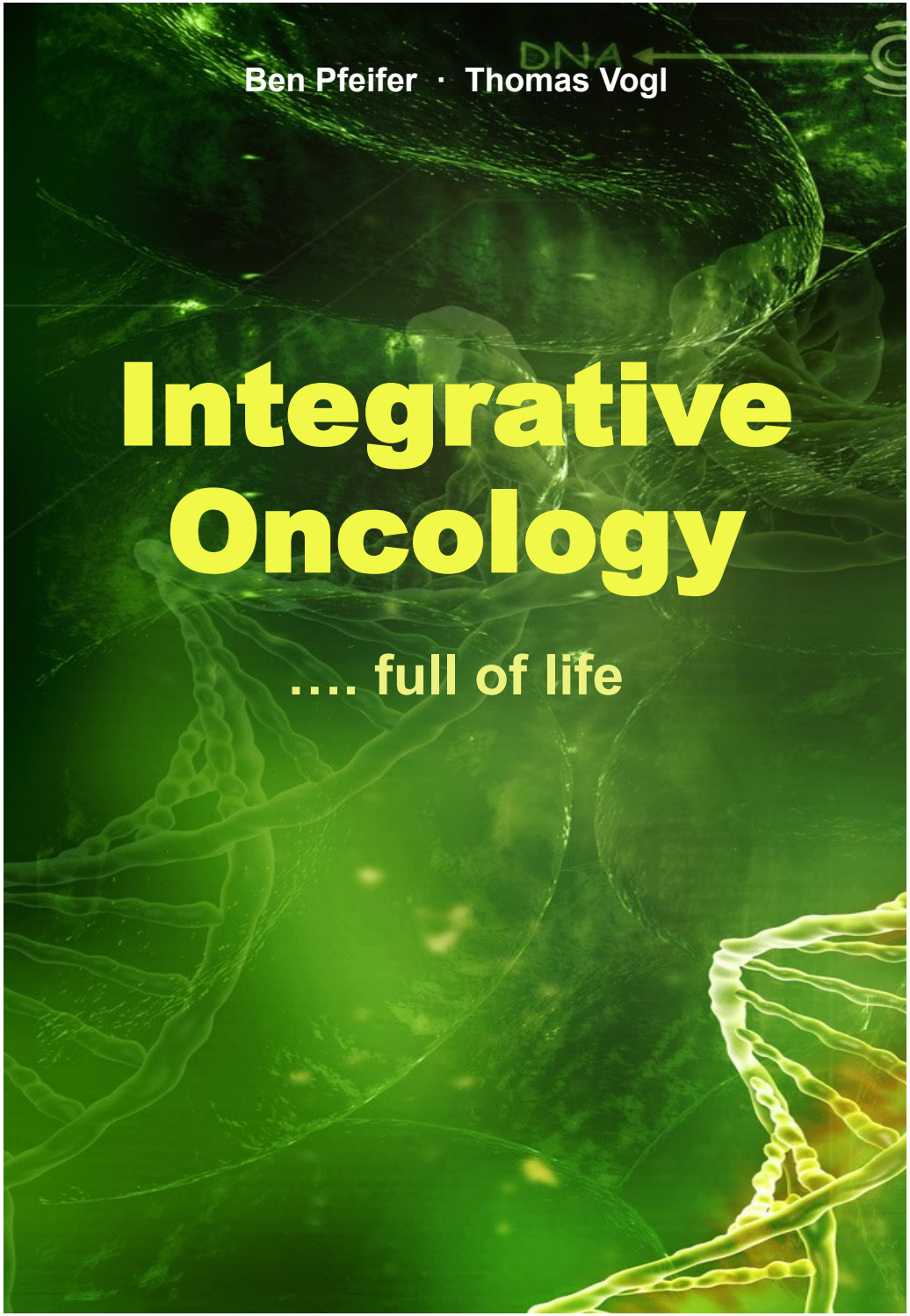
Ben Pfeifer · Thomas Vogl

Integrative Oncology

…. full of life



Univ. Prof. Dr. med. Thomas Vogl

Institute for Diagnostic and Interventional Radiology University Hospital of Frankfurt

He has been a physician for 35 years and is deeply committed to his work. Studied medicine in Munich, Germany, and also trained as a specialist there at the Großhadern hospital. Guest professor at the Massachusetts General Hospital in Boston, USA. Qualified as a radiologist and nuclear medicine specialist in 1989. Three years later, directing senior physician at the radiology clinic of Freie Universität Berlin. Since 1998, director of the Institute of Diagnostic and Interventional Radiology at the University Hospital of Frankfurt. National and international awards.

'The constant exchange of experiences with colleagues, continued training at the highest level, and timely implementation of research results have special significance in our profession.'

