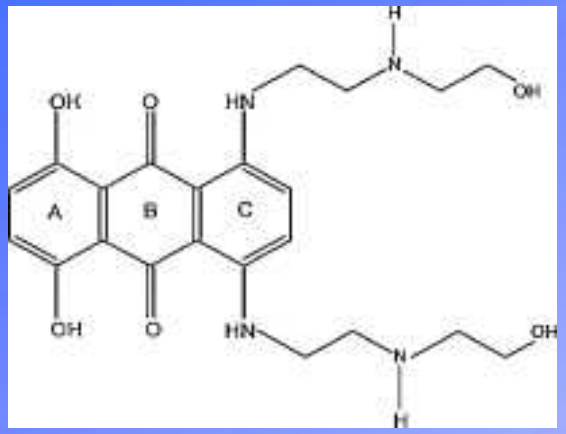
Figure 1. *The pyrimidine ring and the two 5-FU tautomers: lactam and lactim forms.*

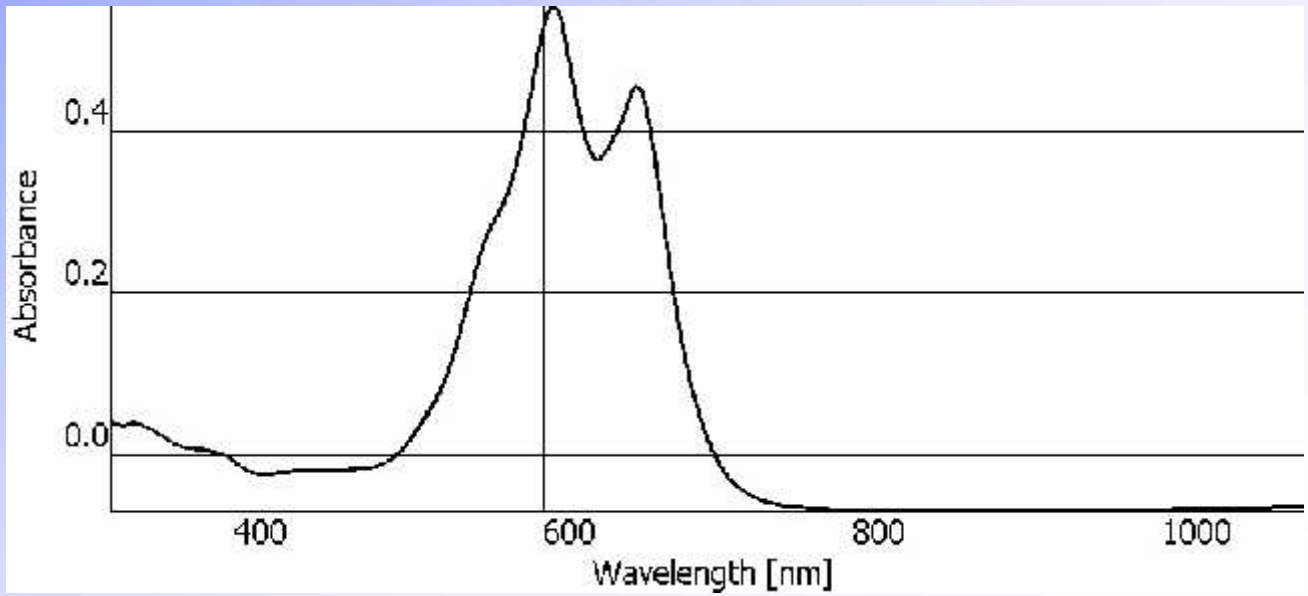
Mitoxantron as photosensitizer

- Mitoxantron is a blue substance
- Mitxantron is activated by yellow and red light
- Mitoxantron is a strong chemo-photosensitizer
- Is effective in multiple cancer varieties

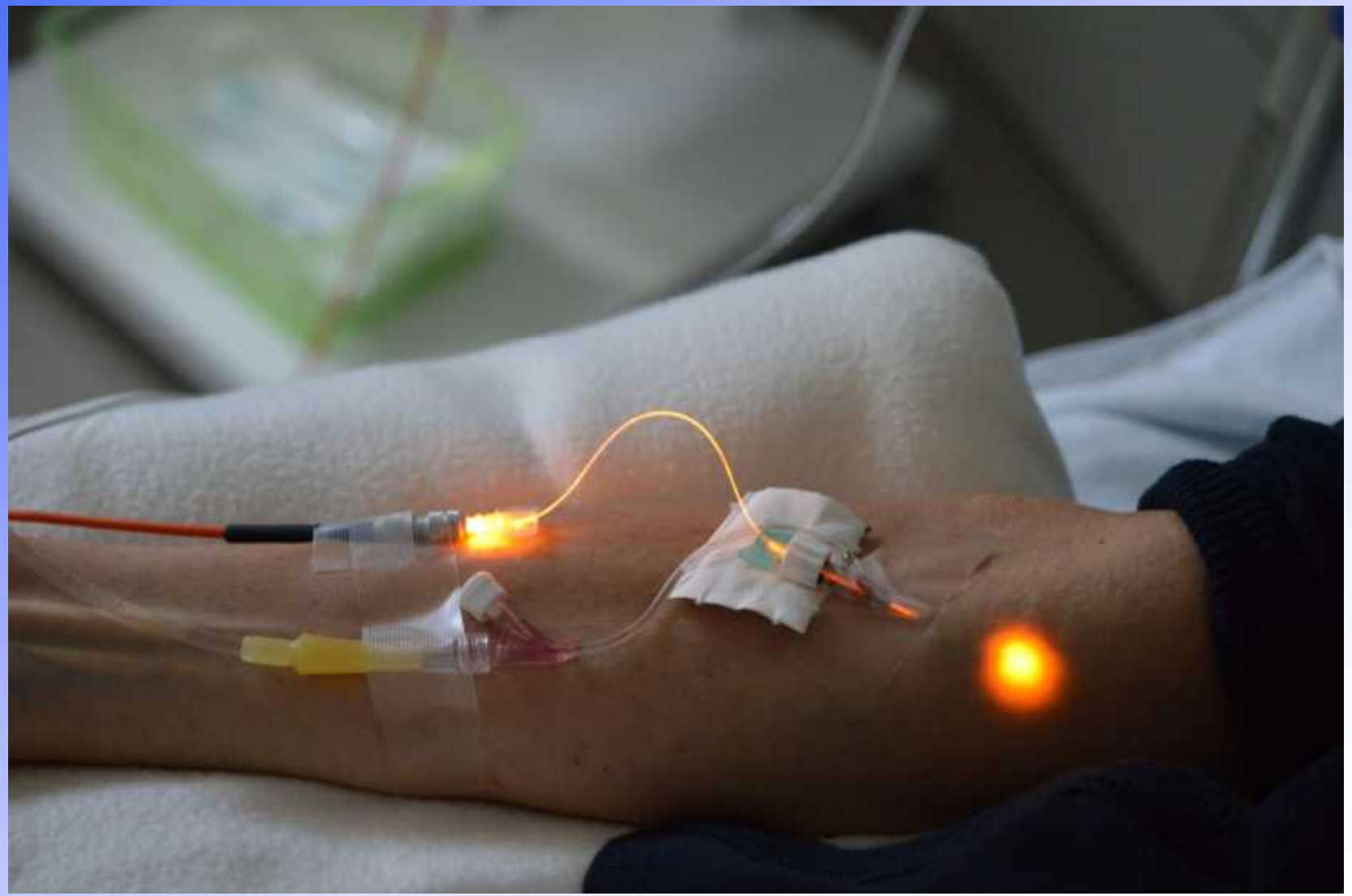
Mitoxantron

Mitoxantron as photosensitizer





Mitoxantron stimulation (Y-cannula)

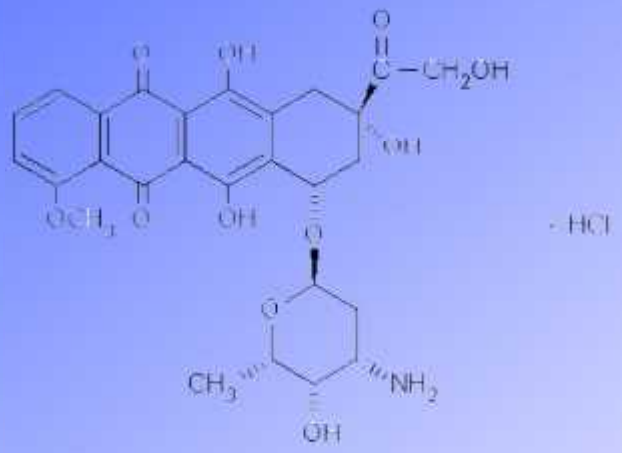


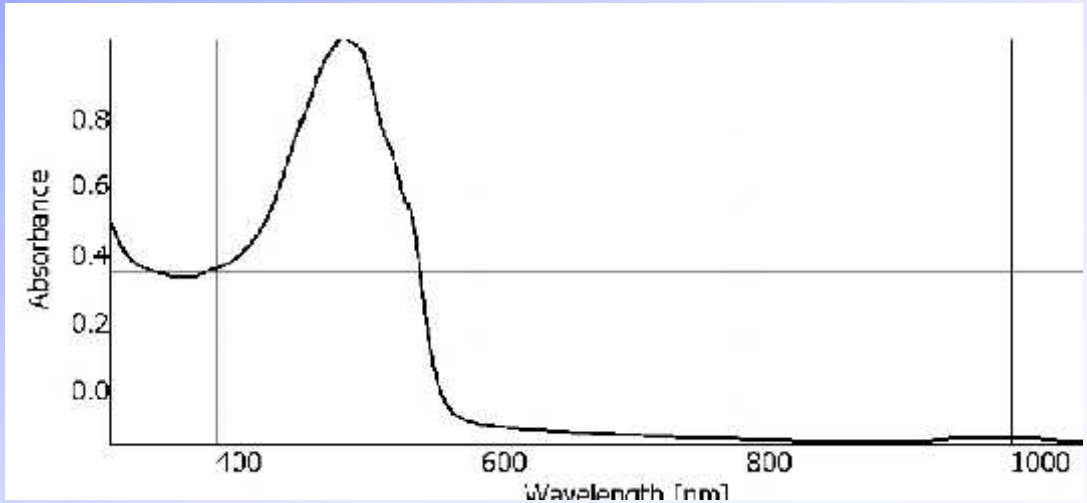
Doxorubicin (liposomal) as photosensitier

- Is widely used for many different cancers (Anthracyclin antibiotics)
- Is an orange solution and is stimulated by visible laser light
- Can be enhanced by liposomal delivery (Doxil)
- Stimulation by blue-green light