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Aeskulap INTERNATIONAL

Passionate physician, scientist and 'world explorer' for 45 years; trained as a specialist in Germany and the USA.

Specialization and interests: Anaesthesiology and intensive therapy, immunology, oncology, stem cell research. Recipient of the Humboldt Prize; worked in complementary cancer treatment for 22 years, always searching for new and better treatment methods for his patients.

'Nature is the best physician – it can heal many illnesses and never speaks badly of its colleagues.'

Ernst Ferdinand Sauerbruch

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How to effectively combine the most modern therapy methods of interventional radiology with complementary oncology measures

'Integrative oncology' has become a catchphrase. From the smallest village doctor's practice to renowned university hospitals – anyone who has something to say in oncology advertises the 'integrative' approach.

However, this seldom goes beyond good intentions or lip service. This is unfortunate, since our many years of experience show that an integrative treatment approach can improve the quality of life and life expectancy of seriously ill cancer patients. In order to make this opportunity attainable for all cancer patients, academic and complementary medicine must work together closely to find better solutions for patients.

The individual goal of combining the most modern conventional treatment methods with successful complementary treatments to benefit patients is, however, often torpedoed by an inability to cooperate. Such failures are often due to the egos of therapists. University-trained oncologists are frequently unwilling to engage in conversation, let alone cooperate, with a 'complementary oncologist'. There is often a lack of interest or even curiosity regarding complementary therapy protocols. The use of complementary treatment methods is rejected with 'convinced ignorance'. This is easier than it would be to deal with the subject! On the other hand, physicians working in complementary oncology are often not sufficiently critical of their own methods, often categorically advising against chemotherapy and radiation even if patients can expect survival benefits from these toxic treatment methods, at least in statistical terms.

This places cancer patients under unnecessary pressure, potentially robbing them of benefits in terms of quality of life and life expectancy. My colleagues and I already recognized this problem of a lack of cooperation between complementary and academic medicine specialists and discussed it in detail in 2006 in our textbook 'Onkologie integrativ' [Integrative Oncology] (ELSEVIER; ISBN: 978-3-437-56420-8). Many things have, however, improved for our patients and for myself personally in terms of interdisciplinary cooperation since the work on this book. Over the years, we built direct access to academic medicine both domestically and in foreign countries, and cooperate closely with oncologists, gynaecologists, immunologists, and other specialists.

Most colleagues were able to see with their own eyes that our complementary treatment protocols benefit patients. Persistence and an honest, personal connection to academic medicine have led us to our goal. The cooperation with a leading interventional radiologist in particular has been very worthwhile for many of our patients, and also for myself personally.

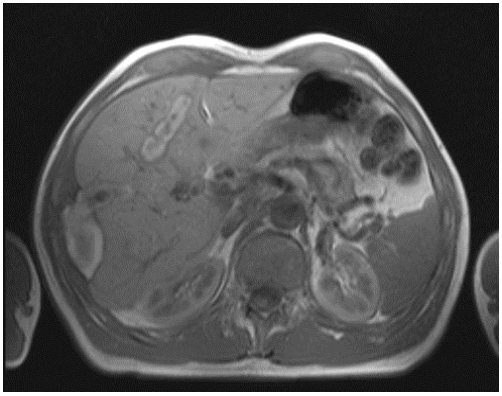
Professor Vogl, director of the Institute for Diagnostic and Interventional Radiology at the University Hospital of Frankfurt am Main and I would like to present some of our joint patients here who have benefited from our friendly and interdisciplinary cooperation, both in terms of improving their quality of life and in terms of extending their lifespan.

T.CH. – a 53-year-old male patient from Switzerland who saw his doctor in May 2006 with bowel movement problems and received a diagnosis of colon cancer with liver metastases after a few weeks. The poor prognosis (less than 10% probability of living five years with this illness) was very much on the mind of this young tax official when he came to us for a consultation. Since he did not accept the toxic side effects of systemic chemotherapy, he was searching for a 'gentler' treatment. The patient tolerated the complementary oncological treatment that was recommended to him very well.

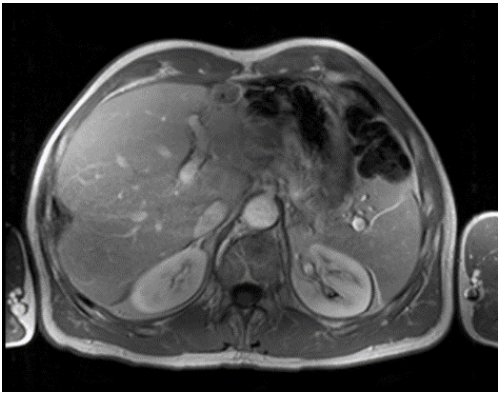
He increasingly felt more energetic and took pleasure in life again. His laboratory parameters improved within two months. Our complementary oncological treatment protocol initially consisted of locoregional hyperthermia for the liver and drug therapy with high dosed curcuminoids (Curcumin combi extra forte), proteoglycan (Aeskulap-CA statin), arabinoxylan (BioBran), milk

thistle combined with quercetin (HEPASAN), and fermented wheat germ extract (AVEMAR). The patient also took a strict ketogenic diet that he followed cyclically (two months of strict ketogenic diet, two months of low-carbohydrate diet).