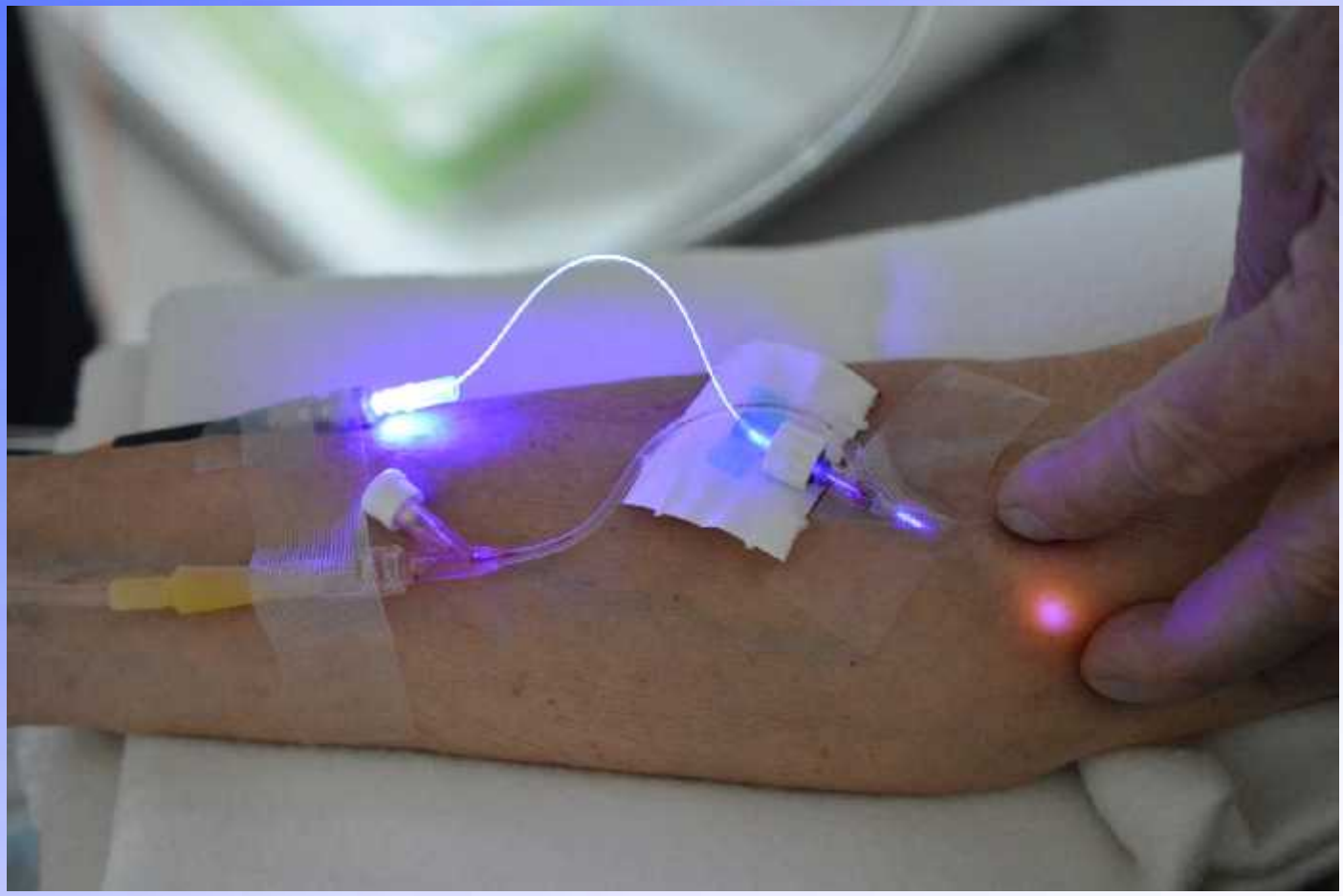
Doxorubicin liposomal

Doxorubicin (liposomal) as photosensitizer





Doxorubicin stimulation

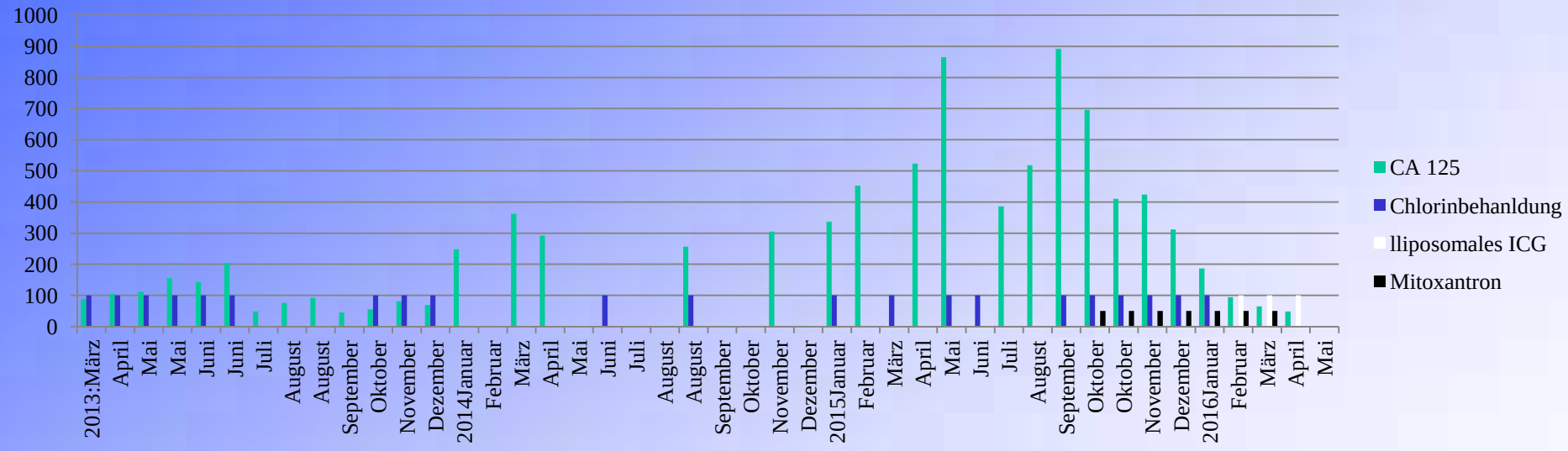


Case report: ovarian cancer with peritoneal carcinosis (patient 45 y.

- **First check: 19.03.13:** CA 125: 88,4 + ascites in Ultrasound
- **02.04.13: 1. PET-CT Scan: O**varial cancer, peritoneal carcinosis, ascites
- **18.06.13: 2. PET-CT Untersuchung**: Metastasen in pelvis, metastases perihepatic perihepatisch, ascites
- **12.11.13: 1. MRI Abdomen:** peritoneal carcinosis, metastases subphrenic, liver and right kidney, ascites
- **08.01.15: 2. MRI pelvis**: Cervix carcinoma grade I, ascites, nodular peritoneal carcinosis, no lymph nodes or metastases in bones
- **27.08.15: 3. PET-MR scan:** progredient peritoneal metastases,perihepatic and in pelvis, 2 new big tumors in ovarial area both sides, recurrence o the ovarial cancer, lympfh nodes rechts epiphrenic

Case report: ovarian cancer with peritoneal carcinosis

Case report: ovarian cancer with peritoneal carcinosis



Sonodynamic therapy

Sonodynamic therapy (SDT) is an emerging approach that involves a combination of low-intensity ultrasound and specialized chemical agents known as sonosensitizers. Ultrasound can penetrate deeply into tissues and can be focused into a small region of a tumor to activate a sonosensitizer which offers the possibility of non-invasively eradicating solid tumors in a site-directed manner. At the same time, the breath of evidence from SDT-based studies suggests that SDT is promising for cancer treatment.

Cancer Biol Med 2016. doi: 10.20892/j.issn.2095-3941.2016.0068

Ultrasound application methods

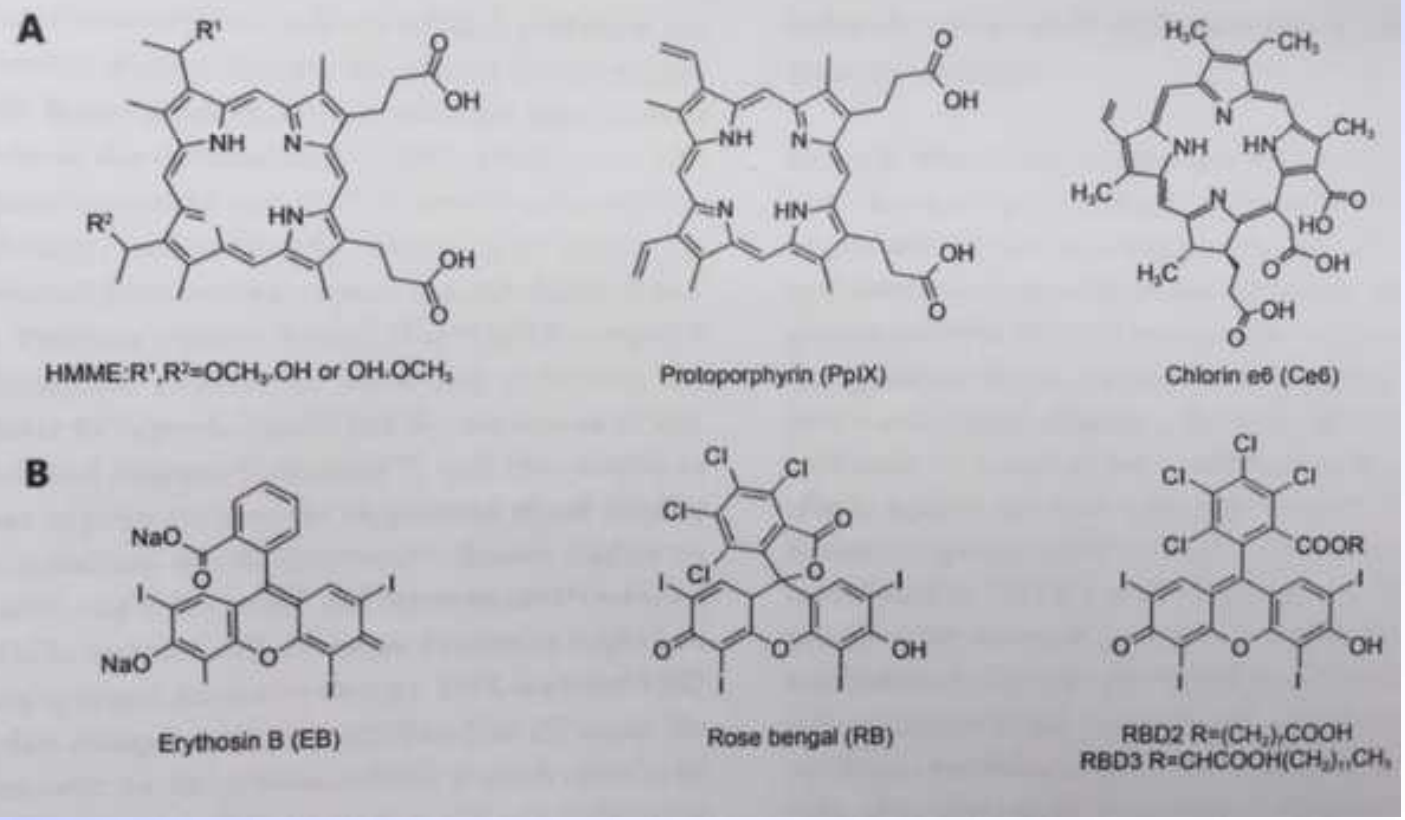
- Low power ultrasound (1 – 2 W/sqcm)
- High frequency ultrasound 300 – 500 W (HIFU)
- Ultrasound schock waves

Sonosensitizers

Cancer Biol Med Vol 13, No 3 September 2016

teroidal anti-inflammatory drug-based sonosensitizers, and
other sonosensitizers. Their chemical structures are shown in

Figure 2. These sonosensitizers have been exten
in some investigations of SDT in cancer treatme



Sonosensitizers

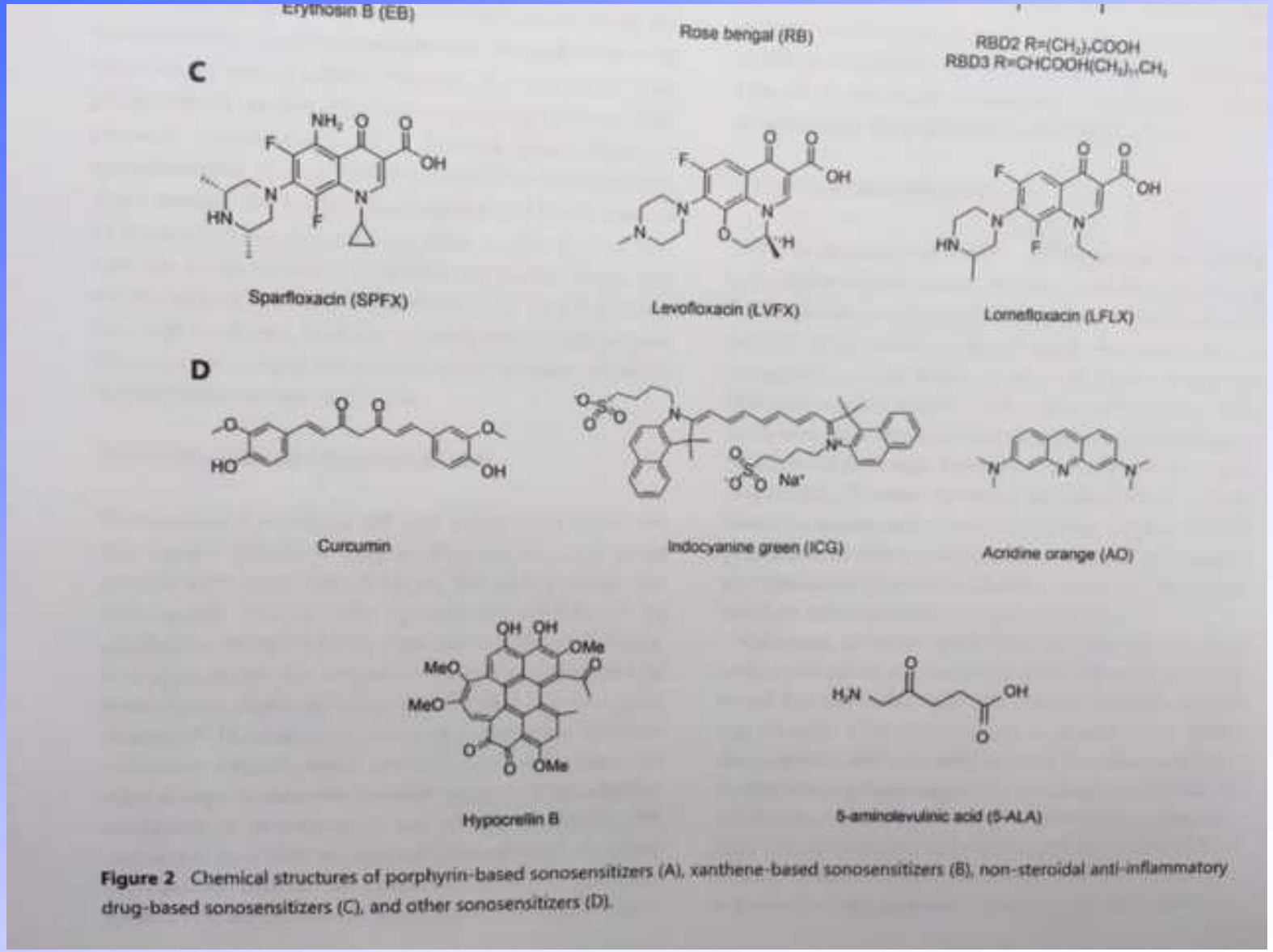
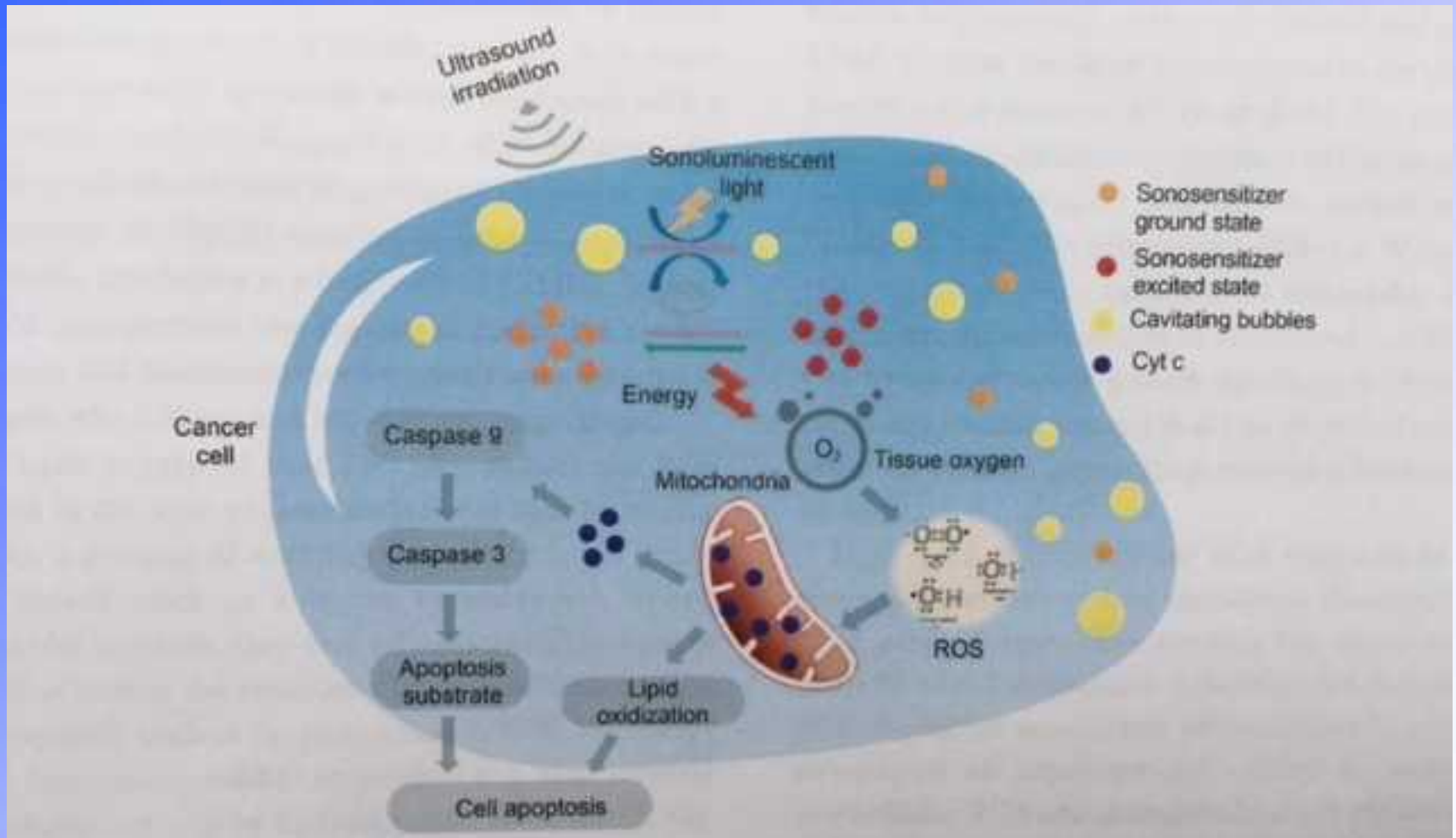


Figure 2 Chemical structures of porphyrin-based sonosensitizers (A), xanthene-based sonosensitizers (B), non-steroidal anti-inflammatory drug-based sonosensitizers (C), and other sonosensitizers (D).



Possible mechanisms of SDT. Ultrasound irradiation induces cavitation around the surface of cancer cells. The energy pro
ose of cavitating bubbles initiates the formation of sonoluminescent light in cancer cells. Thus, sonosensitizer is activated
tate into an excited state. As the activated sonosensitizer returns to the ground state, the released energy can be transferre
nbient oxygen to produce a large amount of ROS including oxygen ion, peroxide and singlet oxygen, which subsequently

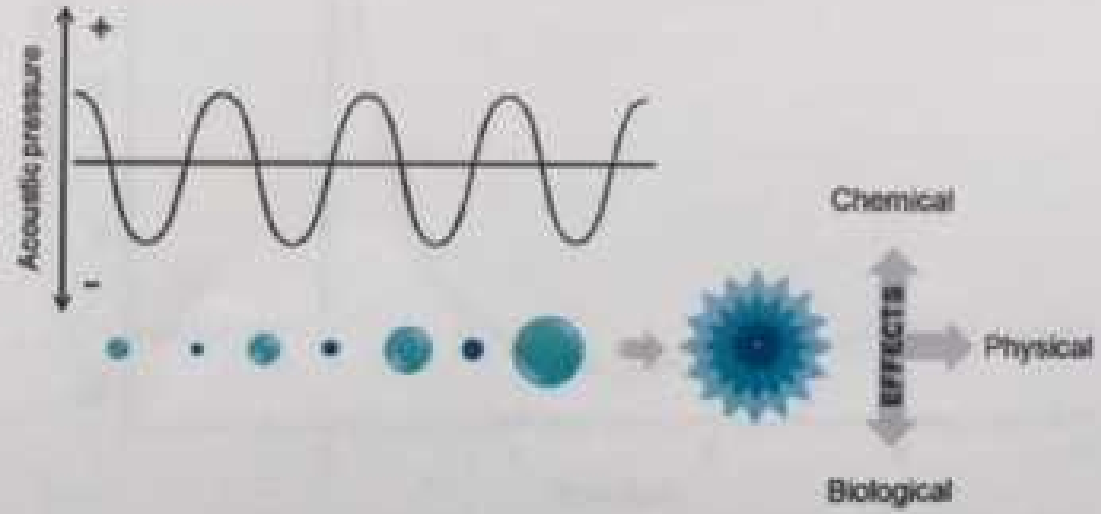


Figure 1 Drawing showing the formation, growth, and collapse of a cavitation bubble.

Current Drug Therapy, 2009, *4*, 179-193

Activated Cancer Therapy Using Light and Ultrasound - A Case Series of Sonodynamic Photodynamic Therapy in 115 Patients over a 4 Year Period

J.N. Kenyon[1,*], R.J. Fuller[1] and T.J. Lewis[2]

[1]*The Dove Clinic, Twyford, Winchester, Hampshire, SO21 1NT, England;* [2]*SonneMed, LLC, 10 Mt. Vernon St. Suite 208, Winchester, MA 01890, USA*

Abstract: Activated Cancer Therapy (ACT), also known as Sonodynamic Photodynamic Therapy (SPDT) is a novel therapeutic modality that utilises a non-toxic photosensitive agent with reported ultrasound-activated properties. SPDT has previously demonstrated significant tumour cell inhibition in animal studies. There has been much research into the efficacy of photodynamic therapy and development in understanding of the underlying mechanism of tumour cytotoxicity. Synergistic ultrasound activation represents a promising development to activated sensitiser therapy, as photo-activation is limited by access and penetrance issues. Ultrasound has been demonstrated to activate a number of sono-sensitive agents allowing the possibility of non-invasive targeted treatment of deeper tumour sites than is currently achievable with photodynamic therapy. This case series of 115 patients with a variety of cancer diagnoses reports on experiences of this treatment over a 4 year period using sublingual administration of a new dual activation agent, Sonnelux-1, followed by a protocol of LED light and low-intensity ultrasound exposure. Initial clinical observation suggests SPDT is worthy of further investigation as an effective and well tolerated treatment for a wide variety of primary and metastatic tumours, including those refractory to chemotherapy.

Key Words: Sonodynamic therapy, photodynamic therapy, activated cancer therapy, ultrasound activated therapy, metastatic cancer, sonnelux-1, dove clinic, sonnemed.

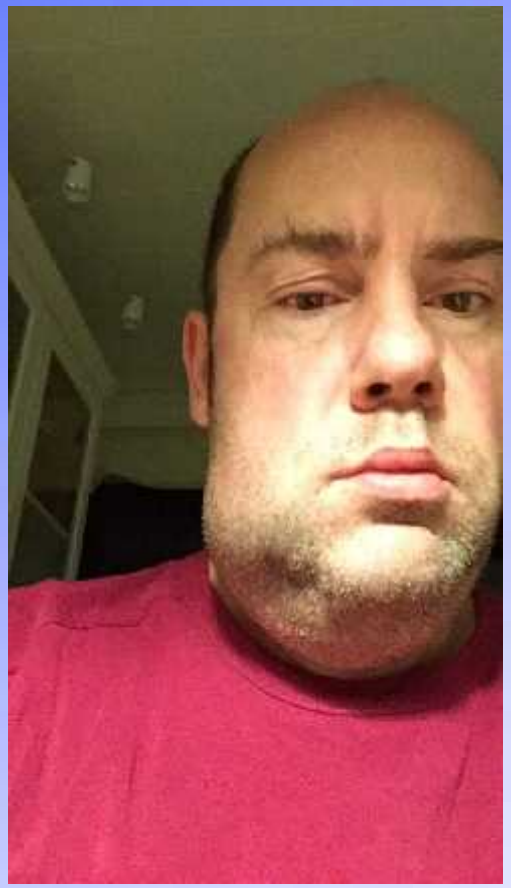
Low power ultrasound device (0,2 – 2,0W/sqcm)

High frequency ultrasound device (HIFU)

Ultrasound schock wave device

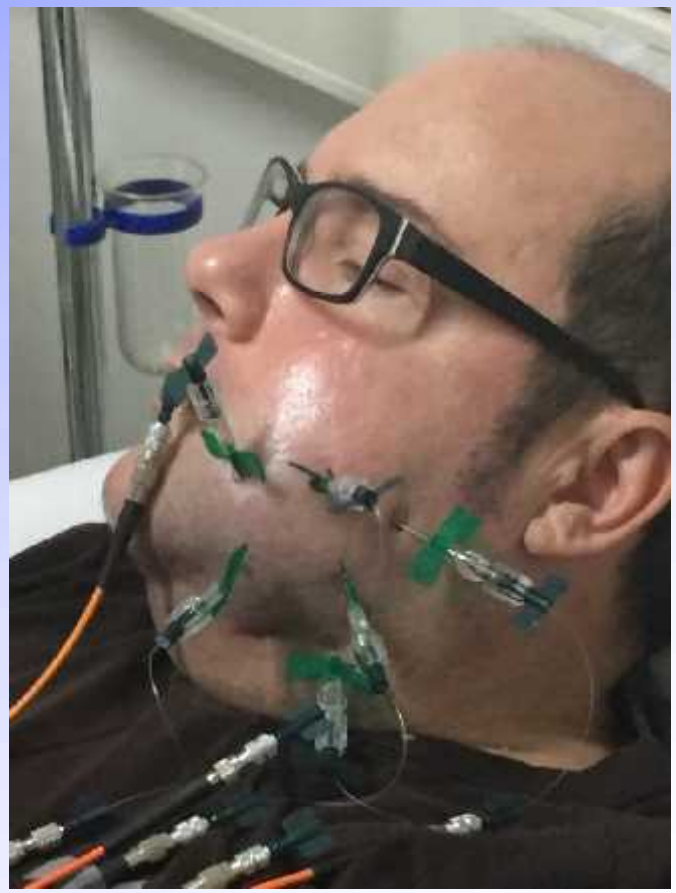
Lymphoma

B-cell lymphoma




SonoScape
LASERZENTRUM WEBER
L752/Breast
MI 0.3
TIS 0.1
GETH THOMAS GERUNG
19/12/2016 12:01:19
FPS 20
D/G 140/4
GN 37
I/P 0/30
PWR 70
FRQ 9.8-15.8
D 6.0cm
0
5
199 199
THI

B-cell lymphoma



B-cell lymphoma


SonoScape
LASERZENTRUM WEBER
L752/Breast
GETH THOMAS GERUNG
FPS 22
GN 9
FRQ 9.8-15.8
SonoScape
LASERZENTRUM WEBER
L752/Breast
GETH THOMAS GERUNG
FPS 22
GN 16
FRQ 9.8-15.8

10 days later


SonoScape
LASERZENTRUM WEBER
L752/Breast
MI 0.3
TIS 0.1
GETH THOMAS GERUNG
23/01/2017 11:26:22
FPS 20
D/G 140/4
GN 37
I/P 0/30
PWR 70
FRQ 9.8-15.8
D 6.0cm
0
5
0 199 199
THI