To gain control of his liver metastasis more quickly, we suggested additional treatment with trans-arterial chemoembolization (TACE) to the patient. This less damaging local chemotherapy significantly reduced the size of the liver metastases; the remainders of these cancer lesions were then successfully destroyed with laser-induced thermotherapy (LITT).



MRI before LITT therapy in December 20, 2006



MRI check-up after three years (October 19, 2009)

During and after this combined treatment, the patient did extremely well for the next four years. He pursued his career, flew to Colorado every year to ski, and enjoyed unrestricted quality of life. In April 2010, however, the thoracic CT check-up showed lung lesions, paratracheal, and mediastinal lymph node enlargements for the first time. The patient's drug therapy was then expanded by IMUSAN (a combination of medicinal herbs with immunological and antimetastatic effects) and Aeskulap-MCP (modified citrus pectin) and again applied consistently.

The patient was also successfully treated twice with regional chemoperfusion and subsequent thermoablation using microwave energy and LITT. When the lung metastases had been destroyed by local therapy and with the expanded complementary drug therapy, long-lasting remission of the lung lesions was achieved. The patient felt excellent for the next six years: liver and lungs in full remission, no further metastases, good quality of life, and skiing in Colorado every year.

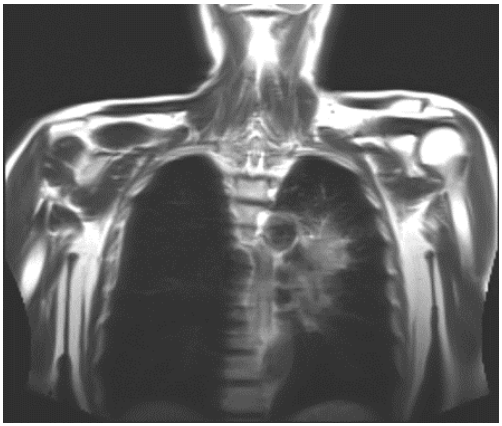
In early 2017, the patient unfortunately had a relapse with rapidly growing mediastinal metastases from which he died in April 2017.

This example shows 11-year survival of a patient with metastasized colon cancer. Complementary oncological treatment combined with multiple radiological interventions using TACE and LITT of the liver and lung metastases have proven themselves very well for this patient.

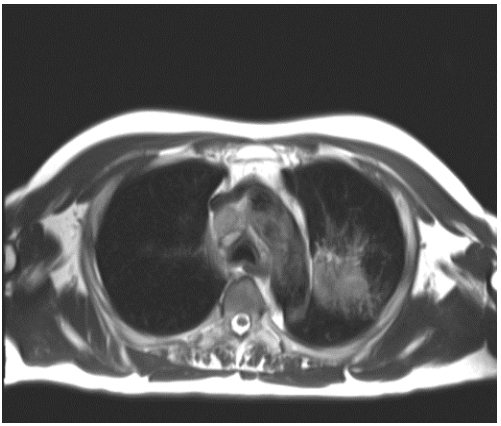
E.H. - a 63-year-old male patient from Los Angeles who was diagnosed with metastasized bronchial cancer in September 2017 and declines palliative chemotherapy. The patient's primary tumour extends from the left hilus region into the upper lobe for a distance of more than 5 cm.

Comparative CT examinations show that the cancer grows quickly and begins to compress the left main bronchus. The patient starts our complementary oncological treatment protocol based on high dosed infusions therapy with curcumin, artesunate, Vitamin C, Q-10, and a haematoxylin/DMSO mixture daily, while also taking various drugs (IMUSAN, Curcumin combi extra forte, artemisinine, Aeskulap-CA statin and Aeskulap-MCP). Due to the risk of compression of the left main bronchus by the rapidly growing tumour, complementary oncological treatment was combined with regional chemo-embolization from the outset.