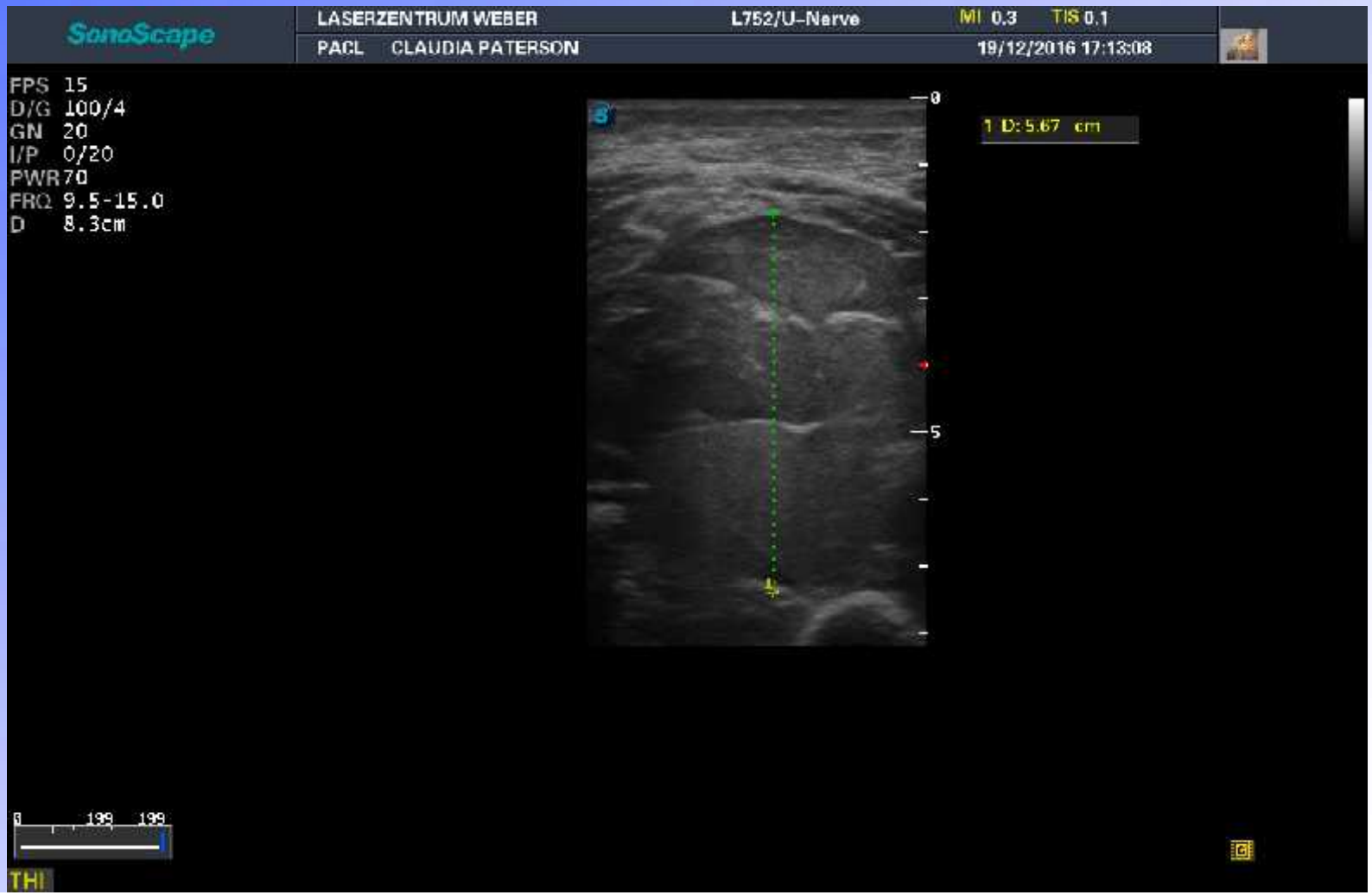

SonoScape
LASERZENTRUM WEBER
L752/Breast
MI 0.3
TIS 0.1
GETH THOMAS GERUNG
23/01/2017 11:28:52
FPS 20
D/G 140/4
GN 29
I/P 0/30
PWR 70
FRQ 9.8-15.8
D 6.0cm
THI

Sarcoma

Patient liposarcoma
12.12.2016

Patient liposarcoma
16.12.2016

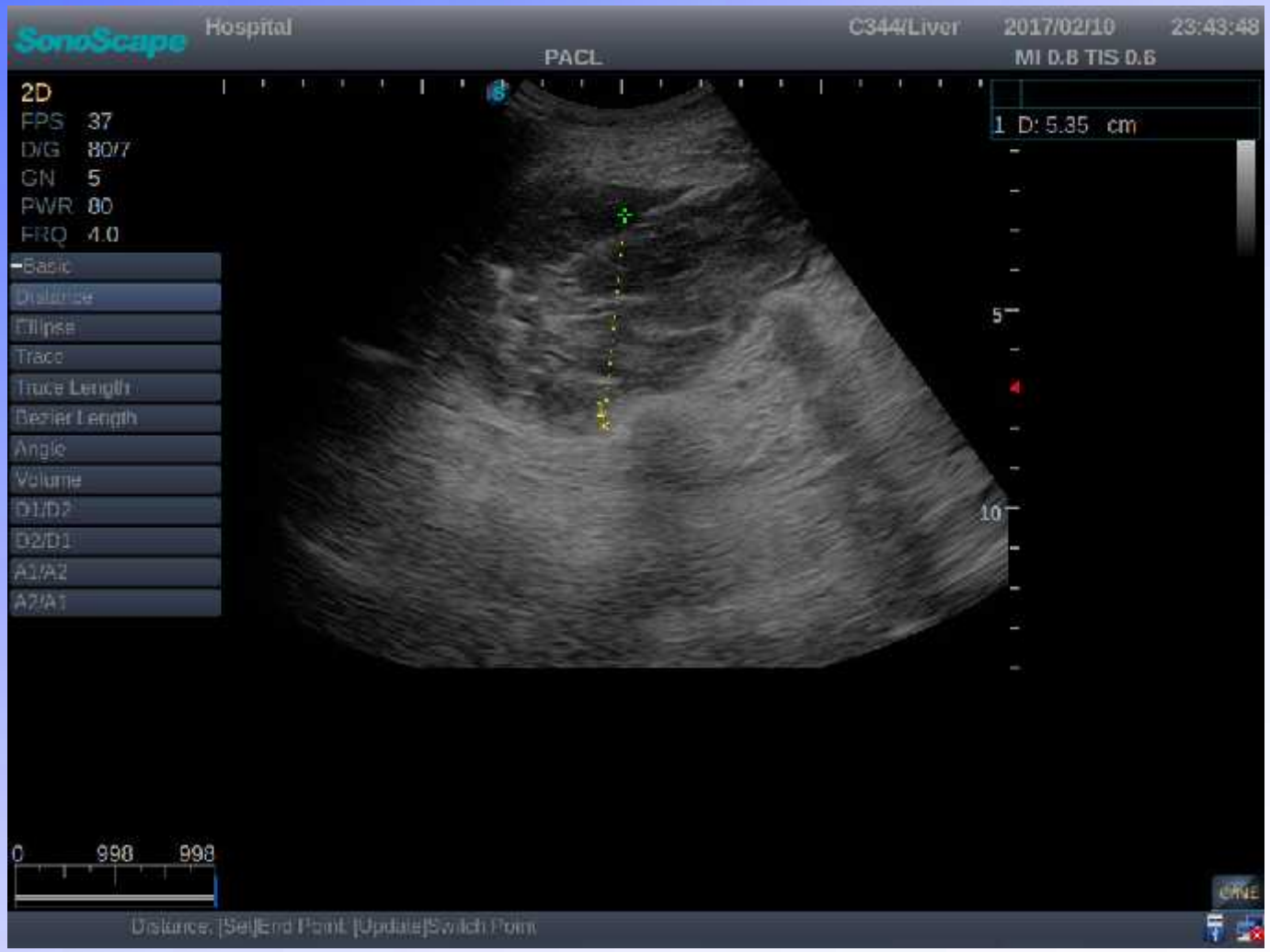
Patient liposarcoma
19.12.2016



Patient liposarcoma
22.12.2016

Patient liposarcoma
10.2.2017

Patient liposarcoma
10.2.2017



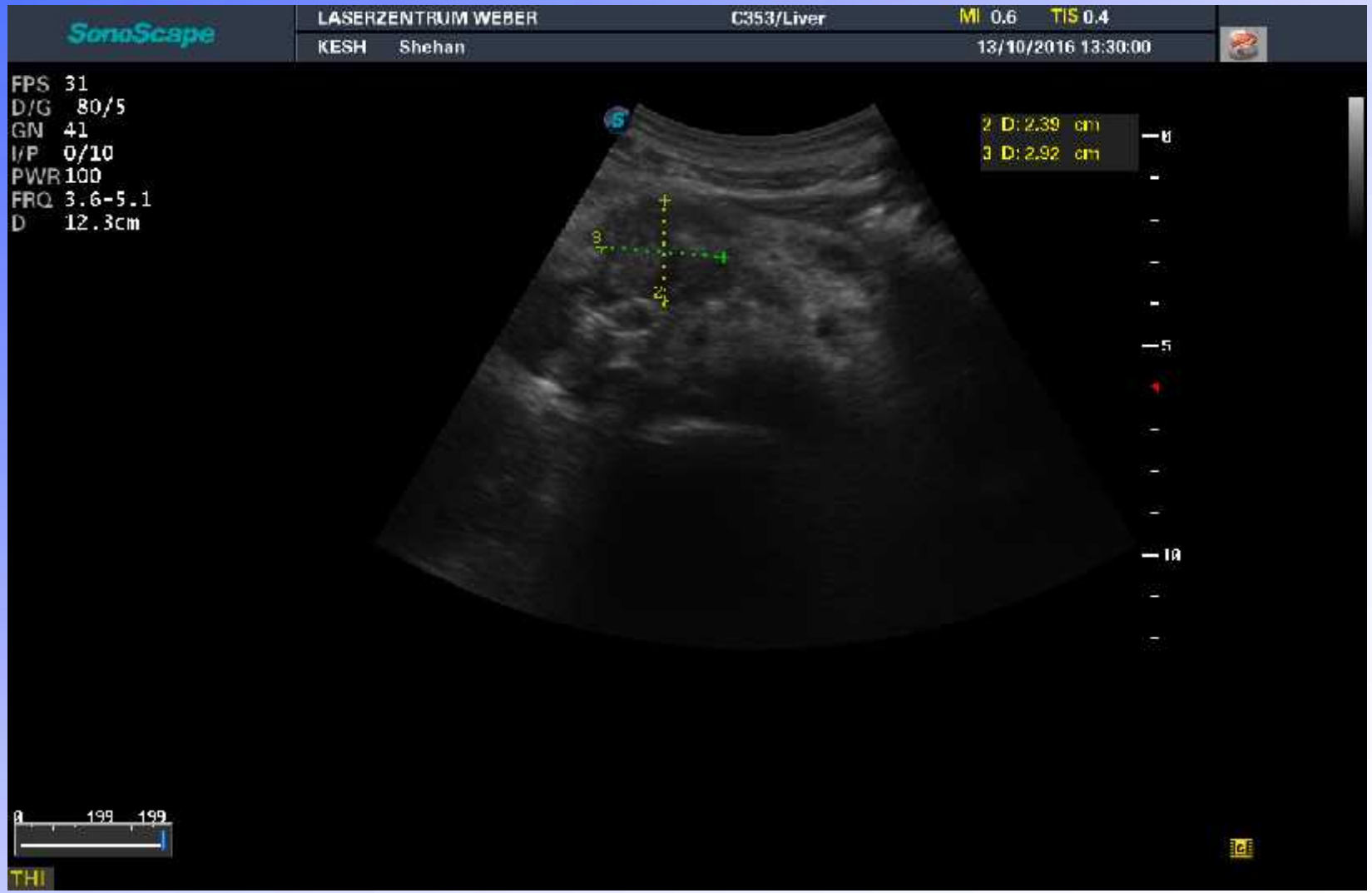
Patient liposarcoma
10.2.2017

Patient liposarcoma
10.2.2017

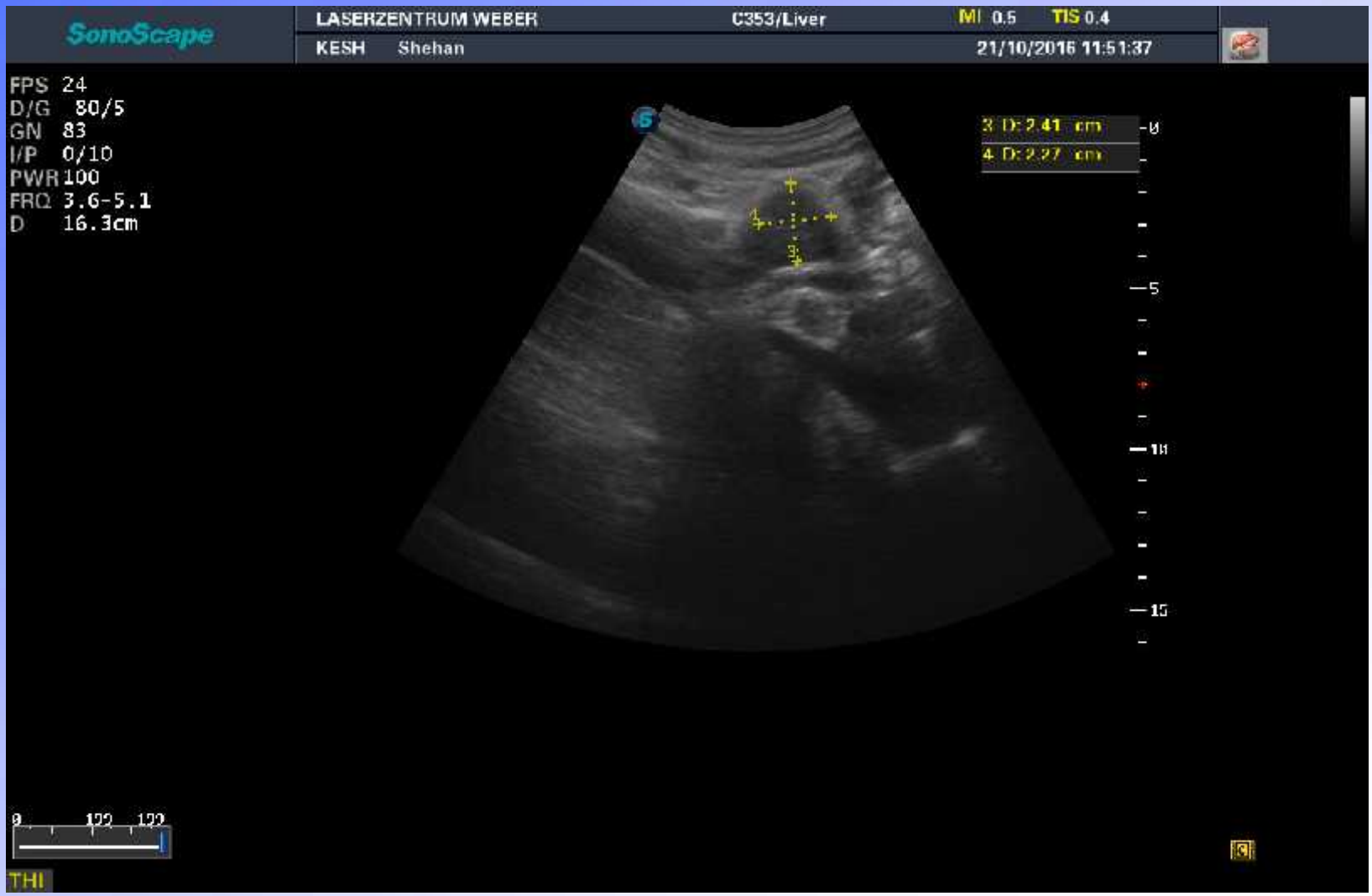
Pancreatic cancer

Case report: pancreatic cancer, male, 45 y. (10.10.2016)

Case report: pancreatic cancer (13.10.2016)



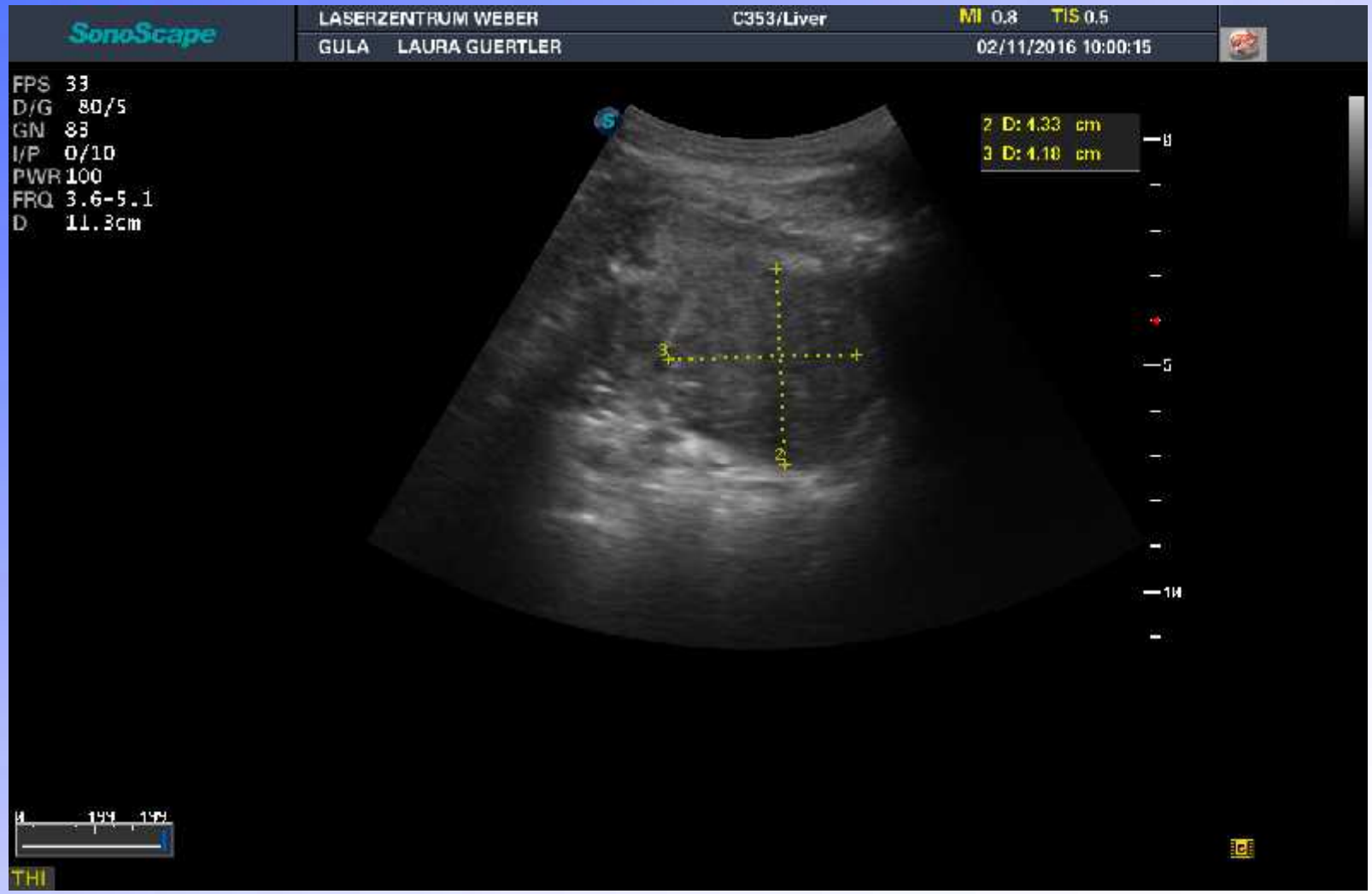
Case report: pancreatic cancer (21.10.2016)



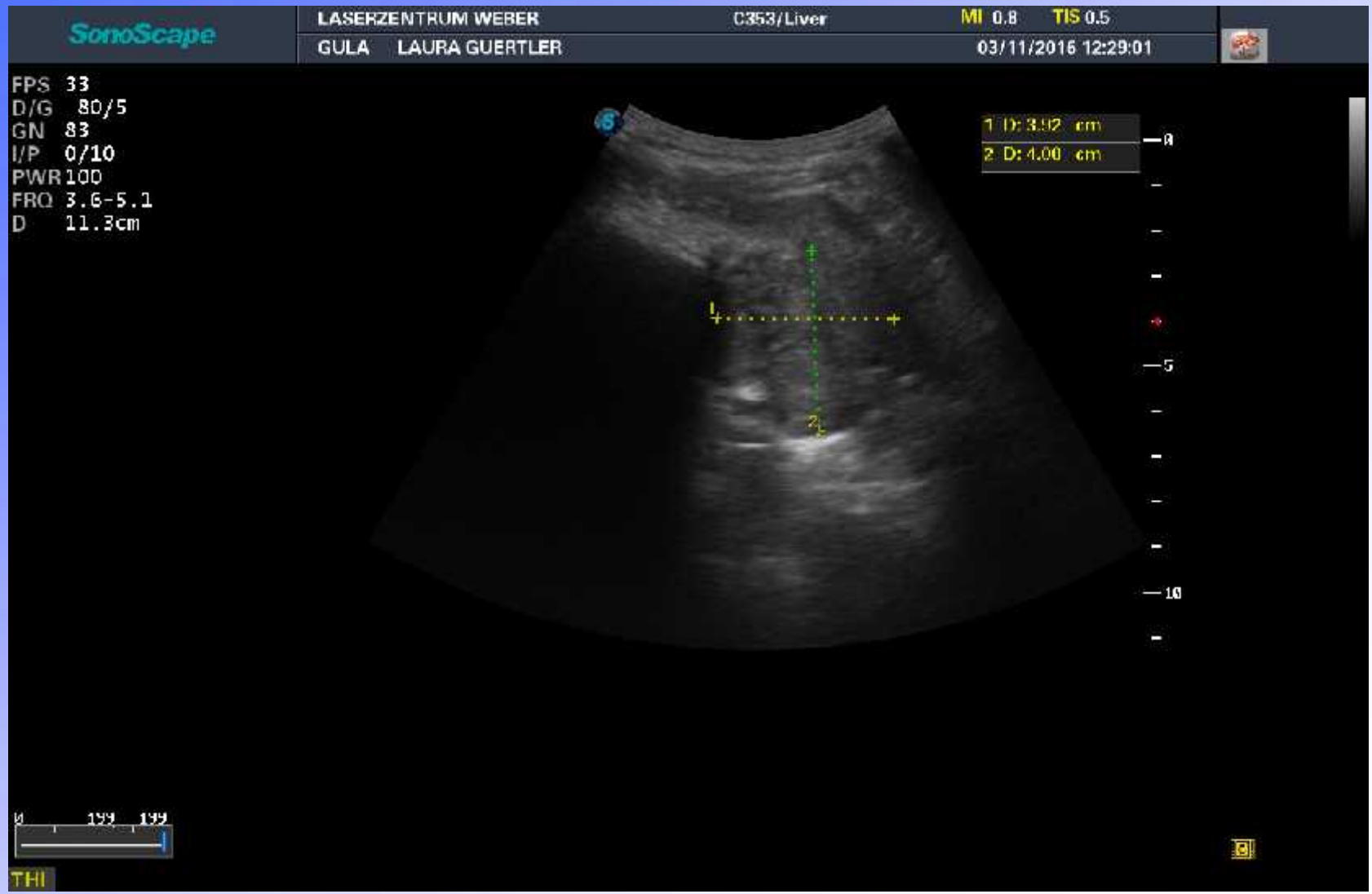
Ewing sarcoma

Case report, Ewing sarcoma, sacrum, female,14 y. (31.10.2016)

Case report, Ewing sarcoma, sacrum, female,14 y. (2.11.2016)



Case report, Ewing sarcoma, sacrum, female,14 y. (3.11.2016)



Patient, 45 y, f, lung cancer with 15 brain metastases

Hello Dr Weber,

Yesterday I had review scans at Royal Marsden
and I want to tell you my good news.

The scans showed reduction of tumours both in
my lung and lesions in my head. The lung reduced around
40% in mass (that's my rough calculation based on 2d
measurements given) as did the smaller cancer in my lung.

The doctor could not see the other lesions (there were about 14)

CT review for NT9LP680539, Sally Bowen DOB 14/1/62

The external CT chest and abdomen scan of 28/12/2016 has been reviewed and compared with the previous scan from 11/11/2016.

The superior right perihilar mass has further reduced in size, measuring 23 x 23mm (series 7 image 37) compared to 29 x 28mm previously. The hilar node inferiorly is now subcentimetre. No other focal lung lesions. No mediastinal or left hilar adenopathy.

No change in the liver cysts. The gallbladder, spleen, pancreas, kidneys and adrenal glands are unremarkable and unchanged. No abdominal lymphadenopathy. No bone lesions.

Comment: Further reduction in size of the right hilar mass and adjacent adenopathy consistent with further partial response.

Dr Anthony Aylwin Consultant Radiologist

Alliance Medical If you have any queries regarding this report, please contact Alliance Medical on +44 (0)20 7935 7711

*** END OF REPORT ***
Private & Confidential 01483 303106 Dr. L A Parkinson Brain HealthTen Harley Street Ltd 10 Harley Street W1G 9PF