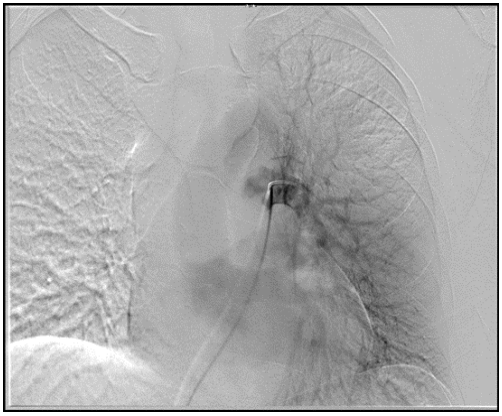
Over a period of two months, both the primary tumour and the lymphatic metastases subsided noticeably, and the risk of bronchial compression was initially eliminated.



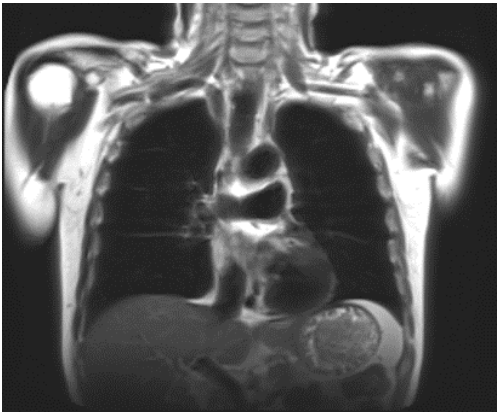
MRI before TACE October 17, 2017



MRI before TACE October 17, 2017



Angiography on October 17, 2017



MRI of February 5, 2018

The patient tolerated the therapies well and did not suffer any significant impairments of his quality of life. His situation was stable, and our hope was to keep the greatly reduced tumour mass under control with

immunological treatment using a checkpoint inhibitor, NK cell therapy, and a peptide vaccine, and perhaps even reduce it further. From January to August 2018, the patient received low dosed Keytruda therapy (up to 150 mg every three weeks), a single treatment with autologous NK cell therapy (1.8 billion cells), and a peptide vaccine once monthly.

However, a PET-CT check-up in the middle of August 2018 showed that the primary tumour volume had increased slightly and the paratracheal lymph node metastases showed increased metabolic activity, giving cause for another TACE treatment and adjustment of the oral medication and infusion protocol at the beginning of October.

One hopes that our combined therapy will once again be able to stop the tumour growth and give the patient more time with a good quality of life.

This example shows that complementary oncological measures combined with regional chemo-embolization were well suited to slowing down rapid tumour growth and averting the risk of bronchial compression for this patient.

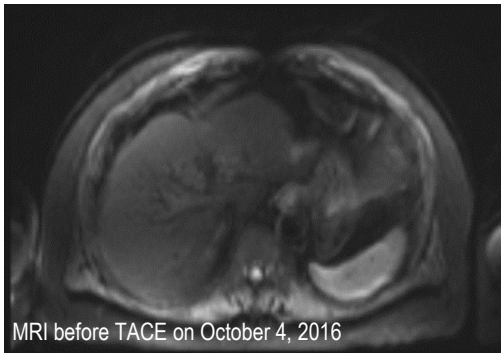
A.L. – a 78-year-old patient from Djakarta who was diagnosed with primary liver cancer in June 2016 comes to see us with AFP parameters far above 1000 ng/ml; his MRI shows a liver lesion in segment 2.

The patient had had a Hepatitis C infection about 20 years ago which was successfully treated with interferon. An RT-PCR showed no viral burden. Known comorbidities include diabetes mellitus type 2 and prostate cancer that was diagnosed last year.

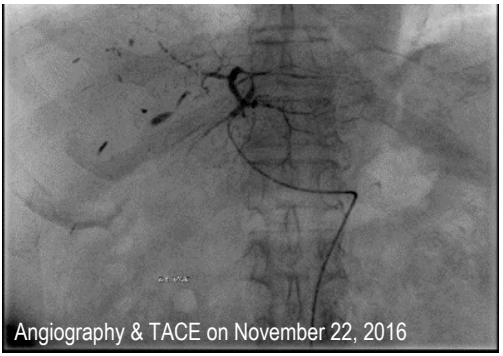
The latter is currently being treated with precision irradiation at the University Hospital of Zurich (Universitätsklinik Zürich). The patient's primary liver cancer was first treated with our complementary oncological basis protocol.

This consists of daily oral administration of IMUSAN, Curcumin combi extra forte, BioBran, quercetin and Aeskulap-CA statin, and parallel infusion therapy with high dosed curcumin, artesunate, coenzyme Q10, Vitamin C and B complex, glutathion, and thymus extract.