Hyperbaric oxygen chamber

New therapeutic strategies for cancer therapy

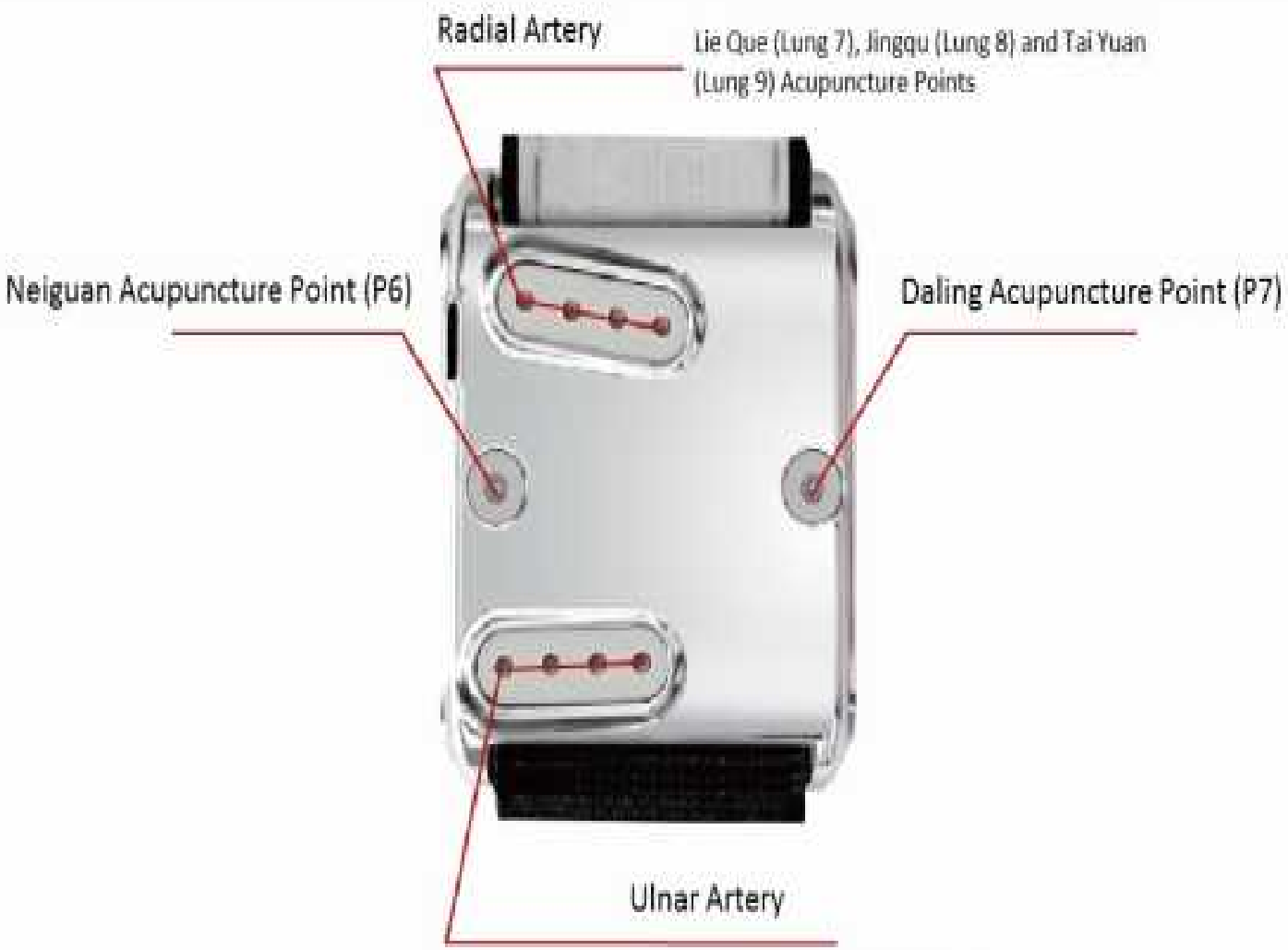
- **Photodynamic and sonodynamic therapy with liposomal ICG, Chlorin E6, Hypericin and Curcumin**

  (external, interstitial, intratumoral irradiation)
- Hyperbaric oxygene therapy
- Low dose chemotherapy using chemodrugs as photosensitizers
- Immunotherapy with intravenous laser blood irradiation
- Immunotherapy with GcMAF, TBL12, dendritic cells, oncolytic viruses and other methods

The new laser watch

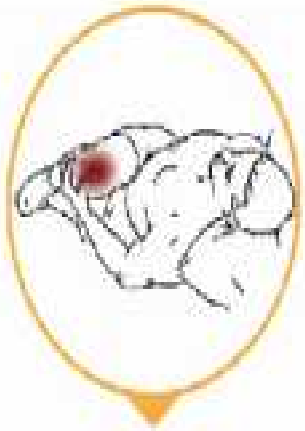
The Laser watch

- 18 Laser diodes
- wavelength 650nm
- power 5mW each


Radial Artery
Lie Que (Lung 7), Jingqu (Lung 8) and Tai Yuan (Lung 9) Acupuncture Points
Neiguan Acupuncture Point (P6)
Daling Acupuncture Point (P7)
Ulnar Artery
Lingdao (Heart 4), Tongli (Heart 5), Yinxi (Heart 6) and Shenmen (Heart 7) Acupuncture Points

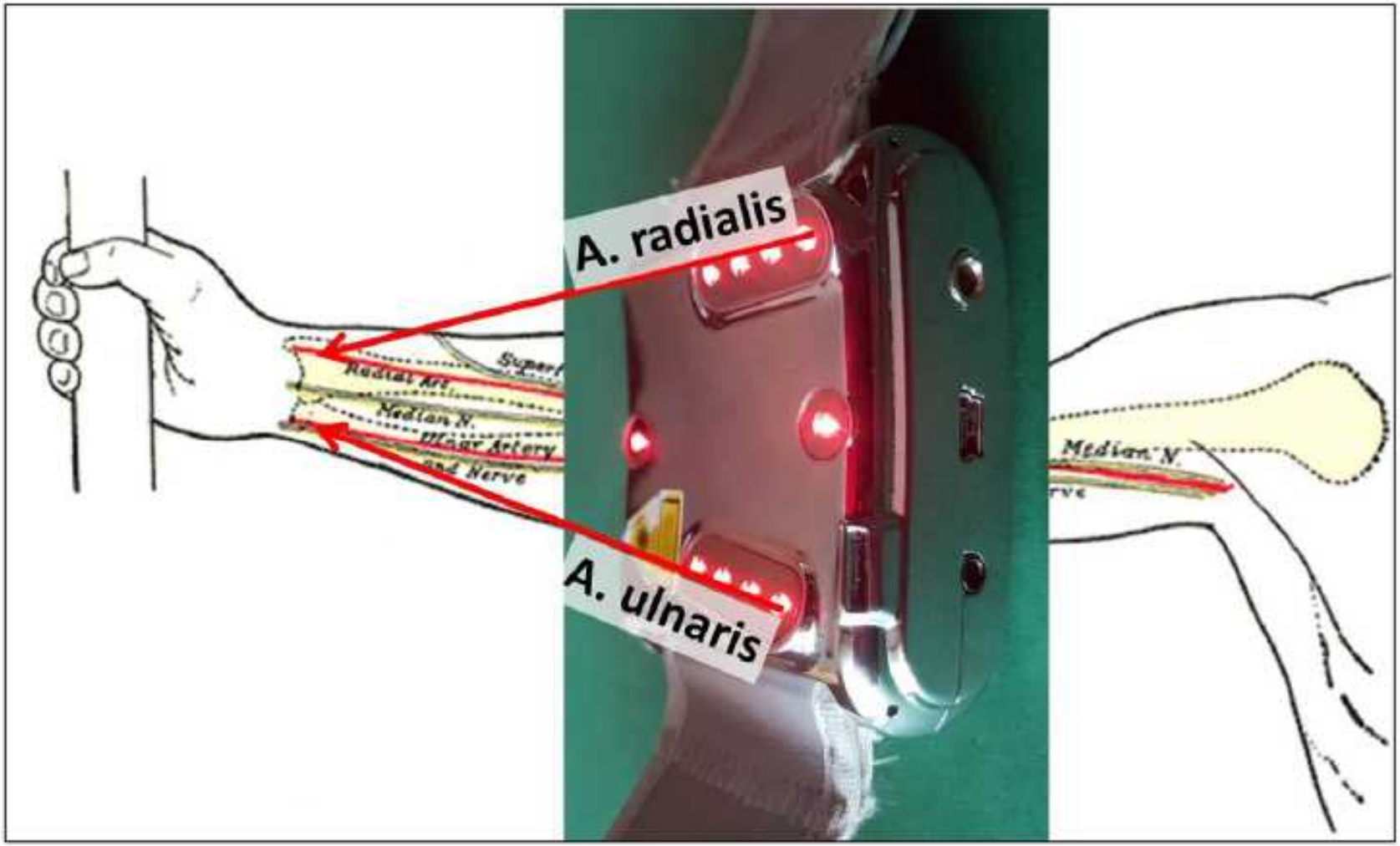
Laser Pad for Local Pain Treatment

The 650nm laser can directly penetrate the Ashi points (= pain points). It activates the lysozyme and phagocytic cell activity and thereby demonstrates anti-inflammatory effects.



1. Connect the pad to the corresponding jack and place it over the area you want to treat.

Please note that a jointly use of the laser pad and the nasal probe or the laser watch is not possible.



ig. 2: Laser blood irradiation with the laser watch

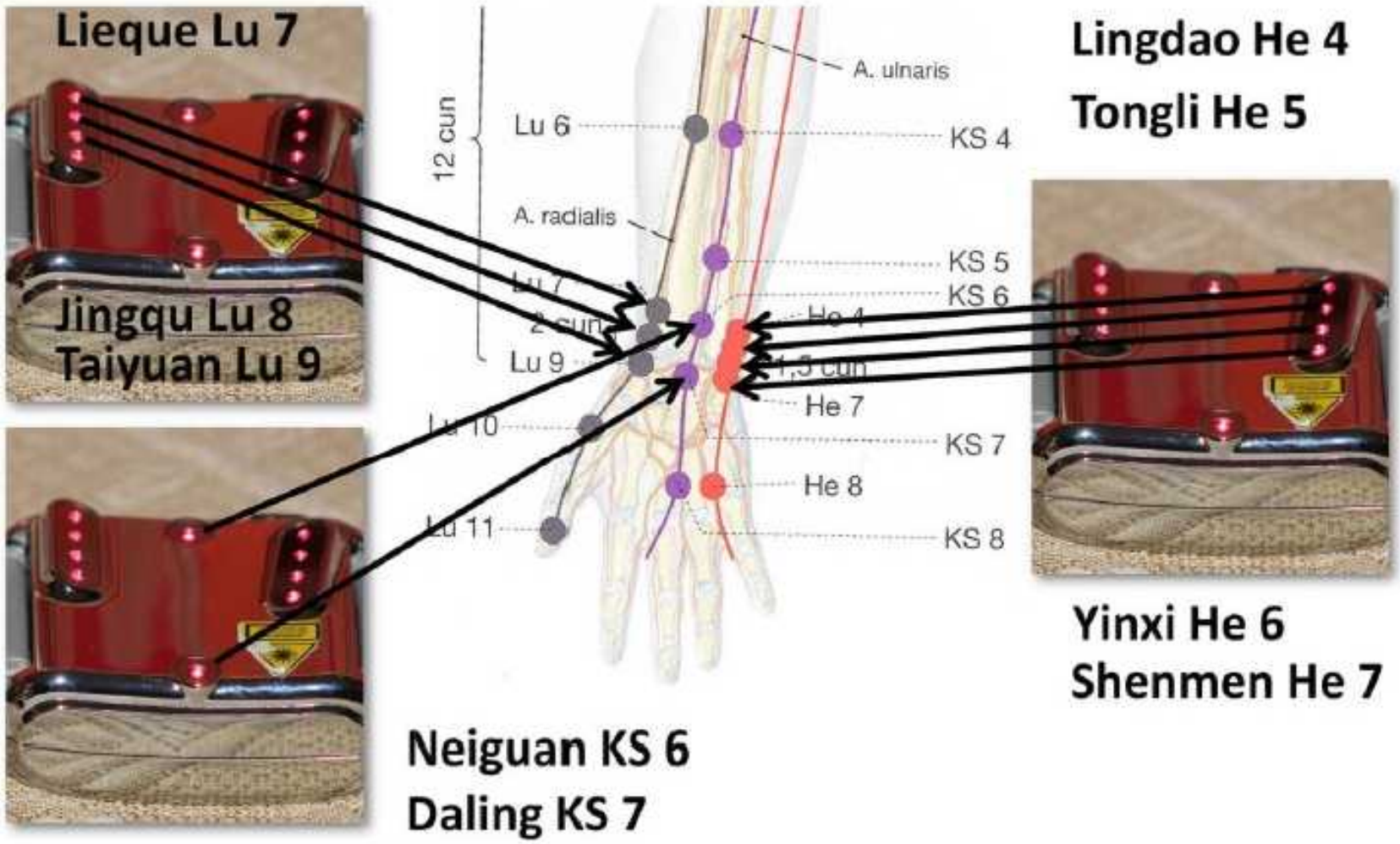


Fig. 3: Acupuncture points which are stimulated through the laser watch (mod. from [5]).