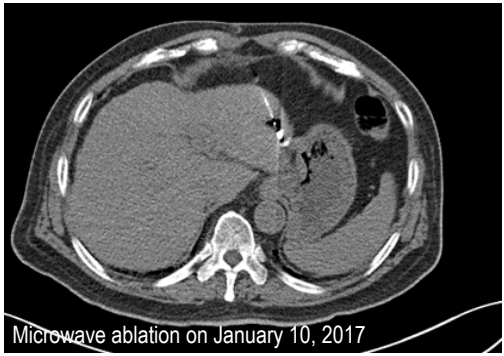
The patient tolerated these therapies very well; we observed an AFP drop of approximately 20% with this complementary oncological therapy, which was completed with 3x TACE treatment of the affected liver segment and subsequent RF ablation of the remaining hepatoma about two months later, with good success.



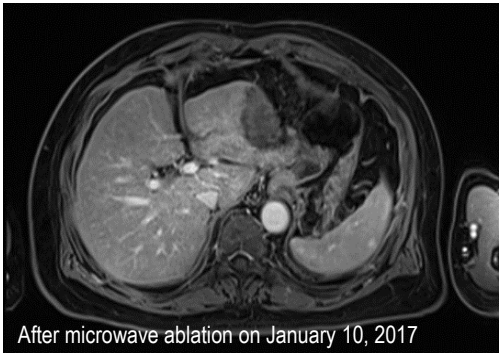
MRI before TACE on October 4, 2016



Angiography & TACE on November 22, 2016



Microwave ablation on January 10, 2017



After microwave ablation on January 10, 2017

This example shows how TACE followed by RF ablation in combination with a complementary oncological treatment protocol was successfully used to treat hepatocellular cancer in a comorbid patient. Since this patient was not a candidate for liver surgery, one can assume that this combination therapy saved his life.

S.P. – a 76-year-old male patient from Venezuela with lymphatic and bone-metastasized prostate cancer was discharged home from the Memorial Sloan Kettering Cancer Centre in New York in 1999 to die because there was no effective treatment for the hormone-resistant and metastasized prostate cancer at that time.

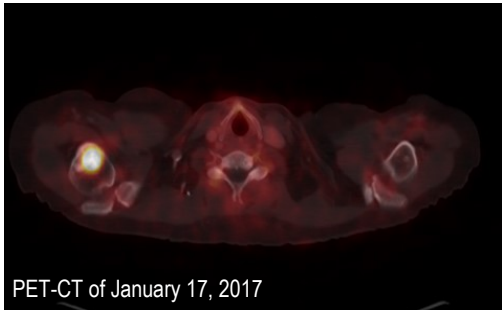
In early 2000, the patient entered our complementary oncological treatment at the Aeskulap Clinic in Switzerland and started our phytotherapy protocol with the precursor products of ProstaSol and IMUSAN, as well as Curcumin combi and BioBran.

This protocol was complemented by a biphosphonate (Zometa) and whole-body hyperthermia, particularly to relieve bone pain due to metastases. Bone pain rapidly improved with this treatment, and PSA levels dropped from slightly over 1000 ng/ml in the course of the first treatment year to less than 1 ng/ml.

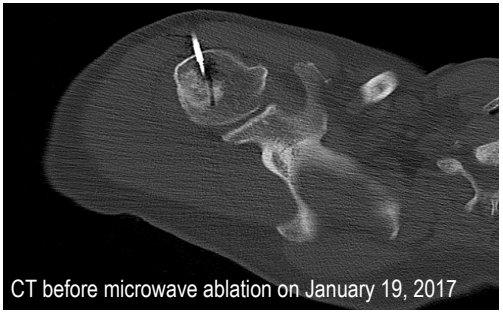
The patient continued the phytotherapy in a modified form and had an astonishingly stable disease course over the next 15 years. Repeated check-ups with whole-body MRIs and PET-CTs showed no cancer activity.

At the end of 2015, PSA levels rose for the first time, to barely over 1.5 ng/ml; this took place after elective knee surgery that was associated with infection and wound healing problems.

A gallium-68 PSMA PET-CT that was done at this time showed an active metastasis in the right humerus and definite tracer absorption in the entire prostate. It was then decided to treat the active metastasis of the humerus with microwave ablation.



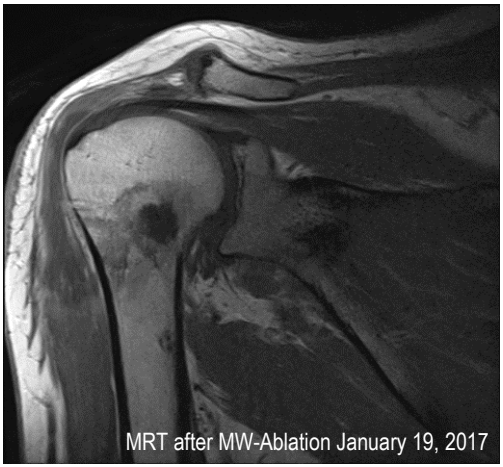
PET-CT of January 17, 2017



CT before microwave ablation on January 19, 2017

Unfortunately, this did not go as well as hoped. After the treatment, the patient developed osteomyelitis in the humerus with muscle necrosis; the bone metastasis remained active, however.