Indications

1. Improvement of blood viscosity and microcirculation as a protection against heart attacks and stroke
2. Improvement of hypertension
3. Improvement of the immune system by stimulation of the different white blood cells
4. General energising effects which act against fatigue and contribute to improved performance
5. Improved sleep by increased release of serotonin and melatonin
6. Prevention of jet lag after long flights by enhanced release of melatonin
7. Protection against thrombosis (on long flights)
8. Anti-inflammatory effects in combination with UltraCur+ (Curcumin)
9. Additive cancer therapy and prevention in combination with chlorophyll

From laser research

Zeitschrift für Akupunktur & Aurikulomedizin
Magazine for acupuncture and auricular medicine

5th October 2015

Daniela Litscher und Gerhard Litscher

LASER WATCH – SIMULTANEOUS LASER ACUPUNCTURE AND LASER BLOOD IRRADIATION AT THE WRIST

Research unit for Complementary and Integrative Laser Medicine,
Research unit for Biomedical Technology in Anaesthesia and Intensive Care
TCM Forschungszentrum (Research centre) Graz, Medizinische Universität Graz (Medical University of Graz), 8036 Graz, Austria

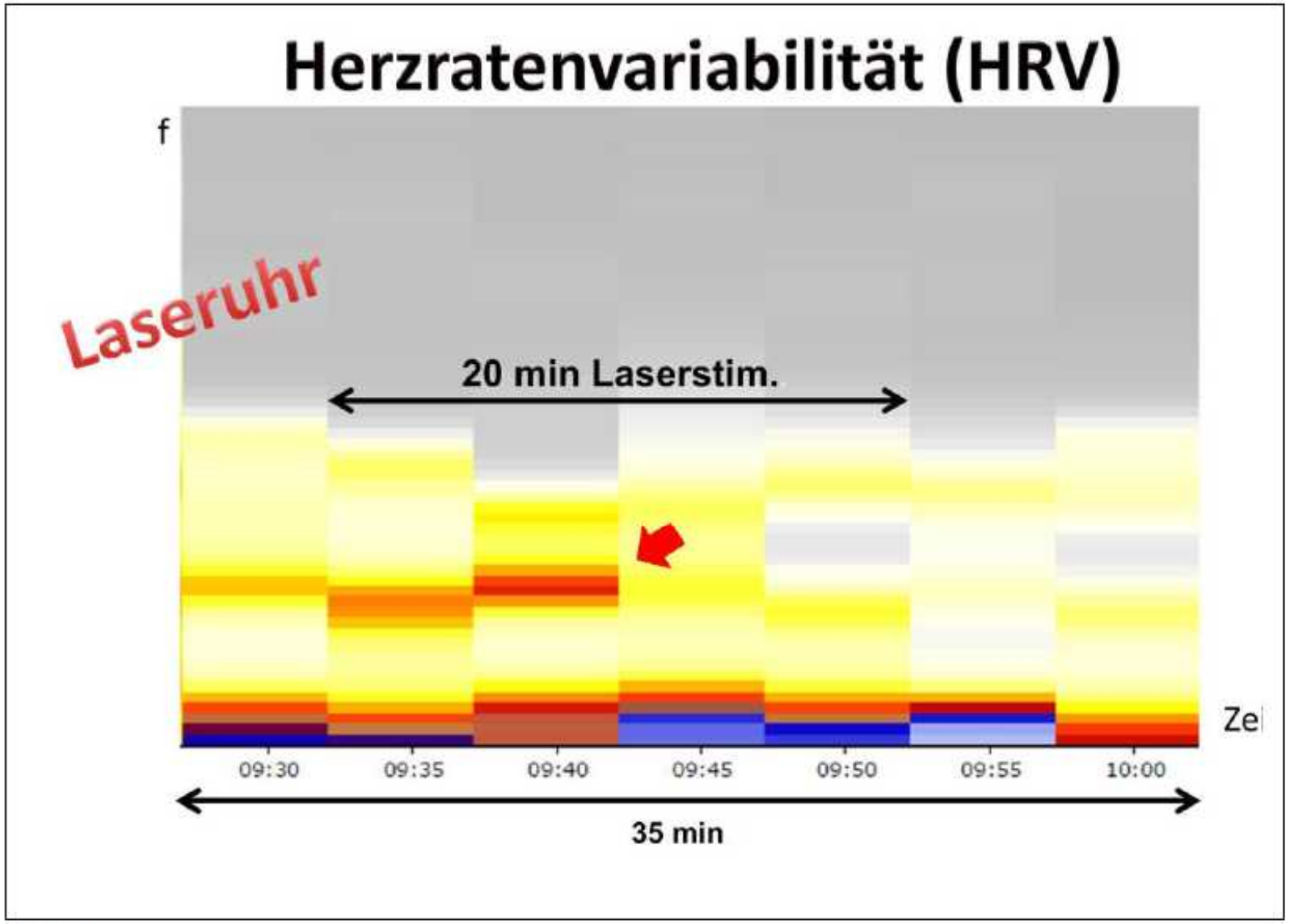


Diagram:

Heart Rate Variability (HRV)

Laser watch

20 minute laser stimulation

Time

Laseruhr

Mikrozirkulation

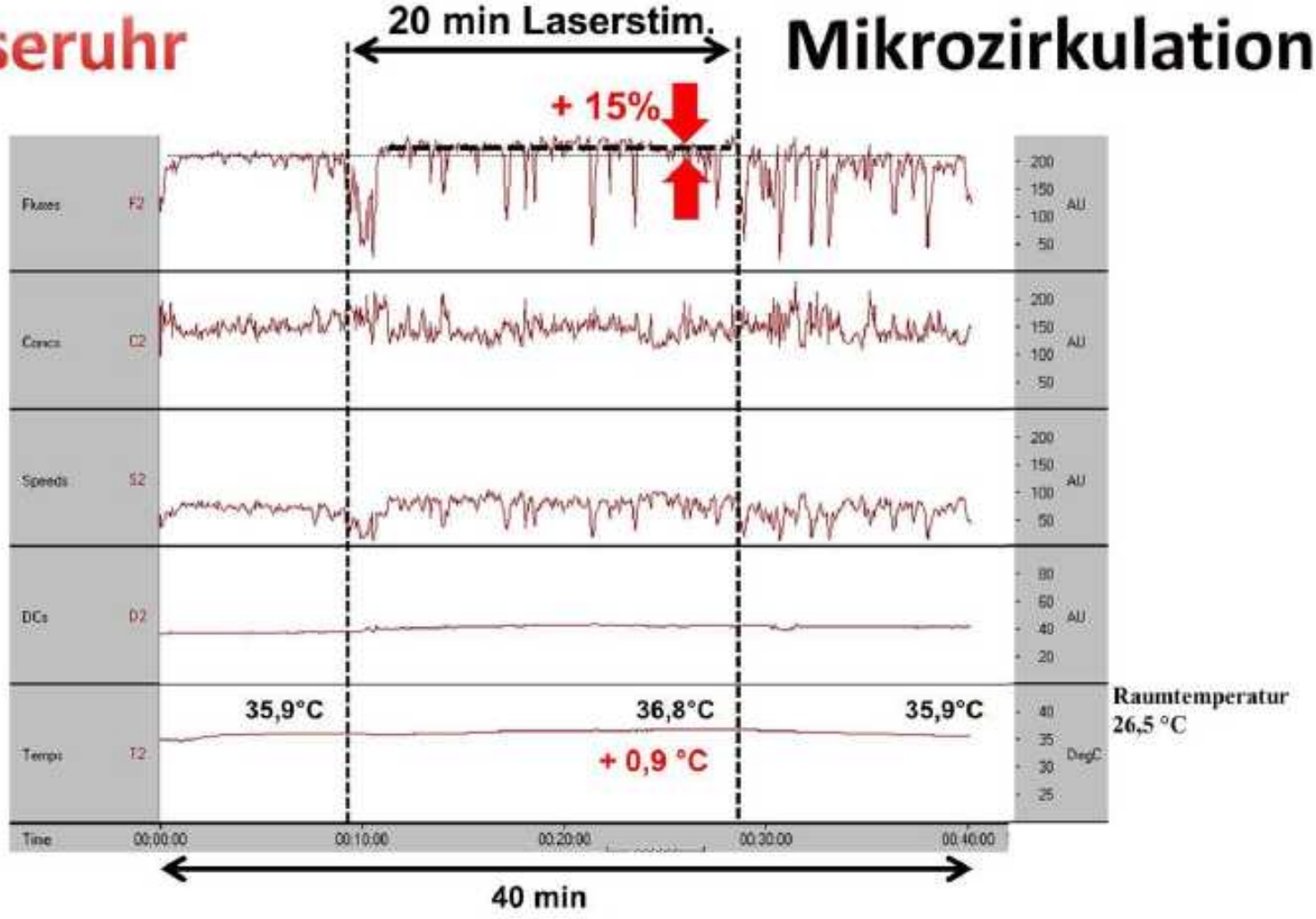


Diagram:

Laser watch 20 minute laser stimulation Microcirculation

Room temperature

The new laser watch first multi center study in Switzerland

Dr. med. Andreas Wirz-Ridolfi,
Reinach/Schweiz
Prof. VRC, Chirurgie FMH,
Akupunktur/TCM ASA

MEDI-CHINA
中国传统医学中心
Zentrum für Traditionelle Chinesische Medizin

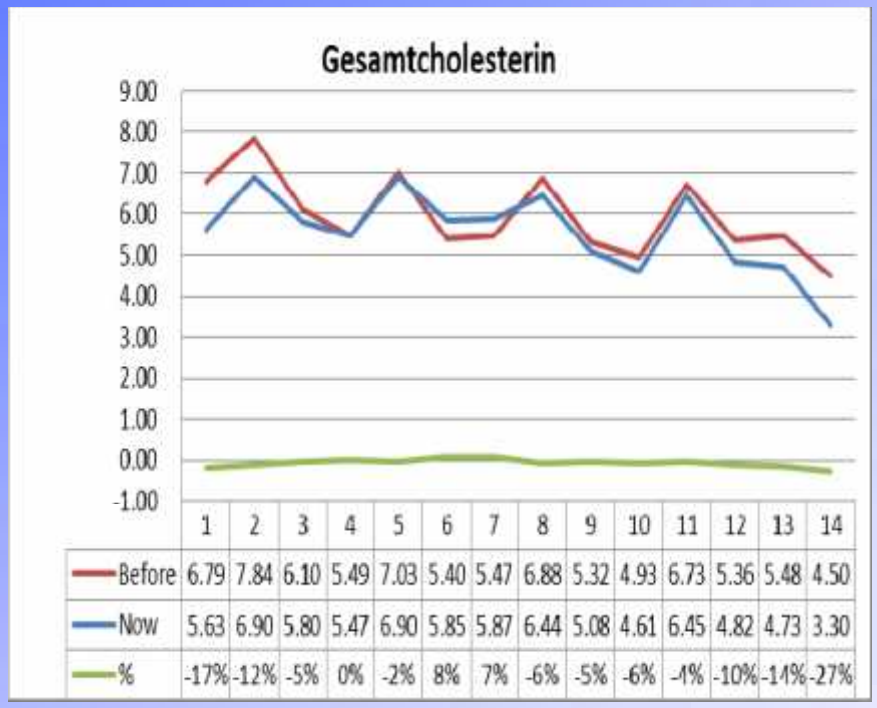
Participants

- 20 patients (12 male,8 female), 18 bis 76 y.
- 2 patients with type 1 diabetes
- 18 patients with type 2 diabetes

Results: Blood pressure

- Highest value:
- Before: 170/90, after: 140/85 mmHg
- Lowering of blood pressure in avarage:
- Systolic 10,04, Diastolic 6,54 mmHg
- In percentage: 7,9 %

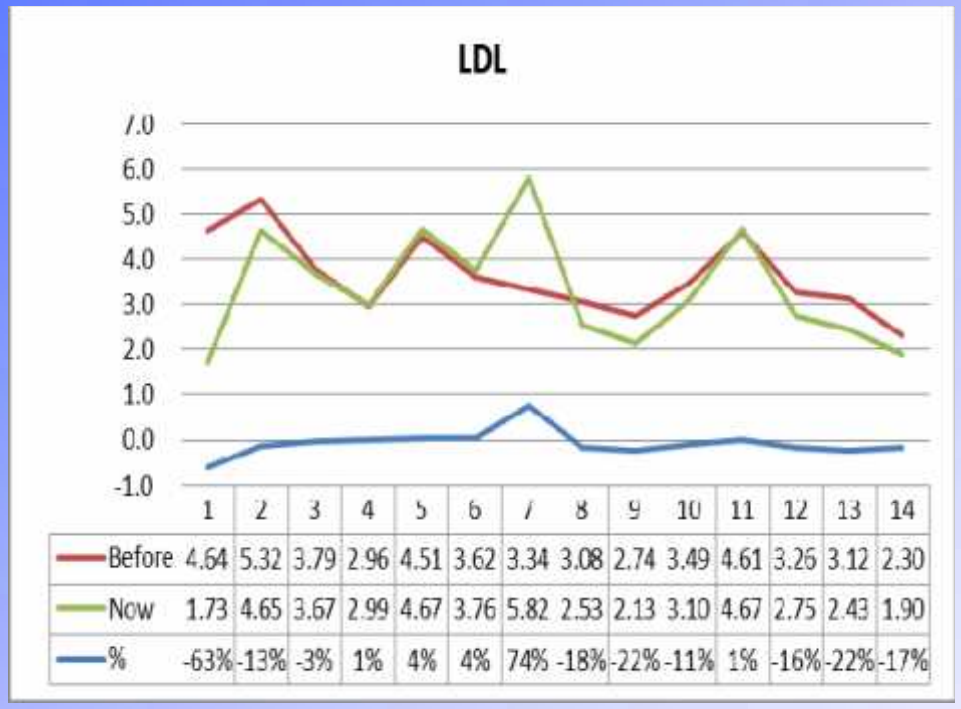
Lipids: Cholesterol



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Before	6.79	7.84	6.10	5.49	7.03	5.40	5.47	6.88	5.32	4.93	6.73	5.36	5.48	4.50
Now	5.63	6.90	5.80	5.47	6.90	5.85	5.87	6.44	5.08	4.61	6.45	4.82	4.73	3.30
%	-17%	-12%	-5%	0%	-2%	8%	7%	-6%	-5%	-6%	-4%	-10%	-14%	-27%

- Average before:5,95, after: 5,5mmol/l
- Lowereing in avarage: - 0,39 mmol/l
- In percentage: - 6,6 %