After the osteomyelitis had healed, the upper arm metastasis was externally irradiated.



MRT after MW-Ablation January 19, 2017

Since the patient's PSA levels had meanwhile risen to 6.5 ng/ml despite irradiation of the active metastasis, the patient is currently receiving an intensified oral medication protocol combined with infusion therapy using high doses of artesunate, curcumin and haematoxylin / DMSO.

After nearly 20 years of successful complementary therapy of metastasized prostate cancer, precision irradiation of the prostate is now planned as well.

This example shows that long-term survival of 20 years with metastasized and hormone-resistant prostate cancer is possible despite widespread bone and lymphatic metastases if one repeatedly combines complementary oncological measures with the most modern therapeutic procedures.

These examples illustrate that the overall effect of today's cancer medicine – conventional and complementary – decisively depends on the willingness to take interdisciplinary and integrative action.

Treatment Techniques of Interventional Oncology

Minimally invasive treatments for tumours of the lungs, liver, kidneys, and bones are performed at our clinic after a consensus decision for the indication by a corresponding tumour conference. The following procedures are differentiated as locoregional treatment measures within the scope of the interventional oncological therapy spectrum:

Vascular treatment procedures

- Regional trans-arterial chemoembolization (TACE)
- Regional trans-arterial chemoperfusion (TACP)
- Transarterial embolization (TAE)
- Selective internal radiotherapy (SIRT)
- Radioembolization with tetraspheres
- 'Drug-eluting Beads'(DEB)

Thermo-ablative procedures

- Radiofrequency ablation (RFA)
- Microwave ablation (MWA)
- Laser ablation (LITT)
- Cryotherapy

Electroporation

- Percutaneous ethanol injection (PEI)

The therapy indication can be symptomatic, palliative, curative, or neoadjuvant in each case.

Interventional oncological treatment measures for liver metastases

In accordance with the updated S3 guideline on the diagnostics and therapy of colorectal cancer, primary or secondary resection of the metastases should be evaluated when metastases are present. This applies particularly if an R0 resection is possible. Five-year survival data after complete resection of colorectal metastases indicate 25-40%. If a surgical procedure is not possible, local ablative procedures can also be used. According to the consensus-based recommendations, this can be followed with thermal ablation (RFA, MWA, LITT) if the liver metastases cannot be resected or the patient's condition does not permit surgical removal of the metastases, particularly if a liver resection was already previously performed.

The combination of thermal ablation and subsequent surgical treatment is also a proven therapy approach. Current indication for radiofrequency ablation: Liver metastases =3 cm. Data differ depending on the tumour location and subject expertise of the radiologist. The benefits of local treatment for patient survival are not yet proven, according to the guideline. However, current data indicate that this may be the case. The prognosis of a patient with liver metastases depends on the options for treating the primary tumour, presence of other metastases, and the extent and treatment options for the liver metastasis.

TACE Trans-Arterial Chemoembolization is a minimally invasive treatment procedure to treat inoperable hepatocellular cancer and in select cases, also liver metastases (e.g. in neuroendocrine cancer). This angiographically performed procedure combines locoregional chemotherapy with simultaneous, targeted embolization of arteries that supply the tumour. Following puncture of the inguinal artery, a special probing catheter is inserted via the aorta into the truncus coeliacus and used to perform imaging of the tumour and the position of the catheter tip by using a contrast agent.

A catheter is then advanced into the main artery of the liver or the right or left hepatic artery via the probing catheter. The catheter tip is positioned according to the position of the liver tumours. It is beneficial to position the catheter tip close to the tumour because this results in more intensive embolization, meaning that the chemotherapy drug will be more effective in the tumour. TACE treatment is not curative in most cases (exception: small, individual haematoma nodes) but tends to extend tumour control and life expectancy with repeated application of TACE treatments.

RFA Radiofrequency ablation, also called high-frequency ablation, is a medical method to locally destroy tissues. An applicator is introduced into the tissues to be treated and thermonecrosis (destruction by heat) brought about by means of a sinusoidal high-frequency alternating current. The resulting tissue friction produces protein denaturation and coagulation necrosis in the tissues. Tissue resistance increases continuously and is measured by the generator.

The ablation is deemed to be complete when resistance rises over 200 Ohm. The procedure is used in various therapy forms such as treatment of heart rhythm disorders or destruction of liver metastases. With CT guidance and local anaesthesia or analgosedation, an RFA probe measuring approximately 3 mm is introduced e.g. into the liver via the skin, and placed in the centre of the tumour.

A radiofrequency generator produces a high-frequency alternating current that generates temperatures of up to 125°C in the tumour tissue. This temperature elevation destroys the tumour tissues. RFA is increasingly used as an alternative to removing part of the liver when treating liver metastases. Benefits of this method include the minimally invasive procedure, ability to repeat the therapy, and saving surrounding liver tissues.

Treatment is performed by making a skin puncture and introducing the RF probe with CT imaging. RFA can also be applied after liver surgery or to treat repeated

metastases. There is currently no major prospectively randomized study comparing RFA with other treatment methods. However, available data thus far indicate that this therapy form is equal to other methods.

MWA Microwave ablation is similar to radiofrequency ablation in that it generates local heating of the tissues, causing irreversible destruction of tumour cells. The success of MWA significantly depends on the size of the target tumours and organ perfusion.

The greater the tumour diameter and organ perfusion, the higher the likelihood that not all tumour cells will attain a temperature of 60° Celsius, thereby meaning that vital tumour tissues remain in the marginal areas of the tumour and produce a relapse. Ideal tumour diameters for complete treatment are therefore up to 3 cm; tumours with diameters of up to 5 cm can, however, also be treated successfully by suitably adapting the technique. In this thermo-ablative method, the water molecules in the tissues are made to vibrate with electromagnetic waves, thereby being heated more intensely than in radiofrequency ablation. Protein denaturation commences at 60°.

The benefits of MWA compared with wedge resection include technical feasibility, negligible intraoperative blood loss, less operating time, no significant patient morbidity, and rapid patient recovery with restoration of the preoperative condition. Complications such as mild pain, fever, and subcutaneous haematomas (frequency up to 20%) generally do not require separate therapy.

LITT To perform Laser-Induced Interstitial Thermotherapy, the liver metastasis is first punctured via the skin with local anaesthesia and CT imaging. The treating physician then introduces a fibre-optic probe into the puncture canal; this probe is used to apply high-energy laser light, destroying the malignant tissues within a diameter of approximately 2 cm.

Therapy is performed with constant monitoring in an MRI, making it possible to precisely track and control the spread of the heat. The entire procedure takes about one and a half hours. LITT has numerous benefits compared with open resection. It is performed on an outpatient basis with local anaesthesia; the 30-day mortality rate after treatment is significantly lower than in surgical removal of liver metastases.

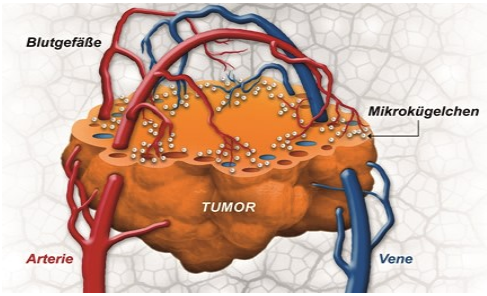
Laser ablation can be repeated without problems as needed; on the other hand, multiple liver resections are often not possible, since a large amount of healthy tissue must also be resected for safety reasons.

CT Cryotherapy is based on the use of very low temperatures in the tumour tissues, resulting in non-specific tissue necrosis and microvascular thromboses in the tumour. The aim of cryotherapy is to destroy the tumour tissues in situ while influencing the surrounding liver tissues as minimally as possible. In this method of freezing the cancer in situ, the tumour tissues near the freezing probe are rapidly cooled to -190 °C, forming ice within the cells with consecutive membrane damage and cell death.

With slower freezing or less low end temperatures, as expected in the periphery of the ice sphere that is formed, extracellular ice formation with resulting increased osmolarity of the remaining extracellular liquids takes place. The resultant osmotic gradient causes water loss of the cells and produces changes in the intracellular environment that can result in cell death.

SIRT Selective Internal Radiotherapy, also called radioembolization or Transarterial Radioembolization (TARE), is a locoregional, minimally invasive therapy method to treat primary cell tumours and liver metastases. SIRT is an uncomplicated therapy option with few side effects for patients who do not (or no longer) respond to other local and systemic treatment methods.

SIRT treatment takes advantage of the liver's dual blood supply: Healthy liver tissues receive more than 80% of their blood supply via the portal vein and signifi-



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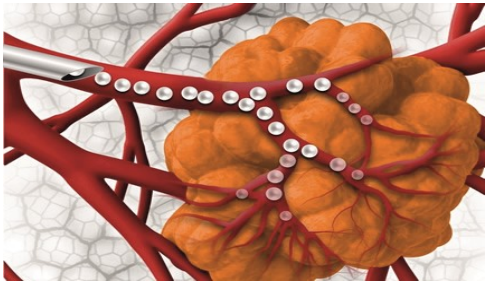
cantly less via the arterial supply route (hepatic artery). Liver tumours, however, are supplied with blood mainly via the hepatic artery, meaning that the microspheres of SIRT treatment that are combined with yttrium-90 can be brought to the tumour directly via the hepatic arteries using an angiographic technique.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The tumour is then specifically irradiated from the inside out, which can destroy the tumour or metastases. At the same time, the microspheres block or restrict the blood supply to the tumour tissues.