Lipids: LDL



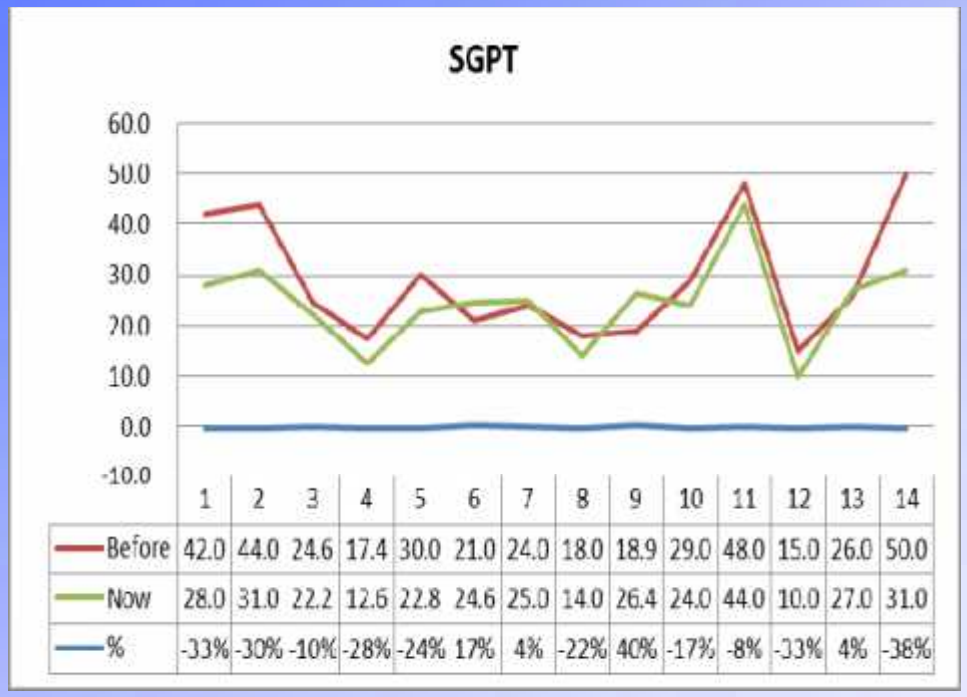
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Before	4.64	5.32	3.79	2.96	4.51	3.62	3.34	3.08	2.74	3.49	4.61	3.26	3.12	2.30
Now	1.73	4.65	3.67	2.99	4.67	3.76	5.82	2.53	2.13	3.10	4.67	2.75	2.43	1.90
%	-63%	-13%	-3%	1%	4%	4%	74%	-18%	-22%	-11%	1%	-16%	-22%	-17%

Avarage before: 3,63, after: 3.34 mmol/l.

Lowering in avarage: - 0,28 mmol/l

- In percentage: - 7,8 %

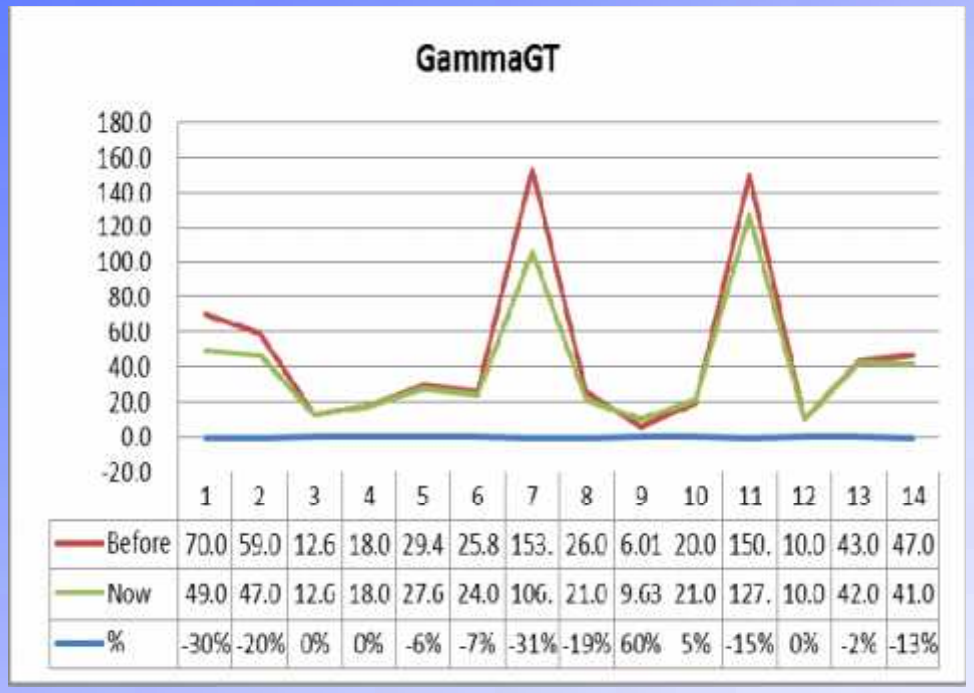
Liver: GPT



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Before	42.0	44.0	24.6	17.4	30.0	21.0	24.0	18.0	18.9	29.0	48.0	15.0	26.0	50.0
Now	28.0	31.0	22.2	12.6	22.8	24.6	25.0	14.0	26.4	24.0	44.0	10.0	27.0	31.0
%	-33%	-30%	-10%	-28%	-24%	17%	4%	-22%	40%	-17%	-8%	-33%	4%	-38%

- Avarage before: 29,14 IU/l. after: 24,47 IU/l
- Lowering in avarage: - 4,66 IU/l
- In percentage: - 16,0 %

Liver: GammaGT



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Before	70.0	59.0	12.6	18.0	29.4	25.8	153.	26.0	6.01	20.0	150.	10.0	43.0	47.0
Now	49.0	47.0	12.6	18.0	27.6	24.0	106.	21.0	9.63	21.0	127.	10.0	42.0	41.0
%	-30%	-20%	0%	0%	-6%	-7%	-31%	-19%	60%	5%	-15%	0%	-2%	-13%

- Average before: 47,84 IU/l, after: 39,70
- Lowering in avarage: - 8,14 IU/l
- In percentage: - 17,0 %

Case report diabetes mellitus type 2

Patient, 62 J., male, therapy with

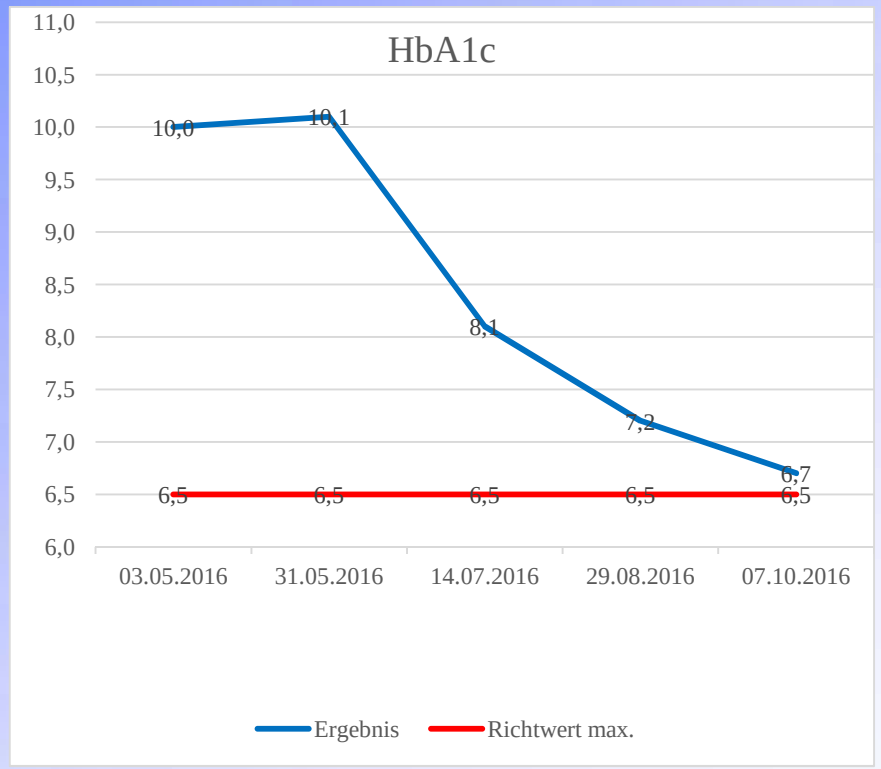
Metformin 2 x 1000 mg, Candesartan 32 mg

Diagnosis: Diabetes Typ 2, Hypertension

Therapy:
3 month red laser watch,
3 months red-blue laser watch in combination with
Curcumin (Ultracur)

Case report: HbA1c

Datum	Parameter	Ergebnis	Richtwert max.
03.05.2016	HbA1c	10,0	6,5
31.05.2016	HbA1c	10,1	6,5
14.07.2016	HbA1c	8,1	6,5
29.08.2016	HbA1c	7,2	6,5
07.10.2016	HbA1c	6,7	6,5

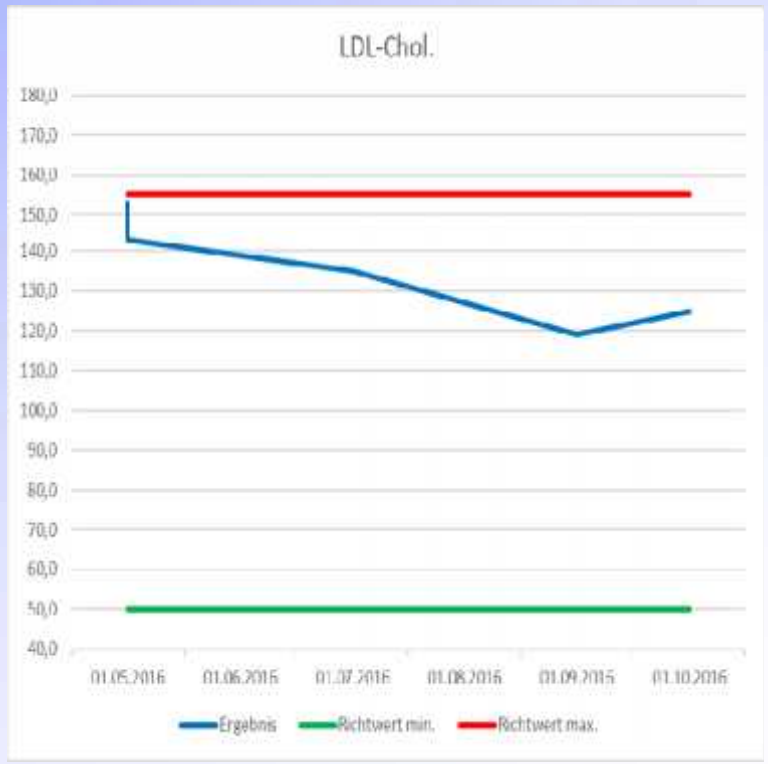


Case report: Cholesterol

Datum	Parameter	Ergebnis	Richtwert max.
03.05.2016	Cholesterin	208,0	200,0
31.05.2016	Cholesterin	210,0	200,0
14.07.2016	Cholesterin	199,0	200,0
05.09.2016	Cholesterin	178,0	200,0
07.10.2016	Cholesterin	189,0	200,0

Case report: LDL-Cholesterol

Datum	Parameter	Ergebnis	Richtwert min.	Richtwert max.
03.05.2016	LDL-Chol.	153,0	50,0	155,0
31.05.2016	LDL-Chol.	143,0	50,0	155,0
14.07.2016	LDL-Chol.	135,0	50,0	155,0
05.09.2016	LDL-Chol.	119,0	50,0	155,0
07.10.2016	LDL-Chol.	125,0	50,0	155,0



Own study results:

Significant increase of Melatonin (30-100 %)

(Dr. Weber in A 380 from Bangkok to Frankfurt)

New laser watch, red-blue

Combination with curcumin

UltraCur +

Curcumin:
Strong antioxidant
with anti-inflammatory and
pain-reducing effects

Highly concentrated curcumin with a 15,000-fold bioavailability

Due to a special protein binding the full potential of this unique medicinal plant can be realized for the first time!

One capsule UltraCur+ has the efficacy of 120g of curcumin.

In relation to conventional curcumin this corresponds to a 15,000-fold bioavailability.

Photodynamic effects:

- Curcumin absorbs blue light 447 nm
- Is a highly effective **Photosensitizer** for PDT for cancer, infectious and autoimmune diseases
- Is in low concentrations phototoxic, works a sonosensitizer, stimulates the immune system, antitumoral, antimetastatic and antiangiogenetic effects

Photoactive+ is an intelligent supplement rom natural plant extracts. It combines water soluble Chlorphyllin (green) with Phycocyanine (blue)

Chlorophyllin

- **Chlorophyllin's** unique molecular structure allows it to act as an *"**interceptor molecule**"* that binds to the harmful carcinogens and excretes them from the body before they can damage your DNA.
- In addition, chlorophyllin has been found to inhibit the growth of cancer cells, reduce excessive oxidative damage that can lead to cancer, support the immune system, and boost the effectiveness of cancer drugs.
- Chlorophyllin's ability to bind to carcinogens and excrete them from the body *before causing DNA damage* makes it a safe and low-cost way of protecting against unavoidable environmental carcinogens.

Chlorophyllin

- **Photosensitizing Effects Of Chlorophyllin**
- ***Photodynamic therapy*** is an exciting new cancer treatment typically used for ***small, local tumors***[55] on or just under the skin, or on the lining of internal organs and cavities, such as the bladder.[56-58] The therapy involves injecting into the bloodstream an agent called a ***photosensitizer***, which is sensitive to a particular type and wavelength of light.[57]

www.isla-laser.org

Next conferences:

-International Laser conference in Bangkok, November 25th and 26th November 2016

-Next international ISLA-conference in Germany June10/11 2017 in Germany

Thank you