Beta-irradiation of yttrium-90 in the microspheres only has a low range of approximately 3-10 mm, sparing the surrounding tumour-free tissues and bringing the irradiation dose to the tumour more effectively than would be possible with external radiation. SIRT is primarily used in the palliative stage of cancer treatment thus far. .

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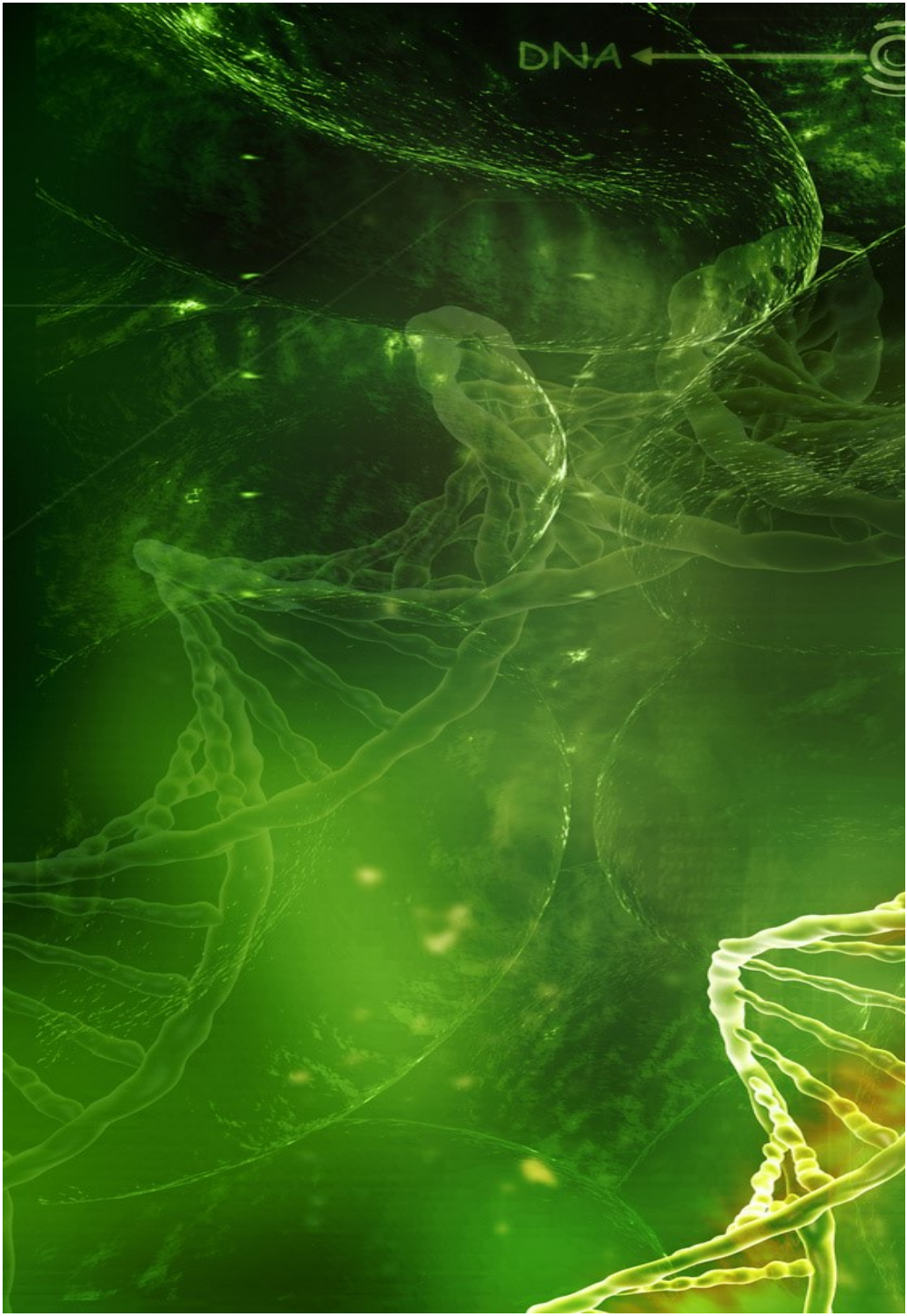
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